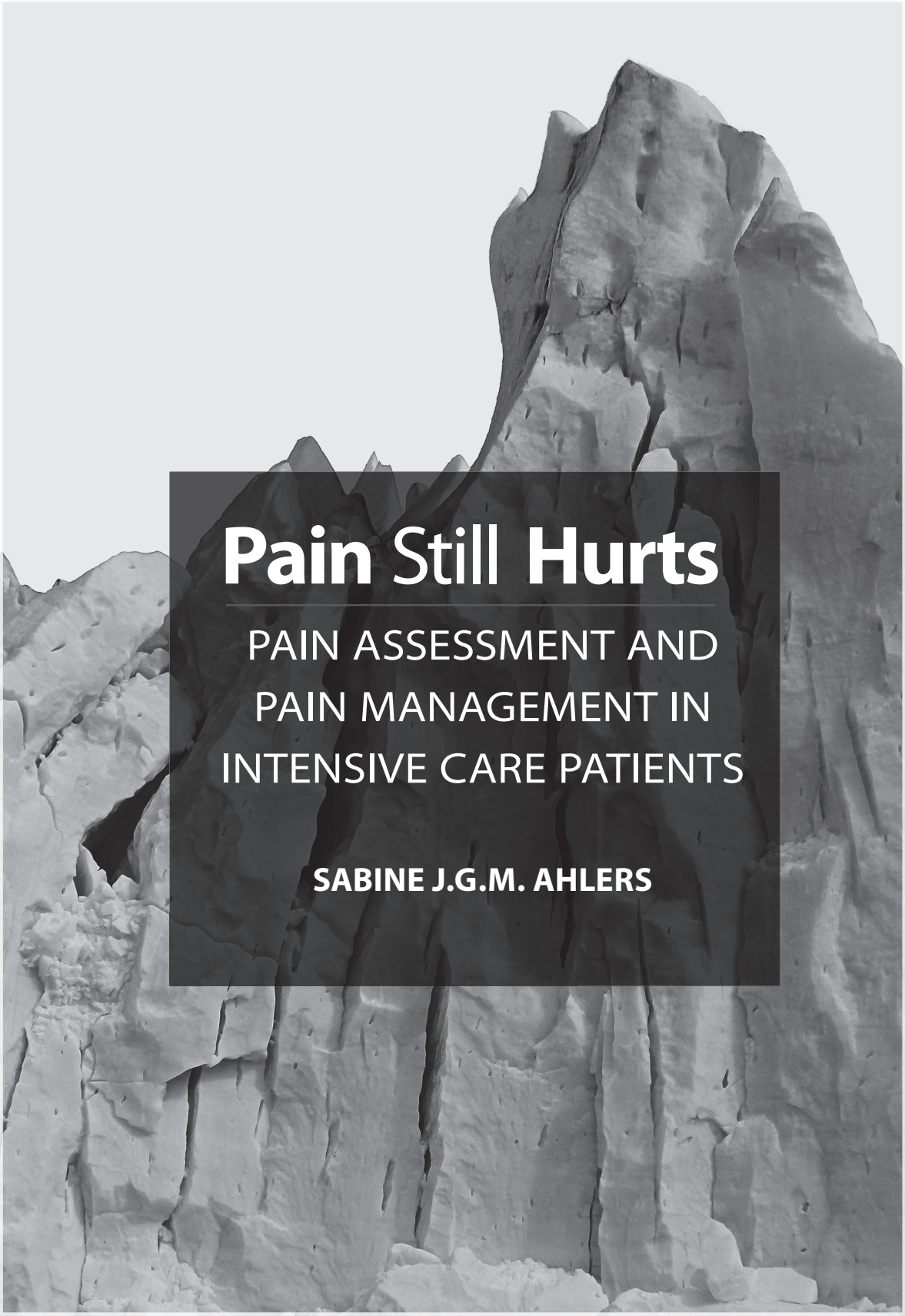

Pain Still Hurts

PAIN ASSESSMENT AND PAIN MANAGEMENT IN INTENSIVE CARE PATIENTS

SABINE J.G.M. AHLERS

De foto op de cover illustreert de pijn die intensive care patiënten kunnen ervaren in rust door onderliggende ziekte of operatie, met daar bovenop de piekpijnen die kunnen ontstaan bij pijnlijke interventies. Deze piekpijnen zijn nooit identiek: iedere patiënt zal zijn of haar pijn anders ervaren, met een verschillende duur en intensiteit. De zon die het ijs verwarmt symboliseert de pijnbehandeling: indien deze effectief is, zal een deel van de pijn verdwijnen.

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Pain Still Hurts

Pain assessment and pain management
in intensive care patients

De pijn doet nog zeer

Pijnmeting en pijnbehandeling
in intensive care patiënten

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.

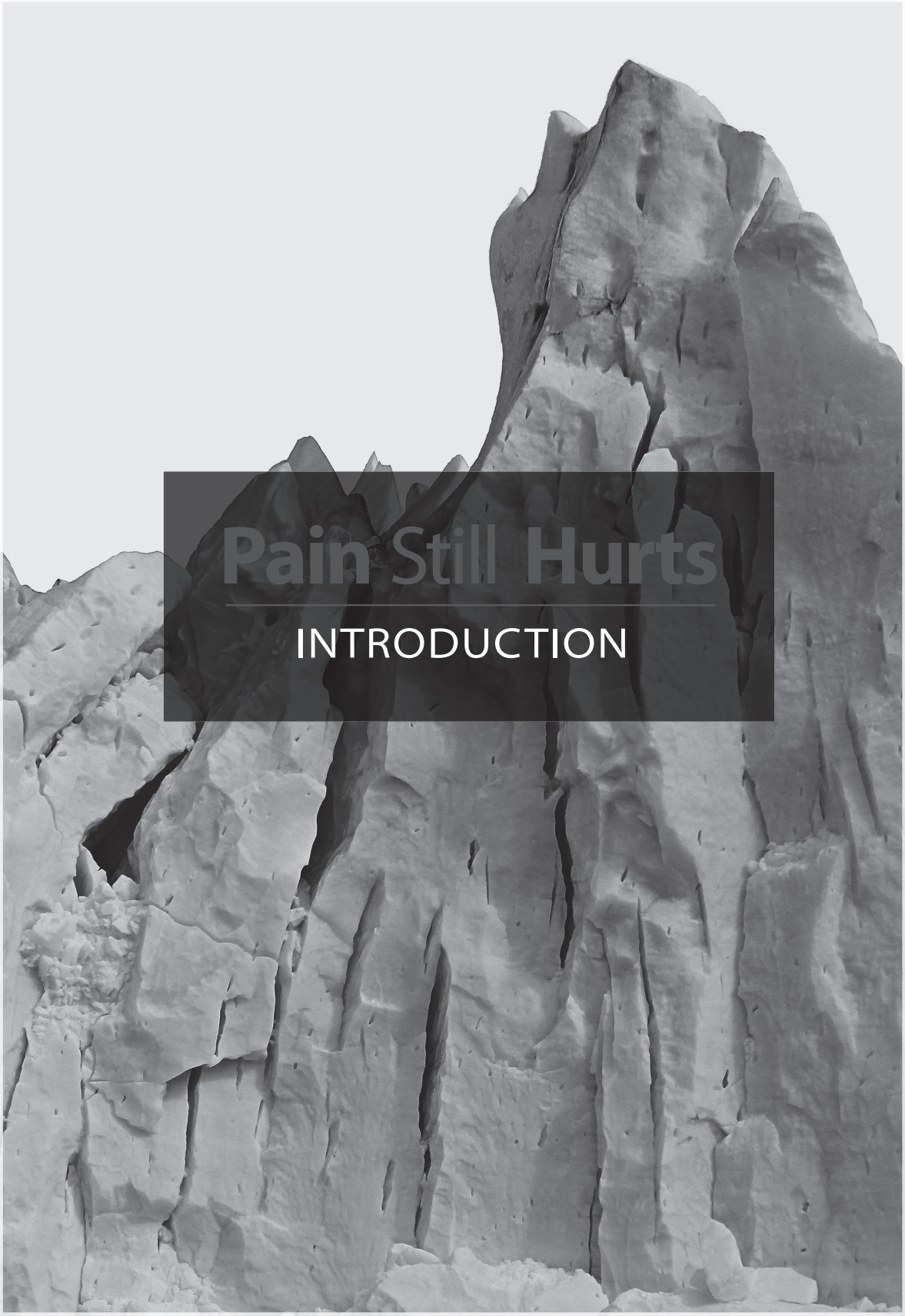
De openbare verdediging zal plaatsvinden op
vrijdag 8 juni 2012 om 11.30 uur

Sabine Josefina Geraldine Maria Ahlers
geboren te Sittard

PROMOTIECOMMISSIE

Promotoren:	Prof.dr. D. Tibboel
	Prof.dr. C.A.J. Knibbe
Overige leden:	Prof.dr. A.H.J. Danser
	Prof.dr. R.J. Stolker
	Prof.dr. L.P.H.J. Aarts
Copromotor:	Dr. E.P.A. van Dongen

CONTENTS



Pain Still Hurts

INTRODUCTION

Chapter 1

PAIN ASSESSMENT AND PAIN MANAGEMENT IN INTENSIVE CARE PATIENTS

INTRODUCTION

Intensive care patients are subject to many factors that may influence the patients' state of comfort or distress. Pain is the main cause of distress experienced by many adult intensive care patients [1], which can be caused by different factors like underlying disease, prolonged immobility and standard routine nurse care such as mobilization or chest drain removal [2]. In previous studies, 45-83% of conscious intensive care patients rated their pain intensity as moderate to severe, at rest as well as during procedures [3-5]. Also most sedated mechanically ventilated patients experience some degree of pain even in the absence of surgical incisions or trauma [6-7]. Researchers have recognized that pain and inadequate pain relief are major causes of physiological adversity and emotional stress [2,8-9], disorientation and sleep deprivation [2]. As a result, adequate use of analgesics may decrease morbidity and mortality [10] and improve the quality of life in intensive care patients [3].

PAIN ASSESSMENT IN INTENSIVE CARE PATIENTS

In order to manage pain adequately, effective methods for the recognition, evaluating and monitoring of pain are essential. Although regular assessment and documentation of pain and response to therapy is recommended by the Society of Critical Care Medicine (SCCM) [2] and the Netherlands Society of Intensive Care (NVIC) [11], a previous study revealed that the observed rates of assessment during procedural pain in mechanically ventilated patients remain below 40% [12]. Besides, 35% to 55% of the nurses have been reported to underrate patients' pain [1,13]. Additionally, pain assessment in intensive care patients may be complicated by mechanical ventilation and decreased consciousness as a result of the severity of illness and the use of sedatives in these patients, particularly when high doses of sedatives are administered [3-4]. Every patient in the intensive care unit will pass different phases of consciousness from deep sedation in the first stage of the disease or after surgery to a fully conscious and communicative patient. Apart from conscious patients and deeply sedated patients, a third group can be identified, i.e. conscious sedated (mechanically ventilated) patients. Current intensive care unit practice strives to restrict sedation to a conscious level whenever possible, in agreement with the landmark report [14] that showed that ventilated patients benefit from daily interruption of sedative infusions. The suitability of the pain assessment instrument depends on the psychometric characteristics of the available pain scales, the sedation state of the patient and the ability for abstraction and comprehension of the patient at the moment of pain assessment.

In conscious patients, self-report is still the 'gold standard' for pain assessment according to the guidelines of the International Association for the Study of Pain [2]. So far, the numeric rating scale (NRS; range 1 to 10) and the visual analogue scale (VAS; range 1 to 100) have

been validated for acute pain only. Both scales are not validated in mechanically ventilated patients in the intensive care unit [15]. However, in sedated patients, the self-report of the patient is usually not available [16-17]. For these patients, several observational pain scales are available. The behavioral pain scale (BPS; range 3-12) for example, was developed specifically for measuring the severity of pain in sedated, mechanically ventilated, unresponsive patients [18], and consisted of three pain related behaviours; facial expression, upper limbs movements and compliance of mechanical ventilation. In conscious sedated mechanically ventilated patients, self-reporting using the NRS or VRS-4 (range 1-4) may be complicated or unreliable in these patients due to their temporarily limited capacities of abstraction and concentration, and lack of comprehension [1-2]. From this point of view, it is of interest which health care worker (nurse, physician or consultant) should score pain in case the patient cannot communicate verbally. While the attending nurse is involved in daily care of the patient, the physician seems to have a more distant relation to the patient. Until now, the most appropriate health care worker, who should score pain in case the patient is not able to report pain is not known. Furthermore, it is unknown which pain assessment instrument is most adequate in intensive care patients.

PAIN MANAGEMENT FOR INTENSIVE CARE PATIENTS AFTER CARDIAC SURGERY

When pain is measured with appropriate pain scales, this will result in the ability to manage pain adequately. Despite the high incidence of pain, physicians may be uncomfortable treating pain using opioids, because of impaired mental status and altered pharmacokinetics and pharmacodynamics of analgesics as result of organ system dysfunction in intensive care patients [3]. Additionally, opioid analgesia is commonly associated with adverse effects, including hypotension and respiratory depression, and worse outcomes as increased mechanically ventilator days and depressed neurological status [19]. Puntillo et al. [4] confirmed this observation in an observational study, in which 64% of the patients did not even receive analgesics before or during a painful procedure, such as wound care or drain removal. However, preventing pain is more effective than treating established pain. When patients receive drugs on an 'as needed' basis, they may receive less than the prescribed dose and encounter significant delays in treatment [2]. Thus, analgesics should be administered on a continuous or scheduled basis, with supplemental bolus doses as required. On the other hand, higher doses of continuous infusions of analgesics may result in more side effects as respiratory depression, constipation or nausea. Therefore, a pain management plan and therapy goal should be established for each patient and re-evaluated as the clinical condition changes [2]. While to date, the implementation of protocols improves with a more patient-orientated regime for analgesia and sedation, a trend is observed away from a hypnosis-based approach

towards an analgesia-based approach. Although these changes may improve pain and sedation practice, further efforts are needed for widespread implementation of pain scoring systems and analgesia protocols [20-21].

MORPHINE AND PARACETAMOL ANALGESIA IN INTENSIVE CARE PATIENTS

Both the SCCM [2] and the NVIC guidelines [11] recommend the use of morphine or fentanyl as intravenous opioid analgesics for postoperative pain relief [2]. Overall, opioids have minimal haemodynamic effects in euvolemic patients [22]. Besides, morphine may provide cardioprotection and anti-inflammatory response in contrast to fentanyl in patients after cardiac surgery [23-25], and is therefore one of the most commonly used drug in pain management [26].

Morphine is metabolised via glucuronidation by phase II metabolism enzyme UDP-glucuronosyl transferase-2B7 (UGT2B7). Regardless of the mode of administration, approximately 44–55% of a morphine dose is converted to M3G, which is the main metabolite, and is suggested to have antagonistic or hyperalgesic effects [27-28]. The metabolite morphine-6-glucuronide (M6G), is formed in 9-10% of the morphine dose, and may have analgesic activity [29]. The morphine dose required to produce analgesia for pain relief is characterized by a large inter-individual variability. This variability may partly be explained by environmental factors, as age, gender or anxiety [30-32]. Some genetic polymorphisms have also been described and may partly explain the variability of morphine's analgesic effects [33-34], although its clinical relevance is unknown.

Especially intensive care patients, who may suffer from a variety of diseases, which can range from patients undergoing elective (cardiothoracic) surgery to patients suffering from sepsis with multi-organ failure and circulation failure, the pharmacokinetic and pharmacodynamic parameters of analgesics may be altered in these patients. Additionally, the use of sedatives in these patients may influence the effect of the analgesics. Eventually, this results in a complex treatment of each individual intensive care patient [16-17].

OBJECTIVE OF THE THESIS

The overall goal was to improve pain management in patients after cardiac surgery and critically ill patients in the intensive care unit.

Therefore, the first main objective is to study the most optimal method for measuring pain in intensive care patients.

The second aim was to improve pain management at rest and during routine care procedures in patients after cardiac surgery in the intensive care unit.

At last, we studied the pharmacokinetics of morphine and metabolites in intensive care patients and the safety of paracetamol in intensive care patients after cardiac surgery.

OUTLINE OF THE THESIS

Pain assessment in intensive care patients

Improvement of effective pain management can only be achieved with accurate pain assessment. In **Chapter 2** we evaluated three pain rating scales for pain at rest, e.g. the numeric rating scale (NRS), the behavioral pain scale (BPS) and visual analogue scale (VAS) in (non-) ventilated intensive care patients, who were conscious or sedated. In **Chapter 3**, the behavioral pain scale (BPS) and the verbal rating scale (VRS-4) were compared for pain assessment at rest in conscious sedated patients.

Pain management for intensive care patients after cardiac surgery

In order to reduce the incidence for pain at rest, in **Chapter 4** the impact of the implementation of a pain management programme, which consisted of systematic pain assessment by trained personnel, was evaluated in intensive care patients for postoperative pain at rest after cardiac surgery. In order to improve pain management during unavoidable routine care procedures, in **Chapter 5** we evaluated the efficacy of two doses of a bolus morphine in intensive care patients who already receive continuous pain relief using morphine infusions and intermittent paracetamol according to a pain titration protocol. **Chapter 6** investigated the influence *COMT* Val158Met polymorphism on pain sensitivity in morphine-treated patients undergoing an unavoidable painful routine healthcare procedure after cardiac surgery. In a follow-up study in these patients, the development of chronic pain after sternotomy was evaluated in **Chapter 7**.

Morphine and paracetamol analgesia in intensive care patients

Morphine was studied in the population of postoperative cardiac patients and critically ill patients, who are characterized by high variability in dosing requirements between and within patients. In **Chapter 8** morphine glucuronidation and elimination clearances in intensive care patients receiving continuous morphine infusions were studied, and compared to healthy volunteers. Finally, **Chapter 9** describes the safety of short-term use of paracetamol four grams daily in postoperative cardiac patients.

Conclusions and perspectives

The results of the investigations described in this thesis are reviewed and discussed in **Chapter 10.** Additionally, the implications for clinical practice and recommendations for future research are provided.

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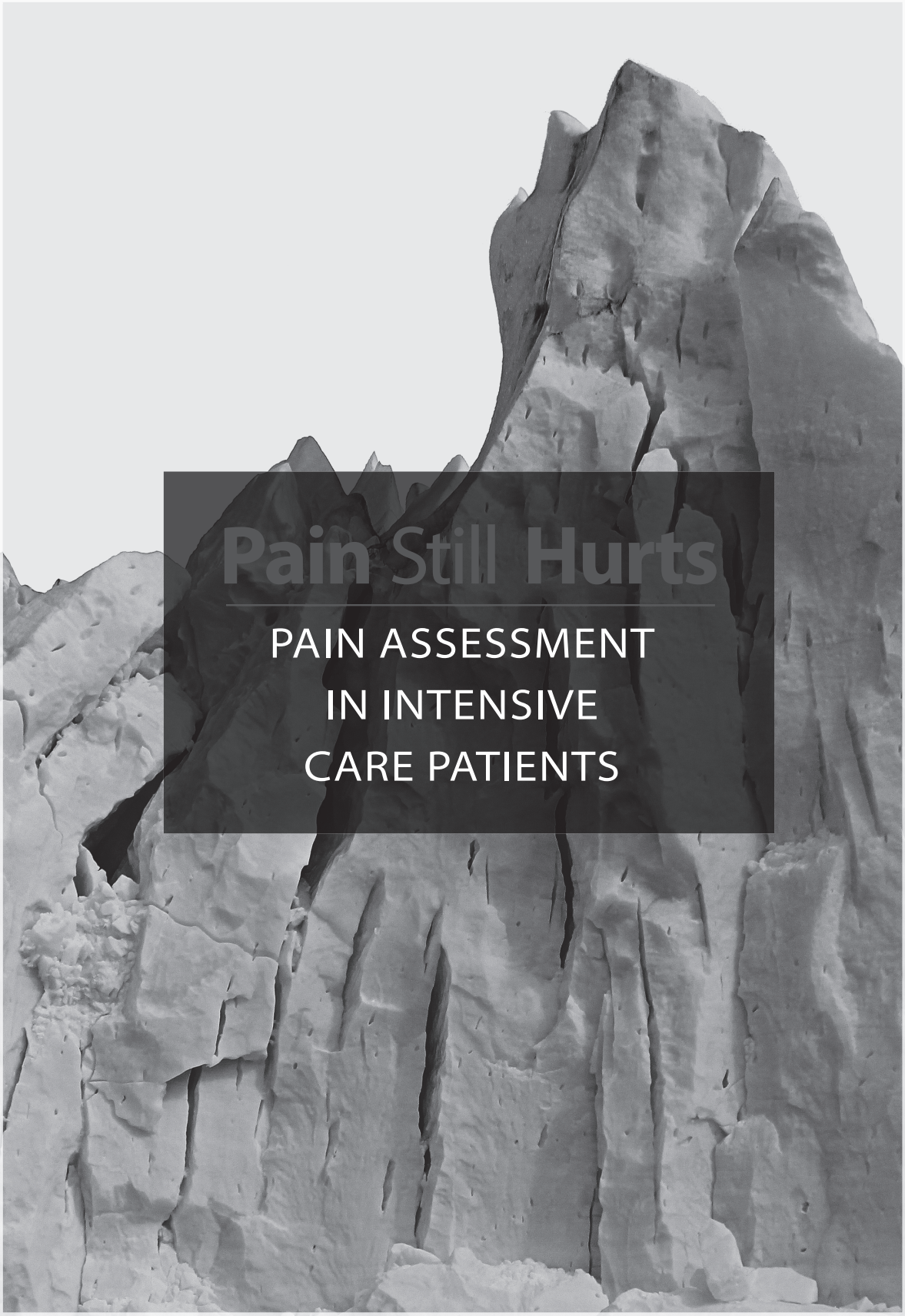

Pain Still Hurts

PAIN ASSESSMENT IN INTENSIVE CARE PATIENTS

Chapter **2**

COMPARISON OF DIFFERENT PAIN SCORING SYSTEMS IN CRITICALLY ILL PATIENTS IN A GENERAL ICU

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Critical Care. 2008;12(1):R15

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ABSTRACT

Background and objectives Pain in critically ill patients in the intensive care unit (ICU) is common. However, pain assessment in critically ill patients is often complicated because these patients are unable to communicate effectively. Therefore, we designed a study (a) to determine the inter-rater reliability of the numeric rating scale (NRS) and the behavioral pain scale (BPS), (b) to compare pain scores of different observers and the patient, and (c) to compare NRS, BPS, and the visual analogue scale (VAS) for measuring pain in patients in the ICU.

Methods We performed a prospective observational study in 113 non-paralyzed critically ill patients. The attending nurses, two researchers, and the patient (when possible) obtained 371 independent observation series of NRS, BPS, and VAS. Data analyses were performed on the sample size of patients (n=113).

Results Inter-rater reliability of the NRS and BPS proved to be adequate (kappa = 0.71 and 0.67, respectively). The level of agreement within one scale point between NRS rated by the patient and NRS scored by attending nurses was 73%. However, high patient scores (NRS ≥4) were underestimated by nurses (patients 33% *vs.* nurses 18%). In responsive patients, a high correlation between NRS and VAS was found (r_s = 0.84, P<0.001). In ventilated patients, a moderate positive correlation was found between the NRS and the BPS (r_s = 0.55, P<0.001). However, whereas 6% of the observations were NRS of greater than or equal to 4, BPS scores were all very low (median 3, range 3 to 5).

Conclusions The different scales show a high reliability, but observer-based evaluation often underestimates the pain, particularly in the case of high NRS values (≥4) rated by the patient. Therefore, whenever this is possible, ICU patients should rate their pain. In unresponsive patients, primarily the attending nurse involved in daily care should score the patient's pain. In ventilated patients, the BPS should be used only in conjunction with the NRS nurse to measure pain levels in the absence of painful stimuli.

INTRODUCTION

Pain is a frequently experienced problem in critically ill patients in the intensive care unit (ICU) [1]. Pain may increase morbidity and mortality and may decrease the comfort of patients and health related quality of life. The adequate use of analgesics and sedatives therefore may decrease morbidity and mortality [2]. Measurement of pain in ICU patients however, may be complicated by decreased consciousness, severity of illness, mechanical ventilation and the use of sedatives in these patients, particularly when high doses of sedatives are administered [3-4]. Although self-report is still the 'gold standard' in pain measurement according to the guidelines of the International Association for the Study of Pain [5], one segment of the ICU patients is unable to communicate effectively. In these cases, the gold standard (that is, the pain intensity reported by the patient) is not possible or potentially unreliable. This is also a common problem in, for example, neonates and children, who are not able to report pain in a reliable manner [6].

Therefore, pain assessment in the ICU remains a challenge for clinicians and researchers. There is no specific neurobiological parameter for the evaluation of pain, nor does an objective quantification of pain intensity or relief exist [7]. Various pain scales are available, but it remains unclear whether they can be applied reliably in the diverse patient population of the ICU, where patients may not only be mechanically ventilated but also are subject to repeated painful procedures. Therefore, it is of interest to define which score should be used for which patient (for example, ventilated, responsive or unresponsive) and by which health care worker, in case the patient cannot communicate. These results can be used to implement a systematic evaluation of pain in all ICU patients. While, to date, the use of scoring systems for pain severity and sedation depth and the implementation of protocols increase with a more patient-orientated regime for analgesia and sedation, a trend is observed away from a hypnosis-based approach and towards an analgesia-based approach. Although these changes may improve pain and sedation practice, further efforts are needed for widespread implementation of pain scoring systems and analgesia protocols [8-9]. Of the available pain scales, the numeric rating scale (NRS; range 0-10) and visual analogue scale (VAS; range 0-100) have been validated for acute pain only, and not in mechanically ventilated patients in the ICU [10]. The behavioral pain scale (BPS) was developed specifically for measuring the severity of pain in sedated, mechanically ventilated, unresponsive patients [11], but this pain scale still is not generally accepted for routine use. Another question in pain management in the ICU is which health care worker (nurse, physician or consultant) should rate pain, in case the patient cannot communicate verbally. While the attending nurse is involved in close daily care of the patient, the physician seems to have a more distinct relation to the patient. Therefore, we designed a study (a) to determine the inter-rater reliability of the NRS and BPS, (b) to compare pain scores of different observers and the patient and (c) to compare NRS, VAS, and BPS for measuring pain in ventilated and non-ventilated patients in the ICU.

MATERIALS & METHODS

Design

A prospective observational study was performed in a 30-bed surgical/medical ICU in a teaching hospital in Nieuwegein, The Netherlands. The Medical Ethical Committee of the St. Antonius Hospital approved the study protocol and waived the need for informed consent because the observational study design and pain measurements are part of the standard care.

Participants

All patients in the ICU who were at least 18 years old were included between 27 June and 4 August, 2005. Patients who received neuromuscular blocking medications or muscle-paralysing drugs continuously, who were unconscious after resuscitation, who were quadriplegic, who suffered from a critical illness (poly)neuropathy, or who had an epidural catheter were excluded. Paralysis, whether caused by a pre-existing condition or by medication, makes the BPS unreliable.

Pain measurement instruments

To assess pain intensity, three pain scales (that is BPS, NRS, and VAS) were used.

The BPS is used after an observation of the patient for about one minute and was validated in critically ill, sedated, and mechanically ventilated patients [10-11]. The BPS is a pain scale for sedated and ventilated patients exclusively and is based on a sum of three subscales: facial expression, upper limb movements, and compliance with mechanical ventilation (Table 1). Each subscale is scored from 1 (no response) to 4 (full response). Therefore, BPS scores range from 3 (no pain) to 12 (maximal pain) [10-11]. The BPS has a maximal acceptable pain score of 5 [12].

Table 1. The behavioral pain scale [11]

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened	2
	Fully tightened	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

The NRS is based on a scale from 0 to 10; 0 represents no pain and 10 represents worst possible pain [13-14]. The NRS has a maximal acceptable pain score of 3 [15].

The VAS is a 100 mm ruler with a movable cursor. At the left side is written 'no pain', at the right side is written 'worst possible pain'. The patient marks the intensity of pain [16-17]. The VAS has a maximal acceptable pain score of 30 mm.

Depth of sedation

The Ramsay scale (RS) was used to assess the sedation level [18]. The RS on a scale from 1 to 6, with higher levels indicating increased degrees of sedation, and considers the following levels: (1) patient anxious, agitated, restless, (2) patient cooperative, orientated and tranquil, (3) patient drowsy or asleep, responds easily to commands, (4) patient asleep, brisk response to a light glabellar tap, (5) patient asleep, sluggish response to a light glabellar tap and (6) patient asleep, no response to a light glabellar tap [19].

Standard pain medication in the ICU

All patients received pain medication according to the local standard protocol, consisting of 1 gram of paracetamol rectally three times daily and morphine 10 mg subcutaneously four times daily or 30-50 mg morphine per day using a continuous intravenous infusion, if required.

Procedures

Before this study, levels of pain were not systematically scored and recorded. During this study, assessments took place in all patients in the ICU twice a day (at 8.30 a.m. and 3.00 p.m.) during 1 month. Assessments were initiated by two researchers who were trainees in pharmacy and who had been working for 6 months under close supervision of two anaesthesiologists of the Department of Anaesthesiology and Intensive Care, and one ICU nurse. These researchers were not involved in the patient's care but took notice of the clinical and medical situation of the patient, similar to physicians on ward rounds. All assessments were made during non-nociceptive procedures, in order to obtain basal pain scores. First, the researchers observed every patient about one minute. Assessments of the researchers were made simultaneously but independent of each other. Then, the researchers scored the BPS, NRS, and RS in order to prevent the outcome from being influenced by the patient's or nurse's score. The BPS was scored only in patients who were ventilated. Then, the attending nurse was asked to score the pain of the patient with the NRS. If the patient was responsive, the patient was asked to score the pain using the NRS and VAS. Gender, length, weight, year of birth, ICU indication, and relevant history were collected. Patients were classified in one of the two ICU indications, 'cardiothoracic surgery' or 'non-cardiothoracic surgery' with a skewed distribution for 'cardiothoracic surgery'.

In this study, the 'NRS researcher' and 'BPS researcher' are defined by NRS rating and BPS rating by the researcher. The 'RS researcher' is defined by the RS rating by the researcher. 'NRS nurse' is defined by the NRS rating by the nurse. 'NRS patient' and 'VAS patient' are defined by the NRS rating and VAS ratings by the patient (Table 2).

Table 2. Pain and sedation scales performed by researcher, nurse and patients

	BPS (if ventilated)	NRS	VAS	RS
Researcher	X	X		X
Nurse		X		
Patient (whenever possible)		X	X	

BPS = behavioral pain scale; NRS = numeric rating scale; VAS = visual analogue scale; RS = Ramsay Scale

Training pain measurement instruments

For adequate use of the BPS, NRS, VAS, and RS, the two researchers attended a 4-hour training session (conducted by a trained ICU nurse), during which the BPS and RS were explained with examples of patients who were in the ICU at the time of the training. When the inter-rater reliability was acceptable according to a quadratic weighted Cohen's kappa of greater than 0.6, the researchers were allowed to score patients for the study [20].

Data analysis

Data were analysed with the statistical software S-Plus® version 6.2 (Insightful Corporation, Seattle, Washington, USA). To correct for the different numbers of measurements per patient, one observation per patient was randomly selected. All statistical analyses were performed using this independent sample, while all measurements were plotted in the figures for better illustration.

Kappa coefficients with quadratic weights were used to reflect agreement for ordinal scales (NRS, BPS, and RS) between the independent researchers. Weighted kappa penalizes disagreement in terms of their seriousness [20]. Theoretically, the value of kappa can range from 0 (disagreement) to 1 (perfect agreement). A value larger than 0.6 was regarded as satisfactory [21]. The 95% confidence intervals for kappa coefficients were calculated.

Spearman non-parametric rank correlation coefficients (r_s) were used to measure the degree of correlation for two ordinal variables. The null hypothesis that the correlation coefficient is zero was tested. A *P*-value <0.05 was considered statistically significant.

RESULTS

Patients characteristics and data

A total of 138 intensive care patients entered the study, with a median of two observation series per patient (range 1 to 15). In total, 25 patients were excluded (15 patients because of incomplete collection of the data and 10 patients because of exclusion criteria), resulting in a total of 113 included patients. Table 3 shows the baseline characteristics of the patients. The body mass index was recorded for 87 of 113 patients (77%).

In total, 371 observations were scored by the researchers and 322 observations were scored by the nurses. In a total of 75 patients (180 observations), the patient could report his or her pain using the NRS. In 141 observations, the patient could also report his or her pain using the VAS. Of the 57 ventilated patients, 13 patients were communicative and could report their pain.

Table 3. Baseline patient characteristics

	All patients
Number of patients	113
Age (years)	66 ± 15
Male gender, n (%)	78 (69%)
BMI (kg/m^2)*	26.6 ± 4.7
Diagnostic categories, n (%)	
Cardiothoracic surgery	83 (73%)
Non-cardiothoracic surgery	30 (27%)
Mechanical ventilation, n (%)	
None	56 (50%)
Pressure Support	36 (32%)
Volume Controlled	21 (19%)
Median Ramsay score (range)	2 (1 -5)

Values expressed as mean ± SD or number (percentage).

* = 26 missing values

Inter-rater reliability

Table 4 depicts the exact agreement, the agreement within one scale point and the quadratic weighted kappa for the NRS, BPS, and RS scale in different groups of patients for the two independent researchers. There was no difference between the ICU indications 'cardiothoracic surgery' (n=83) and 'non-cardiothoracic surgery' (n=30) in exact agreement (60% *vs.* 57%) and agreement within one scale point (94% *vs.* 93%).

NRS patient versus NRS nurse or NRS researcher

For the patients who were able to report their own pain levels (n=75), the level of agreement within one scale point between NRS patient and NRS nurse was 73% compared to 58% for the NRS researcher, corrected for multiple observations per patient. Similar results were found

Table 4. Inter-rater reliability of the NRS, BPS, and RS score

Agreement between	Exact agreement	Agreement within 1 scale point	Kappa (CI)	N
All patients				
NRS	59%	94%	0.71 (0.61-0.81)	113
BPS	80%	100%	0.67 (0.54-0.80)	57
RS	91%	100%	0.66 (0.36-0.97)	44
Non-ventilated patients				
NRS	66%	95%	0.63 (0.45-0.82)	56
Volume Controlled ventilated patients				
NRS	56%	94%	0.64 (0.48-0.81)	36
BPS	81%	100%	0.59 (0.36-0.82)	36
Pressure Support ventilated patients				
NRS	48%	90%	0.80 (0.68-0.93)	21
BPS	81%	100%	0.76 (0.62-0.90)	21
Cardiothoracic patients				
NRS	60%	94%	0.65 (0.53-0.77)	83
Non-cardiothoracic patients				
NRS	57%	93%	0.80 (0.65-0.93)	30

RS = Ramsay scale; NRS = numeric rating scale; BPS = behavioral pain scale

for the exact agreement (42% *vs.* 19%, respectively). The correlation between NRS of patient and nurses (Figure 1) and between NRS of patient and researcher was moderate and low respectively (r_s= 0.55, *P*<0.001 *vs.* r_s=0.38, *P* =0.009). Whereas 33% of the patients scored NRS values of greater than or equal to 4, only 18% of the attending nurses scored NRS values in that range, particularly when the patient rated his or her pain as unacceptable, nurses tend to underestimate the pain level of the patient on the NRS.

NRS patient and VAS patient

In responsive patients, there was a strong positive correlation between the NRS patient and the VAS patient. (r_s=0.84, *P*<0.001, n=75, Figure 2). The correlation between NRS patient and VAS patient was slightly lower in cardiothoracic patients than in non-cardiothoracic patients (r_s= 0.79, *P*<0.001, n=25 patients *vs.* r_s=0.95, *P*<0.001, n=11 patients).

NRS nurse and BPS researcher

While a moderate positive correlation was found between the NRS nurse and the BPS researcher in ventilated patients (r_s=0.55, *P*<0.001, n=57 patients, Figure 3), Figure 3 also shows that using the NRS, only 5% of the observations (n=151 observations of 57 patients) was NRS=0 (no pain), whereas on the BPS, 68% of the observations were BPS=3 (no pain). Besides, using the NRS, 6% of the observations were greater than or equal to 4, considered to be unacceptable pain. However, corresponding BPS scores were all low (median 3, range 3-5) and below the acceptable BPS of 5, which means that no unacceptable pain was observed using the BPS.

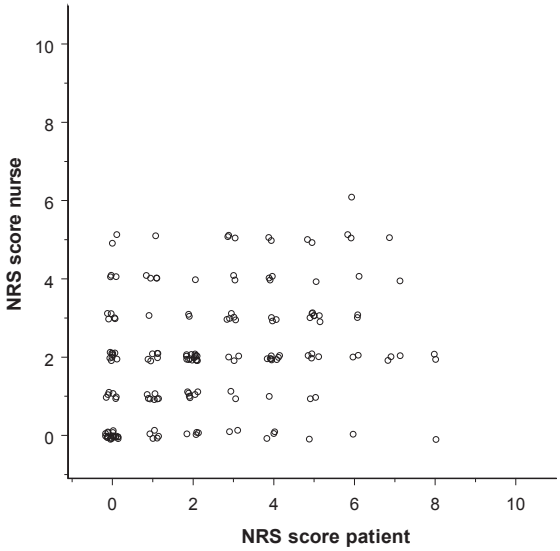

Figure 1. Correlation between numeric rating scale (NRS) scores of patient and nurses. Data of 75 responsive patients with 165 measurements are presented.

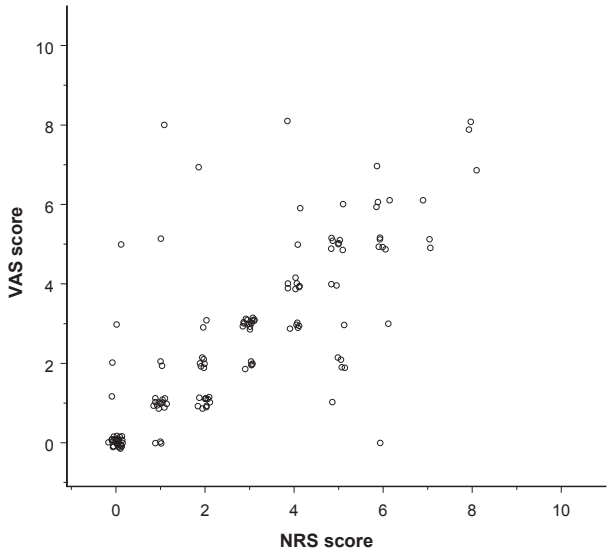

Figure 2. Correlation between numeric rating scale (NRS) score and visual analogue scale (VAS) score of the patient. Data of 75 responsive patients with 131 measurements are presented.

