Voor mijn grootouders
  Jan & Pia
  Paul & Lenie
The studies described in this thesis were supported by:
- Stichting Erasmus Fonds Pijnbestrijding
- EFIC-Grünenthal Grant
- National Children’s Research Centre (Ireland)
- Sophia Children’s Hospital Foundation (the Netherlands)

Printing of this thesis was financially supported by:
- J.E. Jurriaanse Stichting
- Covidien Nederland B.V.


Cover design: Griet Menschaert
Photographer: Bas Wilders
Lay-out: Maya Timmer, MAT ONTWERP, bno
Printed by: Gildeprint Drukkerijen, Enschede, the Netherlands

© 2012 A.J. Valkenburg, Rotterdam, the Netherlands

All rights reserved. No part of this thesis may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, without prior permission from the author, or when appropriate, from the publisher.
Without Uttering a Word
Pain assessment and management
in intellectually disabled children

Zonder een woord uit te brengen
Het meten en behandelen van pijn
bij verstandelijk gehandicapte kinderen

Proefschrift
ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
vrijdag 30 november 2012 om 11.30 uur

doors

Abraham Johannes Valkenburg
geboren te Zwolle
PROMOTIECOMMISSIE

Promotor
Prof.dr. D. Tibboel

Overige leden
Prof.dr. F.J.P.M. Huygen
Prof.dr. R.J. Stolker
Prof.dr. E.J.A. Scherder

Copromotor
Dr. M. van Dijk
## CONTENTS

Prologue ........................................................................... 7

**PART I  INTRODUCTION**

Chapter 1: General introduction ........................................... 15

Chapter 2: Pain management in intellectually disabled children: Assessment, treatment, and translational research .......................... 27

Chapter 3: Pain management in intellectually disabled children: A survey of perceptions and current practices among Dutch anesthesiologists ...................................................... 51

**PART II  ASSESSMENT**

Chapter 4: Extremely low preanesthetic BIS values in two children with West syndrome and Lissencephaly .................................................. 71

Chapter 5: Lower bispectral index values in children who are intellectually disabled ................................................................. 81

Chapter 6: The COMFORT-behavior scale is useful to assess pain and distress in 0- to 3- year old children with Down syndrome .................. 99

Chapter 7: Skin conductance peaks could result from changes in vital parameters unrelated to pain .................................................. 119

**PART III  QUANTITATIVE SENSORY TESTING**

Chapter 8: Pain sensitivity of children with Down syndrome and their siblings: Quantitative Sensory Testing versus parental reports ........... 137

Chapter 9: Long-term effects of neonatal continuous morphine infusion on pain sensitivity: Follow-up of a randomized controlled trial .................. 159

**PART IV  MANAGEMENT**

Chapter 10: Anaesthesia and postoperative analgesia in surgical neonates with or without Down’s syndrome: Is it really different? 185

Chapter 11: Pharmacodynamics and pharmacokinetics of morphine after cardiac surgery in children with and without Down syndrome .... 205

**PART V  DISCUSSION**

Chapter 12: General discussion ........................................... 231

Chapter 13: Summary / Samenvatting .................................. 253

**APPENDICES**

References for the poems ................................................. 264
Definitions ........................................................................... 265
Acknowledgements ............................................................... 266
Curriculum Vitae ................................................................. 269
PhD Portfolio .................................................................. 270
PROLOGUE
Before you start reading this thesis, I would like to share some of my experiences during the years I was working on the various projects that form the basis for this thesis.

**How it all started...**
Before I applied to medical school I said I would never be interested in doing research. However, my perception of research changed quickly enough; in June 2006 Heleen Blussé needed students to interview postoperative patients for her awareness study in the Erasmus MC - Sophia Children’s Hospital. I decided to apply. That was the first research project I worked on.

Shortly after Heleen introduced me to Tom de Leeuw. He was looking for a student to assist with his study on Bispectral index monitoring in intellectually disabled children. I recruited patients for this study before, sometimes during, and after my classes. One of the recovery nurses once joked with me “Does your mother know you’re here”?

**Supervisors**
At some point it became clear that the Bispectral index monitoring study wouldn’t be my last research project. Prof. Tibboel asked me if I would consider doing a PhD on pain in intellectually disabled children. Something I didn’t have to thing about for too long! Dr. Monique van Dijk would be my copromotor (supervisor).

In 2008, Prof. Tibboel sent in a proposal for the Academische Jaarprijs; a competition for teams from Dutch universities. The project aimed at creating awareness for pain in neonates, intellectually disabled children and cognitively impaired elderly patients. Although we left without the money, this was the start of the Meetbus project.

**“De Meetbus”**
The Meetbus is a Citroen HY van; build in 1974 and once owned by landscape photographer Hans Aarsman.
Ingeborg Griffioen from Panton and her husband Wouter transformed the van into the Meetbus; a beautifully designed mobile research unit. The Meetbus enabled us to visit the children with Down syndrome and their siblings at home so they did not have to come down to the hospital to participate in the study. The official launch party in June 2010 was a great event. Everyone loved the Meetbus and it received a lot of attention. There was one thing I didn’t realize at the time, that it is not easy to drive a 1974 Citroen HY.
Launch party of the Meetbus

Weekend with PhD students from Erasmus MC -Sophia Children’s Hospital

With Heleen Blussé
With Brendan O’Hare and Cormac Breatnach

With Monique van Dijk and Prof. Tibboel
Our Lady’s Children’s Hospital Crumlin
Monique had visited the PICU of Our Lady’s Children’s Hospital in Dublin to advise on pain and distress assessment with the COMFORT-B scale. This marked the start of an international collaboration between the two PICUs. In March 2011 Monique and I went over to talk about the ideas for a study on morphine pharmacokinetics and the analgesia and sedation requirements of children with Down syndrome after cardiac surgery.

This was the first of many visits to Dublin and in December 2011 I moved to Dublin. The local hospital ethics committee had already approved the study and the National Children’s Research Centre kindly provided funding. I could start recruiting patients in January 2012. Dr. Cormac Breatnach and Dr. Brendan O’Hare were my local supervisors; they made sure that I not only learned everything about cardiac anesthesia and intensive care medicine, but also about one of the three national sports in Ireland - rugby.

Moving to Ireland brought me to an exciting workplace, a new city, and a new country. I enjoyed every minute of working in Crumlin. Children and their families from all over Ireland travel to Crumlin for cardiac surgery, it has a big impact on the entire family.

Three other things I learned in Ireland:
1. Part of working in Crumlin is going for breakfast. I so enjoyed having a planned breakfast at work. And during the weekends the nurses manage to prepare a full Irish in the tiny kitchen. It is the best break of the day.
2. “And where are ye from?” Number one question in Ireland. It might sound trivial, but it is not. There is nothing so important as “home”. Whether it is in Mayo, west Cork or Zwolle.
3. Things will be ok. Stop worrying. Seen from here, the Netherlands looks so organized. Perhaps there is less need to be so organized.

Looking back at my PhD period
The research aimed at learning more about pain assessment and appropriate management in intellectually disabled children. I hope this thesis shows caregivers that assessing pain and distress in intellectually disabled children requires a little extra attention, but that current perceptions of different analgesia and sedation requirements seem to not necessarily be true.

I absolutely enjoyed doing the research, writing this thesis, but most of all working together with so many people. Prof. Tibboel and Dr. Monique van Dijk taught me a great deal about doing clinical research. Their feedback, innovative ideas and support were key ingredients for this thesis.

A good preparation is essential, but things will be ok and a little bit of patience and persistence goes a long way.

Bram
INTRODUCTION
Chapter 1

GENERAL INTRODUCTION
“Common sensation is generally much less acute than in ordinary persons. Pain is born with wonderful callousness. It is not uncommon for children of this class to allow a thecal abscess to be opened with a scalpel without a grimace or without uttering a word.”

This is what John Langdon Down back in 1887 wrote in his treatise on what we now refer to as individuals with Down syndrome(1). Around 1 in every 700 children is born with trisomy 21 (Down syndrome), which makes it the primary cause of congenital intellectually disability. The vast majority of children with Down syndrome is intellectually disabled; the mean intelligence quotient (IQ) is 50 (range 30 to 70)(2).

More than 80 different comorbidities have been associated with Down syndrome(3) and some – such as a congenital heart defect – are present in the majority of the children with Down syndrome(4). Up to 20 years ago, Down syndrome was a reason to withhold surgery for congenital duodenal obstruction or congenital heart defects(5). This is no longer the case; together with improved therapy for pulmonary hypertension and leukemia the 10-year survival of children with Down syndrome improved to 91%(6). Morbidity is higher in those who survive; therefore adequate pain assessment and management is highly relevant in these children.

The studies in this thesis address pain assessment and management, as well as general anesthesia and sedation, in intellectually disabled children - with a focus on children with Down syndrome. Furthermore, there are parallels with pain assessment and management in neonates and infants. The different topics are introduced below.

**Measuring depth of anesthesia**

General anesthesia is a drug-induced, reversible condition that includes specific behavioral and physiological traits - unconsciousness, amnesia, analgesia, and akinesia - with concomitant stability of the autonomic, cardiovascular, respiratory, and thermoregulatory systems(7). Several electroencephalogram (EEG)- derived monitors have been developed to measure depth of anesthesia; predominantly the depth of the hypnotic component of anesthesia. Bispectral index (BIS) monitoring, initially developed to prevent intraoperative awareness, is the best studied instrument to measure depth of anesthesia in children(8). Given the high incidence of comorbidities in intellectually disabled children, they will often require general anesthesia for surgery, dental treatments or diagnostic procedures(9). Anesthesiologists could well face communication problems, difficulties in assessing the level
of consciousness, and unexpected consequences of pharmacokinetic or pharmacodynamic interactions when caring for intellectually disabled children. A reliable measure of depth of anesthesia could help titrate anesthetic agents in these children. However, it has been noted that BIS values tend to be lower in intellectually disabled patients\(^{(10, 11)}\). The validity of BIS in these patients requires therefore more attention.

**Clinical aspects of pain assessment and management**

Although self-report is the gold standard for pain assessment, it is not always feasible or appropriate. Health professionals have had to find other methods to assess pain in infants and young children, in mechanically ventilated or sedated patients, and in intellectually disabled patients. Consequently, various observational pain assessment tools have been developed and validated to measure pain in these groups, such as the COMFORT-B scale for children below the age of 3 years\(^{(12)}\) and various scales for intellectually disabled children\(^{(13-15)}\). Nevertheless, there is still a paucity of evidence for the proper pain management in intellectually disabled patients and they are often excluded from prospective randomized trials on analgesic regimens. Their participation in such trials is badly needed since retrospective studies revealed that intellectually disabled children received lower doses of intraoperative opioids compared to controls\(^{(16, 17)}\). Furthermore, Malviya et al. reported that 89% of the physicians they surveyed tended to prescribe sub-therapeutic doses of analgesics to children with an intellectual disability\(^{(18)}\).

Especially children with Down syndrome are often described as more agitated and “difficult to sedate” after surgery\(^{(19)}\). This was confirmed in a retrospective chart review study; it showed that children with Down syndrome more often received sedatives and muscle relaxants after cardiac surgery than children without Down syndrome\(^{(20)}\); however, these claims have not been evaluated in prospective trials.

**Experimental pain research**

Since 1960 we have seen substantial growth in the research on pain in humans (see Figure 1). Initially focusing on adults, 20 years later this research picked up on pain in children, with for example the key publications by Anand and colleagues on pain in neonates\(^{(21, 22)}\). The output is in sharp contrast with the number of studies in intellectually disabled children: between 2005 and 2009 no more than 30 of the 100 000 articles on pain in humans addressed pain in this vulnerable patient group. We are still waiting for the dashed line in the graph to incline.

Since the publication of John Langdon Down’s report in 1887\(^{(1)}\), the pain sensitivity of intellectually disabled children and adults has been widely debated but rarely studied\(^{(23, 24)}\). The first systematic investigation of their pain sensitivity was published in 2000; it showed that individuals with Down syndrome have more problems to localize pain and perceived an ice-cold stimulus later as painful than controls\(^{(25)}\). Defrin et al. were the first to apply quantitative sensory testing (QST) and found that intellectually disabled adults are
even more sensitive to painful stimuli than controls(26). The QST procedure systematically documents alterations and reorganization in nervous system function and, in particular, the nociceptive system(27). One of the most frequently applied QST modalities in both children and adults is the assessment of the thermal detection and pain thresholds with the Thermal Sensory Analyser(28, 29).

Pain sensitivity has also been investigated in one of the mouse models for Down syndrome. Compared to control littermates, the Tn65Dn mouse showed an overall reduced responsiveness to painful stimuli(30). However, the claim that children with Down syndrome are less sensitive to pain has not been systematically evaluated.

![Graph showing publications on pain in PubMed between 1960 and 2009](image)

**FIGURE 1** Publications on pain in PubMed between 1960 and 2009
Adapted from Belew et al.(31) The dotted line represents numbers of publications on adults and children together; the solid line numbers of publications in children separately; and the dashed line publications on pain in intellectually disabled children. The upper diagram shows the number of publications for the three groups and the lower diagram only publications on children and intellectually disabled children.
Pain in neonates and infants

Pain management can be challenging as well in other groups of pediatric patients in which self-report of pain is not an option. Randomized controlled trials have investigated the optimal analgesic therapies in neonates and infants(32, 33). However, concerns have been raised that analgesic and anesthetic agents might have long-term adverse effects on the developing nervous system of neonates and infants, in particular the induction of neuroapoptosis(34). Analgesics are titrated based on observational pain assessments; nevertheless observational pain assessment is regarded as a silver standard; one keeps searching for a more objective method to measure pain such as skin conductance(35), near-infrared spectroscopy(36), or heart-rate variability(37). However, Berde and McGrath recently emphasised that “there is a strong bias among clinicians and clinical researchers to find an objective measure of pain”(38). They postulated criteria for the ideal physiologic measure of pain intensity (See Table 1).

### TABLE 1
Criteria for physiologic measures of pain intensity

<table>
<thead>
<tr>
<th></th>
<th>Low cost, portable, reliable, easy to use, low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Strong agreement with self-report pain scales in articulate subjects ages 4 years and older.</td>
</tr>
</tbody>
</table>

Strong agreement means:

- High sensitivity and high specificity
- Excellent positive and negative predictive value over the full range from mild to severe pain intensities
- For patients/subjects with:
  - Experimental pain, including repetitive stimulation
  - Acute postoperative pain
  - Several distinct types of recurrent episodic pain and chronic persistant pain

Adapted from Berde and McGrath(38)
STUDY QUESTIONS

The studies presented in this thesis addressed the following questions:

Part II Assessment
- Are instruments for pain and distress assessment, such as BIS-monitoring, the COMFORT-B scale and skin conductance monitoring, also valid in non-verbal infants and children?

Part III Quantitative sensory testing
- Do children with Down syndrome show reduced sensitivity to pain according to their parents and in experimental pain tests?
- Does continuous morphine administration at neonatal age affect thermal detection and pain thresholds, chronic pain, or neurological functioning at 8-9 years of age?

Part IV Management
- Do postoperative analgesia and sedation requirements or the morphine pharmacokinetics of children with Down syndrome differ from those of other children?
OUTLINE

Part I introduces the topic of pain assessment and management in intellectually disabled children. Chapter 2 is a review of the literature on pain assessment, management and translational research in these children. The results of a survey among Dutch anesthesiologists on their perceptions and practice with regard to pain management in intellectually disabled children are presented in Chapter 3.

Part II reports on the validation and use of pain and distress assessment tools. The use of BIS-monitoring to measure the depth of the sedative component of anesthesia is reported in Chapters 4 and 5. The COMFORT-B scale is evaluated for the assessment of pain and distress in children with Down syndrome in Chapter 6. Skin conductance monitoring as a real-time measure of sympathetic nervous system activations (such as pain and distress) was applied in Chapter 7.

Part III focuses on quantitative sensory testing. The study in Chapter 8 describes the thermal detection and pain thresholds as well as the results of parental questionnaires on the pain behaviour of children with Down syndrome versus siblings. The study in Chapter 9 evaluates the effects of neonatal continuous morphine infusion on thermal detection and pain thresholds, chronic pain and neurological functioning at 8 to 9 years of age.

Part IV describes the results of a retrospective study on the analgesia and sedation requirements of neonates with Down syndrome in Chapter 10 and the results of a prospective study on the pharmacokinetics and pharmacodynamics of morphine after cardiac surgery in infants and children with and without Down syndrome in Chapter 11.

Part V discusses the results of this thesis in a broader perspective and gives an overall summary of the thesis in Chapter 12 and 13.
REFERENCES

1. Down JL. On some of the mental affections of childhood and youth: Being the Lettsomian lectures delivered before the Medical society of London in 1887, together with other papers. London: J. & A. Churchill; 1887.


‘I put you from your pain, I can no more.’
Chapter 2

PAIN MANAGEMENT IN INTELLECTUALLY DISABLED CHILDREN: ASSESSMENT, TREATMENT, AND TRANSLATIONAL RESEARCH

Abraham J. Valkenburg, Monique van Dijk, Annelies de Klein, Johannes N. van den Anker, Dick Tibboel

*Developmental Disabilities Research Reviews* (2010); 16: 248 - 257
The primary focus of pain research in intellectually disabled individuals is still on pain assessment. Several observational pain assessment scales are available, each with its own characteristics, its own target group and its own validated use. Observational studies report differences in the treatment of intra- and postoperative pain of intellectually disabled children and almost all children with intellectual disability have comorbidities that need to be addressed. The scope of research has started to broaden. In this review we aim to answer the question: Can we integrate validated ways of pain assessment and postoperative pain treatment in intellectually disabled children in order to develop specific analgesic algorithms? Regrettably there is little knowledge on possible interaction effects and other relevant pharmacological issues. Possible genotype-phenotype associations related to pain in children with Down’s syndrome have several promises as six possible candidate genes are located on chromosome 21.

In conclusion, the pain assessment tools for intellectually disabled children are there. We should now focus on tailoring the pain treatment. To this aim we need to perform pharmacokinetic and pharmacodynamic studies of analgesics and obtain information about the genotype - phenotype relationships for pain. This can lead to the development of specific analgesic algorithms.
INTRODUCTION

Pain in intellectually disabled individuals
What makes pain management in intellectually disabled individuals so challenging? Are there alterations in neurobiological processes involved in nociception, is it more difficult for them to express pain or are caregivers unaware of methods to assess pain? More than half a century ago, Couston presented seven cases of intellectually disabled adults who did not show any pain in situations where he expected pain expression(1). But times have changed and several pain assessment tools specially geared to persons with an intellectual disability are available now. These pain assessment tools rely on observation by caregivers, as self-report usually is not possible or is considered to be unreliable nowadays. The primary focus of pain research in intellectually disabled individuals is still on pain assessment. The scope of research has started to broaden. Several experimental pain studies have been reported, for example a quantitative sensory testing (QST) study among individuals with Down’s syndrome (2), the postoperative pain treatment has retrospectively been evaluated (3, 4) and the first steps towards translational genetic studies have been made(5).

Epidemiology
The American Association on Intellectual and Developmental Disabilities (AAIDD) defines intellectual disability as “A disability characterized by significant limitations both in intellectual functioning and in adaptive behavior, which covers many everyday social and practical skills. This disability originates before the age of 18.” Epidemiological studies have reported prevalence of intellectual disability ranging from 0.3% to 0.78%(6, 7). The causes of intellectual disability are very diverse, from chromosomal abnormalities to hereditary diseases or acquired disorders. Westerinen et al. provide a number of inclusion diagnoses based on the International Classification of Diseases (ICD) 10 that are used for the epidemiological analysis(6). Another aspect is the epidemiology of health conditions among intellectually disabled children. For example gastroesophageal reflux disease, a condition that will cause significant discomfort and pain, is present in up to 50% of intellectually disabled children and adults(8, 9). Albeit that children with an intellectual disability form a heterogeneous group, it would be worthwhile to identify common traits in pain expression and grounds for tailor-made pain management of this group.

Outline of this review
First, recent advances in pain assessment of intellectually disabled children will be explored. The second part of this review will evaluate the pain treatment and the influence of co-medication in this group. Third, (translational) genetic studies in Down’s syndrome will be discussed from the perspective of pain research. In this review we aim to answer the question: Can we integrate validated ways of pain assessment and postoperative pain treatment in intellectually disabled children in order to develop specific analgesic algorithms?
PAIN ASSESSMENT

Why focus on assessment?
The International Association for the Study of Pain considers a person’s self-report of pain as the gold standard for pain assessment. Apart from the presence of pain, medical professionals will want to know the location, duration, intensity, type of sensation and so on. There are self-report tools to quantify the intensity of pain, for example the Visual Analogue Scale or Numeric Rating Scale(10). After surgery for example, patients should be assessed on a regular basis and pain scores should be recorded. Pain assessment is an essential part of history taking and daily clinical practice. Providing adequate analgesic therapy is virtually impossible when not based on reliable pain assessment. In addition, reassessment of pain after intervention is important to ensure effective and safe pain management(11).

What if people cannot say they have pain or what if we have reasons to doubt that the answer is reliable? This is considered to be the case in young children up to the age of three years, intellectually disabled children and adults and cognitively impaired elderly persons as well as patients who are sedated during intubation for artificial ventilation. In this review article we will focus on intellectually disabled children. Kingston et al. state that caregivers should take care not to regard the behavior of persons with intellectual disability as challenging only, because that brings the risk of ‘diagnostic overshadowing’(12). In other words, clinicians shouldn’t attribute all symptoms to the intellectual disability, but see it as an attempt to communicate. A survey among parents about pain in intellectually disabled children made clear that the degree of intellectually disability influences the pain expression of their child. Children with mild or moderate intellectually disability made verbal statements about pain and children with profound intellectual disability used indirect behaviors (crying, behavioral and emotional changes) to express pain(13). In a recent review article about pain assessment in intellectual disabilities the results of the two studies that examined the quality of self-report are found inconclusive(14). More evidence is needed before self-report can be recommended as a first-line assessment approach for children with even mild intellectual disability. How do we then assess their pain? The answer is observational assessment.

Observational pain assessment
Several observational pain assessment scales are available, each with its own characteristics, its own target group and its own validated use. But all of them are based on observation of manifestations that are considered indicators of pain. Our own research group has developed and validated the Checklist Pain Behavior for intellectually disabled children(15).

Postoperative pain assessment
The presence of intellectual disability influences the decisions of caregivers regarding pain assessment and treatment(16, 17). Caregivers should use appropriate and valid observa-
# TABLE 1
Validated Observational Pain Assessment Scales for Intellectually Disabled Children

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age range</strong></td>
<td>6-33</td>
<td>3-19</td>
<td>1 - 18</td>
<td>3-19</td>
<td>4-19</td>
<td>6 -18</td>
<td></td>
</tr>
<tr>
<td>in years</td>
<td>Mean age 10 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of</strong></td>
<td>112</td>
<td>49</td>
<td>24</td>
<td>140</td>
<td>73</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td><strong>patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patient</strong></td>
<td>non-verbal patients</td>
<td>non-verbal</td>
<td>non-verbal</td>
<td>non-verbal</td>
<td>intel-lectually disabled children</td>
<td>intel-lectually disabled children</td>
<td>non-verbal</td>
</tr>
<tr>
<td>group</td>
<td>non-verbal</td>
<td>intel-lectually disabled children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with cerebral</td>
<td>intellectually disabled</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>palsy</td>
<td>disabled children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>Pain</td>
<td>Pain</td>
<td>Postoperative Pain</td>
<td>Postoperative Pain</td>
<td>Postoperative Pain</td>
<td>Postoperative Pain</td>
<td></td>
</tr>
<tr>
<td><strong>Indicators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facial</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocal</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consolability</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiological</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>indicators</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Items</strong></td>
<td>10 (0 - 10)</td>
<td>6 (0 - 24)</td>
<td>27 (0 - 81)</td>
<td>20 (0 - 60)</td>
<td>10 (0 - 10)</td>
<td>5 (0 - 10)</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>(score range)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>2/10: Pain is possible</td>
<td>Not available</td>
<td>11/ 81: Moderate to severe pain</td>
<td>Not available</td>
<td>14/60: Moderate or worse pain</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td><strong>cut-off</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>scores</strong></td>
<td>6/10: Definite pain that requires treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical cut-off scores:**
- Not available
- Moderate to severe pain
- Moderate or worse pain
- Moderate pain (not based on sensitivity/specificity)
- Not available
tion postoperative pain assessment scales immediately after surgery. Table I provides an overview of validated observational pain assessment skills for intellectually disabled children. The review articles of Voepel-Lewis et al., Ghai et al., Breau et al., and Van Dijk et al., and the book chapter by Breau et al. discuss the characteristics of the different scales in a solid way(14, 18-21). Complexity, clinical utility, compatibility, validity and the items of the scales are topics that have been addressed in the reviews.

**Behavioral versus physiological indicators of pain**

Pain assessment scales are either unidimensional or multidimensional. This classification refers to the factor structure (are all items a measure for the same construct?), to the construct of the results (only pain or pain and, for example, distress) or to the nature of the items (behavioral or physiological) Most of the above mentioned pain assessment scales are composed of behavioral indicators of pain. Physiological indicators such as heart rate variability(22), skin conductance(23) and near-infrared spectroscopy (NIRS)(24) could be seen as biomarkers of both the stress or pain system. Stevens et al. identified three different purposes of biomarkers, namely as outcome measure, as predictor of health and development, and as probe of central nervous system integrity(25). Anand et al. state that a physiological response to a painful stimulus should be regarded as evidence of pain reactivity(26). Researchers generally seem to be biased towards physiological measures(27). They provide a list with criteria that should be met for a candidate physiologic measure of pain intensity. Based on these criteria a well-validated multidimensional pain assessment scale should be developed, including behavioral indicators and for example skin conductance or heart rate variability measurement.

**Recent advances in pain assessment**

Recent advances in pain assessment include a pain assessment protocol and the Individualized Numeric Rating Scale (INRS). The peer reviewed pain assessment protocol of Kingstone et al. includes a pain diary kept by caregivers, a pain story, assessment of chronic pain, a baseline pain assessment, a simple visual analogue scale, the pain faces tool and a body map. Especially the pain diary and pain story with the appropriate use of symbols could improve communication of pain in intellectually disabled children. However, this protocol should be prospectively evaluated to validate its use(12). The INRS is based on individual pain indicators that parents and caregivers proposed(28). The individual descriptions are ranked on a scale from 0 to 10. This makes the INRS an observational pain assessment tool, not a self-report tool. The INRS was validated in a study exploring postoperative pain in 50 children with profound intellectual disability, aged 6 - 18 years. In the accompanying editorial, Breau points out that there will always be a pull between clinical utility and psychometric soundness of a pain assessment scale(29). Furthermore, she states that standardized scales are possible for this population and that individualized pain tools are not necessary.
**Individualized pain assessment**

The question remains how individualized the pain assessment should be. On the one hand, standardized scales can easily be implemented in clinical practice. Nurses and doctors can be trained to use the scale, and the results can be used to guide pain management or serve as an outcome parameter in research. On the other hand, we should not forget the individual patient. Such standard scales will never cover the wide variability in the degree of intellectual disability. It could be helpful to use information about a child’s adaptive behavior. The Vineland Adaptive Behavior Scale assesses domains of adaptive behavior such as communication and social skills that are also necessarily to convey pain(30, 31). The Pediatric Pain Profile also makes it possible to relate a child’s normal behavior with his/her pain behavior. The profile is completed by parents and yields information about a child’s behavior when it is on its best and when it suffers from pain(32).

**Experimental Research (Quantitative Sensory Testing)**

Pain assessment can now encompass more than just measuring the frequency and intensity of pain by behavioral parameters. A psychophysical method has been introduced, Quantitative Sensory Testing (QST), which systematically documents alterations and reorganization in nervous system function and, in particular, the nociceptive system(33). It is hoped that its application will clarify the mechanisms involved in nociception. In their review article, Arendt-Nielsen et al. distinguish three different purposes of QST regarding pain assessment: First, basic mechanistic studies in healthy volunteers. Second, clinical studies for diagnostic and monitoring purposes. Third, pharmacological studies to evaluate analgesic efficacy of new and existing compounds. As QST quantifies the reactions to sensory stimuli, it is well suited to measure a person’s pain sensitivity, for example. Results of standardized QST measurements could be compared between persons and between groups. The German research network on neuropathic pain has published reference values for their QST protocol in healthy children(34), healthy adults(35) and in adults with neuropathic pain syndromes(36). Nielsen et al. state in a review article that both clinical and experimental pain studies consistently reveal large individual differences in reported pain(37). It is recommended to study the sources of variation (for example environmental and genetic factors), so that measures of pain sensitivity could be used to predict clinical outcomes and to individualize pain treatment regimens. A systematic review by Werner et al. revealed that preoperative pain tests may predict 4 to 54% of the variance in postoperative pain experience, depending on the stimulation methods and test paradigm used(38). This predictive strength is higher than demographics or psychological factors. This is a promising field that needs evidence from more and larger studies with an appropriate design.

**QST in intellectually disabled persons**

Through the years, conflicting reports about the pain sensitivity of intellectually disabled persons have been published. In 1954 Couston reported reduced pain sensations in seven
adults(1). In 1958 Stengel et al. reported that insensitivity to pain was not observed in any of the 97 intellectually disabled patients in their study(39). Several decades later, Biersdorff estimated that the incidence of pain insensitivity/indifference in intellectually disabled persons was 25.2%(40). Quantitative sensory testing can help us to quantify and study the reaction to nociceptive stimuli in intellectually disabled. In a QST pilot study, Hennequin et al. found that individuals with Down’s syndrome (n=26), aged 4 to 30 years, expressed pain more slowly and less precisely than did control subjects (n=75)(2). Defrin et al. found that the heat pain thresholds in 25 intellectually disabled adults (11 of them had Down’s syndrome) were lower than those in the 14 control subjects, i.e. when assessed with the reaction-time independent method. The heat pain thresholds assessed with the reaction-time dependent method were comparable, but this could be explained by the longer reaction times of the intellectually disabled subjects(41). In a sham-controlled sensory-testing protocol, Symons et al. studied the facial behavior of 44 intellectually disabled adults before, during and after sensory-stimulation modalities(42). This study shows that individuals with significant intellectual impairments are sensitive to tactile stimulation consistent with QST protocols. In conclusion, QST is feasible in intellectually disabled. Studying the influences of developmental age, earlier painful events and major surgery, reaction time and genetic factors on the reaction to nociceptive stimuli might be worthwhile.
The area of postoperative pain treatment is as broad as or even broader than the area of pain assessment. There are many different analgesics, dosages, routes of administration and almost each hospital has its own pain protocols. There are only a few randomized controlled trials in this area, but other types of studies provide evidence for the most appropriate analgesia for specific groups and indications. Taddio and Oberlander provide an overview of most used medications for chronic conditions in intellectually disabled children and specific considerations to assure good analgesia(43). As to the latter, would they need adapted postoperative analgesia because of their intellectual disability?

What do we know from chart review studies?
A review article about Down’s syndrome and anesthesia provides a nice overview on the implications of Down’s syndrome for perioperative management(44). Apart from the notice that these children are regarded as gregarious and friendly and the mention of a higher incidence of postoperative agitation, Mitchell et al. do not report any other recommendations regarding postoperative analgesia. Gakhal et al. reported that children with Down’s syndrome (n=16) were more likely to receive morphine on postoperative day 3 after cardiac surgery and received more additional sedatives and muscle relaxants than children without Down’s syndrome (n=16)(3). Malviya et al. found that intellectually disabled children (n=19) received smaller doses of opioids after spinal fusion surgery than did children without intellectual disability (n=23) and that fewer intellectually disabled children were assessed for pain after surgery(45). Koh et al. prospectively evaluated the intra- and postoperative pain treatment of 152 children with intellectual disability (mean age 10 years old) and 138 children without (mean age 8 years old)(4). During surgery, children with intellectual disability received less amounts of opioids. The researchers found no differences in the amounts and types of postoperative analgesics. However, of the children who received morphine postoperatively, children with intellectual disability were less likely to receive it by a patient controlled analgesia (PCA) pump. The authors acknowledge the concern of many pediatric anesthesiologists that intellectually disabled children are more sensitive to respiratory and CNS depressive effects of opioids as a possible explanation for the difference in intraoperative opioid administration. The lesser use of the PCA pump might be explained by the difficulty in explaining its concepts to intellectually disabled children. Czarnecki et al. have evaluated the safety of postoperative parent/nurse-controlled analgesia (PNCA) in 71 intellectually disabled children (mean age 10 years)(46). Two patients needed naloxone administration because of respiratory depression or sedation. The authors conclude that through proper education and diligent monitoring, PNCA may be a safe and effective modality for postoperative analgesia in intellectually disabled children(46).

A recent study by Long et al. examined intra- and postoperative analgesia for orthopedic
TABLE 2
Comparison of analgesic consumption between intellectually disabled children and controls

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group</td>
<td>Retrospective case-control study</td>
<td>Retrospective cross-sectional study</td>
<td>Prospective cohort study</td>
<td>Retrospective cross-sectional study</td>
<td>Retrospective cross-sectional study</td>
</tr>
<tr>
<td>Control group</td>
<td>16 children with Down’s syndrome (mean age: 5 years)</td>
<td>19 intellectually disabled children (mean age: 11 years)</td>
<td>152 intellectually disabled children (mean age: 10 years)</td>
<td>71 children with cerebral palsy (29 intellectually disabled) (mean age: 11 years)</td>
<td>24 children with Down’s syndrome (median age: 3 days)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>Cardiac surgery</td>
<td>Spinal fusion surgery</td>
<td>Various</td>
<td>Orthopedic surgery</td>
<td>Congenital duodenal obstruction repair</td>
</tr>
<tr>
<td>Intra-operative analgesia of the study group</td>
<td>Not available</td>
<td>=</td>
<td>↓</td>
<td>↓</td>
<td>=</td>
</tr>
<tr>
<td>Post-operative analgesia of the study group</td>
<td>↑</td>
<td>↓</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
</tbody>
</table>

*A Analgesic doses compared to the control group* 

Surgery in 71 children with cerebral palsy and 77 children without. Of the children with cerebral palsy, 41% were intellectually disabled(47). However, the findings of Long et al. were comparable to those of Koh et al. since children with cerebral palsy received less amounts
of opioids intraoperatively and comparable amounts of postoperative analgesia(4). Also the children with cerebral palsy were less often assessed for postoperative pain, as reported by Malviya et al. as well. Our own research group compared the analgesic consumption after congenital duodenal obstruction repair between neonates with and without Down’s syndrome. We observed no differences in morphine doses or pain scores between the two groups(48).

Table II provides a summary of the results of these comparative studies regarding perioperative pain treatment in intellectually disabled children versus controls.

In conclusion, these observational studies report differences in the treatment of intra- and postoperative pain of intellectually disabled children. It seems that intellectually disabled children receive less intraoperative analgesia and fewer of them are assessed for postoperative pain. No differences in the amount of postoperative analgesia have been reported, but children with intellectual disability are less likely to receive a PCA pump. Most importantly, it is not clear in any of these studies why the children with intellectually disability received less intraoperative analgesia. Do pediatric anesthesiologists only believe that those children need less analgesia or is this finding a result of methodological issues of those studies or do they really need less amounts of analgesia for the same analgesic effect?

Co-medication in intellectually disabled children

Almost all children with intellectual disability have comorbidities that need to be addressed. For example, about 10% of the intellectually disabled children in a Dutch cohort study were treated with psychotropic drugs(49). The nature of the comorbidity depends mostly on the underlying cause of the intellectual disability. Thyroid disorders have been reported in up to 54% of children with Down’s syndrome (50) and they are therefore more often treated with supplemental thyroid hormones(51). There is, however, one comorbidity that is more common among all individuals with intellectual disability, namely epilepsy. A review article by Beavis et al. reported a 14 to 75% prevalence of epilepsy in patients with intellectual disability(52). For example, in a cohort of 48 children with spastic tetraplegia 50% suffered from epilepsy and all of them were treated with antiepileptic drugs(53). A larger study described that 20% of 818 children with cerebral palsy had seizures in the past 12 months(54). Glaze et al. found that 60% of 602 patients with RETT syndrome had seizures. Eighty percent of the patients with seizures were treated(55). Lastly, 8% of 350 children with Down’s syndrome suffered from seizures and all of them received antiepileptic drugs(56).

Chronic treatment with antiepileptic drugs could have implications for anesthetic and postoperative care. Antiepileptic drugs have many physiologic and pharmacologic effects that can have impact on an anesthetic. Kofke et al. described that the protein binding and enzyme induction effects of common antiepileptic drug, could influence the pharmacokinetics of sedative and analgesic drugs used for anesthesia and postoperative analgesia(57).
Tempelhoff et al. found that patients treated with antiepileptic drugs required higher doses of fentanyl for maintenance of general anesthesia compared with patients who had never received antiepileptic drugs (58). Eriksson et al. found lower plasma concentrations of clonazepam in children treated with lamotrigine (59). The use of antiepileptic drugs has also been associated with different pharmacodynamic effects such as depth of anesthesia (60).

This area definitely will need more attention, as all children treated with those drugs will benefit from this information.

**Pharmacological research in children**

Regrettably there is little knowledge on possible interaction effects and other relevant pharmacological issues. Up to 70% percent of the drugs used in a children’s hospital are unapproved or off-label (61). Tailor-made drug therapy in children, first of all requires more information about the drugs that are used in children. We must know what the body does with the drug, the pharmacokinetics, and what the drug does to the body, the pharmacodynamics. These processes considerably change when a newborn develops into a child, an adult and an elderly person. Apart from the developmental stage, also body composition, use of co-medication, presence of hepatic or renal failure are known to influence a drug’s pharmacokinetics and pharmacodynamics (62). Combining the information on the pharmacokinetics and pharmacodynamics of a drug could lead to a model that describes the efficacy and concentrations of that drug. Based on this model, dosing recommendations can be generated. The validity of these dosing recommendations should then be tested in a prospective study. The process leading to validated dosing recommendations used to be long and difficult in children (63), but is made easier by recent advantages such as better sample analysis equipment and statistical software packages (64, 65). This will also benefit the patient since fewer and smaller blood samples are required. A good example is the pharmacology of morphine, a widely used analgesic in children and adults of any age. A recent study by Knibbe et al. provided new dosing recommendations based on a population pharmacokinetic model of intravenous morphine in children up to the age of three years old. Simulations showed that a different dosing regimen would result in a more narrow range of morphine and metabolite concentrations (65).

We have learned that healthcare professionals assess and treat pain differently in intellectually disabled children. This is why special pain assessment scales have been developed for this group of children. Some researchers might have anticipated the question if analgesic dosing regimens need to be adjusted for intellectually disabled children since they excluded these children from analgesics pharmacokinetics and pharmacodynamics studies (66-70). Evidence for (hypothetical) differences in pharmacokinetics and pharmacodynamics in intellectually disabled children is very scarce. We know that co-medication can influence the pharmacokinetics of analgesics. Measuring the pharmacodynamic effects requires the use of adjusted pain assessment tools. Few studies have investigated the pharmacokinetics of specific drugs in children with Down’s syndrome. A small study on vincristine, a chemo-
therapeutic, found no altered pharmacokinetics in children with Down’s syndrome(71). Three other studies reported only subtle alterations in children with Down’s syndrome. Griener et al. reported that only the metabolism of the acetaminophen could be increased to glutathione-derived conjugates and decreased to the sulfate-derived conjugates(72). Clearance of theophylline, a drug that treats reactive airway diseases, was found to be prolonged in children with Down’s syndrome(73). The clearance of methotrexate in children with Down’s syndrome was 5% lower than in children without Down’s syndrome(74). The authors of the latter study conclude they found no evidence for differences in the pharmacokinetics of methotrexate that explained lower tolerance in children with Down’s syndrome for this drug.

In conclusion, the advanced methods of pharmacological research make it possible to study smaller groups of patients. The focus of pharmacological research should be on the influence of co-medication on analgesics. Both children with and without intellectual disabilities will benefit from these studies.
DOWN’S SYNDROME

What is so special about children with Down’s syndrome?

Down’s syndrome, occurring in about 1 in 700 live births, is the most common genetic cause of intellectual disability. Each year 275 - 300 children with Down’s syndrome are born in the Netherlands(75). About 95% of the individuals with Down’s syndrome have a trisomy 21, the others show Robertsonian translocation involving chromosome 21 or mosaic trisomy 21.

Despite the shared genetic cause, the phenotype of children with Down’s syndrome is highly variable. Therefore we will address several possible risk factors for altered pain experience and pain expression in these children. Throughout their whole life children with Down’s syndrome are more at risk to experience pain. Several major congenital abnormalities that require surgical intervention occur more often in children with Down’s syndrome than in the general population. For example, from a large population-based study in the US(76) it appeared that 6.7% of the children with Down’s syndrome were born with a congenital gastrointestinal defect such as duodenal atresia and Hirschsprung’s disease(77).

Furthermore, many more children with Down’s syndrome are born with congenital heart defects(78-80). Especially atrial septal defects, ventricular septal defects, and atrioventricular septal defects are more common in this group. These defects will require endovascular or surgical treatment. These children with Down’s syndrome are more at risk to develop pulmonary hypertension compared to children without Down’s syndrome(80). Pulmonary hypertension requires adjusted management during intensive care treatment or surgery since this state is associated with more perioperative complications.(81) Also later in life, several specific diseases that might cause pain are more common in children with Down’s syndrome. For example, they have an increased risk of developing acute leukemias(82). Both the disease and its treatment might cause pain. Ear, nose and throat problems, such as chronic middle ear disease and chronic rhinorrhea, are frequently seen in children with Down’s syndrome and cause considerable morbidity(50). Orthopedic problems such as upper cervical spine instability, scoliosis, hip problems or foot problems are present in approximately 20% of the children with Down’s syndrome. A great deal of these disorders can become symptomatic, cause pain and disability and require surgical intervention(83).

Intellectual disability is present in almost all children with Down’s syndrome. However, there is a great variety in development of these children. Intelligence Quotients average 50 with a range from 30 to 70(84). Children with Down’s syndrome are especially delayed in expressive communication and some researchers suggest this delay increases when the children get older(30). Dykens et al. suggested that there is an age-related plateau in the development of adaptive behavior during the middle childhood years. Chapman et al. provide a useful overview of the developmental emergence of the behavioral phenotype of Down’s syndrome from infancy to adulthood(84). Other associated disorders such as hearing and visual impairments, hypothyroidism, seizures and obstructive sleep apnea can have a
negative impact on cognitive functioning(85). The developmental delay across the different domains will certainly influence the pain expression abilities of most children with Down’s syndrome.