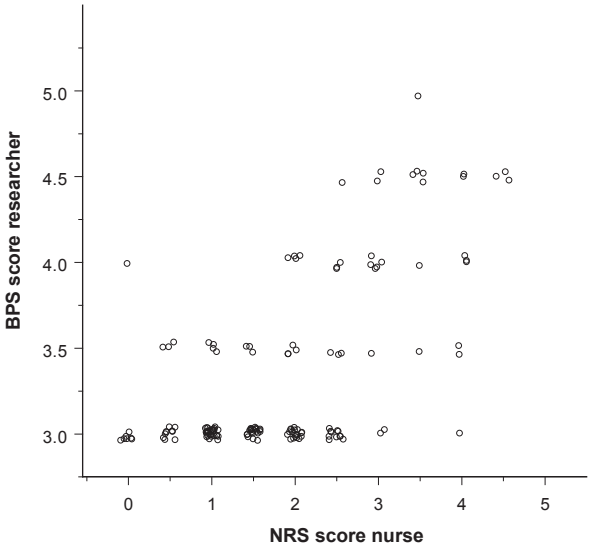

Figure 3. Correlation between numeric rating scale (NRS) score and behavioral pain scale (BPS) score. Data of 57 ventilated patients with 151 measurements are presented.

There was no difference in the correlation between cardiothoracic patients and non-cardiothoracic patients (r_s=0.54, *P*<0.001, n=47 patients *vs.* r_s= 0.53, *P*=0.047, n=10 patients) or between pressure-supported ventilated patients compared to volume-controlled ventilated patients (r_s=0.64, *P*=0.004, n=21 patients *vs.* r_s=0.49, *P*=0.004, n=36 patients).

NRS researcher and RS researcher

The correlation between the NRS researcher and the RS researcher was low (r_s= 0.28, *P*=0.078, n=40). The correlation was weak in both cardiothoracic patients and non-cardiothoracic patients (r_s=0.24, *P* =191, n=31 patients *vs.* r_s=0.04, *P* =0.9, n=13 patients).

DISCUSSION

In our study, we found that the inter-rater reliability for the NRS and BPS was good, which proves that it is possible to train medical personnel to use these scales in a reliable way in ICU patients. However, although the different pain scales show a high reliability, an important finding of our study is that especially unacceptably high patient scores (NRS≥4) were underestimated by both the nurses and the researchers as 33% of the NRS patient values were greater than or equal to 4 compared to 18% for the nurses. As it is known that the patients may underestimate pain by themselves (caused by factors like culture and the environment [22-23]), the risk of underestimation seems to be an important issue when scoring pain in

ICU patients. The underestimation of patients' pain scores by the nurses is already supported in the literature. However, the finding that underestimation occurs in especially high patient scores was never reported. Therefore, it is of utmost importance to use restrictive sedation protocols aiming at cooperative sedation levels instead of unconscious levels [4], allowing for response to questions about pain evaluation and thereby reducing observed-based pain evaluations and allowing for self-report of pain.

The correlation between the NRS and the BPS in our study is in accordance with the study of Payen et al. [11], which showed that the BPS is reliable for measuring the severity of pain in sedated and ventilated patients. Also, Aissaoui et al. [10] concluded that the BPS is valid and reliable for measuring intervention pain in non-communicative ICU patients. In our study however, in 57 ventilated patients of which 13 were communicative, only 5% of the observations (n=151 observations of 57 patients) was NRS of 0 (no pain), whereas on the BPS, a remarkable 68% of the observations were BPS of 3 (no pain). In addition, although 6% of our observations were greater than or equal to 4 (unacceptable pain according to [24]), the BPS scores were all low with a median value of 3 (range 3-5), which is the lowest possible value of the BPS in a scale with a maximum value of 12. Also in the study of Payen et al. [11] a high non-response on the BPS was found in assessments completed at rest (BPS score of 3 in 88% to 97% of the observations) and 82% of the observations at rest and during interventions were clustered around BPS 3 to 6.

The high non-response on the BPS can be explained by the short time of observation. During one minute of observation, the patient may seem pain free (BPS of 3). However, using the NRS, a higher score may be rated, as the nurse tends to include more background information of the patient (for example, the pain levels from the last hours while caring for the patient). So the BPS reflects the objective visible behavior at one specific time point, whereas the NRS represents a global impression of pain, including several contextual factors during a longer time period. It seems, therefore, that the BPS should be used only in conjunction with the NRS nurse to measure pain levels the ICU.

Various studies concluded that, compared with the NRS, the VAS is not an adequate tool in patients with a decreased consciousness [25-26]. This appears to be related to the lack of ability for abstraction and comprehension and provides difficulties in patients who are injured to the upper limbs. In our study, the correlation between the NRS and VAS estimated by the patient is strong (r_s=0.84, P<0.001, n=75), suggesting that the VAS is also an adequate tool for measuring pain in about two thirds of the patients in our ICU. However, the VAS could be used in only 75 patients of the 113 patients, in particular in patients with intact comprehension and abstraction, when recovering from critical illness and just before leaving the ICU following cardiac surgery. Therefore, it is unknown whether this finding can be extrapolated to other ICUs.

The correlation between the NRS score and RS score was low (r_s= 0.28, P=0.078, n=40). So the degree of pain intensity does not seem to depend on the level of sedation. This is impor-

tant because these two scores should be able to distinguish between the level of analgesia and the level of sedation. Whereas high RS levels (deep sedation) may be expected in more severely ill patients experiencing more pain, patients with low RS levels (light sedation), in contrast, have more ability to show painful behaviours, resulting in absence of a significant correlation.

This study had several limitations. In the present study, we collected pain scores of ICU patients at rest and without painful stimuli. In the ideal study design in which different pain scoring systems in the ICU are compared, the pain scores in the absence and presence of an unavoidable painful stimulus should be tested in order to be able to study the sensitivity to change for each pain scale. In further studies, therefore, basal pain scores should be obtained together with intervention pain scores in order to evaluate and judge pain scales for different purposes (for example, at rest and during painful interventions).

Furthermore, the patients included in this study are characterized by a high percentage (73%) of post-cardiothoracic surgery patients and a 50% rate of mechanical ventilation, which was partly due to pain measurements before leaving the ICU, so extrapolation of the result to other ICUs may be limited. In addition, in our ICU, sedation levels are aimed at cooperative levels comparable to those of Kress et al. and Brook et al. [27] whenever possible. Both these characteristics of our ICU may have resulted in the relatively high percentage of responsive patients (66%) who were able to report pain using NRS and VAS. This should still be considered when the results of our study are extrapolated to other ICUs. On the other hand, in our study, there were no significant differences when the results were divided between 'cardiothoracic surgery' patients and 'non-cardiothoracic surgery' patients.

In conclusion, the different scales show a high reliability, but observer-based evaluation often underestimates the pain, particularly in the case of high NRS values (NRS≥4) rated by the patient. Therefore, whenever this is possible, ICU patients should rate their pain. In unresponsive patients, primarily the attending nurse involved in daily care should score the patient's pain. The BPS should be used only in conjunction with the NRS nurse to measure pain levels in the absence of painful stimuli.

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Chapter 3

USE OF THE BEHAVIORAL PAIN SCALE TO ASSESS PAIN IN CONSCIOUS SEDATED PATIENTS

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ABSTRACT

Background and objectives Assessing pain in mechanically ventilated critically ill patients is a great challenge. There is a need for an adequate pain measurement tool for use in conscious sedated patients because of their questionable communicative abilities. In this study, we evaluated the use of the behavioral pain scale (BPS) in conscious sedated patients in comparison to its use in deeply sedated patients, for whom the BPS was developed. Additionally, in conscious sedated patients the combination of the BPS and the patient-rated verbal rating scale (VRS-4) was evaluated.

Methods We performed a prospective evaluation study in 80 non-paralyzed critically ill adult intensive care unit (ICU) patients. Over two months, nurses performed 175 observation series: 126 in deeply sedated patients and 49 in conscious sedated patients. Each observation series consisted of BPS ratings (range 3-12) at four points: at rest, during a non-painful procedure, at retest rest, and during a routine painful procedure. Patients in conscious sedated state also self-reported their pain using the 4-point VRS-4.

Results BPS scores during painful procedures were significantly higher than those at rest, both in deeply sedated patients (5.1 [4.8-5.5] *vs.* 3.4 [3.3-3.5], respectively) and conscious sedated patients (5.4 [4.9-5.9] *vs.* 3.8 [3.5-4.1], respectively) (mean [95% confidence interval]). For both groups, scores obtained during the non-painful procedure and at rest did not significantly differ. There was a strong correlation between nurses' BPS ratings and conscious sedated patients' VRS-4 ratings during the painful procedure (r_s=0.67, P<0.001). At rest and during non-painful procedures, 98% of the observations were rated as acceptable pain (VRS 1 or 2) by both nurses and patients. During painful procedures, nurses rated the pain higher than patients did in 16% of the observations and lower in 12% of the observations.

Conclusions The BPS is a valid tool for measuring pain in conscious sedated patients during painful procedures. Thus for non-communicative and mechanically ventilated patients it may be regarded as a bridge between the observational scale used by nurses and the VRS-4 used by patients who are able to self-report pain.

INTRODUCTION

Many critically ill patients in the intensive care unit (ICU) suffer from pain [1-3], notably those on mechanical ventilation [4-5]. From 35% to 55% of nurses have been reported to underrate patients' pain [6-7], and a current practices study revealed that the observed rates of assessment during procedural pain in mechanically ventilated patients remain below 40% [8]. Researchers have recognized that pain and inadequate pain relief are major causes of physiological adversity and emotional stress [9-11]. Therefore, it would seem important to achieve effective management of analgesia, first by measuring pain in a valid and reliable manner.

Various pain scales are available, but there is insufficient evidence of their reliability in the diverse ICU population. The Society of Critical Care Medicine recommends self-reporting by communicative patients using the numeric rating scale (NRS, range 0-10) [7]. This scale requires a certain level of comprehension, so one may opt for an alternative, the 4-point verbal rating scale (VRS-4), which has shown good reliability and validity [12]. Postoperative patients even prefer the VRS-4 over the NRS because of its ease of use [12].

The observational behavioral pain scale (BPS, range 3-12), applied by nurses, has been validated in deeply sedated, mechanically ventilated patients [13-14]. It is composed of three subscales: facial expression, movement of the upper limbs, and compliance with mechanical ventilation [13]. The BPS reflects objective visible behavior at one specific time point, whereas the NRS represents a global impression of pain, including several contextual factors during a longer time period [15]. Gélinas et al. [16] recently developed the Critical Care Pain Observation Tool (range 0-8). Based on the BPS, the Critical Care Pain Observation Tool has not yet been tested among different critical care populations and requires additional validation [17].

Apart from communicative and deeply sedated patients, a third group can be identified, i.e. conscious sedated mechanically ventilated patients. Current ICU practice strives to restrict sedation to a conscious level whenever possible, in agreement with the landmark report [18] that showed that ventilated patients benefit from daily interruption of sedative infusions. Ventilation could be stopped earlier in these patients, resulting in shorter ICU stays, and they showed no adverse psychosocial outcomes [19].

Self-reporting using the NRS or VRS-4 may be complicated or unreliable in these patients due to their temporarily limited capacities of abstraction and concentration, and lack of comprehension [7,11]. Furthermore, the BPS has been validated only in deeply sedated and non-communicative patients.

For this growing group of conscious sedated patients, an observational pain scale such as the BPS, which can be used by the nurse, can add value to VRS-4 scores, because patients' self-reporting may be complicated and/or unreliable. Therefore, we designed a study to compare use of the BPS_{nurse} in conscious sedated patients and in deeply sedated patients, for whom the BPS was developed. Additionally, in conscious sedated patients, the combination of the BPS_{nurse} and the patient-rated VRS-4 was evaluated.

MATERIALS AND METHODS

Design

A prospective, observational study was performed in a 30-bed surgical/medical ICU in a teaching hospital in Nieuwegein, the Netherlands. The Medical Ethical Committee of the St. Antonius Hospital approved the study protocol and waived the need for informed consent because the observational study design and pain measurements are considered as standard care.

Patients and classifications

During the two-month study period, all patients admitted to the ICU were evaluated for inclusion in the study once a day (between 8:00 a.m. and 12 noon). ICU patients who were 18 years and older, sedated irrespective of sedation depth, and ventilated for at least 8 hours before assessment were eligible for inclusion. Patients who received neuromuscular blocking medications or muscle-paralyzing drugs, who were unconscious after resuscitation, quadriplegic, had a critical illness (poly) neuropathy, or had an epidural catheter, were excluded.

Included patients were classified as 'sedated' or 'conscious sedated' on the specific day. Sedated patients were defined as patients who were not able to communicate during all 4 consecutive assessments (at rest, during non-painful procedures, at retest rest and during painful procedures) on that particular day. Conscious sedated patients were defined as patients who were able to communicate during at least one part of the assessment. Patients could be included on multiple days, an approach also used in the first BPS validation study in non-responsive critically ill patients [13].

Eighty patients were included during the two-month study period. Fifty patients were classified as sedated on all study days, 17 as conscious sedated on all study days, and 13 as either sedated or conscious sedated on different days in the study period.

Pain measurement instruments

BPS. The BPS is an observational pain scale, preferably applied by the attending nurse. It has been validated for use in deeply sedated, mechanically ventilated patients [13,20]. Easy to use and well accepted by nurses, the BPS contains three subscales: facial expression, upper limb movements, and compliance with mechanical ventilation (Table 1). Each subscale is scored from 1 (no response) to 4 (full response). Therefore, BPS scores range from 3 (no pain) to 12 (maximal pain) [13]. A BPS score of 6 or higher is considered to reflect unacceptable pain [2].

VRS-4. The VRS-4 is a 4-point verbal rating scale (range 1-4) used for patient self reporting. It was adapted from the verbal graphic scale [21], which includes four categories: 1) free of pain (NRS 0), 2) mild pain (NRS 1-3), 3) moderate pain (NRS 4-6), and 4) severe pain (NRS 7-10). This shorter version was used because conscious sedated patients may temporarily lack full comprehension of the more complex 11-point NRS. Unacceptable pain using the 11-point

Table 1. The behavioral pain scale [13]

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened	2
	Fully tightened	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

NRS is defined as NRS>3 (moderate pain and severe pain) [6-7], thus unacceptable pain using the 4-point VRS was defined as a score of 3 or 4. In this study, the 'BPS_{nurse}' is defined based on a BPS rating by the attending nurse. The '$VRS\text{-}4_{patient}$' is defined by the VRS-4 rating by the patient.

Study procedures and intervention

Pain was assessed during two routine nursing procedures. One was an arterial catheter dressing change, identified as a non-painful procedure from a pilot study in our ICU. The second was turning, a procedure that patients have described as painful [22-23]. In addition, pain was assessed at rest, i.e. before the first of these procedures, and in between these procedures, at least 30 minutes after the first procedure.

At each of these four points, a nurse researcher (AV, critical care nurse and student in nursing sciences) and an attending nurse simultaneously observed the patient for about one minute, with the observers' assessments made independently. The attending nurse then determined the Ramsay score (RS). Next, the nurse researcher and the attending nurse independently determined the BPS_{nurse} score. Communicative patients were then asked to apply the $VRS\text{-}4_{patient}$. This order was decided upon to prevent the nurses' scores from being influenced by the patient's score.

Demographic data such as gender, age, intensive care indication and the Sequential Organ Failure Assessment (SOFA) score [24] were collected.

Training

The 72 nurses who participated in the study all attended a 4-hour training session, given by a BPS-trained ICU nurse. Attention was paid to the essentials of pain and the difficulties of scoring pain in ventilated and sedated patients. The use of the BPS was explained by means of pictures of ICU patients. All received a protocol explaining the study and the BPS.

Depth of sedation

Depth of sedation was assessed by the Ramsay scale (RS), which is a single-item, six-level scale (scores range from 1 to 6) [25]. The levels are: (1) patient anxious, agitated, restless, (2) patient cooperative**,** oriented and tranquil, (3) patient drowsy or asleep, responds easily to commands, (4) patient asleep, brisk response to a light glabellar tap, (5) patient asleep, sluggish response to a light glabellar tap, and (6) patient asleep, no response to a light glabellar tap [9]. The RS was rated in the morning (between 7:30 and 8:00 a.m.), whereas the pain assessments were completed between 8:00 a.m. and 12:00 noon). In 8 patients, the RS was different during sedation assessment and pain assessment. The RS score for the conscious sedated patients (median 6, range 3-6) was significantly lower ($P<0.001$) than that for the sedated patients (median 3, range 2-5).

Standard pain and sedative medication in the ICU

All patients received pain medication by protocol, i.e., four times daily 1 gram of paracetamol rectally plus either four times daily 10 mg morphine subcutaneously if in moderate pain or 30-50 mg morphine per day by continuous intravenous infusion when in severe pain. Pain severity was evaluated on a daily basis. For procedural pain, patients received either no morphine, or a bolus of 5 to 10 mg morphine, depending on the attending nurse's judgement. Patients were sedated preferably with propofol or midazolam, according to local standard practice.

Data analysis

Data were analyzed using the SPSS software (version 15.0, Chicago, ILL, USA). The statistical analysis was performed by calculation on all measurements of all patients, including one measurement per day per patient. This approach was used by Payen et al. [13] when they first validated the BPS in non-responsive critically ill patients, and can be justified because a critically ill patient's condition may rapidly change over 24 hours, e.g. when taken off mechanical ventilation, with consequences in terms of organ failure, neurological or respiratory situation, sedation levels, pain levels, and communication abilities.

Kappa coefficients with quadratic weights were used to reflect agreement between the nurse researcher and the attending nurse regarding the BPS. Weighted kappa penalizes disagreement in proportion to its severity [26]. Theoretically, the value of kappa can range from 0 (no agreement) to 1.0 (perfect agreement). A value larger than 0.6 was regarded as satisfactory [27]. The 95% confidence intervals (95%CI) for kappa coefficients were calculated.

Internal consistency, a measure of how the items within a scale are interrelated, was expressed in Cronbach's α. A high Cronbach's α value reflects high internal consistency. Generally, a value larger than 0.7 is regarded as satisfactory [28].

The effect size is a standardized way to express the magnitude and meaning of an instrument's capacity to change, in this case the BPS. The effect sizes of the BPS total and BPS items

were calculated as the difference between the score at rest and the score during the painful procedure, divided by the standard deviation (SD) at rest [29]. An effect size of around 0.20 is generally considered to be small, one of 0.50 indicates moderate differences, and those of 0.80 or above indicate large differences [30].

Values are expressed as mean and standard deviation (SD) or 95% confidence interval [95%CI]. Spearman non-parametric rank correlation coefficients (r_s) were used to measure the degree of correlation for two ordinal variables. The unpaired t-test and the Mann-Whitney U test served to compare differences in quantitative and non-parametric data, respectively. The test-retest procedure was analyzed by the paired Student's t-test. A *P*-value of <0.05 was considered statistically significant.

RESULTS

Patients and data

Table 2 shows the characteristics of the 80 enrolled patients, classified by state of sedation. The mean amount of propofol administered (± SD) was 130.4 mg/h ± 58.8 for conscious sedated patients *vs.* 175.6 mg/h ± 72.6 for sedated patients (*P*<0.05). The mean amount of midazolam administered in conscious sedated patients and sedated patients was 3.3 mg/h ± 1.2 *vs.* 4.8 mg/h ± 2.5 (*P*=0.32). The mean ICU stay at time of pain assessment (± SD) was 4.5 days ± 3.6 for conscious sedated patients *vs.* 5.4 days ± 8.1 for sedated patients (*P*=0.43). One hundred seventy-five observation series were completed: 126 in 63 sedated patients and 49 in 30 conscious sedated patients. The latter also included 49 $VRS\text{-}4_{patient}$ scores for 30 patients.

Table 2. Baseline patient characteristics of all 80 patients participating in the study, with patients in sedated state at all study days (n=50), patients in conscious sedated state at all study days (n=17) and patients in either sedated or conscious sedated state on different days (n=13).

	Patients in sedated state on all days	Patients in conscious sedated state on all days	Patients in both states on different days
Number of patients	50	17	13
Age (years) (SD)	66 ± 12	61 ± 15	60 ± 11
Males/ females, n	30/20	12/5	7/6
Median SOFA score (range)	5 (1-14)	5 (1-10)	6 (2-9)
Diagnostic categories, n			
Cardiac surgery	22	9	3
Abdominal surgery	9	6	4
TAAA	5	0	0
Non-surgical	14	2	6

TAAA = thoracoabdominal aortic aneurysm; SOFA = Sequential Organ Failure Assessment.

Inter-rater reliability

Table 3 gives the quadratic weighted kappa and the exact agreement (EA) for the BPS_{nurse} in sedated patients (126 observation series) and conscious sedated patients (49 observation series) between the nurse researcher and the attending nurse. Kappa values were excellent (0.80 to 0.83). There was no difference in exact agreement for sedated and conscious sedated patients (0.83 [95%CI 0.76-0.87] *vs.* 0.80 [95%CI 0.72-0.88]).

Table 3. Inter-rater reliability of the BPS total and separate BPS items as evaluated by nurses in sedated patients (126 observation series) and conscious sedated patients (49 observation series).

	Kappa	EA (%)	No. of observation series
Sedated patients			
BPS total	0.83 (0.79-0.87)	67	126
BPS facial expression	0.80 (0.75-0.85)	82	126
BPS upper limb movement	0.72 (0.64-0.79)	82	126
BPS compliance ventilation	0.62 (0.52-0.72)	88	126
Conscious sedated patients			
BPS total	0.80 (0.72-0.88)	70	49
BPS facial expression	0.78 (0.69-0.87)	81	49
BPS upper limb movement	0.67 (0.52-0.82)	87	49
BPS compliance ventilation	0.61 (0.45-0.70)	89	49

EA = exact agreement, BPS = behavioral pain scale

Pain scores in conscious sedated patients and sedated patients

BPS_{nurse}

BPS_{nurse} scores were significantly higher during painful procedures than at rest in both sedated patients (5.1 [95%CI 4.8-5.5] *vs.* 3.4 [95%CI 3.3-3.5]) and conscious sedated patients (5.4 [95%CI 4.9-5.9] *vs.* 3.8 [95%CI 3.5-4.1]) (Figure 1). There was no difference in BPS_{nurse} scores between the non-painful procedure and rest in sedated patients (3.4 [95%CI 3.3-3.6] *vs.* 3.3 [95%CI 3.2-3.4]) and conscious sedated patients (3.7 [95%CI 3.5-3.9] *vs.* 3.6 [95%CI 3.3-3.8]). BPS_{nurse} scores did not differ between sedated patients and conscious sedated patients at rest or during non-painful or painful procedures.

Table 4 shows that the effect size for responsiveness of BPS total scores was large in sedated patients (126 observation series) and conscious sedated patients (49 observation series) (2.5 and 1.8, respectively). The effect size of the item 'facial expression' was largest in both sedated patients (3.6) and conscious sedated patients (2.4). It was also large for 'compliance with ventilation' (1.4 and 0.9), but moderate for 'upper limbs' in both groups (0.7 and 0.5) (Table 4). During painful procedures, internal consistency was moderate in both sedated patients and conscious sedated patients (Cronbach's α 0.63 and 0.66, respectively).

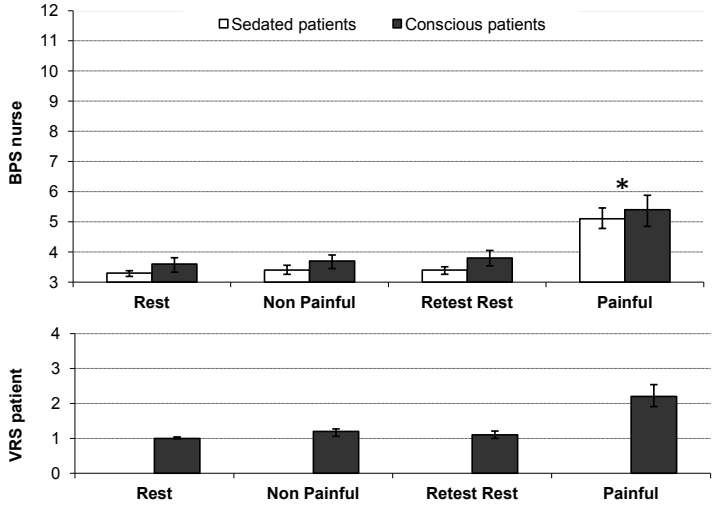

Figure 1. Change in behavioral pain scale $(BPS)_{nurse}$ and verbal rating scale (VRS)-$4_{patient}$ at rest, during non-painful procedures, at retest rest, and during painful procedures (mean [95% confidence interval]) in sedated patients (126 observation series) and conscious sedated patients (49 observation series).

Table 4. BPS total scores and BPS items scores (mean ± SD) at rest and during painful procedure, with effect size in sedated patients (126 observation series) and conscious sedated patients (49 observation series).

	Retest rest	Painful procedure	*P*	Effect size
Sedated patients				
BPS total	3.4 ± 0.7	5.1 ± 1.0	<0.001	2.5
BPS facial expression	1.1 ± 0.3	2.1 ± 1.0	<0.001	3.6
BPS upper limb movement	1.2 ± 0.4	1.4 ± 0.7	<0.001	0.7
BPS compliance ventilation	1.1 ± 0.4	1.6 ± 0.7	<0.001	1.4
Conscious sedated patients				
BPS total	3.8 ± 0.9	5.4 ± 1.8	<0.001	1.8
BPS facial expression	1.1 ± 0.4	2.0 ± 1.0	<0.001	2.4
BPS upper limb movement	1.5 ± 0.6	1.8 ± 0.8	0.003	0.5
BPS compliance ventilation	1.2 ± 0.4	1.6 ± 0.5	<0.001	0.9

BPS = behavioral pain scale

VRS-4$_{patient}$

In conscious sedated patients, VRS-$4_{patient}$ scores were significantly higher during painful procedures than at rest (2.2 [95%CI 1.9-2.5] *vs.* 1.1 [95%CI 1.0-1.2]). Scores did not differ between the non-painful procedure and rest (1.0 [95%CI 1.0-1.0] *vs.* 1.0 [95%CI 1.0-1.0]).

Comparison between BPS_{nurse} and $VRS\text{-}4_{patient}$ in conscious sedated patients

During the painful procedure, there was a strong positive correlation between BPS_{nurse} and $VRS\text{-}4_{patient}$ (r_s=0.67, P<0.001, 49 observation series) (Figure 2). The four boxes in Figure 2 each have been divided into four quadrants, separating acceptable pain and unacceptable pain scores (unacceptable pain VRS-4>2 and BPS>5).

During painful procedures, in 16% of the observations the patient rated pain as acceptable (VRS scores 1 or 2) whereas the nurse rated it as unacceptable (BPS>5). Conversely, in 12% of the observations, the patient rated pain as unacceptable (scores VRS>2) whereas the nurse rated it as acceptable (BPS 3-5). At rest, during the non-painful procedure, and at retest rest, 98% of the observations were in the quadrant with acceptable pain scores. In these cases, both the patient and the nurse assigned acceptable pain scores.

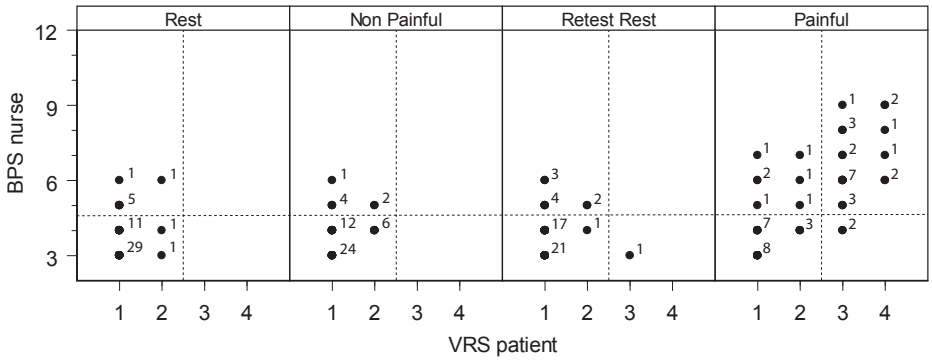

Figure 2. Correlation between behavioral pain scale $(BPS)_{nurse}$ and verbal rating scale $(VRS)\text{-}4_{patient}$ (49 observation series) at rest, during non-painful procedures, at retest rest, and during painful procedures. The dotted line divides acceptable pain scores from unacceptable pain scores (VRS-4 >2 and BPS >5). Each number reflects how many similar results were observed per paired evaluation.

DISCUSSION

The findings from this study are consistent with the notion that the BPS is reliable for pain assessment in conscious sedated patients. This is of interest in that so far, the BPS has been validated for deeply sedated patients only [13]. All ICU patients recovering from a deeply sedated state will pass through this conscious sedated state. Thereby, patients who experience agitation or delirium, in whom self reporting will be complicated, benefit from this pain assessment in the conscious sedated state.

BPS_{nurse} scores during painful procedures were significantly higher than those at rest in both sedated patients and conscious sedated patients. Payen et al. [13] made a similar observation in deeply sedated patients, i.e., BPS scores were significantly higher for painful procedures such as turning or tracheal suctioning. Therefore, it would seem that the BPS can detect and discriminate pain and is a valid measure of pain in both sedated and conscious

sedated patients. Furthermore, the internal consistency was comparable for observations in both groups, demonstrating similar homogeneity of the items. The fact that the effect size was large in both groups shows that the BPS is able to quantify change in clinical status and detect painful procedures. In both groups, the BPS subscale 'facial expression' was the most sensitive to change, as in a previous study [20]. The value of facial expression has been proven for both acute and chronic pain not only in adults [31-32], but also in infants and children [33].

Underestimation of patients' pain by nurses is a well-known problem [5]. Surprisingly, using the BPS, nurses also tend to overestimate patients' pain. On the other hand, conscious sedated patients' pain scores are not always reliable. Therefore, use of the BPS in combination with the VRS-4 during painful procedures may lead to a more reliable rating of patients' pain. A previous study from our group [34] also concluded that a combination of self-reporting and observational measures is recommended when credibility of self-reporting is doubted. Each method yields unique information. Self-reporting primarily reflects expressive pain behavior that is under control of higher mental processes. Observational measures capture behavior that is less subject to voluntary control and more automatic [34].

The level of agreement between the research nurse and the attending nurse was high for both sedated patients and conscious sedated patients (kappa 0.83 and 0.80, respectively). The fact that the kappa values in this study pertained to 72 nurses and generally remained good, shows that nurses can be trained to use the BPS in a reliable way in both sedated and conscious sedated patients.

In the ideal study design, nurses would be blinded to the nature of the procedure (painful or non-painful) that is being performed at the point of assessment. This could be achieved by videotaping the scenes and having the nurses rate the scenes afterwards. Care should be taken then to conceal the procedure. A limitation of video recordings is the likelihood that some aspects are missed because the general overview of the patients' situation is necessarily is not provided.

In this study, we used the VRS-4 instead of the 11-point NRS, because of the lack of capability in conscious sedated patients. This approach was inspired by a study from Briggs and Closs [12], who showed that postoperative patients prefer the VRS. It would be of interest to test whether our assumption that conscious sedated patients are indeed incapable of using an 11-point scale is valid.

In this study, most patients were in a sedated state, although it is desirable for patients to be in a conscious sedated state. This suggests that the health staff should give more attention to the sedation state of the patients in our ICU.

Nevertheless, as the BPS may both overrate and underrate patients' pain, and the patient's self-report is not always reliable, a combination of the nurse-rated BPS and the patient-rated VRS-4 is perhaps ideal for estimating patients' pain. Within this context, patients' sedation

levels must be frequently assessed as well, and conscious patients' own self-reported pain scores must be considered the 'gold standard'.

In conclusion, the BPS_{nurse} is valid for use in conscious sedated patients during painful procedures. Thus, the BPS thus can be regarded as a bridge between the observational scale for non-communicative and mechanically ventilated patients and the VRS-4 used by patients who are able to self-report pain.

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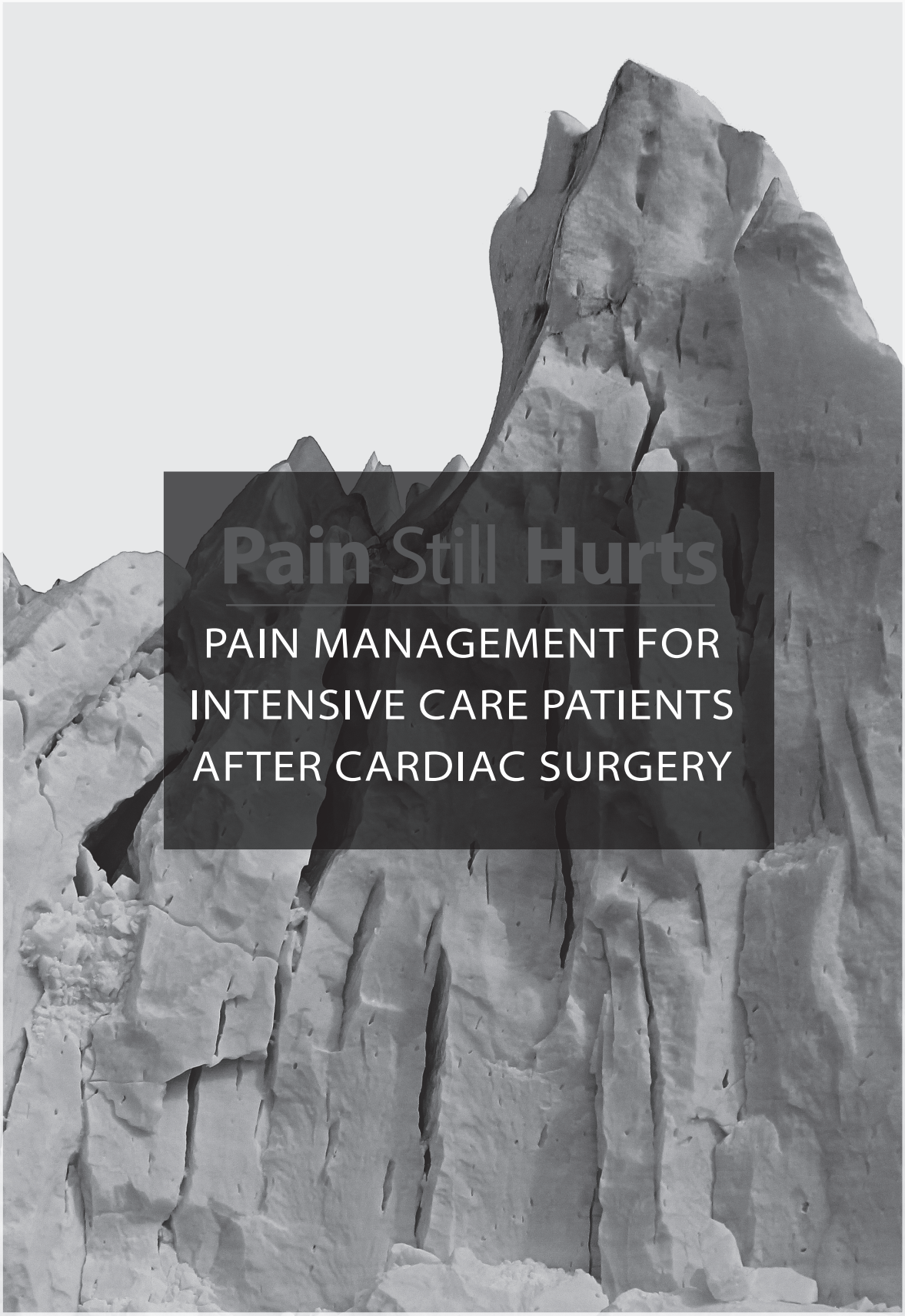

Pain Still Hurts

PAIN MANAGEMENT FOR INTENSIVE CARE PATIENTS AFTER CARDIAC SURGERY

Chapter **4**

IMPROVED ANALGESIA AFTER THE REALISATION OF A PAIN MANAGEMENT PROGRAMME IN ICU PATIENTS AFTER CARDIAC SURGERY

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ABSTRACT

Background and objectives Although clinical guidelines recommend systematic evaluation of pain in intensive care patients, we know little about the effects from such systematic pain evaluation. This study aims to quantify the effect of a pain management programme in the intensive care unit (ICU).

Methods In this prospective two-phase study, pain levels scored by ICU patients after cardiac surgery through sternotomy were compared before and after the implementation of a pain management programme. The pain management programme consisted of a three-fold strategy; all staff was trained in assessing pain and in providing adequate analgesia, a new patient data management system obliged nurses to ask patients for their pain score three times a day and the preferred analgesic treatment was optimized. The numeric rating scale (NRS 0-10) was used by the 190 patients. A NRS≥4 was considered unacceptable. A generalized linear mixed-effects model was used for analysing repeated measurements data.

Results The occurrence of unacceptable pain (NRS≥4) was significantly lower in the intervention group (OR 2.54 [95%CI 1.22 - 5.65; P=0.01 for the control group). Patients in the intervention group received significantly more morphine (29.3 mg [IQR 10.0-36.0] *vs.* 22.6 mg [IQR 0-42.7] a day, P<0.01), with higher morphine amounts administered to patients with higher NRS scores (P=0.01). In the control group no such relation was observed (P=0.66). There was no difference in length of stay in the ICU or in ventilation time.

Conclusions The intervention programme successfully reduced the occurrence of unacceptable pain. Further improvement of pain management should focus on the prevention of pain.

INTRODUCTION

Pain is a frequently experienced phenomenon in patients in the intensive care unit (ICU) [1-2]. Of these patients, 63-77% reported pain during their stay in the ICU [3-4]. Negative effects of inadequate analgesia, such as a stress response with increased myocardial oxygen consumption and tachycardia [5-7], an increased risk of respiratory insufficiency [8-10] contributing to a prolonged duration of mechanical ventilation and in consequence prolonged ICU length of stay [11], warrant a good pain management system for every ICU. Moreover, good pain management reflects a standard quality in daily patient care and is considered an important health care benchmark. A reduction of postoperative pain scores and increased use of analgesics have been shown after the implementation of a pain management system for patients in the post anaesthesia care unit (PACU) and in the wards after various types of surgery [12-13].

Also in the ICU, clinical practice guidelines recommend systematic evaluation of pain in patients for optimal pain management [14], but how to introduce this evaluation and in which form is not specified. Literature search revealed only little information concerning the effects of the introduction of a pain management system and pain education programme in the ICU [11,15]. This is in particular of relevance since it is known that even in the context of observational studies where caregivers knew their pain evaluations were being monitored, pain assessment was not performed according to acceptable standards [16]. Similar results were shown by Watt-Watson and colleagues [17], who showed that only 33-47% of the prescribed dose of analgesics was actually administered despite the fact that the patients after coronary artery bypass grafting (CABG) experienced considerable pain. Most patients would not voluntarily ask the nurse for analgesics.

In this study, we describe an ICU pain management system consisting of 3 steps: a pain education programme for the health staff, the introduction of systematic pain measurement and registration using an automated patient data management system (PDMS), and an optimization of the analgesia protocol. The current study was conducted to evaluate the effect of this new ICU pain management system on pain levels in patients after cardiac surgery in the ICU, the use of analgesics, and possible influences on ventilation time or ICU length of stay.

MATERIALS AND METHODS

Study design

The two-phase prospective controlled study was performed in the ICU of the St. Antonius Hospital, Nieuwegein, The Netherlands. The Medical Ethical Committee of the St. Antonius Hospital approved the study protocol and waived the need for informed consent. The trial was registered under number NCT00773045.

Patients

All patients after cardiac surgery through sternotomy i.e. CABG, valve surgery, aortic root, ascending aorta and aortic arch surgery, admitted to the ICU in the period from June to August 2005 and in the same period in 2006 were included. Patients who were under 18 years old, who received muscle paralysing agents continuously, or patients with debilitating neuromuscular illnesses such as critical illness polyneuropathy or severe encephalopathy and patients unable to speak Dutch or English were excluded from the study. Demographic patient data and both prescribed and administered analgesics were obtained from the medical records (see below for details).

Pain measurements

The numeric rating scale (NRS) was chosen as scoring system [6,14]. As pain scores reported by the patients themselves are the gold standard for measuring pain, in this study only pain scores reported by the patients themselves are evaluated [18-19]. The NRS has been validated for acute pain and is commonly accepted for pain assessment, particularly for postoperative patients [20]. The NRS has also been proven to be useful in ICU patients [19]. The NRS is an 11-point scale from 0 to 10, where 0 represents 'no pain' and 10 represents 'worst pain imaginable'. A NRS≥4 was considered unacceptable, while a NRS≥6 was considered extreme pain [6]. Pain scores were recorded during a maximum of 3 postoperative days in the ICU, as most patients were expected to have left the ICU by then after uncomplicated cardiac surgery.

Control phase

During the control phase, pain was not systematically evaluated and registered by the nursing staff in the ICU. Therefore, twice a day from Monday till Friday, two trained independent researchers [19] paid visits to all patients and their attending nurses and then asked all patients to score their pain. This evaluation of pain occurred when patients were at rest between 9.00 and 10.00 a.m. and between 2.00 and 3.00 p.m.

Directly following cardiac surgery at ICU admittance, the anaesthesiologist prescribed 1 gram of paracetamol 3-4 times daily (rectal or oral administration) and either subcutaneous morphine "when required" 4 times daily or morphine by continuous intravenous infusion. The intensive care doctors could adjust this prescribed morphine dose if clinically judged necessary. All analgesic medication was prescribed manually on the medical order sheet at the patient's bedside.

Pain management programme

Following the control phase a pain management programme was introduced consisting of 3 steps; the entire health staff was trained in assessing pain, an automated PDMS (Metavision suite, version 5.43.15, SP07, iMDsoft Ltd, Massachusetts, USA, 2005) was introduced to record pain scores, and the analgesics protocol was optimized. The steps of the pain training

programme and the differences between the control and the intervention phase are summarized in Table 1.

Training sessions for nurses, intensive care doctors and anaesthesiologists were given twice in 2006. The sessions based on the available literature discussed various possible pain scoring systems, the difficulties of scoring pain in ventilated and sedated patients, the importance of adequate analgesia, and the effect of pain on morbidity and ICU length of stay. Furthermore, the sessions confronted both groups with the high percentage of unacceptable pain levels found during the control phase. The sessions especially for nurses concentrated further on the importance of self-report by patients, the need to ask patients actively about their pain levels using the NRS, and the fact that in the control phase analgesics had been administered relatively infrequent although adequately prescribed. The sessions for the doctors (intensive care doctors, anaesthesiologists and their trainees) emphasized on the fact that in the control phase accurately prescribed analgesics, had not been administered adequately. They were encouraged to activate a standard analgesic protocol in the PDMS which consisted of intravenous morphine as a continuous infusion instead subcutaneously or "when required", in combination with the administration of paracetamol directly upon ICU arrival.

The training sessions for the nurses took place in groups of maximum 10 persons. Approximately 80 of the 100 regularly working nurses took part in the training, which was repeated

Table 1. Steps of the pain management programme during the control and intervention phase

	Control phase	Intervention phase
Step 1: Pain education programme		
Structure	none	- 2 training sessions per group of 10 nurses or doctors - e-mail - weekly info bulletins
Contents		- presentation of actual pain scores in ICU during control phase - relevance of analgesia - different pain measurement instruments - clinical signs of pain
Step 2: Pain registration		
When	not regularly	at least 3 times a day
Where	no predefined space in medical record	PDMS, predefined space
How	no defined scoring system	similar as vital signs NRS (0-10)
Step 3: Analgesia protocol		
Paracetamol		
Route	rectal or oral	intravenous, rectal or oral
First dose	on first routine administration time after ICU admittance	immediately after surgery
Morphine		
Route	preferably subcutaneously	preferably intravenously
Start administration	no specific timing	immediately after surgery

after a few months. Apart from the training sessions, all information was repeated in weekly and monthly information bulletins and emailed to all nurses and doctors.

Intervention phase

During the intervention phase the attending nurses asked patients their pain levels upon preset times by alarms of the PDMS three times a day (7 days a week) at 8:00 a.m., 4:00 p.m. and midnight. They were allowed to record pain scores next to the appointed times. Nurses were instructed to refer directly to the attending intensive care doctor for the administration of more analgesics in case of unacceptably high pain levels (NRS≥4).

At ICU admittance, the anaesthesiologist activated a standard pain protocol in the PDMS, prescribing a starting dose of morphine left to his discretion, and paracetamol. Intensive care doctors were free to adjust the prescribed analgesics if necessary during the stay in the ICU. Paracetamol could be administered intravenously in addition to the rectal and oral route. Morphine through continuous intravenous infusion was preferred over morphine subcutaneously and dosing "when required". Administration of analgesics was started directly upon admittance to the ICU.

Endpoints

Primary endpoint was the occurrence of unacceptable pain (NRS≥4) reported by the patients themselves before and after the introduction of the pain management programme. Secondary endpoints were the administered postoperative doses of morphine and paracetamol during the ICU stay, the ICU length of stay, and duration of mechanical ventilation.

Statistical analysis

Data were analysed using SPSS software (version 14.0, Chicago, ILL, USA). The Mann-Whitney test was used for quantitative data. In order to correct for the different numbers of measurements per patient between the control and the intervention group, a linear mixed-effects model was used (statistical software R, version 2.6.1). A generalized linear mixed-effects model was used for binomial variables. A *P*-value of <0.05 was considered to be statistically significant. Data are presented as mean with interquartile range (IQR) or range, unless stated otherwise.

RESULTS

Patient characteristics and data

Table 2 shows patient characteristics of the control group (n=60) and the intervention group (n=130). There were no significant differences between the groups.

Table 2. Patient characteristics

	Control group n = 60	Intervention group n = 130	P
Age (years)	68 [35-92]	66 [27-86]	NS
Male gender, n (%)	40 (67%)	88 (68%)	NS
Type of cardiac surgery (n) (%)			NS
CABG or valve surgery	37 (62%)	86 (66%)	
CABG & valve surgery	14 (23%)	26 (20%)	
Aorta surgery (& valve surgery)	7 (12%)	12 (9%)	
Other	2 (3%)	7 (5%)	
EuroSCORE (median)	5 [0-16]	5 [0-16]	NS

Data is expressed in mean [range] or number (percentage). NS = not significant
EuroSCORE: European System for Cardiac Operative Risk Evaluation score [21]

Because in the intervention group, the automatic requests by the PDMS for pain evaluations were thrice daily in all patients admitted to the ICU including during the weekends, more patients and more pain scores per patient were available during the intervention phase compared to the control phase (130 *vs.* 60 patients, and 716 *vs.* 127 scores, respectively). All self-reported pain scores from the intervention phase (during and after regular office hours) were used for analysis because there were no differences between patients admitted to the ICU during or after regular office hours (Monday till Friday from 8:00 to 17:00 *vs.* Monday till Friday 17:00-8:00 and during weekends, respectively), e.g. age (mean 65 years [range 27-86] *vs.* mean 67 years [range 37-83], respectively; *P*=0.25) and gender (male 71% *vs.* 67%, respectively; *P*=0.67). In the intervention group, 113 patients of the 130 patients (87%) were able to report their pain, resulting in 185 self-reported pain scores over the first three days. In the control group, 48 patients from the 60 patients (80%) were able to report their pain themselves resulting in 64 pain scores within three days.

NRS pain scores

Only pain scores that were scored by patients themselves were evaluated. Unacceptable pain events (NRS≥4) occurred in 23% (42 of 185 pain scores) of all measurements in the intervention group and in 41% (26 of 64 pain scores) in the control group during the first 3 days in the ICU (Figure 1). Not all patients were able to report a pain score on the day of surgery and some patients left the ICU early on postoperative day 1 or day 2. This explains the differences in number of pain scores between days.

Unacceptable pain scores were significantly reduced in the intervention group with an odds ratio of 2.54 [95%CI 1.22 - 5.65], *P*=0.01) for unacceptable pain in the control group. This odds ratio was calculated with a generalized mixed-effects model for repeated measurements correcting for the differences of number of pain scores per patient between groups.

The percentage of patients who developed *at least one* unacceptable pain event (NRS≥4) or *at least one* extreme pain event (NRS≥6) was comparable between the groups (intervention *vs.* control group: 46% *vs.* 49%; *P*=0.74 and 17% *vs.* 19%, *P*=0.72).

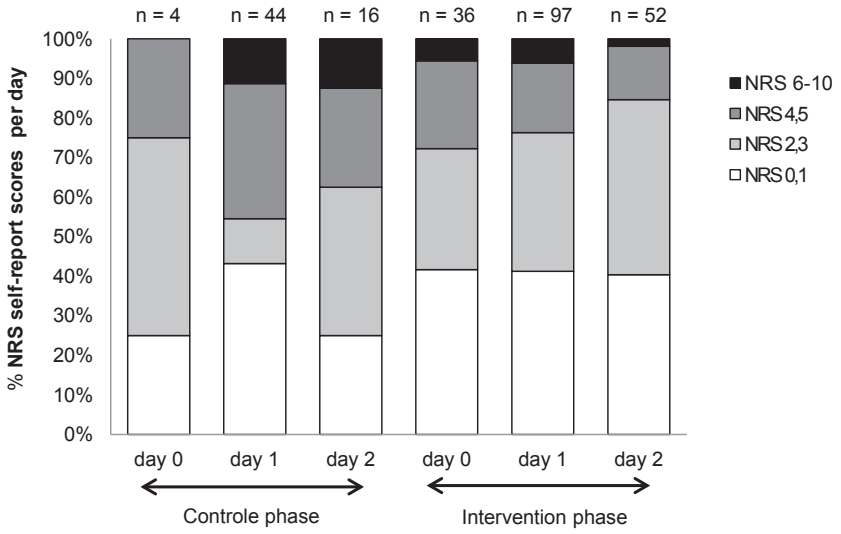

Figure 1. Patient self-report pain levels on postoperative days 0, 1 and 2 in the ICU after cardiac surgery

Use of paracetamol and morphine

ICU patients in the intervention group received significantly more morphine than in the control group (mean 29.3 mg *vs.* 22.6 mg per day, $P<0.01$, Table 3). Linear mixed effects model for repeated measures detected a significant positive relation between the amount of morphine administered and the NRS scores in the intervention group (0.015 [95%CI 0.0035-0.027], $P = 0.01$), showing that more morphine was administered to patients with higher pain scores. In the control group no such relation was observed (-0.0075 [95%CI -0.042-0.02], $P=0.66$). There was no difference in paracetamol administration between groups (median 2.8 gram *vs.* 2.7 gram per day; $P=0.61$, Table 3).

Table 3. Morphine and paracetamol administration, length of ICU stay and duration of mechanical ventilation

	Control group (n = 60)	Intervention group (n = 130)	P
Paracetamol, gram per day *	2.7 (2.0 - 4.0)	2.8 (2.1 - 3.3)	0.61 †
Morphine, mg per day *	22.6 (10.0 - 36.0)	29.3 (11.8 - 44.1)	<0.01 †
Morphine iv	12.2 (0 - 24.1)	22.9 (0 - 42.7)	<0.001†
Morphine sc	10.4 (0 - 19.5)	6.4 (0 - 10.0)	0.03 †
ICU stay, hr	42 (23 - 46)	38 (23 - 51)	0.54 ‡
Mechanical ventilation, hr	10 (7 - 16)	11 (7 - 16)	0.82 ‡

Data are expressed as mean (interquartile range). iv = intravenous, sc = subcutaneous

* 2 missing values; † general mixed-effect model; ‡ Mann-Whitney U test

Length of stay and duration of mechanical ventilation

The ICU length of stay was not significantly different between the intervention group (median 38 hours [IQR 23-51]) and the control group (median 42 hours [IQR 23-46]; *P*=0.54). Neither was there a difference in the duration of mechanical ventilation between groups (intervention, median 11 hours [IQR 7-16] *vs.* control, median 10 hours [IQR 7-16]; *P*= 0.82) (Table 3).

DISCUSSION

While optimal pain management is considered as one of the main features in benchmarking and grading the quality of care, only a very limited number of studies has evaluated the effect of systematic pain assessment and pain training in the ICU. It has been shown before in a heterogeneous population of ICU patients by Chanques et al. [11], that systematic pain assessment may result in a decrease of unacceptable pain levels from 63% to 42% in the ICU. In our study, we focussed in particular on patients in the ICU after cardiac surgery in order to optimize pain treatment in a more homogenous group of ICU patients and observed a clinically relevant reduction of 56% in unacceptable pain scores. Diby et al. [15] also described the implementation of a postoperative pain treatment programme for patients in the ICU after cardiac surgery. After the implementation, pain intensity at rest decreased significantly, morphine was more adequately administered and patients' sleep quality was improved. Our study not only underlines their finding that a pain management programme reduces pain in patients in the ICU after cardiac surgery, but moreover shows that the same applies for an ICU population with co morbidities such as history of pulmonary oedema and renal failure, which were excluded in the study by Diby et al. [15].

The currently described three-step pain management programme, that consisted of a health staff pain education program, systematic pain measurement and registration, and an optimization of the analgesia protocol, successfully reduced the occurrence of unacceptable pain (NRS≥4) in patients after cardiac surgery with an odds ratio for unacceptable pain of 2.54 in the control group. Although this seems a major reduction in unacceptable pain levels, we even think that various influences may have contributed to an underestimation of the decrease of these pain scores. As this study was derived from a practical wish to improve the quality of care, several limitations to the methodology and consequently the interpretation of results have to be considered. The pain scores in the control group were asked when patients were at rest, not undergoing interventions, which may lead to relatively low pain levels at that particular moment. The pain scores in the intervention group however were taken at preset times initiated by PDMS, regardless of an intervention at that time. This may have resulted in higher pain scores in the intervention group, thereby underestimating the actual effect of the pain management programme.

Additionally, during the intervention phase, nurses were trained to be more alert of high NRS levels compared to the control phase and they were allowed to rate pain at any other time in addition to the appointed times. This may have resulted in recording especially high pain levels more frequently in the intervention group. On the other hand, a bias may have been introduced by letting nurses, being the patients' caregiver, ask for the patients' actual pain scores that provide a reflection of the quality of care being provided by them. The patients in the intervention group reported their pain scores to nurses in a care dependent relation, as opposed to the fact that the patients reported their actual pain scores to the independent researchers in the control group. We think however, that differences in reporting pain between the groups are not relevant for the conclusions of this study for three reasons; first in the control phase the ICU nurses were also present when the researchers asked the patient their actual pain scores. So, any restriction that patients may have felt in reporting their pain score in the presence of their caregiver would be present in both situations. Secondly, the patients were neither aware of nor trained in the pain management programme and they were asked exactly the same question in both phases, albeit by different persons. Thirdly, in order to avoid a difference in interpretation between the two phases, we only used pain scores given by the patients themselves.

The comparison of the pain levels between groups was complicated by the difference in the number of scores per patient and the total number of patients per group. This was a result of the difference in registration of pain scores. We managed to overcome this difficulty via a generalized mixed-effects model for repeated measurements. Another way to achieve the pain scores during the control phase would potentially have influenced the results as it seems logical that the registration of pain itself would have led to an intervention at the time, which would have made it impossible to compare the groups before and after the introduction of the pain management programme.

The intervention phase showed reduced pain levels, higher doses of intravenous morphine and lower doses of subcutaneous morphine. Although it seems obvious that higher doses of morphine resulted in lower pain levels, our study also shows that the increased morphine doses were administered in cases of higher NRS values (P=0.01). This indicates that the right patient, i.e. the patient in need for analgesia, received more morphine, which was in contrast with the control group in which there was no such relation. As little is known of the bioavailability of subcutaneously administered morphine in the individual ICU patient with possible impaired perfusion and an altered volume of distribution, the programme intended and succeeded in a 38% reduction of the total amount of morphine administered subcutaneously.

In this study no reduction in ventilator days or ICU length of stay could be demonstrated in contrast with another study [22], where such an effect after the implementation of drug administration algorithms directed by levels of analgesia occurred. On the other hand, a prolongation of ventilator days as a possible negative influence of the increase in morphine administration did not occur either. The fact that we observed no difference in duration

of mechanical ventilation may also have been influenced by both the use of short-acting medication, e.g. propofol, a short-acting sedative, for sedation in both phases, and by the fact that most patients after cardiac surgery followed a fast-track regimen with anticipated short ventilation times.

Following the implementation of the pain management system, still 23% of all measurements had an unacceptable outcome (NRS≥4). These results are comparable to the previously referred study in a diverse group of ICU patients [11] and approximately 3 times lower than in other reports [3-4]. Furthermore, 46% of the patients experienced at least one painful event during their stay in the ICU. Even though the results of our pain management programme were promising and of clinical importance, this still leaves us with a number of reports of unacceptable pain, which cannot be resolved by pain measurements and the suggested kind of programme, but needs to be addressed by new pain programmes which focus especially on prevention of for example intervention related pain, which has been suggested before [15].

Thus , we conclude that the pain management system containing 3 steps, i.e. a pain education programme, systematic pain measurement and registration with a PDMS and an optimized analgesia protocol significantly reduces the overall occurrence of unacceptable pain, and leads to the administration of more morphine in the patients in need for analgesia. Moreover, concerning patient safety, the increase of morphine administration does not increase ventilation time or ICU length of stay. Therefore, we conclude that the effort invested in such a programme is very much worthwhile and should be implemented in all ICUs. Nonetheless, as 46% of the patients in the intervention group still experienced at least one unacceptable pain event during their ICU stay, we suggest that the next step in optimising pain management will focus on more individually tailored analgesia and the prevention of pain and intervention related pain.

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Chapter **5**

EFFICACY OF AN INTRAVENOUS BOLUS OF MORPHINE 2.5 VERSUS MORPHINE 7.5 MG FOR PROCEDURAL PAIN RELIEF IN POSTOPERATIVE CARDIOTHORACIC PATIENTS IN THE INTENSIVE CARE UNIT: A RANDOMISED DOUBLE-BLIND CONTROLLED TRIAL

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ABSTRACT

Background and objectives As pain in the intensive care unit (ICU) is still common despite important progress in pain management, we studied the efficacy of an intravenous bolus of morphine 2.5 versus 7.5 mg for procedural pain relief in patients after cardiothoracic surgery in the ICU.

Methods In a prospective double-blind randomised study, 117 ICU-patients after cardiothoracic surgery were included. All patients were treated according to a pain titration protocol for pain at rest, consisting of continuous morphine-infusions and paracetamol, which is applied during the entire ICU stay. On the first postoperative day, patients were randomised to intravenous morphine 2.5 (n=59) or 7.5 mg (n=58) at thirty minutes before a painful intervention (turning of the patient and/ or chest drain removal). Pain scores using the numeric rating scale (NRS, range 0-10) were rated at rest (baseline), and around the painful procedure.

Results At rest (baseline), overall incidence of unacceptable pain was low (NRS≥4; 14% *vs.* 17%, *P*=0.81) for patients allocated to morphine 2.5 mg and 7.5 mg respectively. For procedural related pain, there was no difference in incidence of unacceptable pain (NRS≥4; 28% *vs.* 22%, *P*=0.53) and mean pain scores (2.6 [95%CI 2.0-3.2] *vs.* 2.7 [95%CI 2.0-3.4]) between patients receiving morphine 2.5 and 7.5 mg, respectively.

Conclusions In intensive care patients after cardiothoracic surgery with low pain levels for pain at rest, there was no difference in efficacy between a bolus of intravenous morphine 2.5 mg or morphine 7.5 mg for pain relief during a painful intervention.

INTRODUCTION

Despite important clinical progress in pain management [1], patients after cardiothoracic surgery in the intensive care unit (ICU) may suffer from postoperative pain [2-3]. Procedural related pain is the most common form of health care induced pain [4], of which turning of the patient and chest drain removal have been identified as the most painful procedures [5-6]. More specifically, patients recall repeated painful procedures as strong negative memories of the time in intensive care unit [7]. Additionally, it has been demonstrated that postoperative pain is a predictor for the development of chronic thoracic pain [8]. When receiving adequate pain relief, ICU patients are reported to be more comfortable, thereby also improving patients' outcome like mortality or morbidity [9].

For pain at rest, recent studies [2,10-11] showed that a pain training programme, in which pain scores were systematically recorded by trained personnel, results in a successful reduction in the occurrence of unacceptable pain at rest. In the study conducted in our ICU [11], 46% of the patients treated after the introduction of the pain training programme, experienced at least one unacceptable pain event at rest during their stay. In order to reduce this incidence, a pain titration protocol for pain management at rest is implemented in our ICU, because individualized titration of analgesia is associated with shorter ICU- and hospital length of stay a lower mortality [12].

Apart from pain at rest, ICU patients may suffer from routine health care painful procedures. However, according to available evidence, procedural pain is difficult to treat, in which one part of the patients will experience unacceptable pain despite treatment [13-15]. No studies are available in which a bolus of analgesics is studied for procedural pain relief in ICU patients who are already treated with individualized titration of analgesia for pain at rest. Therefore, we designed a randomised controlled study to compare the efficacy of a bolus of intravenous morphine 2.5 versus 7.5 mg for procedural pain relief in postoperative patients after cardiothoracic surgery in the ICU, who were already treated according to a pain titration protocol for pain at rest.

MATERIALS & METHODS

Design

A prospective, double-blind, randomised clinical trial was performed in a 30-bed surgical/medical intensive care unit (ICU) in a teaching hospital, Nieuwegein, The Netherlands. The study was approved by the local Ethics Committee of the St. Antonius Hospital, Nieuwegein, The Netherlands. Written informed consent was obtained from the patients before the cardiothoracic surgical procedure. The study was registered at ClinicalTrials.gov (identifier NCT00558090).

Patients

During a 10-month period, patients admitted to the ICU after cardiothoracic surgery though sternotomy, between 18-85 years old and weighting between 45-140 kg were included. Exclusion criteria were planned postoperative admission to the postoperative anaesthesia care unit (PACU) instead of ICU (depending on their co-morbidities), pregnancy or breast-feeding, a language barrier, coma or brain death, patients with a known morphine or paracetamol allergy and patients who refused informed consent. Participant flow is summarized in the CONSORT diagram (Figure 1). Of 528 patients who were scheduled for cardiothoracic surgery

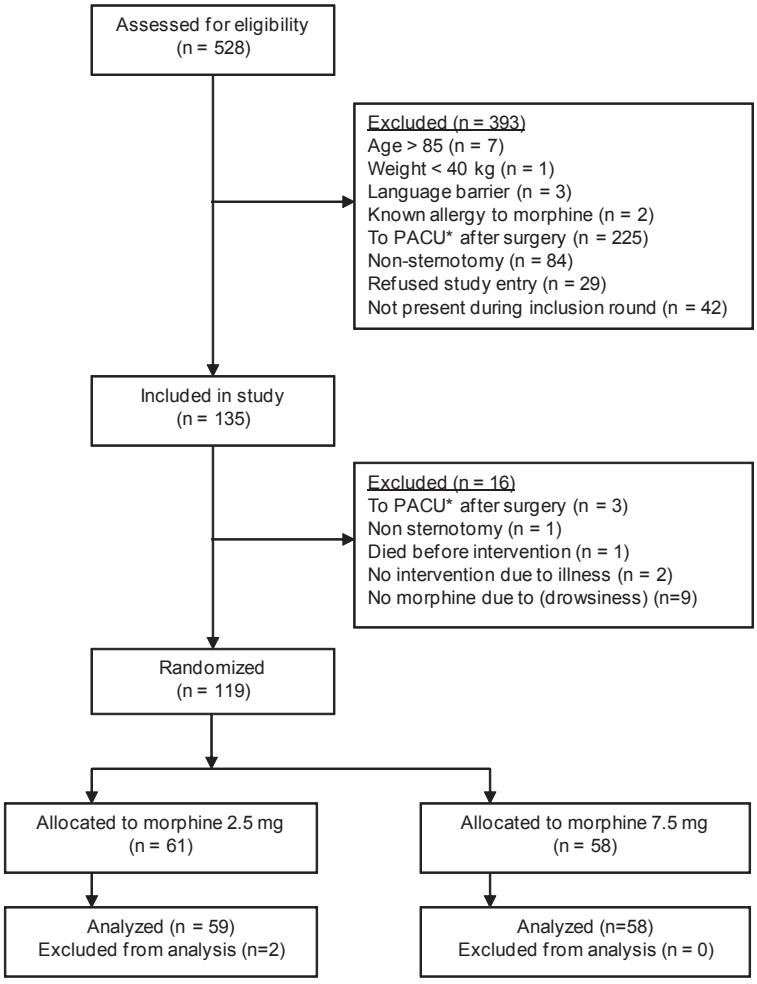


Figure 1. CONSORT diagram

and assessed for eligibility, 393 were excluded and 135 patients were enrolled in the study. The 42 patients who were excluded because they were not present on the ward during inclusion rounds due to medical examination, did not differ from included study patients in terms of demographic characteristics, i.e. mean age (68 years ± 15 *vs.* 69 years ± 11, *P*=0.51), mean BMI (26 kg/m^2 ± 3 *vs.* 27 kg/m^2 ± 4, *P*=0.14), and mean baseline pain scores (NRS 1.4 ± 1.5 *vs.* 1.5 ± 1.7, *P*=0.93) or incidence of unacceptable pain scores at baseline (NRS≥4; 10% *vs.* 13%, *P*=0.78).

Of the 135 patients enrolled in the study, 16 patients were excluded before randomisation of the study medication (Figure 1). Random allocation resulted in 61 patients assigned to 2.5 mg morphine and 58 patients assigned to the 7.5 mg morphine group. In the patients receiving 2.5 mg morphine, one patient was excluded from analysis, because the pain score during the painful procedure was not recorded. One patient was excluded because the intervention was not executed according study protocol.

Intra-operative anaesthetic technique during cardiothoracic surgery

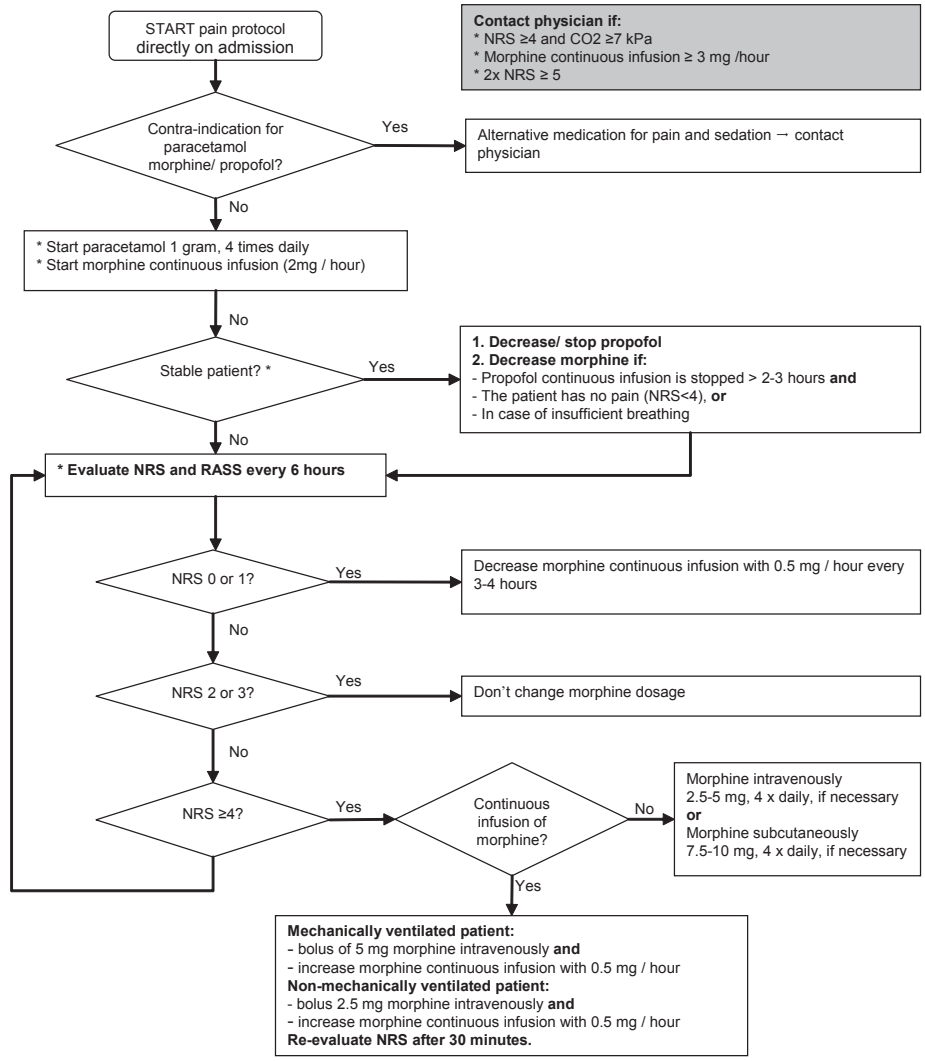
In all patients, midazolam or diazepam, fentanyl and propofol was used for induction of anaesthesia. All patients were paralyzed with pancuronium. Anaesthesia was maintained with propofol, sevoflurane, nitrous oxide and either fentanyl or remifentanil as preferred by the attending anaesthesiologist.

Pain measurements instruments

The NRS was scored by the patient which is considered the gold standard for pain measurement [16]. The NRS was explained to participating patients before cardiothoracic surgery. The NRS is based on a scale from 0 to 10; 0 represents no pain, and 10 represents worst possible pain [17-18]. The NRS has a maximal acceptable pain score of 3 [19]. Severe pain was defined as a NRS≥7 [20]. The minimum clinically significant difference in pain reduction has been determined to be 1.3 to 1.5 [21-22]. In case the patient was not able to report his or her pain, the NRS was scored by the nurse, which has been proven to be a reliable measure [23]. There was no difference between mean NRS scores by the patient and mean NRS scored by the nurse before administration of the study dose morphine (1.7 [95%CI 1.3-2.0] *vs.* 1.3 [95%CI 0.7-1.9]; *P*=0.38) and during intervention (2.7 [95%CI 2.2-3.2] *vs.* 2.3 [95%CI 1.5-3.0].

Standard pain titration protocol for treatment of pain at rest

For basic pain relief, a standard pain titration protocol (Figure 2), consisting of intravenous morphine infusions and intermittent paracetamol, was used in all patients, which is current practice in this ICU since 2007. When patients had an NRS score of ≥4, the attending nurse together with the responsible physician administered additional analgesic medication.



* Hemodynamicly stable, acceptable leakage through thoracic drains, adequate time after muscle relaxation, adequate core temperature
NRS = numeric rating scale
RASS = Richmond Agitation Sedation Scale
ICU = Intensive Care Unit

Figure 2. Pain titration protocol for pain at rest

Study procedures

According a standard pain titration protocol for pain at rest, patients were treated with continuous morphine infusions. The painful intervention took place during routine healthcare procedures on the first postoperative day after cardiothoracic surgery (day 1), between 7.30 a.m. and 9.30 a.m.. Patients received either morphine 2.5 or 7.5 mg intravenously, 30 minutes prior to an unavoidable painful routine intervention, i.e. turning of the patient and/ or chest drain removal, which were both described as painful by patients [5,24]. Pain levels using the NRS were assessed at rest (baseline, before administration of a bolus morphine 2.5 or 7.5 mg), and 5 minutes before, during and 5 minutes after the painful intervention. If necessary, rescue medication (fentanyl) could be administered.

Sample size calculation

With an incidence of unacceptable pain (NRS≥4) of 60% [13] during a painful intervention, the sample size needed for a 25% reduction in incidence of unacceptable pain, is 120 patients. The sample size was calculated with a power of 0.80 and an alpha of 0.05, two sided. Turning of the patient and drain removal have been identified as the most painful routine procedures performed for adults [5-6], in which pain intensity between chest drain removal and turning of the patient was comparable (NRS 6.5 ± 3.9 *vs.* NRS 4.1 ± 3.4) [6]. In our study, there was no difference in pain intensity between turning of the patient and chest drain removal as well (NRS 2.2 ± 2.0 *vs.* 3.1 ± 2.7 respectively; *P*=0.07).

Study medication

Morphine 2.5 and 7.5 mg syringes were prepared using morphine HCl 10 mg = 1 ml solution for injection (Pharmachemie, Haarlem, The Netherlands), which was diluted with sodium chloride 0.9% for a final concentration of morphine 2.5 mg = 10 ml and morphine 7.5 mg = 10 ml respectively. The preparation, packaging and labelling was performed by the Department of Clinical Pharmacy. Syringes were blinded for patients, nurses, physicians and researchers.

Randomisation to morphine 2.5 or 7.5 mg before the painful intervention

Randomisation to one of the two groups was performed using a random allocation schedule generated in blocks of 6 using SPSS. Randomization was performed in blocks of 6 patients to ensure that the morphine 2.5 mg group and 7.5 mg group would be of approximately equally size through the course of the study. The studied dose of 7.5 mg was chosen because it corresponds - in combination with the baseline morphine dosage according to the pain titration protocol - to the morphine dosage of 0.15 mg/kg, which was shown to be effective for pain relief in patients with severe pain [20]. The studied dose of 2.5 mg results from our hypothesis that a pain titration pain protocol combined with a low dose or placebo is sufficient to prevent or treat procedural pain.

Endpoints

Primary endpoint of the study was the percentage of patients with an unacceptable pain score (NRS≥4) at baseline and during painful intervention, in both the group receiving morphine 2.5 mg or 7.5 mg. Secondary endpoints were mean NRS scores during intervention, extreme pain (NRS≥7) during painful intervention, and clinically relevant decrease or increase in the NRS during intervention compared with the NRS before intervention.

Data-analysis

The SPSS statistical package (version 15.0.1 for Windows; SPSS, Chicago, IL) was used for the statistical analyses. Analysis was conducted in patients allocated to receive morphine 2.5 mg and 7.5 mg, although at baseline (at rest), patients still had to receive the study medication. Descriptive statistics are reported as means with SDs, medians with ranges, and proportions. Means were compared using a t-test for normally distributed data or the non-parametric Mann Whitney two-sample rank sum test for data not fitting the assumptions of parametric testing. Proportions were compared by using chi-square tests or Fisher's exact test when appropriate. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Baseline patient characteristics

Baseline demographic and clinical characteristics of patients are described in Table 1. Patients allocated to 7.5 mg morphine were significantly older (72 years ± 9 *vs.* 66 years ± 12, $P<0.002$), had a higher median euroSCORE (8 [range 0-13] *vs.* 6 [range 2-12], $P=0.03$), and were less often exposed to the combination of turning and drain removal (22 patients *vs.* 36 patients, $P=0.03$).

NRS scores at baseline (before administration of a bolus morphine 2.5 or 7.5 mg)

At rest (baseline), overall incidence of unacceptable pain (NRS≥4) was low (16%), and comparable between patients planned for randomization to morphine 2.5 mg and 7.5 mg (14% *vs.* 17%, $P=0.81$) (Table 2, Figure 3). Mean baseline NRS scores at rest were not different between patients receiving 2.5 mg and 7.5 mg morphine (1.5 [95%CI 1.2-2.0] *vs.* 1.7 [95%CI 1.1-2.2]; $P=0.62$). Patients planned for randomization to morphine 7.5 mg received significantly less morphine (13.1 ± 5.9 mg *vs.* 15.9 ± 5.5 mg, $P=0.03$) compared to the patients planned for randomization to morphine 2.5 mg.

Table 1. Baseline characteristics of patients receiving morphine according to the pain titration protocol for pain at rest and a bolus of morphine 2.5 or 7.5 mg thirty minutes before a painful intervention.

	Pain titration protocol + Morphine 2.5 mg (n = 59)	Pain titration protocol + Morphine 7.5 mg (n = 58)	P
Male gender, n (%)	46 (78%)	41 (71%)	0.40
Age (years)	66 [63-69]	72 [70-74]	0.002
Body Mass Index (kg/m^2)	27 [26-28]	27 [26-29]	0.68
History of sternotomy, n (%)	5 (8%)	10 (17)	0.17
History of Diabetes Mellitus, n (%)	10 (17%)	9 (16%)	1.00
History of pain [a], n (%)	11 (18%)	16 (28%)	0.28
Preoperative Pain score NRS ≥ 4 n (%)	3 (5%)	9 (16%)	0.12
Preoperative chronic use, n (%)			
Benzodiazepines [#]	7 (12.3%)	10 (18%)	0.30
Analgesics [b#]	7 (10.3%)	12 (21%)	0.22
Median euroSCORE (range)	6 (2-12)	8 (0-13)	0.03
Intraoperative dose fentanyl			
Total dose (mg)	1.7 [1.5-1.9]	1.6 [1.5-1.7]	0.35
Dose (mcg/kg)	21.1 [19.0-23.2]	20.0 [18.6-21.4]	0.45
Intraoperative dose remifentanil			
Total dose (mg)	1.1 [0.7-1.4]	1.2 [0.9-1.5]	0.49
Dose (mcg/kg)	13.2 [9.1-17.3]	15.2 [11.6-18.9]	0.46
Surgery in the morning/ afternoon	44/15	34/24	0.08
Median RASS score before intervention (range)	0 (-4-2)	0 (-5-1)	0.41
Intervention			
Turning/ Turning & Drain removal, n	23/36	35/23	0.03
Mechanical ventilation, n (%)	9 (15%)	11 (19%)	0.63
NRS scored by patient / nurse, n	48/11	49/9	0.81
Duration between bolus morphine 2.5/7.5 mg and procedural intervention (min)	32 [28-35]	30 [28-32]	0.42

Data are mean [95%CI], median (range), number (percentage) or number/number. [a] Includes chronic back pain, rheumatoid arthritis, polyneuropathy, Herniated Nucleus Pulposus (HNP). [b] Includes paracetamol, NSAID's and opioids. euroSCORE = European System for Cardiac Operative Risk Evaluation score [25]; RASS = Richmond Agitation and Sedation Scale [31]; NRS = numeric rating scale

Table 2. Baseline NRS scores at rest and baseline morphine consumption in patients planned for randomization to morphine 2.5 mg (n=59) vs. 7.5 mg (n=58)

	Pain titration protocol + Morphine 2.5 mg (n = 59)	Pain titration protocol + Morphine 7.5 mg (n=58)	P
Baseline (at rest)			
NRS ≥ 4, n (%)	8 (14%)	10 (17%)	0.81
NRS ≥ 7, n (%)	0 (10%)	3 (5%)	0.12
Mean NRS [95% CI]	1.5 [1.2-2.0]	1.7 [1.1-2.2]	0.62
Median NRS [IQR]	1 [0-3]	1 [0-3]	0.95
Baseline cumulative dose morphine on day of intervention (mg)	15.9 ± 5.5	13.1 ± 5.9	0.03
Baseline cumulative dose morphine on day of intervention (mg/kg)	0.19 ± 0.08	0.15 ± 0.08	0.03
Dose bolus morphine 2.5 / 7.5 mg (mg/kg)	0.03 ± 0.005	0.09 ± 0.016	<0.001

Data are expressed as number (percentage), mean (95%CI) or median (interquartile range [IQR])

NRS = numeric rating scale

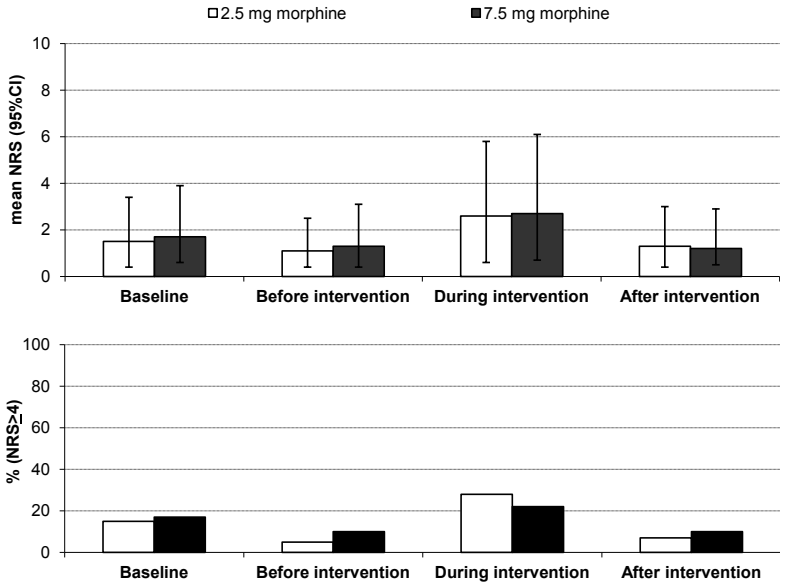


Figure 3. Mean NRS scores (95%CI) and the percentage of patients with unacceptable pain (NRS≥4) at rest (baseline) and before, during and after intervention in patients randomised to receive 2.5 mg (n=59) or 7.5 mg morphine (n=58).