On the one hand, children with Down’s syndrome are more at risk to experience pain due to, for example, associated congenital abnormalities and orthopedic problems. On the other hand, they face more challenges in expressing their pain due to the developmental delay, poor expressive language and speech intelligibility skills, and hearing and visual impairments(86).

**Translational research and pain management**

Mouse models for Down’s syndrome are more and more used to study the genotype - phenotype relationships(87). Murine chromosome 16 contains about 80% orthologous genes of human chromosome 21.

One of the mouse models for Down’s syndrome has been used for studying the pain responsiveness compared to control litter-mates(5). Pain behavior was tested by the hot plate test and exposure to tonic pain from a formalin injection in a paw. Responsiveness to these nociceptive stimuli was overall decreased in the Down’s syndrome mice compared to control litter-mates. The authors suggest that overexpression of several genes might alter transmission of sensory and nociceptive stimuli. The human orthologues of these genes are located on chromosome 21 and could affect in a similar manner pain perception in Down syndrome patients.

This is just one example of translational pain research focused on pain and Down’s syndrome. The Pain Genes Database gives access to all published pain-related phenotypes of mutant mice(88). Six possible candidate genes for further research about genotype-phenotype relationships for pain in Down’s syndrome emerge from combining the information of the DNA sequence of human chromosome 21(89), the orthologues genes on murine chromosome 16(87), the Pain Genes Database(88) and the study about the pain responsiveness of the mouse model for Down’s syndrome (5). Table III provides further information about these six genes and the phenotype of the specific mice models. These six genes can be explored for alterations in the genome, for example the presence of polymorphisms influencing the level of gene expression of these genes in the dorsal root ganglia and peripheral nerve fibers, in combination with information about the pain phenotype. This research can be conducted both in humans using quantitative sensory testing (see above) or in the mouse model using tests as described by Martinez-Cue et al.

Studies in humans by Hennequin and Defrin showed that overall the reaction of adults with Down’s syndrome to nociceptive stimuli differs from the reaction of control individuals(2, 41). Combining this finding with that from the study of Martinez-Cue et al. about the reaction to nociceptive stimuli of the mouse model for Down’s syndrome, one could suggest
### TABLE 3 Possible candidate genes for the study of genotype - phenotype relationships in Down's syndrome

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Full name</th>
<th>Encodes for</th>
<th>Nociception</th>
<th>Hypersensitivity</th>
<th>Analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAMTS5</td>
<td>A disintegrin and metalloproteinase with thrombospondin motifs 5</td>
<td>Enzyme that functions as aggreganase to cleave aggregan, a major proteoglycan of cartilage</td>
<td>No differences</td>
<td>Mutant less sensitive</td>
<td>Not tested</td>
</tr>
<tr>
<td>GRIK1</td>
<td>Glutamate receptor, ionotropic, kainate 1</td>
<td>1 of the 4 subunits of a glutamate receptor</td>
<td>Mutant less sensitive</td>
<td>No differences</td>
<td>Not tested</td>
</tr>
<tr>
<td>S100B</td>
<td>S100 calcium binding protein B</td>
<td>Member of the S100 family of proteins containing 2 EF-hand calcium-binding motifs.</td>
<td>Not tested</td>
<td>Mutant less sensitive</td>
<td>Not tested</td>
</tr>
<tr>
<td>RUNX1</td>
<td>Runt-related transcription factor 1</td>
<td>α subunit of core binding factor; 3 isoforms</td>
<td>Mutant less sensitive</td>
<td>Mutant less sensitive</td>
<td>Not tested</td>
</tr>
<tr>
<td>KCN6</td>
<td>G protein-activated inward rectifier potassium channel 2</td>
<td>Integral membrane protein and inward-rectifier type potassium channel</td>
<td>Mutant more sensitive</td>
<td>Not tested</td>
<td>Mutant less sensitive</td>
</tr>
<tr>
<td>KCNE1</td>
<td>Potassium voltage-gated channel subfamily E member 1</td>
<td>Transmembrane protein known to associate with the product of the KVLQT1 gene to form the delayed rectifier potassium channel</td>
<td>Suggestion from Martinez-Cue et al.; No information from knockout mice study.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
that there is a pain phenotype in Down’s syndrome. It will be very difficult to distinguish
the effects from the pain phenotype on the pain expression from those of the intellectual
disability. Yet, if it would be possible, one could study the variability of the pain phenotype
across children with Down’s syndrome taking into account information about the genotype
of for example the six candidate genes. This translational approach would provide valuable
information about genotype - phenotype relationships for pain in Down’s syndrome.

TAILOR-MADE PAIN TREATMENT

The time has come to move on from studying pain assessment to studying postoperative
pain treatment in intellectually disabled children. In the first part of this review, it appeared
that self-report is seen as unreliable or impossible in intellectually disabled children and
that therefore researchers put a big effort in developing observational pain assessment
tools. Information about the adaptive behavior of a child could help selecting the appropri-
ate assessment tool for that individual. Future research will need to focus on multimodal
pain assessment and quantitative sensory testing, but for now, the observational pain as-
essment tools make it possible to assess pain in intellectually disabled children.

The second part of this review summarized the knowledge about postoperative pain treat-
ment in intellectually disabled children. The observational studies reported conflicting
results about the pain treatment. Considering the significant use of co-medication and the
possible pharmacokinetic nuances, we think it is time to prospectively evaluate these chil-
dren’s pain treatment. The pharmacokinetics and pharmacodynamics of analgesics should
also be examined in intellectually disabled children. We should start with studies in chil-
dren with Down’s syndrome as they are frequently subjected to major surgical procedures.

This brings us to the third part of this review, from which it is clear that it will be possible
to examine pain in children with Down’s syndrome more precisely - i.e. by studying geno-
type - phenotype relationships for pain in Down’s syndrome.

In conclusion, the pain assessment tools for intellectually disabled children are there. We
should now focus on tailoring the pain treatment. To this aim we need to perform pharma-
cokinetic and pharmacodynamic studies of analgesics and obtain information about the
genotype - phenotype relationships for pain. This can lead to the development of specific
analgesic algorithms.
REFERENCES


I only know that all we know comes from you
PAIN MANAGEMENT IN INTELLECTUALLY DISABLED CHILDREN: A SURVEY OF PERCEPTIONS AND CURRENT PRACTICES AMONG DUTCH ANESTHESIOLOGISTS

Abraham J. Valkenburg*, Sylvia M. van der Kreeft*, Tom G. de Leeuw, Robert J. Stolker, Dick Tibboel, Monique van Dijk

*Both authors contributed equally to this work

Pediatric Anesthesia (2012); 22: 682–689
ABSTRACT

Background
Intellectually disabled children are more likely to undergo surgical interventions and almost all have comorbidities that need to be managed. Compared with controls, intellectually disabled children tend to receive less intraoperative analgesia and fewer of them are assessed for postoperative pain.

Aim
To evaluate perceptions and practices of anesthesiologists in the Netherlands concerning pain management in intellectually disabled children.

Methods/Materials
We surveyed members of the Section on Pediatric Anesthesiology of the Netherlands Society of Anesthesiology in 2005 and 2009, using a self-designed questionnaire.

Results
The response rate was 47% in both years. In 2005, 32% of the anesthesiologists rated intellectually disabled children as “more sensitive to pain” than non-intellectually disabled children - versus 25% in 2009. But no more than 7% in 2005 versus 6% in 2009 agreed with the statement “children with intellectually disabled children need more analgesia”. Most anesthesiologists gave similar doses of intraoperative opioids for intellectually disabled and non-intellectually disabled children, 92% in 2005 versus 89% in 2009. In 2005, only 3% applied a pain assessment tool validated for intellectually disabled children, versus 4% in 2009.

Conclusions
Anesthesiologists in the Netherlands take a different approach when caring for intellectually disabled children and they were not aware of pain observation scales for these children. However, the majority think intellectually disabled children are not more sensitive to pain or require more analgesia. These opinions did not change over the four-year period. One way to proceed is to implement validated pain assessment tools and to invest in education.
INTRODUCTION

In 1954, Couston postulated that intellectually disabled persons are indifferent to pain(1). Over the years, however, opinions have changed; caregivers now generally consider that intellectually disabled children experience pain as other children(2). The American Association on Intellectual and Developmental Disabilities (AAIDD) defines intellectual disability as “a disability characterized by significant limitations both in intellectual functioning and in adaptive behavior, which covers many everyday social and practical skills. This disability originates before the age of 18.”(3). Around 18 of 1000 children are intellectually disabled(4). Intellectually disabled children often suffer from conditions that require painful and surgical interventions(5). Several observational pain assessment tools have been developed for these patients as recently reviewed by Voepel-Lewis et al.(6) and us(7). Epilepsy is also common and chronic treatment with anticonvulsants may have consequences for anesthetic and postoperative care(8-10). Compared to controls, intellectually disabled children tend to receive less intraoperative analgesia and fewer of them are assessed for postoperative pain(7). Justification for this disparity is lacking, apart from observations that intellectually disabled adults show altered pain sensitivity(11, 12). For this and other reasons we were interested in current practices of anesthesiologists treating intellectually disabled children.

Aim

The primary aim was to evaluate perceptions and practices of anesthesiologists in the Netherlands concerning pain management in intellectually disabled children. The secondary aim was to study changes in perceptions and practices between 2005 and 2009.
METHODS/MATERIALS

We surveyed the members of the Section on Pediatric Anesthesiology (SKA) of the Netherlands Society of Anesthesiology (NVA) in 2005. According to Dutch law Institutional Review Board (IRB) approval was not required. The survey was repeated in 2009 to evaluate if perceptions or practice have changed over time. On both occasions, a questionnaire was sent by mail. The anesthesiologists were asked to complete the questionnaire – anonymously – and to return it in a prepaid return envelope. A reminder was sent to all SKA members a few weeks later.

The 29-item questionnaire was developed in 2005 by our research group consisting of an experienced pediatric anesthesiologist (T.d.L.), a psychologist (M.v.D.) and a health scientist (J.P.). They all worked in the Erasmus University Medical Center – Sophia Children’s Hospital (Rotterdam, the Netherlands).

The respondents were asked about their perceptions on the pain sensitivity of intellectually disabled children, their pre-, intra- and post-operative practices when caring for these children, and any pain assessment tools they used.

Returned questionnaires were handled anonymously. Questionnaires of anesthesiologists who indicated they did not treat children with intellectual disability were excluded, and so were questionnaires in which more than 25% of the closed questions were not answered.

Two researchers (S.v.d.K., A.V.) independently analyzed the responses to the open questions and the free text responses and grouped these using the thematic analysis method(13). The classifications were compared and any discrepancies were resolved by discussion between the two researchers.

Data were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, IL, US). The results from the survey in 2005 were compared to those from 2009 using the t-test. The Chi-square test (or Fisher exact test in the case of predicted cell counts lower than 5) was used to compare nominal data for the two years. All reported P values are two-sided, and P values of less than 0.05 are considered to indicate statistical significance.
RESULTS

In 2005, the questionnaire was sent to all 192 SKA members; in 2009 to all 214. The response rate was 47% in 2005 as well as in 2009. On both occasions only one respondent stated never to have treated intellectually disabled children. These two questionnaires were excluded. Furthermore, one 2009 questionnaire was excluded because more than 25% of the closed questions were not answered (see Figure 1).

The background characteristics of the anesthesiologists, such as years of experience and type of hospital, were statistically not significantly different between the two evaluations (see Table 1).

![Flow diagram of inclusion in 2005 and 2009](image)

**FIGURE 1** Flow diagram of inclusion in 2005 and 2009

<table>
<thead>
<tr>
<th>TABLE 1 Characteristics of the anesthesiologists, by year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Experience in years, mean (SD)</td>
</tr>
<tr>
<td>2005 (n=89)</td>
</tr>
<tr>
<td>13.8 (8.3)</td>
</tr>
<tr>
<td>2009 (n=98)</td>
</tr>
<tr>
<td>14.8 (8.3)</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td>0.40&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>District hospital, n (%)</td>
</tr>
<tr>
<td>51 (57.3)</td>
</tr>
<tr>
<td>60 (61.9)</td>
</tr>
<tr>
<td>Specialist pediatric hospital, n (%)</td>
</tr>
<tr>
<td>23 (25.8)</td>
</tr>
<tr>
<td>19 (19.6)</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td>0.78&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Teaching hospital, n (%)</td>
</tr>
<tr>
<td>15 (16.9)</td>
</tr>
<tr>
<td>18 (18.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of times of giving anesthesia to intellectually disabled children, per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20, n (%)</td>
</tr>
<tr>
<td>36 (40.4)</td>
</tr>
<tr>
<td>42 (43.3)</td>
</tr>
<tr>
<td>20-50, n (%)</td>
</tr>
<tr>
<td>30 (33.7)</td>
</tr>
<tr>
<td>36 (37.1)</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td>0.67&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>50-100, n (%)</td>
</tr>
<tr>
<td>12 (13.5)</td>
</tr>
<tr>
<td>12 (12.4)</td>
</tr>
<tr>
<td>&gt;100, n (%)</td>
</tr>
<tr>
<td>11 (12.4)</td>
</tr>
<tr>
<td>7 (7.2)</td>
</tr>
</tbody>
</table>

<sup>a</sup> t-test
<sup>b</sup> Chi-square test
Perceptions
In 2005, 32% of the anesthesiologists rated the pain sensitivity of intellectually disabled children as “more sensitive” than that of non-intellectually disabled children versus 25% in 2009 \( (P = 0.31) \) (see Figure 2). Moreover, 7% in 2005 and 6% in 2009 \( (P=0.25) \) agreed with the statement “children with intellectual disabilities need more analgesia than children without intellectual disabilities” (see Table 2). Thematic analysis of an open question revealed that anesthesiologists ask more involvement of parents, that they pay more attention and take more time when caring for an intellectually disabled child (see Table 2).

![FIGURE 2 Anesthesiologists’ perceptions about the pain sensitivity of intellectually disabled children compared to nonintellectually disabled children](image)

Pre- and intra-operative
Most anesthesiologists continue the co-medication of the patient preoperatively, namely 99% in 2005 and 97% in 2009 \( (P=0.62) \). However, if patients use co-medication, 80% of the anesthesiologists in 2005 versus 86% of the anesthesiologists in 2009 \( (P=0.28) \) adjust the dose of anesthetics. In Table 3 the policy for different types of co-medication is further detailed.
### TABLE 2 Anesthesiologists’ perceptions on pain management in intellectually disabled children compared to non-intellectually disabled children, by year

<table>
<thead>
<tr>
<th>Perception</th>
<th>2005 (n=89)</th>
<th>2009 (n=98)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectually disabled children are at high risk for pain because of...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>less developed communication skills</td>
<td>85 (96.6)</td>
<td>92 (94.8)</td>
<td>0.56 b</td>
</tr>
<tr>
<td>co-morbidity</td>
<td>30 (34.1)</td>
<td>37 (38.1)</td>
<td>0.57 b</td>
</tr>
<tr>
<td>pain is considered to be less important</td>
<td>23 (26.1)</td>
<td>25 (25.8)</td>
<td>0.96 b</td>
</tr>
<tr>
<td>other reasons</td>
<td>8 (9.1)</td>
<td>9 (9.3)</td>
<td>0.97 b</td>
</tr>
<tr>
<td>The lower the level of functioning the lower the pain sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disagreed</td>
<td>66 (75.0)</td>
<td>76 (78.4)</td>
<td>0.48 c</td>
</tr>
<tr>
<td>Neither agreed nor disagreed</td>
<td>16 (18.2)</td>
<td>19 (19.6)</td>
<td></td>
</tr>
<tr>
<td>Agreed</td>
<td>6 (6.8)</td>
<td>2 (2.0)</td>
<td></td>
</tr>
<tr>
<td>The lower the level of functioning the harder it is to distinguish pain from other emotions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disagreed</td>
<td>14 (15.9)</td>
<td>9 (9.4)</td>
<td>0.55 b</td>
</tr>
<tr>
<td>Neither agreed nor disagreed</td>
<td>11 (12.5)</td>
<td>9 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Agreed</td>
<td>63 (71.6)</td>
<td>78 (81.2)</td>
<td></td>
</tr>
<tr>
<td>Intellectually disabled children need more analgesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disagreed</td>
<td>44 (50.0)</td>
<td>49 (50.0)</td>
<td>0.25 b</td>
</tr>
<tr>
<td>Neither agreed nor disagreed</td>
<td>38 (43.2)</td>
<td>43 (43.9)</td>
<td></td>
</tr>
<tr>
<td>Agreed</td>
<td>6 (6.8)</td>
<td>6 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Differences in approach</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No differences in treatment</td>
<td>36 (43.9)</td>
<td>28 (35.9)</td>
<td>0.30 b</td>
</tr>
<tr>
<td>Ask more involvement of the parent(s)/caretaker(s)</td>
<td>22 (26.8)</td>
<td>21 (26.9)</td>
<td>0.99 b</td>
</tr>
<tr>
<td>Less developed communication skills</td>
<td>12 (14.6)</td>
<td>21 (26.9)</td>
<td>0.06 b</td>
</tr>
<tr>
<td>Pay more attention</td>
<td>9 (11.0)</td>
<td>9 (11.5)</td>
<td>0.91 b</td>
</tr>
<tr>
<td>More time</td>
<td>8 (9.8)</td>
<td>10 (12.8)</td>
<td>0.54 b</td>
</tr>
</tbody>
</table>

* More than one answer possible
b Chi-square test
Fischer exact test
TABLE 3 Preoperative continuation and dose adjustments in children with chronic use of co-medication, by year

<table>
<thead>
<tr>
<th></th>
<th>2005 (n=89)</th>
<th>2009 (n=98)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose adjustment of anesthetics in patients that use</strong>(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analgesics</td>
<td>67 (93)</td>
<td>64 (77)</td>
<td>0.004(^a)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>59 (82)</td>
<td>71 (85)</td>
<td>0.91(^a)</td>
</tr>
<tr>
<td>Spasmolytics</td>
<td>33 (46)</td>
<td>32 (38)</td>
<td>0.62(^a)</td>
</tr>
<tr>
<td>Antiepileptic drugs</td>
<td>54 (76)</td>
<td>66 (79)</td>
<td>0.71(^a)</td>
</tr>
<tr>
<td>Anti-reflux drugs</td>
<td>14 (20)</td>
<td>12 (14)</td>
<td>0.37(^a)</td>
</tr>
<tr>
<td><strong>Preoperative continuation of</strong>(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analgesics</td>
<td>85 (97)</td>
<td>91 (96)</td>
<td>1.00(^b)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>81 (92)</td>
<td>88 (92)</td>
<td>0.93(^a)</td>
</tr>
<tr>
<td>Spasmolytics</td>
<td>77 (88)</td>
<td>86 (90)</td>
<td>0.66(^a)</td>
</tr>
<tr>
<td>Antiepileptic drugs</td>
<td>85 (97)</td>
<td>93 (97)</td>
<td>1.00(^b)</td>
</tr>
<tr>
<td>Anti-reflux drugs</td>
<td>89 (100)</td>
<td>90 (94)</td>
<td>0.03(^b)</td>
</tr>
</tbody>
</table>

\(^a\) More than one answer possible
\(^b\) Chi-square test
\(^c\) Fisher-exact test

In both evaluations, 99% of the anesthesiologists used inhalational agents for induction of anesthesia (P=1.00). Furthermore, 98% of the anesthesiologists in 2005 versus 93% in 2009 (P=0.17) used intravenous sedative agents for induction of anesthesia. Twelve anesthesiologists (15%) in 2005 versus 10 (10%) in 2009 (P=0.33) used other sedative agents for induction in intellectually disabled children. Dose adjustments of sedative agents for induction of anesthesia were more common. In 2005 26% of the anesthesiologists used other doses in intellectually disabled children, versus 25% of the anesthesiologists in 2009 (P=0.92). In 2005, 8% responded they use lower doses versus 11% in 2009 (P=0.93). Seven per cent responded in 2005 they use higher doses versus 10% in 2009 (P=0.57).

For maintenance of anesthesia, only four anesthesiologists in 2005 (4%) versus three in 2009 (3%) gave other sedative agents to intellectually disabled children (P=0.71). They explained this as follows: “For dental surgery I prefer intravenous agents”, “No inhalational anesthetics for children with a neuromuscular disorder”, “No propofol for children with mitochondrial disorders”, “No long-acting agents”, “No sevoflurane in children with a syndrome”, “Another agent in children with epilepsy” and “Only another agent in children with mitochondrial disorders”. Differences in dosing of maintenance were more common:
14 (16%) of the anesthesiologists in 2005 versus 10 (11%) in 2009 ($P=0.30$) used other doses in intellectually disabled children to maintain anesthesia. In 2005, 6% responded they use lower doses versus 7% in 2009 ($P=0.93$). In 2005, 3% responded that they use higher doses versus 1% in 2009 ($P=0.57$).

The majority of anesthesiologists used similar doses of intraoperative opioids for intellectually disabled and non-intellectually disabled children, 77 (92%) in 2005 versus 83 (89%) in 2009. In 2005, 6 (7%) of the anesthesiologists prescribed lower doses to intellectually disabled children versus 9 (10%) in 2009 (See Table 4). The differences between both evaluations were statistically non-significant ($P=0.80$). In both years, the main reasons for a higher or lower dose were the chronic use of co-medication, the underlying syndrome and the type of procedure.

**TABLE 4 Dosing of intraoperative opioids in intellectually disabled children compared to non-intellectually disabled children, by year**

<table>
<thead>
<tr>
<th></th>
<th>2005(n=84)</th>
<th>2009(n=93)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Similar dose</strong></td>
<td>77 (91.7)</td>
<td>83 (89.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Lower dose</strong></td>
<td>6 (7.1)</td>
<td>9 (9.7)</td>
<td>0.80*</td>
</tr>
<tr>
<td><strong>Higher dose</strong></td>
<td>1 (1.2)</td>
<td>1 (1.1)</td>
<td></td>
</tr>
</tbody>
</table>

* Fischer Exact Test

Anesthesiologists used intraoperative bispectral index (BIS) monitoring in 2005 as often in intellectually disabled children (27%) as in non-intellectually disabled children (28%). This was also the case in 2009, but BIS monitoring was now significantly more often applied: in 43% of intellectually disabled children (up from 27%; $P=0.04$) and in 45% of non-intellectually disabled children (up from 28%; $P=0.03$).

**Postoperative**

In 2005, 6% of the anesthesiologists were aware of a special pain assessment tool for intellectually disabled children (FLACC, CPB or COMFORT-B) versus 16% in 2009 ($P=0.02$). Only 3% in 2005 and 4% in 2009 actually used one of these tools ($P=1.00$).
In this survey we asked anesthesiologists in the Netherlands about their opinions on pain management in intellectually disabled children. We also asked whether they adapted their practice, for example by adjusting dosing of analgesic and sedative agents. The key finding is that perceptions do not fully match practice of anesthetic care for intellectually disabled children.

Perceptions
Around a third of the anesthesiologists in our survey thought that intellectually disabled children are more sensitive for pain (see Figure 2). A previous study, by Malviya et al., reported that 89 per cent of a group of nurses and physicians believed intellectually disabled children experience pain in the same way as other children(2). Findings cannot be validly compared, however, because our target group consisted of anesthesiologists only. Furthermore, definitions differed: Malviya et al. asked about ‘pain experience’ whereas we used the term ‘pain sensitivity’.

More and more, anesthesiologists take the less developed communication skills of intellectually disabled children into account; in 2005 15% reported a different approach for this reason, versus 27% in 2009 (P=0.06). Although a third of the surveyed anesthesiologists considered intellectually disabled children more sensitive to pain, but no more than 6 per cent thought they need more analgesia. A recent systematic review found that preoperatively measured thermal pain sensitivity correlates with postoperative analgesic requirements in adults(14). Thus there could be a mismatch between perceived pain sensitivity and the analgesia intellectually disabled children receive, however experimental pain is not the same as postoperative pain. A promising avenue of research would be quantitative sensory testing in verbal children with intellectual disabilities to determine thermal detection and pain thresholds(15).

Practices
Seven percent in 2005 and 10% in 2009 gave lower doses of intraoperative opioids to intellectually disabled children. This could be seen as an improvement, since a previous survey found that 89% of the physicians have a tendency to prescribe subtherapeutic doses of opioids(2). In addition, two other studies report lower doses of intraoperative opioids in intellectually disabled children(16, 17). One previous study by Malviya et al. reported that anesthesiologists gave comparable doses of intraoperative opioids to intellectually disabled children and non-intellectually disabled children undergoing spinal fusion surgery(18). Around a quarter of the respondents adjust doses of sedative agents for induction of general anesthesia and around 15% adjust doses of sedative agents for maintenance of general anesthesia. The dosing of sedative agents used during general anesthesia was not evaluated in the previous studies.
More than half of the respondents in both evaluations report that they pay more attention, take more time, and ask more involvement of parents, when caring for intellectually disabled children. A possible explanation is that it requires more effort to explain to intellectually disabled children the need for general anesthesia and to make sure they are as comfortable as possible at induction of general anesthesia. It might be necessary to adapt the education materials preparing intellectually disabled children for anesthesia and to study whether these children are more distressed or anxious than other children.

Previous studies found that the majority of intellectually disabled children have comorbidities such as thyroid disorders, gastro-intestinal diseases, psychiatric disorders or epilepsy(7). Epilepsy rates from 14 to 75% have been reported(19). Most children with epilepsy are chronically treated with a combination of antiepileptic drugs. The protein binding and enzyme inducing properties of antiepileptic drugs could influence the pharmacokinetics of drugs used for anesthesia and postoperative analgesia(9, 10). Seventy-six percent of the respondents in 2005 and 79% in 2009 adjusted the dose of anesthetics in children treated with antiepileptic drugs.

Based on our results and previous studies, we conclude that intellectually disabled children tend to receive lower doses of intraoperative opioids and sedatives. There is hardly any evidence for these dose adjustments, apart of the few studies in adults who are treated with antiepileptic drugs(9). Pharmacokinetic and pharmacodynamic evaluations should provide evidence for dose adjustments in intellectually disabled children. For children who are chronically treated with antiepileptic drugs, interactions with anesthetics as well as possible toxicity and side effects need to be studied.

**Pain assessment**

Pain assessment is a corner stone of adequate postoperative treatment(20). As reliable self-report of pain is impossible in most intellectually disabled children, observational pain assessment tools have been developed and validated for this group(21-23) as recently reviewed by us(7). Although up to 27% of the respondents adapt their practice in intellectually disabled children because of perceived less developed communication skills, no more than 4% of all respondents uses such a tool. A recent developed observational pain assessment scale is the individualized numeric rating scale (INRS)(24). It is based on individual pain indicators that parents and caregivers proposed. The individual descriptors are ranked on a scale from 0 to 10. Postoperative pain management protocols should include the use of a pain assessment tool that has been validated for intellectually disabled children.

**BIS monitoring**

Anesthesiologists in our survey use BIS monitoring as often in intellectually disabled children as in non-intellectually disabled children. Moreover, in 2009 they used it significantly
more than in 2005. Nevertheless, the value of BIS monitoring in intellectually disabled patients remains debatable. Choudhry et al. observed that BIS values of intellectually disabled children did not differ from those of controls(25). Sarıaoğlu et al. found that children with cerebral palsy needed less propofol than controls to reach a BIS value of 35(26). Our group observed that BIS values in intellectually disabled children were lower than those in controls(27). Most recently, Ponnudurai et al. found that degree of intellectual disability did not influence BIS values in intellectually disabled adults(28). Although the BIS monitor still is being used as a device to measure depth of anesthesia in intellectually disabled children, it is not clear whether the commonly used target values for general anesthesia (40 to 60) should be aimed for in intellectually disabled children as well. Frei et al. found lower MAC values for halothane in intellectually disabled children(29). One way to proceed could be to investigate the MAC values of different volatile anesthetics in patients treated with anticonvulsants and the relationship with BIS values.

**Education**

We observed only minor differences between the survey in 2005 and the survey in 2009 although the intervening period saw the publication of several important articles about pain assessment in intellectually disabled children, namely the validation of the revised FLACC(22), the Checklist Pain Behavior(30), a review about pain assessment scales(6) as well as the book about pain in children and adults with developmental disabilities by Oberlander and Symons(31).

Our institution has developed an observational tool for use in intellectually disabled children entitled ‘Checklist Pain Behavior’. It was widely distributed since its publication in 2006 and train-the-trainer sessions for caregivers are frequently held. In spite of all this, the Dutch anesthesiologists’ knowledge on pain in intellectually disabled children does not seem to have much improved, given the results of the survey in 2009. Dutch national guidelines for postoperative pain treatment were published in 2003(32). These guidelines are currently being revised to include a section about pain assessment in intellectually disabled children.

In the near future we should invest in targeted education and training of anesthesiologists and other caregivers, for example by offering Continuing Medical Education (CME) modules(33).

**Limitations**

A weakness of this survey was that we asked questions about intellectually disabled children in general. Intellectual disability encompasses a few common etiologies (for example Down’s syndrome or cerebral palsy) and a variety of very rare etiologies. In a large proportion of children with an intellectually disability the origin is unknown. In addition, it is a very heterogeneous group with varying levels of intellectual functioning and a variety of comorbidities and comediations. Therefore we chose to develop a survey that evaluates
the care for intellectually disabled children in general. Around 40% of the respondents reported they treat less than 20 intellectually disabled patients per year (see Table 1). Therefore it is difficult to expect them to have sufficient experience with all the different etiologies. Future prospective studies should account for the level of intellectual functioning and the cause of intellectual disability, by studying for example, only children with Down’s syndrome. Second, selection bias may have occurred. The response rate was 47% on both occasions, comparable to other survey studies in the field of pediatric anesthesia(34, 35). Thirdly, we did not ask questions about the use of opioids in the postoperative period. Postoperative pain management is as well highly relevant in these children and studies are needed to provide an evidence base. In the fourth place, we cannot rule out bias since we did not investigate the internal or external validity of the questionnaire that was used for this survey(36-38).

**Conclusions and implications**

We conclude that there are differences in anesthetic care for intellectually disabled children in the Netherlands compared to non-intellectually disabled children. Respondents tend to use a different approach when taking care for these patients and they were not aware of pain observation scales for intellectually disabled children. However, the majority of respondents think that intellectually disabled children are not more sensitive to pain or require more analgesia. These opinions did not change over the four-year period. We acknowledge, however, the paucity of evidence in this field. With limited research resources, we feel it is more and more important to select the most important questions. It will be impossible to study the pharmacokinetics and pharmacodynamics of each anesthetic agent in the heterogeneous population of intellectually disabled children. Therefore, we should strive to establish valid pharmacodynamic outcome measures that may be used to titrate anesthetics, taking into account their specific metabolic disease influencing drug metabolism and/or the way the abnormally developed CNS processes nociceptive stimuli. One way to proceed is to actively implement validated postoperative pain assessment tools and to invest in education of anesthesiologists and caregivers.
REFERENCES


ASSESSMENT
What calculation, number, measurement, replied?
EXTREMELY LOW PREANESTHETIC BIS VALUES IN TWO CHILDREN WITH WEST SYNDROME AND LISSENCEPHALY

Abraham J. Valkenburg, Tom G. de Leeuw, Andreas Machotta, Frank Weber

*Pediatric Anesthesia* (2008); 18: 446 - 448
Infantile spasms (IS) is a convulsive disorder of infancy and early childhood. The spasms involve the muscles of the neck, trunk and extremities. Most children with IS have the electroencephalographic (EEG) pattern known as hypsarrhythmia. A classic hypsarrhythmia pattern consists of high voltage slow waves and spikes, present in all cortical areas. The EEG can show ictal and interictal patterns of hypsarrhythmia. The combination of spasms, hypsarrhythmia and arrest of psychomotor development is known as West syndrome. Hrachový et al.(1) described in a review of 67 studies the long-term outcome of IS, with an average follow-up of 31 months. The mortality rate was 13%, 51% continued to have seizures, persistent neurological deficits were present in 44% of patients and 61% had abnormal EEG findings.

Miller Dieker syndrome is an autosomal recessive syndrome, associated with a deletion on chromosome 17p13.3. It is a combination of epilepsy like West Syndrome, lissencephaly and severe mental deficiency.

Anticonvulsants such as vigabatrin and phenobarbital exert their effect by facilitating gamma aminobutyric acid (GABA) mediated inhibition via allosteric interaction with neuronal postsynaptic GABA_A receptors. Barbiturates can also, in the absence of GABA, activate the GABA_A receptor directly, an effect that may underlie their sedative properties(2). Propofol and volatile anesthetics also act on the GABA_A receptor in the central nervous system. In this way anticonvulsants may influence the depth of anesthesia.

An objective measure of the effects of anesthetics on the brain and the level of consciousness is the Bispectral Index (Aspect Medical Systems, Natick, MA, USA). BIS is an empirically calibrated number derived from adult EEG data that correlates with the depth of the sedative component of general anesthesia in adults. It is validated for children older than one year(3).

Choudhry et al.(4) demonstrated that during general anesthesia in children with quadriplegic cerebral palsy and mental retardation (CPMR) BIS values exhibit a pattern of change, similar to that observed in normal children. The mean BIS value after premedication in the CPMR group was 92 compared to 97 in the group of normal children. It is questionable if this significantly lower BIS value is also clinically relevant because it is still a normal preanesthetic value. Saricaoglu et al.(5) described that children with cerebral palsy needed less propofol during induction of general anesthesia to obtain a BIS value between 35 and 45 than otherwise healthy children.

Many children with mental retardation also have seizures as a comorbidity of their disease and use anticonvulsants. One questions the validity and usefulness of BIS as a measure of sedation in this particular group of patients.
CASE 1

A 2 years and 7 months old boy, weighing 15 kg, diagnosed with West syndrome and lissencephaly. He was born at a gestational age of 37 weeks, there were no perinatal problems. After an admission for his spasms he was diagnosed with West syndrome and lissencephaly. Despite anticonvulsant medication, oral valproic acid (2 x 360 mg/day) and phenobarbital (2 x 30 mg/day), convulsions still occurred at a frequency of 8–10 times a day. Because of feeding difficulties and recurrent aspiration pneumonias he received a percutaneous gastrostomy (PEG).

He was scheduled for a PEG replacement under general anesthesia. The anticonvulsants were continued until the evening before the procedure. No additional sedatives were given. With approval from the local medical ethics committee and written informed parental consent (as for case 2), the BIS electrodes (BIS Pediatric Sensor, Aspect Medical Systems) were placed on the patient’s forehead and temple according to the manufacturers recommendation, before inhalational induction of general anesthesia. The range of BIS values before induction was 28–33.

Because of anticipated difficulties in obtaining venous access, we choose an inhalational induction with 8% sevoflurane (fraction inspired) in 100% oxygen with a fresh gas flow of 10 L/min. During inhalational induction we observed a significant increase of BIS values, after loss of consciousness (LOC), up to a maximum of 67. Thereafter BIS values returned to a range of 33–45.

Intravenous access was obtained after which alfentanil (20 mcg/kg) and propofol (2 mg/kg) were administered to facilitate tracheal intubation. The inspiratory sevoflurane concentration was decreased to 4%. Pulse oximetry, noninvasive blood pressure, ECG, BIS and endtidal concentration of sevoflurane, oxygen and CO₂ were monitored throughout the procedure. All these physiological parameters were within age related normal limits. During the procedure, the patient’s hypnotic level was assessed by measures of the University of Michigan Sedation Scales (UMSS)(6). Anesthesia was maintained with isoflurane 1.5% expired fraction and prior to the introduction of the gastroscope another dose of alfentanil (10 mcg/kg) was administered. The PEG was replaced endoscopically. During the procedure, the BIS values showed a range of 37–53 with a mean of 45. The patient was extubated once he was fully awake. After the patient returned to his preanesthetic level of consciousness, BIS values showed a range of 17–51 with a mean value of 35. The time course of BIS values of this patient is displayed in Figure 1.
FIGURE 1 Time course of BIS values of patient 1
We report about a 2 years and 4 months old boy, weighing 15 kg, diagnosed with Miller Dieker syndrome, confirmed by a deletion on chromosome 17p13.3. He was born at a gestational age of 42 weeks, in the presence of meconium stained amniotic fluid. Magnetic Resonance Imaging (MRI) showed lissencephaly. Despite anticonvulsant medication, oral valproic acid (2 x 200 mg/day), vigabatrin (2 x 750 mg/day) and nitrazepam (2 x 1.25 mg/day), convulsions still occurred at a frequency of 5–10 times a day. Because of feeding difficulties and recurrent aspiration pneumonias he received a PEG.

He was scheduled for a PEG replacement under general anesthesia. After our experience with the previous case we decided to place the BIS monitor the evening prior to the day of the procedure, in order to measure BIS values while the patient was fully awake, during natural sleep and probably during an episode of epilepsy. The range of the awake BIS values was 14–22 and the range of the BIS values during natural sleep was 14–33. During an observed spasm there was no change in the BIS values. The anticonvulsants were continued until the morning of the procedure. No additional sedatives were given. After venous access was obtained, induction of general anesthesia was performed as follows: an initial dose of alfentanil (20 mcg/kg) was administered, followed by propofol (4 mg/kg). After LOC, we administered isoflurane (3% fraction inspired) in 100% oxygen with a fresh gas flow of 10 L/min. During the intravenous induction, the range of the BIS values was 3–35. The patient was intubated two minutes after LOC.

Intraoperative monitoring and the anesthesia technique was exactly the same as for patient 1. The PEG was replaced endoscopically. During the procedure, the BIS values showed a range of 1–23. The level of anesthesia was also scored using the UMSS(6), during anesthesia the patient was unarousable. The patient was extubated once he was fully awake. After the patient had returned to his preanesthetic level of consciousness, BIS values showed a range of 30–36.

CASE 2

We report about a 2 years and 4 months old boy, weighing 15 kg, diagnosed with Miller Dieker syndrome, confirmed by a deletion on chromosome 17p13.3. He was born at a gestational age of 42 weeks, in the presence of meconium stained amniotic fluid. Magnetic Resonance Imaging (MRI) showed lissencephaly. Despite anticonvulsant medication, oral valproic acid (2 x 200 mg/day), vigabatrin (2 x 750 mg/day) and nitrazepam (2 x 1.25 mg/day), convulsions still occurred at a frequency of 5–10 times a day. Because of feeding difficulties and recurrent aspiration pneumonias he received a PEG.

He was scheduled for a PEG replacement under general anesthesia. After our experience with the previous case we decided to place the BIS monitor the evening prior to the day of the procedure, in order to measure BIS values while the patient was fully awake, during natural sleep and probably during an episode of epilepsy. The range of the awake BIS values was 14–22 and the range of the BIS values during natural sleep was 14–33. During an observed spasm there was no change in the BIS values. The anticonvulsants were continued until the morning of the procedure. No additional sedatives were given. After venous access was obtained, induction of general anesthesia was performed as follows: an initial dose of alfentanil (20 mcg/kg) was administered, followed by propofol (4 mg/kg). After LOC, we administered isoflurane (3% fraction inspired) in 100% oxygen with a fresh gas flow of 10 L/min. During the intravenous induction, the range of the BIS values was 3–35. The patient was intubated two minutes after LOC.

Intraoperative monitoring and the anesthesia technique was exactly the same as for patient 1. The PEG was replaced endoscopically. During the procedure, the BIS values showed a range of 1–23. The level of anesthesia was also scored using the UMSS(6), during anesthesia the patient was unarousable. The patient was extubated once he was fully awake. After the patient had returned to his preanesthetic level of consciousness, BIS values showed a range of 30–36.
DISCUSSION

To our best knowledge no case reports have described the use of BIS monitoring in children with West syndrome and lissencephaly. Having measured extremely low BIS values prior to anesthesia, we advise a preassessment of the BIS values in these children during states of wakefulness.

It is difficult to communicate with children with severe psychomotor retardation. In order to obtain information regarding the level of consciousness before and after anesthesia we asked the parents to assign their children to a particular level. Parents are better able to assess their child's level of consciousness since they see them every day and recognize responses of their children during verbal and nonverbal communication. The parents of both children confirmed that their children were awake before and after anesthesia at the same moment that we thought they were awake.

Kochs et al. (7) described the tendency of the EEG power spectrum to shift towards higher frequencies with a concentration 1.2% isoflurane compared to a concentration of 0.6%. Furthermore paradoxical increases of the BIS during increasing isoflurane concentration (8) have been published. This might be an explanation for the increase of the BIS during the induction with sevoflurane in case 1. After a decrease of the inspired sevoflurane concentration to 4% the BIS value decreased.

We have no definite explanation for extremely low preanesthesia BIS values in these two children. We think it might be a consequence of the EEG abnormalities in children with West syndrome, with their reduced cortical neuronal mass, and partially a result of anticonvulsant medication, but there is no evidence in the literature.

Because of limited experience with the use of the BIS monitor in patients with a combination of neurological disorders, epilepsy and regular anticonvulsant medication, ASPECT Medical Systems advises caution in the interpretation of BIS values in this group of patients (http://www.biseducation.com/assets/collaborate/2005/10/17/Trifold-English.PDF). Further research of BIS monitoring in this particular group of patients is necessary.
REFERENCES

Take, if you must, this little bag of dreams; Unloose the cord, and they will wrap you round.
LOWER BISPECTRAL INDEX VALUES IN CHILDREN WHO ARE INTELLECTUALLY DISABLED
ABSTRACT

Background
Very few data are available on the use of Bispectral index (BIS) monitoring in children who are intellectually disabled. Epileptiform electroencephalogram activity, underlying cerebral pathology, or anticonvulsant/spasmolytic therapy might influence BIS monitoring. Our aim in this exploratory study was to first compare BIS values at 4 different stages of anesthesia between intellectually disabled children and controls. Our second aim was to investigate the discriminative properties of BIS between consciousness and unconsciousness for intellectually disabled children and for controls.

Methods
Eighteen intellectually disabled children and 35 control children, aged 2–13 yr, were included. BIS values, landmark events, and standard monitoring values of vital functions were recorded throughout the whole procedure. The performance of BIS in distinguishing between a conscious and unconscious state was assessed from receiver operating characteristic curves.