Pain scores before, during and after the painful intervention in patients randomised to receive morphine 2.5 mg versus 7.5 mg

During intervention, overall incidence of unacceptable pain (NRS≥4) was low (25%), and comparable between patients allocated to morphine 2.5 and 7.5 mg (28% and 22% respectively) (Table 3, Figure 3). In both the 2.5 morphine and 7.5 morphine groups, mean NRS scores were low (2.6 [95%CI 2.0-3.2] *vs.* 2.7 [95%CI 2.0-3.4]). 8% and 14% of the patients experienced severe pain (NRS≥7) during the intervention in the morphine 2.5 and 7.5 mg group, respectively. There were no significant differences in mean NRS scores 5 minutes before, during and 5 minutes after the painful intervention between patients receiving morphine 2.5 mg and patients receiving morphine 7.5 mg (Table 3, Figure 3).

No difference was found between the groups morphine 2.5 and 7.5 mg in clinically relevant (ΔNRS≥1.3) decrease (0% *vs.* 3%; *P*=0.24) or increase (42% *vs.* 38% *P*=0.71) in NRS scores. There was also no difference in mean change in NRS scores between both groups (1.5 [95%CI 1.1-1.9] *vs.* 1.4 [95%CI 0.1-2.6] respectively, *P*=0.64) (Table 4). Additionally, in patients with unacceptable pain at rest (baseline), the mean change in NRS score was similar between patients allocated to morphine 2.5 and 7.5 mg (-1.1 [95%CI -2.9-0.7] *vs.* 0.4 [95%CI -2.1-2.9], *P*=0.27). None of the patients received fentanyl rescue medication.

Table 3. NRS scores before, during and after the painful intervention (turning and/or drain removal) in patients randomised to receive morphine 2.5 mg (n = 59) vs. 7.5 mg (n = 58).

	Pain titration protocol + Morphine 2.5 mg (n = 59)	Pain titration protocol + Morphine 7.5 mg (n=58)	P
Before painful intervention (5 minutes before intervention)			
NRS ≥ 4, n (%)	2 (5%)	6 (10%)	0.16
NRS ≥ 7, n (%)	0 (0%)	1 (2%)	0.50
Mean NRS [95% CI]	1.1 [0.7-1.4]	1.3 [0.9-1.8]	0.35
Median NRS [IQR]	1 [0-2]	1 [0-2]	0.66
During painful intervention			
NRS ≥ 4, n (%)	17 (28%)	13 (22%)	0.53
NRS ≥ 7, n (%)	5 (8%)	8 (14%)	0.39
Mean NRS [95% CI]	2.6 [2.0-3.2]	2.7 [2.0-3.4]	0.86
Median NRS [IQR]	2 [1-4]	2 [1-3]	0.81
After painful intervention (5 minutes after intervention)			
NRS ≥ 4, n (%)	3 (7%)	6 (10%)	0.32
NRS ≥ 7, n (%)	0 (0%)	2 (3%)	0.24
Mean NRS [95% CI]	1.3 [0.9-1.7]	1.2 [0.7-1.7]	0.70
Median NRS [IQR]	1 [0-2]	0 [0-2]	0.21

NRS=numeric rating scale

Table 4. Change in mean NRS scores in patients randomised to receive morphine 2.5 mg (n = 59) vs. 7.5 mg (n = 58).

	Pain titration protocol + Morphine 2.5 mg (n = 59)	Pain titration protocol + Morphine 7.5 mg (n=58)	P
Mean Δ NRS [95%CI]			
Between 'baseline intervention' and 'during intervention'	1.1 [0.5-1.7]	1.0 [0.4-1.6]	0.92
Between 'baseline intervention' and 'before intervention'	-0.4 [-0.7- 0.1]	-0.3 [-0.6 -0.0]	0.59
Between 'before intervention' and 'during intervention'	1.5 [1.0-2.1]	1.4 [0.8-1.9]	0.64
Between 'during intervention' and 'after intervention'	-1.3 [0.8-0.1.8]	-1.5 [1.0-2.0]	0.58
Clinically relevant decrease NRS, n (%)*			
Between 'before intervention' and 'during intervention'	0 (0)	2 (3)	0.24
Between 'during intervention' and 'after intervention'	20 (33)	23 (40)	0.57
Clinically relevant increase NRS, n (%)*			
Between 'before intervention' and 'during intervention'	25 (42)	22 (38)	0.71

Clinically relevant decrease/ increase = Δ NRS> 1.3

DISCUSSION

In this study, we evaluated the efficacy of morphine 2.5 versus 7.5 mg for the prevention and treatment of a non-avoidable painful intervention in ICU patients after cardiothoracic surgery, who were already treated according to a pain titration protocol for pain at rest. In patients with low pain levels for pain at rest, there was no difference in efficacy between a

bolus of intravenous morphine 2.5 mg or morphine 7.5 mg for pain relief during a painful intervention.

During the painful intervention, we found a substantially lower incidence of unacceptable NRS scores (25%), compared to previous reports. In these studies, incidences of 32% to 62% were reported during endotracheal suctioning and movement in patients with various morbidities [13-15]. In addition, mean NRS scores during the painful intervention were low (Table 3) compared to other studies, in which mean NRS scores of 5 and 7 were recorded during turning and drain removal, respectively [5-6]. In these studies, pain was managed with standard doses of analgesics for pain relief at rest or during procedural interventions only [26-28], in contrast to our study using a pain titration protocol. As such, the pain titration protocol which is applied during the entire ICU stay may not affect pain scores at rest alone, but may also lead to a decrease of pain intensity during painful procedures. This is partly explained by the study of Aubrun et al. [20], who concluded that patients with an initial visual analogue scale (VAS) ≥6 need more often rescue medication after morphine titration compared to patients with VAS<6 in the treatment of postoperative pain.

The dose of morphine 7.5 mg in our study was in accordance with the described literature for the prevention of procedural pain. Aubrun et al. [20] reported that a threshold of 0.15 mg/kg morphine is needed for pain relief in patients with severe pain (NRS≥7) during postoperative pain titration. A lower dose of 0.10 mg/kg was less effective compared to 0.15 mg/kg for pain reduction in emergency department patients with acute pain. A higher dose of 0.25 mg/kg morphine was reported to lead to respiratory depression compared to 0.15 mg/kg [29]. Our dose of morphine 7.5 mg combined with the standard titration protocol is therefore the most optimal dose as it is in accordance with the maximum dose of 0.15 mg/kg. In contrast, the dose of morphine 2.5 mg results from our hypothesis that a pain titration protocol for managing pain at rest combined with only a low dose morphine is sufficient to prevent or treat procedural pain. However, we cannot exclude that morphine 2.5 mg is comparable to placebo. In that case, the pain titration protocol is more important for procedural pain management than a bolus of morphine.

Concerning pain at rest, previous reports showed that systematic pain measurement reduced incidences of unacceptable pain (NRS≥4) at rest to approximately 40% [2,10-11]. In our study, we were able to reduce the incidence of unacceptable pain at rest to 16%, as result of morphine titration adapted to individual pain. In the group patients allocated to morphine 7.5 mg, similar NRS scores could be achieved by a lower baseline morphine consumption compared to the patients allocated to morphine 2.5 mg. The difference in morphine consumption can be explained by the difference in baseline characteristics, as patients allocated to morphine 7.5 mg were significantly older and had a higher euroSCORE. It is well known that older patients need less analgesics for pain relief than younger patients [30]. Patients with a high euroSCORE are probably more vulnerable for the effects of medication, due to impaired condition of elimination organs, e.g. kidney and liver. This condition may result in

a slower elimination of morphine, thereby leading to lower morphine consumption in these patients. Thus, the pain titration protocol leads to an individual dosing regimen of analgesics, thereby resulting a low incidence of unacceptable pain at rest (16%).

Some remarks must be included concerning the limitations of our study. First, patients receiving 7.5 mg were more often exposed to the intervention 'drain removal', which may be more painful than the intervention 'turning' and thus may have reduced the difference in effect of pain relief between the patients receiving 2.5 mg and 7.5 mg. However, there was no significant difference in pain intensity between turning and drain removal. Secondly, the low procedural pain levels may theoretically have contributed to the reported lack of difference in pain levels between the morphine 2.5 and 7.5 mg group. I.e. as a result of the low overall pain scores which the patients reported within the context of the pain titration protocol, further decrease of pain intensity is more difficult to detect. In the ideal study design, we compared morphine 7.5 mg with placebo in combination with the pain titration protocol. However, for ethical considerations we preferred to treat these patients with a low dose of morphine. In this context, morphine may be dosed on kg bodyweight instead of a fixed dose. Finally, it cannot be excluded that the low overall pain scores in a context of studying the clinical trial itself. During a clinical trial with relation to pain management, all health care workers in the ICU will be "affected" in their approach to pain treatment.

In conclusion, in intensive care patients after cardiothoracic surgery with low pain levels for pain at rest, there was no difference in efficacy between a bolus of intravenous morphine 2.5 mg or morphine 7.5 mg for pain relief during a painful intervention.

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Chapter **6**

THE VAL158MET POLYMORPHISM OF THE CATECHOL-O-METHYLTRANSFERASE (*COMT*) GENE IS ASSOCIATED WITH INCREASED PAIN SENSITIVITY IN MORPHINE TREATED-PATIENTS UNDERGOING A PAINFUL PROCEDURE AFTER CARDIAC SURGERY

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ABSTRACT

Background and objectives The catechol-O-methyltransferase (*COMT)* Val158Met polymorphism affected healthy volunteers' pain sensitivity upon experimental pain stimuli. The relevance of these findings in morphine-treated postoperative cardiac patients undergoing painful health care procedures is unknown. Therefore, we aimed to investigate whether the *COMT* Val158Met polymorphism influences pain sensitivity in morphine-treated patients undergoing an unavoidable routine painful procedure after cardiac surgery.

Methods 117 non-paralysed postoperative cardiac patients in the intensive care (ICU) were genotyped for the *COMT* Val158Met polymorphism. All patients were treated with continuous morphine infusions for pain at rest, and received a bolus of morphine (2.5 or 7.5 mg) before a painful procedure (turning and/or chest drain removal) on the first postoperative day. NRS scores were evaluated at four time points, i.e. at baseline (at rest), and before, during, and after the painful procedure.

Results Overall mean NRS scores were significantly higher in patients carrying the Met-variant allele. During the painful procedure, the mean NRS score was significantly higher for Met/Met patients compared to Val/Met and Val/Val patients (mean NRS 3.4 ± 2.8, 2.7 ± 2.4 and 1.7 ± 1.7, respectively; P=0.04). In Met/Met patients, the increase in NRS scores during the painful procedure compared with baseline NRS score was clinically relevant (ΔNRS≥1.3) and statistically significant and appeared independent of sex and the morphine bolus dose.

Conclusions Our results show that the *COMT* Val158Met polymorphism contributes to variability in pain sensitivity in morphine treated-patients after cardiac surgery in the ICU, as Met-allele carriers were more sensitive to overall pain and procedure-related pain.

INTRODUCTION

Postoperative pain is a frequent problem in cardiac surgery [1]. It is characterized by a large inter-individual variability, even when the patient is at rest [2]. On the other hand, the numerous unavoidable painful health care procedures in the intensive care unit (ICU) produce pain levels that may differ largely between patients. Turning of the patient and chest drain removal have been identified as the most painful procedures [3-4]. This inter-patient variability in pain sensitivity may partly be explained by environmental factors such as age, sex or anxiety [5-7]. Furthermore, some candidate genes have been associated with differential pain sensitivity [2,8].

The cathechol-*O*-methyltransferase (*COMT*) enzyme may contribute to the variability in pain sensitivity because it has a role in pain processing. *COMT* metabolizes dopamine, epinephrine and norepinephrine, and is a key modulator of dopaminergic and adrenergic neurotransmission [9]. *COMT* contains a common functional coding polymorphism corresponding to a valine-to-methionine substitution at codon 158 (Val158Met). This substitution has been associated with a three- to four fold decrease in *COMT* activity [10]. Zubieta et al. [11] have suggested that lower *COMT* activity leads to an enhanced activation of the dopaminergic neurotransmission, with lower endogenous levels of enkephalins and thus exaggerated pain sensitivity as a result [11]. More specifically, in an experimental study these authors showed that healthy volunteers with the Met/Met genotype reported higher pain ratings than did those with the Val/Val genotype. In addition, subjects with the Met/Met genotype showed weaker activation of the endogenous opioid system on experimental pain stimuli than did subjects with the Val/Val genotype. These results were confirmed in two other experimental studies with healthy volunteers [12-13], and in one study evaluating morphine consumption in patients with chronic cancer pain [9]. There are however no reports on the relevance of this polymorphism on acute postoperative pain, i.e. after cardiac surgery, experienced either at rest or upon an unavoidable painful healthcare procedure, such as chest drain removal or turning of the patient, when patients were treated with intravenous morphine infusions.

In a recent clinical trial in postoperative cardiac patients of our group [14], pain levels were studied around an unavoidable routine painful procedure, *i.e.* turning of the patients and/or chest drain removal. Despite continuous morphine infusions and a bolus dose of morphine before the procedure, 25% of the patients experienced unacceptable pain rated on the numeric rating scale (NRS≥4, range 0-10 [15]) [14]. In the present study we tested the hypothesis that the *COMT* Val158Met polymorphism may explain these high pain levels upon the unavoidable painful procedure in these postoperative cardiac patients. Therefore, the aim of this study was to investigate the influence of the *COMT* Val158Met polymorphism on pain sensitivity during an unavoidable painful routine healthcare procedure in morphine-treated adult patients after cardiac surgery in the ICU.

METHODS

Design

A prospective observational study was performed in a 30-bed surgical/medical ICU in a teaching hospital, St Antonius Hospital, Nieuwegein, The Netherlands. The study was part of a randomised controlled trial (registered at ClinicalTrials.gov, identifier NCT00558090) evaluating postoperative cardiac patients' pain levels around an unavoidable painful procedure in the ICU. The clinical trial was approved by the St. Antonius Hospital Ethics Committee and written informed consent was obtained from all patients before the cardiac surgical procedure.

Patients

During a 10-month period, we considered eligibility of all patients aged from 18 to 85 years admitted to the ICU after cardiac surgery though sternotomy, as described in a previous report [14]. Within the randomised controlled trial for the prevention and treatment of procedural pain, 135 patients were considered, 129 of whom were enrolled in the study according to the eligibility criteria. Nine of those 129 patients were excluded from analysis because they underwent a second sternotomy in the first 48 postoperative hours. Two patients were excluded because the painful procedure was not executed. One other patient was excluded because genotyping failed. Hence, 117 patients were included in the analysis.

Pain measurements instrument

The patients themselves, in principle, rated their pain levels on the numeric rating scale (NRS), as this is considered as the gold standard for pain measurement [16]. The NRS is based on a scale from 0 to 10; 0 represents no pain, and 10 represents worst possible pain [17-18]. A NRS score of 4 and higher is considered as unacceptable pain [15]. Pain increase or decrease is considered as clinically significant when the NRS change is at least 1.3 to 1.5 [19]. The NRS was used to assess postoperative pain at rest and during procedural pain. Scoring was explained to all participating patients before cardiac surgery. If a patient was not able to self-report, the NRS was scored by the nurse, which has been proven to be a reliable measure [20].

Standard pain titration protocol for treatment of pain at rest

For basic pain relief, a standard pain titration protocol, consisting of intravenous morphine infusions and intermittent paracetamol administration, was used in all patients, which is current practice in our ICU since 2007. Postoperatively patients rated their pain using the NRS at three standardised times, which is routine nursing care. At NRS scores of ≥4, the attending nurse, along with the responsible physician, prescribed and administered additional analgesic medication [21].

Procedures

On day 0, patients underwent (non)-elective cardiac surgery through sternotomy. Before surgery, one blood sample (10 ml) for *COMT* genotype determination was collected. After surgery, patients were admitted to the ICU, and were treated with continuous morphine infusions according to the standard pain titration protocol to manage pain at rest [14].

On the first postoperative day, thirty minutes prior to the unavoidable routine care painful procedure, i.e. turning of the patient and/or chest drain removal between 7.30 a.m. and 9.30 a.m., patients received an intravenous bolus dose of morphine of either 2.5 or 7.5 mg [14]. Pain levels were assessed using the NRS at four time points, i.e. at baseline (immediately before administration of the morphine bolus dose), and 5 minutes before, during, and 5 minutes after the procedure. Patients' characteristics and perioperative data were collected.

Genotype analysis

Genomic DNA was isolated from 200 µl ethylenediaminetetraacetic acid-treated whole blood using a MagnaPure LC (Roche Diagnostics GmbH, Mannheim, Germany). The *COMT* rs4680G>A polymorphism (Val158Met) was determined through allelic discrimination analysis using TaqMan® (Applied Biosystems, CA, USA) genotyping assays (C__25746809_50) on the ABI PRISM 7500® Fast real-time PCR Systems (Applied Biosystems, CA, USA). The PCR cycle consisted of an initial step of 1 min at 60°C, followed by a denaturation step at 95°C for 30 sec and 40 cycles with 95°C for 3 sec and 60°C for 30 sec. The final post-PCR read was made in 1 min at 60°C. The volume for each reaction was 12 µl, consisting of 5 µl TaqMan® GTXpress™ Master Mix, 0.125 µl of TaqMan® SNP genotyping assay (80x), containing the primers (64 µM) and the probes (16 µM), and 20 ng genomic DNA.

Statistical analysis

Statistical analyses were made with the SPSS statistical package (version 18.0 for Windows; SPSS, Chicago, IL). Continuous data are expressed as mean ± SD or median (range) where appropriate. To estimate the effect of genotype on the outcome variables (NRS scores), NRS scores were compared between genotypes by a linear mixed-model analysis based on the maximum likelihood ratio with the patient genotype status as fixed factors and the time point of pain assessment as repeated measurement. No structure was imposed on variances and covariances between and within times of the repeated measurements. To adjust for potential confounding, linear mixed-model analysis was also performed by adding sex and the dose of morphine as covariates.

One-way ANOVA was performed to compare means between the three genotype groups (Val/Val, Val/Met and Met/Met genotype) at a single time point under the null hypothesis that the means of the compared groups were equal. Potentially confounding effects of patient's sex status and the morphine dose (2.5 *vs.* 7.5 mg) were assessed with multiple linear regression analyses. For these models, the homozygous genotype for the most frequent allele was

set as the reference. Student's paired t-tests served to test the significance of the change in NRS scores during the painful procedure (third time point) when compared to baseline (i.e. before morphine bolus dose; first time point), either for the entire population or for sub-groups stratified by COMT genotype. Categorical data are expressed as percentage of total in each category and the associations were tested by Pearson's Chi Square test. A *P*-value of ≤ 0.05 was considered as statistically significant.

RESULTS

Patient characteristics

Thirty-two women and eighty-five men were included in the study, all Caucasian except two patients, who were of Asian and African American origin. Thirty patients were homozygous for the wild-type allele (Val/Val) with regard to the *COMT* Val158Met polymorphism; 66 were heterozygous (Val/Met); and 21 were homozygous for the variant allele (Met/Met). This yielded a 46.2% frequency of the Met-allele, in line with previous data [13], while the genotype distribution did not deviate from the Hardy-Weinberg equilibrium (χ^2=2.1, *P*=0.14). Patient characteristics are presented in Table 1; there were no differences between the three genotype groups with respect to sex, age, type of surgery, intraoperative use of analgesics,

Table 1. Patients' characteristics

	Val/Val	Val/Met	Met/Met	P
Number of patients	30	66	21	
Age (yrs)	71 ± 11	69 ± 11	66 ± 12	0.45
Sex (male/ female), n	22/8	49/17	14/7	0.79
BMI (kg/m^2)	27.7 ± 4.3	27.5 ± 4.2	26.6 ± 3.9	0.59
Type of cardiac surgery, n (%)				0.41
CABG	7 (23%)	16 (24%)	2 (10%)	
Valve	5 (17%)	16 (24%)	7 (33%)	
CABG and Valve surgery	14 (47%)	23 (35%)	6 (29%)	
Aorta surgery	4 (13%)	11 (17%)	6 (29%)	
Mean duration of anaesthesia (hours)	4.2 ± 1.2	4.2 ±1.0	3.7 ± 1.1	0.24
Mean intraoperative dose of fentanyl (mg)	1.6 ± 0.5	1.6 ±0.5	1.7 ±0.6	0.68
Mean intraoperative dose of remifentanil (mg)	1.0 ± 1.0	1.2 ±1.3	1.3 ±1.3	0.71
Cumulative postoperative dose morphine (mg) before morphine bolus	12.6 ± 6.8	13.6 ± 6.7	14.7 ± 6.6	0.55
Dose morphine bolus 2.5 or 7.5 mg *	14/13	30/33	15/6	0.16
Unavoidable routine care procedure				
Turning/ turning & drain removal	11/19	36/30	8/13	0.18
Mean ICU stay (days)	2.1 ± 1.6	2.3 ± 2.2	2.4 ± 1.5	0.83

All values are expressed as mean ± SD or as number (percentage). COMT = catechol-*O*-methyltransferase; BMI = body mass index; CABG=coronary artery bypass graft; ICU=intensive care unit

* 6 missing values.

or cumulative morphine consumption before the painful procedure. Finally, proportions of patients randomised to receive either a 2.5 or 7.5 mg bolus dose of morphine did not differ between the three genotype groups (χ^2=3.6, *P*=0.16, Table 1).

NRS scores around the painful procedure

Figure 1 illustrates the NRS pain scores at the four time points for the three genotype groups. In a linear mixed-model considering all four time points, analysis of repeated measurement demonstrated that the overall mean NRS scores estimated from the model were significantly different across *COMT* genotype clusters, being on average 1.2 ± 0.2, 1.6 ± 0.1 and 1.9 ± 0.2 for Val/Val, Val/Met and Met/Met patients, respectively (*P* ANOVA=0.03) (Figure 1).

Pair-wise analyses revealed that the mean difference in NRS score significantly differed between patients with the Met/Met genotype and patients with the Val/Val genotype (ΔNRS = 0.7 ± 0.3; *P*=0.01). This difference was not significant between Val/Met patients versus Met/Met patients (ΔNRS = -0.3 ± 0.2; *P*=0.19) and versus Val/Val patients (ΔNRS = 0.4 ± 0.2, *P*=0.07) (Figure 1). When sex was introduced as a covariate in the linear mixed-model analysis,

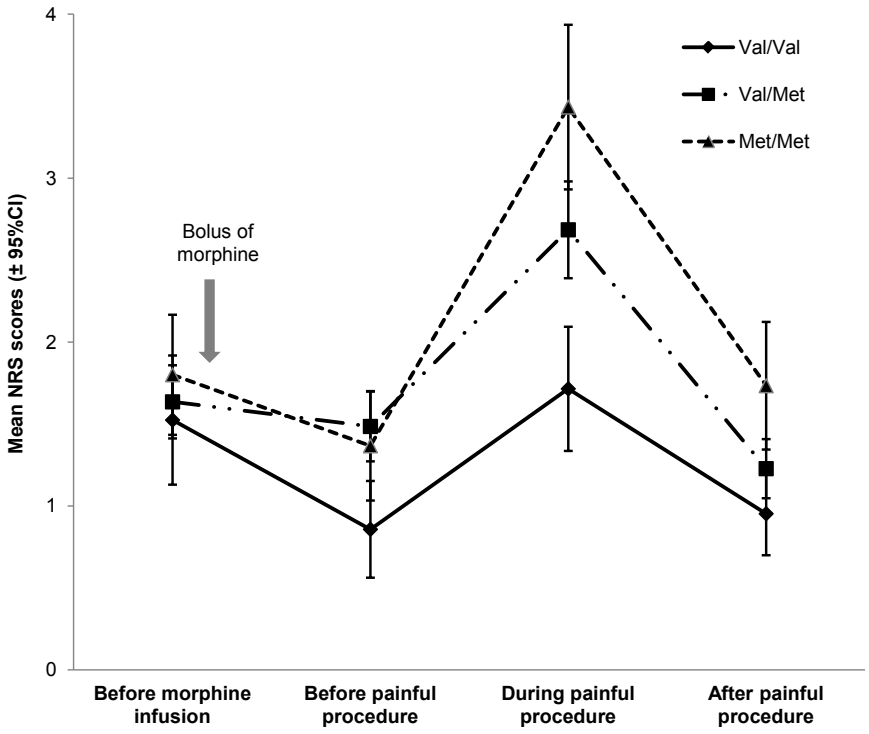

Figure 1. Mean NRS scores around the painful procedure.
Pain was rated at four individual times using the numeric rating scale (NRS). A bolus morphine was administered after time point 'at baseline'. Linear mixed model analysis revealed a significantly higher overall NRS score in patients with the Met/Met genotype compared to patients with the Val/Met patients and Val/Val patients.

adjusted mean NRS scores were 1.1 ± 0.23, 1.5 ± 0.15 and 1.8 ± 0.20 for Val/Val, Val/Met and Met/Met patients, respectively (*P* ANOVA=0.03), indicating that the effect of *COMT* genotype was independent of sex.

Table 2 reports mean NRS scores for the four time points separately. Only the mean NRS scores during the painful procedure were significantly different between the genotype groups (*P*=0.04). The highest pain score was recorded for patients with the Met/Met genotype (mean NRS 3.4 ± 2.8), followed by heterozygous patients with the Val/Met genotype (mean NRS 2.7 ± 2.4) and patients with the Val/Val genotype (mean NRS 1.7 ± 1.7). At this time point, the difference in mean NRS scores between Val/Val and Met/Met patients was thus 1.7, which is considered clinically relevant (ΔNRS≥1.3-1.5). In an additional analysis, we adjusted for potential confounding by sex. In a multiple linear regression model, the difference in mean NRS score between the genotype groups at any of the four time points remained significant (*P*=0.01).

At last, unacceptable pain scores (NRS≥4) during the painful procedure were considered. In total, 26% of the 117 patients experienced unacceptable pain (NRS≥4) during the painful procedure. Proportions of patients reporting such high scores did not differ between the three genotype groups (*P* = 0.14).

Table 2. NRS scores at individual time points

	Baseline (pain at rest)	Before painful procedure	During painful procedure	After painful procedure
NRS score				
Val/Val	1.5 ± 1.8	0.9 ± 1.4	1.7 ± 1.7	1.0 ± 1.2
Val/Met	1.6 ± 1.8	1.5 ±1.7	2.7 ± 2.4	1.2 ± 1.5
Met/Met	1.8 ± 2.0	1.4 ±1.8	3.4 ± 2.8	1.7 ± 2.1
P – value	0.86	0.34	0.04	0.20

All values are expressed as mean ± SD

COMT = catechol-*O*-methyltransferase; NRS = numeric rating scale

Increase in NRS scores upon the painful procedure compared with baseline

For all patients, the NRS increase (ΔNRS), corresponding to the NRS score recorded during the painful procedure minus the baseline NRS score recorded before the bolus administration of morphine, was a mean of 1.1 ± 2.3, indicating a statistically significant increase (*P*<0.001), albeit not a clinically significant increase (ΔNRS<1.3).

Regarding the subgroups, the Met/Met homozygote group showed a statistically significant and clinically relevant increase in the NRS score during the painful procedure compared with baseline, with a mean ΔNRS of 1.6 ± 2.5 (*P*=0.001). The mean ΔNRS for the Val/Met group was 1.1 ± 2.2 (*P*<0.001), which is not considered clinically relevant; that for the Val/Val homozygote group 0.2 ± 1.8 (*P*=0.63), thus neither statistically significant nor clinically relevant. In a multiple linear regression model to adjust for potential confounding by sex, the ΔNRS score was significantly related with the *COMT* allelic status (*P*=0.03) and this relationship was not

modified when sex was introduced as an independent variable. Similar results were observed after stratification according to the bolus dose of morphine (*i.e.* 2.5 or 7.5 mg), indicating that the change in NRS scores was independent of the bolus morphine dose (data not shown). Altogether, 29 patients (24%) who reported acceptable pain (NRS<3) at baseline, reported unacceptable pain (NRS≥4) during the painful procedure; proportions of these patients did not differ between the genotype groups ($P = 0.20$).

DISCUSSION

We evaluated the influence of the *COMT* Val158Met polymorphism in postoperative cardiac patients treated with continuous morphine infusions to manage pain at rest and with an additional bolus dose of morphine before an unavoidable postoperative painful procedure (chest drain removal and/or turning of the patient) in the ICU. The main finding was that patients carrying the Met-variant allele experienced both significantly increased overall pain and significantly increased pain during the painful procedure, compared to patients with the Val/Val genotype. More specifically, patients with the Met/Met genotype showed a statistically significant and clinically relevant increase in pain scores during the painful procedure, unlike patients with the Val/Val genotype. To our knowledge, this is the first study evaluating the impact of the *COMT* Val158Met polymorphism on pain sensitivity within a clinical research design in morphine-treated postoperative patients undergoing an unavoidable painful stimulus. So far, only healthy volunteer studies have evaluated this polymorphism in relation to pain sensitivity applying experimental pain stimuli, with similar results as in the present study (Table 3). Loggia et al. [22] demonstrated that individuals with the Met/Met genotype exhibit stronger pain signals in numerous cortical and subcortical structures after repeated noxious stimulation when compared to other genotype groups. This is also consistent with other studies evaluating the impact of the *COMT* Val158Met polymorphism on pain sensitivity. Zubieta et al. [11] demonstrated that Met/Met subjects were characterized by higher sensory and affective pain ratings; two other studies [12-13] found that Met/Met individuals were more susceptible to pain after repeated thermal stimuli. Jensen et al [13] showed that, after remifentanil bolus injection and repeated heat pain stimuli, Met/Met subjects reported higher pain scores than did Val/Val subjects, while heterozygous subjects reported intermediate scores. Thus, the results of our clinical study confirm the results of the experimental pain studies in healthy volunteers, where pain sensitivity of patients carrying the Met-allele experience was higher than that of patients with the Val/Val genotype. As such, we showed that this genotype-related difference in pain sensitivity is clinically relevant in morphine-treated patients after cardiac surgery undergoing an unavoidable – instead of experimental – pain stimulus in the ICU.

Table 3. Overview of studies which investigated the COMT Val158Met polymorphism in relation to pain sensitivity

Study design	Study population	Intervention	Main outcome	Reference
Experimental	29 Healthy volunteers	Binding potential of the mu-receptor and muscle pain was measured twice: during intensity controlled sustained pain induced by infusion of 5% hypertonic saline into the masseter muscle and during the infusion of non-painful 0.9% isotonic saline.	Subjects with the Met/Met genotype of the COMT Val158Met polymorphism showed diminished regional μ-opioid system responses to pain compared with Met/Val and Val/Val subjects. These effects were accompanied by higher sensory and affective ratings of pain.	[11]
Experimental	202 Female healthy volunteers	Threshold and tolerance to thermal, ischemic, and mechanical stimuli, as well as temporal summation to heat pain, were determined.	The Val158Met polymorphism was associated with sensitivity to painful heat stimuli, which suggest that the Val158Met polymorphism plays a primary role in variation in temporal summation of pain.	[12]
Experimental	43 Healthy volunteers	Five blocks of thermal heat pain were induced to the hand. After each stimulus subjects rated pain on a VAS. Before the second and the fourth stimulus, respectively an intravenous injection of remifentanil (0.08 mg/kg) and placebo was administered.	Met/Met subjects reported significantly more pain compared to Val/Val subjects in case of repeated pain stimuli, although not during an initial response of the descending pain system. The opioid intervention induced analgesia without a separating effect for genotype.	[13]
Experimental	54 healthy volunteers	Subjects received two heat pain stimuli on the right forearm during functional Magnetic Resonance Imaging (fMRI). After each stimulus, subjects rated their pain intensity using the Gracely Sensory scale (GSS).	Met/Met subjects showed stronger pain-related fMRI signals than Val/Val subjects in several brain structures, only for high intensity pain stimuli after repeated administration	[22]
Clinical research design	207 morphine-treated patients for chronic cancer pain	Between the genotype groups, morphine doses, serum concentrations of morphine and morphine metabolites were compared.	After a mean treatment period of 3.5 months, patients with the Val/Val genotype needed more morphine when compared to the Val/Met and the Met/Met genotype groups. Pain scores were not reported.	[9]

VAS = visual analogue scale, range 0-10

Although, we found a clinically relevant increase in NRS score in patients with the Met/Met genotype, proportions of patients whose pain increased from an acceptable level (NRS<4) at baseline to an unacceptable level (NRS≥4) during the painful procedure did not differ between the genotype groups. We realize that in our study the mean NRS scores generally were low (NRS<4), and that especially the increase to unacceptable pain during the painful procedure should be prevented. However, the knowledge that patients with the Met/Met genotype are at higher risk for a clinically relevant increase in pain during a painful intervention may be of value for procedural-related pain management.

The results of our study suggest that patients carrying the Met-allele may benefit from a more individualized therapy in case of a second surgery. Higher morphine doses may be anticipated, although only a small increase in efficacy may be expected at an increased inci-

dence of adverse events. In this respect, non-opioid analgesics may be preferable, as they act independent of endogenous enkephalin levels and the μ-receptor density. However, agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) may be disadvantageous in post-operative cardiac patients as they carry the risk of cardiovascular side effects. Thus, further research should focus on these and other aspects of individualized pain management.

In our study, patients received continuous morphine infusions for pain at rest, and a bolus dose of morphine before a painful procedure. Morphine requirement did not differ between the genotype groups during ICU stay and during the painful procedure. Interestingly, at first sight our results deviate from the observation made by Rakvåg et al. [9] that Met/Met homozygous cancer patients required less morphine compared to patients with the Val/Val variant. The authors suggest this may be explained by an increase in μ-opioid receptor density in Met/Met patients, which causes morphine to be more effective. However, those patients were treated for prolonged cancer pain for approximately 3.5 months [9], in contrast with our patients who were treated for postoperative acute pain (maximum for 48 hours). It is possible that an increase in μ-opioid receptor density may occur after a more prolonged period of opioid treatment. Moreover, the study of Rakvåg et al. [9] concerned a heterogeneous group of patients, with differences in disease severity and progression, and thus several nociceptive stimuli, whereas in our study all patients underwent the same painful procedure.

Considering the bolus morphine (2.5 *vs.* 7.5 mg), we observed no significant effect of the genotype on the analgesic response of morphine. These results are supported by the study of Jensen et al. [13] (Table 3), in which a single dose of remifentanil before a heat stimulus induced analgesia, without a separating effect for genotype. They also found that Met/Met subjects reported significantly more pain than did Val/Val subjects in case of repeated pain stimuli, except after the initial pain stimulus. As our patients underwent cardiac surgery the day before the painful procedure, it is likely that the pain system was already triggered at the time of the painful procedure. Therefore, we suggest that Met/Met patients receiving the same dose as Val/Val patients are more sensitive to pain as a result of repeated painful stimuli, which is independent of a morphine bolus dose.

Two limitations of our pilot study should be addressed. Firstly, our study was in fact underpowered because this analysis was conducted within a randomised controlled trial, and was thus not designed primarily as a pharmacogenetic study. However, even with these low numbers of patients, we found a significant effect of genotype on both overall pain levels and pain during the painful procedure. Secondly, pain sensitivity is influenced by many factors, including probably genetic contributions of more than one gene. Therefore, this study cannot determine the relative importance of the *COMT* Val158Met polymorphism compared to other genes involved in pain.

In conclusion, the results of the present clinical study suggest that the *COMT* Val158Met polymorphism is correlated to pain sensitivity in morphine treated-patients undergoing a

painful healthcare procedure after cardiac surgery, showing that Met-allele carriers are more sensitive to overall pain and procedural pain.

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Chapter **7**

REMIFENTANIL DURING CARDIAC SURGERY IS ASSOCIATED WITH CHRONIC THORACIC PAIN ONE YEAR AFTER STERNOTOMY

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ABSTRACT

Background and objectives Chronic thoracic pain after cardiac surgery is a serious condition affecting many patients. The aim of the study was to identify predictors for chronic thoracic pain after sternotomy in cardiac surgery patients by analysing patient and perioperative characteristics.

Methods A follow-up study was performed in 120 patients who participated in a clinical trial on pain levels in the early postoperative period after cardiac surgery. The presence of chronic thoracic pain was evaluated by a questionnaire one year after surgery. Patients with and without chronic thoracic pain were compared. Associations were studied using multivariable logistic regression analysis.

Results Questionnaires of 90 patients were analysed. Chronic thoracic pain was reported by 18 patients (20%). In the multivariable regression model, remifentanil during cardiac surgery, age below 69 years and a body mass index above 28 kg/m^2 were independent predictors for chronic thoracic pain (Odds ratios 8.9 [95%CI 1.6-49.0], 7.0 [95%CI 1.6-31.7], 9.1 [95%CI 2.1-39.1], respectively). No differences were observed in patient and perioperative characteristics between patients receiving remifentanil (58%, n=52) compared to patients not receiving remifentanil (42%, n=38).The association between remifentanil and chronic thoracic pain appeared dose-dependent, both for total dose and for dose corrected for kg Lean Body Mass and duration of surgery (*P* for trend <0.01 and <0.005, respectively).

Conclusions In this follow-up study in cardiac surgery patients, intraoperative remifentanil was predictive for chronic thoracic pain in a dose-dependent manner. Randomized studies designed to evaluate the influence of intraoperative remifentanil on chronic thoracic pain are needed to confirm these results.

INTRODUCTION

Chronic thoracic pain after cardiac surgery via sternotomy is a serious condition affecting many patients. Recent studies report incidences varying from 11 to 56% [1-6], depending on the definition and the study population [7]. Patients suffering from chronic thoracic pain experience a significantly lower physical and mental health status compared with patients without chronic thoracic pain [1-2,8-9]. In order to prevent chronic pain, studies are needed to identify factors that may predict an increased likelihood [7].