Results
Median (interquartile range) BIS values for the intellectually disabled group were significantly lower than those for controls in the awake state (72 [48–77] vs 97 [84–98], \( P<0.001 \)), during stable intraoperative anesthesia (34 [21–45] vs 43 [33–52], \( P=0.02 \)), and during return of consciousness (59 [36–68] vs 73 [64–78], \( P=0.009 \)). The discriminative properties of the BIS monitor for the state of consciousness were comparable between the 2 groups according to the receiver operating characteristic curves. Nevertheless, the optimal cutoff BIS value for discrimination between conscious and unconscious state was 28 points lower for the intellectually disabled group.

Conclusions
We advise anesthesiologists to be alert to possible lower BIS values in intellectually disabled children. There is a risk that they will inadvertently misinterpret the state of consciousness in intellectually disabled children. New multicenter studies must find the optimal manner of evaluating (un)consciousness in intellectually disabled patients with documented and confirmed specific etiologies of their intellectual disability.
In pediatric anesthesia, monitoring the depth of anesthesia has received increasing attention with the advent of electroencephalogram (EEG)-derived devices(1). One of these is the bispectral index monitor (BIS, Aspect Medical Systems, Newton, MA). The BIS is an empirically calibrated number, derived from adult EEG data, which correlates with depth of the hypnotic component of general anesthesia in adults. It is a validated monitor of depth of anesthesia for children older than 1 yr(2).

In children with intellectual disability, the EEG could show abnormal activity due to the underlying cerebral pathology and/or epileptiform activity. Many intellectually disabled children also have epilepsy or cerebral palsy(3, 4) and thus may be treated with anticonvulsants and/or spasmyotics. As a consequence, one might question the validity and usefulness of BIS as a measure of sedation in this particular group of patients. There is little evidence about the use of BIS in children with intellectual disability and/or those who are treated with anticonvulsants. Choudhry and Brenn(5) described BIS values in 20 children with quadriplegic cerebral palsy and mental retardation changing similarly to those in 21 nonretarded children during general anesthesia. After premedication, the mean BIS value in the cerebral palsy and mental retardation group was 92 compared with 97 in the group of normal children. Saricaoglu et al.(6) demonstrated that 20 children with cerebral palsy needed less propofol to obtain a BIS value between 35 and 45 during induction of general anesthesia than did 20 otherwise healthy children. Twelve of the children with cerebral palsy had a history of seizures, 10 of whom were treated with anticonvulsants. Because of limited experience with the use of the BIS monitor in patients with a combination of neurological disorders, epilepsy, and regular anticonvulsant medication, ASPECT Medical Systems, the manufacturer of the BIS monitor, advises caution in the interpretation of BIS values in this group of patients.

A reliable depth of anesthesia monitor would be very helpful in titrating anesthesia in children with intellectual disability for various reasons. First, they often present with many congenital anomalies, syndromes, and disorders that might require surgical intervention. Second, anesthesiologists face communication problems, difficulties in assessing level of consciousness, and unexpected consequences of pharmacodynamic interactions when anesthetizing children with intellectual disability, severe neurological disorders, or epilepsy. The first aim of this exploratory study was to compare BIS values at different stages of anesthesia between intellectually disabled children and controls. The second aim was to investigate the discriminative properties of BIS between consciousness and unconsciousness for intellectually disabled children and for controls.
METHODS

This prospective, observational study was performed at the Erasmus University Medical Center–Sophia Children’s Hospital, Rotterdam, The Netherlands, between September 2006 and September 2007. The study protocol and data collection were approved by the local ethics review board. Written informed consent was obtained from the parents.

Study Population
Children eligible for this study (aged 2–13 yr) were scheduled for elective, diagnostic gastroduodenoscopy under general anesthesia and when indicated combined with percutaneous endoscopy gastrostomy (PEG) placement. Any contraindication for the standard anesthetic regimen was an exclusion criterion. The study group included intellectually disabled children who underwent gastroduodenoscopy combined with PEG placement because of severe feeding difficulties and inability to adequately feed those children(7). The control group included children without intellectual disabilities, neurological diseases, or epilepsy, and who were not being treated with anticonvulsant medication or spasmodytics.

Diagnosis of Intellectually Disabled
The diagnosis of intellectually disabled was made by a pediatric neurologist after multiple patient clinic visits. In 16 of 17 patients, this diagnosis was further supported by magnetic resonance imaging and/or specific genetic or serum tests.

Study Protocol
All patients received a standardized anesthetic regimen without premedication. Immediately before induction of general anesthesia, BIS electrodes (BIS Pediatric Sensor [4 sensors], Aspect Medical Systems) were placed on the patient’s forehead and temple, as recommended by the manufacturer. However, if a child resisted placement, no other attempt was made until after loss of consciousness (LOC, defined as loss of eyelash reflex). Electrodes were connected to a BIS monitor (A-2000, version 3.2; Aspect Medical Systems). Before induction of general anesthesia, 1 attempt was made to secure IV access. If successful, the patients received alfentanil (20 mcg/kg IV) and propofol (2–4 mg/kg IV) to facilitate tracheal intubation. Whenever IV access could not be achieved in 1 attempt, inhaled induction with 8% sevoflurane (fraction inspired) in 100% oxygen with a fresh gas flow of 10 L/min was chosen and IV access was secured after LOC. In the case of inhaled induction, tracheal intubation was also facilitated by alfentanil (20 mcg/kg) and propofol (2–4 mg/kg). After tracheal intubation, anesthesia was maintained with isoflurane (1.5% fraction expired). The timepoint of stable intraoperative anesthesia was defined as 30 s before introduction of the gastroscope. Administration of anesthetics was then stable and a (surgical) painful stimulus was absent. All children received another dose of alfentanil (10 mcg/
kg) before introduction of the gastroscope. Patients’ lungs were mechanically ventilated to normocapnia (end-tidal CO \textsubscript{2} 35–40 mmHg). Pulse oximetry, noninvasive arterial blood pressure, electrocardiogram, BIS, and concentrations of isoflurane, carbon dioxide, and oxygen were monitored throughout the procedure. At the end of the procedure, isoflurane administration was discontinued. After sufficient spontaneous breathing returned, the anesthesiologist checked for a response to verbal commands. Return of consciousness was identified on the basis of the patient’s preoperative reactions to verbal commands. Patients were tracheally extubated immediately after return of consciousness and then transferred to the postanesthesia care unit.

**Statistical Analysis**

Data for previously defined landmark events (all medication administrations, loss of consciousness, intubation, start and end of the procedure, discontinuation of isoflurane administration, return of consciousness, extubation, and unexpected events) were recorded using Rugloop software (Demed, Temse, Belgium). Recorded data included BIS and related values (signal quality, electromyography, and suppression ratio) and standard monitoring values (pulse oximetry, non-invasive arterial blood pressure, electrocardiogram, and concentrations of isoflurane, carbon dioxide, and oxygen).

Data were analyzed using SPSS version 15.0 (SPSS, Chicago, IL) and Labgrab (Demed). A P value less than 0.05 was considered statistically significant.

Normal distribution of the data was tested by the 1-sample Kolmogorov-Smirnov test. To compare frequencies of normally distributed data, parametric tests (independent-samples t-test) were used. Non-parametric tests (Mann-Whitney U-test) served to compare the frequencies of ordinal data (e.g., all BIS values). A Fisher’s exact test was used to test differences in the distribution of nominal data. Data are given in mean (standard deviation) or median (interquartile range), as appropriate. For compensating the considerable time delay of signal processing, BIS values 0 and 30 s after each landmark event were analyzed. For both groups, we used a receiver operating characteristic (ROC) curve to describe the discriminating performance of the BIS monitor between consciousness and unconsciousness. We used 4 BIS values per patient in this analysis. The awake value and the value 30 s after return of consciousness were marked as conscious values, and the value 30 s after LOC and intraoperative values were marked as unconscious values. First, we plotted the true-positive rate against (sensitivity) the false-positive rate (1-specificity) for the measured BIS values. Second, for each group, the BIS value with the highest combination of sensitivity and specificity was selected as the optimal cutoff BIS value for discrimination between conscious and unconscious state. Third, the area under the curve (AUC) was calculated. A large AUC corresponds with high discriminative properties. Fourth, we compared the ROC curve of the intellectually disabled group with the ROC curve of the control group by testing the statistical significance of the difference between the AUCs.
**FIGURE 1** Bispectral index values for both groups during different stages of anesthesia. Median (horizontal line), 25th and 75th percentiles (box), and range (whiskers) of Bispectral index values for the intellectually disabled (ID) and the control group. * = P<0.05 (from Mann-Whitney U-test). LOC= Loss of consciousness; RoC = Return of consciousness
RESULTS

Patient Characteristics
Seventeen patients were enrolled in the intellectually disabled group and 35 in the control group. The demographic characteristics of both groups were comparable (Table 1). None of the children in the control group was treated with anticonvulsants or spasmolytics. Ten intellectually disabled patients were treated with anticonvulsants (benzodiazepines, barbiturates, and/or antiepileptic drugs) for seizure control and 3 other patients with spasmolytics (baclofen). The etiology of underlying neurological disorders in the intellectually disabled group comprises 12 different disorders (Table 2).

**TABLE 1 Characteristics of the 52 subjects by group**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ID group (n=17)</th>
<th>Control group (n=35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>12 (71)</td>
<td>19 (54)</td>
<td>0.37</td>
</tr>
<tr>
<td>Age (yr), mean (SD)</td>
<td>5.4 (3.6)</td>
<td>6.2 (3.8)</td>
<td>0.50</td>
</tr>
<tr>
<td>Weight (kg), median (IQR)</td>
<td>17 [14 to 26]</td>
<td>19 [14 to 37]</td>
<td>0.68</td>
</tr>
<tr>
<td>Duration of anesthesia (min),</td>
<td>54 (25)</td>
<td>44 (15)</td>
<td>0.12</td>
</tr>
<tr>
<td>mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of gastroscopy (min),</td>
<td>8 [7 to 13]</td>
<td>10 [8 to 16]</td>
<td>0.25</td>
</tr>
<tr>
<td>median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous induction of</td>
<td>13 (76)</td>
<td>27 (77)</td>
<td>1.00</td>
</tr>
<tr>
<td>anesthesia, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ID = Intellectually Disabled; IQR = Interquartile Range
### TABLE 2 Underlying neurological disorders in the intellectually disabled group (n=17)

<table>
<thead>
<tr>
<th>Neurological disorder</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congenital</strong></td>
<td></td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>1</td>
</tr>
<tr>
<td>Carbohydrate-Deficient Glycoprotein Syndrome Type 1c</td>
<td>1</td>
</tr>
<tr>
<td>Triple A Syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Lesch-Nyhan Syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Lissencephaly + Epilepsy</td>
<td>1</td>
</tr>
<tr>
<td>Miller-Dieker Lissencephaly Syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Klinefelter syndrome</td>
<td>1</td>
</tr>
<tr>
<td>West syndrome</td>
<td>1</td>
</tr>
<tr>
<td><strong>Posthypoxic encephalopathy</strong></td>
<td></td>
</tr>
<tr>
<td>Perinatal</td>
<td>3</td>
</tr>
<tr>
<td>Post resuscitation</td>
<td>3</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Syndromal disorder of unknown origin</td>
<td>1</td>
</tr>
<tr>
<td>Neurodegenerative disorder of unknown origin</td>
<td>1</td>
</tr>
</tbody>
</table>

**Differences in BIS values between the intellectually disabled and control groups**

BIS values (median [interquartile range]) for the intellectually disabled group were significantly lower than those for controls in the awake state (72 [48–77] vs 97 [84 –98], P<0.001), during stable intraoperative anesthesia (34 [21–45] vs 43 [33–52], P=0.02), and during return of consciousness (59 [36–68] vs 73 [64–78], P=0.009) (Table 3 and Fig. 1). The Fisher’s exact test revealed that the proportion of missing awake BIS values was significantly higher in the control group: 24 of 35 vs 5 of 17 in the intellectually disabled group (P=0.02). In the intellectually disabled group, 8 of 17 of the loss of consciousness values was missing versus 25 of 35 in the control group (P=0.13). None of the intraoperative values was missing in the intellectually disabled group versus 3 of 35 in the control group (P=0.54). On the return of consciousness values, 3 of 17 were missing in the intellectually disabled group versus 5 of 35 in the control group (P=1.00).
### TABLE 3 Bispectral index values at four stages of anesthesia, by group

<table>
<thead>
<tr>
<th>Stage</th>
<th>ID group (n=17)</th>
<th>Control group (n=35)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td></td>
</tr>
<tr>
<td>Conscious</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Awake</td>
<td>72 (48 to 77)</td>
<td>97 (84 to 98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30 s after return of consciousness</td>
<td>59 (36 to 68)</td>
<td>73 (64 to 78)</td>
<td>0.009</td>
</tr>
<tr>
<td>Unconscious</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 s after loss of consciousness</td>
<td>41 (32 to 61)</td>
<td>56 (42 to 71)</td>
<td>0.15</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>34 (21 to 45)</td>
<td>43 (33 to 52)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

ID = Intellectually Disabled; IQR = Interquartile Range

* Mann-Whitney U test

### ROC analysis

The discriminative properties of the BIS monitor for the state of consciousness were comparable between the groups. The AUC for the control group was not statistically significantly larger than the AUC for the intellectually disabled group (0.92 vs 0.78, \( P=0.07 \)). In Figure 2, the ROC curve for each group is displayed and optimal cutoff BIS values have been marked.

For the control group, the optimal cutoff BIS value was 65 (sensitivity=0.81 and specificity=0.93) and for the study group it was 47 (sensitivity=0.73 and specificity=0.81).
FIGURE 2 Discriminative properties of the Bispectral index monitor between consciousness and unconsciousness in the intellectually disabled and control group. Receiver operating characteristic curve of the intellectually disabled and the control group.
DISCUSSION

BIS values observed in the awake state, during stable intraoperative anesthesia, and during return of consciousness were significantly lower for intellectually disabled children compared with controls. The differences between the 2 groups ranged from 9 to 25. BIS distinguished the conscious and unconscious state equally well in the 2 groups. Nevertheless, the optimal cutoff BIS value for discrimination between the conscious and unconscious state was 28 points lower for the intellectually disabled group.

On the BIS scale from 100 (fully awake) to 0 (isoelectric EEG), differences of these magnitudes could easily give rise to misinterpretation of the patient’s state of consciousness.

Comparison with previous studies

These data confirm and supplement the observations of Choudhry and Brenn(5) and Saricaoglu et al.(6). Both groups reported lower BIS values in intellectually disabled children. However, contrary to our findings, in those previous studies, the BIS values of intellectually disabled children remained within the defined ranges for the different stages of anesthesia. Still, we should be aware of essential differences between these 2 studies and this study. First, anesthesia management was substantially different. We administered both IV and inhaled anesthetics, whereas Saricaoglu et al. administered only propofol. Patients in the study by Choudhry and Brenn were premedicated with midazolam, received inhaled induction with sevoflurane, and tracheal intubation was facilitated with rocuronium. Second, children in the study groups of both previous studies had been diagnosed with cerebral palsy and intellectual disability, but details on the underlying causes of cerebral palsy or the severity of intellectual disability were lacking.

Possible explanations for lower BIS values in intellectually disabled children

The small sample size and the heterogeneity of the group of intellectually disabled children in this study do not allow establishing causal relationships that might explain the lower BIS values in this group. Alternatively, we suggest 3 possible explanations based on findings from the literature.

1. A review by Dahaba(9) summarizes a large variety of conditions (anesthetic drugs, clinical conditions, and electric device interference) that could result in the BIS indicating an incorrect hypnotic state. The effect of most of those conditions on the EEG signal is clear. Dahaba gives no definite explanation for lower BIS values in intellectually disabled children. We suggest that the underlying cerebral pathology could cause epileptiform and nonepileptiform EEG abnormalities and thus affect BIS values. For example, nonepileptiform EEG abnormalities were observed in the majority of a cohort of children with tetraplegia/diplegia(10).

2. Epileptiform activity during general anesthesia has been reported to affect BIS values. Verma and Radtke(11) reviewed studies about ictal and interictal EEG activity. Interictal
activity in partial epilepsy concerns several patterns of δ waves. The frequency band for δ waves is between 1 and 4 Hz. Those low-frequency waves are generated during natural sleep but are also seen during general anesthesia as an effect of hypnotic drugs(9, 12). These interictal δ waves could artificially decrease BIS values in children with epilepsy.

3. Not only epileptiform activity but also anticonvulsants might influence BIS values. Most anticonvulsants exert their effect by facilitating γ-aminobutyric acid (GABA)-mediated inhibition via allosteric interaction with neuronal postsynaptic GABA_A receptors. Propofol and volatile anesthetics also act on the GABA_A receptor in the central nervous system. In this way, anticonvulsants may directly influence depth of anesthesia. Ten of the intellectually disabled children in our study were treated with anticonvulsants versus none of the control children.

Limitations of this study

Major Limitation
A considerable number of awake BIS values for the control group is missing. However, the obtained BIS values in the control children were comparable to those reported in other pediatric studies(13, 14). We assume that the awake BIS values of the other control children in our study would have been comparable to those reported by Denman et al.(13) and by Blussé et al.(14). The crux of the matter is that the awake BIS values of intellectually disabled children were much lower than the ones measured in the control group. Furthermore, for logistical reasons and the fact that one-quarter of the patients received inhaled induction, a larger proportion of the loss of consciousness data is missing for both groups. Therefore, the loss of consciousness data should be interpreted with caution.

Second Limitation
Heterogeneity in neurological diagnoses (Table 2) is a realistic reflection of the intellectually disabled patient population in need of a PEG but makes it difficult to generalize the results of the study to all intellectually disabled patients.
CONCLUSIONS

We advise anesthesiologists to be alert to possible lower BIS values in children who are intellectually disabled. There is a risk that they will inadvertently misinterpret the state of consciousness in these children.

Given the variety and rarity of underlying neurological disorders, only large multicenter trials might provide decisive information about BIS monitoring in intellectually disabled children. In addition, the effects of epileptiform EEG activity and anticonvulsant therapy on BIS should be studied. It would also be advisable to study other depth of anesthesia monitors in an attempt to find the optimal manner of evaluating (un)consciousness in intellectually disabled patients with documented and confirmed specific etiologies of their intellectual disability.
REFERENCES

W.B. YEATS
In toils of measurement
Beyond eagle or mole,
Beyond hearing or seeing
Or Archimedes’ guess,
To raise into being,
That loveliness?
THE COMFORT-BEHAVIOR SCALE IS USEFUL TO ASSESS PAIN AND DISTRESS IN 0-TO 3-YEAR-OLD CHILDREN WITH DOWN SYNDROME

Abraham J. Valkenburg, Anneke A. Boerlage, Erwin Ista, Hugo J. Duivenvoorden, Dick Tibboel, Monique van Dijk

PAIN (2011); 152: 2059-2064
Many pediatric intensive care units use the COMFORT-behavior scale (COMFORT-B) to assess pain in 0- to 3-year old children. The objective of this study was to determine whether this scale is also valid for the assessment of pain in 0 to 3 year old children with Down syndrome. These children often undergo cardiac or intestinal surgery early in life and therefore admission to a pediatric intensive care unit. Seventy-six patients with Down syndrome were included and 466 without Down syndrome. Pain was regularly assessed with the COMFORT-B scale and the Numeric Rating Scale (NRS). For either group, confirmatory factor analyses revealed a 1-factor model. Internal consistency between COMFORT-B items was good (Cronbach’s α=0.84 to 0.87). Cutoff values for the COMFORT-B set at 17 or higher discriminated between pain (NRS pain of 4 or higher) and no pain (NRS pain below 4) in both groups. We concluded that the COMFORT-B scale is also valid for 0-to 3-year old children with Down syndrome. This makes it even more useful in the pediatric intensive care unit setting, doing away with the need to apply another instrument for those children younger than 3.
INTRODUCTION

Children receiving intensive care often undergo many painful, invasive procedures, including mechanical ventilation. Many are recovering from major surgery. The resulting pain and distress are treated with analgesic and or sedative agents. Assessment of pain and distress is therefore an important cornerstone of pediatric intensive care treatment and is increasingly used as a performance indicator. Observational tools are needed in preverbal infants and nonverbal children - i.e. mechanically ventilated or sedated children. The Multidimensional Assessment of Pain Scale (MAPS) and the COMFORT-behavior (COMFORT-B) scale are suitable to assess pain and have been validated for the pediatric intensive care unit (PICU) setting. These instruments are based on the observation of typical pain behaviors such as grimacing, cry, body movements and muscle tension. Other tools may be needed in critically ill infants with intellectual disabilities or neurological impairment because their pain expression may be atypical or less vigorous. The Non-communicating Children’s Pain Checklist-Postoperative Version, the Pediatric Pain Profile, the revised Faces, Legs, Activity, Cry and Consolability, and the Checklist Pain Behavior have been validated for postoperative pain in children with intellectual disabilities, from the age of 3 to 4 years onwards. These scales require a long observation period, up to 10 minutes, or require a description of idiosyncratic behaviors. To our knowledge, no such tools are available for younger children with a suspected or known intellectual disability, let alone for the intensive care unit setting.

Individuals with Down syndrome have a 40 to 60% risk of congenital heart diseases and congenital gastrointestinal anomalies that require surgical repair at a young age. We have been using the COMFORT-B scale in daily practice since 1999 in 0 to 3 year old children with Down syndrome as well. The manual of the original COMFORT scale does not exclude children with this condition, but validity of the scale for use with Down syndrome patients was not analyzed separately (Dr. Bruce Ambuel, personal communication). Many of those children show hypotonia, which could affect their behavior, and thus the score on the item ‘Muscle Tone’. Also, Down syndrome has been associated with a low-pitched, hoarse cry, which could affect the score on the item ‘Crying’. We wondered, therefore, whether the COMFORT-B scale is really valid in 0-to 3-year old children with Down syndrome.

The objective of the study reported here was to evaluate the psychometric properties of the COMFORT-B scale for the assessment of pain and distress in 0-to 3-year old children with Down syndrome and to determine whether different cut-off values should apply for them.
METHODS

Subjects and Setting
The ICU of Erasmus University Medical Center - Sophia Children’s Hospital, Rotterdam, the Netherlands serves as the only level III facility for children in a referral area comprising about 4 million inhabitants and 35,000 newborns per year. Admission criteria are major surgery or other conditions requiring intensive care such as trauma, sepsis and the need for mechanical ventilation. Treatment almost always involves painful and invasive procedures. To counteract the consequences, we introduced a standardized pain and distress management protocol in 1999, which has not changed substantially since that time. The key element is application of the COMFORT-B scale and Numeric Rating Scale by observation (NRS_{obs}) for pain every 8 hour shift at set times (2-10-18 hrs) and on suspicion of pain or distress (3, 5, 16). Since November 2002, all COMFORT-B and NRS_{obs} scores are being prospectively recorded in our Patient Data Management System (PDMS). The study was approved by the local ethics committee of Erasmus University Medical Center. The need for informed parental/guardian consent was waived.

The study group consisted of patients with Down syndrome, who met the following criteria: ICU stay between November 2002 and April 2009, confirmed diagnosis of trisomy 21 by genetic analysis, age 0 to 36 months and scores of at least two assessments available. Children without Down syndrome admitted in the reference year 2007 served as a control group. This year is the middle year of the period 2005 (start of PDMS) up to and including 2009. We assume that 2007 is a representative reference year because the standardized mean differences (SMD) in COMFORT-B scores between 2007 versus the other years were small (0.02 to 0.08). Inclusion criteria for the control group were: ICU stay between January 2007 and January 2008, age 0 to 36 months and scores of at least two assessments available.

Instruments
The COMFORT-B scale is a pain and distress assessment instrument that asks observers to consider intensity of six behavioral manifestations: Alertness, Calmness, Respiratory response (for mechanically ventilated children) or Crying (for spontaneously breathing children), Body movements, Facial tension and Muscle tone. For each of these items, five descriptions, rated from 1 to 5, are provided reflecting increasing intensity of the behavior in question. Summating the ratings of the six behavioral manifestations leads to a score ranging from 6 to 30. Clinical cutoff scores for the COMFORT-B and NRS_{obs} for pain have been determined. The pain management protocol dictates some kind of intervention (non-pharmacological and/or pharmacological) when COMFORT-B scores of 17 or higher are combined with NRS_{obs} pain ratings of 4 or higher(16).

All nurses undergo a 2 hour COMFORT-B training program when they start to work in our unit. The program includes 10 assessments in different patients, with a qualified nurse
performing the same assessments. Agreement is assessed from the linearly weighted Cohen’s kappa calculated from these 10 paired assessments. This coefficient corrects for chance agreement (17). The minimal Cohen’s kappa that nurses needed to reach was 0.65. If Cohen’s kappa value was below 0.65, the nurse was asked to repeat assessments until the required kappa value had been reached. Median linearly weighted kappa values were 0.81 (interquartile range 0.77 to 0.87) for 103 nurses.

The NRS is a validated tool that asks patients themselves or proxies to rate pain intensity by number (0=no pain at all and 10= worst imaginable pain)(18). We refer to the NRS as applied by proxy raters as NRS_{obs} to avoid confusion with the NRS for self-report. The NRS_{obs} expresses the observer’s expert opinion of the patient’s level of pain, taking the patients’ circumstances (disease-related, treatment related, environmental and patient specific) into account. Several studies compared the NRS_{obs} or observed visual analog scale to observational pain assessment tools in 0 to 3 year old children(19). These NRS_{obs} assessments – part of the pain management protocol since 1999 – serve to differentiate between pain and distress. For instance, a high COMFORT-B score may coincide with a low NRS_{obs} for pain if the nurse knows that the child requires sedation rather than analgesia. The nurse takes this knowledge into account when applying the NRS_{obs}. Repeating the assessments after interventions is required to monitor the effect of the intervention.

The Nurses Interpretation of Sedation Scale (NISS) is the nurse’s expert opinion of the level of sedation, reflected by one of these categories: Insufficient sedation, Adequate sedation, Oversedation. The NISS is applied to infants who receive sedatives and/or opioids. This instrument is comparable to the one used by Marx et al.(20). The NISS was validated in our unit in 2005 (5).

**Procedure**

All COMFORT-B, NRS_{obs} and NISS scores for the included patients were retrieved from our PDMS. The following patient data were collected from the medical records: sex; age at first assessment; reason of admission to the PICU; opioid, sedative and paracetamol administration during admission; and ventilatory status.

**Statistical analysis**

Data were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, IL, US). All reported P values are two-sided, and P values of less than 0.05 are considered to indicate statistical significance. Summary statistics (mean values and percentages) of repeated pain assessments per patient served to compare results among groups and to correlate COMFORT-B scores with NRS_{obs} pain scores at patient level (21). Pearson product moment correlation coefficient was applied to test the linear association between continuous variables. The Chi-square test (or Fisher exact test in the case of low predicted cell counts) was used to compare nominal data for the two independent groups. Continuous data were presented
as median [IQR]. Data were compared between the two independent groups with the Mann-Whitney test or with the t test for normally distributed variables. For these tests, we used all scores of the first seven days of a patient’s admission. If patients had been admitted more than once, the data of the longest admission were used. This strategy was aimed at limiting the variability in number of assessments per patient.

First, to test the internal consistency of the COMFORT-B scale, Cronbach’s α and corrected inter-item correlations were calculated for each of the two groups. Second, to test whether the factor structure of the COMFORT-B scale is comparable between the two groups, a confirmatory factor analysis was performed with the Mplus software version 5.21 (Muthén & Muthén, Los Angeles, CA, US). This analysis was based on a maximum of 5 COMFORT-B scores per patient, randomly selected from all scores of the first seven days of the patient’s longest admission. The following method was applied: each score was assigned a random number using the UNIFORM function in SPSS. The scores numbered 1 through 5 were entered in the analysis. Seventeen percent of patients had been assessed only 2 or 3 times because of a short admission. In those cases all scores were used in the analysis. The analysis aimed at finding a parsimonious factor model that adequately represents the empirical structure of the COMFORT-B scale for both the Down syndrome and the control group. We also tested a 1-factor model, because Van Dijk et al. earlier found a 1-factor model that adequately described the COMFORT-B scale (3). The following performance measures of overall fit were used: 1. χ² test for model fit: a non-significant value indicates that the model at issue cannot be rejected. To account for the effect of sample size on χ² test, the χ²/df was also used. 2. Standardized root mean square of residuals (SRMR): the lower the SRMR the better the model fits. 3. Root mean squares error of approximation (RMSEA): A value of 0.05 indicates a close fit and values up to 0.08 represent reasonable errors of approximation in the population. Parameters were estimated by the maximum likelihood mean and variance adjusted procedure.

Four models were tested: 1. Invariant error variances for corresponding items across groups; 2. Equal factor loadings across groups; 3. Equal factor means across groups; 4. Invariant residual variances for corresponding items across groups. Because the prefinal model showed that the residual covariances of two items were substantial, the final model allowed for freeing the residual covariances of these two items.

Third, for each group, the COMFORT-B score with the optimal combination of sensitivity and specificity was selected as the clinical cut-off score for pain. NRS_OBS values of 4 or higher served as reference value for pain. Furthermore, the positive and negative predictive values of the COMFORT-B scale were determined for either group. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve of the Down syndrome group was compared with the AUC of the control group by testing the statistical significance of the difference between these two groups.
FIGURE 1 Receiver operating characteristic curve for COMFORT-Behavior with NRS\textsubscript{obs} pain of 4 - 10 as state variable. Down syndrome group (solid line) and control group (dashed line).
RESULTS

Patient characteristics
Seventy-six patients with Down syndrome and 466 without Down syndrome were included. The demographic characteristics are listed in Table 1. A total of 46.8% of children in the control group were mechanically ventilated, versus 73.7% in the Down syndrome group ($P<0.001$). Children with Down syndrome underwent significantly more often surgery for associated congenital anomalies ($P<0.001$). Morphine administration was significantly more frequent in the Down syndrome group (62% versus 45%, $P=0.006$); the same held true for midazolam (68% versus 51%, $P=0.005$).
### TABLE 1 Characteristics of the 542 subjects, by group

<table>
<thead>
<tr>
<th></th>
<th>Down syndrome (n=76)</th>
<th>Controls (n=466)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male sex</strong>, n (%)</td>
<td>45 (59.2)</td>
<td>273 (58.6)</td>
<td>0.92 a</td>
</tr>
<tr>
<td><strong>Age in days</strong>, median [IQR]</td>
<td>81 [42 to 273]</td>
<td>119 [22 to 355]</td>
<td>0.22 b</td>
</tr>
<tr>
<td><strong>Study period</strong>, median [IQR]</td>
<td>3 [1 to 6]</td>
<td>1 [1 to 6]</td>
<td>0.014 b</td>
</tr>
<tr>
<td><strong>Mechanically ventilated</strong>, n (%)</td>
<td>56 (73.7)</td>
<td>218 (46.8)</td>
<td>&lt;0.001 a</td>
</tr>
<tr>
<td><strong>Morphine</strong>, n (%)</td>
<td>47 (62)</td>
<td>209 (45)</td>
<td>0.006 a</td>
</tr>
<tr>
<td><strong>Paracetamol</strong>, n (%)</td>
<td>58 (76)</td>
<td>332 (71)</td>
<td>0.36 a</td>
</tr>
<tr>
<td><strong>Midazolam</strong>, n (%)</td>
<td>52 (68)</td>
<td>238 (51)</td>
<td>0.005 a</td>
</tr>
<tr>
<td><strong>ECMO</strong> treatment, n (%)</td>
<td>4 (5.3)</td>
<td>21 (4.5)</td>
<td>0.77 c</td>
</tr>
</tbody>
</table>

**Reason of admission**

<table>
<thead>
<tr>
<th>Reason of admission</th>
<th>Total surgical, n (%)</th>
<th>Controls (n=466)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>54 (77.1)</td>
<td>313 (67.2)</td>
<td>0.014 a</td>
</tr>
<tr>
<td>Cardiothoracic</td>
<td>32 (59.3)</td>
<td>73 (23.3)</td>
<td>&lt;0.001 c</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>15 (27.8)</td>
<td>102 (32.6)</td>
<td></td>
</tr>
<tr>
<td>Ear-nose-throat</td>
<td>5 (9.3)</td>
<td>23 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Craniofacial</td>
<td>2 (3.7)</td>
<td>99 (31.6)</td>
<td></td>
</tr>
<tr>
<td>Other surgery°</td>
<td>0 (0)</td>
<td>16 (5.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22 (28.9)</td>
<td>153 (32.8)</td>
<td>0.014 a</td>
</tr>
<tr>
<td>Cardiorespiratory failure</td>
<td>17 (77.3)</td>
<td>102 (66.7)</td>
<td>0.29 c</td>
</tr>
<tr>
<td>Gastrointestinal / urogenital</td>
<td>3 (13.6)</td>
<td>11 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>2 (9.1)</td>
<td>5 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>0 (0)</td>
<td>13 (8.5)</td>
<td></td>
</tr>
<tr>
<td>Infection / sepsis</td>
<td>0 (0)</td>
<td>11 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Other °</td>
<td>0 (0)</td>
<td>11 (7.2)</td>
<td></td>
</tr>
</tbody>
</table>

* Chi-square test  
° Mann-Whitney test  
°° Exact test  
° Extracorporeal Membrane Oxygenation  
°° Other surgery includes urogenital, orthopaedic, dermatological surgery and tumor extirpations  
°°° Other diagnoses includes intoxication, neurological problems and malignancies

### Pain assessments

Median number of COMFORT-B scores significantly differed between the two groups (P=0.023): a median [IQR] of 9 [4 to 22] in the control group versus a median (IQR) of 16 [8 to 22] in the Down syndrome group. Mean COMFORT-B score was 12.1 (SD 1.7) in the Down syndrome group versus 12.3 (SD 1.8) in the control group (P=0.31). A total of 7% of the 7439 COMFORT-B scores across both groups were 17 or higher. The percentage of
COMFORT-B scores of 17 or higher was calculated for each patient. Median (IQR) percentage per patient was 8.3 (0 to 20) in the Down syndrome group versus 6.7 (0 to 20) in the control group (P=0.48). The median percentage of NRS\textsubscript{obs} ratings of 4 or higher per patient was 0 in both groups. NRS\textsubscript{obs} pain ratings of 4 or higher were seen in 4.8% of all 6954 NR-S\textsubscript{obs} pain assessments.

The Pearson product moment correlation between mean NRS\textsubscript{obs} for pain and mean COMFORT-B scores per patient was 0.45 for the Down syndrome group (P<0.01) and 0.57 for the control group (P<0.01).

| TABLE 2 COMFORT-B item scores and internal consistency measures, by group |
|-------------------------------------------------|-----------------|----------|-----------------|
| **Items**, mean (SD)                           | Down syndrome (1163 scores) | Controls (6276 scores) | P value \(^a\) | SMD \(^b\) |
| Alertness                                      | 2.2 (1.1)         | 2.1 (1.1) | 0.10            | -0.05         |
| Calmness                                       | 1.3 (0.7)         | 1.4 (0.7) | 0.50            | 0.02          |
| Respiratory response \(^c\)                   | 1.8 (0.8)         | 1.8 (0.8) | 0.61            | 0.02          |
| Crying \(^c\)                                 | 1.3 (0.7)         | 1.5 (1.0) | <0.001          | 0.23          |
| Physical movements                             | 2.3 (1.0)         | 2.2 (0.9) | <0.001          | -0.12         |
| Facial tension                                 | 2.0 (0.6)         | 2.0 (0.6) | <0.001          | 0.12          |
| Muscle tone                                    | 2.8 (0.6)         | 2.9 (0.5) | <0.001          | 0.21          |
| Corrected item-total correlation               | 0.54 to 0.72      | 0.57 to 0.76 |
| Cronbach’s \(\alpha\) unstandardized          | 0.84              | 0.87      |
| Cronbach’s \(\alpha\) standardized            | 0.86              | 0.88      |

\(^a\) t test
\(^b\) Standardized Mean Difference (SMD): Values of Down’s syndrome group minus values of control group
\(^c\) 54.6% of the scores were scored in mechanically ventilated patients (respiratory response) and 45.4% in spontaneously breathing patients (crying)

**Sedation assessments**

A median [IQR] number of 10 [1 to 41] NISS assessments in 41.1% of the 542 patients (37.7% in the control group versus 44.7% in the Down syndrome group) were recorded in the PDMS. The median [IQR] percentage of adequate sedation scores was 90.5% [78 to 100] in the control group versus 87.8% [79 to 100] in the Down syndrome group (P=0.33).

**Item descriptives and internal consistency**

Table 2 lists the mean COMFORT-B item scores and SDs for both groups; the mean scores were derived from all scores of the first 7 days of the longest admission. There were signifi-
cant differences for four items. However, the SDM between the two groups was low. The standardized Cronbach’s $\alpha$’s varied from 0.84 to 0.87 and all corrected item-total correlations were above 0.54 (Table 2).

**Confirmatory factor analysis**

Confirmatory factor analysis was applied on 347 scores in the Down syndrome group and 2067 scores in the control group. The most plausible model included equal factor loadings, equal residual variances, unequal error variances and unequal factor means. In this model, the item ‘Calmness’ appeared to be correlated with ‘Respiratory response / crying’. ‘Facial expression’ was correlated with ‘Muscle tone’. The fit indices were satisfactory ($\chi^2$ of 101 with 19 degrees of freedom, $\chi^2$/df of 5.3, SRMR of 0.03 and a RMSEA of 0.06). The unstandardized factor loadings varied from 0.36 for muscle tone to 0.86 for body movements both groups. The unstandardized and standardized loadings of the COMFORT-B items for the two groups are listed in Table 3.

**TABLE 3 Unstandardized and standardized factor loadings for the COMFORT-B scale**

<table>
<thead>
<tr>
<th>Item</th>
<th>Down syndrome scores (347 scores)</th>
<th>Controls (2067 scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alertness</td>
<td>Unstandardized 1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Standardized 0.74</td>
<td>0.78</td>
</tr>
<tr>
<td>Calmness</td>
<td>Unstandardized 0.63</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>Standardized 0.76</td>
<td>0.76</td>
</tr>
<tr>
<td>Physical movement</td>
<td>Unstandardized 0.86</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>Standardized 0.75</td>
<td>0.81</td>
</tr>
<tr>
<td>Facial tension</td>
<td>Unstandardized 0.48</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>Standardized 0.70</td>
<td>0.69</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Unstandardized 0.36</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>Standardized 0.54</td>
<td>0.57</td>
</tr>
<tr>
<td>Respiratory response / Crying *</td>
<td>Unstandardized 0.66</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>Standardized 0.68</td>
<td>0.63</td>
</tr>
</tbody>
</table>

* These two items were combined in the confirmatory factor analysis. Respiratory response was scored in mechanically ventilated patients and crying in spontaneously breathing patients.

**Optimal clinical cut-off values**

For both groups the clinical cut-off COMFORT-B score of 17 presented with good sensitivity (82% in the Down syndrome group and 83% in the control group) and excellent specificity (92% in the Down syndrome group and 91% in the control group). The positive predic-
tive value was 0.32 in both groups. The negative predictive value was excellent (0.99) for both groups. The AUC for the Down syndrome group did not statistically significantly differ from the AUC of the control group ($P=0.85$), see Figure 1.
DISCUSSION

Psychometric properties of the COMFORT-B scale were comparable between 0-to 3-year old patients with and without Down syndrome. Confirmatory factor analysis revealed that a 1-factor model was sufficient to represent the six items of the COMFORT-B scale. The finding that more children in the Down syndrome group were mechanically ventilated and received morphine and midazolam can be explained by the fact this group included more surgical patients.

The current study confirms the 1-factor structure of the COMFORT-B scale when applied in children with and without Down syndrome in the ICU setting. Previous studies have evaluated the original COMFORT scale (eight items) in the pediatric ICU setting using exploratory (4, 22) and confirmatory factor analysis(3). All three studies identified a 1-factor solution for the six behavioral items and one or more factors for the two physiological items blood pressure and heart rate. Omitting the items blood pressure and heart rate resulted in the six-item COMFORT-B scale, which is now often used(3, 4). However, in contrast to the previous studies, the items ‘Calmness’ and ‘Respiratory response / crying’ were intercorrelated in the present study, and so were ‘Facial expression’ and ‘Muscle tone’. These additional intercorrelations were required to reach an adequate fit of the model. Confirmatory factor analysis as applied in the present study has important advantages over exploratory factor analysis because it allows for statistical inference modeling. Exploratory factor analysis does not allow for this and gives no information about intercorrelations or significant differences in factor loadings(23, 24). Hence, we recommend the use of confirmatory factor analysis for all future studies in this field.

The mean COMFORT-B scores did not differ significantly between the two groups. The prevalence of pain was low in both groups: COMFORT-B scores were 17 or higher in about 7% of the assessments. NRS\textsubscript{obs} pain scores of 4 or higher (an indication for moderate to severe pain) were even more rare (5% of scores). The correlation coefficients between COMFORT-B and NRS pain scores were acceptable in both groups. The number of COMFORT-B scores was higher in the Down syndrome group because they were more often admitted after surgery. In practice, surgical patients are assessed more frequently. Other PICUs have reported comparable prevalences of pain using the same assessment instruments as in the present study. One study by Johansson et al. in 40 PICU patients reported a median COMFORT-B score of 12 in the children who were adequately sedated(6). The NRS\textsubscript{obs} pain ratings in that study were 4 or higher in only 6% of the assessments.

Comparing the mean item scores between the 1163 scores of the Down syndrome group and the 6276 scores of the control group, we observed some statistically significant differences. The item scores on the four items “Crying”, “Physical Activity”, “Facial Tension” and “Muscle Tone” were significantly different between the two groups. The standardized mean
differences (SMD) for these items ranged from -0.12 to 0.23; therefore we see these differences as clinically not relevant. Because the mean item score for “Crying” was lower, future studies using spectrographic analysis could evaluate the character of the cry of children with Down syndrome. Lind et al. observed that children with Down syndrome have a low-pitched, hoarse cry(15). The COMFORT-B scale evaluates the intensity of the crying, not its characteristics.

Children with Down syndrome are reported to have a weaker muscle tone(25). The mean item score for “Muscle Tone” was lower in the Down syndrome group, with a SMD of 0.21. The small magnitude of this difference may be explained by the fact that the COMFORT-B observer assesses muscle tone by lifting the child’s arm or leg, whereas the pediatrician applies an overall assessment of hypotonia. Another explanation may be that nurses will anticipate hypotonia when assessing muscle tone in children with Down syndrome.

The optimal clinical cut-off value of the COMFORT-B scale for pain was 17 for both groups of patients with good sensitivity, specificity and negative predictive value. The positive predictive value was relatively low in both groups. This may be because distress without pain also results in a high COMFORT-B score. In our study, the NISS scores suggest that more than 80% of the children were adequately sedated. Children were treated according to the pain management protocol. More children with Down syndrome received morphine and midazolam, probably because of the higher rate of surgery in this group. The doses of morphine and midazolam did not differ between the groups. Reducing the incidence of pain is highly desirable and PICUs around the world strive for this, but this low incidence of pain may influence the psychometric evaluation of pain assessment scales.

A possible limitation of this study is that background characteristics were collected from charts. Nevertheless, all pain assessment data were retrieved from the patient data management system (PDMS) in which these data are prospectively collected at set time points during a patient’s admission. The use of the PDMS assures a satisfactory level of quality and reliability of the data. The second limitation is that the sample size of the Down syndrome group was small. This is in line with other studies in this patient group and is because the incidence of Down syndrome in the Netherlands is 16 per 10,000 live births(26). In general, it is preferable to have a smaller discrepancy between group sizes.

Previous studies validated the COMFORT-B scale for the assessment of pain and distress in children admitted to the PICU. Nowadays, the COMFORT-B scale has gained wide acceptance in PICUs around the world. Because the COMFORT-B scale now proved valid for 0 to 3 year old children with Down syndrome as well, there is no need to introduce yet another scale. The COMFORT-B scale may also serve as a validated outcome parameter in pharmacodynamic studies in children with Down syndrome.
REFERENCES


Until imagination, ear and eye,
Can be content with argument and deal
In abstract things;
or be derided by
A sort of battered kettle at the heel.
SKIN CONDUCTANCE PEAKS COULD RESULT FROM CHANGES IN VITAL PARAMETERS UNRELATED TO PAIN

Abraham J. Valkenburg, Sjoerd P. Niehof, Monique van Dijk, Esther J.M. Verhaar, Dick Tibboel

Pediatric Research (2012); 71: 375 - 379
ABSTRACT

Introduction
Pain is usually assessed by the interpretation of behavior, which can be subjective. Therefore, there is an ongoing search for more objective methods. Performance of skin conductance measurement as a pain assessment tool is variable, as some studies report low specificity and a low predictive value of the method. The aim of this pilot study was to test whether autoregulation of the skin temperature influences the skin conductance of pain-free infants.

Methods
We included 11 infants, median (interquartile range (IQR)) age of 34 (13–76) d, who were admitted to the surgical high-care unit for monitoring after surgery. None was treated with opioids or sedatives, and observational pain scores were low.

Results
Skin conductance was highly correlated with skin temperature in all subjects. Moreover, a significant change in all other vital parameters was observed on comparing before- and after-peak data.

Discussion
These results indicate that sympathetic neural activity to maintain homeostasis (such as autoregulation of skin temperature) results in skin conductance peaks. Real-time evaluation of the sympathetic nervous system would be valuable for pain assessment. However, the technique should be better defined to increase both sensitivity and specificity for the measurement of pain before use in daily practice can be advocated.
INTRODUCTION

Pain management and ideally pain prevention are cornerstones of optimal postoperative care. In verbal children and adults, self-report is the generally accepted gold standard for the assessment of pain. Self-report is impossible, however, in neonates and infants, intubated or sedated patients and intellectually disabled patients. In those cases, caregivers have to rely on observational pain assessment scales such as the COMFORT-behavior scale(1), the Numeric Rating Scale for pain, or physiological parameters such as heart rate or blood pressure(2).

Still, researchers are in search for more objective methods. Recently studied methods include near-infrared spectroscopy(3), heart rate variability(4) and skin conductance measurement(5-7). The last is based on the following theory: Sweat glands are sympathetic innervated and will produce sweat, and thereby salt, which increases the electrical conductance of the skin. Pain is known to stimulate sympathetic nerve activity, but animal and human studies have shown that several other physiological responses have the same effect. The primary function of the eccrine sweat glands is to enable evaporative heat loss in the autoregulation of body temperature. The following receptors and simple maneuvers influence skin sympathetic nerve traffic: temperature receptors in the central nervous system and skin, arousal and stress, respiration, cardiopulmonary receptors, sleep, and pain(8). However, Rutter reports that palmar and plantar sweat glands respond more to emotional stimuli than to thermal stimuli(9).

Measurement of skin conductance as a pain assessment tool has been studied during heel lancing(10), intraoperatively(11), directly postoperatively(12), during postoperative care(13, 14) and during intensive care(15). Performances were variable, as some studies report good sensitivity (12) and others low specificity and a low predictive value(16). It could be possible that sympathetic nerve activity, other than caused by pain, influences skin conductance and therefore has impact on the performance of skin conductance measurement.

Aim

The aim of this pilot study was to test whether autoregulation of the skin temperature influences the skin conductance of pain-free infants.
METHODS

Design
We performed an observational pilot study in which we measured simultaneously the infants’ skin conductance and vital parameters such as skin temperature, respiratory rate, heart rate, peripheral oxygen saturation ($\text{SpO}_2$) and Peripheral Flow Index (PFI).

Subjects and Setting
The study protocol was approved by the local ethics review committee of the Erasmus University Medical Center (Rotterdam, the Netherlands). Written informed consent was obtained from all the parents. The pilot study was performed at the surgical high-care unit of Erasmus University Medical Center - Sophia Children’s Hospital between July and September 2008.

Inclusion criteria were: Age up to and including 12 months, and being monitored in the surgical high-care unit. Exclusion criteria were: Mechanical ventilation, treatment with opioids or sedatives in the 24 hours before the study, and a COMFORT-B score of 17 or higher (indicating moderate to severe pain or distress) before measurement.

Measurements
The infants underwent routine medical examination and nursing care in the morning. Skin conductance electrodes (see below) were placed after nursing care, and data recording started 5 to 10 minutes later. Data were recorded for 60 minutes, thereafter the electrodes were removed.

Pain and distress assessment
On the test day, the nurse who provided the morning care assessed the infant’s distress and pain using the COMFORT-Behavior scale. The COMFORT-B scale is an observational assessment tool and includes 6 items; each item is rated with a score from 1 to 5. Adding all six items together provides a pain rating between 6 and 30. The COMFORT-B has been validated for pain and distress assessment in critically ill and postoperative children(1, 17, 18).

Skin conductance
Skin conductance was assessed using the Stress Detector (MedStorm, Oslo, Norway). The three pediatric skin electrodes (MedStorm) were attached to the heel of the neonate according to the manufacturers’ recommendations. The software automatically defines peaks above the amplitude threshold of 0.02 microSiemens. The sample frequency of the Stress Detector is 65 Hz. The Stress Detector records the skin conductance in microSiemens and in terms of signal quality. The other parameters, such as number of fluctuations in skin conductance per second (NFSC) and area under the curve, are derived from the change of
skin conductance over time. The other parameters, such as number of fluctuations in skin conductance per second (NFSC) and area under the curve, are derived from the change of skin conductance over time. The NFSC was calculated over the entire measurement period (approximately one hour) as this would be more precise than considering a 15 or 30 seconds time frame.

Vital parameters
Our surgical high-care unit uses the Philips Intellivue MP-30 monitor (Philips, Eindhoven, the Netherlands) for monitoring. The Oxisensor II neonatal probe (Covidien-Nellcor™, Boulder, USA) was attached to the sole of the foot to measure peripheral oxygen saturation and to calculate the Peripheral Flow Index (PFI). Kendall Medi-Trace neonatal 3 lead ECG electrodes (Covidien-Nellcor™) were used to measure heart rate and respiratory rate. The skin temperature surface probe (Philips) was attached next to the skin conductance electrodes on the heel to measure the skin temperature. During the study, the monitor was connected to a laptop computer with TrendFace software (iexellence, Wildau, Germany) to record the vital parameters. Data were recorded with a sample frequency of 0.97 Hz.

Statistical analysis

Data extraction
The Stress Detector stores the skin conductance data in a text file with a sample frequency of 65 Hz. The raw data as well as signal quality data were imported in MATLAB (MathWorks, Natick, MA, USA), a high-level technical computing language and interactive environment for algorithm development, data visualization, data analysis and numeric computation. TrendFace software exported the vital parameter data into an Excel file with a sample frequency of 0.97 Hz (1.032s). We, therefore, used skin conductance values with the same sample frequency of 0.97 Hz.

Data analysis in MATLAB
The Stress Detector software detects peaks and hills in the skin conductance data, but does not export this information. In MATLAB we therefore defined peaks and troughs according to the definition used in the MedStorm software, i.e. the minimal amplitude of a peak is 0.02 microSiemens. The number of fluctuations in skin conductance per second (NFSC) per subject were compared between the Stress Detector and the MATLAB analysis to verify the similarity between the calculations.

Because the absolute skin conductance values in microSiemens can be influenced by accumulation of sweat in the electrodes, Med-Storm advises the use the number fluctuations in skin conductance per second (NFSC) instead of the absolute skin conductance. A peak is a burst of sympathetic activity; however, not only caused by pain or distress. Mean values of
vital parameters measured during fifteen seconds before and after each peak were statistically compared using the t-test.

Data analysis in SPSS
First, we analyzed patient characteristics using descriptive statistics. As the sample size is small in this pilot study, we report median and interquartile range values for the group.

Second, we analyzed the skin conductance and vital parameter data per patient using descriptive statistics. Thereafter the mean values of the group were calculated. Also the Spearman rank order correlation coefficients between the skin conductance and vital parameters were calculated per patient.

Third, the differences in vital parameter values before and after a peak were analyzed in SPSS 19 (Chicago, IL, USA). For each vital parameter, we calculated the percentage of values that significantly differed before and after a peak and applied the Friedman test to compared these percentages between the different vital parameters(19).

![Percentage of significant differences before and after skin conductance peaks for the vital parameters. Median (horizontal line), 25th and 75th percentiles (box), and range (whiskers) of significant differences in vital parameters before and after a skin conductance peak. PFI = Peripheral Flow Index, SpO2 = peripheral oxygen saturation](image_url)
RESULTS

Patient characteristics
We included 11 subjects with a median [interquartile range (IQR)] age of 34 [13 to 76] days. Six had had gastrointestinal surgery, three surgical closure of a congenital diaphragmatic hernia, one repair of esophageal atresia, and one a rigid bronchoscopy. Table 1 shows their baseline characteristics. Patients were studied at a median [IQR] of 11 [5 to 17] days after surgery. The median [IQR] COMFORT-behavior score prior to the study was 10 [9 to 10], indicating that none was in pain or distress.

TABLE 1 Characteristics of the 11 subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median [IQR]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (M/F)</strong></td>
<td>5 / 6</td>
</tr>
<tr>
<td><strong>Gestational Age</strong>, in weeks</td>
<td>36 [29 to 38]</td>
</tr>
<tr>
<td><strong>Age</strong>, in days</td>
<td>34 [13 to 76]</td>
</tr>
<tr>
<td><strong>Post-conceptional age</strong>, in days</td>
<td>275 [259 to 280]</td>
</tr>
<tr>
<td><strong>Days after surgery</strong></td>
<td>11 [5 to 17]</td>
</tr>
<tr>
<td><strong>Duration of measurement</strong>, in minutes</td>
<td>63 [61 to 65]</td>
</tr>
<tr>
<td><strong>COMFORT-B score before measurement</strong></td>
<td>10 [9 to 10]</td>
</tr>
<tr>
<td><strong>Skin Conductance</strong></td>
<td></td>
</tr>
<tr>
<td>Number of peaks</td>
<td>36 [19 to 312]</td>
</tr>
<tr>
<td>Skin Conductance, in microSiemens</td>
<td>6.42 [3.13 to 9.21]</td>
</tr>
<tr>
<td>Number of Fluctuations</td>
<td>0.0098 [0.0047 to 0.0825]</td>
</tr>
<tr>
<td>in Skin Conductance per second</td>
<td></td>
</tr>
<tr>
<td><strong>Vital parameters</strong></td>
<td></td>
</tr>
<tr>
<td>Heart rate, in beats/minute</td>
<td>154 [130 to 167]</td>
</tr>
<tr>
<td>Skin Temperature, in °C</td>
<td>32.19 [30.54 to 32.88]</td>
</tr>
<tr>
<td>Peripheral Flow Index</td>
<td>0.66 [0.37 to 1.20]</td>
</tr>
<tr>
<td>Peripheral oxygen saturation, in %</td>
<td>98.67 [97.65 to 99.50]</td>
</tr>
<tr>
<td>Respiratory rate, in breaths/minute</td>
<td>44.37 [37.39 to 60.85]</td>
</tr>
</tbody>
</table>

Descriptive results
Monitoring lasted a median [IQR] of 63 minutes [61 to 65] during which a median [IQR] number of 3576 [3099 to 3678] samples was obtained. The median [IQR] number of skin conductance peaks was 36 [19 to 312]. The median values of the vital parameters are shown in Table 1.
Significant differences before and after skin conductance peaks

The median percentages of statistically significant differences in vital parameters before and after a skin conductance peak are displayed in Figure 1. Percentages varied from a median [IQR] of 62 % [59 to 68] for heart rate to a median [IQR] of 88 % [82 to 94] for skin temperature (Friedman test: P = 0.003). In one subject, peripheral oxygen saturation changed significantly after all 18 peaks (see Figure 1).

Correlations

In all 11 subjects, skin temperature (in ° Celsius) was statistically significantly correlated with the skin conductance value (in microSiemens; P <0.001). In eight subjects, this was a positive correlation: Median [IQR] Spearman’s rho correlation coefficient of 0.86 [0.78 to 0.94]. In the remaining three subjects, it was a negative correlation: Spearman’s Rho correlation coefficient of -0.48, -0.49 and -0.99. Background characteristics (postnatal age, type of surgery, sex and environmental circumstances) and vital parameters of these three patients did not differ from those of the eight patients for whom a positive correlation was found.

An example of the positive correlation between skin temperature and skin conductance for one subject is displayed in Figure 2; the Spearman’s Rho correlation coefficient for this subject was 0.92.

![Graph showing correlation between skin temperature and skin conductance](image)

**FIGURE 2** Correlation between skin temperature and skin conductance for Subject 10. This figure is based on 2837 paired observations (skin conductance and skin temperature) in one subject during a measurement of 1 h. The Spearman’s rho correlation coefficient is 0.92.
DISCUSSION

We found that in infants without evident pain, skin conductance was correlated with skin temperature. Using TrendFace and MATLAB software, we were able to analyze skin conductance and vital parameters in detail, focusing on the skin conductance peaks, which represent bursts of skin sympathetic nerve activity. Vital parameters before and after a peak mostly were significantly different. For skin temperature this was even the case in a median of 88% of the peaks. Percentages for all other four vital parameters were lower. In all 11 infants, skin temperature was highly correlated with the skin conductance. However, this pilot study does not explain why there should be both positive and negative correlations since none of the background characteristics or vital parameters differed between patients for whom a negative correlation was found and those for whom a positive correlation was found. The possibility of coincidence cannot be excluded. Our results suggest that sympathetic neural control of vital functions to maintain homeostasis (such as autoregulation of skin temperature) results in skin conductance peaks.

Analysis of skin sympathetic nerve activity is not a new technique. In a review article on microneurographic recordings, Wallin et al. conclude that skin sympathetic nerves are mostly involved in thermoregulation(8). Other maneuvers that influence the sympathetic nerve activity are arousal, stress, respiration, sleep, cardiopulmonary receptors and pain. Four types of skin sympathetic nerves are distinguished vasoconstrictor, vasodilator, sudomotor and pilomotor. Sudomotor nerves are cholinergic and cause sweat secretion (measured as a peak in skin conductance) at increased activity, for example thermoregulation. Microneurographic recordings from the sudomotor nerves simultaneously with skin conductance measurement are scarce. Macefield et al. made microneurographic recordings combined with skin conductance, electrocardiogram and skin blood flow(20). Sudomotor nerve activity appeared to be correlated with cardiac activity and skin conductance but not with skin blood flow.

Studies that evaluated skin conductance as a means to measure (postoperative) pain reported different degrees in clinical performance(12, 16). For example, Choo et al. found a weak correlation between skin conductance and numeric rating scale for pain (NRS-pain) in 90 postoperative children, namely 0.21(13). They determined a cutoff value of 0.23 skin conductance peaks per second for the detection of severe pain (NRS-pain 7 or higher) with a sensitivity of 56% and a specificity of 78%. The other study in children, by Hullett et al.(12), reports a better sensitivity of 90% but a lower specificity of 64%. Other relevant studies are listed in Table 2. Comparison between the studies is difficult, since cutoff points for the number of skin conductance peaks and gold standards differ between the studies. Compared to skin conductance measurement, the COMFORT-behavioral scale performed better with a reported sensitivity of 83% and a specificity of 91%(21). Results from Loggia et al.,
who compared skin conductance and visual analogue scale (VAS) scores in healthy adults, suggest that skin conductance is not a very reliable predictor of pain(22). The authors advise caution when using autonomic measures to infer pain. The reported poor sensitivity and specificity of skin conductance to measure (postoperative) pain could be a result of the correlation of skin conductance with for example autoregulation of the skin temperature, as confirmed in our study.

**TABLE 2 Studies that evaluated the performance of skin conductance as a measure of postoperative pain**

<table>
<thead>
<tr>
<th>Study group</th>
<th>Ledowski (14)</th>
<th>Ledowski (7)</th>
<th>Hullett (12)</th>
<th>Ledowski (16)</th>
<th>Choo (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>21 to 67 years</td>
<td>19 to 81 years</td>
<td>1 to 16 years</td>
<td>18 to 82 years</td>
<td>7 to 17 years</td>
</tr>
<tr>
<td>Cutoff value in skin conductance peaks per second</td>
<td>0.10</td>
<td>0.10</td>
<td>0.13</td>
<td>0.10</td>
<td>0.23</td>
</tr>
<tr>
<td>Gold standard</td>
<td>NRS (by proxy) &gt;3</td>
<td>NRS &gt;3</td>
<td>VAS &gt;3</td>
<td>NRS &gt;3</td>
<td>NRS &gt;5</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>89%</td>
<td>89%</td>
<td>90%</td>
<td>50%</td>
<td>58%</td>
</tr>
<tr>
<td>Specificity</td>
<td>74%</td>
<td>68%</td>
<td>64%</td>
<td>64%</td>
<td>61%</td>
</tr>
</tbody>
</table>

NRS = Numeric Rating Scale, VAS = Visual Analog Scale

**Limitations**

None of the subjects had an arterial line for blood pressure monitoring. Therefore we were not able to evaluate the correlation between skin conductance and blood pressure.

**Implications**

Preclinical and clinical studies in neonates, children and adults are needed to make skin conductance a clinically more useful measure for postoperative pain. Preclinical studies should use microneurography as the gold standard and measure skin conductance simultaneously. These studies should not only evaluate the influence of pain and other sympathetic activity on skin conductance, but also find certain rhythms, if any, in skin conductance peaks. The algorithms of the skin conductance monitor could then be made more specific for the measurement of pain by correcting for other sympathetic influences. The clinical studies then should validate the skin conductance monitor in different age groups such as neonates, children and adults for the measurement of (postoperative) pain(23). Furthermore, it could be difficult to compare pain-free and painful states in the same subjects and to assure stable circumstances. The clinical studies should therefore also integrate, for example, observational pain assessment and electroencephalography in a multimodal approach as applied by Slater et al.(24). This strategy could lead to a validated,
objective pain assessment tool that can be used in clinical practice and serve as a pharmaco-dynamic parameter in pain research.

**Conclusions**

In this pilot study we observed that, in a pain-free state, other sympathetic nerve activity, such as skin temperature autoregulation, also results in skin conductance peaks that are usually seen in pain states. Real-time evaluation of the sympathetic nervous system would be valuable for pain assessment. However, the technique should be better defined to increase both the sensitivity and specificity for the measurement of pain before use in daily practice can be advocated.
REFERENCES

PART 3

QUANTITATIVE SENSORY TESTING
Hoe zal ik dit uitleggen, dit waarom wat wij vinden niet is wat wij zoeken?
Chapter 8

PAIN SENSITIVITY OF CHILDREN WITH DOWN SYNDROME AND THEIR SIBLINGS: QUANTITATIVE SENSORY TESTING VERSUS PARENTAL REPORTS

Abraham J. Valkenburg, Monique van Dijk, Dick Tibboel
ABSTRACT

Background
Children with Down syndrome are claimed to be less sensitive to pain. Previous studies showed that parents have difficulties in perceiving if their child is in pain and to identify the location of the pain. The aim is to compare thermal detection and pain thresholds between children with Down syndrome and their siblings, using qualitative and quantitative methods, as well as parental questionnaires on pain coping, pain behaviour and chronic pain.

Methods
Forty-two children with Down syndrome (mean age 12 years) and 24 siblings (mean age 14 years) participated in this study. Tests included qualitative sensory tests, assessment of thermal pain and detection thresholds and parental questionnaires on developmental age, pain coping, pain behavior, chronic pain and the medical history.

Results
The different sensory tests proved to be feasible in 33% to 88% of children in the Down syndrome group. Children with Down syndrome were less sensitive for the detection of cold and warmth than their siblings, but only when measured with the reaction time dependent method. Children with Down syndrome were more sensitive for heat pain. They also used less pain coping strategies than their siblings. Only 14% of the children with Down syndrome were able to adequately give self-report of pain versus 92% of the controls (P<0.001). Sixty-six percent of the children with Down syndrome were rated as less sensitive to pain versus 10% of the controls (P<0.001).

Conclusion
Children with Down syndrome will remain dependent of pain assessment by proxy, since self-report is not adequate. Parents rate their children with Down syndrome as less sensitive to pain, but this is not confirmed by quantitative sensory testing.
As early as 1887 John L. Down made the following observation about persons with what we now call Down syndrome: “common sensation is generally less acute than in ordinary persons. Pain is borne with wonderful callousness.”(1). More than a century later, a study reported that around 30% of parents of children with Down syndrome had difficulty perceiving if their child is in pain and that 70% of the parents had difficulty identifying the location of the pain(2). These results were confirmed in a prospective study among a group of individuals with Down syndrome versus a control group. The individuals with Down syndrome had more problems to locate a painful stimulus and also reacted to the painful stimulus later than did the controls(3). Defrin et al. applied quantitative sensory testing to assess the heat pain sensitivity of 11 adults with Down syndrome and 14 controls and concluded that the individuals with Down syndrome were more sensitive to heat pain than controls (borderline significance; P=0.06)(4).

Down syndrome is the primary cause of congenital intellectual disability worldwide. More than 80 different associated anomalies have been identified in children with Down syndrome, such as congenital heart defects, congenital duodenal obstruction, leukemia, hypothyroidism, vision and hearing disorders(5, 6). Many children with Down syndrome suffer from such anomalies are therefore likely to experience pain from inevitable operations but also from, for example, orthopedic problems later on(7, 8). More knowledge on the pain sensitivity of children with Down syndrome and the pain coping strategies they use could lead to better, individualised pain management.

The aim of the present study was to compare thermal detection and pain thresholds between children with Down syndrome and their siblings, using qualitative and quantitative methods, as well as parental questionnaires on pain coping, pain behaviour and chronic pain.
METHODS

Subjects and setting
This study has been approved by the local medical ethics committee of Erasmus University Medical Center – Sophia Children’s Hospital, Rotterdam, the Netherlands. Participants were recruited through the Zuid-Holland branch of the national parental organization for Down syndrome in the Netherlands. Around 80% of parents of children with Down syndrome are members of that organization. The Zuid-Holland area covers more than 20% of the Dutch population. Members with 8 to 18-year-old children received a letter from the organization informing them about the study and inviting them to participate. Those willing to participate were asked to complete a form with their contact details and return it in a prepaid envelope to the researcher (AJV). The researcher then contacted the parents to provide further information and to arrange a date for a home visit. Parents of 42 children with Down syndrome gave written informed consent for the study, as well for 24 siblings without Down syndrome. Siblings of 12 years or older were asked to give written informed consent themselves for the study.

Qualitative sensory testing
The child’s discriminative abilities for the perception of touch and sharpness were tested with the Neuropen (Owen Mumford Ltd., Oxford, UK). To test the perception of touch the monofilament is pressed to the skin (approximately a force of 10 gram); the sharp end of the device is calibrated to exert a force of 40 gram. To test the feasibility of testing the discriminative abilities with the Neuropen, the researcher demonstrated both ends of the Neuropen to the subject and asked the participant “does this feel blunt or sharp?”. If the subject could describe the difference between blunt and sharp, the researcher then asked the participant to close the eyes. The Neuropen was applied to the non-dominant arm of the participant (blunt – sharp – blunt – blunt – sharp). After each stimulus, the researcher asked “does this feel blunt or sharp?”.

The child’s discriminative abilities for the perception of warmth and cold were tested with the Senselab Rolltemp (Somedic AB, Hörby, Sweden). The cold roller is 25 °C and the warm roller is 40 °C. To test the feasibility of testing the discriminative abilities with the Rolltemp, the researcher demonstrated both rollers to the participant and asked for each roller “does this feel warm or cold?”. If the subject could describe the difference between warmth and cold, the researcher then asked the participant to close the eyes. The rollers were applied five times to the non-dominant arm of the participant (warm – warm – cold – warm – cold). After each stimulus the researcher asked “does this feel warm or cold?”.

Reaction time
The visual-motor reaction time for the dominant hand was measured with open-source
software (http://delphiforfun.org/Programs/Reaction_times.htm). The participant was asked to click the mouse as soon as the blue ball appeared on the white screen. The first sequence of 10 repetitions served to familiarize the participant with the test and to assess the feasibility. The second sequence of 10 repetitions served to measure the reaction time. The program calculated the mean of the 10 values.

Quantitative sensory testing
The mechanical perception threshold was tested with the Von Frey Aesthesiometer (Somedic AB, Hörby, Sweden). The 20 nylon monofilaments each have another diameter. The force that is needed to buckle the hair ranges from 0.026 gram to 110 gram. The researcher first showed the Von Frey hairs and then asked the participant to close the eyes and to say “yes” as soon as the stimulus is perceived. The researcher applied the Von Frey hairs to the skin of the non-dominant arm, starting with the smallest hair. The test was regarded as feasible if the participant was able to keep the eyes closed and reacted verbally to the application of the Von Frey hairs.

Skin temperature was measured at the thenar eminence of the non-dominant hand to ensure it was within the range of 27 to 37 degrees Celsius(9).

We anticipated that testing the thermal perception thresholds and pain thresholds would perhaps not be feasible in the children with Down syndrome. We therefore made a comic book to prepare the participants. The main character was a plush animal that we brought with us to the home visit. Her plush ‘tail’ was the thermode of the thermal sensory analyzer. The comic book was available online for parents and children; parents were asked to read the story with the child before the home visit. During the test, a hard copy of the book was used. Before the start of the test, the comic was read with the child and the plush animal was again introduced. Parents were asked to be present during the introduction and the test but to minimize interference with their child. Feasibility was defined by the following elements: the ability to indicate a change in the temperature of the thermode, the ability to retain attention for at least three successive stimuli, and the ability to distinguish between testing the detection threshold and the pain threshold (i.e. mere perception of the stimulus versus painfulness of the stimulus).

Thermal thresholds were measured at the thenar eminence of the non-dominant hand, using the Thermal Sensory Analyzer-II (Medoc Ltd, Ramat Yishai, Israel) with the 30 by 30 mm thermode. Baseline temperature for all measurements was 32 degrees Celsius, the minimum temperature was 0.0 °C and the maximum temperature was 50.0 °C. Detection thresholds were measured using both the method of limits (reaction time dependent) and the method of levels (reaction time independent). The standardized instructions were in accordance with other quantitative sensory testing studies in children(10-12). The only
adjustment was that the children were asked to release a button as soon as a stimulus was perceived since this is considered easier than pressing a button as in other studies. Six modalities were tested in the following order. 1) Detection threshold for cold (method of limits): Six repetitions, temperature decreased by 1.0 °C/s. Children were asked to release the button as soon as the cold stimulus was perceived. 2) Detection threshold for warmth (method of limits): Six repetitions, temperature increased by 1.0 °C/s. Children were asked to release the button as soon as the warm stimulus was perceived. 3) Pain threshold for cold (method of limits). Five repetitions, temperature decreased by 1.5 °C/s. Children were asked to release the button as soon as the stimulus was so cold it became painful. A note was made when the minimum temperature (0.0 °C) was reached. 4) Pain threshold for heat (method of limits): Five repetitions, temperature increased by 1.5 °C/s. Children were asked to release the button as soon as the stimulus was so hot it became painful. A note was made when the maximum temperature (50.0 °C) was reached. 5) Detection threshold for cold (method of levels): Children were asked per step if the cold stimulus was perceived, until the difference between two steps was less than 0.1 °C/s. The number of steps needed was recorded. 6) Detection threshold for warmth (method of levels): Children were asked per step if the warm stimulus was perceived, until the difference between two steps was less than 0.1 °C/s. The number of steps needed was recorded.

Detection thresholds established by the method of limits were calculated as the mean value of the final four of the six measurements. The first two measurements served to assure that the child understood the test correctly. Pain thresholds established by the method of limits were calculated as the mean value of the final four of five measurements. The first measurement served to assure that the child understood the test correctly. Detection thresholds established by the method of levels were measured once. If the minimum or maximum temperature is reached, the device records the minimum temperature (0.0 °C) / maximum temperature (50.0 °C) as the result.

**Questionnaires**
Parents were asked to complete five questionnaires for the child with Down syndrome and the sibling (if applicable). The questionnaires could be completed either online (on a password-protected website) or in writing.

1. Questionnaire on the child’s medical history (medication prescriptions, surgical history, other medical issues), education and the family’s socioeconomic status (according to the standardized classification of occupations, provided by Statistics Netherlands, version 2010).

2. The Vineland Adaptive Behavior Scale - Screener (Dutch version, PITS B.V., Leiden, the Netherlands)(13) asks parents to assess the child’s adaptive behavior. Adaptive behav-
ior is defined as “the collection of conceptual, social and practical skills that have been learned by people in order to function in their everyday lives”. The questionnaire consists of 90 items in four domains: communication, daily living, socialization and motor skills (score range 0 to 180). Reference values for Dutch children with and without Down syndrome are available(14).

3. Self-developed questionnaire with qualitative and quantitative questions on pain and anxiety in medical and non-medical situations. Parents were asked to compare the pain behavior of their child with Down syndrome to children of the same age without Down syndrome. For example: Is your child with Down syndrome (less – equally – more) sensitive for pain than children without Down syndrome?

4. The Pain Coping Questionnaire, is developed and validated by Reid et al.(15). Parents were asked to rate how often their child uses each of 39 pain coping strategies that represent 8 coping subscales: Information seeking, problem solving, seeking social support, positive self-statements, behavioural distraction, cognitive distraction, externalizing, internalizing/catastrophizing. The questionnaire was translated into Dutch using forward-backward translation by two independent translators.

5. The Chronic Pain Questionnaire, is developed and validated by Perquin et al.(16). This questionnaire asks for the incidence of pain in the past 3 months and additional information about the pain (location, frequency, duration and intensity). A pain episode with duration of 3 months or longer is defined as chronic pain. The original language is Dutch.

Statistical analysis
Summary statistics of continuous variables are presented as median [interquartile range] and as percentage for ordinal and categorical variables. Data were compared between the children with and without Down syndrome using the Mann-Whitney test for continuous, non-normal data and the chi-square test (or Fisher exact test in case of low predicted cell counts) for nominal data. Binary logistic regression analysis was performed with the feasibilities of the different tests as outcome variables and chronological age, developmental age and socioeconomic status as predictor variables. P values (two-sided) of less than 0.05 are considered statistical significantly. Data were analysed by SPSS software, version 19.1 (IBM, Armonk, NY, USA).
RESULTS

Background
Background characteristics are presented in Table 1. Children with Down syndrome underwent more often cardiac surgery and were more often treated for hypothyroidism.

TABLE 1 Background Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Down syndrome (n= 42)</th>
<th>Controls (n= 24)</th>
<th>P value *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median [IQR] or number (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex, n(%) male</strong></td>
<td>21 (50%)</td>
<td>16 (67%)</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Age in years</strong></td>
<td>11.9 [10.6 to 14.7]</td>
<td>13.8 [11.5 to 17.3]</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Reaction time in seconds</strong></td>
<td>0.84 (0.35)</td>
<td>0.38 (0.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Number of surgical interventions</strong></td>
<td>2 [1 to 3]</td>
<td>0 [0 to 1]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Surgery for congenital heart defect</strong></td>
<td>14 (34%)</td>
<td>0 (0%)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Hypothyreoidism</strong></td>
<td>9 (22%)</td>
<td>0 (0%)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Socioeconomic status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>7 (17%)</td>
<td>4 (17%)</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>13 (32%)</td>
<td>6 (26%)</td>
<td>0.87</td>
</tr>
<tr>
<td>High</td>
<td>21 (51%)</td>
<td>13 (57%)</td>
<td></td>
</tr>
<tr>
<td><strong>Vineland Adaptive Behavior Scale</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communication</td>
<td>32 [24 to 38]</td>
<td>52 [50 to 52]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daily skills</td>
<td>31 [26 to 36]</td>
<td>44 [42 to 45]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Social</td>
<td>33 [28 to 35]</td>
<td>45 [42 to 46]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Motor</td>
<td>32 [27 to 35]</td>
<td>36 [36 to 36]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>123 [108 to 141]</td>
<td>175 [169 to 177]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% of maximum score</td>
<td>68 [60 to 78]</td>
<td>97 [94 to 98]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Developmental age in years</td>
<td>4.6 [4.1 to 5.3]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* P value from Mann Whitney U test or Fisher Exact test  
IQR= Interquartile Range

Feasibility
All qualitative and quantitative sensory tests were feasible in 100% of the controls. The feasibility in the children with Down syndrome ranged from 88% for the Rolltemp test and the Von Frey hair test to 33% for the detection thresholds for warmth (method of levels) (see Figure 1). Logistic regression analysis revealed that chronologic age was a significant covariable for the feasibility of the warm detection threshold as well as for cold and heat pain threshold testing (P=0.02, P=0.04 and P=0.02 respectively), i.e. the tests were more often feasible in older children than in younger children. The feasibility of the tests was not predicted by developmental age or socioeconomic status.
FIGURE 1 Feasibility rates of sensory tests in children with Down syndrome. The striped sections of the bars represent percentages of children in whom testing was feasible; numbers in the bars are the numbers of children. Not all tests were applied to every subject.

Qualitative sensory tests
Twenty-one (70%) of the children with Down syndrome made one or more mistakes with the Neuropen test (distinguishing sharp and blunt) versus 8 (35%) of the controls ($P=0.01$). Ten (32%) of the children with Down syndrome made one or more mistakes with the Rolltemp test (distinguishing warmth and cold) versus none of the controls ($P=0.003$).

Quantitative sensory tests
The mechanical detection threshold determined with the Von Frey hairs was 0.026 gram (the first hair) in 21 (91%) of the control group versus in 16 (53%) of the Down syndrome group ($P=0.003$).
The reaction time of the children with Down syndrome was significantly longer than that of the controls ($P<0.001$), see Table 1.
The results for the detection thresholds and pain thresholds are displayed in Table 2. Detection thresholds for cold and warmth (method of limits) were significantly higher in the Down syndrome group compared to the control group (P=0.001 and P<0.001 respectively). However, when measured with the method of levels, the detection thresholds for warmth and cold were not statistically significant between both groups. This difference between the method of limits and method of levels for the Down syndrome group could be explained by the longer reaction time of the children with Down syndrome. The detection threshold for warmth measured with the method of limits (a reaction time dependent method) is statistically significantly correlated with the reaction time (0.59; 95% CI 0.25 to 0.80; P=0.002), but the detection threshold for warmth measured with the method of levels (a reaction time independent method) is not statistically significantly correlated with the reaction time (0.19; 95%CI -0.40 to 0.67; P=0.54). Pain thresholds in the Down syndrome group were lower than those in controls; the heat pain thresholds were statistically significantly lower (P=0.03) and the cold pain threshold were borderline statistically significantly lower (P=0.06). There was a trend that more controls perceived no heat or cold pain before reaching 50 °C or 0 °C, respectively, than did children with Down syndrome, however this was not statistically significantly different (P=0.10 and P=0.09 respectively).

TABLE 2 Quantitative sensory testing

<table>
<thead>
<tr>
<th></th>
<th>Down syndrome (n=41)</th>
<th>Controls (n=21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection threshold cold (MLI)</td>
<td>26.4 (3.7)</td>
<td>30.5 (0.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Detection threshold warmth (MLI)</td>
<td>37.1 (2.0)</td>
<td>34.1 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain threshold cold (MLI)</td>
<td>13.5 (7.8)</td>
<td>7.2 (7.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Threshold not reached</td>
<td>1 (8%)</td>
<td>4 (36%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Pain threshold heat (MLI)</td>
<td>44.7 (3.0)</td>
<td>47.0 (3.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Threshold not reached</td>
<td>3 (15%)</td>
<td>8 (38%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Detection threshold cold (MLE)</td>
<td>29.4 (3.0)</td>
<td>30.6 (1.1)</td>
<td>0.23</td>
</tr>
<tr>
<td>Detection threshold warmth (MLE)</td>
<td>34.6 (2.8)</td>
<td>33.4 (0.9)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

MLI = Method of Limits, MLE = Method of Levels

**Questionnaires**

The questionnaires were completed for 41 (98%) of the children with Down syndrome and 22 (92%) of the controls.

Of the children with Down syndrome, 36 (85%) were able to verbalize pain versus 20 (95%) of the controls (P=0.65). However, only 6 (14%) of the children with Down syndrome were able to verbalize, localize and tell the intensity of the pain according to their parents, versus
22 (92%) of the controls (P<0.001).
Sixty-six percent of the children with Down syndrome were rated as less sensitive to pain versus 10% of the controls (P<0.001). Children with Down syndrome were seen as more anxious in a medical situation than controls, especially during venepuncture (73% versus 14%; P<0.001), see Table 3. Incidence of an episode of pain in the last three months was comparable between both groups, as well as the incidence of chronic pain (duration > 3 months) (See Table 3)

**TABLE 3 Pain behaviour and chronic pain**

<table>
<thead>
<tr>
<th>Chronic Pain Questionnaire</th>
<th>Down syndrome (n=41)</th>
<th>Controls (n=22)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episode of pain in last 3 months</td>
<td>15 (37%)</td>
<td>9 (41%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Duration of pain &gt; 3 months</td>
<td>3 (7%)</td>
<td>1 (4%)</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Anxiety in medical situations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visiting a doctor</td>
<td>10 (24%)</td>
<td>0 (0%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Visiting a dentist</td>
<td>13 (32%)</td>
<td>3 (14%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Undergoing a vaccination</td>
<td>24 (59%)</td>
<td>2 (9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Undergoing a venepuncture</td>
<td>30 (73%)</td>
<td>3 (14%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Difficulties to assess if your child is in pain?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain sensitivity, compared to other children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less sensitive</td>
<td>27 (66%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td>Equally sensitive</td>
<td>11 (27%)</td>
<td>17 (85%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>More sensitive</td>
<td>3 (7%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Difficulties to console my child, in comparison with other children</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less difficult</td>
<td>7 (17%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td>Equally difficult</td>
<td>30 (73%)</td>
<td>17 (85%)</td>
<td>0.71</td>
</tr>
<tr>
<td>More difficult</td>
<td>4 (10%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Difficulties to explain the episode of pain, compared to other children</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less difficult</td>
<td>2 (5%)</td>
<td>3 (15%)</td>
<td></td>
</tr>
<tr>
<td>Equally difficult</td>
<td>16 (39%)</td>
<td>16 (80%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>More difficult</td>
<td>23 (56%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Abilities to locate the pain, compared to other children</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less able to</td>
<td>21 (52%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Equally able to</td>
<td>19 (46%)</td>
<td>16 (80%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>More able to</td>
<td>1 (2%)</td>
<td>3 (15%)</td>
<td></td>
</tr>
<tr>
<td><strong>Abilities to verbalize the intensity of the pain, compared to other children</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less able to</td>
<td>32 (78%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Equally able to</td>
<td>8 (20%)</td>
<td>17 (85%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>More able to</td>
<td>1 (2%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
</tbody>
</table>

Missing data: n=1 with Down syndrome; n=2 controls
Pain coping
The results of the pain coping questionnaire are displayed in Table 4. The children with Down syndrome were rated significantly lower than controls on the subscales information seeking, problem solving, seeking social support and positive self-statements. For the Down syndrome group, the use of information seeking, problem solving and seeking social support coping strategies was significantly correlated with their developmental age (respectively 0.56, 95% CI 0.30 to 0.74, (P<0.001, 0.50, 95%CI 0.23 to 0.70, (P=0.002) and 0.44, 95%CI 0.15 to 0.66, (P=0.004)).

TABLE 4 Pain Coping

<table>
<thead>
<tr>
<th></th>
<th>Down syndrome (n=41)</th>
<th>Controls (n=22)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information seeking</td>
<td>1.8 [1.0 to 2.3]</td>
<td>3.1 [2.4 to 3.8]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Problem solving</td>
<td>1.5 [1.0 to 2.5]</td>
<td>3.3 [2.5 to 3.7]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Seeking social support</td>
<td>2.4 [1.6 to 3.2]</td>
<td>3.0 [2.6 to 3.6]</td>
<td>0.009</td>
</tr>
<tr>
<td>Positive self-statements</td>
<td>1.0 [1.0 to 2.4]</td>
<td>2.7 [2.2 to 3.6]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Behavioural distraction</td>
<td>3.0 [2.0 to 3.2]</td>
<td>3.0 [2.4 to 3.6]</td>
<td>0.30</td>
</tr>
<tr>
<td>Cognitive distraction</td>
<td>2.8 [1.6 to 3.5]</td>
<td>3.0 [2.6 to 3.2]</td>
<td>0.45</td>
</tr>
<tr>
<td>Externalizing</td>
<td>1.4 [1.0 to 1.8]</td>
<td>1.2 [1.0 to 1.8]</td>
<td>0.91</td>
</tr>
<tr>
<td>Internalizing / catastrophizing</td>
<td>1.4 [1.0 to 1.9]</td>
<td>1.5 [1.0 to 2.2]</td>
<td>0.38</td>
</tr>
<tr>
<td>Cronbach's alpha</td>
<td>0.68</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Cronbach's alpha (standardized)</td>
<td>0.67</td>
<td>0.73</td>
<td></td>
</tr>
</tbody>
</table>

Missing data: n=1 with Down syndrome; n=2 controls
DISCUSSION

Summary
Qualitative sensory testing is feasible in the majority of children with Down syndrome, whereas quantitative sensory testing is more difficult and therefore less feasible in children with Down syndrome. The results show that it takes longer for children with Down syndrome to detect a warm or cold stimulus and that there is a trend for lower heat and cold pain thresholds, compared to siblings without Down syndrome. Two-third of the parents reported that their child with Down syndrome is less sensitive to pain and that the child uses fewer pain coping strategies than do the siblings.