Previous studies recognized younger age [2-3,8,10], increased body mass index (BMI) [8] and female gender [6] as predictors for chronic thoracic pain. Furthermore, in different studies severe immediate postoperative pain [6,10], non-elective surgery [6] or a resternotomy in the early postoperative period [6] have been suggested. The variety in the identified predictors may result from the different definitions for chronic pain and heterogeneity of the patient populations, as well as the retrospective design of most studies. The majority of the studies lacked detailed information from the perioperative period, such as pain levels before surgery or the choice and dose of anaesthetics and analgesics used during cardiac surgery. In this respect, it has been shown that the anaesthetics used during surgery may have long-term effects regarding chronic pain, as Salengros et al. [11] showed for remifentanil in patients who underwent a thoracotomy.

We performed a follow-up study of patients who participated in a clinical trial on pain levels in the early postoperative period in the intensive care unit (ICU) after cardiac surgery. The present study aimed to identify predictors for chronic thoracic pain one year after cardiac surgery via sternotomy by analysing detailed patient and pre-, intra- and postoperative characteristics.

METHODS

Design and patients

A follow-up study was conducted in 120 patients who participated in a prospective, double blind randomised clinical trial on procedural analgesia in the ICU after cardiac surgery (ClinicalTrials.gov identifier: NCT00558090). The inclusion criteria for this clinical trial were patient informed consent, admittance to the ICU after cardiac surgery via sternotomy, age between 18 and 85 years and body weight between 45 and 140 kg. Exclusion criteria were pregnancy or breast-feeding, an inability to communicate in either Dutch or English, coma or brain death and a known morphine or paracetamol allergy. For the clinical trial, informed consent was given by 135 patients. Four patients were excluded directly after surgery because they were not admitted to the ICU but to the post anaesthesia care unit (n=3) or did not undergo a sternotomy (n=1). Eleven patients died within one year after surgery, resulting

in 120 patients eligible for the follow-up study. The follow-up study was approved by the Ethics Committee (VCMO, Nieuwegein, The Netherlands) as an amendment to the clinical trial. Additional written informed consent was obtained from the patients. Participant flow is summarized in a flow chart (Figure 1).

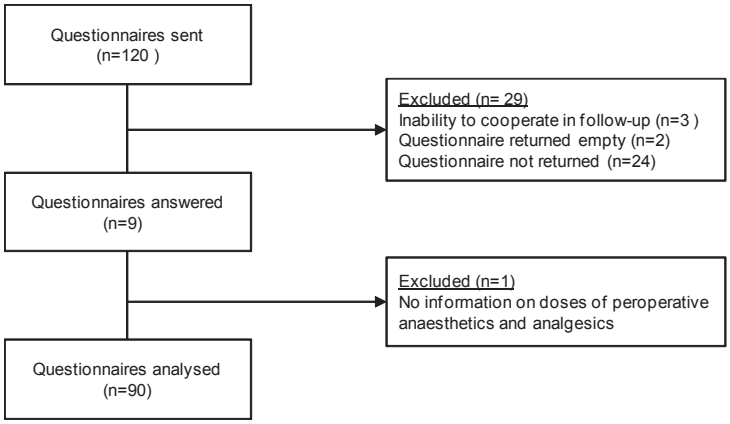

Figure 1. Participant flow

Preoperative evaluations

Preoperatively, patient characteristics were collected and patients were questioned about their pain history, the use of analgesics and preoperative pain score. For the latter the numeric rating scale (NRS) (range 0-10, with "0" representing "no pain" and "10" representing "the worst pain imaginable") was used [12-13].

Intraoperative anaesthesia and analgesia

For induction of anaesthesia, midazolam and propofol bolus injections were administered together with fentanyl. Patients were paralyzed with pancuronium. Anaesthesia was primarily maintained with propofol, with optional use of nitrous oxide. According to local practice, sevoflurane 0.25 – 1.00 minimum alveolar concentration was added for cardio-protection until the start of the extra corporeal circulation. For intraoperative analgesia, intermittent fentanyl doses were used, while remifentanil continuous infusion was initiated directly after the induction of anaesthesia at the discretion of the attending anaesthesiologist. Total dose of remifentanil and remifentanil dose corrected for kg Lean Body Mass (LBM) and duration of surgery in minutes were calculated. LBM was defined for male (1.1 * weight (kg) - 128 (weight/ height (cm)) and female 1.07 * weight (kg) - 148 (weight/ height (cm)) [14]. Perioperative data were registered in the clinical trial registration form. In total, eighteen anaesthesiologists and ten surgeons were involved during surgery. The specific combination of a surgeon and an anaesthesiologist was unique for 43 patients and did not occur more than five times.

Postoperative pain measurement and analgesia in the ICU

According to standard care in our ICU, a patient data management system (PDMS) obliged nurses to ask patients for their pain score three times a day (8.00 a.m., 4.00 p.m. and midnight) [15]. A pain titration protocol was used in all patients as part of standard care, consisting of intermittent paracetamol 4 grams daily and a continuous intravenous infusion of morphine, which was started directly upon admittance to the ICU. According to the pain titration protocol, in case of a NRS score of more than 3, an extra bolus of morphine and/or an increase in continuous morphine infusion was applied. Pain scores were registered in the patient data management system (PDMS).

Follow-up study one year after cardiac surgery

A questionnaire enquiring after the presence of chronic thoracic pain was sent to the patients one year (13 months ± 0.6) after cardiac surgery. This previously used questionnaire [6] was based on the McGill Pain Questionnaire [16]. Chronic thoracic pain was defined as sternal and/or thoracic pain (NRS>0), which the patient identified as related to surgery, which was different from angina and which was present in the 2 weeks preceding the interview [6].

Data-analysis

All statistical analyses were performed using IBM SPSS Statistics (version 19.0 for Windows; SPSS, Chicago, IL). Descriptive statistics of demographic and clinical variables were expressed as frequencies with percentages (%), median with interquartile range [IQR] or mean with standard deviation (SD) where appropriate. Categorical data were analyzed by $\chi 2$ or Fisher's exact tests and continuous data by Student's t-tests or Mann-Whitney U-tests. In case of significant differences in frequencies between patients with and without chronic pain in continuous or ordinal variables, receiver operating characteristic (ROC) curves were constructed to identify cut-off points with most discriminative value. By using these cut-off points (dichotomization) and adding all other associated clinical variables ($P<0.10$), a backward stepwise logistic regression analysis was performed to identify variables with most predictive value. Additionally, as a sensitivity analysis, the regression analysis was repeated without dichotomization. Imputation has been applied for 5 data-entries (0.3% of all data entries). A two-tailed *P*-value <0.05 was considered significant for all tests.

RESULTS

Patients and data

Of the 120 sent questionnaires, 96 (80%) were returned. Two were returned empty and three questionnaires were accompanied by a note that these patients were unable to fill in the questionnaire. This resulted in 91 answered questionnaires. Responders of the question-

naire were more often men compared to non-responders (76% (69/91) versus 55% (16/29), respectively, *P*=0.03). Otherwise no differences were observed between responders and non-responders, i.e. mean age (69 years ± 11 *vs.* 70 years ± 12, *P*=0.69), median European System for Cardiac Operative Risk Evaluation score (euroSCORE [17]) (7 [range 0-13] *vs.* 6 [range 2-13], *P*=0.39) and mean BMI (27 kg/m^2 ± 4 *vs.* 28 kg/m^2 ± 5, *P*=0.41, respectively). One patient was excluded during the analysis because details of intraoperative anaesthetics and analgesics could not be retrieved. Patient characteristics of the 90 included patients are summarized in Table 1.

Table 1. Patient characteristics

	All patients
Number of patients	90
Male/female, n	69/21
Age, years (range)	68.9 (32-85)
BMI, kg/m^2 (±SD)	27.3 ±3.8
Type of cardiac surgery, n (%)	
CABG	22 (24.4%)
CABG and valve surgery	30 (33.3%)
Valve surgery	19 (21.1%)
Aortic surgery	19 (21.1%)
Diabetes, n (%)	16 (17.8%)
EuroSCORE, median [IQR]	7 [4-9]

SD =standard deviation, IQR = Interquartile Range. EuroSCORE = European System for Cardiac Operative Risk Evaluation score [18]

Univariate analysis of patient and pre-, intra- and postoperative characteristics

One year after cardiac surgery, 20% of the patients (n=18) reported chronic thoracic pain (NRS >0). Table 2 compares patient and perioperative characteristics of patients with and without chronic thoracic pain. Patients with chronic thoracic pain were significantly younger (mean age 63 years ± 12 *vs.* 70 years ± 10), had a higher mean BMI (30.2 kg/m^2 ± 4.6 *vs.* 26.6 kg/m^2 ± 3.3), a lower median euroSCORE (4.5 [IQR 3-7] *vs.* 7 [IQR 5-9]), and used more preoperative analgesics (27.8% *vs.* 11.1%) compared to patients without chronic thoracic pain. Furthermore, mean preoperative NRS scores were higher in patients with chronic pain compared to patients without chronic thoracic pain (1.9 ± 3.1 *vs.* 0.5 ± 1.3). During anaesthesia, patients with chronic thoracic pain received significantly more often remifentanil compared to patients without chronic thoracic pain (83.3% *vs.* 51.4%). The dose of fentanyl during anaesthesia was not different between patients with and without chronic thoracic pain (1.7 mg ± 0.6 *vs.* 1.7 mg ± 0.4, *P* = 0.44). Postoperative pain scores in the ICU were not significantly different between patients with chronic thoracic pain and without chronic thoracic pain (Table 2).

Cut-off points identified via ROC curve analysis were 69 years for age, 28 kg/m^2 for BMI and an euroSCORE of 6. These three variables, together with preoperative pain (NRS>0), chronic use of analgesics before surgery and anaesthesia that included remifentanil, were selected for multivariate logistic regression analysis with stepwise backward elimination.

Table 2. Patient and perioperative characteristics of patients with and without chronic thoracic pain one year after surgery

	No chronic pain n=72	Chronic pain n=18	*P*-value
Patient characteristics			
Male gender, n (%)	53 (74%)	16 (89%)	0.19
Age, years (±SD)	70.2 (±9.6)	63.4 (±12.4)	0.02
BMI, kg/m^2 (±SD)	26.6 (±3.3)	30.2 (±4.6)	<0.0001
EuroSCORE, median [IQR]	7 [5-9]	4.5 [3-7]	0.01
Preoperative NRS, mean (±SD)	0.5 (±1.3)	1.9 (±3.1)	0.01
History of chronic pain, n (%) [a]	16 (22%)	4 (22%)	0.98
Previous sternotomy, n (%)	8 (11%)	1 (6%)	0.49
Use of analgesics before surgery (%) [b]	8 (11%)	5 (28%)	0.08
Intraoperative characteristics			
Type of surgery, n (%)			0.93
CABG	18 (25%)	4 (22%)	
CABG and valve surgery	23 (32%)	7 (39%)	
Valve surgery	15(21%)	4 (22%)	
Aortic surgery	16 (22%)	3 (17%)	
Non-elective surgery, n (%)	7 (9.7%)	0 (0%)	0.17
Anaesthesia that included nitrous oxide, n (%)	46 (64%)	13 (72%)	0.32
Anaesthesia that included remifentanil (%)	37 (51%)	15 (83%)	0.02
Fentanyl during anaesthesia, mg, (mean) (±SD)	1.7 (±0.4)	1.7 (±0.6)	0.44
Duration of surgery, minutes, mean (±SD)	242 (±79)	255 (±59)	0.53
Postoperative characteristics			
Mechanical ventilation, hours, mean (±SD)	13.6 (±19.6)	14.2 (±16.2)	0.93
Length of stay in the ICU, days, mean (±SD)	2 (2)	2 (2)	0.48
Resternotomy during admittance, n (%)	7 (10%)	3 (17%)	0.41
NRS at 16:00 on day of surgery, mean (±SD) *	0.9 (±0.9)	1.2 (±2.0)	0.37
NRS at 23:59 on day of surgery, mean (±SD) #	1.4 (±1.3)	1.8 (±1.9)	0.51
NRS at 8:00 on first POD, mean (±SD)	1.6 (±1.8)	2.1 (±2.0)	0.28

SD=standard deviation, IQR=interquartile range, BMI=body mass index, EuroSCORE = European System for Cardiac Operative Risk Evaluation score [18], NRS=numeric rating scale, CABG=Coronary artery bypass grafting, ICU=intensive care unit; POD = postoperative day. [a] Includes chronic back pain, rheumatoid arthritis, polyneuropathy, hernia. [b] Includes paracetamol, non steroidal anti inflammatory drugs (NSAID's) and opioids. * 15 missing values. # 3 missing values

Multivariate analysis of patient and pre-, intra- and postoperative characteristics

In the multivariate logistic regression analysis, anaesthesia that included remifentanil, age younger than 69 years and a BMI above 28 kg/m^2 all appeared independent predictors for chronic thoracic pain with corresponding odds ratios as shown in Table 3. The goodness-of-fit of the final model was excellent (*P*-value by Hosmer and Lemeshow test 0.94). Preoperative pain, chronic use of analgesics before surgery and EuroSCORE were not statistically significant associated with chronic pain in the multivariate analysis. In analysis without dichotomization of continuous variables, remifentanil was confirmed as independent predictor of chronic thoracic pain (OR 1.7; [95%CI 1.1-2.8]).

Table 3. Multivariate analysis for independent predictive factors of chronic thoracic pain one year after sternotomy

	Odds Ratio	95% CI	*P*-value
Anaesthesia that included remifentanil	8.93	1.6 - 49.0	0.01
Age <69 years	7.03	1.6 - 31.7	0.01
BMI ≥28 kg/m^2	9.05	2.1 - 39.1	0.003

Backward stepwise binary logistic regression, variables entered: age, BMI, EuroSCORE, preoperative NRS score, use of analgesics in history and anaesthesia that included remifentanil

BMI = body mass index, NRS=numeric rating scale, EuroSCORE=European System for Cardiac Operative Risk Evaluation score [17]

Based on these findings, the association between remifentanil and chronic thoracic pain was examined in more detail. In total, 52 patients (58%) received remifentanil during cardiac surgery. Table 4 shows that there were no differences in patient characteristics or perioperative characteristics between patients who received remifentanil and patients who did not receive remifentanil.

Table 4. Characteristics of patients with and without anaesthesia with remifentanil during cardiac surgery

	Remifentanil n=52 (58%)	No remifentanil n=38 (42%)	*P*-value
Patient characteristics			
Male gender, n (%)	40 (77%)	29 (76%)	0.95
Age, years (±SD)	69 ± 10	68 ± 11	0.79
BMI, kg/m^2 (±SD)	28 ±4	27 ±4	0.60
EuroSCORE, median [IQR]	6 [4-8]	7 [4-9]	0.24
Preoperative NRS, mean (±SD)	0.8 ±1.9	0.8 ± 2.0	0.59
Intraoperative characteristics			
Type of cardiac surgery, n (%)			0.03
CABG	17 (33%)	5 (13%)	
CABG and valve surgery	18 (35%)	12 (32%)	
Valve surgery	11 (21%)	8 (21%)	
Aortic surgery	6 (12%)	13 (34%)	
Length of surgery, minutes, mean (±SD)	244 ±68	246 ±84	0.85
Anaesthesia that included nitrous oxide, n (%)	34/52 (65%)	25/37 (68%)	0.83
Fentanyl during anaesthesia, mean (±SD)			
in mg	1.7 ± 0.44	1.7 ± 0.65	0.69
in mcg/kg LBM/ minute	0.13 ± 0.05	0.12 ± 0.04	0.94
Propofol during anaesthesia, gram, mean (±SD)	1.1 ± 0.6	1.0 ± 0.5	0.86
Postoperative characteristics			
Mechanical ventilation, hours, mean (±SD)	11.7 ± 7.7	16.5 ± 27.6	0.87
Length of stay in the ICU, days, mean (±SD)	1.7 ± 1.5	2.0 ± 2.0	0.90
Resternotomy during admittance, n (%)	5 (10%)	5 (13%)	0.60
Mean NRS at 16:00 hours on the day of surgery, (±SD)*	1.2 ±1.4	0.7 ± 0.8	0.11
Mean NRS at 23:59 hours on the day of surgery, (±SD)#	1.5 ±1.5	1.5 ±1.3	0.55
Mean NRS at 8:00 hours on the first postoperative day, ±SD	1.8 ± 2.0	1.5 ± 1.7	0.61

EuroSCORE=European System for Cardiac Operative Risk Evaluation score [17]

* 15 missing values; # 3 missing values

Table 5 shows the association between remifentanil dose administered during anaesthesia for cardiac surgery and Odds ratio for chronic thoracic pain one year after surgery. Both with increasing total amounts of remifentanil (mg) and with increasing remifentanil dose corrected for kg Lean Body Mass (LBM) and duration of surgery, the Odds ratio for chronic thoracic pain increased with a significant *P*-value for trend (*P* for trend <0.01 and <0.005, respectively). This table shows the division of patients into 3 groups; the first group contains patients who did not receive remifentanil (n=38), while the patients who received remifentanil during anaesthesia (n=52) were equally divided over the second and third group. This resulted in cut-off points between the second and third group of 1.7 mg for total dose of remifentanil and 0.12 mcg of remifentanil/kg LBM/minute of surgery. The correlation (r_2) between remifentanil total dose and dose flow rate related to lean body mass was 0.82.

Table 5. Association between intraoperative total dose of remifentanil and the remifentanil dose corrected for lean body mass (LBM) and duration of surgery, and Odds ratio for chronic thoracic pain one year after surgery.

	No chronic pain n=72	Chronic pain n=18	Odds ratio	95% CI	*P* -value	*P* -value for trend
Total dose of remifentanil in mg, n (%)						
0	35 (49%)	3 (17%)	1.00		0.04	0.01
> 0 and <1.7	19 (26%)	6 (33%)	3.68	0.8 - 16.4		
≥ 1.7	18 (25%)	9 (50%)	5.83	1.4 - 24.3		
Remifentanil in mcg /kg LBM/ minute, n (%)						
0	35 (49%)	3 (17%)	1.00		0.02	0.005
> 0 and <0.12	19 (26%)	5 (28%)	3.07	0.7 - 14.3		
≥ 0.12	18 (25%)	10 (55%)	6.48	1.6 - 26.5		

LBM= lean body mass

DISCUSSION

Besides younger age and increased BMI, remifentanil during cardiac anaesthesia appears an independent predictor for chronic thoracic pain one year after sternotomy. To our best knowledge, so far, chronic thoracic pain has not been associated with remifentanil in patients after cardiac surgery, although a relation between chronic post-thoracotomy pain and remifentanil has been described [11]. Despite the fact that the current study was not designed to investigate the role of remifentanil in chronic pain after surgery, we found the relation between remifentanil and the Odds ratio for chronic thoracic pain to be dose-dependent. There were no other differences in patient and perioperative characteristics between patients who received remifentanil and those who did not. Furthermore, remifentanil was administrated in a substantial percentage of patients (58%) and was either started as a continuous infusion directly after the induction of anaesthesia, or not started at all. Therefore, the present study provided a unique possibility to compare patients with and without remifentanil during

surgery, possibly leading to the identification of a risk factor for chronic pain that can actually be avoided.

Chronic post-surgical pain related to remifentanil during anaesthesia has so far only been described by Salengros et al. [11] in patients after thoracotomy. Remifentanil high dose (0.14-0.26 μg/kg/min) during elective thoracotomy combined with postoperative epidural analgesia was not only associated with a larger area of allodynia around the wound in the first 72 postoperative hours, but also with a significant higher incidence of chronic pain compared with a three times lower dose of remifentanil and epidural analgesia during surgery. In patients after major abdominal surgery, a higher dose of remifentanil (0.3 ± 0.2 μg/kg/min) has been associated with acute opioid tolerance and opioid-induced hyperalgesia compared with a lower dose of remifentanil (0.1 ± 0.0 μg/kg/min), suggested by higher pain scores in the first postoperative hour and exaggerated postoperative opioid consumption in the first 24 postoperative hours [19]. Similar to other studies upon cardiac surgery [20-22], we were not able to evaluate pain scores in the first postoperative hour due to prolonged sedation after cardiac surgery. Therefore, we cannot not report on the actual presence of acute opioid tolerance in our patients. Higher doses of remifentanil during cardiac surgery were, however, shown to be associated with hyperalgesia for the first seven postoperative days compared with a 1.5 times lower dose of remifentanil when applied via target controlled infusion [22]. Unfortunately, in the aforementioned study populations the development of chronic pain was not evaluated. It can be anticipated that hyperalgesia is linked to peripheral and central pain sensitization and thereby correlates with the development of postoperative chronic pain [23]. This suggests that hyperalgesia due to remifentanil in the early postoperative period may explain the higher incidence of chronic pain.

In addition to the finding of a dose-dependent association between remifentanil and development of chronic thoracic pain, the present study also confirmed an increased BMI (>28 kg/m2) and a younger age (<69 years) as risk factors [2-3,8,10]. As surgery may be more difficult in the obese patient, with both a larger surface of tissue damaged and a longer retraction time [8], this may explain the association between an increased BMI and chronic thoracic pain. For the observed association between younger age and the presence of chronic thoracic pain after surgery, Bruce and colleagues [8] have suggested that younger patients have a lower pain threshold and are less likely to accept, and more likely to report pain. Another explanation is that younger patients are more active and more likely to be hampered by pain in their activities, whereas older patients may be more likely to accept their limitations.

We consider some limitations of our study. First, the studied patients participated in a clinical trial on pain levels in the early postoperative period after cardiac surgery. This may have led to a selection bias because patients may have had either a specific reason not to participate or on the contrary, may have been eager to participate in a study with the expectation of additional attention for pain and analgesia. On the other hand, the fact that the patients participated in this clinical trial, which resulted in a carefully prospectively monitored group

of patients with amongst others, detailed information on patient and perioperative characteristics, could be considered as a strength of the present study. Second, despite the high response rate of 75% of the questionnaires, another selection bias cannot be excluded, as we are not informed about the patients who did not respond. Moreover, the association between remifentanil and chronic pain was not suspected until the analysis of the study. Third, continuous infusion of remifentanil during cardiac anaesthesia could be initiated after induction of anaesthesia at the discretion of the attending anaesthesiologist. Surgeons, surgical techniques and anaesthesiologists were not randomized or standardized for the study, even though the large number of surgeons (n=10) and anaesthesiologists (n=18) without fixed combinations between the two, could be considered a strength as well. These limitations make it impossible to draw any more conclusions than the reported association between remifentanil and chronic thoracic pain after cardiac surgery. Unmeasured confounding can therefore not be ruled out, even though there were no significant differences in patient or other characteristics between the patients who received remifentanil and those who did not. As such, the results of this study, with higher amounts of remifentanil being significantly associated with higher Odds ratios for chronic pain, warrant further blinded, randomized and prospective studies as this may prevent the development of chronic thoracic pain or at least part of this serious condition. In further research, a follow-up at 3-6 months after cardiac surgery should be considered, thereby identifying chronic pain in an earlier period, which would increase the response rate.

In conclusion, chronic thoracic pain after sternotomy was associated with the use of remifentanil during cardiac surgery, younger patients and an increased BMI. Higher doses of remifentanil were positively associated with significantly higher Odds ratios for chronic pain. As this is the second study that reports an association between remifentanil and chronic pain, further research is needed through randomized controlled trials with and without remifentanil during cardiac surgery is called for to investigate the relation between remifentanil and the development of chronic thoracic pain.

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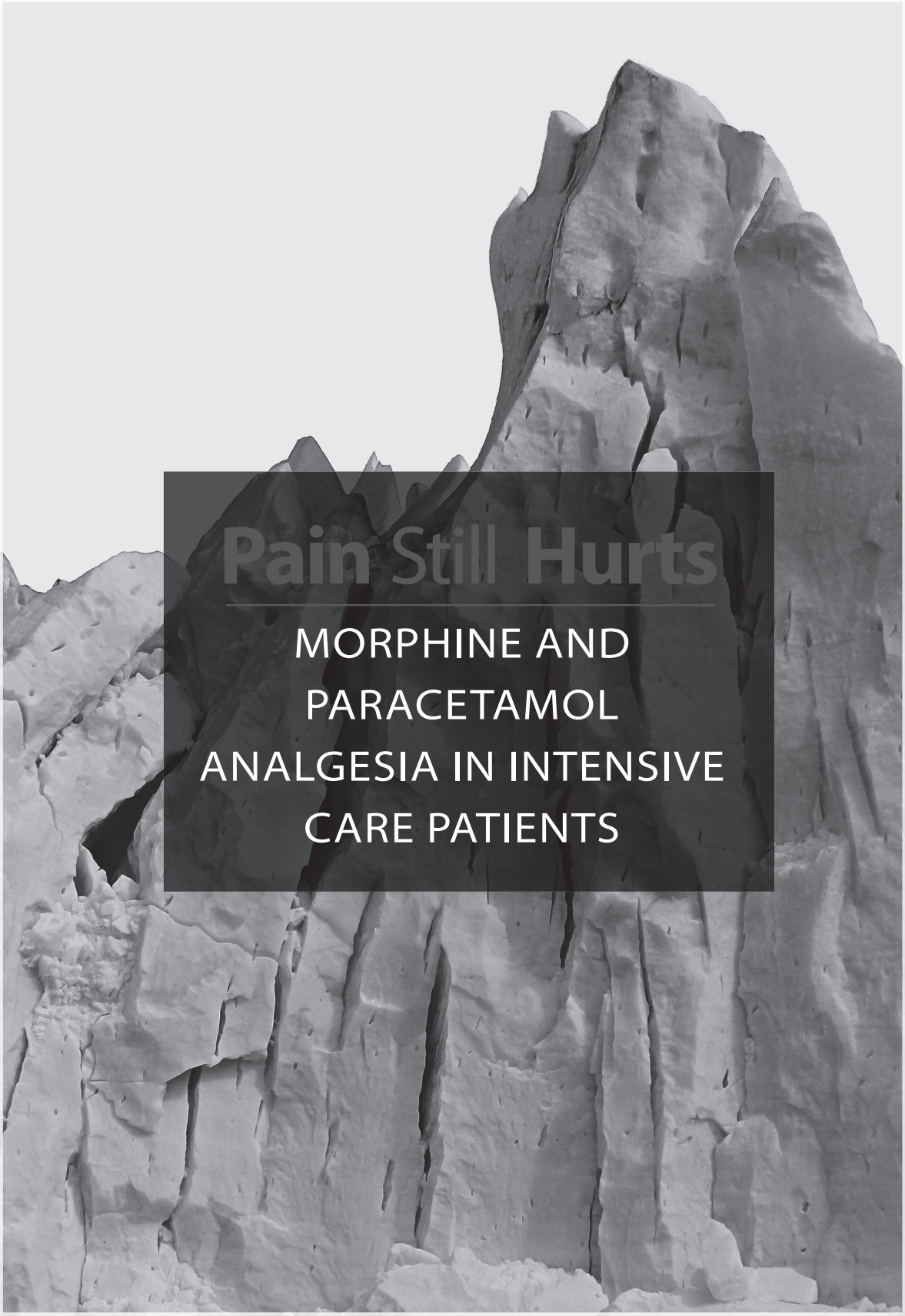

Pain Still Hurts

MORPHINE AND PARACETAMOL ANALGESIA IN INTENSIVE CARE PATIENTS

Chapter **8**

MORPHINE GLUCURONIDATION AND ELIMINATION IN INTENSIVE CARE PATIENTS: A COMPARISON WITH HEALTHY VOLUNTEERS

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ABSTRACT

Background and objectives While morphine is the preferred analgesic for moderate to severe pain in the intensive care unit, its pharmacokinetics have not been adequately quantified in these patients. The aim of this study was to evaluate the glucuronidation and elimination clearance of morphine in intensive care patients in conjunction with healthy volunteers, on the basis of morphine and morphine-3-glucuronidation (M3G) concentrations.

Methods A population pharmacokinetic model with covariate analysis was developed with the non-linear mixed-effects modelling (NONMEM) VI. The analysis included 3012 morphine and M3G concentrations from 135 intensive care patients (117 cardiothoracic surgery patients and 18 critically ill patients), who received continuous morphine-infusions adapted to individual pain levels, and 622 morphine and M3G concentrations from a previously published study of 20 healthy volunteers, who received an intravenous bolus of morphine followed by a 1-hour infusion.

Results For morphine a three-compartment model best described the data, while for M3G a one-compartment model was used. In intensive care patients, glucuronidation clearance of morphine to M3G and elimination clearance of M3G were significantly decreased with 17% and 81% respectively, compared to healthy volunteers. Moreover, serum creatinine concentration was identified as a covariate for both elimination clearance of M3G within the group of intensive care patients and for non-M3G clearance of morphine in both intensive care patients and healthy volunteers.

Conclusion In intensive care patients, glucuronidation of morphine to M3G and elimination of M3G appeared significantly decreased compared to healthy volunteers. As a result, substantially elevated M3G concentrations may be anticipated in intensive care patients, which is even more pronounced in case of increased serum creatinine concentrations.

INTRODUCTION

Morphine is the preferred analgesic for moderate and severe (postoperative) pain in the intensive care unit (ICU) [1-2]. However, the clinical use of morphine is characterized by a large inter-individual variability in analgesic effect, which may be related to patient characteristics, such as age [3], sex [4], ethnic origin [5], anxiety [6] and genetic polymorphisms [7]. More specifically, this variability may also be caused by differences in morphine pharmacokinetics as a result of variability in health status, hepatic metabolic capacity and renal clearance, particularly when intensive care patients are concerned [8]

Morphine is mainly metabolized in the liver via glucuronidation by phase II metabolism enzyme UDP-glucuronosyltransferase (UGT)2B7 [9] to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Both metabolites and unchanged morphine are excreted by the kidneys [10]. The main metabolite M3G is suggested to have antagonistic or hyperalgesic effects, which may potentially result in reduced morphine efficacy [11]. While M6G concentrations are usually low, its clinical analgesic potency appeared recently lower than previously found in animals [11-13] and therefore M6G concentrations now seem of limited interest. As a consequence, insight in the pharmacokinetics of morphine and its main metabolite M3G seems of relevance in guiding dosing regimes in specific patient groups such as intensive care patients who may receive prolonged infusions of morphine.

To date, there are no reports on the pharmacokinetics of morphine and M3G in intensive care patients, even though morphine is extensively investigated in terms of efficacy and side effects in a variety of patient groups [10,14-18]. In intensive care patients, glucuronidation of morphine through UGT2B7 to M3G and/or renal excretion of morphine and M3G may be impaired as a result of major surgery such as cardiac surgery with cardiopulmonary bypass, or critical illness related to septic shock, or multiple organ failure. Furthermore, some of these patients may suffer from acute renal failure. Therefore, in this study a population pharmacokinetic model of morphine and its main metabolite M3G was developed in order to study the glucuronidation of morphine to M3G and elimination of M3G and morphine in intensive care patients in conjunction with healthy volunteers.

METHODS

Study design

This analysis was based on observations obtained in intensive care patients participating in a clinical trial in which pain management for procedural related pain was evaluated (registered at ClinicalTrials.gov (identifier NCT00558090)). In this study, both intensive care patients after cardiac surgery through sternotomy [19] and critically ill patients with an expected duration of mechanical ventilation of more than 48 hours were included. The study was performed in

a 30-bed surgical/medical ICU in a teaching hospital, Nieuwegein, The Netherlands and was approved by the Ethics Committee of the St. Antonius Hospital. Written informed consent from cardiac surgery patients was obtained the day before the cardiac surgery. Written informed consent from critically ill patients was obtained by their next of kin on the first day of admission to the intensive care. Whenever possible, (written) informed consent was also obtained from the critically ill patient himself during or after the study.

Patients

Intensive care patients after cardiac surgery through sternotomy and critically ill patients with an expected duration of mechanical ventilation of more than 48 hours, were included. Additional inclusion criteria were age between 18-85 years and weight between 45-140 kg. Exclusion criteria were patients with a known morphine or paracetamol allergy, planned admission to the postoperative anaesthesia care unit (PACU), pregnancy or breast-feeding, serious neurological deficits (e.g. coma or brain death), a language barrier, and patients who refused informed consent [19].

Twenty healthy volunteers were enrolled earlier as part two other studies and detailed information can be found in the references [20-21].

Morphine dosing schemes

Upon admission to the ICU, in all intensive care patients a morphine continuous infusion (2 mg/hour) was started, with subsequent doses adapted to individual pain levels resulting in morphine doses ranging from 0.5 to 2.5 mg/hour [19]. In addition, before a painful procedure (turning of the patient and/or chest drain removal), patients received a bolus dose of morphine (2.5 or 7.5 mg) on the first postoperative day (cardiac surgery patients) or on the first or second day after admission in the ICU (critically ill patients) [19]. Also for other procedures, additional bolus doses of morphine could be administered at the discretion of the attending intensivist which were registered on the case report form.

In the previously published study in healthy volunteers, 20 young men and women (10 of each sex) received intravenous morphine bolus 0.10 mg/kg dose followed by an infusion of 0.03 mg/kg/h for 1 hour [20-21].

Blood sampling

In the intensive care patients, 2 ml arterial blood was drawn for determination of serum concentrations of morphine and M3G four times daily (3.00 a.m., 7.00 a.m., 3.00 p.m. and 9.00 p.m.), during their ICU stay. Additionally, a blood sample was collected at 5 minutes before and 5 minutes after the painful procedure (turning of the patient and/ or chest drain removal) which corresponded to 30 and 40 minutes after the bolus dose of morphine of 2.5 or 7.5 mg, respectively, on the first day of ICU admittance.

In the previously published healthy volunteer study [20-21], blood samples were collected at fixed times (t=5, 10, 20, 30, 40, 50, 60, 65, 70, 80, 100, 130, 180, 300, and 420 minutes after the morphine bolus dose).

Analytical Method

Blood samples were rapidly centrifuged and serum was stored at -20ºC until analysis. Morphine and M3G serum concentrations were determined using a high-performance liquid chromatography tandem mass spectrometry (LC-MS-MS) method (*see appendix I*). The Lower Limit of Quantification was 1 µg/L for morphine and 2 µg/L for M3G. For morphine, within-day coefficients of variation were 5.5% at 5 µg/L and 3.5% at 250 µg/L. For M3G within-day coefficients of variation were 10.4% at 10 µg/L and 3.5% at 500 µg/L. The molecular weights of morphine and M3G are 285 and 461 Da, respectively.

Data analysis

The non-linear mixed-effects modelling software NONMEM® VI (Globomax LLC, Hanover, MD, USA) was used, with S-plus® version 6.2 (Insightful Software, Seattle, WA, USA) for visualization of the data.

Model building was performed in four different steps: (i) selection of the structural model (one, two or three compartment model); (ii) choice of a statistical sub-model; (iii) covariate analysis; and (iv) model evaluation. Discrimination between different models was made by comparison of the objective function (-2 log likelihood). A value of $P<0.05$, representing a decrease of 3.84 in the objective function, was considered statistically significant. In addition, goodness-of-fit plots (both observed *vs.* individual- and population-predicted concentrations, and time as well as population predictions *vs.* weighted residuals) were evaluated, with specific emphasis on observed *vs.* population-predicted concentrations. Furthermore, visual improvement of the individual plots, the confidence interval of the parameter estimates and the correlation matrix were used to evaluate the model.

Pharmacokinetic model

The concentrations of morphine and M3G were expressed as microgram (µg) morphine units per L, logarithmically transformed and fitted simultaneously (NONMEM VI, ADVAN5). For morphine, a three-compartment model was preferred over a two-compartment model, since it was able to describe the datasets more accurately. For the metabolite M3G, a one-compartment model was used (Figure 1). Due to the large number of observations in steady state and the relative sparse sampling after bolus injection in intensive care patients, minimization difficulties occurred when all parameters of the four compartment model (Figure 1) were independently estimated, with particularly instable results for volume of distribution of central compartment of morphine (V_1). As a result, V_1 in the intensive care patients was modelled as a multiplication factor of V_1 in the 'healthy volunteers' while according to previ-

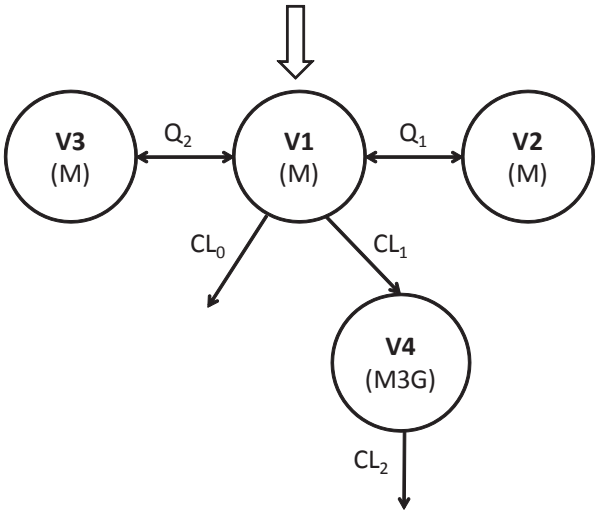

Figure 1. Schematic representation of the model
M = morphine; M3G = Morphine-3-glucuronide; Cl_0 = non-M3G clearance; Cl_1 = glucuronidation clearance of morphine to M3G; Cl_2 = elimination clearance of M3G;; Q_1 and Q_2 = intercompartmental clearance of morphine; V_1 = volume of distribution of central compartment of morphine; V_2 and V_3 = volume of distribution of peripheral compartment of morphine; V_4 = volume of distribution of M3G

ous analyses of the healthy volunteers in this study [20-21], V_1 in the 'healthy volunteers' was fixed to 3.67 litre (0.052 litre/kg*70.6 kg bodyweight). As an alternative approach, V_1 in the intensive care patients was fixed to 14.2 litre, as reported by Mazoit et al. [13] in postoperative patients. This alternative approach was rejected because diagnostics deteriorated, even though the estimates for the parameters of the model other than V_1 were stable. Based on previous studies in adults, the metabolite volume of distribution of M3G was fixed at 23 litre [22].

The inter-individual value (*post hoc* value) of the parameters of the *i*th subject was modelled by;

$$\theta_i = \theta_{mean} \cdot e^{\eta i} \qquad \text{(Eq.1)}$$

where θ_{mean} is the population mean and η_i is a random variable with mean zero and variance ω^2, assuming lognormal distribution in the population. The intra-individual variability, resulting from assay errors, model misspecifications, and other unexplained sources, was best described with a proportional error model. This means for the j^{th} observed log-transformed morphine and M3G concentration of the i^{th} individual, the relation (Y_{ij}) is described by equation 2:

$$Y_{ij} = \log c_{pred,ij} + \varepsilon_{ij} \qquad \text{(Eq. 2)}$$

where c_{pred} is the predicted morphine and M3G concentration and ε_{ij} is a random variable with a mean of zero and variance of σ^2.

Covariate analysis

Covariates were plotted independently against the individual *post hoc* parameter estimates and the weighted residuals to visualize potential relationships. The following covariates were tested; study group (cardiac surgery patients, critically ill patients and healthy volunteers), age, sex, bodyweight, body mass index (BMI), type of cardiac surgery, and serum creatinine concentration. For the covariate study group, besides exploring differences between the three study groups, also differences between two groups were evaluated (intensive care patients *vs.* healthy volunteers). Continuous covariates (age, bodyweight, BMI and serum creatinine concentration) were tested linear centred $\theta_i = \theta_1 + (COV - COV_{median}) \times \theta_2$ or exponential $\theta_i = \theta_1 \times (\frac{COV}{COV_{median}})^{\theta_2}$ in which θi represents the individual parameter estimate, COV denotes the covariate and COV_{median} the median value of the covariate for the population. Categorical covariates (study group as three or two groups, sex, type of surgery) were tested fractional by estimation of an additional parameter on a structural parameter for each subgroup.

Covariates were separately incorporated into the model and considered statistically significant if the objective function decreased 3.84 points or more ($P<0.05$). When more than one significant covariate 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. Beside the objective function, other criteria as presented under data analysis were considered. This procedure was in particular applied to covariates that could be related such as study group, age and serum creatinine concentration. Finally, after forward inclusion, a backward exclusion procedure was applied to justify the covariate, and was considered statistically significant if the objective function decreased with 6.63 points or more ($P<0.01$), while also the criteria as discussed under data analysis were considered.

Internal validation

For internal validation of the model, the normalized prediction distribution errors (NPDE) method was used [23-24], because there was a wide range in the administered morphine doses within the intensive care patients, and between the intensive care patients and the healthy volunteers. Besides, blood sampling schemes differed largely between intensive care patients and healthy volunteers. The NPDE method was implemented using the NPDE add-on software package, which was run in R. In this study, each observation was simulated 2000 times. The results of NPDE method are visualized in different graphs: (i) a histogram showing the distribution of the NPDEs, which are expected to follow a normal distribution; (ii) a scatterplot NPDE *vs.* time; and (iii) a scatterplot NPDE *vs.* predicted concentrations.

Simulations

With the developed pharmacokinetic model, simulations were performed to establish what serum concentrations of morphine and M3G would be achieved in healthy volunteers, in intensive care patients with a normal renal function (creatinine serum concentration 80 µmol/L) and in intensive care patients with renal failure (creatinine serum concentration 250 µmol/L), after receiving a continuous infusion of 2 mg/hour for 24 hours.

RESULTS

Patients

The analysis was based on 1506 morphine and 1506 M3G serum concentrations obtained from 135 intensive care patients, i.e. 117 cardiac surgery patients and 18 critically ill patients. From the 20 healthy volunteers, 311 serum concentrations of morphine and 311 serum concentrations of M3G were available [20-21]. Patients' characteristics and healthy volunteer characteristics are summarized in Table 1.

Table 1. Background characteristics

	Cardiac surgery patients (n=117)	Critically ill patients (n=18)	Healthy volunteers (n=20)
Male gender, n (%)	87 (74%)	12 (67%)	10 (50%)
Age (yr)	69 [32-85]	67 [50-79]	26 [20-36]
BMI (kg/m^2)	27 [18-43]	28 [21-35]	22 [18-27] *
Type of cardiac surgery, n (%)			
CABG	23 (20%)	-	-
Valve surgery	26 (22%)	-	-
CABG & valve surgery	43 (37%)	-	-
Aortic surgery	25 (21%)	-	-
Diagnostic group, n (%)			
Sepsis	-	14 (78%)	-
Cardiac failure	-	3 (17%)	-
Respiratory failure miscellaneous	-	1 (5%)	-
Median euroSCORE	7 [0-13]	-	-
Median SOFA-score on the first day of admission	-	9 [6-16]	-
Median serum creatinine concentration (µmol/L)	80 [54-464]	132 [51-433]	80 [-]
Median length of ICU stay (days)	2 [1-13]	10 [3-52]	-
Morphine infusion duration (hour)	21 [5-132]	123 [14-337]	1 [-]
Number of available samples			
Morphine	982	524	311
Morphine-3-glucuronide	982	524	311

Data are expressed in number (percentage) or mean [range] unless when stated as median [range]. BMI=body mass index; CABG= coronary artery bypass graft; euroSCORE= European System for Cardiac Operative Risk Evaluation score [25] * = 1 missing value

Structural model

The pharmacokinetic model used is depicted in Figure 1. The morphine data were best described with a three-compartment model, parameterized in terms of volume of the central compartment (V_1), two peripheral compartments (V_2 and V_3), intercompartmental clearances (and Q_1 and Q_2), glucuronidation clearance of morphine to M3G (CL_1) and non-M3G clearance (CL_0). The volume of distribution (V_1) for the intensive care patients was modelled as multiplication factor of the V_1 of the healthy volunteers, and was estimated 32.2. The formation of M3G was best described with a one-compartment model, parameterized in terms of the volume of distribution of M3G (V4) and elimination clearance (CL_2). For the residual or intra-individual variability, a proportional error model was used, with different errors for the study groups 'healthy volunteers' and 'intensive care patients'.

Covariate model

In the covariate analysis, study group (healthy volunteers *vs.* intensive care patients) proved the most significant covariate when implemented on CL_2 (elimination clearance of M3G). Addition of this covariate as a study group multiplication factor on CL_2 resulted in a decrease of objective function value by 754 points ($P<0.001$), and diagnostic plots of the model largely improved in comparison with the simple model. CL_2 proved 5.37 times higher in healthy volunteers compared to intensive care patients with a median creatinine concentration of 80 µmol/L (Table 2), which equals a reduction of 81% in intensive care patients. Further differentiation in three study groups (healthy volunteers, cardiac surgery patients and critically ill patients) did not improve the results.

Within the group 'intensive care patients', serum creatinine concentration was an additional covariate for CL_2, resulting in a decrease in objective function value by 523 points ($P<0.001$). The influence of serum creatinine concentration on clearance was best described using an exponential scaling factor (k_2) and was estimated -0.71 (Table 2). Implementation of the creatinine concentration to CL_2 resulted in improved diagnostics, especially for the intensive care patients (diagnostic plot 'population predicted *vs.* observed concentrations').

As a third covariate, serum creatinine concentration proved the most predictive covariate for CL_0 (non-M3G clearance) in all patients, which resulted in a decrease in objective function value of 89 points ($P<0.001$). The influence of serum creatinine concentration on CL_0 was best described using an exponential scaling factor (k_1) and was estimated -1.34 (Table 2). Implementation of creatinine concentration as covariate to CL_0 resulted in improved diagnostics, especially the diagnostic plot 'population predicted *vs.* observed concentrations' for the healthy volunteers.

Finally, addition of the covariate study group (healthy volunteers *vs.* intensive care patients) on CL_1 (glucuronidation clearance of morphine to M3G) further improved the model, with the objective function value decreasing by 4 points ($P<0.05$). Diagnostic plots improved, especially the diagnostic plot 'population predicted *vs.* observed concentrations'

for the healthy volunteers. CL_1 proved 1.20 times higher in healthy volunteers compared to intensive care patients (Table 2), which equals a reduction of 17% in intensive care patients. Further differentiation within the group of intensive care patients (cardiac surgery patients and critically ill patients) did not improve the results any further. No other covariates could be identified. Table 2 lists all parameter estimates with their confidence intervals obtained of the final model. Final diagnostics plots for morphine and M3G are shown in Figure 2 and Figure 3, respectively.

Table 2: Population pharmacokinetic parameters estimates of the final model

	Equation	Value	CV (%)
Fixed effects			
Cl_0 (L/min)	$= CL_{0pop}*(CRE/80)^{k1}$		
CL_{0pop}		0.694	9.86
k_1		-1.34	-24.7
CL_1 (L/min)			
ICU-patients	$CL_{1poplCU}$	0.537	8.83
Healthy volunteers	$CL_{1poplCU}*mf$		
mf		1.20	10.5
Cl_2 (L/min)			
ICU-patients	$= CL_{2poplCU}*(CRE/80)^{k2}$		
$CL_{2poplCU}$		0.0325	14.2
k_2		-0.71	-30.4
Healthy volunteers	$= CL_{2poplCU}*mf$		
mf		5.37	15.7
V_1 (L)			
Healthy patients	$V_{1pophealthy}$	3.67 FIX	-
ICU patients	$V_{1pophealthy}*mf$		
mf		32.2	37.9
V_2 (L)		90.9	5.81
V_3 (L)		502	13.5
V_4 (L)		23 FIX	-
Q_1 (L/min)		1.33	5.21
Q_2 (L/min)		0.184	10.1
Interindividual variability			
ω^2 (Cl_0)		0.684	20.5
ω^2 (Cl_1)		0.091	16.9
Residual error			
σ^2 (ICU patients)		0.285	11.6
σ^2 (healthy volunteers)		0.049	13.4

CV = coefficient of variation; Cl_0 = non-M3G clearance of morphine; Cl_1 = glucuronidation clearance of morphine to M3G; Cl_2 = elimination clearance of M3G; Q_1 and Q_2 = intercompartmental clearance; V_1 = volume of distribution of central compartment of morphine; V_2 and V_3 = volume of distribution of peripheral compartments of morphine; V_4 = volume of distribution of M3G; pop = study population in general (both ICU patients and healthy volunteers); poplCU = population of intensive care patients pophealthy = population of healthy volunteers; CRE = median serum creatinine concentration; k_1 = exponential scaling factor for Cl_0 (non M3G clearance) k_2= exponential scaling factor for Cl_2 (elimination clearance of M3G) in intensive care patients; mf = multiplication factor; ω^2 = interindividual variance; σ^2 = proportional intraindividual variance.

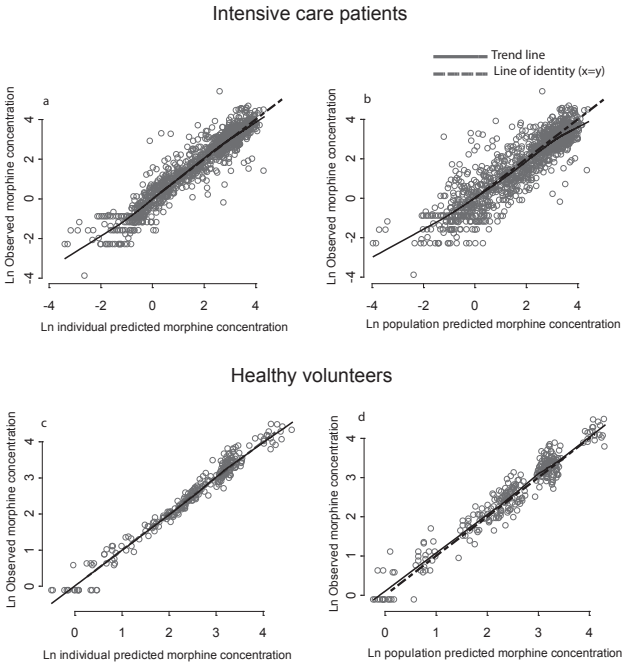

Figure 2. Observed *vs.* individual-predicted concentrations (left plots) and observed *vs.* population-predicted concentrations (right plots) of morphine in intensive care patients (a, b), and healthy volunteers (c, d).

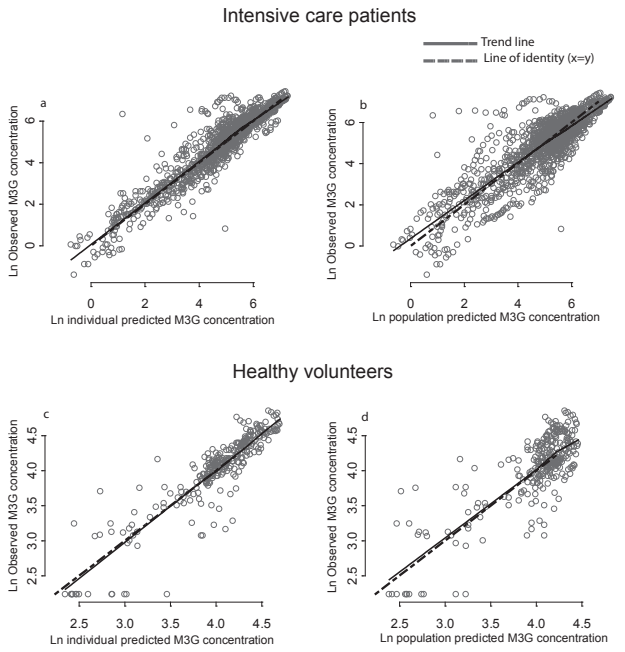

Figure 3. Observed *vs.* individual-predicted concentrations (left plots) and observed *vs.* population-predicted concentrations (right plots) of M3G in intensive care patients (a, b), and healthy volunteers (c, d).

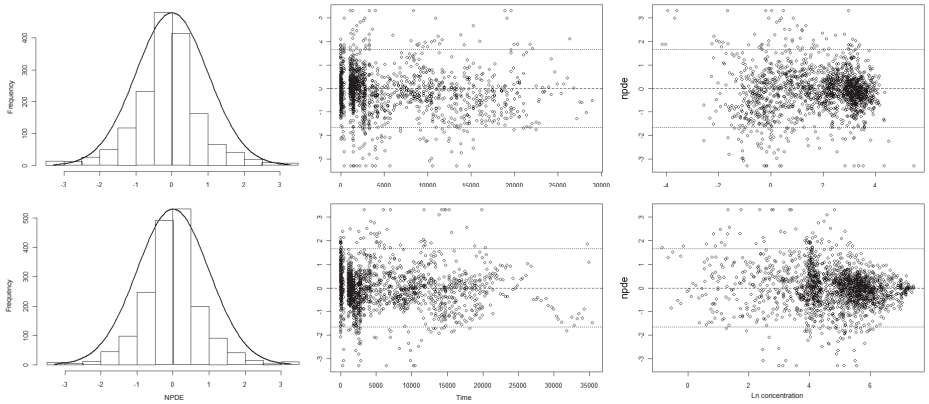

Figure 4. Results of the internal validation with the normalized prediction distribution error (NPDE) method.
The histograms show the NPDE distribution for morphine (upper panel) and morphine-3-glucuronide (lower panel), with solid lines indicating normal distribution (left plots). The distribution of the NPDE *versus* time, and NPDE *versus* the log of the concentration are shown (middle and right plots). The dotted lines represent the 90% distribution of the NPDE.

Internal validation

Figure 4 shows the results of the NPDE for morphine and M3G. The histogram follows a normal distribution expected by the solid line. Although there was a slight overestimation of the interindividual variability, no trend was observed in the NPDE *versus* time or versus predicted concentrations.

Simulations

The simulations based on the final pharmacokinetic model presented in Figure 5a and 5b, show morphine and M3G serum concentrations in a typical healthy volunteer, a typical intensive care patient with normal renal function (creatinine concentration 80 µmol/L), and a typical intensive care patient with an impaired renal function (creatinine concentration 250 µmol/L) upon a 24 hour morphine infusion of 2 mg/h. Figure 5a shows that similar morphine concentrations can be expected in intensive care patients compared to healthy volunteers, except in case of impaired renal function. Figure 5b shows that in intensive care patients increased M3G concentrations can be expected in comparison to healthy volunteers. When renal function is impaired in intensive care patients, even higher M3G concentrations are anticipated.

DISCUSSION

In order to quantify the glucuronidation and elimination clearance of morphine in intensive care patients in comparison to healthy volunteers, a pharmacokinetic model of morphine

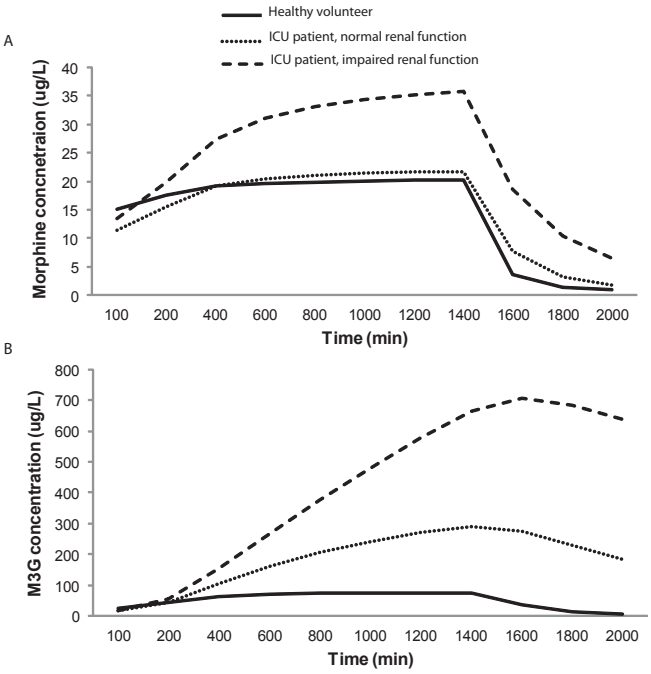

Figure 5. Simulated concentrations of morphine (A) and M3G expressed as morphine equivalents (B) in healthy volunteers, intensive care patients with normal renal function (creatinine concentration 80 µmol/L) and intensive care patients with impaired renal function (creatinine concentration 250 µmol/L), upon on a dosing regimen of a continuous infusion of morphine 2 mg/hour for 24 hours.

and morphine-3-glucuronide (M3G) was developed. In this model, 135 intensive care patients and 20 healthy volunteers were included. In the pharmacokinetic analysis, it was found that intensive care patients had a significantly decreased glucuronidation clearance of morphine to M3G (17%) and elimination clearance of M3G (81%) compared to healthy volunteers. Furthermore, serum creatinine concentrations proved a covariate for elimination clearance of M3G in intensive care patients, and for the non-M3G clearance in all patients. Simulations of these results illustrate that substantial accumulation of in particular M3G can be expected in intensive care patients upon 24 hour infusion, which is even more pronounced upon impaired renal function.

While in our study, glucuronidation clearance of morphine to M3G in healthy volunteers of 0.644 L/min (38.6 L/h) was found comparable to the results of Hasselstrom et al. [26], we identified a decrease of 17% in this glucuronidation clearance parameter in intensive care patients. In this respect, no differences between cardiac surgery patients and critically ill patients were observed. Nowadays, no data are available on glucuronidation clearance of morphine to M3G in intensive care patients. Studies so far focused on patients with cirrhosis, in whom glucuronidation clearance of morphine was shown to be decreased, probably due to reduction in hepatic clearance [27]. We hypothesize that in intensive care patients, the

amount and/or activity of the metabolism enzyme UDP-glucuronosyltransferase (UGT)2B7 may be (temporarily) decreased. Although no specific information is available on the UGT2B7 enzyme in this specific study population, there is some evidence that the activity of other liver enzymes, such as cytochrome P-450 enzymes, is decreased in case of critically illness [28] or after surgery [29]. The consequences of this finding are illustrated in the simulations depicted in Figure 5A in which morphine concentrations in intensive care patients compared to healthy volunteers are only slightly increased, provided normal renal function is assumed. As such, the decrease of 17% in the glucuronidation clearance of morphine in intensive care patients by itself does not lead to morphine accumulation upon prolonged infusion.

This study identified a very large reduction (81%) in elimination clearance of M3G (CL_2) in intensive care patients compared to healthy volunteers. While elimination clearance of M3G in healthy volunteers of 0.175 L/min (10.5 L/h) is similar to those reported in literature [26], the reduction of 81% in this parameter in intensive care patients was independent of renal function. Thus, in intensive care patients with normal renal function substantially higher M3G levels may be expected upon 24 hour continuous infusion, with even higher M3G levels upon renal failure (Figure 5B). So far, the relevance of high M3G levels in intensive care patients is unknown. Although controversial, M3G is thought to antagonize the analgesic effect, and to play a role in the development of tolerance and hyperalgesia [10]. Most studies arise from animal studies, in which M3G has been demonstrated to antagonize morphine and M6G analgesia [30-32]. Two healthy volunteer studies [22,33] were however not able to confirm these results, although this may be explained by the short study period of 2 hours. In contrast, in the study of Mazoit et al. [13], it was shown that M3G does have an antinociceptive effect. The authors discuss that this effect is moderate, and because of the very long transfer half-time from injection site to effect compartment, a significant effect of M3G is not though to occur before the 9^{th} – 18^{th} hour after initiation of analgesic treatment. In our study, the cardiac surgery patients had a mean infusion duration of 21 hours, while the critically ill patients received intravenous morphine infusions for a mean duration of 123 hours. In this respect, animal studies have found that M3G and high dose morphine produced altered pain behavior, such as hyperalgesia, allodynia and motor excitation [10]. In humans, these symptoms have mostly been observed in cancer patients treated with high dose morphine. In several of these case reports very high levels of morphine and M3G, as well as accumulation of M3G relative to morphine or M6G has been demonstrated [10]. Thus, the very large decrease in elimination clearance of M3G in intensive care patients resulting in substantially elevated M3G concentrations, may be clinically relevant, in particular upon prolonged administration of morphine infusion.

In our study, serum creatinine concentration proved a covariate for elimination clearance for M3G (CL_2) within the group of intensive care patients, and in addition to the decrease of 81% in this parameter in intensive care patients in comparison to healthy volunteers. Also for non-M3G clearance (CL_0), serum creatinine concentration was a significant covariate in all

patients, which may be explained by the fact that for this parameter study group could not be identified as a significant covariate. While the influence of serum creatinine concentration on these clearance parameters was best described using a negative exponential function, it is well known from literature in a diverse patient population that clearance of morphine and its metabolites deteriorates as result of renal failure [34-38]. In these studies, clearance of M3G and M6G were significantly correlated with creatinine clearance [34-35]. Additionally, a recent pharmacokinetic-pharmacodynamic study of Mazoit et al. [13] showed that M3G clearance was markedly decreased in postoperative patients after several types of surgery, receiving intravenous and intramuscular morphine during 48 hours. Thus, as illustrated in Figure 5, in intensive care patients with impaired renal function, morphine will cumulate compared to intensive care patients without renal failure and healthy volunteers. Also for M3G, higher concentrations than those anticipated in intensive care patients without renal failure will be reached, while these concentrations were already largely increased in intensive care patients without renal dysfunction compared to healthy volunteers (Figure 5B). Overall, these results suggest that significant accumulation of M3G may occur in intensive care patients, with or without renal failure. Considering the potential anti-nociceptive and hyperalgesic activity of M3G, this finding may be clinically relevant, and should be taken into account in this special patient group, particularly upon prolonged use of morphine infusions.

We consider some limitations of our study. In this analysis, we were not able to differentiate between the two subgroups of intensive care patients in our study population, i.e. cardiac surgery patients versus critically ill patients. We realize that there are many physiological differences between these two subgroups that may result in different pharmacokinetic parameters. An explanation for the lack of difference between these two groups may be the imbalance in patient numbers (117 *vs.* 18 patients). On the other hand it can be hypothesized that differences in pharmacokinetic parameters between these two groups are mainly located in volumes of distribution, which are expected to be larger in critically ill patients. Obviously, there were insufficient data to properly estimate central volume of distribution due to the relative lack of data directly after bolus injection in the intensive care patients. As such, future research in intensive care patients should focus on obtaining more samples after bolus injection to study the influence of the intensive care subgroups on volume of distribution. This would also allow the resulting model to be used for simulations of concentrations after bolus injection, which was not performed in this study (Figure 5) as the result of this relative lack of data. In our opinion, it may hypothesized that clearance values are not that different between these two intensive care patient subgroups given the fact that many samples were obtained to estimate these parameters. Another issue may be the correlation between covariates within the study groups. Intensive care patients were older and had on average higher serum creatinine concentrations. By systematically testing of the influence of all these covariates in different functions on the basis of predefined statistical criteria, we were however able to identify which parameter was the most predictive which has ultimately

resulted in the model presented in this study. Finally, we were not able to differentiate among non-M3G clearance (CL_0), which theoretically consists of unchanged morphine clearance, M6G clearance and potentially clearance through other pathways. Therefore, in the ideal study design, concentrations of M6G and/or excretion of morphine and metabolites in urine should be included in the analysis in order to distinguish between these routes. This may also lead to different covariates for sub-parameters of Cl_0 as in our analysis serum creatinine could be identified for this parameter only. It seems reasonable that serum creatinine will account for the part of this parameter that is responsible for excretion of unchanged morphine but not for glucuronidation to M6G for instance. Nonetheless, the results of our final model seem valid as the percentage of the intravenous morphine dose that was converted through Cl_1 to M3G and through CL_0 was 46% and 54% respectively, which is in line with previous reports. In those reports, it was reported that 44-55% of the morphine dose was converted to M3G regardless of the morphine dose [10].

In conclusion, in intensive care patients, glucuronidation of morphine to M3G and elimination clearance of M3G appeared significantly decreased compared to healthy volunteers. As a result, in particular elevated M3G concentrations may be anticipated in intensive care patients, which is even more pronounced upon increased serum creatinine concentrations.

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Appendix I: Determination of morphine and morphine-3-glucuronide in serum by LC-MS-MS

For the construction of the calibration line, human pool serum was spiked with adequate volumes of morphine and morphine-3-glucuronide (M3G)(Cerilliant, Texas, USA) in methanol/water to give a concentration of 0-2500 µg/L. 50 µl of the standards was stored in Eppendorf vials (VWR, Amsterdam, The Netherlands) at -20 degrees Celcius until analysis. 200 µl samples, standards, blanco's and quality controls were transferred in a Eppendorf 1,5 ml vial. The protein was precipitated with 700 µl acetonitril which contained an adequate amount of ^{2}H3-Morphin ($^{2}H_3$-M) (Cerilliant, Texas, USA) and ^{2}H3-Morphin-3-glucuronide ($^{2}H_3$-M3G) (Cerilliant, Texas, USA) as internal standard and 100 µl 1mM zinc sulphate. The vials were vortexed for 2 minutes and centrifuged for 5 minutes at 13000 rpm. 200 µl of the supernatant was transferred in a glass tube and dried under a gentle stream of nitrogen at 50 degrees Celcius. The residues were reconstituted in 100 µl of 0.1 % (v/v) formic acid in water. 20 µl was injected by an Ultimate 3000 autosampler (Dionex, Amsterdam, The Netherlands) and pumped by a HPG680 pump (Dionex, Amsterdam, The Netherlands) on a 3 µm, 120Å, 50 x 2.1 mm YMC-pack ODS-AQ column (YMC Inacom, Overberg, The Netherlands) with an ODS precolumn (Phenomenex, Utrecht, The Netherlands) at 30 degrees Celcius. This HPLC part of the equipment was controlled by Chromeleon (Dionex, Amsterdam, The Netherlands). The eluent was monitored by a Quattro micro API tandem mass spectrometer (Waters, Etten-Leur, The Netherlands). Peak areas of reaction ions from morphine and M3G and the internal standards $^{2}H_3$-M, and $^{2}H_3$-M3G were obtained in the multiple reaction mode and integrated by data software Masslynx 4.1 (Waters, Etten-Leur, The Netherlands). m/z was 165.0 (285.9>165.0) for morphine and 286.0 (461.9>286.0) for M3G. For the internal standards m/z was 165.0 (288.9>165.0) for $^{2}H_3$-M and m/z (464.9>289.0) for $^{2}H_3$-M3G. All the samples were calculated by the internal standard method with weighing factor 1/(Y^2). The mobile phase consisted of 0.1% formic acid in water with 3% acetonitril (Lichosolv) (Merck BV, Amsterdam, The Netherlands) as modifier. At a flow rate of 0.5 ml/min the retention times of morphine, M3G, $^{2}H_3$-M and $^{2}H_3$-M3G were respectively 6.70, 7.18, 6.65 and 5.10 minutes. Total analysis time was 10 minutes. All analytes were analyzed within one run.

Chapter 9

AMINOTRANSFERASE LEVELS IN RELATION TO SHORT-TERM USE OF PARACETAMOL FOUR GRAMS DAILY IN POSTOPERATIVE CARDIOTHORACIC PATIENTS IN THE ICU

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ABSTRACT

Background A volunteer study suggested that taking paracetamol 4 grams daily could result in elevated alanine aminotransferase (ALT) plasma levels in a substantial proportion of healthy volunteers. The safety of this dose of paracetamol for acute postoperative pain remains controversial.

Aim To study the incidence of alanine aminotransferase (ALT) elevations after short-term use of paracetamol 4 grams daily, as part of the standard pain management protocol, for 93 consecutive patients after cardiothoracic surgery.

Methods ALT-levels and other liver function tests were measured preoperatively as baseline and once daily after surgery during the ICU-stay.

Results Preoperative ALT-levels of more than 1 time the Upper Limit of Normal (ULN, >40 U/L) was observed in 11% (n=10) of the patients but none of these baseline ALTlevels exceeded 3 times the ULN (>3x ULN). The average daily dose of paracetamol administered was 50 mg per kg (standard deviation = 16) after surgery. Postoperative ALTlevels of >1x ULN was observed in 17% (n=16), and 4% (n=4) exceeded >3x ULN. The other liver function tests of the latter four patients, including AST (range 173-5590 U/L), γ-glutamyltransferase (range 56-103 U/L), Lactate Dehydrogenase (range 376-3518 U/L) and the International Normalized Ratio (range 2.0-6.6), were all abnormal. These four patients all had right ventricular failure or cardiogenic shock during the postoperative period which could explain the significant rises in ALT after surgery.

Conclusion The incidence of significant ALT elevations after using daily paracetamol as an analgesic agent for cardiac surgery, at a dose of 4 grams per day, was low and mostly due to complications after surgery. Our results, albeit still very limited, provided some reassurance about the safety of paracetamol 4 grams daily, as a supplementary analgesic agent for adult patients undergoing cardiac surgery.

INTRODUCTION

Paracetamol is the most commonly used analgesic agent to treat mild to moderate postoperative pain [1]. For more severe pain, paracetamol in combination with an opioid produces a greater analgesic effect than higher doses of the opioid alone [2-4]. Moreover, paracetamol has few contraindications or side effects and lacks significant drug interactions [5], which makes it a valuable analgesic for postoperative pain management (e.g. after cardiothoracic surgery). Severe hepatotoxicity may, however, occur in significant paracetamol overdoses (>140 mg/kg) [6] through an increased production of the reactive metabolite N-acetylbenzoquinoneimine (NAPQI) which reacts with the cysteine group of hepatocellular proteins, resulting in hepatic cell death.

Although hepatotoxicity (defined as alanine aminotransferase [ALT] levels >1000 U/L [7]) after therapeutic dosages of paracetamol has not been not reported [8-9], Watkins and colleagues [10] observed a high incidence of alanine aminotransferase (ALT) elevations (31-44%) of more than three times the Upper Limit of Normal (ULN) in paracetamol-treated healthy subjects after 3 days of its use. In this clinical trial, a total of 145 healthy subjects were randomly assigned into 5 groups (placebo *vs.* either paracetamol four grams daily, or a combination of paracetamol with one of three different opioids). As a result of this publication, physicians and pharmacists are now well aware of possible liver injury associated with therapeutic dosage of paracetamol for the treatment of acute and chronic pain [6,11-12]. If an elevated ALT level can be observed in healthy subjects after taking paracetamol four grams per day, it is possible that this problem can be more prevalent for critically ill patients due to concomitant usage of drugs that may affect the liver and impaired perfusion of the liver, especially in postoperative cardiothoracic patients after cardiopulmonary bypass [13]. Although other analgesic agents, such as NSAID or opioids, are also available, these agents also have significant side effects and may not be safer than paracetamol [6]. As such, it is pivotal to evaluate the safety profile of paracetamol as an analgesic agent for critically ill patients. Currently the incidence of ALT elevations after using paracetamol, as part of an analgesic protocol, after cardiothoracic surgery remains uncertain [14]; in this study we aimed to evaluate the profile of ALT levels, in a cohort of postoperative cardiothoracic patients who had been treated with rectal or intravenous paracetamol 4 grams daily.

METHODS AND MATERIALS

Study Design

A prospective observational study was performed in a 30-bed surgical/medical ICU in a teaching hospital, St Antonius Hospital, Nieuwegein, The Netherlands. The study was part of a clinical trial (registered at ClinicalTrials.gov, identifier NCT00558090), in which the pain

management for intervention-related pain was evaluated in postoperative cardiothoracic patients. The clinical trial was approved by the local Ethics Committee of the St. Antonius Hospital (approval number R0715A, November 7th, 2007). Written informed consent was obtained from the patients before the cardiothoracic surgical procedure.

Patients

Between February 18 and November 13 2008, 135 consecutive patients aged between 18 and 85 years old were admitted to the ICU after cardiothoracic surgery requiring sternotomy and cardiopulmonary bypass (CPB). Exclusion criteria were patients with a known morphine or paracetamol allergy, planned postoperative admission to the postoperative anaesthesia care unit (PACU), pregnancy or breast-feeding, serious neurological deficits (e.g. coma or brain death), patients not able to communicate in either Dutch or English, and patients who refused informed consent. In 93 of the 135 patients, we were able to collect ALT and AST values and were therefore included in this prospective observational study.

Standard pain titration protocol for treatment of pain at rest

According to standard care in our ICU, physicians and nurses were trained in assessing pain and in providing adequate analgesia, a patient data management system (PDMS) obliged nurses to ask patients for their pain score three times a day, and the preferred analgesic treatment was optimized [15].

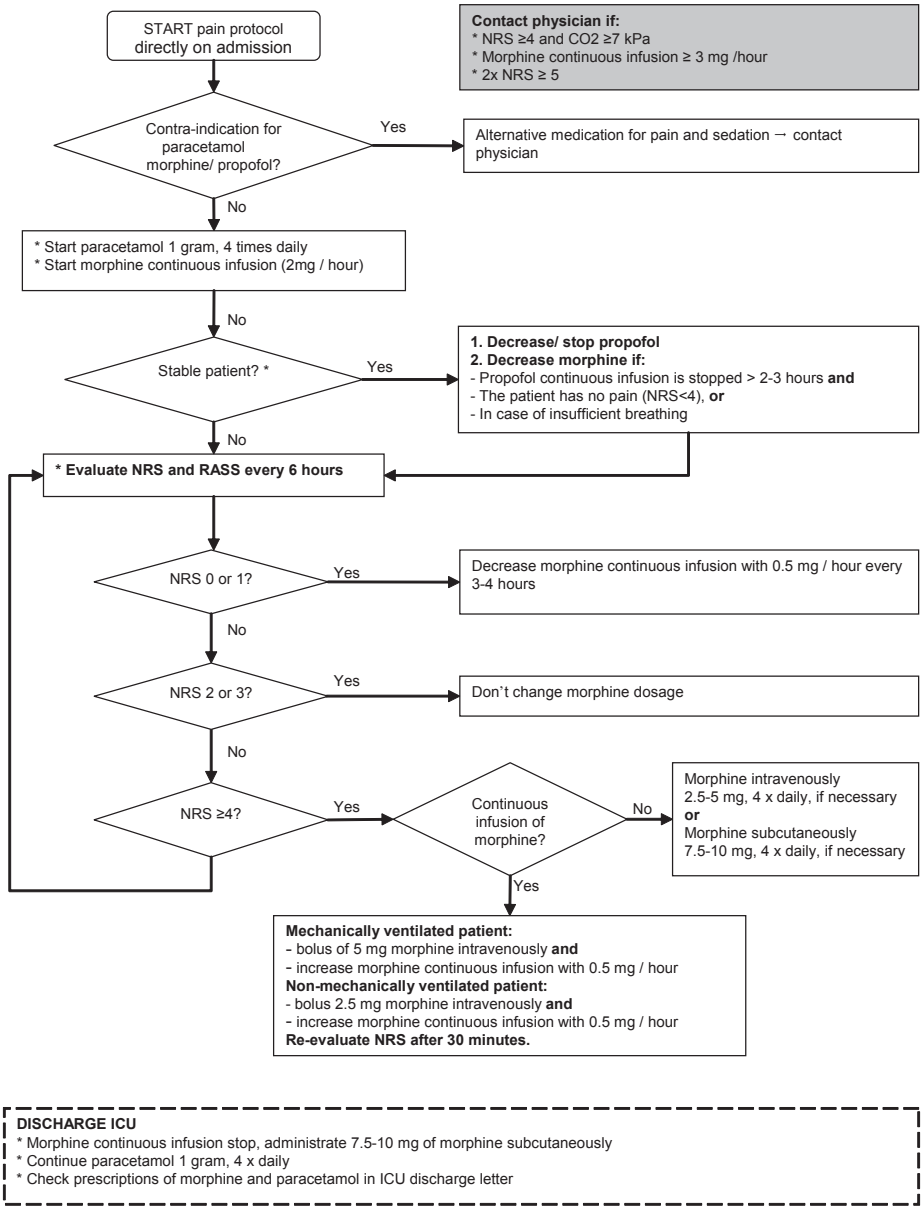
For basic pain relief, a standard pain titration protocol was used in all patients, which is current practice in the ICU since 2007, consisting of continuous intravenous infusion of morphine and a standard dose of rectal or intravenous paracetamol 4 grams daily (Figure 1).

Liver function tests

Arterial blood plasma samples (4 ml) for determination of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were taken from the arterial line. Of each patient, samples were obtained just after the induction of anaesthesia (baseline) and thereafter once daily at 15.00 hr as long as the patients were still in the ICU, for a maximum of 10 days. The results of the liver function test were available to the attending clinicians. The Upper Limit of Normal (ULN) for both ALT and AST was defined as 40 U/L [10], in which 2x ULN equals 80 U/L and 3x ULN equals 120 U/L. Other liver function tests, such as γ-glutamyl transpeptidase (GGT), Lactate Dehydrogenase (LD), International Normalized Ratio (INR) and bilirubin were taken as part of their routine clinical care.

Study procedure

On the day of cardiothoracic surgery, patients received one gram of paracetamol orally. Thereafter, patients received rectal or intravenous paracetamol upon automatic signals by the Patient Data Management System (PDMS) 4 times a day (7 days a week). When patients



* Hemodynamicly stable, acceptable leakage through thoracic drains, adequate time after muscle relaxation, adequate core temperature
NRS = numeric rating scale
RASS = Richmond Agitation Sedation Scale
ICU = Intensive Care Unit

Figure 1. Pain titration protocol for pain at rest

were transferred to the ward, paracetamol one gram four times daily was prescribed in the ICU-discharge letter for the ward.

Data-analysis

The SPSS statistical package (version 15.0.1 for Windows; SPSS, Chicago, IL) was used for the statistical analyses. Descriptive statistics are reported as mean with standard deviation (SD), median with range, or proportion. Means were compared using a t-test for normally distributed data or the nonparametric Mann Whitney two-sample rank sum test for data not fitting the assumptions of parametric testing. Proportions were compared by using chi-square tests or Fisher's exact test when appropriate. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Patients and data

Patient demographics of the 93 patients are presented in Table 1. The mean number of measured ALT tests performed per patient was 3.4 (range 2-8). Of all the 93 patients included in this study, 8 patients (9%) used preoperative paracetamol 4 grams daily. In 69 patients,

Table 1. Patients' characteristics

	All patients
Number of patients	93
Male gender, n (%)	69 (74%)
Age (years)	69 ± 11
Body Mass Index (kg/m^2)	27 ± 4
Body Weight (kg)	82 ± 14
Median EURO score (range)	8 (0-13)
Type of cardiothoracic surgery, n (%)	
CABG	15 (16%)
Valve surgery	21 (23%)
CABG + valve surgery	33 (36%)
Aortic surgery (+ valve)	24 (26%)
Non-elective surgery, n (%)	5 (5%)
Duration of mechanical ventilation in the ICU (hours)	20 ± 31
Median ICU stay (days) (range)	2 (1-13)
Pre-operative use of paracetamol, n (%) [a]	8 (9%)
Pre-operative chronic use of alcohol, n (%) [b]	25 (36%)
Paracetamol received in the ICU	
Dose (mg/kg/day)	50 ± 16

Data are expressed as mean ± standard deviation (SD) or median (range).