Feasibility
The different qualitative and quantitative sensory tests were feasible in only 33% to 88% of the children with Down syndrome. De Graaf et al. found that measuring warm and cold detection thresholds was feasible in 81% of 5-year-old children(11). Testing the pain thresholds with quantitative sensory testing is generally feasible in children of 7 years and older(17). Defrin et al. did not report any results on the feasibility of quantitative sensory testing in intellectually disabled adults(4). Feasibility of the more complicated quantitative sensory testing tests (such as pain thresholds and detection thresholds according to the method of levels) was limited in the children with Down syndrome and was significantly lower in the children with a lower chronological age but not in children with a lower developmental age. The limited variability in the developmental age of children with Down syndrome could explain why it is not found as a covariate for the feasibility, since the interquartile range for developmental age was 1.2 years versus 4.1 years for the chronological age. The limited feasibility of the different tests is an important finding, but it makes it difficult to draw overall conclusions on the pain sensitivity of children with Down syndrome.

Sensory testing
Children with Down syndrome were well able to distinguish between a warm and a cold stimulus. Distinguishing between sharp and blunt was more difficult, seeing that 70% made one or more mistakes.
Quantitative sensory testing is more complex, since the intensity of the stimulus increases during the test. Children with Down syndrome responded slower to a hot or cold stimulus (detection threshold), probably due to delayed peripheral conduction of the stimulus and delayed cerebral processing, since previous studies found that the sensory nerve conduction velocities of children with Down syndrome are prolonged(18) and the inter-hemispheric transmission time of adults with Down syndrome is longer than in controls(19). With regard to the hot and cold pain thresholds; children with Down syndrome are more sensitive for heat pain and there is a trend that they are more sensitive to cold pain. Defrin et al. also found that adults with Down syndrome are more sensitive for heat pain, but this
did not reach statistical significance (4). The reaction time of the subjects in their study based on the difference in pain thresholds obtained with the method of limits (reaction time dependent) and the method of levels (reaction time independent) was prolonged and the authors therefore recommended the method of levels in intellectually disabled subjects. Our findings support this recommendation, since the visuomotor reaction time was significantly correlated (r 0.59) with the detection threshold for warmth measured with the method of limits, but not when measured with the method of levels. The method of levels would therefore be preferable over the method of limits, but the feasibility of the method of levels was poor in the children with Down syndrome compared to the feasibility of the method of limits. A small-scale study found that pain thresholds in children were stable over short retest intervals, but that thresholds significantly decreased over longer retest intervals (mean interval of 16 months) (20). Future quantitative sensory studies should therefore assess the detection and pain thresholds over time to verify stability of the thresholds.

**Quantitative sensory testing versus proxy (parental) report**

Although the quantitative sensory testing results suggest that children with Down syndrome are more sensitive to heat and cold pain, their parents reported in 66% of the cases that their child was less sensitive to pain. What could be the reason for this discrepancy? Parents see their child daily, whereas we tested the thermal detection and pain thresholds only on one occasion and the pain thresholds only in a subset of the children. In addition, Edwards et al. showed that there is no correlation between self-report of pain sensitivity and results of pain threshold testing in adults (21). We assume that parents will rate their child as less sensitive based on occasions when the child did not respond to an obvious painful stimulus or event in the way the parents expected. The lesser ability of children with Down syndrome to rate the intensity of the pain or to localize the pain supports this idea. The verbal and non-verbal pain expressions of children with Down syndrome are probably different from what we expect. Parents see this as less sensitive to pain, but this perception is not confirmed by quantitative sensory testing.

**Pain coping**

The children with Down syndrome used fewer pain coping strategies than did their siblings. The four less often used coping strategies all belong to the high-order factor approach (attempts to deal with pain and emotional distress when in pain) (15). The use of coping strategies of the two other high-order factors (problem- and emotion-focused avoidance) was comparable between the children with Down syndrome and their siblings. Burkitt et al. found that pain coping of intellectually disabled children and adults is highly dependent of their cognitive age, as was confirmed in the present study (22). Caregivers should be aware that children with Down syndrome do not make many attempts to deal with the pain, but use primarily distraction coping styles.
Self-report
LaChapelle et al. found that 65% of intellectually disabled adults was able to provide self-report of pain(23). Adequate self-report of pain requires the ability to quantify the pain and localize the pain(24, 25). Although 85% of the children with Down syndrome in the present study could verbalize the pain, no more than 20% was able to quantify the pain and only 46% was able to localize the pain. The abilities of children with Down syndrome to provide an adequate self-report for pain are rather limited, so that they will have to rely on caregivers for their pain assessment.

Limitations
We tested more children with Down syndrome than siblings, since not all children with Down syndrome had a sibling who met the inclusion criteria. By recruiting the subjects through the parental organization for Down syndrome in the Netherlands, we hoped to reach a more representative population than by recruiting children seen in the outpatient clinics of our hospital. However, this strategy could also have resulted in a selection bias, since parents who did not participate often motivated this by pointing out that their child had many medical problems. Furthermore, around 80% of parents of children with Down syndrome in the Netherlands are members of the organization, so this could have resulted in a potential selection bias as well.

Implications
From a clinical point of view, it will be important to investigate the pain expression of children and adults with Down syndrome after surgery and to find appropriate assessment tools for chronic pain. Even if the individual can verbalize pain, it will still be necessary for caregivers to apply observational pain assessment tools. Caregivers should anticipate that children with Down syndrome do use problem and emotion avoidance pain coping styles, and they should support the use of those coping styles with (developmental) age appropriate distraction methods.

From a research point of view, the poor feasibility of currently used quantitative sensory tests necessitates the use of other methods to quantify the pain behaviour of children with Down syndrome. Functional Magnetic Resonance Imaging (fMRI)(26) or electroencephalography (EEG)(27) could help elucidate the cerebral processing of sensory and painful stimuli in children with Down syndrome. Another quantitative sensory testing modality, diffuse noxious inhibitory control (DNIC), could give insight into the inhibitory potential of individuals with Down, but this test may be too complex to be feasible(28).

Conclusions
Only a minority of children with Down syndrome is able to use adequate self-report of pain according to their parents. This skill is probably required for quantitative sensory testing as well, since the feasibility of the tests was poor. In accordance with previous studies in
adults with Down syndrome, we found that children with Down syndrome were less sensitive for the detection of cold and warmth than their siblings, but they were more sensitive for heat pain than their siblings.
REFERENCES

1. Down JL. On some of the mental affections of childhood and youth: Being the Lettsomian lectures delivered before the Medical society of London in 1887; together with other papers. London: J. & A. Churchill; 1887.
zoals een pasgeboren kind kijkt alsof het kijkt naar iets in zichzelf, iets ziet daar wat het meekreeg
Chapter 9

LONG-TERM EFFECTS OF NEONATAL CONTINUOUS MORPHINE INFUSION ON PAIN SENSITIVITY: FOLLOW-UP OF A RANDOMIZED CONTROLLED TRIAL

Short-term and long-term effects of neonatal pain and its analgesic treatment have been topics of translational research over the years. The present study aimed to identify possible long-term effects of continuous morphine infusion on thermal pain sensitivity, incidence of chronic pain and neurological functioning. Eighty-nine of the 150 participants of a neonatal RCT on continuous morphine infusion versus placebo during mechanical ventilation underwent quantitative sensory testing and neurological examination at the age of 8 or 9 years. Forty-three children from the morphine group and 46 children from the placebo group participated. Thermal detection and pain thresholds were compared to data of 139 historical controls. Multivariate analyses revealed no statistically significant differences in thermal detection thresholds and pain thresholds between the morphine and placebo group. More children in the morphine group experienced an episode of pain in the three months before the follow-up visit compared to the placebo group, but the incidence of chronic pain (>3 months) was comparable. Neurological examination was normal in the majority of the children; mild deviations in coordination and balance were present in 7/9 (78%) of the morphine group versus 5/16 (31%) of the placebo group (P=0.04). We found in the present study that neonatal continuous morphine infusion (10 mcg/kg/hr) has no adverse effects on thermal detection and pain thresholds or overall neurological functioning eight to nine years later.
Providing adequate and evidence-based analgesia and sedation to newborns receiving intensive care is an ongoing challenge; one has to account for developmental changes in drug pharmacokinetics and pharmacodynamics as well as in the human nervous system\(^1,\)\(^2\). The short-term and long-term effects of neonatal pain and its analgesic treatment have become topics of translational research. The repeated painful procedures in intensive care can lead to short-term hyperalgesia\(^3\). Long-term follow-up of the extremely preterm born showed a generalized decrease of thermal sensitivity, probably due to tissue injury and modulation of nociceceptor pathways\(^4\). Opioids have both beneficial and adverse short-term effects. Morphine is an effective analgesic agent for newborns’ postoperative pain but not acute procedural pain\(^5\)\(^-\)\(^8\). However, continuous morphine infusion does not lower the risk of poor neurological outcome after intensive care\(^7\). Animal studies have shown negative long-term effects of neonatal morphine on cognitive functioning and proliferation of damaged astrocytes\(^9\)\(^-\)\(^11\). Participants of two RCTs on neonatal morphine administration were studied again five years after the original RCT\(^7,\)\(^8\). The one, a small-scale follow-up of the NEOPAIN trial, showed that children who had received morphine (n=14) had a smaller head circumference, weighed less, and had more social problems than children who had received placebo (n=5)\(^12\). The other, performed in our institution, showed that children who had received morphine (n=49) performed more poorly on one subtest of the intelligence scale than did the children who had received placebo (n=41); other neurobehavioral outcomes and the incidences of chronic pain were comparable between the two groups\(^13\). This unique cohort is being followed and at the age of 8 years, participants were old enough for quantitative sensory testing\(^14\).

Morphine is used worldwide for opioid analgesia in neonates, infants and children. In the present study we aimed to identify any adverse effects of continuous morphine infusion on thermal detection thresholds and pain thresholds, incidence of chronic pain, and neurological functioning at 8 to 9 years of age.
METHODS

Original study
Between 2000 and 2002, 150 neonates who received mechanical ventilation in two level III neonatal intensive care units participated in a multi-center randomized controlled trial. Seventy-three neonates were randomly assigned to the continuous morphine group (loading dose of 100 mcg/kg followed by infusion of 10 mcg/kg/hr) and 77 to the placebo group (normal saline). If pain or distress was noted, children in both groups received open-label morphine bolus of 50 mcg/kg and, if indicated, open-label morphine infusion (5-10 mcg/kg/hr) as rescue medication. Open-label morphine was administered to 27% of the children in the morphine group versus 40% of the placebo group (P=0.10). Further details, including background characteristics of the participants, can be found in the original article(7).

Follow-up study (8 to 9 year)
The institutional ethics review boards of the two study sites (Erasmus University Medical Center - Sophia Children’s Hospital, Rotterdam, the Netherlands and Isala Clinics, Zwolle, the Netherlands) approved the study plan. Parents of the 132 survivors were informed of the study and were asked for written informed consent. Seventeen participants from the morphine group were lost to follow-up and 5 parents refused informed consent for the follow-up study. Sixteen patients of the placebo group were lost to follow-up and 5 parents refused informed consent for the follow-up study. The remaining 89 children and their parents were then invited for a follow-up visit in their hospital (either Rotterdam or Zwolle)(See Figure 1).

Parents were asked to complete several questionnaires (see below) before the visit. The visit consisted of three parts: Quantitative sensory testing by a trained researcher, medical examination by a pediatrician and neuropsychological testing by a psychologist. These health professionals were blind to the participants’ study condition (continuous morphine infusion versus placebo) in the original RCT.

Quantitative sensory testing
Participants underwent quantitative sensory testing in a quiet hospital room, with a stable room temperature (20 to 22 degrees Celsius). Parents were present in the room and were instructed ‘not to interfere during the test’. Reaction time was measured using the baseline speed task for the dominant hand (Amsterdam Neuropsychological Tasks, Version 3.1, Boom test publishers, Amsterdam, the Netherlands). This computerized visual-motor task includes 32 repetitions. Skin temperature was measured at the thenar eminence of the non-dominant hand to confirm it was within the range of 27 to 37 degrees Celsius(15). Thermal thresholds were measured at the thenar eminence of the non-dominant hand, using the Thermal Sensory Analyzer-II (Medoc Ltd, Ramat Yishai, Israel) with the 30 by 30 mm thermode. Baseline temperature for all measurements was 32 degrees Celsius,
the minimum temperature was 0.0 °C and the maximum temperature was 50.0 °C. Detection thresholds were measured using both the method of limits (reaction time dependent) and the method of levels (reaction time independent). The standardized instructions were in accordance with other quantitative sensory testing studies in children(14, 16, 17). Six modalities were tested in the following order. 1) Detection threshold for cold (method of limits): Six repetitions, temperature decreased by 1.0 °C/s. Children were asked to press the button as soon as the cold stimulus was perceived. 2) Detection threshold for warmth (method of limits): Six repetitions, temperature increased by 1.0 °C/s. Children were asked to press the button as soon as the warm stimulus was perceived. 3) Pain threshold for cold (method of limits). Five repetitions, temperature decreased by 1.5 °C/s. Children were asked to press the button as soon as the stimulus was so cold it became painful. A note was made when the minimum temperature (0.0 °C) was reached. 4) Pain threshold for heat (method of limits): Five repetitions, temperature increased by 1.5 °C/s. Children were asked to press the button as soon as the stimulus was so hot it became painful. A note was made when the maximum temperature (50.0 °C) was reached. 5) Detection threshold for cold (method of levels): Children were asked per step if the cold stimulus was perceived, until the difference between two steps was less than 0.1 °C/s. The number of steps needed was recorded. 6) Detection threshold for warmth (method of levels): Children were asked per step if the warm stimulus was perceived, until the difference between two steps was less than 0.1 °C/s. The number of steps needed was recorded.

Detection thresholds established by the method of limits were calculated as the mean value of the final four of the six measurements. The first two measurements were used to assure that the child understood the test correctly. Pain thresholds established by the method of limits were calculated as the mean value of the final four of five measurements. The first measurement was used to assure that the child understood the test correctly. Detection thresholds established by the method of levels were measured once. In case the participant did not establish a pain threshold before the minimum or maximum temperature was reached, the device recorded the minimum temperature (0.0 °C) / maximum temperature (50.0 °C) as the result.

Reference data quantitative sensory testing (historical controls)
Reference values for quantitative sensory testing in 139 children between 7 and 11 years have been collected by our group.(http://repub.eur.nl/res/pub/8210/Early%20Pain.pdf). Subjects (ages 7 through 11 years) were recruited at two elementary schools in the reference area of the Erasmus University Medical Center – Sophia Children’s Hospital, Rotterdam, the Netherlands. The local ethics committee and the Dutch Central Committee on Research involving Human Subjects approved the study. Parents provided written informed consent for the study. Exclusion criteria were a history of surgery or admission to a neonatal intensive care unit.
The cold/warm detection and cold/heat pain thresholds were obtained using the method of limits. Instructions and methods were the same as in the present study. The only difference was that the lower limit for the cold pain threshold was -10 °C, where nowadays 0.0°C is the lower limit.

All 139 subjects were tested between July 2004 and August 2005. Eighty-one (58%) of them were male. The median [IQR] age was 8 [7 to 9] years.

**Questionnaires**
The participants’ parents completed the Vineland Adaptive Behavior Scale - Screener (Dutch version, PITS B.V., Leiden, the Netherlands)(18); the four domains of this scale are communication, daily living, socialization and motor skills. Parents also completed the Chronic Pain Questionnaire (Dutch version)(19); this questionnaire asks for the incidence of pain in the 3 months before the visit and additional information about the pain (location, frequency, duration and intensity).

**Medical examination**
All children were examined by a pediatrician and were, if indicated, referred for further diagnosis or treatment. Weight, height and head circumference were measured and plotted against sex-matched reference values for the Netherlands (4th nation-wide growth study 1997). The neurological examination was based on the Touwen assessment of minor neurological dysfunctions.(20) We assessed 41 items in 5 domains (posture/muscle tone, reflexes, involuntary movements, coordination/balance and cranial nerve dysfunctions). Minor neurological dysfunctions were defined as the presence of 2 or more deviant items in at least one domain.

**Neuropsychological testing**
A trained psychologist tested the children’s intelligence quotient (IQ) with the Wechsler Intelligence Scale for Children - III (Dutch version).

**Statistical analysis**
Summary statistics of continuous variables are presented as median [interquartile range] and as percentage for ordinal and categorical variables. Data were compared between the continuous morphine and the placebo group using the Mann-Whitney test for continuous, non-normal data and the chi-square test (or Fisher exact test in case of low predicted cell counts) for nominal data. The quantitative sensory testing data is compared to reference values of 139 historical controls using analysis of variance with post-hoc Bonferroni correction for multiple comparisons.

For the multivariate analysis of the quantitative sensory testing data, we built step-wise robust regression models for each of the six modalities, using robust regression procedure with MM estimation(21). We applied this method for the very reason that the outcome vari-
ables were non-normally distributed. Tukey bisquare estimator was the weight function. In
the first model, we added the treatment condition (continuous morphine versus placebo)
and the amount of additional morphine in the first 28 days after birth as covariables. In the
second model, we added sex and study site (Rotterdam versus Zwolle) as additional covariables. In the third model, we added the intelligence quotient as additional covariable. For
the model on the cold pain threshold we added floor (pain threshold was not reached at
minimum) and for the heat pain threshold ceiling (pain threshold was not reached at max-
imum) as covariable in all three models. For each model, we present the unstandardized
regression estimates, including the 95% confidence intervals and P values (chi-square test).
Logistic regression analyses were applied with prevalence of pain and chronic pain as
dichotomous outcome variables and the treatment condition (continuous morphine versus
placebo) and the amount of additional morphine in the first 28 days after birth as predictor
variables.
P values (two-sided) of less than 0.05 are considered statistical significantly. Data were ana-
lyzed by SPSS software, version 19.1 (IBM, Armonk, NY, USA) and SAS, version 9.2 (SAS,
Cary, NC, USA).

**FIGURE 1** Flowchart based on the CONSORT flowchart
RESULTS

Background characteristics
Of the 132 survivors, 43 children from the morphine group and 46 children from the placebo group participated in this follow-up study (See Figure 1). Their mean age was now 8.9 years. Background characteristics were comparable between the two groups (see Table 1). Mean IQ was 101 (SD 18) for the placebo group versus 99 (SD 19) for the morphine group (P = 0.63).

<table>
<thead>
<tr>
<th>TABLE 1 Background Characteristics (distinguished by group)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Sex, n(%) male</strong></td>
</tr>
<tr>
<td><strong>Birth characteristics</strong></td>
</tr>
<tr>
<td>Gestational age in weeks</td>
</tr>
<tr>
<td>Birthweight in grams</td>
</tr>
<tr>
<td><strong>Age in years</strong></td>
</tr>
<tr>
<td><strong>Height in cm</strong></td>
</tr>
<tr>
<td><strong>SDS height for age</strong></td>
</tr>
<tr>
<td><strong>Weight in kg</strong></td>
</tr>
<tr>
<td><strong>SDS weight for age</strong></td>
</tr>
<tr>
<td><strong>Head circumference in cm</strong></td>
</tr>
<tr>
<td><strong>SDS head circumference for age</strong></td>
</tr>
<tr>
<td><strong>IQ</strong></td>
</tr>
<tr>
<td><strong>Developmental age in months</strong></td>
</tr>
<tr>
<td><strong>Reaction time in ms</strong></td>
</tr>
<tr>
<td><strong>Test location Rotterdam, n(%)</strong></td>
</tr>
</tbody>
</table>

* Mann-Whitney test for continuous variables and Fisher exact test for categorical variables
* According to reference values (the Netherlands 1997)
* Intelligence Quotient (Wechsler Intelligence Scale for Children), mean (SD), P value from t test
* Vineland Adaptive Behavior Scale
* Amsterdam Neuropsychological Tasks
IQR = Interquartile Range ; cm = centimeter ; kg = kilogram ; ms = milliseconds

Quantitative Sensory Testing
Quantitative Sensory Testing (QST) was performed in 41(89%) of the placebo group and in 37(86%) of the morphine group. Nine children did not attend the follow-up visit (but completed the questionnaires) and the equipment was not available in the remaining 2 oc-
casions. QST was feasible in all subjects with regard to understanding the instructions and completing the test.

Univariate analysis showed that these children (both morphine and placebo group) were more sensitive for the detection of cold (method of limits), compared to the historical controls \( (P=0.002 \text{ and } P=0.005 \text{ respectively}) \). The children in the morphine group were more sensitive for the detection of cold than the children in the placebo group (method of levels, \( P=0.045 \)) (see Table 2).

Ten (24%) of the children in the placebo group did not establish a pain threshold for cold before the minimum temperature (0.0 °C) was reached, versus 9 (25%) of the morphine group \( (P=0.82) \). Ten (24%) of the children in the placebo group did not establish a pain threshold for heat before the maximum temperature (50.0 °C) was reached, versus 8 (22%) of the children in the morphine group \( (P=0.95) \).

**TABLE 2 Results of quantitative sensory testing, distinguished by group**

<table>
<thead>
<tr>
<th></th>
<th>Placebo group (n= 41)</th>
<th>Morphine group (n= 37)</th>
<th>Historical controls (n=139)</th>
<th>P value *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method of Limits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold detection threshold in °C</td>
<td>29.6 (2.4)</td>
<td>29.9 (1.4)</td>
<td>28.1 (3.1)</td>
<td>&lt;0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Warm detection threshold in °C</td>
<td>34.8 (1.4)</td>
<td>34.5 (1.4)</td>
<td>34.7 (2.2)</td>
<td>0.70</td>
</tr>
<tr>
<td>Cold pain threshold in °C</td>
<td>11.8 (8.4)</td>
<td>12.3 (8.9)</td>
<td>8.5 (9.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Threshold not reached&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10 (24%)</td>
<td>9 (25%)</td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>Heat pain threshold in °C</td>
<td>45.0 (3.5)</td>
<td>44.9 (4.3)</td>
<td>44.8 (4.7)</td>
<td>0.97</td>
</tr>
<tr>
<td>Threshold not reached&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10 (24%)</td>
<td>8 (22%)</td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Method of Levels</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold detection threshold in °C</td>
<td>30.7 (1.2)</td>
<td>31.1 (0.7)</td>
<td></td>
<td>0.045</td>
</tr>
<tr>
<td>Number of stimuli</td>
<td>11 (3)</td>
<td>10 (2)</td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Warm detection threshold in °C</td>
<td>33.3 (1.1)</td>
<td>33.2 (1.1)</td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>Number of stimuli</td>
<td>11 (4)</td>
<td>10 (2)</td>
<td></td>
<td>0.15</td>
</tr>
</tbody>
</table>

* ANOVA test for the comparison between the three groups, t-test for continuous variables and Fisher exact test for categorical variables

<sup>b</sup> Patients in whom 1 or more times the pain threshold was not reached (the child did not press the button before the temperature of the thermode reached its minimum/maximum (0.0 °C and 50.0 °C respectively)

<sup>c</sup> Post-hoc Bonferroni correction: Placebo group versus Controls \( P=0.005 \) and Morphine group versus Controls \( P=0.002 \)
### TABLE 3 Regression estimates of intervention, with and without adjustment for different covariables: Detection thresholds (method of limits)

<table>
<thead>
<tr>
<th>DETECTION TRESHOLD FOR COLD</th>
<th>Estimate</th>
<th>95% CI limits</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Intercept</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment condition a</td>
<td>0.21</td>
<td>-0.18 to 0.60</td>
<td>0.29</td>
</tr>
<tr>
<td>Additional morphine b</td>
<td>0.00</td>
<td>-0.0002 to 0.0002</td>
<td>0.81</td>
</tr>
<tr>
<td>2 Intercept</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment condition a</td>
<td>0.22</td>
<td>-0.19 to 0.62</td>
<td>0.29</td>
</tr>
<tr>
<td>Additional morphine b</td>
<td>0.00</td>
<td>-0.0002 to 0.0003</td>
<td>0.85</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.096</td>
<td>-0.51 to 0.32</td>
<td>0.65</td>
</tr>
<tr>
<td>Study site</td>
<td>-0.047</td>
<td>-0.46 to 0.37</td>
<td>0.82</td>
</tr>
<tr>
<td>3 Intercept</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment condition a</td>
<td>0.25</td>
<td>-0.15 to 0.64</td>
<td>0.22</td>
</tr>
<tr>
<td>Additional morphine b</td>
<td>0.0001</td>
<td>-0.0002 to 0.0003</td>
<td>0.57</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.15</td>
<td>-0.56 to 0.26</td>
<td>0.48</td>
</tr>
<tr>
<td>Study site</td>
<td>-0.012</td>
<td>-0.42 to 0.39</td>
<td>0.95</td>
</tr>
<tr>
<td>IQ c</td>
<td>0.012</td>
<td>0.0016 to 0.0228</td>
<td>0.024</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DETECTION TRESHOLD FOR WARMTH</th>
<th>Estimate</th>
<th>95% CI limits</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Intercept</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment condition a</td>
<td>-0.35</td>
<td>-0.98 to 0.29</td>
<td>0.29</td>
</tr>
<tr>
<td>Additional morphine b</td>
<td>0.00</td>
<td>-0.0003 to 0.0004</td>
<td>0.87</td>
</tr>
<tr>
<td>2 Intercept</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment condition a</td>
<td>-0.37</td>
<td>-1.006 to 0.26</td>
<td>0.25</td>
</tr>
<tr>
<td>Additional morphine b</td>
<td>0.00</td>
<td>-0.0003 to 0.0004</td>
<td>0.82</td>
</tr>
<tr>
<td>Sex</td>
<td>0.33</td>
<td>-0.33 to 0.99</td>
<td>0.33</td>
</tr>
<tr>
<td>Study site</td>
<td>0.37</td>
<td>-0.27 to 1.01</td>
<td>0.26</td>
</tr>
<tr>
<td>3 Intercept</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment condition b</td>
<td>-0.50</td>
<td>-1.09 to 0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>Additional morphine c</td>
<td>0.00</td>
<td>-0.0004 to 0.0003</td>
<td>0.88</td>
</tr>
<tr>
<td>Sex</td>
<td>0.39</td>
<td>-0.23 to 1.01</td>
<td>0.21</td>
</tr>
<tr>
<td>Study site</td>
<td>0.44</td>
<td>-0.16 to 1.04</td>
<td>0.15</td>
</tr>
<tr>
<td>IQ c</td>
<td>-0.023</td>
<td>-0.039 to -0.0069</td>
<td>0.005</td>
</tr>
</tbody>
</table>

* Morphine group versus placebo group
* Additional morphine in first 28 days
* Intelligence Quotient (Wechsler Intelligence Scale for Children)
CI = Confidence Interval
### TABLE 4 Regression estimates of intervention, with and without adjustment for different covariables: Pain thresholds (method of limits)

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>95% CI limits</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PAIN TRESHOLD FOR COLD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Intercept</td>
<td>14.26</td>
<td>11.75 to 16.76</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment condition a</td>
<td>1.67</td>
<td>-1.58 to 4.93</td>
<td>0.31</td>
</tr>
<tr>
<td>Additional morphine b</td>
<td>-0.0013</td>
<td>-0.0032 to 0.0007</td>
<td>0.22</td>
</tr>
<tr>
<td>Floor c</td>
<td>-4.49</td>
<td>-5.73 to -3.25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2 Intercept</td>
<td>16.35</td>
<td>13.31 to 19.40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment condition a</td>
<td>2.21</td>
<td>-0.66 to 5.08</td>
<td>0.13</td>
</tr>
<tr>
<td>Additional morphine b</td>
<td>-0.0014</td>
<td>-0.0032 to 0.0004</td>
<td>0.12</td>
</tr>
<tr>
<td>Sex</td>
<td>0.65</td>
<td>-2.34 to 3.65</td>
<td>0.70</td>
</tr>
<tr>
<td>Study site</td>
<td>-5.38</td>
<td>-8.30 to -2.46</td>
<td>0.0003</td>
</tr>
<tr>
<td>Floor c</td>
<td>-4.20</td>
<td>-5.31 to -3.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3 Intercept</td>
<td>15.27</td>
<td>6.98 to 23.56</td>
<td>0.0003</td>
</tr>
<tr>
<td>Treatment condition a</td>
<td>2.23</td>
<td>-0.67 to 5.13</td>
<td>0.13</td>
</tr>
<tr>
<td>Additional morphine b</td>
<td>-0.0014</td>
<td>-0.0032 to 0.0004</td>
<td>0.14</td>
</tr>
<tr>
<td>Sex</td>
<td>0.52</td>
<td>-2.53 to 3.57</td>
<td>0.74</td>
</tr>
<tr>
<td>Study site</td>
<td>-5.42</td>
<td>-8.37 to -2.47</td>
<td>0.0003</td>
</tr>
<tr>
<td>IQ d</td>
<td>0.012</td>
<td>-0.067 to 0.090</td>
<td>0.77</td>
</tr>
<tr>
<td>Floor c</td>
<td>-4.19</td>
<td>-5.31 to -3.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>PAIN TRESHOLD FOR HEAT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Intercept</td>
<td>44.01</td>
<td>42.93 to 45.10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment condition a</td>
<td>0.42</td>
<td>-1.05 to 1.88</td>
<td>0.58</td>
</tr>
<tr>
<td>Additional morphine b</td>
<td>-0.0004</td>
<td>-0.0031 to 0.0005</td>
<td>0.40</td>
</tr>
<tr>
<td>Ceiling c</td>
<td>1.74</td>
<td>1.21 to 2.27</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2 Intercept</td>
<td>44.02</td>
<td>42.48 to 45.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment condition a</td>
<td>0.34</td>
<td>-1.13 to 1.81</td>
<td>0.65</td>
</tr>
<tr>
<td>Additional morphine b</td>
<td>-0.0005</td>
<td>-0.0014 to 0.0004</td>
<td>0.31</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.61</td>
<td>-2.21 to 0.90</td>
<td>0.43</td>
</tr>
<tr>
<td>Study site</td>
<td>0.86</td>
<td>-0.64 to 2.36</td>
<td>0.26</td>
</tr>
<tr>
<td>Ceiling c</td>
<td>1.67</td>
<td>1.13 to 2.20</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3 Intercept</td>
<td>45.50</td>
<td>41.07 to 49.93</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment condition a</td>
<td>0.36</td>
<td>-1.10 to 1.82</td>
<td>0.63</td>
</tr>
<tr>
<td>Additional morphine b</td>
<td>-0.0005</td>
<td>-0.0014 to 0.0004</td>
<td>0.27</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.55</td>
<td>-2.05 to 0.96</td>
<td>0.48</td>
</tr>
<tr>
<td>Study site</td>
<td>0.92</td>
<td>-0.57 to 2.42</td>
<td>0.23</td>
</tr>
<tr>
<td>IQ d</td>
<td>-0.015</td>
<td>-0.056 to 0.026</td>
<td>0.47</td>
</tr>
<tr>
<td>Ceiling c</td>
<td>1.61</td>
<td>1.07 to 2.16</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* a Morphine group versus placebo group  
  b Additional morphine in first 28 days  
  c Pain threshold was not reached in one of more occasions  
  d Intelligence Quotient (Wechsler Intelligence Scale for Children)  
  CI = Confidence Interval
**TABLE 5** Regression estimates of intervention, with and without adjustment for different covariables: Detection thresholds (method of levels)

<table>
<thead>
<tr>
<th>DETECTION TRESHOLD FOR COLD</th>
<th>Estimate</th>
<th>95% CI limits</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Intercept</td>
<td>31.04</td>
<td>30.78 to 31.30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment condition</td>
<td>0.21</td>
<td>-0.14 to 0.56</td>
<td>0.25</td>
</tr>
<tr>
<td>Additional morphine</td>
<td>-0.0001</td>
<td>-0.0003 to 0.0001</td>
<td>0.22</td>
</tr>
<tr>
<td>2 Intercept</td>
<td>31.05</td>
<td>30.66 to 31.44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment condition</td>
<td>0.23</td>
<td>-0.14 to 0.59</td>
<td>0.23</td>
</tr>
<tr>
<td>Additional morphine</td>
<td>-0.0002</td>
<td>-0.0004 to 0.0001</td>
<td>0.17</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.14</td>
<td>-0.52 to 0.24</td>
<td>0.47</td>
</tr>
<tr>
<td>Study site</td>
<td>0.12</td>
<td>-0.25 to 0.50</td>
<td>0.53</td>
</tr>
<tr>
<td>3 Intercept</td>
<td>30.74</td>
<td>29.66 to 31.82</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment condition</td>
<td>0.24</td>
<td>-0.13 to 0.61</td>
<td>0.20</td>
</tr>
<tr>
<td>Additional morphine</td>
<td>-0.0002</td>
<td>-0.0004 to 0.0001</td>
<td>0.18</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.16</td>
<td>-0.54 to 0.23</td>
<td>0.43</td>
</tr>
<tr>
<td>Study site</td>
<td>0.13</td>
<td>-0.24 to 0.51</td>
<td>0.49</td>
</tr>
<tr>
<td>IQ c</td>
<td>0.0030</td>
<td>-0.0069 to 0.013</td>
<td>0.55</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DETECTION TRESHOLD FOR WARMTH</th>
<th>Estimate</th>
<th>95% CI limits</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Intercept</td>
<td>32.98</td>
<td>32.73 to 33.23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment condition</td>
<td>-0.079</td>
<td>-0.42 to 0.26</td>
<td>0.65</td>
</tr>
<tr>
<td>Additional morphine</td>
<td>0.0001</td>
<td>-0.0001 to 0.0003</td>
<td>0.27</td>
</tr>
<tr>
<td>2 Intercept</td>
<td>32.96</td>
<td>32.57 to 33.34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment condition</td>
<td>-0.090</td>
<td>-0.43 to 0.25</td>
<td>0.61</td>
</tr>
<tr>
<td>Additional morphine</td>
<td>0.0001</td>
<td>-0.0001 to 0.0003</td>
<td>0.17</td>
</tr>
<tr>
<td>Sex</td>
<td>0.17</td>
<td>-0.18 to 0.53</td>
<td>0.34</td>
</tr>
<tr>
<td>Study site</td>
<td>-0.14</td>
<td>-0.50 to 0.21</td>
<td>0.43</td>
</tr>
<tr>
<td>3 Intercept</td>
<td>33.95</td>
<td>32.99 to 34.92</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment condition</td>
<td>-0.13</td>
<td>-0.46 to 0.19</td>
<td>0.42</td>
</tr>
<tr>
<td>Additional morphine</td>
<td>0.0001</td>
<td>-0.0001 to 0.0003</td>
<td>0.23</td>
</tr>
<tr>
<td>Sex</td>
<td>0.22</td>
<td>-0.12 to 0.56</td>
<td>0.20</td>
</tr>
<tr>
<td>Study site</td>
<td>-0.14</td>
<td>-0.48 to 0.19</td>
<td>0.39</td>
</tr>
<tr>
<td>IQ c</td>
<td>-0.0098</td>
<td>-0.019 to -0.0010</td>
<td>0.029</td>
</tr>
</tbody>
</table>

* Morphine group versus placebo group
* Additional morphine in first 28 days
* Intelligence Quotient (Wechsler Intelligence Scale for Children)
CI = Confidence Interval
Regression estimates for the six QST modalities are presented in Tables 3 to 5. Neither treatment modality (morphine group versus placebo) nor the amount of additional morphine in the first 28 days was a statistically significant predictor in any of the models. For the cold and warmth detection thresholds (method of limits), IQ was a statistically significant predictor ($P=0.024$ and $P=0.005$ respectively). The higher the IQ, the more sensitive the children were for the detection of cold and warmth, see Table 3. Children who reached the minimum (0.0 °C) or maximum (50.0 °C) at one or more occasions, had statistically significantly higher mean pain thresholds. Children seen in the hospital in Zwolle (n=39) had statistically significant lower mean cold pain thresholds ($P=0.0003$), but we did not see an effect from the study site on the heat pain thresholds ($P=0.26$).(Table 4) For the warm detection thresholds (method of levels), IQ was a statistically significant covariable ($P=0.029$).

**Chronic pain**

Nine (20%) of the children in the placebo group versus 18 (43%) children in the morphine group experienced an episode of pain in the three months before the study visit, as reported by the parents in the Chronic Pain Questionnaire. This prevalence was entered in the logistic regression analysis as dichotomous outcome variable and treatment modality (morphine

![Figure 2](image-url)
versus placebo group) was a significant predictor \((P=0.02)\), but the amount of additional morphine in the first 28 days was not \((P=0.98)\).

Abdominal pain was the most common type of pain; it was present in 4 (44%) of the children in the placebo group versus in 10 (56%) of the children in the morphine group with pain \((P=0.70)\). The second most common type of pain was headache; it was present in 6 (67%) of the children in the placebo group versus in 6 (33%) of the children in the morphine group with pain \((P=0.13)\). Six (67%) children in the placebo group suffered from pain at more than one body site, versus 8 (44%) of the children in the morphine group with pain \((P=0.42)\). The pain was chronic (duration longer than 3 months) in 4 (9%) children in the placebo group versus 5 (12%) in the morphine group \((P=0.42)\), see Figure 2. There was a weak but significant correlation between a reported episode of pain in the last three months at the follow-up visit at 5 years versus a reported episode or pain at 8 to 9 years of age \((64\) subjects, \(r=0.32, P=0.01)\).

**Neurological examination:**

Two children in the placebo group and two children in the morphine group were severe intellectually and developmentally disabled, and did therefore not attend the follow-up visit. Neurological examination was performed in 37 children of the morphine group and 41 of the placebo group, see Table 6. The neurological examination was normal in 28 (76%) of the children in the morphine and in 25 (61%) of the children in the control group \((P=0.14)\). In the children with minor neurological dysfunctions, mild deviations in coordination and muscle tone were more common in the morphine group (7/9 (78%)) than in the placebo group (5/16 (22%)) \((P=0.04)\).

The presence of minor neurological dysfunctions at 8-9 years of age was not related to the presence of intraventricular hemorrhages in the neonatal period \((P=0.26)\).

**TABLE 6 Minor Neurological Dysfunctions (distinguished by group)**

<table>
<thead>
<tr>
<th>Minor Neurological Dysfunctions</th>
<th>Placebo group (n=41)</th>
<th>Morphine group (n=38)</th>
<th>P value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild deviations in posture/muscle tone</td>
<td>6/16 (38%)</td>
<td>2/9 (22%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Mild deviations in reflexes</td>
<td>4/16 (25%)</td>
<td>1/9 (11%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Presence of involuntary movements</td>
<td>0/16 (0%)</td>
<td>0/9 (0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Mild deviations in coordination/balance</td>
<td>5/16 (31%)</td>
<td>7/9 (78%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mild deviations in cranial nerve function</td>
<td>1/16 (6%)</td>
<td>0/9 (0%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* Fisher exact test
DISCUSSION

A cohort of children who as neonates participated in a RCT on continuous morphine infusion versus placebo for mechanical ventilation was seen at the age of 8-9 years. Univariate analysis revealed that children in the morphine group were more sensitive for the detection of cold (according to the method of levels). However, this was not confirmed in the multivariate analysis. The treatment condition (morphine versus placebo) was not a significant covariable in any of the 6 quantitative sensory testing modalities. The multivariate analysis did show correlations between IQ and the detection thresholds, both with the reaction time dependent method of limits and the reaction time independent method of levels. However, all correlations were weak (see Table 3 and Table 5) and clinically not significant. The children in both the placebo and the morphine group were more sensitive for the detection of cold (method of limits), compared to the reference data (1.5°C and 1.8°C, respectively). This might be due to methodological variations; cold detection threshold testing was the first test for the controls, so they might have needed to adapt to a test situation and setting, whereas the children in the present study already did several other tests before the quantitative sensory testing. Analysis of the other three method of limits modalities revealed no differences between the morphine or placebo group on the one hand and the reference data on the other hand.

Numbers of children who did not establish a pain threshold before reaching the minimum or maximum temperature were comparable between the morphine and placebo group. Blankenburg et al. provided an overview of QST studies in children that revealed a wide variation of pain thresholds, probably due to methodological variations (e.g. test site and instructions to participants)(16). The 95% confidence intervals in that study suggest that some children reached the minimum or maximum as well(16). Our multivariate analyses showed that the floor/ceiling effect should be added as a covariable when analyzing QST data.

In two other follow-up studies(4, 22), the lower limit of the thermal sensory analyzer was set at 10.0 °C, instead of the generally accepted 0.0 °C. International and multidisciplinary guidelines on quantitative sensory testing in children are needed to improve reproducibility of testing and reduce methodological variations(23).

**Long-term effects of surgery and morphine**

Hermann et al. reported long-term hypoalgesia for heat pain in both preterm and term born 9 to 14-year-old children who had received neonatal intensive care(24). The preterm neonates in that study underwent a mean number of 172 invasive procedures in the first week of life; however, no more than 53% of them received analgesics.

The hypoalgesia in former extremely preterm born 11-year-olds, reported by Walker et al., was most marked in those who had undergone neonatal surgery(4). In contrast, another study on long-term effects of neonatal surgery (all neonates received opioids postoperatively) showed no differences in the cold and warmth detection thresholds between the
neonatal surgery group and the control group at the age of 9 to 12 years(22).
Combining the previous data with the results of present study, we hypothesize that that neonatal injury or surgery is likely to have more pronounced long-term effects on pain processing than neonatal morphine treatment itself.

**Chronic pain**
In both groups in the present study, prevalence of pain in the three months before the follow-up visit was lower than Dutch reference values (i.e. 58% for boys versus 75% for the girls respectively)(19). Overall, the prevalence of a pain episode in the last three months did not significantly differ between boys and girls. The prevalence of chronic pain was comparable between the two groups and lower than the reference values (i.e. 11% for boys versus 13% for girls)(19). Noteworthily, the prevalence of chronic pain in both groups had dropped since the 5-year follow-up visit, i.e. from 14% to 9% in the placebo group and from 15% to 12% in the morphine group(13).

**Neurological functioning**
The majority of the children had a normal neurological examination. The prevalence of minor neurological dysfunctions (i.e. 39% of the placebo group versus 24% of the morphine group) is comparable to the prevalence in a reference cohort of term born children (i.e. 50% prevalence of minor neurological dysfunctions)(20). Mild deviations in coordination / balance control – a minor neurological dysfunction that could indicate cerebellar dysfunction – were more common in the morphine group of the present study \( (P=0.04) \). Research in rodents suggests that morphine treatment has a negative effect on the development of cerebellar neurons(25). A study in human preterm born found that they were more at risk for cerebellar injuries during the neonatal period than term born and that at adolescent age their cerebellum volume was smaller than that in term born adolescents(26). Minor cerebellar dysfunction could therefore be related to the preterm birth, but we cannot rule out an adverse effect from the higher morphine doses on cerebellar functioning.

The pilot follow-up study of the NEOPAIN trial found an overall lower prevalence of neurological soft signs (i.e. 20% in the placebo group \( n=5 \) versus 14% in the morphine group \( n=14 \)); however, the researchers did not detail which neurological soft signs (comparable to minor neurological dysfunctions) were assessed(12). In that study, the children in the morphine group had 7% smaller head circumference and 4% less bodyweight than children in the placebo group. Although several children in our study were prematurely born or born small for gestational age, most children in both groups now had normal height, weight and head circumference for their age. The difference in height between the two groups found at the age of five was not longer apparent. The preterm neonates in the NEOPAIN trial received higher doses of morphine, up to 30 mcg/kg/hr of morphine(8, 12). At neonatal age, the children in the morphine group of our study received 10 mcg/kg/hr of morphine; in the case of pain or distress children in both groups received open-label morphine as rescue medication.
Limitations

There are various other quantitative sensory testing modalities, such as mechanical or current detection and pain thresholds(27). Because 8-to 9-year old children are expected to have a short attention span, we decided to assess only thermal detection and pain thresholds.

Given the range of variation in data on pain thresholds in other studies(16) and the fact that the study site (Zwolle versus Rotterdam) was a significant covariable for the cold pain thresholds in the present study, we suggest that the determination of pain thresholds is sensitive to variations in instructions and methodology. However, this does not influence the comparison between the morphine and the placebo group in the present study. At both study sites the children received the same instructions, however, we did not investigate the inter-tester reliability for giving the instructions.

Reference data were available only for the four tests according to the Method of Limits, and not for the tests according to the Method of Levels. The reference data were collected in a set-up in which the minimum temperature of the thermal sensory analyzer was -10.0 degrees Celsius, compared to 0.0 degrees Celsius in the present study; this hampered the comparison of the cold pain thresholds between the control group and the present study.
CONCLUSION

We found in the present study that neonatal continuous morphine infusion (10 mcg/kg/hr) had no adverse effects on thermal detection and pain thresholds or overall neurological functioning eight to nine years later. Univariate analysis showed differences in the cold detection thresholds, however, this was not confirmed in the multivariate analysis. Children who had received continuous morphine as neonates experienced more episodes of pain in the three months before the study visit, but the prevalence of chronic pain was comparable between the morphine and the placebo group.
REFERENCES

MANAGEMENT
Je kijkt en je kijkt en je blijft vragen naar wat je ziet, maar wat je ziet is het enige antwoord
ANAESTHESIA AND POSTOPERATIVE ANALGESIA IN SURGICAL NEONATES WITH OR WITHOUT DOWN’S SYNDROME: IS IT REALLY DIFFERENT?

Abraham J. Valkenburg, Monique van Dijk, Tom G. de Leeuw, Conny J. Meeussen, Catherijne A.J. Knibbe, Dick Tibboel

British Journal of Anaesthesia (2012); 108: 295 - 301
ABSTRACT

Background
Reports conflict on optimal postoperative analgesic treatment in children with intellectual disability. We retrospectively compared postoperative analgesia consumption between neonates with Down’s syndrome and neonates without Down’s syndrome in relation to anaesthesia requirements and pain scores.

Methods
We analysed hypnotic and analgesic drugs administration, pain scores (COMFORT-Behaviour scale) and duration of mechanical ventilation during the first 48 hours after surgical repair of congenital duodenal obstruction in neonates between 1999 and 2011. Data of 15 children with Down’s syndrome were compared with data of 30 children without Down’s syndrome.

Results
General anaesthesia requirements did not differ. Median [IQR] maintenance dose of morphine during the first 24 hours postoperatively was 9.5 [7.8 to 10.1] µg kg⁻¹ hr⁻¹ in the Down’s syndrome group versus 7.7 [5.0 to 10.0] µg kg⁻¹ hr⁻¹ in the control group (P=0.46). Also morphine doses at postoperative day 2 and COMFORT-B scores at day 1 did not significantly differ between the two groups. COMFORT-B scores at day two were lower in children with Down’s syndrome (P=0.04). Duration of postoperative mechanical ventilation did statistically not differ between the two groups (P=0.89).

Conclusions
In this study, neonates with and without Down’s syndrome received adequate postoperative analgesia, as judged from comparable analgesic consumption and pain scores. We recommend prospective studies in children of different age groups with Down’s syndrome and in other groups of intellectually disabled children to provide further investigation of the hypothesis that intellectual disability predisposes to different analgesic requirements.
Research on systematic pain assessment and adequate analgesic therapy in children and neonates is on the rise(1). It is not clear whether the “standard” dosing regimens are applicable to intellectually disabled children(2). The evidence nevertheless points at differences in analgesia for intellectually disabled children. Fewer children with intellectually disability were assessed for pain after spinal fusion surgery and they received smaller doses of opioids(3). On the other hand, Gakhal et al. found that children with Down’s syndrome were more likely to receive morphine on day 3 after cardiac surgery than were controls(4).

Most studies in children with intellectual disability are limited by the sample heterogeneity in terms of aetiologies and intellectual disability levels. The reported incidence of congenital duodenal obstruction in children with Down’s syndrome is 369 per 10 000 live births, far exceeding that in children without Down’s syndrome, from 1.16 to 3.06 per 10 000 live births(5). This makes repair of duodenal obstruction eminently suitable for comparison of anaesthesia, analgesia and pain scores between a well-defined group of future intellectually disabled neonates and a group of neonates with a lesser risk of future intellectual disability.
METHODS

Participants and setting
After approval of the local ethics review board, we identified all patients who underwent surgical repair of congenital duodenal obstruction between March 1999 and February 2011 in Erasmus University Medical Centre - Sophia Children’s Hospital, Rotterdam, the Netherlands, and reviewed their medical records. The Erasmus MC Department of Paediatric Surgery and ICU serves as the only level III facility for those patients in a referral area comprising about 4 million inhabitants and 35 000 newborns/year.

Eligible subjects were those who underwent surgical repair of congenital duodenal obstruction within the first 28 postnatal days. Exclusion criteria were: sedation or analgesic treatment during the 24 hours before surgery, other surgical interventions at the same time or within 48 hours after primary surgery for duodenal obstruction or no digital record available.

Anaesthesia management
Anaesthesia management is not standardized in our centre and has changed over the years, reflecting new developments. Management of neonates with Down’s syndrome generally does not differ from neonates without Down’s syndrome, although anaesthetists may anticipate on possible airway management difficulties in neonates with Down’s syndrome. Atracurium was the preferred neuromuscular blocking agent until around 2008, when it was replaced with cisatracurium. Until 2008, most patients received barbiturates (thiopental or pentothal) as the hypnotic agent, which was then replaced with propofol. After 2008, a single shot caudal block was used more frequently as anaesthetists became familiar with this technique. Evidence of specific anaesthesia for surgical repair of congenital duodenal obstruction is missing.

Postoperative pain protocol
A postoperative pain protocol is in place since 1999, see Supplementary figure S1 at the end of this chapter. The first step was regular pain assessment by an intensive care nurse; at least every two hours during the first postoperative days and then every eight hours. The nurse used both the COMFORT-Behaviour (COMFORT-B) scale and the Numeric Rating Scale (NRS) for pain(6-8). The COMFORT-B scale includes 6 items, each rated from 1 to 5. Adding the ratings for all six items provides a pain rating between 6 and 30. The COMFORT-B scale has been validated for the use in children with and without Down’s syndrome(8, 9). The NRS score for pain is a validated tool that asks a proxy (the nurse) to rate pain intensity (0 = no pain at all and 10 = worst imaginable pain). The NRS expresses the observer’s expert rating of the patient’s level of pain, taking the patients’ circumstances (disease-related, treatment related, and environmental and patient specific)
into account(10). The NRS assessments – part of the pain management protocol since 1999 – serve to differentiate between pain and distress. The second step of the protocol is analgesic therapy. Already at the end of surgery, neonates receive a loading dose of 100 µg kg⁻¹ morphine, followed by a maintenance dose of 10 µg kg⁻¹ hr⁻¹. The protocol-associated decision-tree suggests that score combinations of COMFORT-B ≥ 17 and NRS ≥ 4 indicate moderate to severe pain, warranting opioid analgesia. Otherwise, maintenance doses of morphine are gradually decreased on the guidance of COMFORT-B and NRS scores. The pain management protocol makes no difference between children with or without Down’s syndrome. The sedation algorithm has been described previously(11).

In the study period, four children with Down’s syndrome and four without had been included in a randomized controlled trial about the potential morphine-sparing effects of rectal acetaminophen to continuous morphine infusions(12). No differences in outcomes between the two treatment modes were seen; therefore, those neonates were not excluded from our study.

**Measurements**

The following demographic characteristics were recorded: Sex, gestational age at birth, postnatal age at day of surgery, weight at day of surgery, presence of trisomy 21 and diagnosis of associated congenital abnormalities (in particular, cardiac anomalies). We recorded amounts of anaesthetics, neuromuscular blocking agents, and analgesics (intravenous or caudal) given intraoperatively. From the surgeons’ report, we retrieved the cause of duodenal obstruction (duodenal atresia, duodenal web or annular pancreas), duration of the surgery, and whether a central venous catheter had been placed. Furthermore, we recorded all hypnotics and analgesics administered during the first 48 hours postoperatively and the duration of postoperative mechanical ventilation. Prospectively collected COMFORT-B scores and NRS ratings were retrieved from in the Patient Data Management System (PDMS). Postoperative day 1 is defined as 0 to 24 hours after surgery and postoperative day 2 as 24 to 48 hours after surgery.

**Statistical analysis**

Data were analysed using SPSS version 19.0 (IBM, Chicago, IL). The chi-square test (or Fisher exact test in the case of low predicted cell counts) was used to compare nominal data for the neonates with and without Down’s syndrome. Continuous data are presented as median [interquartile range] and the two groups were compared using the Mann-Whitney U test. Duration of morphine use is presented as mean (SD) and the two groups were compared using the t test. All reported P values are two-sided, and P values of less than 0.05 are considered to indicate statistical significance.
FIGURE 1 Flowchart for the 107 children assessed for eligibility
RESULTS

From 1999 to 2011, one hundred and seven children underwent surgical repair of congenital duodenal obstruction in our hospital. Figure 1 gives a flowchart showing that 45 were included in this study; that is 15 with Down’s syndrome (Down’s syndrome group) and 30 without (control group). The excluded neonates are listed in Figure 1.

Background characteristics of both groups are listed in Table 1. During surgery, a central venous catheter was placed in 7 of the patients with Down’s syndrome versus 12 of the controls ($P=0.67$). Children with Down’s syndrome had more often a congenital heart disease ($P=0.001$), notably an atrioventricular septal defect. The causes of the congenital duodenal obstruction were comparable between the two groups (see Figure 1).

### TABLE 1 Characteristics of the 45 subjects, by study group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Down’s syndrome ($n = 15$)</th>
<th>Controls ($n = 30$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male / Female, $n$</td>
<td>12 / 3</td>
<td>9 / 21</td>
<td>0.002 $^b$</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>37 [36 to 40]</td>
<td>36 [33 to 38]</td>
<td>0.021 $^c$</td>
</tr>
<tr>
<td>Presence of congenital heart disease, $n$ (%)</td>
<td>8 (53)</td>
<td>2 (7)</td>
<td>0.001 $^d$</td>
</tr>
<tr>
<td>Age at surgery, days</td>
<td>3 [1 to 10]</td>
<td>2 [1 to 4]</td>
<td>0.30 $^c$</td>
</tr>
<tr>
<td>Weight at surgery (kg)</td>
<td>2.8 [2.5 to 3.0]</td>
<td>2.2 [1.7 to 2.6]</td>
<td>0.005 $^c$</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>187 [149 to 201]</td>
<td>167 [144 to 208]</td>
<td>0.78 $^c$</td>
</tr>
<tr>
<td>Postoperative ventilation, $n$ (%)</td>
<td>12 (80)</td>
<td>25 (83)</td>
<td>1.00 $^d$</td>
</tr>
<tr>
<td>Duration of postoperative ventilation (hours)</td>
<td>32 [16 to 46]</td>
<td>27 [18 to 46]</td>
<td>0.89 $^c$</td>
</tr>
</tbody>
</table>

$^a$ IQR = Interquartile range  
$^b$ Chi-square test  
$^c$ Mann-Whitney U test  
$^d$ Fisher Exact test

**General anaesthesia**

General anaesthesia was induced intravenously in 14 (93%) of the children with Down’s syndrome, of whom 3 received a rapid sequence induction, while 24 (80%) of the controls were induced intravenously, of whom twelve received a rapid sequence induction ($P=1.00$). The hypnotic agents administered during general anaesthesia are listed in Table 2. Five of the children with Down’s syndrome received a bolus of midazolam prior to transport to the
ICU versus one in the control group ($P=0.01$).

Fentanyl was administered to 14 (93%) of the children with Down’s syndrome versus 26 (87%) of the children without Down’s syndrome. The median [IQR] dose was 6.7 [5 to 10] µg kg$^{-1}$ for the Down’s syndrome group versus 6.7 [4 to 10] µg kg$^{-1}$ for the control group ($P=0.69$). The others (1 with and 4 without Down’s syndrome) received sufentanil. Three of the patients with Down’s syndrome versus 6 of the controls received single-shot caudal analgesia during surgery ($P=1.00$). Seven of these patients received 1 to 7 mL ropivacaine 0.2%; the other two patients 4 and 7 mL bupivacaine 0.25%.

Paracetamol was administered intraoperatively as a loading dose in six (40%) of the patients with Down’s syndrome versus 13 (43%) of the controls ($P=0.38$).

**Postoperative intensive care treatment**

Except one neonate in the control group, all patients received morphine after operation (see Table 3). Continuous morphine administration was discontinued within the first 24 hours in 8 (53%) of the neonates with Down’s syndrome versus in 13 (43%) of the controls ($P=0.53$). Mean (SD) total duration of morphine use was 28.2 (15.6) hours in the Down’s syndrome group versus 31.9 (16.8) hours in the control group ($P=0.48$).

Paracetamol was administered after operation in 12 (80%) of the patients with Down’s syndrome versus 16 (53%) of the controls ($P=0.08$). Two patients with Down’s syndrome and three controls received midazolam after operation ($P=1.00$; Table 3).
### TABLE 2 Intra-operative analgesics, hypnotics and neuromuscular blocking agents, by group

<table>
<thead>
<tr>
<th>Type of induction</th>
<th>Down’s syndrome (n = 15)</th>
<th>Controls (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous, n (%)</strong></td>
<td>11 (73)</td>
<td>12 (40)</td>
<td></td>
</tr>
<tr>
<td><strong>Rapid Sequence Induction, n (%)</strong></td>
<td>3 (20)</td>
<td>12 (40)</td>
<td>0.06 a</td>
</tr>
<tr>
<td><strong>Inhalational, n (%)</strong></td>
<td>1 (7)</td>
<td>6 (20)</td>
<td></td>
</tr>
</tbody>
</table>

#### Hypnotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Down’s syndrome (n = 15)</th>
<th>Controls (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Barbiturates, n (%)</strong></td>
<td>12 (80)</td>
<td>18 (60)</td>
<td>0.18 b</td>
</tr>
<tr>
<td><strong>Median [IQR] dose, mg/kg</strong></td>
<td>4.7 [3.6 to 5.1]</td>
<td>4.6 [4.3 to 5.6]</td>
<td>0.63 c</td>
</tr>
<tr>
<td><strong>Propofol, n (%)</strong></td>
<td>3 (20)</td>
<td>6 (20)</td>
<td>1.00 a</td>
</tr>
<tr>
<td><strong>Median [IQR] dose, mg/kg</strong></td>
<td>3.9 [3.6 to 3.9]</td>
<td>3.5 [2.4 to 7.3]</td>
<td>1.00 c</td>
</tr>
<tr>
<td><strong>Sevoflurane, n (%)</strong></td>
<td>5 (33)</td>
<td>5 (15)</td>
<td>0.20 b</td>
</tr>
<tr>
<td><strong>Isoflurane, n (%)</strong></td>
<td>4 (27)</td>
<td>13 (43)</td>
<td>0.28 b</td>
</tr>
<tr>
<td><strong>Midazolam, n (%)</strong></td>
<td>5 (33)</td>
<td>1 (3)</td>
<td>0.01 a</td>
</tr>
<tr>
<td><strong>Median [IQR] dose mcg/kg</strong></td>
<td>118 [55 to 419]</td>
<td>91</td>
<td>0.67 c</td>
</tr>
</tbody>
</table>

#### Neuromuscular blocking agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Down’s syndrome (n = 15)</th>
<th>Controls (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Succinylcholine, n (%)</strong></td>
<td>3 (20)</td>
<td>13 (43)</td>
<td>0.12 b</td>
</tr>
<tr>
<td><strong>Median [IQR] dose, mg/kg</strong></td>
<td>1.9 [1.4 to 1.9]</td>
<td>1.9 [1.6 to 2.2]</td>
<td>0.90 c</td>
</tr>
<tr>
<td><strong>Atracurium, n (%)</strong></td>
<td>10 (67)</td>
<td>11 (37)</td>
<td>0.06 b</td>
</tr>
<tr>
<td><strong>Median [IQR] dose, mg/kg</strong></td>
<td>1.0 [0.5 to 1.3]</td>
<td>1.1 [0.8 to 1.4]</td>
<td>0.39 c</td>
</tr>
<tr>
<td><strong>Cisatracurium, n (%)</strong></td>
<td>4 (27)</td>
<td>14 (47)</td>
<td>0.20 b</td>
</tr>
<tr>
<td><strong>Median [IQR] dose, mcg/kg</strong></td>
<td>197 [155 to 228]</td>
<td>170 [121 to 279]</td>
<td>0.80 c</td>
</tr>
</tbody>
</table>

#### Analgesics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Down’s syndrome (n = 15)</th>
<th>Controls (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fentanyl, n (%)</strong></td>
<td>14 (93)</td>
<td>26 (87)</td>
<td>0.65 c</td>
</tr>
<tr>
<td><strong>Median [IQR] dose, mcg/kg</strong></td>
<td>6.7 [5.0 to 10.1]</td>
<td>6.7 [4.0 to 9.9]</td>
<td>0.69 c</td>
</tr>
<tr>
<td><strong>Sufentanil, n (%)</strong></td>
<td>1 (7)</td>
<td>4 (13)</td>
<td>0.65 a</td>
</tr>
<tr>
<td><strong>Median [IQR] dose, mcg/kg</strong></td>
<td>0.4</td>
<td>0.4 [0.3 to 0.6]</td>
<td>0.80 c</td>
</tr>
<tr>
<td><strong>Caudal block, n (%)</strong></td>
<td>3 (20)</td>
<td>6 (20)</td>
<td>1.00 a</td>
</tr>
<tr>
<td><strong>Paracetamol, n (%)</strong></td>
<td>6 (40)</td>
<td>13 (43)</td>
<td>0.83 b</td>
</tr>
<tr>
<td><strong>Median [IQR] dose, mg/kg</strong></td>
<td>22 [8 to 28]</td>
<td>25 [8 to 35]</td>
<td>0.58 a</td>
</tr>
</tbody>
</table>

*a* Fisher exact test  
*b* Chi-square test  
*c* Mann-Whitney test
TABLE 3 Postoperative administration of analgesics and sedatives, by group

<table>
<thead>
<tr>
<th></th>
<th>Down’s syndrome</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients (%)</td>
<td>15 (100)</td>
<td>29 (97)</td>
<td>1.00 a</td>
</tr>
<tr>
<td>Loading dose, mcg/kg</td>
<td>100 [87 to 107]</td>
<td>107 [96 to 136]</td>
<td>0.09 b</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>day 1, mcg/kg/hr</td>
<td>9.5 [7.8 to 10.1]</td>
<td>7.7 [5.0 to 10.0]</td>
<td>0.46 b</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>day 2, mcg/kg/hr</td>
<td>7.0 [5.0 to 8.6]</td>
<td>5.0 [5.0 to 6.3]</td>
<td>0.47 b</td>
</tr>
<tr>
<td><strong>Paracetamol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients (%)</td>
<td>12 (80)</td>
<td>16 (53)</td>
<td>0.08 c</td>
</tr>
<tr>
<td>Median [IQR] cumulative dose day 1, in mg/kg</td>
<td>46 [29 to 78]</td>
<td>67 [45 to 88]</td>
<td>0.21 b</td>
</tr>
<tr>
<td>Median [IQR] cumulative dose day 2, in mg/kg</td>
<td>72 [44 to 82]</td>
<td>59 [28 to 77]</td>
<td>0.61 b</td>
</tr>
<tr>
<td><strong>Midazolam</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients (%)</td>
<td>2 (13)</td>
<td>3 (10)</td>
<td>1.00 a</td>
</tr>
<tr>
<td>Cumulative dose day 1 and 2, mcg/kg</td>
<td>398 [107 to 398]</td>
<td>703 [200 to 703]</td>
<td>0.40 b</td>
</tr>
</tbody>
</table>

| a Fisher exact test |
| b Mann-Whitney U test |
| c Chi-square test |

Postoperative pain scores

Over the first two postoperative days, 429 COMFORT-B and 431 NRS scores had been recorded (See Table 4). The median [IQR] COMFORT-B score after arrival at the ICU was 9 [8 to 11] in children with Down’s syndrome versus 10 [8 to 11] in controls (P=0.36). The median [IQR] COMFORT-B score at day two was 10 [9 to 11] in children with Down’s syndrome versus 11 [10 to 12] in controls (P=0.04). Almost all NRS scores were 3 or lower (low or no pain): 97% in the Down’s syndrome group versus 96% in the control group (P=0.43). Scores were even 0 (no pain) in 110 (66%) observations in the Down’s syndrome group versus 217 (74%) in the control group (P=0.06). The combined scores suggested moderate to severe pain (NRS score of ≥ 4 combined with a COMFORT-B score of ≥17) only once in no more than two patients with Down’s syndrome and three controls.
### TABLE 4 Postoperative COMFORT-B and NRSa scores, by group

<table>
<thead>
<tr>
<th></th>
<th>Down’s syndrome (n = 15)</th>
<th>Controls (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median number of scores per patient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>6 [3 to 8]</td>
<td>4 [3 to 8]</td>
<td>0.30</td>
</tr>
<tr>
<td>Day 2</td>
<td>4 [3 to 6]</td>
<td>3 [3 to 7]</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>Median scores per patient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMFORT-B day 1</td>
<td>10 [9 to 11]</td>
<td>10 [9 to 11]</td>
<td>0.52</td>
</tr>
<tr>
<td>COMFORT-B day 2</td>
<td>10 [9 to 11]</td>
<td>11 [10 to 12]</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Percentage of NRS a scores of 0, i.e. no pain, per patient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>86 [59 to 100]</td>
<td>75 [52 to 100]</td>
<td>0.65</td>
</tr>
<tr>
<td>Day 2</td>
<td>100 [59 to 100]</td>
<td>100 [69 to 100]</td>
<td>0.63</td>
</tr>
</tbody>
</table>

*a* Numeric Rating Scale  
*b* Two patients without Down’s syndrome were not assessed due to a short stay on the PICU  
*c* Mann-Whitney U test
DISCUSSION

Our analysis did not reveal any substantial differences in anaesthesia and analgesia for congenital duodenal obstruction repair between neonates with and without Down’s syndrome, nor in pain scores. Even the duration of mechanical ventilation was not longer - as often expected - in the neonates with Down’s syndrome. Neonates with Down’s syndrome had a higher gestational age; this could explain their higher weight at surgery. However, it is unlikely that this influenced anaesthetic or postoperative management because medication was calculated per kilogram body weight. Congenital heart disease was more frequent in neonates with Down’s syndrome, which is consistent with findings from previous studies(5, 13, 14). Children with Down’s syndrome received more often a bolus midazolam before transport to the ICU. COMFORT-B scores at day two were lower in children with Down’s syndrome than in children without Down’s syndrome, but the difference is clinically not significant.

The question arises whether our findings tally with those of previous studies? Table 5 provides an overview of previous studies (3, 4, 15, 16) and the present study. Valid comparison, however, is hampered by the different age groups and the heterogeneity of diagnoses and surgical procedures in the previous studies. Two reported that the intellectually disabled children received less intraoperative analgesia than the others. One reported more postoperative analgesia and one less postoperative analgesia in the intellectually disabled children. In addition, a questionnaire among physicians revealed that 89% agreed with the statement that intellectually disabled children receive sub therapeutic doses of analgesics(17). Two of the previous studies also evaluated pain scores. One observed lower pain scores in the intellectually disabled children but lacked statistical testing(3). In the other, pain scores had been documented in only one-third of the children with cerebral palsy and these did not differ from those of the children without cerebral palsy(16). In view of the above, the question remains whether potential differences in pain experience(18, 19), pain expression, or both of intellectually disabled children influence analgesic requirements (what they need) or pain management (what they get) in these children. The COMFORT-B scale has been validated by our group for the use in 0-to 3-year old children with Down’s syndrome as well(9). Therefore, we have reason to believe that at this age the pain expression of children with Down’s syndrome is similar to other children. It does remain possible that neonates with Down’s syndrome experience pain differently. Adults with Down’s syndrome are reported to be more sensitive for heat pain(20). Since several pain-related genes (ADAMTS5, GRIK1, S100B, RUNX1, KCNE1, KCNJ6) are located on chromosome 21(21), it will be important to study the effect of the trisomy 21 on pain experience as well as the pharmacokinetics and pharmacodynamics of analgesics(2).

In the present study, the ICU’s postoperative pain protocol provided for adequate treatment
of potential pain and distress, as demonstrated by generally low COMFORT-B and NRS scores in all children. Results from a recent study by our group suggest that, independent of the presence of Down’s syndrome, neonates, in particular those younger than 10 days, have impaired pharmacokinetic capacity to metabolise morphine. This study provided new dosing recommendations based on a population pharmacokinetic model of intravenous morphine in children up to the age of three years old. Simulations showed that a different dosing regimen would result in a more narrow range of morphine and metabolite concentrations. This new dosing recommendation for morphine entails a 50% dose reduction in children younger than 10 days old. Since most of the children in our study were younger than 10 days, the administered doses may therefore have been to the upside. As such, it might be speculated that the neonates in our analysis may have been pain-free with even less analgesia. A new pharmacodynamics study is needed to validate these new dosing recommendations; specifically also in intellectually disabled children.
### TABLE 5 Comparison of the available evidence

<table>
<thead>
<tr>
<th>Study design</th>
<th>Study group</th>
<th>Control group</th>
<th>Type of surgery</th>
<th>Intraoperative analgesia of the study group</th>
<th>Postoperative analgesia of the study group</th>
<th>Pain scores in the study group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gakhal 1998</td>
<td>Retropective case-control study</td>
<td>16 children with Down’s syndrome (mean age: 5 years)</td>
<td>16 children without Down’s syndrome (mean age: 5 years)</td>
<td>Cardiac surgery</td>
<td>Not available</td>
<td>↓</td>
</tr>
<tr>
<td>Malviya 2001</td>
<td>Retrospective cross-sectional study</td>
<td>19 intellectually disabled children (mean age: 11 years)</td>
<td>23 children without intellectual disability (mean age: 11 years)</td>
<td>Spinal fusion surgery</td>
<td>=</td>
<td>↓</td>
</tr>
<tr>
<td>Koh 2004</td>
<td>Prospective cohort study</td>
<td>152 intellectually disabled children (mean age: 10 years)</td>
<td>148 children without intellectual disability (mean age: 8 years)</td>
<td>Various</td>
<td>↓</td>
<td>=</td>
</tr>
<tr>
<td>Long 2009</td>
<td>Retrospective cross-sectional study</td>
<td>71 children with cerebral palsy (29 intellectually disabled) (mean age: 11 years)</td>
<td>77 children without cerebral palsy (mean age: 11 years)</td>
<td>Orthopedic surgery</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Present study</td>
<td>Retrospective cross-sectional study</td>
<td>15 children with Down’s syndrome (median age: 3 days)</td>
<td>30 children without Down’s syndrome (median age: 2 days)</td>
<td>Congenital duodenal obstruction repair</td>
<td>=</td>
<td>=</td>
</tr>
</tbody>
</table>

* Analgesic doses compared to the control group.

* The difference between the two groups has not been tested in the study by Malviya et al.

* Pain scores were available in only 31% of the study group.
**Study limitations**

Judging from the insignificant differences found between the two groups, the study could have been underpowered. For two important outcome parameters we determined the sample size required to result in a statistically significant difference ($\alpha$ of 0.05 and $\beta$ of 0.80). First, the maintenance dose of morphine on day 1 was higher in children with Down’s syndrome; 76 patients in each group would be required to make this difference statistically significant. Second, 260 patients in each group would be required to make the difference in COMFORT-B scores at day 1 statistically significant. Given the incidence of congenital duodenal obstruction of 1.16 – 3.06 per 10 000 live births, such a study would be challenging, but may be usefully informed by the current work.

Complications and unexpected events were not registered during most years of our study period. Therefore we are not able to present reliable data regarding complications or unexpected events.

**Conclusions**

In this study, both neonates with and without Down’s syndrome received adequate postoperative analgesia, as judged from comparable analgesic consumption and pain scores. The pain scores were low and this finding suggests that these neonates, independent of the presence of Down’s syndrome, might have been pain-free with less analgesia. Since evidence is still scarce and contradictory, we recommend prospective multicentre studies evaluating postoperative pain management in different age groups of children with Down’s syndrome and in other groups of intellectually disabled children. These studies should preferably use a randomized controlled study design comparing different analgesic regimens. In this way, conclusive evidence on the premise that intellectual disability predisposes to different analgesic requirements can be obtained.
**SUPPLEMENTARY FIGURE S1**: Postoperative Analgesia Protocol (Paediatric Intensive Care Unit; Erasmus University Medical Centre – Sophia Children’s Hospital)
REFERENCES

Zo andersom is alles, misschien.
Ik zal dit uitleggen.
PHARMACODYNAMICS AND PHARMACOKINETICS OF MORPHINE AFTER CARDIAC SURGERY IN CHILDREN WITH AND WITHOUT DOWN SYNDROME

Abraham J. Valkenburg, Monique van Dijk, Elke H.J. Krekels, Brendan O’Hare, William Casey, Ron A.A. Mathôt, Catherijne A.J. Knibbe, Dick Tibboel, Cormac Breatnach
ABSTRACT

Background
Approximately 40 to 60% of children with Down syndrome have a congenital heart defect and many therefore undergo major surgery and postoperative intensive care management at a young age. Children with Down syndrome are described as being more agitated and “difficult to sedate” after surgery. The aim of this study was to compare the pharmacodynamics and pharmacokinetics of intravenous morphine after cardiac surgery in two groups of children – those with and without Down syndrome.

Methods
All children received standardized general anaesthesia for cardiac surgery; all received a loading dose of morphine (100 mcg/kg) after cardiopulmonary bypass; thereafter a morphine infusion was commenced at 40 mcg/kg/hr. During intensive care, nurses regularly assessed pain and discomfort with validated observational instruments (COMFORT-B scale and Numeric Rating Scale (NRS) for pain). These scores guided analgesic and sedative treatment. Pain scores and analgesia and sedation requirements were recorded. Blood samples were obtained for pharmacokinetic analysis at preset time intervals.

Results
Eighteen children with Down syndrome and sixteen controls underwent cardiac surgery with cardiopulmonary bypass. Median COMFORT-B and NRS scores were not statistically significantly different between the two groups. Median morphine infusion rate during first 24 hr after surgery was 31.7 [IQR 22.8 to 37.0] mcg/kg/hr in the Down’s syndrome group versus 31.8 [IQR 25.7 to 36.2] mcg/kg/hr in the control group (P=1.00). Morphine requirements during the following days as well as need for additional sedation were comparable between the two groups.
Population pharmacokinetic analysis revealed no statistically significant differences in any of the pharmacokinetic parameters of morphine between the children with and without Down syndrome.

Conclusion
Based on pharmacodynamic and pharmacokinetic analysis, there is no evidence to adjust morphine dosing after cardiac surgery in children with Down syndrome compared to children without Down syndrome.
INTRODUCTION

Approximately 40 to 60% of children with Down syndrome have a congenital heart defect and many will therefore undergo major surgery and require postoperative intensive care management(1). Children with Down syndrome are described as being more agitated and “difficult to sedate” after surgery(2). Walker acknowledged that the provision of analgesia may be influenced by perceptions about a patient’s sensitivity to pain or response to analgesia(3).

The results from retrospective chart review studies on analgesia/sedation requirements of children with Down syndrome do not provide a consensus view: Gakhal et al. found that children with Down syndrome are more likely to require morphine at day 3 after cardiac surgery than are children without Down syndrome. The children with Down syndrome were also more likely to receive additional sedatives and muscle relaxants than those without(4). On the other hand, a more recent study in 15 neonates with and 30 without Down syndrome who had undergone surgical repair of congenital duodenal obstruction revealed no statistically significant differences in postoperative analgesic or sedative requirements, or pain scores, between the two groups(5).

Worldwide, morphine is the first line analgesic and sedative agent in children after cardiac surgery(6, 7). Recent advances have improved the feasibility of pharmacokinetic studies in infants and children, since both the required blood sample volume and number of samples required for analysis has decreased substantially(8). Validated population pharmacokinetic models have been applied to describe the pharmacokinetics of morphine in various groups of critically ill and postoperative neonates, infants and children(9, 10).

Pharmacokinetic analysis of other drugs such as paracetamol(11), theophylline(12) and methotrexate(13) have revealed altered metabolism and lower clearance in children and adults with Down syndrome. However, knowing the pharmacokinetics of a drug alone is not enough: information on the effect of a drug, the pharmacodynamics, is invaluable as well(14). Combining the pharmacokinetics of morphine with pharmacodynamic endpoints, i.e. pain/distress assessments and dosing requirements, in children with and without Down syndrome will provide information on the degree of variability between children with and without Down syndrome. Armed with this information our ability to assess if dosing adjustments are required will be enhanced.

Therefore the aim of this study was to compare the pharmacodynamics and pharmacokinetics of intravenous morphine after cardiac surgery in two groups of children – those with and without Down syndrome.
METHODS

Subjects and setting
This observational, prospective case-control study was conducted at the Department of Anaesthesia and Intensive Care Medicine of Our Lady’s Children’s Hospital, Dublin, between January and May 2012.
The study protocol was approved by the local ethics committee. Written parental informed consent for the study was obtained preoperatively.
The inclusion criteria for the Down syndrome group were: a confirmed diagnosis of Trisomy 21, age 3 to 36 months and cardiac surgery with cardiopulmonary bypass for atrial septal defect (ASD), ventricular septal defect (VSD), atrioventricular septal defect (AVSD), or Tetralogy of Fallot (TOF) repair. The inclusion criteria for the control group were: age 3 to 36 months and cardiac surgery with cardiopulmonary bypass for ASD, VSD, AVSD or TOF repair. The exclusion criteria for both groups were: epilepsy, cerebral palsy or birth asphyxia, history of cardiothoracic surgery through sternotomy, preoperative mechanical ventilation, preoperative treatment with morphine or midazolam and extracorporeal membrane oxygenation (ECMO) treatment after cardiopulmonary bypass.

General anaesthesia
Children received a standardized general anaesthesia regimen without premedication. After IV access was secured, anaesthesia was induced with intravenous midazolam (optional; 100 to 200 mcg/kg), ketamine (1 to 3 mg/kg), pancuronium (100 to 150 mcg/kg) and fentanyl (up to 10 mcg/kg). The anaesthetist had the option to use propofol (1 to 4 mg/kg) for induction of anaesthesia instead of midazolam and ketamine. Anaesthesia was maintained with sevoflurane (0.75 to 2.5% fraction inspired) in an air/oxygen mixture. Arterial and central venous access was secured thereafter. Prior to incision and sternotomy, a further fentanyl bolus was given. The range for the total dose of fentanyl used up to the start of cardiopulmonary bypass was 10 to 25 mcg/kg. During cardiopulmonary bypass, general anaesthesia was maintained with remifentanil (0.25 to 0.50 mcg/kg/min) and isoflurane (0.5 to 1.0% fraction inspired), both delivered through the bypass circuit. After coming off bypass, anaesthesia was maintained with sevoflurane (0.75 to 2.5 % fraction inspired). All patients underwent modified ultrafiltration after cardiopulmonary bypass for 10 minutes. Afterwards the morphine loading dose (100 mcg/kg) was administered and the morphine infusion was commenced at 40 mcg/kg/hr.

Postoperative intensive care management
All patients received standardized postoperative pain and distress management according to the following departmental guidelines, based on pain and distress assessments (see below for clinical cutoff values). Morphine infusion was continued at 40 mcg/kg/hr during intensive care. Three doses of IV paracetamol were prescribed (7.5 mg/kg for children <10
kg and 15 mg/kg for children >10 kg). Morphine boli (20 to 40 mcg/kg) were prescribed as needed (PRN).

For rescue sedation, midazolam boli (50 to 100 mcg/kg) were prescribed as needed (PRN) with escalation to a midazolam infusion (1 to 2.5 mcg/kg/min) if a requirement for further sedation persisted. The second-line sedative agent was enteral chloral hydrate (25 to 50 mg/kg every six hours).

When, based on COMFORT-B and NRS scores, continuous morphine infusion was weaned to 12 mcg/kg/hr or less and patients were ready for discharge to the ward, they were commenced on oral morphine (double the total daily IV dose; divided in six-hourly doses).

Two hours after the first dose of oral morphine, the intravenous morphine infusion was switched off.

Pain and distress were assessed at least every two hours after return to the intensive care unit with the COMFORT-B scale and the NRS for pain. Both instruments are validated for children (0 to 3 years) with and without Down syndrome admitted to an intensive care unit(15, 16). The COMFORT-B scale is a pain and distress assessment instrument that asks observers to consider the intensity of six behavioral manifestations: Alertness, Calmness, Respiratory response (for mechanically ventilated children) or Crying (for spontaneously breathing children), Body movements, Facial tension and Muscle tone. For each of these items, five descriptions, rated from 1 to 5, are provided, reflecting an increasing intensity of the behavior in question. Summating the ratings of the six behavioral manifestations leads to a score ranging from 6 to 30. The NRS for pain (0=no pain at all and 10=worst imaginable pain) expresses the observer’s informed opinion of the patient’s level of pain – taking disease-related, treatment related, environmental and patient-specific circumstances into account.

All nurses follow a 2-hour COMFORT-B training program when they start to work in our unit. The program includes 10 assessments of different patients, with a qualified nurse (trained to teach pain and distress assessment) performing the same assessments. Agreement is assessed from the linearly weighted Cohen k calculated from these 10-paired assessments. Median [IQR] linearly weighted kappa values were excellent; 0.92 [0.88 to 0.96] for 147 nurses.

Clinical cutoff scores for the COMFORT-B and NRS pain have been determined(17). The decision tree suggests that score combinations of COMFORT-B >16 and NRS > 3 indicate moderate to severe pain, warranting additional opioid analgesia. Otherwise, maintenance doses of morphine are gradually decreased on the guidance of COMFORT-B and NRS scores.

**Measurements**

Data collection for the study commenced on arrival of the patient in the operating theatre. Measurements included patient demographics, dose and time of anaesthetic agents administered, details of the cardiac surgery performed, duration of mechanical ventilation and
duration of intensive care admission. The following risk assessment scales were applied: Risk Adjustment for Surgery for Congenital Heart Disease (RACHS-1)(18) on admission (score range 1 to 6 where 6 is the highest risk category), Paediatric Index of Mortality (PIM2) (probability of death in %)(19) on admission and daily Paediatric Logistic Organ Dysfunction scores (probability of death in %) (PELOD-II)(20). Postoperative administration of morphine and other analgesic and sedative agents were recorded. Arterial blood samples for pharmacokinetic analysis were taken at preset time points (see below). COMFORT-B and NRS scores were noted. The end of the data collection period was marked by one of the following events: a switch from intravenous to oral morphine, discharge to the ward, a procedure requiring general anaesthesia and reintubation for any reason other than oversedation.

Samples for pharmacokinetic analysis
Arterial blood samples (1.0 mL) for determination of morphine plasma concentrations were taken at the following time intervals: immediately prior to morphine loading dose (t=0), t=10, t=30 to 60 minutes, t=4 hours, t=8 hours, t=16 hours, t=24 hours; in addition daily at 8.00 am and once just before the end of the study. Blood samples were centrifuged and plasma was stored at -80°C.

Analytical method
Morphine, morphine-3-glucuronide and morphine-6-glucuronide concentrations were analyzed using LC-MS/MS in the positive ionisation mode on a Shimadzu LC-30 (Nishino-kyo-Kuubaracho, Japan) system coupled to an AB SCIEX 5500 QTRAP mass spectrometer (Framingham, MA, US). 75 µl acetonitril/methanol 84:16 (v/v%) containing the internal standard morphine-d3, morphine-3-glucuronide-d3 and morphine-6-glucuronide-d3 was added to 10 µl of patient’s plasma to precipitate proteins. Samples were vortexed, stored at -20°C for 30 minutes, vortexed again and centrifuged. For the determination of morphine, morphine-3-glucuronide and morphine-6-glucuronide 3 µl was injected onto a Thermo Scientific Hypersil Gold HILIC (50 x 2.1 mm, 1.9 µm) column. A stepwise chromatographic gradient was applied using acetonitril and water with a constant 5% addition of 1% ammonium formate / 2% formic acid in water. The flow was 600 µl/min for the HILIC method, column-oven temperature was 40°C. Morphine, morphine-3-glucuronide and morphine-6-glucuronide were measured as [M+H]+, using the mass transition of 286.1/165.1, 462.2/286.2 and 462.2/286.2 respectively. The method was validated over a range of 2 to 500 ng/mL. The accuracies ranged from 93.5% to 105.5%, the intra-day precisions were below 9.6% and the inter-day precisions were below 12.9%.