[a] Defined as paracetamol 4 grams daily

[b] Defined as alcohol >1 IE daily, 24 missing values

EURO score: European System for Cardiac Operative Risk Evaluation score [16]; CABG = coronary artery bypass graft; ICU = intensive care unit

information on history of alcohol use was available, of whom 36% (n=25) used alcohol (>1 unit daily) preoperatively. The mean dose paracetamol administered in the ICU per day for all patients was 50 mg/kg (± 16 mg/kg).

Preoperative ALT levels

Ten patients (11%) had a baseline ALT level of more than one time the upper limit of normal (>1x ULN) (mean ALTlevel 66 U/L, range 42-96). In 3 of these 10 patients, the ALT levels were elevated to >2x ULN (81 U/L, 90 U/L and 96 U/L). None of the patients experienced a preoperative ALT level of >3x ULN (Table 2, Figure 2).

Table 2. (A) Incidence of aminotransferase elevations by multiples of upper limit of normal (ULN) and (B) the incidence of aminotransferase elevations by multiples of patient's preoperative/ baseline (BL).

		Preoperative level n (%)	Postoperative Levels n (%)		
A. Upper limit of Normal					
	N	**> 1x ULN (>40 U/L)**	**> 1x ULN (>40 U/L)**	**> 2x ULN (>80 U/L)**	**>3x ULN (>120 U/L)**
ALT	93	10 (11%)	16 (17%)	5 (5%)	4 (4%)
AST	93	8 (9%)	75 (81%)	40 (43%)	14 (15%)
B. Baseline Limit					
			> 1x BL	**> 2x BL**	**> 3x BL**
ALT	93	-	36 (39%)	14 (15%)	5 (5%)
AST	93	-	89 (96%)	67 (72%)	37 (40%)

ULN = upper limit of normal (<40 U/L); BL = Baseline; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase

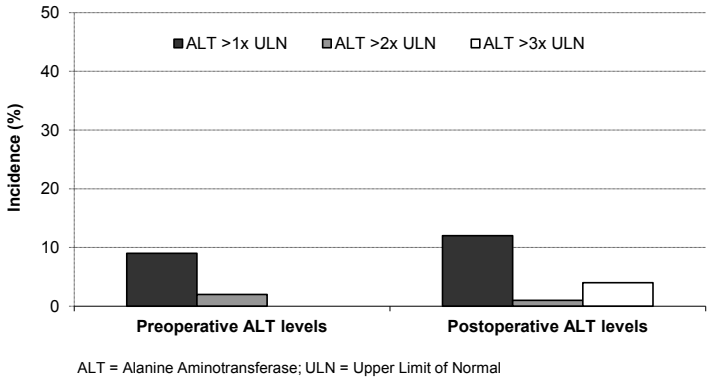


Figure 2. Incidence of preoperative and postoperative aminotransferase elevations by multiples of upper limit of normal (ULN)

Postoperative ALT levels

In Table 2 and Figure 2, the incidences of aminotransferase levels (ALT and AST) by multiples of the ULN (>40 U/L) (A) and the incidence of aminotransferase levels (ALT and AST) by multiples of patients' baseline aminotransferase levels (B) are presented.

Of all the 93 patients included in the study, the incidence of ALT >1x ULN and >2x ULN was 17% (n=16) and 5% (n=5), respectively. Four male patients (4%) experienced an ALT >3x ULN (Table 2, Figure 2).

In the patients experiencing an ALT >1x ULN (n=16), mean dose of paracetamol per day was 50 mg/kg (± 22 mg/kg). The mean cumulative dose of paracetamol received in ICU in these patients was 205 mg/kg (± 110 mg/kg).

Cases with an ALT >2x ULN (>80 U/L)

In total, 5% (n=5) of the patients experienced an ALT >2x ULN. One of these patients had a maximum ALT of 93 U/L, which decreased to normal (< 40 U/L) during follow-up and the other 4 patients experienced ALT values of more than 3 times the upper limit of normal (>3x ULN).

Cases with an ALT of >3x ULN (>120 U/L)

Table 3 presents an overview of the four cases with an ALT of >3x ULN. In all 4 cases, other liver function tests (e.g. AST, GGT, LD, INR), and also creatine kinase (CK) were increased. All four cases also had an elevated AST postoperatively (>3x ULN; range 173-5590 U/L).

Case 1 had a preoperative ALT baseline of 60 U/L, which represents >1x ULN. Case 1 experienced an allergic reaction to protamine administered during surgery, thereby also leading to right ventricular failure. The postoperative course of this patient was further complicated by *S. aureus* pneumonia. The patient recovered promptly after treatment with inotropic agents and antibiotic therapy and left the ICU four days postoperatively.

Cases 2, 3 and 4 had a preoperative baseline ALT level within the reference range (<40 U/L) and developed cardiogenic shock and/or sepsis postoperatively, and died 2 to 5 days later. In case 4, paracetamol was discontinued when the ALT level was 1011 U/L on day 4 of ICU stay.

One of the 4 cases with an ALT of >3x ULN used paracetamol 4 grams daily preoperatively. This case had no serious increased ALT and AST levels at preoperative baseline (60 U/L and 35 U/L respectively). None of the four cases with an ALT of >3x ULN, used alcohol preoperatively.

DISCUSSION

Our results showed that the incidence of maximum ALT of >3x ULN after paracetamol four grams daily in patients after cardiothoracic surgery was low (4%)(n=4) and the significant rises in ALT could easily be explained by severe complications after surgery.

Table 3. Overview of cases with an alanine aminotransferase (ALT) level of >3 x upper limit of normal

	Case 1	Case 2	Case 3	Case 4
Patient characteristics				
Type of surgery	CABG + AVR	Re-AVR + carotid endarterectomy	CABG + AVR	CABG + aneurysm resection
EURO- score	4	13	11	12
Pre-operative paracetamol?	Yes	No	No	No
Pre-operative alcohol?	No	No	No	No
Baseline ALT (U/L)	60	31	20	15
Paracetamol				
Dose (mg/kg/day)	40	41	59	50
Cumulative dose (mg/kg)	150	173	242	236
Route of administration	1 gram IV by ICU arrival, followed by rectal administration	1 gram IV by ICU arrival, followed by rectal administration	Rectal administration	1 gram IV by ICU arrival, followed by rectal administration
Liver function tests and outcome				
Highest ALT (U/L)	293	136	250	2837
Corresponding AST (U/L)	264	836	173	5590
Day of ICU stay of highest ALT	Day 3	Day 4	Day 3	Day 5
Other liver function tests *	Bilirubin 11 µmol/l CK 2206 U/L GGT 103 U/L LD 607 U/L INR 2.0	Bilirubin 7 µmol/l CK 176 U/L LD 376 U/L INR 5.5	Bilirubin 12 µmol/l CK 98 U/L LD 522 U/L INR 6.6	CK 131 U/L GGT 56 U/L LD 3518 U/L INR 4.1
Progression disease	Right ventricle failure after allergic reaction to protamine perioperatively. Suspected for pneumonia (*S. aureus* in sputum)	Cardiogenic shock, sepsis and multi-organ failure	Cardiogenic shock and multi-organ failure	Cardiogenic shock (tamponade)
Outcome	Patient fully recovered, left ICU 3 days postoperatively	Died 4 days postoperatively	Died 2 days postoperatively	Died 5 days postoperatively

* Reference levels: Bilirubin: <17 µmol/l; Creatinekinase (CK): <175 U/L; γ-glutamyltransferase (GGT): <50 U/L; Lactate hydrogenase (LD): <220 U/L; International Normalized Ratio (INR): <1.2. CABG = Coronary Artery Bypass Graft; AVR = Aortic Valve Replacement; EuroSCORE: European System for Cardiac Operative Risk Evaluation score [16]; IV = intravenously; ICU = intensive care unit

The safety of using 4 grams per day of paracetamol as an analgesic and antipyretic agent remains controversial [9]. Increased ALT levels after receiving standard therapeutic doses of paracetamol for various indications have been reported [17-20] and, in a systematic review, Dart and Bailey [9] reported an overall incidence of 0.4% increase in ALT levels in patients, who were treated with therapeutic doses of paracetamol. Furthermore, a remarkably high

incidence of increased ALT levels was also reported in a healthy volunteer study [10]. In some reports, the use of therapeutic doses of paracetamol also appeared to have contributed to the development of severe liver failure and death [21-23]. Our study was different from these previous reports and required careful consideration. First, we had careful documentation of the doses of paracetamol administered to all the patients in this study. It is possible that some of the previous reports of severe liver toxicity induced by paracetamol may due to unintended overdoses because of inaccurate documentation of the doses of paracetamol used [9]. In fact, a number of prospective randomised clinical trials on healthy subjects also did not observe significant ALT elevations after 4, 6 or 8 grams of paracetamol per day for a maximum of 3 days [24-25], even in subjects using alcohol [9,26].

Second, although mild elevations of ALT were not uncommon after therapeutic doses of paracetamol after cardiac surgery, severe elevations of ALT (3xULN) were all associated with significant complications during or after cardiac surgery. It is known that in critically ill patients, the main causes of liver failure are septic shock and a low cardiac output, i.e. cardiogenic shock [27]. In cardiac failure, a low cardiac output causes hepatic ischemia due to reduced hepatic blood flow and venous congestion of the liver [27]. In sepsis, liver failure is mainly the result of insufficient oxygen extraction of the liver despite sufficient or even increased splanchnic and hepatic perfusion [27]. In these conditions of liver failure, liver function parameters like AST, GGT, LD, INR, and bilirubin are often increased similar to those we observed in our 4 cases in our study (Table 3). Therefore, the increased ALT levels in these 4 cases differ from the typical paracetamol induced liver injury, in which an isolated increased ALT and AST level within the first 24 hour-period is observed [28].

Third, in the healthy volunteer study conducted by Watkins and colleagues [10], they included no data on alcohol consumption, diet or paracetamol use before entering the study. We were able to collect these data, and observed that 37% (n=25) and 9% (n=8) of the patients regularly consumed alcohol or used paracetamol preoperatively, respectively, in this study. Of the four patients with ALT levels of >3x ULN, only one patient used preoperative paracetamol 1 to 4 grams daily. However, baseline ALT (60 U/l) and AST (35U/l) levels for this patient were not substantially increased.

Apart from an increase in ALT levels in our patients, we also observed an increase in AST levels in many of our patients after surgery (AST of >1x ULN: 82%, >2x ULN: 43%, and >3x ULN: 15%). Because AST is also a biomarker for myocardial injury, and is formed in the urea cycle after cardiac ischemia [29], it is possible that increases in AST were primarily due to myocardial ischemia during and after surgery.

This study has some limitations. First, the sample size of this study was still small and was underpowered to detect rare adverse events. Second, we did not have a control group in our observational study. The safety of paracetamol should ideally be tested in a randomised placebo-controlled trial in which selection bias and confounding can be reduced. Third, we used different routes to administer paracetamol to the patients during the course of their

stay in ICU. Because bioavailability of rectal paracetamol is not the same as intravenous or oral paracetamol, it is possible that the incidence of liver dysfunction would be higher if only intravenous preparation of paracetamol was used. Finally, we did not have blood paracetamol levels both before and after the occurrence of deranged liver function tests. As such, we cannot assess whether there was any significant relationship between blood paracetamol concentrations and ALT levels in our patients.

In conclusion, in our cohort of postoperative cardiothoracic patients, we found a low incidence of substantial ALT elevations, except those who had severe cardiac complication during or after surgery, and did not appear to affect the clinical outcomes of our patients. With the limited data available, this study provided some reassurance about the safety of therapeutic doses of paracetamol in adult cardiac surgical patients.

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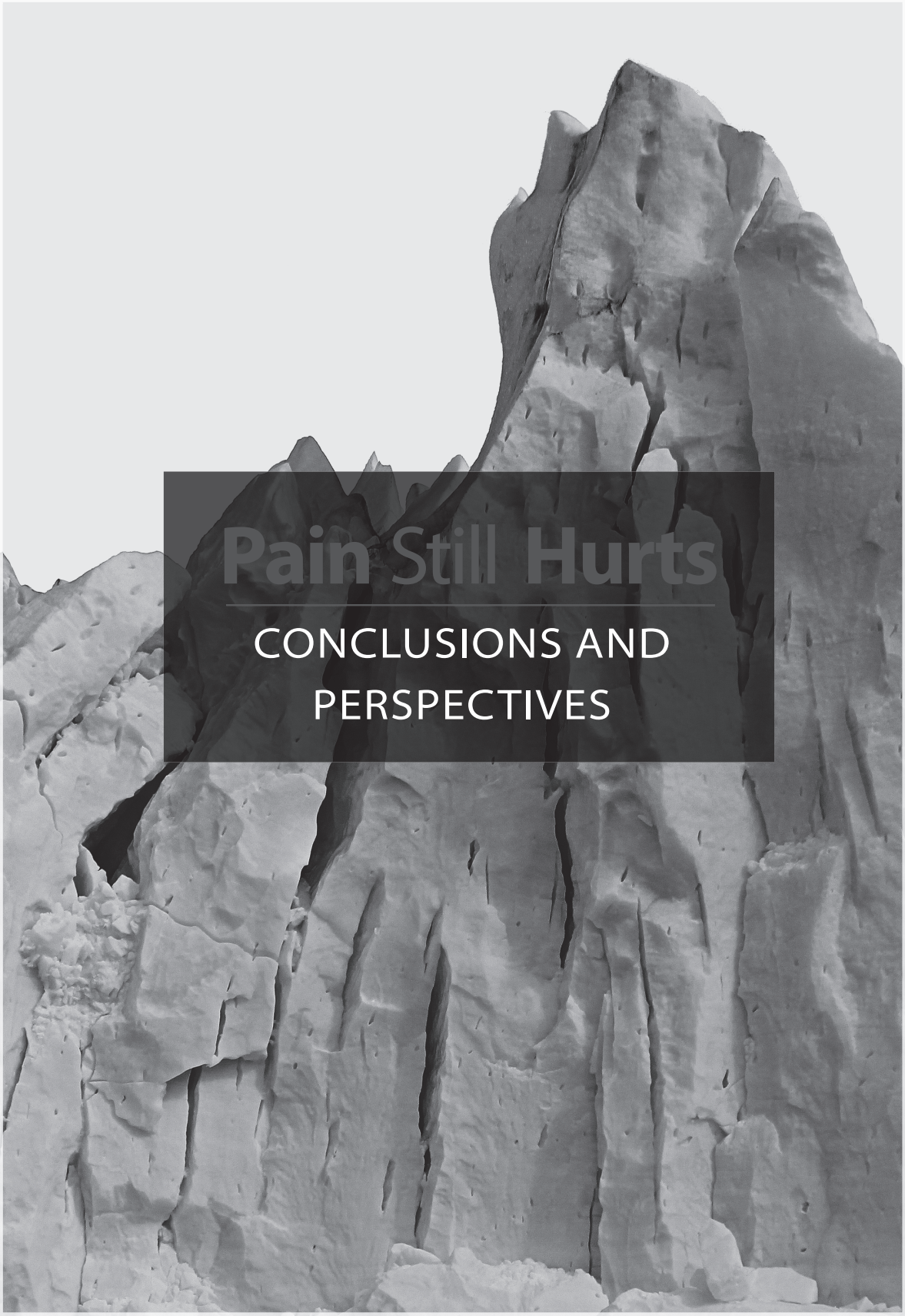

Pain Still Hurts

CONCLUSIONS AND PERSPECTIVES

Chapter **10**

PAIN ASSESSMENT AND PAIN MANAGEMENT IN INTENSIVE CARE PATIENTS

INTRODUCTION

The overall goal of the studies described in this thesis was to improve pain management in adult patients after cardiac surgery and critically ill patients in the intensive care unit (ICU). We focused on pain assessment, pain management at rest and during painful procedures, and the efficacy and safety of analgesics, such as paracetamol and morphine.

Despite efforts in improving pain management in intensive care patients from different research groups [1-3], 63-77% of the patients still report moderate to severe pain during their ICU stay. As pain management programmes may decrease morbidity and mortality, and improve the quality of life in intensive care patients [1,4], pain management has increasingly been recognized as an essential part of the standard care of patients in the ICU. Moreover, pain management became more important as a result of the position statement on sedation of intensive care patients that reported restriction to a conscious level whenever possible, which enables patients to report pain in an earlier phase of their intensive care stay.

PAIN ASSESSMENT IN INTENSIVE CARE PATIENTS

Adequate pain management can only be achieved by using effective methods for the recognition, evaluating and monitoring of pain. Both the Society of Critical Care Medicine (SCCM) [5] and the Netherlands Society of Intensive Care (NVIC) developed guidelines for analgesia and sedation [6], and advice about pain assessment and preferred analgesics and sedatives. However, the most optimal method for pain assessment still needs to be determined, as there are only few evidence based studies available in this specific patient population.

Every patient in the ICU will pass different stages of consciousness, from a deeply sedated state during the first stage of the disease or after surgery, through arousal from sedation to a fully conscious and communicative state. Depending of the sedation level of the patient, different pain scales are available (Appendix I). Therefore, pain assessment should always be in conjunction with assessment of the depth of sedation, for which several sedation scales are validated in clinical practice (Appendix II).

In **Chapter 2**, we evaluated three pain rating scales, i.e. the numeric rating scale (NRS), the visual analogue scale (VAS), and the behavioral pain scale (BPS) in (non-)ventilated intensive care patients, who were conscious sedated or sedated. Furthermore, we determined which health care worker (nurse or consultant) should preferably score this pain in case the patient was not able to report pain himself.

In conscious patients, self report is the 'gold standard' for pain assessment according to the guidelines of the International Association for the Study of Pain [7]. However, the NRS (range 0-10) and VAS (range 1-100) have been validated for acute pain only, and both pain

scales were never validated in mechanically ventilated patients in the ICU [8]. In our study, 66% of the patients were able to score their pain using the numeric rating scale (NRS). The visual analogue scale (VAS) appeared less suitable, and could only be scored by 43% of the patients. The reduced number of patients who were able to rate the VAS may result from the limited ability for abstraction and comprehension of the patients. Furthermore, the VAS cannot be used by patients who are injured to the upper limbs. Although the NRS also needs a certain level of comprehension and abstraction, the NRS is easier to score as pain is scores verbally, with or without some assistance from the attending nurse. The more simple 4-point verbal rating scale (VRS-4) may be an alternative for both the VAS and NRS, as the VRS-4 has shown good reliability and validity in postoperative patients in previous studies [9], and is preferred by patients over the NRS [10]. However, the VRS-4 is less sensitive compared to the NRS and VAS [11]. Therefore, the NRS is in our opinion the preferred pain measurement scale in conscious patients.

In sedated patients, who are not able to report pain, observers have to use behavioral and physiological parameters of the patient. From this point of view, several pain scales were developed (Appendix I). The Non Verbal Pain Scale (NVPS) was modified from the FLACC (Face, Legs, Activity, Cry, Consolability) scale, consisting of three behavioral indicators and four physiological indicators [12]. The NVPS is partly validated for patients after burn trauma and not for intensive care patients in general. Before this pain scale can be applied in the intensive care unit, it has to be evaluated more extensively, especially in terms of inter-rater reliability and psychometric properties.

The Pain Assessment Intervention Notation (PAIN) Algorithm includes behavioral and physiological indicators as well, and involves guidelines for analgesic treatment [13]. Although this method may be a useful tool to standardize pain assessment and management in the ICU, the length of the pain scale limits the clinical applicability. Furthermore, behavioral and physiological indicators of the PAIN Algorithm have not been standardized so far, resulting in nurses making clinical judgements or interpretation based on their experiences [14]. Moreover, using physiological indicators for estimating patients' pain may be misleading, as these parameters, i.e. heart frequency and blood pressure are influenced by medication, such as beta blockers and inotropics. For this reason, the NVPS and PAIN Algorithm may be less applicable for pain measurement in intensive care patients.

The Critical Care Pain Observation Tool (CCPOT) was recently developed from three existing pain scales (BPS [15], COMFORT [16] en PAIN Algorithm [17]), and consists of four behavioral indicators. Gélinas et al. [18] showed that the CCPOT is valid for pain measurement in patients after cardiac surgery, with a high sensitivity and specificity during a painful intervention [18-20]. An advantage of the scale is that it can be applied even in non-ventilated patients. However, the CCPOT is only validated for one painful procedure (turning of the patient), with a low specificity during non-painful procedures. Therefore, further research is necessary before the CCPOT can be implemented in the ICU.

At last, the BPS is a pain scale for sedated and mechanically ventilated patients exclusively and is based on three behavior parameters [15]. The BPS is validated in a diverse case mix population, including surgical patients and patients with respiratory insufficiency, multi-trauma and sepsis. In our study, the BPS appeared to be a valid tool measuring pain in sedated patient, and is most adequately scored by the nurse. The BPS is also quick and simple to score, although an important finding of our study is that especially unacceptably high patient scores (NRS≥4) were underestimated by the nurses. Thereby, it has to be taken into account that the BPS showed a high non-response in deeply sedated patients. The reason for this phenomenon may be that the BPS reflects the objective visible behavior at one specific time point. In contrast, the NRS represents a global impression of pain, including several contextual factors during a longer time period. It seems, therefore, that the BPS should be used only in conjunction with the NRS nurse to measure pain levels in intensive care patients.

In conscious sedated patients, the VAS may be not applicable, resulting from immobility making it impossible to point to a score on the VAS. Furthermore, the NRS or VAS may be unreliable because of limitations in comprehension and abstraction, to capture a range from 0 to 10, or 0 to 100 mm, respectively. However, self report using the VRS-4 may be useful, as this scale consists of only for levels. In **Chapter 3**, we showed that the BPS scored by the nurse proved a valid method in conscious sedated patients. Nevertheless, as the BPS was found to both overrate and underrate patients' pain, and the patient's self-report is not always reliable, a combination of the nurse-rated BPS and the patient-rated VRS-4 is perhaps ideal for estimating patients' pain, as each method yields unique information. Self-reporting primarily reflects expressive pain behavior that is under control of higher mental processes. Observational measures capture behavior that is less subject to voluntary control and more automatic [21].

Sedation assessment in intensive care patients

As mentioned before, the choice for a pain measurement instrument for an individual patient depends on the patients' depth of sedation. Sedation assessment can protect patients from complications associated with under sedation, such as agitation, anxiety and ventilator asynchrony [22], and oversedation on the other hand, which may result in side effects caused by sedatives, increased duration of mechanical ventilation and longer length of stay in the intensive care unit [23-25]. Several sedation scales are available (appendix II), although a true gold standard scale has not been established.

The Ramsay scale is widely used, although the scale attracted criticism because of its lack of clear discrimination, and lack of specific descriptors to differentiate between levels [5,26]. Because of the limited psychometric testing of the Ramsay scale, new sedation scales were developed, i.e. the Sedation Agitation scale (SAS), the Motor Activity Assessment Scal (MAAS) and the Richmond Agitation Sedation Scale (RASS). The SAS [27] scores a patient's level of consciousness and agitation from a seven-point list describing patients behavior,

and showed excellent inter-rater reliability and validity when compared to other sedation scales [27-28]. The MAAS is adapted from the SAS, and has been validated for use in critically ill patients [29]. Although the MAAS appeared sensitive to changes in sedation levels and was shown a reliable tool, the MAAS does not have sufficient psychometric evaluations, and is not significantly different from the SAS. Therefore, the MAAS is not considered a primary and unique method for evaluation of sedation levels [26]. The Richmond Agitation Sedation Scale (RASS) [30] has been validated to detect changes in sedation status over several days, and correlates with doses of sedatives and analgesic medications administered in critically ill patients [31]. The RASS has a good inter-rater reliability and correlates well with the Ramsay score [30,32]. A disadvantage of the RASS are the lengthy and subjective descriptions of the items, which makes the RASS more difficult to interpret for health care workers.

Using the Vancouver Interaction and Calmness Scale (VICS), patients are assessed independently for the ability to interact and communicate and for their level of activities or restlessness. The scale has been validated for the assessment of sedation in adult critically patients [33]. However, the VICS as not been tested to identify optimal sedation endpoints [5].

At last, the ATICE is a sedation scoring system that additionally rates patient agitation and ventilator synchrony [34], and includes more scoring parameters compared to the RASS. It has demonstrated high internal consistency, inter-rater reliability across disciplines, and validity. Although more scoring parameters will result in a more complete sedation assessment, the ATICE is more difficult to perform in daily practice [6].

Finally, the Bispectral index (BIS) is an objective method for depth of anaesthetic or sedation assessment, based on the patients' electroencephalogram (EEG). Most reports showed a strong correlation between BIS and patient recall or level of hypnosis in the operating room [35]. BIS guided anaesthesia is suggested to reduce the risk of awareness in at-risk adult surgical patients undergoing general anaesthesia [36], although the reliability of these results are questionable, as result of the underpowered study and differences in anaesthetic procedure between the BIS guided anaesthesia and the control group [37-38]. In the ICU, the use of the BIS is limited, as the BIS scores may vary between patients at the same subjective level of sedation. Muscle based electrical activity may artificially elevate BIS scores if the patient has not received neuromuscular blockade [5], which is the case in almost all intensive care patients nowadays. Furthermore, the BIS cannot be evaluated in patients with metabolic impairments or structural abnormalities of the brain. At last, there are no prospective comparative studies evaluating patient outcomes of using BIS versus subjective sedation scales [5,26,39]. Therefore, the use of the BIS cannot be recommended until the value and validity are confirmed. Both the SCCM and the NVIC, recommends the use of the SAS, MAAS and VICS [5-6]. The NVIC recommends also the use of the RASS or the ATICE as useful sedation assessment scale [6].

Conclusions and recommendations

- The method of pain assessment depends on the patients' depth of sedation and mode of mechanically ventilation.
- Pain scores should be obtained by self report of patients as much as possible, preferable by using the NRS.
- In sedated patients, who are not able to communicate, pain should be rated by the attending nurse, using the NRS in conjunction with the BPS.
- In conscious sedated patients, a combination of the nurse-rated BPS and the patient-rated VRS-4 should be used for the estimation of patients' pain.
- Specific neurobiological parameters for the evaluation of pain should be identified, which may be used as part of the current pain scales, and may contribute to a more objective pain assessment.

PAIN MANAGEMENT FOR INTENSIVE CARE PATIENTS AFTER CARDIAC SURGERY

Pain management at rest

Adequate pain management reflects a high quality in daily patient care and is considered an important health care benchmark. Clinical practice guidelines recommend systematic evaluation of pain in patients for optimal pain management, but how to implement such a protocol is not specified. More specifically, clinical practice guidelines may have limited effect on changing the health carers' behavior, as result of a variety of barriers to guideline adherence, which may include for example lack of knowledge, lack of awareness or environmental barriers such as time or resources [40].

In our ICU, at baseline 42% of the pain scores at rest were rated as unacceptable pain by patients after cardiac surgery, which is defined as a NRS score of 4 or higher [8]. Although this incidence is substantial, it is rather low compared to previous reports, reporting incidences even between 63-77% [2]. In order to reduce this incidence of pain at rest, in **Chapter 4**, we introduced a pain management system consisting of a pain education programme for nurses and physicians, the introduction of systematic pain assessment and registration of the pain scores. Furthermore, the standard analgesia protocol was optimized, in which intravenous morphine as a continuous infusion was preferred over subcutaneous use or use on demand, and was combined with paracetamol administration directly upon arrival in the ICU. It was shown that this protocol successfully reduced the occurrence of unacceptable pain (NRS≥4) in patients after cardiac surgery from 42% to 23%. This incidence of unacceptable pain of 23% is comparable with a previous study in a diverse group of ICU patients [1], and approximately three times lower than other reports [2,41]. In this study, patients in the intervention group received higher morphine doses compared with baseline, while morphine was administered to patients with high pain levels (NRS≥4). This

confirms that unacceptable pain is more adequately managed in the intervention group compared to patients in the control group. Additionally, patients in the intervention group received more intravenous morphine and less subcutaneous morphine compared to the control group. As little is known of the bioavailability of subcutaneously administered morphine in intensive care patients with possible impaired perfusion and an altered volume of distribution, the programme intended and succeeded in a 38% reduction of the total amount of morphine administered subcutaneously. Thus, efforts so far leads to a successful implementation of a guideline concerning pain management, which could in part be achieved by efforts in improving health carers' knowledge and attitude concerning pain management.

However, in the intervention group, still 46% of the patients experienced at least one unacceptable pain score during their stay in the intensive care unit. Therefore, we focused on more individually tailored analgesia for pain management at rest. To this effect, we implemented a pain titration protocol, consisting of a continuous infusion of morphine and paracetamol 4 grams daily, as individualized titration of analgesia is associated with shorter ICU- and hospital length of stay and a lower mortality [42]. In **Chapter 5**, in which procedure-related pain was studied, all patients were treated according to this pain titration protocol. Within this context, we observed a lower incidence of unacceptable pain at rest (16%) in patients treated according the pain titration protocol, compared with the situation that only the pain training programme was implemented (Chapter 4). The incidence of unacceptable pain of 16% was also remarkably lower compared to previous reports, including patients with a comparable case mix [1,43]. In this patient group, we observed higher morphine consumption in younger patients, and in patients with a low euroSCORE (Chapter 5, Table 1). It is well known that older patients need less analgesics for pain relief than younger patients [44]. Patients with a high euroSCORE are probably more vulnerable for the effects of medication, due to impaired condition of elimination organs, e.g. kidney and liver. This condition may result in a slower elimination of morphine, thereby leading to lower morphine consumption in these patients. The observed differences in morphine consumption between patients with various background characteristics suggest that the pain titration protocol leads to an individual dosing regimen of analgesics, thereby resulting in a low incidence of unacceptable pain at rest.

Conclusions and recommendations

- A successful implementation of a pain training programme, in order to achieve a significant decrease in pain at rest in the ICU can only be realized when health care workers are intensively trained in terms of knowledge and attitude in pain management.
- In an intensive care unit, a pain titration protocol should be implemented, which leads to an individualised dosing regimen of analgesics, thereby resulting in a lower incidence of unacceptable pain at rest.

Procedural pain management

Apart from pain at rest, patients in the ICU may suffer from unavoidable routine care painful procedures. Procedural related pain is the most common form of health induced pain, which has been recalled as strong negative memories of the time in the intensive care unit [45-46]. However, a number of reports showed that procedural pain is difficult to treat [1,47]. Therefore, one part of the patients will experience unacceptable pain despite treatment [47-49]. In **Chapter 5**, we studied the efficacy of a bolus of intravenous morphine 2.5 versus 7.5 mg for procedural pain relief in postoperative patients after cardiac surgery in the ICU, who were already treated according to a pain titration protocol for pain at rest. In patients with low pain levels for pain at rest (16%), there was no difference in efficacy between a bolus of intravenous morphine 2.5 mg or morphine 7.5 mg for pain relief during a painful intervention. As such, a bolus dose of morphine 2.5 mg may be sufficient to prevent procedural pain, in case pain at rest is well controlled on the basis on individually tailored analgesia.

During the painful intervention, we found a substantially lower incidence of unacceptable NRS scores (25%), compared to previous reports. Incidences of 32% to 62% have been reported during endotracheal suctioning and movement in patients with various morbidities [47-49]. In these studies, pain was managed with standard doses of analgesics for pain relief at rest or during procedural interventions only [50-52], which is in contrast with our study in which a pain titration protocol was applied. As such, we suggest that the pain titration protocol which is applied during the entire ICU stay may not affect pain scores at rest alone, but may also lead to a decrease of pain intensity during painful procedures.

Despite adequate pain management, one part of the patients (25%) experienced unacceptable pain during a painful procedure. Pain levels are known to differ largely between patients and may partly be explained by environmental factors such as age, gender or anxiety. Furthermore, some candidate genes genetic polymorphisms have been associated with differential pain sensitivity.

Pharmacogenetics

In a sub-study of the randomised controlled trial of chapter 5, in **Chapter 6** we evaluated the effect of a polymorphism of the catechol-O-methyltransferase (*COMT)* Val158Met polymorphism, which has been shown to affect pain sensitivity upon experimental pain stimuli in healthy volunteer studies. *COMT* metabolizes dopamine, epinephrine and norepinephrine, and is a key modulator of dopaminergic and adrenergic neurotransmission [53]. *COMT* contains a common functional coding polymorphism Val158Met, corresponding to a valine-to-methionine substitution at codon 158 (Val158Met). This Val158Met substitution has been associated with a three- to four fold decrease in *COMT* activity [54], which results in lower endogenous levels of enkephalins and subsequently exaggerated pain sensitivity [55]. In this study, patients received continuous morphine infusions for pain at rest, and a bolus of morphine (2.5 or 7.5) before a painful procedure. All patients were genotyped for

the *COMT* Val158Met polymorphism. Morphine-treated patients carrying the Met-variant allele experienced both significantly higher overall pain scores and significantly higher pain levels during the painful procedure, compared to patients with the Val/Val genotype. More specifically, in patients with the Met/Met genotype a statistically significant and clinically relevant increase (NRS≥1.3) in pain levels was observed during the painful procedure, which was absent in patients with the Val/Val genotype. To our knowledge, this is the first study evaluating the *COMT* Val158Met polymorphism on pain sensitivity within a clinical research design in morphine-treated postoperative cardiac patients undergoing an unavoidable painful stimulus. The *COMT* Val158Met polymorphism thus explained one part of the variability in pain sensitivity. Patients carrying the Met-allele may potentially benefit from another pain management strategy, including treatment with analgesics which are independent of endogenous enkephalin levels and the μ-receptor density.

Furthermore, the results of this study suggest that pharmacogenetics may play an important role in pain management in the future. It seems that more research is needed, in order to determine an adequate set of genes. This set of genes may be of added value in identifying patients who are at high risk for pain, or have experienced an 'abnormal' pain to usual dosages of analgesics. However, a limitation of such pharmacogenetic studies including several polymorphisms at once is the need of extremely large sample sizes in order to detect differences between the genotype groups of the polymorphisms. In our study, we did find a significant effect in both overall pain levels and pain during the painful procedure between the genotype groups of the *COMT* Val158Met polymorphism. In the future, all patients may undergo genotype screening preoperatively, which enables health care workers to adapt pain management. Thus, pain sensitivity is influences by many factors, including genetic contributions of at least one gene.

Perspectives in procedure-related pain management strategies

In our study, morphine was chosen for the prevention and treatment of postoperative pain at rest and during procedures. Morphine is the preferred analgesic for acute pain relief [5], as it may provide cardioprotection and anti-inflammatory response in contrast to fentanyl in patients after cardiac surgery [56-57]. However, one disadvantage of morphine may be the slow onset of action and relatively long half-time compared to other opioids, such as fentanyl or remifentanil. In several studies with different patient populations [58-60], no superiority for one of the three analgesics, morphine, remifentanil, and fentanyl was found within a pain titration model. In two studies on chest drain removal in postoperative cardiac patients, no difference in pain scores was observed between subcutaneous bupivacain 0.5%, intravenous ketorelac 30 mg or inhaled entonox 50% and intravenous morphine [50,52]. Although an intravenous remifentanil bolus of 0.5 μg/kg was shown to be effective for drain removal in post-cardiac surgical patients in comparison to placebo (median NRS score [25-75%] 1 [0-2] *vs.* 5 [3-6] respectively), patients received no baseline infusions of opioids [61]. The results

are therefore difficult to compare to our situation where standard infusions of morphine are given for pain at rest. At last, in most intensive care patients nonsteroidal anti-inflammatory drugs (NSAID's) cannot be used, due to the high risk of provocation in patients with heamodynamic instability and renal dysfunction. An ideal analgesic for procedural related pain is thus not yet available. Therefore, we should focus on other strategies for procedural pain management. Although beyond our research, we suggest that anxiety management may improve pain management.

Pain is based on the perception of the patient, which is influenced by many factors, including the patient's emotional and psychological state, level of anxiety, understanding of the procedure [62] and environmental factors, including the setting and person performing the procedure [63]. Therefore, the attending nurse may have an important role to decrease pain which is caused by one of these factors. Nurses should be trained in an adequate approach of patients undergoing a painful procedure, in which good attitude and communication are essential. This involves listening to any concerns or anxiety of the patient about the procedure. The patients' expectations of pain should be explored, in which a realistic view of what the patient may experience and the degree of pain relief that may be achieved should be discussed, thereby reducing anxiety.

Moreover, in further research, procedural sedation could be considered in patients expressing concern or distress for the potentially painful procedure. An anxiolytic may induce amnesia and increase cooperativeness and willingness to undergo a similar procedure in the future. Examples for procedural sedation may include ketamine, propofol and benzodiazepines, such as midazolam.

S-ketamine is often used in children for procedural sedation, and produces a trance-like state with both sedation and analgesia while maintaining airway reflexes and an intact respiratory drive [64]. In adult intensive care patients undergoing open wound care procedures, S-ketamine in addition to morphine significantly reduced pain scores compared to morphine alone [65]. In a recent study including trauma patients in the emergency department [66], S-ketamine and propofol were equally effective for procedural related pain, although higher ratings of subclinical respiratory depression and recovery agitation were shown in the S-ketamine group. Recovery agitation, ranging from hallucinations and nightmares to violent outburst, limits the use of S-ketamine in adults, with reported incidences as high as 30% [64].

Midazolam and propofol may also be considered for procedural sedation, because of their advantageous characteristics, such as their relatively fast onset and short half-time [67]. So far, research on midazolam or propofol for procedural sedation is only conducted in patients in the emergency department. In these patients, both midazolam and propofol appeared equally effective for procedural sedation, without significant adverse effects [68]. In further research, midazolam or propofol are suggested agents for procedural sedation in intensive care patients. As the anxiolytic provides no analgesia, the anxiolytic should always be used in

conjunction with an analgesic [69]. Because fentanyl has a quick onset and short duration of action, fentanyl may be considered as analgesic [70].

Conclusions and recommendations

- To prevent unacceptable pain scores (NRS≥4) during painful procedures, adequate pain management for pain at rest using a pain titration protocol, is crucial.
- More research is needed to identify patients who are at risk for unacceptable pain (NRS≥4) during a painful procedure. In this respect, the role of pharmacogenetic testing may increase, as a polymorphism of the *COMT* gene is related to higher pain sensitivity.
- In patients at risk for unacceptable pain (NRS≥4) during a painful procedure due to anxiety, an anxiolytic (e.g. midazolam or propofol) in conjunction with an analgesic (e.g. fentanyl) may be a focus in further research.

Chronic thoracic pain

Besides acute postoperative pain, chronic thoracic pain after cardiac surgery is a serious condition affecting many patients. Pain is described as chronic if it persists three months to one year after tissue healing. On the other hand, it has been suggested that chronic postoperative pain should be defined as pain persisting two months after surgery, which cannot be explained by other causes. In chronic pain management, it is generally accepted to ascertain its effect on quality of life and function [71]. Depending on the definition of chronic thoracic pain, recent studies report incidences varying from 11 to 56% [48,72].