Population pharmacokinetic analysis
Morphine concentrations were modeled with the nonlinear mixed-effects modeling software NONMEM VI (ICON, Ellicott City, MD, US), with the First-Order Conditional Estimate
(FOCE) method for fitting and with PLTtools (PLTsoft, San Francisco, CA, USA) for the visualization of the data. The model was developed in the following steps: 1) choice of the structural model, 2) choice of the error model, 3) covariate analysis, and 4) internal validation of the model.

A decrease in objective function of more than 3.8 points between different (sub) models was considered to be statistically significant: this correlates with a $P$ value of $<0.05$ assuming a $\chi^2$ distribution. In addition, the following plots were used for diagnostic purposes: A) observed versus individually predicted, B) observed versus population predicted, C) time versus weighted residuals, D) population predictions versus weighted residuals. Furthermore, the 95% confidence interval of the parameter estimates, the correlation matrix and visual improvement of the diagnostic plots served to evaluate the model.

The following covariates were analysed: bodyweight, age, sex, and Down syndrome. Continuous covariates were tested in linear or exponential equations; categorical covariates were tested by estimating separate parameter values for each category. Potential covariates were separately incorporated into the model and considered statistically significant ($P<0.05$) if the objective function decreased 7.9 points or more and the 95% confidence interval of the additional parameter did not include zero. When more than one significant covariate for the simple model was found, the covariate-adjusted model with the largest decrease in objection function was chosen as a basis to sequentially explore the influence of additional covariates with the use of the same criteria.

The model was internally validated according to a recently developed framework for the evaluation of paediatric population models(10), by the following steps: Initially, the condition number was assessed by taking the ratio of the largest and smallest Eigenvalue of the covariance matrix in the NONMEM output, 2) a bootstrap analysis with 100 resampled datasets was performed, 3) population predicted versus observed plots were made stratified by weight, age, sex and Down syndrome, 4) $\eta$-shrinkage was determined according to Karlsson and Savic(21) and was accepted if less than 20%, 5) NPDE-analysis was performed on the basis of 1000 simulated profiles(22), and 6) individual and population parameter estimates for the distribution volumes were plotted versus bodyweight to visually assess whether the obtained covariate relationship described the trend in individual parameter values accurately.

Morphine-3-glucoronide and morphine-6-glucoronide concentrations were not included in this NONMEM model.
**Statistical analysis**

Data were analysed using SPSS version 20.0 (IBM, Chicago, IL, USA). Nominal data were compared using the Chi-square test (or Fisher's exact test in the case of low predicted cell counts). Continuous data are presented as median [interquartile range] and the two groups were compared with the Mann-Whitney-U-test. Mean (SD) morphine, morphine-3-glucoronide and morphine-6-glucoronide concentrations are calculated per subject. The mean (SD) values are then presented per group and compared with the t test. Risk factors for a COMFORT-B score of <11 (indicating oversedation) were determined with logistic regression analysis (23). All P values are two-sided and a value of <0.05 is considered as statistically significant.

![Flowchart](https://via.placeholder.com/150)

**FIGURE 1** Flowchart recruited patients.
RESULTS

Background
Eighteen subjects with Down syndrome and sixteen without Down syndrome were included in the study between January and May 2012 (see flow chart in Figure 1). There were no statistically significant differences between the demographic characteristics of the two groups (see Table 1).
Medical history taking revealed that one child with Down syndrome group had undergone surgical repair of congenital duodenal obstruction and that two children with Down syndrome had undergone correction of aortic coarctation combined with pulmonary artery banding (both through lateral thoracotomy).
Of the children with Down syndrome, 11 (61%) received diuretics preoperatively versus 5 (31%) of the controls ($P=0.08$). Three controls and 1 child with Down syndrome received an ACE-inhibitor preoperatively. Two controls and 1 child with Down syndrome received a beta-blocker preoperatively. Two children with Down syndrome received levothyroxine preoperatively for hypothyroidism versus none in the control group. Parents of one subject with Down syndrome did not give consent for the pharmacokinetic samples, see Figure 1.

General anaesthesia and surgery
Details of the general anaesthesia and surgery are presented in Table 1 for both groups. Since more children with Down syndrome underwent repair of an AVSD, the RACHS-1 score is higher for the Down syndrome group (see Table 1). Cardiopulmonary bypass times and aortic cross-clamp times were comparable between both groups. More children in the control group were cooled to 28°C than in the Down syndrome group ($P=0.03$), since more children in the control group underwent Tetralogy of Fallot repair. None of the children received muscle relaxants after cardiopulmonary bypass.
One patient in the control group could not be weaned from cardiopulmonary bypass and was commenced on ECMO; thereafter this patient was excluded from the study. One other child in the control group was excluded from the study before admission to the intensive care unit, due to inadvertent disconnection of the IV line for an unknown period during transport from theatre to the intensive care unit.
### TABLE 1 Background characteristics, by group

<table>
<thead>
<tr>
<th></th>
<th>Down syndrome (n=18)</th>
<th>Controls (n=16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median [IQR] or n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>5 (28%)</td>
<td>8 (50%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Gestational age, in weeks</td>
<td>39 [37 to 40]</td>
<td>40 [39 to 41]</td>
<td>0.08</td>
</tr>
<tr>
<td>Age at surgery, in days</td>
<td>175 [130 to 270]</td>
<td>180 [124 to 234]</td>
<td>0.55</td>
</tr>
<tr>
<td>Weight at surgery, in kg</td>
<td>5.9 [4.9 to 7.7]</td>
<td>6.6 [5.5 to 7.3]</td>
<td>0.67</td>
</tr>
<tr>
<td>Height at surgery, in cm</td>
<td>64 [58 to 66]</td>
<td>67 [61 to 68]</td>
<td>0.24</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASD</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>VSD</td>
<td>3 (17%)</td>
<td>5 (31%)</td>
<td></td>
</tr>
<tr>
<td>AVSD</td>
<td>13 (72%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>TOF</td>
<td>0 (0%)</td>
<td>10 (63%)</td>
<td></td>
</tr>
<tr>
<td>AVSD+TOF</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>ASA classification 3</td>
<td>18 (100%)</td>
<td>16 (100%)</td>
<td>1.00</td>
</tr>
<tr>
<td>RACHS-1 score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4 (22%)</td>
<td>15 (94%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>14 (78%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary bypass time, in min</td>
<td>114 [83 to 132]</td>
<td>115 [96 to 139]</td>
<td>0.80</td>
</tr>
<tr>
<td>Aortic cross-clamp time, in min</td>
<td>76 [55 to 99]</td>
<td>74 [47 to 106]</td>
<td>1.00</td>
</tr>
<tr>
<td>Target temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>intraoperative cooling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34 °C</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>32 °C</td>
<td>16 (89%)</td>
<td>10 (63%)</td>
<td>0.03</td>
</tr>
<tr>
<td>28 °C</td>
<td>1 (6%)</td>
<td>6 (38%)</td>
<td></td>
</tr>
<tr>
<td>Sedative agent for induction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>of general anaesthesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>15 (83%)</td>
<td>15 (94%)</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>7 (39%)</td>
<td>10 (63%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Propofol</td>
<td>3 (17%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Cumulative fentanyl dose, in mcg/kg</td>
<td>12 [10 to 16]</td>
<td>12 [10 to 17]</td>
<td>0.80</td>
</tr>
<tr>
<td>Cumulative remifentanil dose, in mcg/kg</td>
<td>28 [20 to 49]</td>
<td>37 [32 to 49]</td>
<td>0.24</td>
</tr>
</tbody>
</table>

**Pain/distress assessment**

Median COMFORT-B and NRS ratings were comparable between both groups (Table 2). The median [IQR] number of pain and distress assessments per subject was not statistically different between both groups, 14[10 to 18] for the Down syndrome group and 18[10 to 24 for the control group (P=0.40). Univariate analysis revealed that 54 (18%) of the scores...
in the Down syndrome group indicate oversedation (COMFORT-B <11) at any time point, versus 18 (7%) of the scores in the control group (P<0.001). This was confirmed in a logistic regression analysis: Children with Down syndrome were more at risk for oversedation [OR = 3.0(95% CI:1.7 to 5.3)] and children in both groups were more at risk for oversedation in the first 3 hours after surgery [OR =7.4(95% CI:4.0 to 13.4)]. However, there was no statistically significant interaction effect between those two covariables.

**TABLE 2 COMFORT-B and NRS scores during the study period, by group**

<table>
<thead>
<tr>
<th></th>
<th>Down syndrome (298 scores)</th>
<th>Controls (264 scores)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMFORT-B, median [IQR]</strong></td>
<td>13 [12 to 16]</td>
<td>14 [12 to 16]</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>COMFORT-B &gt;16, n(%)</strong></td>
<td>71 (24%)</td>
<td>60 (23%)</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>NRS, median [IQR]</strong></td>
<td>2 [0 to 3]</td>
<td>2 [0 to 2]</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>NRS &gt;3, n(%)</strong></td>
<td>39 (13%)</td>
<td>34 (13%)</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>COMFORT-B &gt;16 and NRS &gt;3, n (%)</strong></td>
<td>23 (8%)</td>
<td>17 (6%)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Oversedation (COMFORT &lt;11), n(%)</strong></td>
<td>54 (18%)</td>
<td>18 (7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Undersedation (COMFORT &gt;22), n(%)</strong></td>
<td>7 (2%)</td>
<td>3 (1%)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

**Morphine**

The mean infusion rates during the first 24 hours as well as the second 24 hours were comparable between both groups (see Table 3). Of the children with Down syndrome, 4 (22%) received intravenous morphine at day 3 (48 to 72 hours) versus 5 (36%) of the controls (P=0.45); morphine infusion was discontinued or switched to oral morphine in the others. One child in the control group was switched to an oxycodone infusion after 20 hours of continuous morphine infusion, due to relentless pruritus, a side effect of morphine.

**TABLE 3 Postoperative administration of intravenous morphine, by group**

<table>
<thead>
<tr>
<th></th>
<th>Down syndrome (n=18)</th>
<th>Controls (n=14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAY 1 (0 to 24 hr)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean infusion rate in mcg/kg/hr</td>
<td>31.7 [22.8 to 37.0]</td>
<td>31.8 [25.7 to 36.2]</td>
<td>1.00</td>
</tr>
<tr>
<td>Number bolus</td>
<td>3 [1 to 5]</td>
<td>4 [3 to 4]</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>DAY 2 (24 to 48 hr)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N(%) on IV Morphine</td>
<td>13 (72%)</td>
<td>12 (86%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Mean infusion rate in mcg/kg/hr</td>
<td>16.8 [10.7 to 24.6]</td>
<td>16.1 [12.0 to 19.9]</td>
<td>0.81</td>
</tr>
<tr>
<td>Number bolus</td>
<td>0 [0 to 1]</td>
<td>0 [0 to 2]</td>
<td>0.69</td>
</tr>
</tbody>
</table>
Sedation
The median time before rescue sedation was required - 10 [4 to 15] hours in the Down syndrome group versus 6 [4 to 13] hours in the control group - was not statistically significantly different (P=0.51). The number of midazolam boli and the number of children that required a midazolam infusion was comparable between both groups (Table 4).

**TABLE 4 Postoperative sedation requirements, by group**

<table>
<thead>
<tr>
<th></th>
<th>Down syndrome (n=18)</th>
<th>Controls (n=14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to start of rescue sedation, in hours</td>
<td>10 [4 to 15]</td>
<td>6 [4 to 13]</td>
<td>0.51</td>
</tr>
<tr>
<td>Mean number midazolam boli</td>
<td>3 [0 to 11]</td>
<td>5 [2 to 7]</td>
<td>0.67</td>
</tr>
<tr>
<td>Midazolam infusion, n (%)</td>
<td>7 (39%)</td>
<td>7 (50%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Mean number chloral hydrate boli</td>
<td>0 [0 to 3]</td>
<td>0 [0 to 2]</td>
<td>0.64</td>
</tr>
<tr>
<td>Mean number morphine / midazolam / chloral hydrate boli</td>
<td>7 [3 to 18]</td>
<td>10 [7 to 17]</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Pharmacokinetics of morphine
A total of 333 plasma samples from 17 subjects with Down syndrome and 14 controls were available for the pharmacokinetic analysis. The median [IQR] number of samples was 11 [9 to 13] for the Down syndrome group versus 12 [10 to 13] for the control group (P=0.71). Mean (SD) morphine, morphine-3-glucuronide and morphine-6-glucuronide concentrations per subject, stratified by group, are presented in Table 5.

**TABLE 5 Mean (SD) morphine, morphine-3-glucuronide and morphine-6-glucuronide plasma concentrations per subject, by group**

<table>
<thead>
<tr>
<th></th>
<th>Down syndrome (n=17)</th>
<th>Controls (n=14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine in ng/mL</td>
<td>38 (17)</td>
<td>42 (15)</td>
<td>0.58</td>
</tr>
<tr>
<td>Morphine-3-glucuronide in ng/mL</td>
<td>220 (98)</td>
<td>280 (141)</td>
<td>0.17</td>
</tr>
<tr>
<td>Morphine-6-glucuronide in ng/mL</td>
<td>35 (16)</td>
<td>40 (25)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

The time-course of morphine concentrations was best described with a two-compartment model, with log-normally distributed inter-individual variability in the volume of the central compartment and the total morphine clearance. A proportional error model was used for the residual variability. In the covariate analysis, bodyweight proved to be a significant predictor of the inter-individual variability in the distribution volume in a linear relationship. Including bodyweight as a covariate in a linear relationship on the distribution volume of the peripheral compartment further improved the model fit. No other significant covariate
relationships could be identified. The bootstrap analysis showed that except for the peripheral distribution volume, the bootstrap parameter values were within 10% of the parameter values obtained in the original model fit. Table 6 shows the population parameter estimates for the final model. The observed versus predicted morphine concentrations, stratified by Down syndrome, are plotted in Figure 2.

**TABLE 6 Parameter estimates of the population pharmacokinetic model**

<table>
<thead>
<tr>
<th>Structural parameter</th>
<th>Original value (CV%)</th>
<th>Mean bootstrap value (Δ from original in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1, L/kg</td>
<td>5.49 (11%)</td>
<td>5.49 (0%)</td>
</tr>
<tr>
<td>V2, L/kg</td>
<td>30.4 (34%)</td>
<td>41.5 (37%)</td>
</tr>
<tr>
<td>Q, ml/min</td>
<td>54.9 (18%)</td>
<td>56.3 (3%)</td>
</tr>
<tr>
<td>CL, ml/min</td>
<td>82.2 (12%)</td>
<td>80.3 (-2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interindividual variability</th>
<th>Original value (CV%)</th>
<th>Mean bootstrap value (Δ from original in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \omega^2 V1 )</td>
<td>0.22 (26%)</td>
<td>0.22 (0%)</td>
</tr>
<tr>
<td>( \omega^2 CL )</td>
<td>0.32 (48%)</td>
<td>0.35 (9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Residual variability</th>
<th>Original value (CV%)</th>
<th>Mean bootstrap value (Δ from original in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \sigma^2 ) Morphine concentrations</td>
<td>36.6%</td>
<td>36.8% (0.5%)</td>
</tr>
</tbody>
</table>

CV = coefficient of variation; \( V1 \) = Central volume of distribution; \( V2 \) = Peripheral volume of distribution; \( CL \) = total clearance; \( Q \) = intercompartemental clearance

Individual parameter estimations for the central volume of distribution, peripheral volume of distribution and clearance are displayed in Figure 3, stratified by group. Although the range of the estimations is wider for the Down syndrome group, there were no statistically significant differences between both groups.

Standard paediatric model evaluation and validation steps showed that the condition number of the final model was 32, which is well under threshold for over-parameterisation of 1000. The results from the NPDE-analysis (See Figure 4) show that the model slightly overpredicts the variability in the population; however this overprediction is constant over time and over the predicted morphine concentration range.
Figure 2: Observed versus predicted morphine concentrations, stratified by group. Down syndrome = filled circles; Controls = open circles.

Figure 3: Individual post-hoc parameter estimations, stratified by group. CL = total clearance; V1 = Central volume of distribution; V2 = Peripheral volume of distribution. Down syndrome: No = 0; Yes = 1.
FIGURE 4 Normalized prediction distribution error (NPDE) plots. The histogram (left panel) shows the NPDE distribution for morphine (solid line is the normal distribution). NPDE versus time is displayed in the middle panel and NPDE versus predicted concentrations is displayed in the right panel.

### Intensive care management

The PIM-2 and PRISM-II scores were not statistically different between the two groups. Duration of intensive care admission as well as duration of mechanical ventilation was comparable between both groups (see Table 7). Three children were reintubated (after which data collection was ended); two controls (due to sepsis and pulmonary hypertension) and one child with Down syndrome (due to post-extubation stridor). Following study completion, 5 (28%) of the children with Down syndrome remained mechanically ventilated in the intensive care unit (due to sepsis, obstructive sleep apnea, possible seizures, pulmonary hypertension and reoperation for pacemaker insertion) as did one (6%) control (for pulmonary hypertension) \( (P=0.13) \).

### TABLE 7 Intensive care management, by group

<table>
<thead>
<tr>
<th></th>
<th>Down syndrome (n=18)</th>
<th>Controls (n=16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIM2 score (%)</td>
<td>2 [2 to 3]</td>
<td>2 [1 to 3]</td>
<td>0.99</td>
</tr>
<tr>
<td>PRISM-II score Day 1 (%)</td>
<td>0.55 [0.1 to 1.3]</td>
<td>1.3 [0.1 to 1.4]</td>
<td>0.54</td>
</tr>
<tr>
<td>PRISM-II score Day 2 (%)</td>
<td>1 [0.1 to 1.3]</td>
<td>0.1 [0 to 0.9]</td>
<td>0.14</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, in hours</td>
<td>23 [17 to 29]</td>
<td>28 [19 to 50]</td>
<td>0.48</td>
</tr>
<tr>
<td>Reintubation, n(%)</td>
<td>1 (6%)</td>
<td>2 (13%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Study period, in hours</td>
<td>40 [24 to 55]</td>
<td>46 [30 to 64]</td>
<td>0.57</td>
</tr>
<tr>
<td>Duration intensive care admission, in days</td>
<td>3.9 [2.1 to 7.8]</td>
<td>4.0 [2.2 to 6.2]</td>
<td>0.93</td>
</tr>
</tbody>
</table>

PIM = Paediatric Index of Mortality PELOD = Paediatric Logistic Organ Dysfunction
DISCUSSION

This study showed that children with Down syndrome have comparable analgesia and sedation requirements after cardiac surgery, compared to controls. Pain and distress assessment showed no statistically significantly differences between the two groups, other than the finding that children with Down syndrome are more at risk for oversedation. No differences were observed in the volume of distribution and clearance of morphine between children with and without Down syndrome. Duration of mechanical ventilation and duration of intensive care admission were comparable between both groups.

**Morphine dosing**

To our knowledge, there is no evidence that establishes the optimal morphine infusion rate after cardiac surgery in children. After a loading dose, 40 mcg/kg/hr is a commonly used rate to start with, after which the dose will be titrated based upon effect and pain scores. We did not expect a prolonged effect from residual anaesthetic agents during intensive care, since the anaesthetic agents during cardiopulmonary bypass were short-acting (i.e. remifentanil and isoflurane) and after bypass morphine (100 mcg/kg loading dose followed by an infusion of 40 mcg/kg/hr) and sevoflurane. The mean morphine infusion rate over the first 24 hours after surgery was 32 mcg/kg/hr in both groups.

Gakhal et al. compared the analgesia and sedation requirements of 16 children with Down syndrome and 16 controls after cardiac surgery(4). The mean infusion rate for the first 24 hours after surgery was somewhat lower (26 mcg/kg/hr for the Down syndrome group and 24 mcg/kg/hr for the controls) than in the present study. The authors report that prescribing patterns differed between the physicians and do not mention availability of observational pain/distress assessment or departmental guidelines in their study. These lower infusion rates in the study by Gakhal et al. could account for the higher use of muscle relaxants and sedative agents reported. The children were also older than in the present study (mean age of 4 years for the Down syndrome group and 5 years for the control group), probably because at that time congenital heart defects were corrected at a later age than in the current era. The comparable morphine requirements between children with and without Down syndrome in the present study confirm the laboratory findings by Martinez-Cue et al.; they found that the dose response curve for morphine analgesia is comparable between the animal model for Down syndrome (Ts65Dn mice) and control littermates(24).

**Pain/distress assessment**

The incidence of a high COMFORT-B score combined with a high NRS for pain was low in both groups (8% of the scores in the Down syndrome group versus 6% in the control group). Children in both groups were more at risk for oversedation (a low COMFORT-B score) in the first three hours after surgery; and children with Down syndrome were slightly
more at risk for oversedation. The oversedation in the first three hours after cardiac surgery could be partly attributed to the morphine. However, such oversedation might contribute to hypotension. The median COMFORT-B scores were still comparable between the two groups (13 in the Down syndrome group versus 14 in the control group, \( P=0.56 \)), so the clinical significance of the oversedation in children with Down syndrome may be limited. In a previous study by our group, COMFORT-B and NRS for pain scores were also comparable between the children with and without Down syndrome that were admitted to the intensive care unit after surgical repair of congenital duodenal atresia(5). However, median COMFORT-B scores and NRS for pain scores were lower than in the present study; this maybe due to the difference in age groups (neonates versus infants/children) and the use of regional anaesthesia in 20% of the children in both groups in that study. In another study on pain and distress assessment in children postoperatively admitted to the intensive care unit (primarily after cardiac surgery), COMFORT-B scores were generally lower (median of 12) and the NRS for pain was \( >3 \) in 6% of the scores compared to 13% in the present study. However, the majority of the children in that study received a high dose midazolam infusion; this may explain the lower scores(25).

**Sedation**

Although morphine was the primary analgesic agent (with sedative properties), most children in both groups received rescue sedation at some point, probably to facilitate mechanical ventilation. The time before rescue sedation was required was shorter in the controls than in the Down syndrome group, but this did not reach statistical significance. Additionally, the number of bolus of midazolam, or chloral hydrate, or the number of children requiring a midazolam infusion was not statistically significantly different between both groups. This is not in line with previous reports on higher sedative requirements in children with Down syndrome(2, 4).

**Pharmacokinetics**

The main finding of the pharmacokinetic analysis was that Down syndrome is not a significant covariate for the volume of distribution or total clearance of morphine. Therefore there is no need for dose adjustments in children with Down syndrome on the basis of pharmacokinetic considerations. Our group previously developed a population pharmacokinetic model in 248 children aged 0-to 3-year-old who received morphine after major non-cardiac surgery or to facilitate mechanical ventilation(26). In the current model, the estimation of both central and peripheral volume of distribution was larger compared to the estimations from the previous model in infants and children after non-cardiac surgery. Altered pharmacokinetics of morphine after cardiopulmonary bypass has been described before(6, 27, 28). After cardiopulmonary bypass, it takes some time to restore homeostasis; systemic inflammatory response, haemodilution, low cardiac output as well as impaired hepatic and renal function are com-
mon findings in children after cardiac surgery(29).
Furthermore, body weight was not a significant covariate for the morphine clearance in this study, whereas it was in previous studies(26). The small range in bodyweight in the present study could explain this. The population clearance estimated in the present study was only slightly smaller compared to the predictions in children after non-cardiac surgery. These aspects will have to be addressed in further analysis of morphine clearance post cardiac surgery.

**Future directions**
All children in the present study were below the age of three. The (postoperative) analgesic and sedative requirements of older children and adults with Down syndrome should be carefully investigated in a prospective study. On the other hand, perceptions of caregivers with regard to pain sensitivity and response to sedation of children with Down syndrome require more attention, since they could influence the provision of analgesia and sedation(3). For both children with and without Down syndrome the next step could be to compare different strengths of intravenous morphine in a randomized, double blind controlled trial, in order to find the optimal dose of morphine after cardiac surgery. So far dosing recommendations are based on institutional based guidelines only, not supported by studies of high quality.

**Limitations**
Anaesthetists titrated the sevoflurane concentration to effect but we could not present the end-tidal sevoflurane concentrations because these were not recorded. We did not take plasma samples for pharmacokinetic analysis after discontinuation of the intravenous morphine, since patients were switched to oral morphine. The pharmacokinetic model was based on morphine concentrations only; the next step will be to incorporate the metabolites (morphine-3- and morphine-6-glucuronide) into the model as well.
CONCLUSIONS

Based on pharmacodynamics and pharmacokinetic analysis, there is no evidence to adjust morphine dosing after cardiac surgery in children with Down syndrome compared to children without Down syndrome.
REFERENCES


DISCUSSION
RUTGER KOPLAND
Ik zeg niet dat het erg is, ik zeg alleen wat ik dacht te zien.
GENERAL DISCUSSION
Like anyone else, Oscar Wilde must have known what pain is; as a poet he knew how to put it in words. This quote perfectly hints at the presence of different layers of pain and the personal nature of pain. The different layers of pain were explained in a model, nearly 100 years after Oscar Wilde, by neurosurgeon John D. Loeser, see Figure 1. The model consists of nested circles identifying four components of pain(1).

Loeser defined the different components as follows: “Nociception is the detection of tissue damage by specialized transducers connected to A delta and C fibres. Pain is the perception of a noxious stimulus that begins in the dorsal horn and involves the entire spinal cord and brain. Suffering is the consequence of a physical or psychological threat to the integrity of the human being. Pain behaviors are the things a person says, does, or does not do that you and I would interpret as reflecting tissue damage.”(2).

Around the same time, Loeser was member of a committee of the International Association for the Study of Pain (IASP) that formulated the following definition of pain in 1979: “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”(3).
This definition still stands today. Anand and Craig addressed already in 1996 the limitations of this definition, as it is not applicable to persons incapable of self-report: For example infants, young children and intellectually disabled children and adults(4). In the note that comes with the definition, IASP therefore later added: “The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment.”

The group that may not able to communicate pain verbally is not in particular a small minority; it includes children below the age of 4, intellectually disabled children and adults, and elderly with cognitive impairment or dementia. What do we know about the Dutch situation? The Netherlands has a population of 17 million people; this includes according to Statistics Netherlands approximately 720,000 children below the age of 4, 115,000 intellectually disabled children and adults and 230,000 demented elderly. In other words, more than a million people in the Netherlands could have great difficulty in expressing pain in a way caregivers will recognize it. Over the next decades, the number of demented elderly is likely to increase substantially due to the aging population in the Netherlands(5).

You may ask yourself, why study pain assessment in intellectually disabled children if we still do not have a measure for pain beyond doubt in other patient groups who are not able to reliably report their pain? And on what basis do you treat the pain then?

Over the years much effort was spent on developing good observational pain assessment instruments that now have been implemented in pain management algorithms. These instruments include several specific tools for intellectually disabled children (see Chapter 2 for an overview). Still, these children are often excluded from pain research because of their inability to self-report pain, the variability in intellectually disability, unknown and potential altered pharmacokinetics of analgesics, and use of co-medication. Seeing that they are at high risk for pain, there is every reason to study pain assessment and its management in intellectually disabled children.

In this chapter I will discuss the three different parts of this thesis - pain assessment, quantitative sensory testing, and pain management. The emphasis then shifts to pain processing of children with Down syndrome, since most studies were carried out in children with Down syndrome. I give with recommendations for clinical pain management and pain research in children. I will conclude with a comparison of the components of pain that are affected in intellectually disabled children and neonates admitted to the intensive care unit.
PAIN ASSESSMENT

The ability to accurately measure pain is the foundation for successful clinical pain management(6). Observational pain assessment, usually performed by nurses, is the silver standard in children up to 4 years of age, sedated or mechanically ventilated patients, and intellectually disabled children. Physicians however, tend to prefer physiological parameters for pain and distress assessment(7). Pain increases the heart rate and blood pressure through the connections from the spinoreticular tract to the brainstem and then further on to the sympathetic and parasympathetic efferent pathways. The sensitivity and specificity of heart rate and blood pressure monitoring for the measurement of pain are not high enough; however in many occasions, for example during general anesthesia or in intubated patients, heart rate and blood pressure monitoring is the only available measure of pain. This is why bedside monitors based on “objective surrogate” measures for pain and distress have been developed – such as Bispectral index(8) and skin conductance(9). In this thesis we evaluated one observational pain assessment tool, the COMFORT-B scale, and two objective surrogate measures, the Bispectral index and skin conductance.

COMFORT-B scale
The COMFORT scale has gained popularity in many hospitals since its introduction in 1992(10). The intensive care nurses of the two children’s hospitals where the studies described in this thesis were conducted, were well trained to use this scale, given the high interrater reliability (Chapters 6, 7, 10 and 11). They each perform approximately 1000 assessments annually. Although the scale already showed good psychometric properties, validation is an ongoing process. Two items, crying and muscle tone were thought to be rated differently in children with Down syndrome, compared to other children(11, 12); the validity of the COMFORT-B scale in children with Down syndrome was therefore questioned. In this thesis we showed that the COMFORT-B scale was also valid in children with Down syndrome and that the clinical cut-off values did not need to be adjusted. The observational pain and distress assessment with COMFORT-B scale might then be the best available option; it has its limitations as well. First, because the observation period is as long as 2 minutes, it is not a good measure for short-lasting procedural pain. A study by our group showed that a shorter observation period of 30 seconds increased the risk for underscoring pain(13). Second, next to the COMFORT-B scale, nurses apply the Numeric Rating Scale (NRS), in order to be able to differentiate between pain and distress. This rating (0=no pain at all and 10= worst imaginable pain) expresses the nurse’s informed opinion of the patient’s level of pain – taking disease-related, treatment-related, environmental and patient-specific circumstances into account. Nevertheless there is a certain measure of subjectivity involved here, as the influence of the nurse’s personal perception of pain cannot be ruled out. A study on how observers translate the various circumstances into a rating from 0 to 10 would provide welcome information on the validity of this rating. Third, the
COMFORT-B scale is only applied 3 to 10 times a day. It will therefore not recognize sudden changes in a child’s behaviour as a continuous measure would. Fourth, caregivers will have to apply other observational pain assessment tools for other groups of intellectually disabled children (see Chapter 2 for an overview). However, these scales have been validated only in children aged 4 years and older whereas the COMFORT-B has been validated in 0- to 3-year-old children.

**Surrogate physiological parameters**

Since they do not require self-report, devices that measure physiological reactions to painful or stressful stimuli are potentially helpful for pain and distress assessment in intellectually disabled children and non-verbal patients. The sensitivity and specificity of changes in blood pressure and heart rate are low, since these changes can also be side-effects from general anesthetic agents, effects from comorbidities such as cardiovascular diseases, or from the surgical procedure itself. Furthermore, inotropic and vasoactive drugs that provide hemodynamic support are often titrated based on the blood pressure and heart rate. In those occasions blood pressure and heart rate monitoring for the assessment of pain and distress may be less reliable.

Physiological parameters are regarded as objective, but objective does not automatically mean valid. For example, the algorithm of the BIS monitor is derived from adult data; the validity of that algorithm in infants (age 0 to 12 months) is questionable since their electroencephalogram (EEG) has not matured yet (14, 15). Furthermore, the Bispectral index is based on only two frontal EEG channels. Epileptic activity and anticonvulsant drugs alter the EEG as well (16). Epilepsy is a common comorbidity in intellectually disabled children; prevalences of up to 75% have been reported (17). Sixty percent of the intellectually disabled children in the study on Bispectral index monitoring suffered from epilepsy and were therefore treated with anticonvulsants; this could be an explanation for the lower Bispectral index values in intellectually disabled children compared to controls (Chapters 4 and 5).

Further evaluation of the EEG and the BIS algorithm is required, before the BIS can be used in infants and intellectually disabled children. To investigate the effect of anticonvulsants on depth of anesthesia, a prospective study is needed in which depth of anesthesia is measured in four study groups – based on intellectual disability and use of anticonvulsant drugs – receiving the same standardized anesthetic regimen. Until then, BIS monitoring cannot be recommended for assessing the depth of anaesthesia in intellectually disabled children.

Another example of a supposedly objective measure of pain and distress is skin conductance monitoring. Comparison of this methodology to other measures in various age groups and various settings proved it has to low sensitivity and specificity for measuring pain (9, 18). For instance, we observed that autoregulation of the body temperature during a rest phase results in skin conductance peaks of similar magnitude as in pain (Chapter 7). In order to make skin conductance measurement more useful, preclinical studies should apply
microneurography of both nociceptive C fibres and sympathetic nerve fibres(19) as the gold standard, and measure skin conductance simultaneously. Comparing pain and pain-free recordings would then enable us to single out the influences of pain and other sympathetic activity on skin conductance. Next, the algorithms of the skin conductance monitor could be refined for the measurement of pain by correcting for other sympathetic influences. For now, the sensitivity and specificity of the COMFORT-B scale for pain assessment exceed those of skin conductance monitoring.

Researchers and clinicians keep searching for more objective measures of pain and distress. In order to move forward, the industry, academic researchers and clinicians should make an effort to develop and validate an useful and reliable bedside monitor. We must leave the time of small-scale observational studies aimed at promoting the use of poorly validated and expensive monitors behind us. The proposed monitor would ideally be a combination of EEG monitoring and hemodynamic monitoring. Two recent studies showed the additional value of advanced statistical methods and combining different continuous recordings. Fabrizi et al. recognized patterns in EEG recordings that discriminated between nociception and other tactile stimulation, using advanced statistical analysis of the data with a principal component analysis(20). Treister et al. found that combining hemodynamic parameters such as heart rate variability and skin conductance discriminated better between pain and no pain than the single parameter approach(21). Multimodal assessment of pain has not been studied in intellectually disabled children and adults, although these are the ones who would certainly benefit from more advanced pain assessment methods.

**Self-report**

Self-report is regarded as the gold standard for the measurement of pain in (non-sedated) children aged 4 years and older and in adults(22). However, only a minority (12%) of the children with Down syndrome of 8 year and older were able to provide adequate self-report according to their parents - based on verbalizing, localizing and rating the intensity of the pain(Chapter 8). The Faces Pain Scale-revised is suitable for self-report in children aged 4 years and older; however chronological age was the only relevant predictor for the ability to use this tool(23). We did not investigate if this scale can help the children with Down syndrome to rate the intensity of their pain. Is it fair to classify them as inadequate to provide self-report? There will be few children with Down syndrome that can provide adequate self-report. But overestimating their abilities can have bigger consequences, possibly resulting in under- or overrating their pain.

It is likely that other intellectually disabled children will not be able to adequately report their pain and that they therefore will remain dependent on pain assessment by proxy.
QUANTITATIVE SENSORY TESTING

Quantitative sensory testing systematically documents alterations and reorganization in nervous system function and, in particular, the nociceptive system (24). It is one of the methodologies fit to diagnose sensory abnormalities in patients with neuropathic pain (25). QST gave researchers the opportunity to evaluate sensory processing in a standardized way; it was picked up to investigate pain sensitivity in intellectually disabled children and adults.

Quantitative sensory testing in intellectually disabled individuals

The suggestion that intellectually disabled children and adults are less sensitive for pain (26, 27) is not confirmed by quantitative sensory testing; the results show they are even more sensitive for heat pain, see Table 1. However, their intellectual disability and prolonged reaction time make quantitative sensory testing less feasible. The study in Chapter 10 showed that self-report for pain in children with Down syndrome is not adequate, and in retrospect this is a requirement for quantitative sensory testing. Also, the studies did not investigate the reproducibility of the sensory testing in the intellectually disabled subjects leaving the issue of test-retest reliability unresolved. Reliability of thermal detection and pain thresholds in adults varied considerably between studies as well (28). The value of quantitative sensory testing remains questionable in intellectually disabled children. This could be resolved if the tests could be performed without depending on the subject’s self-report for pain, using continuous monitoring of more objective parameters such as in the study by Treister et al. (21) or preferably with the proposed monitor described above.

TABLE 1 Overview QST studies in intellectually disabled individuals

<table>
<thead>
<tr>
<th>Study group</th>
<th>Hennequin (24)</th>
<th>Defrin (29)</th>
<th>This thesis (Chapter 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group</td>
<td>26 individuals with Down syndrome</td>
<td>14 adults with unspecified intellectual disability</td>
<td>42 children with Down syndrome</td>
</tr>
<tr>
<td>Control group</td>
<td>75 controls</td>
<td>14 adult controls</td>
<td>24 siblings</td>
</tr>
<tr>
<td>QST modality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold</td>
<td>Longer latencies for cold pain</td>
<td>Not assessed</td>
<td>Less sensitive for detection of cold (MLI)</td>
</tr>
<tr>
<td>Warmth</td>
<td>Not assessed</td>
<td>More sensitive for heat pain (MLE)</td>
<td>Less sensitive for detection of warmth (MLI)</td>
</tr>
<tr>
<td>Reaction time</td>
<td>Not assessed</td>
<td>Prolonged</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Other findings</td>
<td>More difficulties with localization of stimulus</td>
<td>Less sensitive for detection of pressure</td>
<td></td>
</tr>
<tr>
<td>Methodological</td>
<td>No conventional QST methods</td>
<td>No data on feasibility of QST</td>
<td>QST feasible in only minority of children with Down syndrome</td>
</tr>
<tr>
<td>considerations</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MLI = Method of Limits  MLE = Method of Levels
Quantitative sensory testing and long-term effects of neonatal morphine / surgery

Morphine is worldwide used for opioid analgesia in (preterm) infants, for example after surgery for congenital anomalies. Given the adverse effects of morphine and neonatal tissue damage in rodents, it is important to investigate those effects in humans as well (30); for example by applying quantitative sensory testing to evaluate thermal detection and pain thresholds.

Quantitative sensory testing was feasible in the former preterm and term born neonates at 8 to 16 years of age. However, differences in instructions and sensory testing methods (temperature settings and for example methods of levels versus methods of limits) hampers test standardization and comparison of study findings (31). In addition, the long-term adverse effects of neonatal pain and morphine treatment vary widely between the various studies reported in Table 2. It would therefore be desirable to develop international QST guidelines and testing protocols and perform a meta-analysis of both the data of study groups and control groups.

The study in Chapter 9 provided input for the translational research continuum on the development of functional nociceptive circuits in early life. Previous research in rodent models gave new insights in the development of neuronal circuits and neuroplasticity of the fetal and neonatal brain (32). Ruda et al. found that neonatal peripheral injury in a rodent model (evoked with complete Freund’s adjuvant) gave long-term alterations of sensory processing and altered nociceptive neuronal circuits (33). It has been argued that a rodent model with repetitive needle pricking better represents the nerve injury in neonates during intensive care admission than does the model with high doses of intraplantar hind paw injections of inflammatory substances such as complete Freund's adjuvant (34).

Neonatal rodents showed impaired learning and enhanced hippocampal gliosis (proliferation of damaged astrocytes) after morphine administration (35-38). Extreme prematurity (gestational age of <28 weeks) combined with neonatal surgery in humans was associated with more pronounced long-term effects on sensory processing than was admission to the NICU for mechanical ventilation and continuous morphine administration (See Table 2). Major limitations of previous studies are the small sample size and absence of prospective data on administered analgesic and sedative agents in the neonatal period.

Analysis of the electroencephalogram (EEG) during heel lancing in neonates suggests that specific neural circuits for nociceptive processing undergo critical developmental changes until a postconceptional age of 35 to 37 weeks (20).

Therefore the influences of neonatal pain and analgesia on human neurodevelopment and neuroplasticity need closer investigation. More importantly, researchers should be extremely wary of classifying a relationship between administration of anesthetic or analgesic agents and long-term adverse effects as causative (39). They should also judge whether the relationship is strong enough to be clinically relevant. Otherwise we might expect a lot of media attention and risk upsetting parents and caregivers of infants and neonates who require surgery or intensive care treatment.
### TABLE 2 QST and long-term effects of neonatal pain and morphine administration on thermal detection and pain thresholds

<table>
<thead>
<tr>
<th>Study group</th>
<th>Hermann(40)</th>
<th>Schmelzel-Lubiecki(41)</th>
<th>Walker(42)</th>
<th>Hohmeister(43)</th>
<th>This thesis (Chapter 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19 former preterm NICU patients</td>
<td>9 former neonatal cardiac surgical patients</td>
<td>43 former extremely preterm NICU patients</td>
<td>9 former preterm NICU patients</td>
<td>43 in continuous morphine group</td>
</tr>
<tr>
<td></td>
<td>20 former term NICU patients</td>
<td></td>
<td></td>
<td>9 former term NICU patients</td>
<td>46 in placebo group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(both preterm and term NICU patients)</td>
<td></td>
</tr>
<tr>
<td>Opioid analgesia</td>
<td>Yes, in 18 (46%)</td>
<td>Yes</td>
<td>No information provided</td>
<td>No information provided</td>
<td>Yes</td>
</tr>
<tr>
<td>Surgery</td>
<td>No</td>
<td>Yes</td>
<td>Yes, 12 (28%)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Control group</td>
<td>20 controls</td>
<td>9 controls</td>
<td>44 controls</td>
<td>9 controls</td>
<td>139 controls</td>
</tr>
<tr>
<td>Age</td>
<td>9 to 14 years</td>
<td>9 to 12 years</td>
<td>11 years</td>
<td>11 to 16 years</td>
<td>8 to 9 years (study group)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 to 11 years (control group)</td>
</tr>
<tr>
<td>QST modality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold</td>
<td>Not assessed</td>
<td>No differences in cold detection thresholds</td>
<td>Study group less sensitive for detection of cold and cold pain</td>
<td>Not assessed</td>
<td>Study group more sensitive for detection of cold; No differences in cold pain thresholds</td>
</tr>
<tr>
<td>Warmth</td>
<td>Both study groups were less sensitive for heat pain</td>
<td>No differences in warmth detection thresholds</td>
<td>Study group less sensitive for detection of warmth and heat pain</td>
<td>No differences in warmth detection or pain thresholds</td>
<td>No differences in warmth detection or heat pain thresholds</td>
</tr>
<tr>
<td>Other findings</td>
<td>Study group was less sensitive for thermal detection at thoracic scar area</td>
<td>Findings more pronounced in neonates that had surgery</td>
<td>Higher fMRI activations in former preterm NICU patients</td>
<td>In multivariate analysis no differences in thermal detection and pain thresholds between continuous morphine and placebo group</td>
<td></td>
</tr>
</tbody>
</table>
PAIN MANAGEMENT

In previous studies intellectually disabled children received lower amounts of intraoperative analgesia than controls (44, 45). Are their analgesic requirements different or is there another explanation? As a possible reason, the provision of analgesia may be influenced by physicians’ perceptions about the patient’s sensibility to pain or response to analgesia (46). We studied the analgesic and sedative requirements of children with Down syndrome initially retrospectively and then prospectively (Chapter 10 and 11). Before the start of those studies, many clinicians assured that children with Down syndrome were more difficult to sedate. In the prospective study, the same standardized anesthetic and postoperative regimen was applied to both the children with and without Down syndrome. Anesthesiologists titrated the dose of anesthetic agents based on specific clinical endpoints (i.e. blood pressure, heart rate or observational pain assessments), not on the presence or absence of intellectual disability. Furthermore, all patients received standardized postoperative pain and distress management, based on COMFORT-B and NRS scores. The incidence of moderate to severe pain was comparable between both groups: 8% of the assessments in the Down syndrome group versus 6% of the assessments in the control group. No differences in intraoperative analgesic or sedative requirements were found between the two groups.

In addition, the analysis of morphine pharmacokinetics gave no reason for different dosing recommendations in children with Down syndrome.

To our knowledge, there is no evidence that establishes the optimal morphine infusion rate after cardiac surgery in children. A next investigation should compare different doses of intravenous morphine in a randomized, double blind controlled trial using the incidence of pain, rescue medication requirements, and side-effects as outcome measures. As 43% of the children in the retrospective study in Chapter 10 and all children in the prospective study in Chapter 11 received paracetamol next to opioid analgesia, further investigations on multimodal postoperative analgesia in children are needed.

Extrapolation to other groups

The study in Chapter 11 addressed the pharmacodynamics and pharmacokinetics of morphine after cardiac surgery in children with Down syndrome. Can the results be extrapolated to other groups of intellectually disabled children, for example those undergoing spinal fusion correction or other orthopedic procedures? It is not easy to answer this question, seeing the differences in age groups, heterogeneity in the etiology of the intellectual disability, in the surgical procedures, and in co-medication. Prospective studies on the analgesic and sedation requirements of intellectually disabled children as well as pharmacokinetics of analgesic and sedative agents are needed to optimize the pain management for these children.
**Optimal pharmacotherapy**

Recent advances have improved the feasibility of pharmacokinetic studies in infants and children, since both the required blood sample volume and number of samples required for analysis have decreased substantially\(^{(47)}\). Data from population pharmacokinetic and pharmacodynamic studies can be used for simulations. These simulations then can form the basis for the design of proof of principal studies, preferably randomized controlled trials\(^{(48)}\). This approach has successfully been applied to for the development of evidence-based pharmacotherapy in (critically ill) neonates, infants and children without intellectual disability – e.g. for midazolam, morphine, propofol and paracetamol\(^{(49)}\).

But is it feasible to study the pharmacokinetics and pharmacodynamics for every group of intellectually disabled children and for every analgesic or sedative agent? Systematic and careful monitoring of pharmacodynamic effects could be a starting point \(^{(50)}\), preferably with a more advanced bedside monitor as described above. Analysis of the pharmacokinetics would be justified when we could expect an effect size of differences in the pharmacodynamics between two groups as well as potential sources for pharmacokinetic variability.
This thesis started quoting John Langdon Down’s observations that individuals with Down syndrome bear pain with wonderful callousness. Parents and caregivers still perceive children with Down syndrome to be less sensitive to pain (Chapter 3 and 8). It is a logical evaluation based on these children’s pain: each parent gave examples of situations where their child did not report an injury and where they had difficulties in perceiving their child’s pain. But medical professionals, too, tell anecdotes on the decreased pain sensitivity and how difficult to sedate children with Down syndrome are - topics that have been prospectively studied in this thesis. We did not exactly find what we expected based on these anecdotes: Children with Down syndrome are not less sensitive to pain (Chapter 8) and are not more difficult to sedate than children without Down syndrome (Chapter 10 and 11). I think we are dealing with confirmation bias here; clinicians will clearly remember individuals with Down syndrome in whom sedation was not easy or who appeared to be less sensitive to pain. They will not remember the children with Down syndrome who responded ‘normally’. This notion, however, represents the wide variability between children with Down syndrome. We should try to avoid preconceptions and bias and focus on assessing pain in children who do not express pain as we would expect. What do the studies in this thesis tell about pain processing in children with Down syndrome?

Nociception
Nociception seems to be intact in children with Down syndrome. Nociception is the neural process of encoding noxious stimuli and pain sensation is not necessarily implied. Applying the qualitative sensory tests most children with Down syndrome were able to distinguish a sharp and blunt stimulus; applying the quantitative sensory tests to assess the pain thresholds revealed that they are even more sensitive for pain. The studies in children with Down syndrome after congenital duodenal atresia repair and cardiac surgery showed that nociception seems to be intact, judging from the fact that the pain and distress ratings as well as analgesic or sedative requirements did not differ between children with and without Down syndrome.

From nociception to pain behaviour
The higher processing of the nociceptive stimuli - from nociception to experiencing and expressing pain – seems to be affected in children with Down syndrome. Children with Down syndrome had difficulties with localizing pain and with rating the intensity of pain; in other words, their ability for self-report of pain is rather limited. Furthermore, they used fewer pain coping strategies than children without Down syndrome. This is likely to have a big impact on the pain experience and pain expression of children with Down syndrome and will therefore explain the observations by their parents and John Langdon Down. Children with Down syndrome may express pain differently than caregivers expect. Adequate pain
expression – preferably using self-report – requires higher cognitive skills that probably are affected by an intellectual disability. Furthermore, it is likely that the pain expression will be less adequate if a child is anxious or distressed. Pain is known to be a subjective experience, but rating pain expression of others as adequate or not is perhaps even more subjective.

**Other methods of evaluating pain processing**

In this thesis we evaluated pain processing using qualitative and quantitative sensory tests, predominantly with the thermal sensory analyser. There are other potential relevant methods available that we did not apply, such as the cold pressor task, magnetic resonance imaging (MRI) and nerve conduction velocity measurement:

The cold pressor task asks the child to submerge their hand in cold water (with a constant temperature, for example 10 degrees Celsius) until it becomes painful (51). The thermal sensory analyser, on the other hand, is based on increasing the intensity of the stimulus. The limited feasibility of the thermal sensory analyser in children with Down syndrome was certainly an issue. It is worthwhile to study whether the cold pressor task would be more feasible.

Structural magnetic resonance imaging (MRI) of the brain in children and adults with Down syndrome showed smaller brain volumes; in particular the volume of the hippocampus and the amygdala (52, 53). Since these MRI scans give no information on the function of these brain areas, it is hard to determine how these findings contribute to our knowledge on pain processing in children with Down syndrome.

Brandt et al. showed that the nerve conduction velocities of sensory nerves of 6 children with Down syndrome were lower than in 10 children without Down syndrome (61). Although this finding could help explain the higher detection thresholds for cold and warmth in the children with Down syndrome, the contribution of this single study is limited. It would have to be replicated in a larger cohort – combined with evaluation of the nociceptive nerve fibres is therefore required.

**Children with Down syndrome: A starting point?**

The studies on the COMFORT-B scale and the morphine pharmacodynamics and pharmacokinetics were conducted in 0 to 3-year-old children with Down syndrome. Future studies should therefore include older children with Down syndrome as well. De Knegt and Scherder carefully reviewed studies on the pain experience of intellectually disabled adults: they concluded that white matter lesions in adults with vascular dementia could cause central pain and that adults with Down syndrome face early and progressive degeneration and are at high risk of developing Alzheimer’s dementia (54). The effect of progressive neurodegeneration should therefore be carefully taken into account when evaluating pain processing in adults with Down syndrome.

Moreover, Down syndrome is only one of the many causes of intellectual disability: the majority of children with Down syndrome is mildly intellectually disabled whereas other
groups might be more profoundly intellectually disabled and experience more problems, such as girls with Rett syndrome(55). Was it too straightforward to study children with Down syndrome? No, it was not: the high incidence of cardiac surgery and comorbidities justified studying children with Down syndrome. Let this thesis be a starting point for studies in children with autism and other groups of intellectually disabled children.

Future clinical studies on pain expression and the interaction between analgesics and co-medication are needed in intellectually disabled children and adults. Preclinical studies in rodents can help to study alterations in nociception and gene expression(56). Over the years, several mouse models have been developed for various causes of intellectual disability: for example the Ts65Dn mouse for Down syndrome(57) and a mouse model with the mutation in the MECP2 gene for Rett syndrome(58). Mouse models also have successfully been used for the study of pain behaviour and effects of repeated skin breaking procedures at the neonatal age(34). Pain behaviour can be observed in rodents using validated methods such as the hot plate test or tail flick test. Investigations that are not ethical in humans, for example as studying the distribution of the opioid receptor, are feasible in rodents(59).

Preclinical animal studies and clinical human studies have complementary roles and will help to improve pain assessment and management in intellectually disabled children and adults.
RECOMMENDATIONS FOR CLINICAL PAIN MANAGEMENT

1. Use valid observational pain and distress assessment tools in non-verbal children and in children who cannot provide adequate self-report of pain

2. Objective tools based on physiological parameters for pain or distress assessment are potentially good pharmacodynamic outcome measures, but validity for the use in infants and intellectually disabled children should be evaluated before routine use can be recommended

3. Doses of intraoperative and postoperative analgesics and sedatives do not need to be adjusted in children with Down syndrome

4. A multidisciplinary pain management and sedation protocol is a prerequisite for adequate pain management. Compliance with the protocol should regularly be evaluated

RECOMMENDATIONS FOR PEDIATRIC PAIN RESEARCH

1. Development of standardized international quantitative sensory testing (QST) guidelines and meta-analysis of the QST data

2. The pain expression of children with Down syndrome and other groups of intellectually disabled children should be systematically evaluated and thereafter be integrated with clinical pain assessment

3. Development and validation of a pain assessment tool based on physiological parameters that can also be used during general anesthesia and intensive care, especially in non-verbal and intellectually disabled children

4. The studies in Down syndrome should be the starting point for pain research in other groups of intellectually disabled children and adults
INDIVIDUAL PREDICTION OF PAIN AND ANALGESIA AND SEDATION REQUIREMENTS

The above recommendations give direction to clinical pain management and further pediatric pain research. In one of the studies in this thesis, morphine plasma concentrations were modelled using NONMEM software in order to estimate population pharmacokinetic parameters such as the volume of distribution and clearance. The ultimate goal is to predict – for an individual – the amount of pain after surgery and the analgesia or sedation requirements.

Potential predictors:
- Genetic make-up
- Age and developmental stage of the patient (both physiological processes as well as cognition)
- Presence of relevant comorbidities
- Pharmacokinetics and pharmacodynamics of the analgesic and sedative agents
- Use of comedication that could interact with other medications
- Preoperative detection and pain thresholds (quantitative sensory testing) and associated brain activations during fMRI
- Pain coping styles

Carefully developing as well as internal and external validation of those clinical prediction models is essential(60). The reliability of the predictions will have to be evaluated and ongoing research will keep improving the predictions.
At the start of this chapter, I introduced the four components of pain processing as identified by Loeser – nociception, pain, suffering and pain behaviour. This thesis addressed pain assessment and management in intellectually disabled children. Two studies focussed on neonates admitted to the intensive care unit – another group at risk for pain and in which self-report of pain is impossible. There even can be overlap between these two groups; neonates with post-hypoxic encephalopathy for example. These children suffer from a variable degree of intellectual disability and spasticity – also known as cerebral palsy. Table 3 shows a comparison of the components of pain that are affected in intellectually disabled children and neonates admitted to the intensive care unit.

**TABLE 3 Pain processing in intellectually disabled children and neonates admitted to the intensive care – according to the pain model by Loeser**

<table>
<thead>
<tr>
<th></th>
<th>Intellectually disabled children</th>
<th>Neonates admitted to intensive care</th>
</tr>
</thead>
</table>
| **Pain behaviour**   | - Expression is different from what caregivers expect  
                        - Require observational pain assessment by proxy  
                        - Only few pain coping strategies are used | Observational pain assessment by proxy |
| **Suffering**        | - More surgery  
                        - More comorbidities | Repeated skin breaking and stressful procedures |
| **Pain**             | Higher brain functions are damaged | At risk for short-term hyperalgesia as a neonate |
| **Analgesia:**       | - Possible interaction of co-medication (e.g. anticonvulsants)  
                        - Normal postoperative requirements | Continuous morphine infusion has no long-term adverse effects on pain processing |
| **Nociception**      | Intact | Intact |
Nociception is classified as intact in both groups, although it is difficult to evaluate solely “nociception” in humans. It is more feasible to study nociception in animal models, using invasive techniques such as microneurography. Furthermore, animal studies will enable to evaluate structural changes to the peripheral and central nervous system. Those studies could provide a more detailed view on the influence of Down syndrome and other causes of intellectual disability on nociception. For now there are no indications of altered nociception in intellectually disabled children and neonates, based on assessment of thermal detection and pain thresholds.

Pain in intellectually disabled children is primarily postoperative pain; as they get older their comorbidities can cause pain as well, such as orthopedic problems, gastroesophageal reflux disease, constipation, and infections of respiratory and urinary tract. Since many intellectually disabled children use medication, for example anticonvulsants, interaction with anesthetic, analgesic and sedative agents should be studied in these children in future studies.

Structural changes in the central nervous system can be explored using functional magnetic resonance imaging (fMRI), for example to study long-term effects of neonatal pain.

Intellectually disabled children will need surgery; preterm or critically ill neonates will need intensive care management with many skin breaking procedures. It is key to reduce suffering by applying both non-pharmacological and pharmacological interventions.

As pain behavior of intellectually disabled children and neonates is different from what caregivers would expect, more objective methods for the assessment of pain and distress are badly needed. This asks joint effort of medical professionals, researchers, the industry and even parents. More than a million people in the Netherlands – intellectually disabled children, children below the age of 4, and demented elderly – will benefit from improved objective methods to measure pain.

Building on this thesis, we may expect that reliable pain assessment and evidence-based pain management will become available to individuals who communicate pain “without uttering a word”.
REFERENCES

Chapter 13

SUMMARY
SAMENVATTING
SUMMARY

This thesis addressed several studies on pain assessment and management, as well as general anesthesia and sedation, in intellectually disabled children with a focus on children with Down syndrome.

PART I INTRODUCTION

Previous studies on pain assessment and treatment are discussed in Chapter 2. This review showed that observational pain assessment tools for intellectually disabled children have become available and that future research should focus on tailoring the pain treatment in these children. Chapter 3 presents the results of a survey on the perceptions and practices of Dutch anesthesiologists concerning pain management in intellectually disabled children. One third of the respondents perceived intellectually disabled children as more sensitive to pain, but this did not result in higher doses of analgesics for these children. Furthermore, they take a different approach when caring for intellectually disabled children and they were not aware of the existence of pain observation scales for these children.

PART II ASSESSMENT

The question was if instruments for pain and distress assessment, such as Bispectral Index (BIS)-monitoring, the COMFORT-B scale and skin conductance monitoring, are also valid in non-verbal infants and children. Anesthesiologists use the BIS monitor during general anesthesia to monitor the depth of anesthesia. Chapter 4 is a case report describing extremely low awake and perioperative BIS values in two intellectually disabled children. These observations prompted the study presented in Chapter 5, which indeed confirmed that BIS values measured in intellectually disabled children were significantly lower than those of controls. Therefore we advised anesthesiologists to be alert to the fact that BIS values in intellectually disabled children may be subnormal, resulting in a risk of misinterpreting these children’s state of consciousness.

The COMFORT-B scale is an observational pain and distress assessment instrument developed for the use in infants and young children after surgery or if they are admitted to the intensive care unit. Chapter 6 describes a study that found that the COMFORT-B scale is also valid for 0 to 3-year-old children with Down syndrome. This makes it even more useful in the pediatric intensive care unit setting.

The conductance of the skin increases if the sympathetic nervous system is activated, for example by pain or distress. This mechanism is reflected by peaks on the monitor. Previous studies found variable performance of skin conductance measurement as a pain assess-
ment tool, with low specificity and a low predictive value reported in some studies. The study in Chapter 7 showed that sympathetic neural activity to maintain homeostasis (such as autoregulation of skin temperature) also results in skin conductance peaks. Before advocating its use in daily practice, the technique should be better defined to increase both sensitivity and specificity for the measurement of pain.

PART III QUANTITATIVE SENSORY TESTING

Quantitative sensory testing systematically documents alterations and reorganization in nervous system function and, in particular, the nociceptive system. The question was if children with Down syndrome show reduced sensitivity to pain according to their parents and in experimental pain tests. The pain sensitivity of children and adults with Down syndrome has been widely debated but rarely studied. The study in Chapter 8 compared thermal detection and pain thresholds between children with Down syndrome and their siblings, using qualitative and quantitative methods, as well as parental questionnaires on pain coping, pain behaviour and chronic pain. The different sensory tests proved to be feasible in 33% to 88% of children in the Down syndrome group. Parents rated their children with Down syndrome as less sensitive to pain, but this was not confirmed by quantitative sensory testing. Children with Down syndrome will remain dependent of pain assessment by proxy, since self-report was not adequate.

The second study in this part addressed the question whether continuous morphine administration at neonatal age affects thermal detection and pain thresholds, chronic pain, or neurological functioning at 8-9 years of age.

A cohort of children who as neonates participated in a randomized controlled trial is being followed over time. The original study compared continuous morphine infusion with placebo in preterm and term neonates on ventilatory support. The authors concluded that routine continuous morphine infusions should not be recommended for neonates on ventilatory support. The study in Chapter 9 showed, however, that neonatal continuous morphine infusion (10 mcg/kg/hr) has no adverse effects on thermal detection and pain thresholds or overall neurological functioning eight to nine years later.

PART IV MANAGEMENT

Previous studies found that intellectually disabled children receive lower doses of analgesics during general anesthesia. On the other hand, children with Down syndrome are often described more agitated and “difficult to sedate” after surgery. The question was if the postoperative analgesia and sedation requirements of children with Down syndrome differ from other children. Chapter 10 is a retrospective study that compared the pain scores
and analgesia and sedation requirements of neonates with and without Down syndrome after surgical repair of a congenital duodenal obstruction. We did not observe any differences between the neonates with and without Down syndrome. This was then confirmed in a prospective evaluation, presented in Chapter 11. Approximately 40 to 60% of children with Down syndrome have a congenital heart defect and many therefore undergo major surgery and postoperative intensive care management at a young age. This study compared the pharmacodynamics, i.e. analgesia and sedation requirements and pain and distress assessments, as well as the morphine pharmacokinetics between children with and without Down syndrome. We found no reasons for different morphine dosing after cardiac surgery in children with Down syndrome compared to children without Down syndrome.

**PART V GENERAL DISCUSSION**

Chapter 12 discussed the studies presented in this thesis and made recommendations for clinical pain management and pediatric pain research.

It concludes with linking the results to the four components of pain processing as identified by Loeser – nociception, pain, suffering and pain behaviour.

There are no indications of altered nociception in intellectually disabled children and neonates, based on assessment of thermal detection and pain thresholds. Pain in intellectually disabled children is primarily postoperative pain. We found normal postoperative analgesia and sedation requirements in children with Down syndrome. Clinicians should be aware of potential interaction with co-medication (e.g. anticonvulsants). Higher brain functions associated with pain processing appear to be altered. Intellectually disabled children are more at risk to suffer, as they require more often surgery and have more comorbidities. As pain behavior of intellectually disabled children and neonates is different from what caregivers would expect, more objective methods for the assessment of pain and distress are badly needed. This asks joint effort of medical professionals, researchers, the industry and even parents. More than a million intellectually disabled children, children below the age of 4, and demented elderly in the Netherlands will benefit from improved objective methods to measure pain, as self-report may be unreliable or impossible.
SAMENVATTING

Dit proefschrift beschrijft verschillende studies op het gebied van het meten en behandelen van pijn bij verstandelijk gehandicapte kinderen – en dan met name kinderen met het syndroom van Down.

DEEL I - INTRODUCTIE

Hoofdstuk 2 geeft een overzicht van de literatuur op het gebied van het meten en behandelen van pijn. Hieruit blijkt dat er verschillende pijnmeetinstrumenten zijn ontwikkeld voor verstandelijk gehandicapte kinderen; de meest gebruikte observatieschalen worden in dit overzicht besproken. We mogen concluderen dat toekomstig onderzoek zich zou moeten richten op de juiste behandeling van pijn bij deze kinderen.

Hoofdstuk 3 gaat over de resultaten van een enquête onder anesthesiologen in Nederland. We vroegen hen onder andere naar hun percepties en beleid rondom het behandelen van pijn in verstandelijk gehandicapte kinderen. Een derde van de respondenten meende dat verstandelijk gehandicapte kinderen gevoeliger zijn voor pijn, maar vond dit geen reden om de dosering van pijnstillers aan te passen. Daarnaast passen de meeste anesthesiologen hun beleid aan op de verstandelijk gehandicapte kinderen, maar ze waren niet bekend met de verschillende pijnmeetinstrumenten voor deze groep kinderen.

DEEL II - METEN

We vroegen ons af of de verschillende instrumenten voor het meten van pijn en onrust, zoals de Bispectral index monitor, de COMFORT-gedragschaal en de skin conductance monitor, ook toepasbaar zijn bij non-verbale kinderen. Anesthesiologen kunnen de diepte van de anesthesie meten met de Bispectral index monitor. In hoofdstuk 4 bespreken we twee gevallen waarin bij een verstandelijk gehandicapte kind veel lagere BIS-waarden werden gemeten dan we verwachtten; zowel toen ze wakker waren als tijdens de algehele narcose. Deze bevindingen waren de aanleiding voor de studie beschreven in hoofdstuk 5. Deze studie bevestigde dat de BIS-waarden van verstandelijk gehandicapte kinderen lager waren dan die van niet verstandelijk gehandicapte kinderen. We adviseren daarom anesthesiologen er alert op te zijn dat de BIS-waarden van verstandelijk gehandicapte kinderen lager waren dan die van niet verstandelijk gehandicapte kinderen. We adviseren daarom anesthesiologen er alert op te zijn dat de BIS-waarden van verstandelijk gehandicapte kinderen afwijkend kunnen zijn en dat daarom de diepte van de anesthesie verkeerd kan worden geschat.

Verpleegkundigen gebruiken de COMFORT-gedragschaal om pijn en onrust te observeren bij jonge kinderen – na een operatie of als ze behandeld worden op een intensive care afdeling. In hoofdstuk 6 bespreken we een studie die liet zien dat de COMFORT-gedragschaal
ook te gebruiken is voor kinderen met het syndroom van Down. Deze schaal is daarmee nu nog breder toepasbaar op een intensive care afdeling.

De huidgeleiding verandert als het sympathisch zenuwstelsel wordt geactiveerd, bijvoorbeeld tijdens pijn of onrust. Deze veranderingen (pieken) zijn te meten met de skin conductance monitor. Eerdere studies lieten zien dat deze niet altijd even betrouwbaar is: in sommige studies waren de specificiteit en de voorspellende waarde voor het meten van pijn aan de lage kant. Het onderzoek beschreven in hoofdstuk 7 laat zien dat het in standhouden van een constant intern milieu (homeostase; bijvoorbeeld het regelen van de lichaamstemperatuur) ook terug te zien is in de huidgeleiding. De sensitiviteit en specificiteit voor het meten van pijn moet verbeteren voordat deze monitor van toegevoegde waarde is voor het meten van pijn en onrust in de dagelijkse praktijk.

**DEEL III - QUANTITATIVE SENSORY TESTING**

Quantitative sensory testing is het in kaart brengen van veranderingen in het zenuwstelsel – en dan vooral het deel dat pijnprikkels verwerkt – door bijvoorbeeld de waarnemings- en pijndrempels te meten. We vroegen ons af of deze waarnemings- en pijndrempels voor temperatuur anders zijn in kinderen met het syndroom van Down, en of ouders van kinderen met het syndroom van Down het idee hebben dat hun kinderen minder pijngevoelig zijn.

Er werd namelijk gedacht dat kinderen en volwassenen met het syndroom van Down minder pijngevoelig zijn; dit is nog maar zelden echt onderzocht. In hoofdstuk 8 worden de resultaten beschreven van een studie waarin we de waarnemings- en pijndrempels voor temperatuur van kinderen met het syndroom van Down vergeleken met die van een broer of zus. Daarnaast vroegen we hun ouders vragenlijsten in te vullen over hoe hun kind omgaat met pijn en of hun kind last had van chronische pijn. Het percentage van kinderen met het syndroom van Down dat de testen begreep varieerde van 33% tot 88% voor de verschillende testen. Veel ouders zagen hun kind met het syndroom van Down als minder pijngevoelig. Dit werd alleen niet bevestigd met afwijkende pijndrempels.

Omdat zelfrapportage door kinderen met het syndroom van Down vaak niet voldoende betrouwbaar is zullen zorgverleners pijn moeten schatten met bijvoorbeeld een pijnmeetinstrument.

In het tweede hoofdstuk van dit deel onderzochten we of toediening van morfine op de neonatale leeftijd effect heeft op de waarnemings- en pijndrempels, de incidentie van chronische pijn en het neurologisch functioneren op 8 tot 9 jarige leeftijd. We volgden daarom een groep kinderen die als pasgeborene deelnamen aan een gerandomiseerde gecontroleerde studie. Deze studie vergeleek een infuus met morfine met een infuus met placebo in De helft van een groep pretermo en à terme geboren kinderen die beademing nodig hadden kreeg een continu infuus met morfine, de andere helft een infuus met placebo en alleen
morfine als pijn werd gemeten door de verpleegkundigen. Deze studie vond dat een continu morfine infuus niet geadviseerd is voor neonaten die alleen beademd moeten worden. De studie in hoofdstuk 9 laat zien dat dit continu morfine infuus (10 mcg/kg/hr) geen nadelige gevolgen heeft op de waarnemings- en pijndrempels of het neurologisch functioneren 8 of 9 jaar later.

DEEL IV – PIJNBEHANDELING

Voorgaande studies lieten zien dat kinderen met een verstandelijke handicap lagere doseringen van pijnstillers kregen tijdens algehele narcose. Daarentegen worden kinderen met Down syndroom vaak gezien als onrustiger na een operatie en zouden ze hogere doseringen slaapmedicatie nodig hebben. De vraag is daarom of kinderen met Down syndroom andere doseringen pijnstillers en slaapmedicatie nodig hebben na een operatie, vergeleken met kinderen zonder het syndroom van Down.

Hoofdstuk 10 beschrijft een retrospectief onderzoek naar pijn scores en doseringen van pijnstillers en slaapmedicatie bij kinderen met en zonder Down syndroom na een operatie voor een aangeboren obstructie van de dunne darm. Deze studie liet geen verschillen zien tussen kinderen met en zonder Down syndroom. Dit werd bevestigd in de prospectieve studie beschreven in hoofdstuk 11. Ongeveer de helft van de kinderen met het syndroom van Down heeft ook een aangeboren hartafwijking, en velen ondergaan daarom al op jonge leeftijd een ingrijpende operatie met daarna behandeling op een intensive care afdeling. In deze studie vergeleken we de farmacodynamiek – de doseringen van pijnstillers en slaapmedicatie en de pijn/onrust scores – alsmede de farmacokinetiek van morfine (de processen waaraan morfine in het lichaam wordt onderworpen, tussen kinderen met en zonder het syndroom van Down. We concludeerden dat de doseringen van morfine niet te hoeven worden aangepast in kinderen met Down syndroom na een open hartoperatie.

DEEL V – DISCUSSIE

Hoofdstuk 12 is een reflectie op de verschillende studies in dit proefschrift; daarnaast geeft ik aanbevelingen voor de behandeling van pijn en voor toekomstige studies op het gebied van pijn bij kinderen.

Ik sluit af met het bespreken van de resultaten aan de hand van het pijn model van Loeser. Dit model kent vier componenten: nociceptie, pijngewaarwording, pijnbeleving en pijngedrag.

We hebben geen aanwijzingen gevonden dat de nociceptie van verstandelijk gehandicapte kinderen afwikkend is – gebaseerd op de gevonden waarnemings- en pijndrempels voor temperatuur.
De voornaamste oorzaak van pijn in verstandelijk gehandicapte kinderen is postoperatieve pijn. De doseringen van pijnstillers en slaapmedicatie waren hetzelfde voor kinderen met en zonder Down syndroom. Zorgverleners moeten alleen wel bedacht zijn op mogelijke interactie tussen deze medicijnen en de medicijnen die verstandelijk gehandicapte kinderen vaak gebruiken, zoals anti-epileptica. Hogere hersenfuncties die pijnherinneringen verwerken (bijvoorbeeld het interpreteren van pijn) lijken te zijn aangedaan in verstandelijk gehandicapte kinderen.

Verstandelijk gehandicapte kinderen zullen vaker pijn ervaren. Ze ondergaan namelijk vaker operaties en hebben meer aandoeningen zoals infecties of gewrichtsklachten. Het pijngedrag van verstandelijk gehandicapte kinderen is anders dan sommige zorgverleners verwachten. Daarom zijn objectievere maten voor het meten van pijn en onrust hard nodig. Dit vraagt een gezamenlijke aanpak van zorgverleners, onderzoekers, de industrie en ook de ouders. In totaal zijn er in Nederland meer dan een miljoen verstandelijk gehandicapte kinderen, kinderen onder de leeftijd van 4, en dementerende ouderen. Zij zullen veel baat hebben bij verbeterde instrumenten voor het meten van pijn anders dan door zelfrapportage.
APPENDICES

REFERENCES FOR THE POEMS
DEFINITIONS
ACKNOWLEDGEMENTS
CURRICULUM VITAE
PHD PORTFOLIO
REFERENCES FOR THE POEMS

William Butler Yeats  
Yeats (1865 – 1939) was born in Dublin, Ireland. He was a poet, playwright and senator. Yeats was influenced by symbolism and Irish legends. His early work is seen as romantic; in the 20th century his work became more influenced by politics. In 1923 he was awarded the Nobel Prize in Literature.

Chapter 2: Cuchulain’s Fight with the Sea  
Chapter 3: I walked among the seven woods of Coole  
Chapter 4: The Statues  
Chapter 5: Fergus and the Druid  
Chapter 6: A woman’s beauty is like a white  
Chapter 7: The Tower


Rutger Kopland  
Kopland (1934 – 2012) was born in Goor, the Netherlands. He was a poet and professor of psychiatry. His style is described as quiet, conversational and nostalgic. Kopland’s poems are reassuring and demonstrate the ‘mechanics of emotion’. He was awarded the P.C. Hooft Prize in 1988.

Chapter 8: Enkele andere overwegingen  
Chapter 9: Tijd  
Chapter 10: Mijn minnaar en ik  
Chapter 11: Enkele andere overwegingen  
Chapter 12: Drie wintergedichten

DEFINITIONS

Intellectual disability
A disability characterized by significant limitations both in intellectual functioning and in adaptive behaviour, which covers many everyday social and practical skills. This disability originates before the age of 18. *American Association on Intellectual and Developmental Disabilities*

Pain
An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. *International Association for the Study of Pain*

Nociception
The neural process of encoding noxious stimuli. *International Association for the Study of Pain*

Quantitative Sensory Testing
Determination of thresholds or stimulus response curves for sensory processing under normal and pathophysiological conditions. Group of psychophysical methods that systematically document alterations and reorganization in nervous system function and, in particular, the nociceptive system. Arendt-Nielsen L, Yarnitsky D. The Journal of Pain 2009; 10: 556-572

Method of limits
Scheme for sensory threshold determination. A subject is required to indicate as soon as an increasingly strong stimulus is detected. A reaction time inclusive technique. Shy ME et al. Neurology 2003; 60: 898 - 904

Method of levels
Scheme for sensory threshold determination. Stimuli of defined intensity levels are tested with the subject signalling whether a specific level is detected. Technique is independent of subject’s reaction time. Shy ME et al. Neurology 2003; 60: 898 - 904

Pharmacokinetics

Pharmacodynamics
ACKNOWLEDGEMENTS

First of all, I would like to thank all the children and their parents who participated in the studies described in this thesis. Without you there would have been no clinical research! Allereerst zou ik alle kinderen en hun ouders willen bedanken voor hun deelnamen aan de studies beschreven in dit proefschrift. Zonder jullie geen klinisch onderzoek!

Prof. Tibboel: Ik wil u bedanken voor de geboden mogelijkheden om aan zoveel interessante onderzoeken te werken, voor uw haast onuitputtelijke kennis en uw geduld om mensen te blijven motiveren en superviseren.

Monique: jij maakt echt het verschil in begeleiding! De tijd, kennis & liefde die jij daarin stopt! Heel veel dank daarvoor!

Prof. Huygen, Prof. Stolker en Prof. Scherder bedank ik voor het beoordelen van het manuscript.

Prof. Mathôt, Dr. Holstege en Dr. Weijerman bedank ik voor het plaats nemen in de commissie.

Ko Hagoort: Dank voor je kritisch oog en je eindeloze bereidheid om alles te lezen.

Annemarie Illsley: Bedankt voor alle hulp en je lekker nuchtere kijk op dingen.

Heleen Blussé: Een beetje de aanstichter van dit proefschrift! Thanks Heleen!

Tom de Leeuw, Frank Weber en Andreas Machotta, en alle anderen van OK-Sophia wil ik bedanken voor hun bijdrage aan de BIS studies en de enquête.

Sjoerd Niehof, Anne van der Eijk, Esther Verhaar, en de verpleegkundigen van de high-care kinderchirurgie wil ik bedanken voor de hulp bij de skin conductance studie.

Ingeborg en Wouter Griffioen, Iris Hobo, Céline Joosten, en alle anderen bij Panton; Martin Slooff, Regina Lamberts, Erik de Graaf, Gert de Graaf en alle anderen bij Stichting Downsyndroom; Nanda de Knecht en Prof. Scherder van de Vrije Universiteit Amsterdam; Arjan van der Plas van de Medische Instrumentatie Techniek; Annelies de Klein van de Klinische Genetica, wil ik bedanken voor alle hulp bij de Ken Hun Pijn studie!

Liesbeth Groot Jebbink en Richard van Lingen van de afdeling Neonatologie, Isala Klinieken Zwolle; Nienke Weisglas-Kuperus, Joke de Graaf, Marlous Madderom, Gerbrich
van den Bosch, Sylvia van der Kreeft wil ik bedanken voor de hulp bij de follow-up studie.

I would like to thank all the medical, nursing and bioengineering staff of Our Lady’s Children’s Hospital, Crumlin who provided support for the Pk/Pd study. In particular Cormac Breatnach, Brendan O’Hare, Billy Casey, Martina Healy, Professor Redmond, Mr. Nolke, Mr. McGuinness, Tracey Wall, Claire Magner, Erika Brereton, Ian Dawkins, the anaesthetists and registrars, OT 1 staff, cardiac nurses, PICU 1 and 2 staff and NCRC staff.

Verder wil ik Prof. Mathôt en de medewerkers van de apotheek van het AMC bedanken voor het bepalen van de morfine spiegels, en Elke Krekels en Prof. Knibbe voor de super snelle NONMEM modelling.

Hugo Duivenvoorden: Bedankt voor alle weloverwogen statistische adviezen.

Saskia de Wildt, Joke Dunk, en alle andere stafleden, (research) verpleegkundigen en collega’s van de afdelingen Kinderchirurgie en Intensive Care Kinderen van het Erasmus MC - Sophia.


Sophie van der Mark en Marie-Chantal Struijs wil ik bedanken dat ze als paranimfen naast me staan. Sophie, van college tot Kopenhagen; hoe vaak wij koffie, thee of een drankje (met de eventuele sultana) hebben gedaan. Thanks :-)! MC, thanks voor het kibbelen, alle scherpe en slechte grappen, maar vooral je super toffe support.

Vanaf dag 1 van geneeskunde: studiegroep 8: Jeff, Marjolein, Nina, Sigrid, Sophie

The Morning After: Jullie zijn geweldig! Bob, Feline, Florence, Gert, Job, Lindsay, Philip, Remco, Renee, Simone, Sophie

Ludo, Yie Roei, Markus, Thomas, Judith, Lotte, Suzan, Mirjam, Anne, Tom

Oma, Opa, Christine, Sandra, Bas, en alle andere familie

Mijn twee broers: Jan-Paul en Jaap

Pap en mam, jullie zijn er gewoon. Wat ik ook doe en waar ik ook ben...
CURRICULUM VITAE

Bram Valkenburg was born on the 13th of September 1987 in Zwolle, the Netherlands. In 2005 he completed secondary school at the Carolus Clusius College, Zwolle. That same year, he started his medical training at the Erasmus MC - University Medical Center Rotterdam. From 2006 onwards, he combined medical training with research projects at the departments of Anesthesiology and Pediatric Surgery, Erasmus MC - Sophia Children’s Hospital. These projects resulted in a case-report and an article on Bispectral index monitoring, presented in Chapter 4 and 5 of this thesis respectively. He took a research elective at the Children’s National Medical Center, Washington DC, USA, in 2008. In May 2009 he passed his doctoraal examen (master’s degree).

In April 2009 he commenced his Ph.D. studying pain assessment and management in intellectually disabled children at the department of Pediatric Surgery, Erasmus MC - Sophia Children’s Hospital, under the supervision of Prof.dr. D. Tibboel and Dr. M. van Dijk. In 2010 he became trainee member of Pain in Child Health (PICH) – a strategic research training initiative of the Canadian Institutes of Health Research. He was awarded with the EFIC-Grüenthal Grant for young scientists in 2011. In the final year of his Ph.D. training he carried out a research project at the department of Paediatric Anaesthesia and Intensive Care Medicine, Our Lady’s Children’s Hospital, Dublin, Ireland (Supervisors Dr. C. Breatnach and Dr. B. O’Hare).

In February 2013 Bram will commence his internships at the Erasmus MC - University Medical Center Rotterdam.
PHD PORTFOLIO
SUMMARY OF PHD TRAINING AND TEACHING

Name PhD student: A.J. Valkenburg
Erasmus MC Department: Pediatric Surgery
Research School: PhD period: 2009 - 2012
Promotor(s): Prof.dr. D. Tibboel
Supervisor: Dr. M. van Dijk

1. PHD TRAINING

<table>
<thead>
<tr>
<th>GENERAL COURSES</th>
<th>YEAR</th>
<th>WORKLOAD (ECTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- BRÖK (‘Basiscursus Regelgeving Klinisch Onderzoek’)</td>
<td>2009</td>
<td>1</td>
</tr>
<tr>
<td>Erasmus University</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Grant Writing Course Dutch Pediatric Society</td>
<td>2009</td>
<td>1</td>
</tr>
<tr>
<td>- English Course (level Advanced 1) Erasmus University</td>
<td>2010</td>
<td>2</td>
</tr>
<tr>
<td>- Good Clinical Practice Course for Paediatrics Dublin, Ireland</td>
<td>2012</td>
<td>0.25</td>
</tr>
</tbody>
</table>

SPECIFIC COURSES

- SNPs and human disease MolMed, Erasmus MC | 2010 | 1 |

SEMINARS AND WORKSHOPS

- Pain in Child Health (PICH) webconferences (monthly) | 2010 – 2012 | 0.5 |
- 13th PICH institute “The Future of Research for Pain in Children” | 2011 | 0.5 |
| White Point, Canada | | |
- Various anesthesiology, intensive care and pain medicine evening symposia | 2009 – 2012 | 1 |

PRESENTATIONS

- Oral presentation at the 2nd Research and Audit Day Our Lady’s Children’s Hospital Dublin, Ireland | 2012 | 1 |
- Oral presentation at the Irish Congenital Cardiac Association Meeting, Maynooth, Ireland | 2012 | 1 |
### INTERNATIONAL Conferences

<table>
<thead>
<tr>
<th>Event</th>
<th>Year</th>
<th>Workload (ECTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6th Congress of the European Federation of IASP Chapters “Pain in Europe VI” Lisbon, Portugal</td>
<td>2009</td>
<td>1</td>
</tr>
<tr>
<td>8th International Symposium on Pediatric Pain (Poster presentation) Acapulco, Mexico</td>
<td>2010</td>
<td>1</td>
</tr>
<tr>
<td>7th Congress of the European Federation of IASP Chapters “Pain in Europe VII” (Poster Presentation) Hamburg, Germany</td>
<td>2011</td>
<td>1</td>
</tr>
<tr>
<td>International Forum on Pediatric Pain “New Concepts in Complex and Recurrent Pain” (Poster presentation) White Point, Canada</td>
<td>2011</td>
<td>1</td>
</tr>
<tr>
<td>Annual Scientific Meeting of the Intensive Care Society of Ireland (Poster presentation) Dublin, Ireland</td>
<td>2012</td>
<td>0.5</td>
</tr>
<tr>
<td>Paediatric Intensive Care Society Annual Scientific Meeting (Poster presentation) Dublin, Ireland</td>
<td>2012</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### Other

<table>
<thead>
<tr>
<th>Event</th>
<th>Year</th>
<th>Workload (ECTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology research meetings (weekly) (Oral presentations) Erasmus MC – Sophia</td>
<td>2009 – 2011</td>
<td>2</td>
</tr>
<tr>
<td>Pain Committee meetings (monthly) (Oral presentations) Erasmus MC – Sophia</td>
<td>2010 – 2011</td>
<td>1</td>
</tr>
<tr>
<td>Pain / Sedation / Research meetings (monthly) (Oral Presentations) Our Lady’s Children’s Hospital, Dublin, Ireland</td>
<td>2012</td>
<td>1</td>
</tr>
</tbody>
</table>

### 2. Teaching

### Supervising Master’s Theses

- Co-supervision of E. Verhaar 2009 1
- Co-supervision of S. van der Kreeft 2010 1
- Co-supervision of E. Janssen 2011 0.5
- Co-supervision of N. Verweij 2011 0.5

ECTS = European Credit Transfer and Accumulation System
1 ECTS credit represents 28 hours