In order to identify predictors for chronic thoracic pain one year after cardiac surgery via sternotomy, in **Chapter 7**, we performed a follow-up study in patients included in the randomised clinical trial of chapter 5. Chronic thoracic pain was defined as sternal and/or thoracic pain (NRS>0), which the patient identified as related to surgery, which was different from angina and which was present in the 2 weeks preceding the interview [73]. As such, in our study 35% of the patients reported chronic thoracic pain. Besides age below 69 years and a body mass index (BMI) above 28 kg/m^2, intraoperative remifentanil appeared an independent predictor for chronic thoracic pain, which association was dose-dependent. So far, chronic post-surgical pain related to remifentanil during anaesthesia has only been described by Salengros et al. [74], who defined chronic pain as a dichotomic variable (pain: yes or no) one, three and six months after surgery, combined with questions about the intensity of the pain, use of analgesics and type of pain. Remifentanil high dose (0.14-0.26 µg/kg/min) during elective thoracotomy combined with postoperative epidural analgesia was not only associated with a larger area of allodynia around the wound in the first 72 postoperative hours, but also with a significant higher incidence of chronic pain compared with a three times lower

dose of remifentanil and epidural analgesia during surgery. Moreover, in patients after major abdominal surgery, a higher dose of remifentanil (0.3 ± 0.2 µg/kg/min) has been associated with acute opioid tolerance and opioid-induced hyperalgesia compared with a lower dose of remifentanil (0.1 ± 0.0 µg/kg/min), suggested by higher postoperative pain scores in the first postoperative hour and exaggerated postoperative opioid consumption in the first 24 postoperative hours [75]. It can be anticipated that hyperalgesia is linked to peripheral and central pain sensitization via activation of N-methyl-D-aspartate (NMDA) receptors at spinal and central levels, and thereby correlates with the development of postoperative chronic pain [76]. This suggests that hyperalgesia due to remifentanil in the early postoperative period may explain the higher incidence of chronic pain. In our study, we were not able to evaluate this phenomenon, as the patients in our study were sedated in the first postoperative hours. Higher postoperative pain scores may however also be due to inadequate postoperative use of analgesics, based on the misleading assumption that remifentanil has a prolonged analgesic effect. Thus, in this follow-up study, intraoperative remifentanil was predictive for chronic thoracic pain in a dose-dependent manner. Randomised studies designed to evaluate the influence of intraoperative remifentanil on chronic thoracic pain are needed to confirm these results.

Conclusions and recommendations

- There is a need for a uniform definition of chronic thoracic pain to obtain more reliable and clinically relevant data for research purposes and clinical practice.
- To determine long-term outcomes and to clarify whether chronic pain decreases over time, prospective studies should include at least a six months postoperative follow-up.
- Randomised controlled trials are necessary to confirm that remifentanil is associated with the development of chronic thoracic pain in patients after cardiac surgery.

MORPHINE AND PARACETAMOL ANALGESIA IN INTENSIVE CARE PATIENTS

In pain management for moderate and severe postoperative pain in the ICU, both morphine and paracetamol are commonly used analgesics. Although both analgesics have been used for decennia, and have been extensively investigated, there are still questions about the use in terms of efficacy and safety, as well as their interaction to diminish pain and need for analgesics.

Pharmacokinetics of morphine

Morphine is the preferred analgesic for moderate and severe (postoperative) pain in the ICU [5,6]. However, the clinical use of morphine is characterized by a large inter-individual variability in analgesic effect, which may partly be caused by differences in morphine pharmacokinetics as a result of variability in health status, hepatic metabolic capacity and renal clearance, particularly when intensive care patients are concerned. Morphine is mainly metabolized in the liver via glucuronidation by phase II metabolism enzyme UDP-glucuronosyltransferase (UGT)2B7 to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Both metabolites and unchanged morphine are excreted by the kidneys [77]. The main metabolite M3G is suggested to have antagonistic or hyperalgesic effects, which may potentially result in reduced morphine efficacy. In order to quantify the glucuronidation and elimination clearance of morphine in intensive care patients in comparison to healthy volunteers, a pharmacokinetic model of morphine and morphine-3-glucuronide (M3G) was developed. The analysis included 135 intensive care patients (117 cardiac surgery patients and 18 critically ill patients), who received continuous morphine-infusions adapted to individual pain levels, and 20 healthy volunteers, who received an intravenous bolus of morphine followed by a 1-hour infusion [78]. In intensive care patients, glucuronidation clearance of morphine to M3G and elimination clearance of M3G were significantly decreased with 17% and 81% respectively, compared to healthy volunteers. Nowadays, no data are available on glucuronidation clearance of morphine to M3G in intensive care patients. Studies so far focused on patients with cirrhosis, in whom glucuronidation clearance of morphine was shown to be decreased, probably due to reduction in hepatic clearance [79]. We hypothesize that in intensive care patients, the amount and/or activity of the metabolism enzyme UDP-glucuronosyltransferase (UGT)2B7 may be (temporarily) decreased. Although no specific information is available on the UGT2B7 enzyme in this specific study population, there is some evidence that the activity of other liver enzymes, such as cytochrome P-450 enzymes, is decreased in case of critically illness [80] or after surgery [81]. However, the decrease of 17% in the glucuronidation clearance of morphine in intensive care patients by itself does not lead to substantial morphine accumulation upon prolonged infusion. In contrast, we identified a very large reduction (81%) in elimination clearance of M3G in intensive care patients compared to healthy volunteers, which was independent of renal function. Thus, in intensive care patients with normal renal function substantially higher M3G levels may be expected upon 24 hour continuous infusion, with even higher M3G levels upon renal failure. Although controversial, M3G is thought to antagonize the analgesic effect, and to play a role in the development of tolerance and hyperalgesia [77]. Most studies arise from animal studies, in which M3G has been demonstrated to antagonize morphine and M6G analgesia [82-84]. In the study of Mazoit et al. in postoperative patients [85], it was shown that M3G does have an antinociceptive effect. The authors discuss that this effect is moderate, and that a significant effect of M3G is not though to occur before the 9^{th} – 18^{th} hour after initiation of analgesic treat-

ment, because of the very long transfer half-time from injection site to effect compartment. In our study however, cardiac surgery patients had a mean infusion duration of 21 hours, while critically ill patients received intravenous morphine infusions for a mean duration of 123 hours. Thus, the very large decrease in elimination clearance of M3G in intensive care patients resulting in substantially elevated M3G concentrations, may be clinically relevant, in particular upon prolonged administration of morphine infusion.

Moreover, serum creatinine concentration was identified as a covariate for both elimination clearance of M3G within the group of intensive care patients and for non-M3G clearance of morphine in both intensive care patients and healthy volunteers. It is well known from literature in a diverse patient population that clearance of morphine and its metabolites deteriorates as result of renal failure [85-90]. Thus, in intensive care patients with impaired renal function, morphine will cumulate compared to intensive care patients without renal failure and healthy volunteers. Also for M3G, higher concentrations than those anticipated in intensive care patients without renal failure will be reached, while these concentrations were already largely increased in intensive care patients without renal dysfunction compared to healthy volunteers. A limitation of our study was that we were not able to differentiate between the two subgroups of intensive care patients in our study population, i.e. cardiac surgery patients versus critically ill patients, even though we realize that there are many physiological differences between these two subgroups that may result in different pharmacokinetic parameters. Another issue may be the correlation between covariates within the study groups. Intensive care patients were older and had on average higher serum creatinine concentrations. However, the use of non linear mixed-effects modelling techniques allowed to differentiate in part for these correlated covariates, as was demonstrated by the identified statistically significant covariates for each of the clearance parameters. In conclusion, glucuronidation of morphine to M3G and elimination clearance of M3G in intensive care patients appeared significantly decreased compared to healthy volunteers. As a result, in particular elevated M3G concentrations may be anticipated in intensive care patients, which is even more pronounced upon increased serum creatinine concentrations. Considering the potential anti-nociceptive and hyperalgesic activity of M3G, this finding may be clinically relevant, and should be taken into account in this special patient group, particularly upon prolonged use of morphine infusions.

Safety of paracetamol

Concerning the safety of paracetamol, physicians and pharmacists may be reluctant to use paracetamol in intensive care patients, as volunteer study suggested that taking paracetamol four grams daily could result in elevated alanine-aminotransferase (ALT) levels in a substantial proportion (31-44%) of healthy volunteers [91]. As such, it can be anticipated that this problem can be more relevant in intensive care patients due to concomitant usage of drugs that may affect the liver and impaired perfusion of the liver during cardiopulmonary bypass.

Severe hepatotoxicity upon paracetamol use may occur through an increased production of the reactive metabolite N-acetylbenzoquinoneimine (NAPQI) which reacts with the cysteine group of hepatocellular proteins resulting in hepatic cell death, which was shown in significant paracetamol overdoses (>140 mg/kg) [92]. In **Chapter 9**, we studied the incidence of ALT elevations after short-term use of paracetamol 4 grams daily, as part of the standard pain management protocol in 93 consecutive patients after cardiac surgery. Postoperative ALT-levels of >1x Upper Limit of Normal (ULN) was observed in 17% (n=16), and 4% (n=4) exceeded >3x ULN. These four patients all suffered from right ventricular failure or cardiogenic shock during the postoperative period which could explain the significant rises in ALT after surgery. Thus, the incidence of significant ALT elevations after using paracetamol as an analgesic agent for cardiac surgery at a dose of 4 grams per day, was low and most likely due to effects of cardiac surgery.

However, the safety of using paracetamol 4 grams daily as an analgesic and antipyretic agent remains controversial [93]. In several reports, the use of therapeutic doses of paracetamol appeared to have contributed to the development of severe liver failure and death [94-96]. Our study was different from these previous reports and requires careful consideration. First, we had careful documentation of the doses of paracetamol administered to all the patients in this study. It is possible that some of the previous reports of severe liver toxicity induced by paracetamol may due to unintended overdoses because of inaccurate documentation of the doses of paracetamol used [93]. Thereby, a number of prospective randomised clinical trials on healthy subjects did not observe significant ALT elevations after 4, 6 or 8 grams of paracetamol per day for a maximum of 3 days [97-98], even in subjects using alcohol [93,99]. Second, severe elevations of ALT (3xULN) were all associated with significant complications during or after cardiac surgery, i.e. in case of cardiac shock or sepsis. In these conditions of liver failure, liver function parameters like AST, GGT, LD, INR, and bilirubin are often increased similar to those we observed in our 4 cases. Therefore, the increased ALT levels in these 4 cases differ from the typical paracetamol induced liver injury, in which an isolated increased ALT and AST level within the first 24 hour-period is observed [100]. Third, in the healthy volunteer study conducted by Watkins and colleagues [91], they included no data on alcohol consumption, diet or paracetamol use before entering the study. We were able to collect these data, and observed that 37% (n=25) and 9% (n=8) of the patients regularly consumed alcohol or used paracetamol preoperatively, respectively, in this study. However, a limitation of our study was that the sample size of this study was small and was underpowered to detect rare adverse events. Moreover, we did not have a control group in our observational study. The safety of paracetamol should ideally be tested in a randomised placebo-controlled trial in which selection bias and confounding can be reduced. Our results, albeit still very limited, provided some reassurance about the safety of paracetamol 4 grams daily. As paracetamol combined with morphine induced a significant morphine-sparing effect [101-

102], paracetamol can thus be used as a supplementary analgesic agent for adult patients undergoing cardiac surgery.

Conclusions and recommendations

- In intensive care patients, glucuronidation clearance of morphine to M3G and elimination clearance of M3G appeared significantly decreased compared to healthy volunteers. As a result, in particular elevated M3G concentrations may be anticipated in intensive care patients, which is even more pronounced upon increased serum creatinine concentrations. This knowledge is of added value in the development of individualized dosing regimens for intensive care patients.
- With the current knowledge, there is no reason not to administer paracetamol in intensive care patients after cardiac surgery. However, in case of an increased ALT level of more than three times the upper limit of normal, paracetamol should be reconsidered.

MAIN CONCLUSIONS AND PERSPECTIVES

In this thesis, we focused on pain assessment, pain management at rest and during painful procedures, and the efficacy and safety of analgesics, such as paracetamol and morphine.

We identified which pain scale should be used in intensive care patients, depending on the level of sedation (Figure 1). In conscious patients, the NRS should be used, reported by the patient. In sedated patients, who are not able to communicate, pain should be assessed

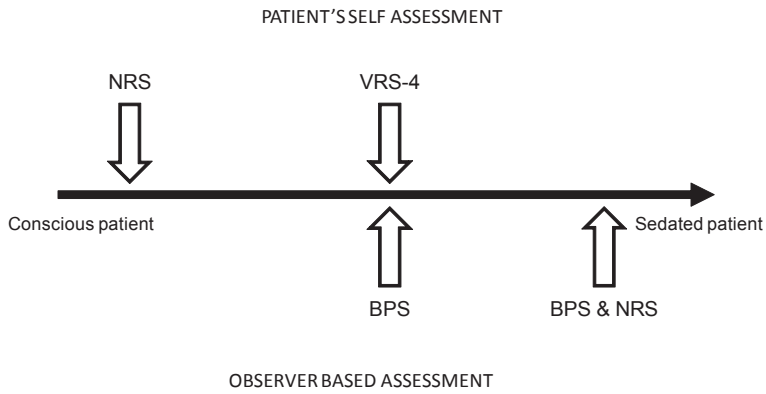

Figure 1. Pain scales associated with the level of consciousness.

by the nurse, using the BPS in conjunction with the NRS. Patients who are conscious sedated may be able to score their pain on the VRS-4. This pain rating should be combined with a pain score of the attending nurse, using the BPS. More research is needed to identify specific neurobiological parameters for the evaluation of pain. These parameters may be used as part of the current pain scales, and may contribute to a more objective pain assessment.

Pain management at rest was improved in postoperative cardiac patients, using a multiple approach. A pain training programme was implemented, consisting of a pain education programme for nurses and physicians, the introduction of a systematic pain assessment, and registration of the pain scores. These efforts resulted in a successful reduction of unacceptable pain scores (NRS≥4) at rest, which could be achieved by improving health carers' knowledge and attitude concerning pain management. Pain scores at rest could be further decreased by the implementation of a pain titration protocol, consisting of paracetamol four grams daily and a continuous morphine infusion, which was adapted to individual pain levels.

During painful procedures, in a randomised controlled trial there was no difference in efficacy between a bolus of morphine 2.5 mg or morphine 7.5 for pain relief in patients treated according to a pain titration protocol. As such, a bolus of morphine 2.5 mg may be sufficient to prevent and treat procedural pain in postoperative cardiac patients. However, despite adequate treatment, 25% of the patients experienced unacceptable pain during the painful procedure, which may be explained by environmental factors or genetic polymorphisms in pain sensitivity. As such, the polymorphism of the *COMT* Val158Met gene proved associated with changes in pain sensitivity, as morphine treated patients carrying the Met-allele, experienced both significantly higher overall pain scores and significantly higher pain levels during the painful procedure, compared to patients with the Val/Val genotype. Although this polymorphism explained one part of the inter-individual variability in pain sensitivity, more research is needed to identify patients who are at risk for unacceptable pain during painful procedures. Unacceptable pain during painful procedures may potentially be further decreased by decreasing patients' anxiety. Hereby, the nurse may play an important role in approaching patients undergoing a painful procedure, in which a good attitude and communication are essential. Furthermore, more research is needed to evaluate procedural sedation, for which midazolam or propofol - combined with an analgesic such as fentanyl - are suggested agents.

Studying chronic thoracic pain, it appeared that there is a need for a uniform definition, which is of added value in obtaining more reliable and clinically significant data on the incidence of this phenomenon. In a follow up study of patients included in the randomised clinical trial, remifentanil was associated with the development of chronic thoracic pain, in a dose dependent manner. These results must be confirmed in a randomised controlled trial.

Both morphine and paracetamol were investigated in terms of efficacy and safety in intensive care patients. In a population pharmacokinetic model, which was developed with nonlinear mixed-effects modelling, glucuronidation capacity and elimination clearances of

morphine and morphine-3-glucuronide (M3G) were significantly decreased in intensive care patients, compared to healthy volunteers. This knowledge is of added value for the development of individualized dosing regimens in intensive care patients.

Concerning the safety of paracetamol, physicians and pharmacists may be reluctant to use paracetamol in intensive care patients, as a volunteer study suggested that taking paracetamol four grams daily could result in elevated alanine-aminotransferase levels in a substantial proportion of healthy volunteers. However, with the current knowledge of our study, there is no reason not administering paracetamol in intensive care patients. However, in case of an increased ALT level of more than three times the upper limit of normal, the use paracetamol should be reconsidered.

In conclusion, we significantly improved the pain management in the intensive care unit. More specifically, we were able to reduce pain levels which are substantially lower compared to other studies. However, despite the efforts for pain management at rest and during painful procedures, one part of the patients is subject to unacceptable pain levels during their intensive care stay. More research is needed to identify objective parameters which may be used for pain measurement in case the patient is not able to report pain. Furthermore, there is a need of identifying the high risk patient for unacceptable pain scores during painful procedures, thereby including pharmacogenetics, potentially in the preoperative evaluation. In this way, individual pain treatment regimens can be implemented, and studies can be designed to identify the real contribution of genetics in the individual patient. These high risk patients may potentially benefit from another pain treatment during painful procedures, in which procedural sedation may be useful in the anxious patient. At last, the results of pharmacokinetic study, in which the glucuronidation capacity and elimination of morphine and M3G was studied, can be used to develop more individualized dosing regimens [103].

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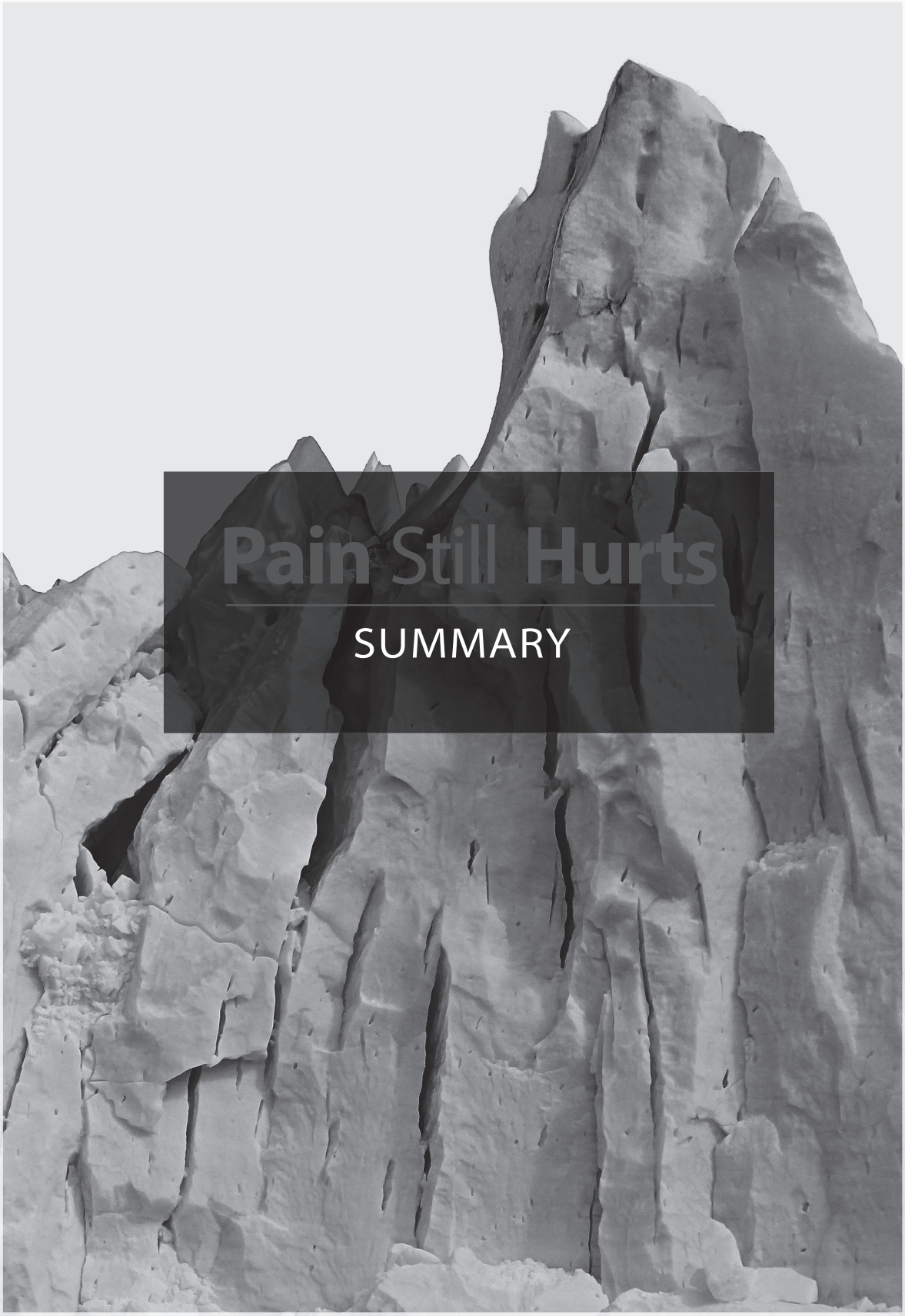
Appendix 1: Overview pain scales for conscious patients and sedated patients in the ICU

Pain scale	Dimension	Total Range	Items	Range Items
Pain scales for patients´ self report				
Visual Analogue Scale (VAS) [104]	0 (no pain) -100 (maximal pain)	0-100	-	-
Numerical Rating Scale (NRS) [105]	0 (no pain) -10 (maximal pain)*	0-10	-	-
Verbal Rating Scale (VRS-4) [106]	1. No pain (NRS=0) 2. Mild pain (NRS 1-3) 3. Moderate pain (NRS 4-6) 4. Severe pain (NRS 7-10)	0-4	-	-
Objective pain scales scored by the nurse				
Non Verbal Pain Scale (NVPS) [12]	Sum of 3 behavior indicators + 2 physiological indicators	0-10	*Behavior indicators* **1**.Facial expression **2**. Body movement **3**. Guarding *Physiological indicators I* **4**. Changes in vital symptoms in last 4 hours *Physiological indicators II* **5**. Changes in skin, pupil diameter or body temperature	 0-2 0-2 0-2 0-2 0-2
PAIN-Algorithm [13]	0 (no pain) -10 (maximal pain) Based on 3 behavior indicators + 8 physiological indicators	0-10	*Behavior indicators* **Facial expression**: **1**. grimacing **2**. Drawn around mouth and eyes. **3**. Teary- crying **4**. Wrinkled forehead **Movements**: **5**. none **6**. Slow **7**. Restlessness **8.** Seeking attention **9.** Vocalization **Posturing/Guarding: 10**. Rigid **11.** Splinting **12**. Tense, stiff. *Physiological indicators* **1**. Increased *or* **2**. Decreased Heart rate **3**. Increased *or* **4**. Decreased blood pressure **5**. Increased *or* **6**. Decreased respiratory rate **7**. Perspiration **8.** Pallor	Present / Absent Present / Absent
Critical Care Pain Observation Tool (CPOT) [18]	Sum of 4 behavior indicators	0-8	**1**. Facial expression **2.** Body movements **3**. Muscle tension **4a**. compliance with the ventilator *or* **4b**. vocalization for extubated patients	0-2 0-2 0-2 0-2
Behavioral Pain Scale (BPS)[15]	Sum of 3 behavior indicators	3-12	**1.** Facial expression **2.** Upper limb movements **3.** Compliance with mechanical ventilation	1-4 1-4 1-4

Appendix 2. Sedation scales for intensive care patients

Pain scale	Dimension	Total Range	Items
Ramsay score [107]	Six levels, with higher levels indicating increased degrees of sedation.	1 - 6	*Level of sedation: 1.* patient anxious, agitated, restless, *2.* patient cooperative, orientated and tranquil, *3.* patient drowsy or asleep, responds easily to commands, *4.* patient asleep, brisk response to a light glabellar tap, *5.* patient asleep, sluggish response to a light glabellar tap and *6.* patient asleep, no response to a light glabellar tap
Sedation agitation scale (SAS) [27]	7 levels with lower levels indicating increased levels of sedation	1-7	*Level of sedation: 1.*Unarousable *2.* Very sedated *3.* Sedated *4.* Calm, cooperative, *5.* Agitated *6.* Very agitated *7.* Dangerous agitation
Motor activity assessment Scale (MAAS) [29]	Seven levels, with higher levels indicating increased degrees of sedation.	0 - 6	*Agitation:* three levels (4 to 6), *Calm and cooperative level:* one level (level 3), *Sedation:* 3 levels (levels 0 to 2) All levels are defined by multiple criteria.
Vancouver Interaction and calmness scale (VICS)	Contains two domains ('interaction' and 'calmness').	0-30 per domain	Each domain has five questions, and each question has six responses from 'strongly agree' to 'strongly disagree'. Patient stimulation required for some questions. Scores are summed, with higher scores for calm and interactive
Richmond Agitation Sedation Scale (RASS) [30]	Ten levels with lower levels indicating increased degrees of sedation. Levels were defined by response to verbal then physical stimulation, plus consideration of cognition and sustainability	-5 - 4	*Level of sedation: 0.* Unresponsive **1**. Responsive only to noxious stimulus *2.* Responsive to touch or name *3.* Calm and cooperative *4.* Restless and cooperative *5.* Agitated *6.* Dangerously agitated, uncooperative
Adaption to the intensive care environment (ATICE) [34]	Five tests in two domains: consciousness and tolerance domains.	0-20	*Consciousness domain:* (**a**) awakeness scale (five levels from 0 = eyes closed, no mimic, to 5 = eyes open spontaneously, based on verbal then physical stimulation) and (**b**) comprehension scale (score based on summing 1 point each for positive response to five commands). *Tolerance domain:* (*a*) calmness scale (four levels from 3 = calm to 0 = life-threatening agitation), (*b*) ventilator synchrony scale (score based on summing 1 point for each of four observed events) and (**c**) face relaxation scale (four levels from 3 = relaxed face to 0 = permanent grimacing)
Bispectral index (BIS) [108]	Objective method for sedation assessment, based on the patients' electroencephalogram (EEG)	0-100	100 represents an 'awake' clinical state, whereas 0 denotes an isoelectric state.



Pain Still Hurts

SUMMARY

INTRODUCTION

In the recent past, pain management has become an essential part of the standard care of patients in the intensive care unit (ICU), as these days 63-77% of intensive care patients reported pain during their stay in the ICU. Adequate pain management may reduce physiological adversity and emotional stress, and will therefore result in a decrease in morbidity and mortality. Adequate pain management reflects a certain quality in daily patient care and is considered an important healthcare benchmark. The topic became more important, as result of new position statement of the ideal depth of sedation, which is changed away from deep sedation in combination with muscle relaxants towards a restricted sedation policy to a conscious level whenever possible. Adequate pain management can be achieved only by using effective methods for the recognition, evaluating and monitoring of pain. Knowledge of the optimal pain measurement instrument and insight which health care worker should rate pain in case the patient cannot communicate verbally, are necessary. However, pain measurement in intensive care patients can be complicated as result of underlying diseases and decreased consciousness.

Analgesic treatment with morphine and paracetamol is the cornerstone of pain management. Although both analgesics are commonly used and are extensively investigated, the most optimal dose is still not known in terms of efficacy and safety. Especially the morphine dose required to produce analgesia for pain relief is characterized by a large inter-individual variability.

In this thesis, we studied the most optimal method for measuring pain in intensive care patients, in which we evaluated several pain measurement instruments and identified the health care worker who should score pain in case the patient is not able to communicate. Secondly, we aimed to improve pain management at rest and during routine care procedures in patients after cardiothoracic surgery. Moreover, we studied the influence of genetics on pain sensitivity during an unavoidable painful procedure, and tried to identify predictors for development of chronic thoracic pain in cardiac patients. At last, we studied the pharmacokinetics of morphine in intensive care patients, on the basis of population pharmacokinetic modelling and the safety of paracetamol in postoperative patients after cardiac surgery.

PAIN ASSESSMENT IN INTENSIVE CARE PATIENTS

Various pain measurement instruments are available, but it remains unclear whether they can be applied reliably in the diverse patient population of the ICU. Furthermore, it is of interest which health care worker (nurse, physician or consultant) should score pain in case the patient cannot communicate verbally.

In **Chapter 2**, we designed a prospective observational study to compare the visual analogue scale (VAS), numeric rating scale (NRS) and the behavioral pain scale (BPS), and to compare pain scores of different observers and the patient for measuring pain in patients in the ICU. So far, the VAS and NRS were validated for acute pain only, but not for pain measurement in intensive care patients specifically. Furthermore, the BPS was validated for pain measurement in sedated and mechanically ventilated patients, but this pain scale still is not generally accepted for routine use. This study showed that whenever this is possible, intensive care patients should rate their pain using the NRS. In sedated patients, the attending nurse involved in daily care should score the patient's pain, in which the BPS should be used only in conjunction with the NRS rated by the nurse to measure pain levels in the absence of painful stimuli. Although the different scales show a high reliability, observer-based evaluation often underestimates the pain, particularly in case of high NRS values (≥4) rated by the patient.

Apart from conscious patients and sedated patients, a third group of patients can be identified, i.e. conscious sedated mechanically ventilated patients. Current intensive care practice strives to restrict sedation to a conscious level whenever possible, in agreement with the landmark report that showed that ventilated patients benefit from daily interruption of sedative infusions. These patients may be communicative, but self-reporting using the NRS or VRS-4 may be complicated or unreliable in these patients due to their temporarily limited capacities of abstraction and concentration, and lack of comprehension. Therefore, in **Chapter 3**, we evaluated the use of the behavioral pain scale (BPS) in conscious sedated patients in comparison to its use in deeply sedated patients, for whom the BPS was developed. Additionally, in conscious sedated patients the combination of the BPS and the patient-rated verbal rating scale (VRS-4) was evaluated. In a prospective evaluation study in 80 non-paralyzed critically ill adult intensive care unit patients, the BPS appeared a valid tool for measuring pain in conscious sedated patients during painful procedures. Thus, for non-communicative and mechanically ventilated patients the BPS may be regarded as a bridge between the observational scale used by nurses and the VRS-4 used by patients who are able to self-report pain.

PAIN MANAGEMENT IN INTENSIVE CARE PATIENTS AFTER CARDIAC SURGERY

In order to improve pain management for patients at rest in the ICU, in **Chapter 4** the effect of a pain management programme in the intensive care unit was evaluated, consisting of (1) a pain education programme for the health staff, (2) the introduction of systematic pain measurement and registration using an automated patient data management system (PDMS), and (3) optimization of the analgesia protocol. In this prospective two-phase study, pain levels scored by intensive care patients after cardiac surgery through sternotomy were compared before and after the implementation of a pain management programme. The

intervention programme successfully reduced the occurrence of unacceptable pain (NRS≥4) (OR 2.54 [95%CI 1.22 - 5.65; *P*=0.01] for the control group). Further improvement of pain management should focus on more individually tailored analgesia and procedural related pain, as 46% of the patients in the intervention group still experienced at least one unacceptable pain event during their ICU stay. Therefore, a pain titration protocol was implemented, consisting of paracetamol 4 grams per day, and continuous morphine infusions. In Chapter 5, in which procedure-related pain was studied, all patients were treated according to the pain titration protocol. Within this context, we observed a lower incidence of unacceptable pain at rest (16%) in patients treated according the pain titration protocol, compared with the situation that only the pain training programme was implemented (Chapter 4).

In **Chapter 5** we studied the efficacy of an intravenous bolus of morphine 2.5 versus 7.5 mg for procedural pain relief in patients after cardiac surgery in the intensive care unit. In a prospective double-blind randomised study, all patients were treated according to a pain titration protocol for pain at rest. On the first postoperative day, patients were randomised to intravenous morphine 2.5 or 7.5 mg before a painful intervention (turning of the patient and/ or chest drain removal). This study demonstrated that patients treated according to a pain titration protocol show low incidences of pain at rest (NRS≥4; 16%) and during a painful intervention (NRS≥4; 25%). Within this context, an intravenous bolus of morphine 2.5 mg is sufficient for pain relief during a painful intervention.

Despite adequate treatment, one part of the patients (25%) experiences unacceptable pain during the unavoidable painful procedure. Pain sensitivity is known to differ largely between patients and may partly be explained by genetic polymorphisms. In **Chapter 6**, we investigate whether the catechol-O-methyltransferase (*COMT)* Val158Met polymorphism influences pain sensitivity in 117 morphine-treated intensive care patients undergoing unavoidable routine care painful procedures after cardiac surgery. While overall mean NRS score was significantly higher in patients carrying the Met-variant allele, also during the painful procedure mean NRS score was significantly higher for Met/Met patients compared to Val/Met and Val/Val patients. In the Met/Met patients, the increase in NRS scores due to the painful procedure compared with baseline NRS score was statistically significant and clinically relevant. So far, the *COMT* Val158Met polymorphism has been shown to affect pain sensitivity in experimental healthy volunteer studies. Our results suggest that the *COMT* Val158Met polymorphism contributes to variability in pain sensitivity in morphine treated-patients after cardiac surgery, as Met-allele carriers were found to be more sensitive to overall pain and procedure related pain. As a result, patients carrying the Met-allele may benefit from another pain management strategy, including analgesics which are independent of endogenous enkephalin levels and the μ-receptor density.

Besides acute postoperative pain, chronic thoracic pain after cardiothoracic surgery is a serious condition affecting many patients, with reported incidences varying from 11 to 56%. In **Chapter 7**, we aimed to identify predictors for chronic thoracic pain after sternotomy. A

follow-up study was performed in 120 patients who participated in the randomised clinical trial for procedural pain. In this study, 20% of the 90 responders reported chronic thoracic pain one year after cardiothoracic surgery. Besides age below 69 years and a body mass index (BMI) above 28 kg/m^2, intraoperative use of remifentanil was an independent predictor for chronic thoracic pain in a dose dependent manner. Randomised studies designed to evaluate the influence of intraoperative remifentanil on chronic thoracic pain are needed to confirm these results.

MORPHINE AND PARACETAMOL ANALGESIA IN INTENSIVE CARE PATIENTS

In pain management for moderate and severe (postoperative) pain in the ICU, both morphine and paracetamol are commonly used analgesics. Although both analgesics are used for decennia, and are extensively investigated, there are still questions about the efficacy and safety of morphine and paracetamol.

The clinical use of morphine is characterized by a large inter-individual variability in analgesic effect, which may partly be caused by differences in morphine pharmacokinetics as a result of variability in health status, hepatic metabolic capacity and renal clearance, particularly in intensive care patients. Morphine is mainly metabolized in the liver via glucuronidation by phase II metabolism enzyme UDP-glucuronosyltransferase (UGT)2B7 to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Both metabolites and unchanged morphine are excreted by the kidneys. As the pharmacokinetics of morphine have not been adequately quantified in these patients, in **Chapter 8** the glucuronidation and elimination clearance of morphine was evaluated in intensive care patients in conjunction with healthy volunteers. The population pharmacokinetic model with covariate analysis included 135 intensive care patients (117 cardiac surgery patients and 18 critically ill patients), who received continuous morphine-infusions adapted to individual pain levels, and 20 healthy volunteers, who received an intravenous bolus of morphine followed by a 1-hour infusion. In intensive care patients, glucuronidation clearance of morphine to M3G and elimination clearance of M3G were significantly decreased with 17% and 81% respectively, compared to healthy volunteers. Moreover, serum creatinine concentration was identified as a covariate for both elimination clearance of M3G within the group of intensive care patients and for non-M3G clearance of morphine in both intensive care patients and healthy volunteers. As a result, substantially elevated M3G concentrations may be anticipated in intensive care patients, which is even more pronounced upon increased serum creatinine concentrations. Considering the potential anti-nociceptive and hyperalgesic activity of M3G, this finding may be clinically relevant, and should be taken into account in this special patient group, particularly upon prolonged use of morphine infusions.

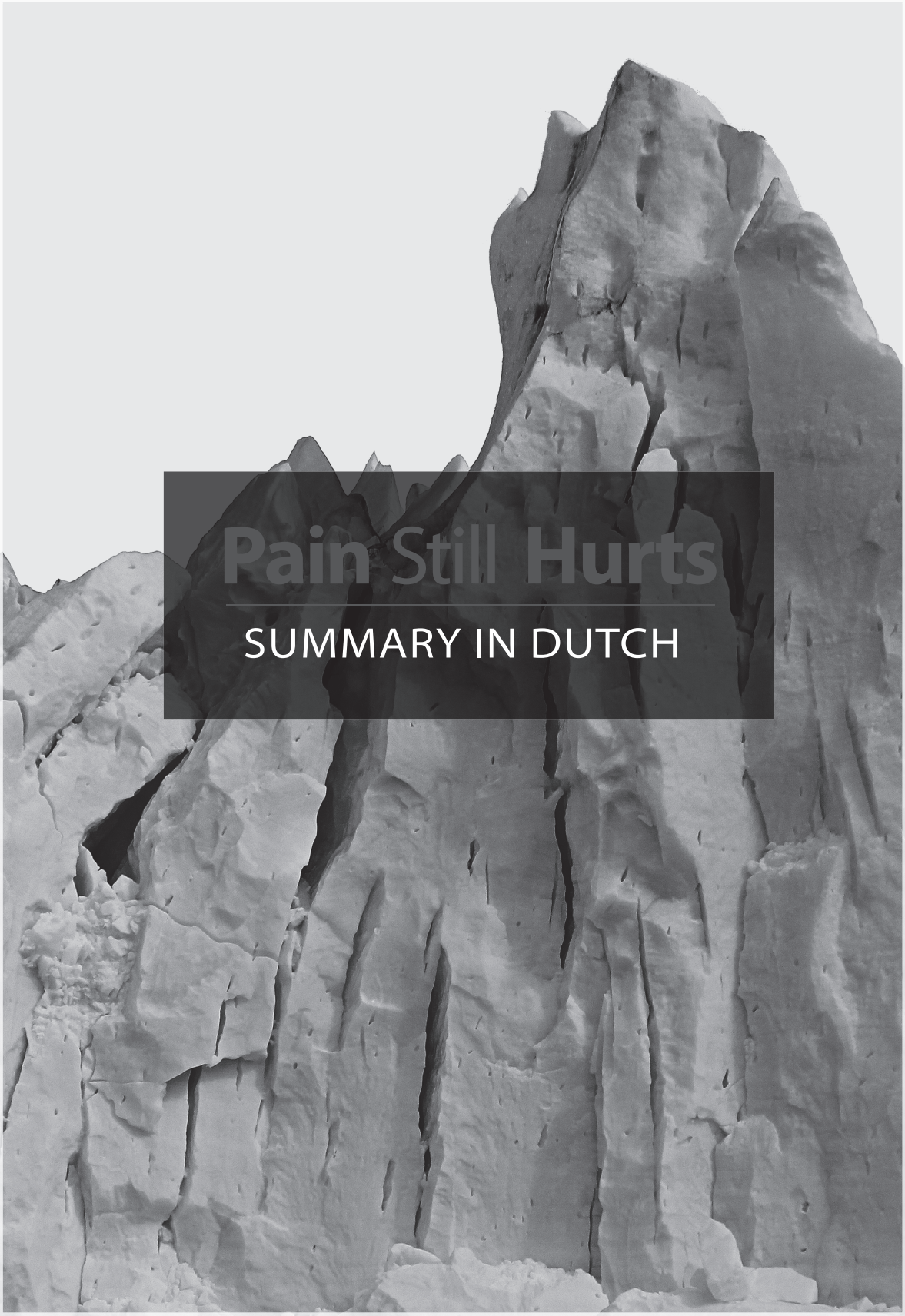
Considering the safety of paracetamol in intensive care patients, physicians and pharmacists may be reluctant to use paracetamol in intensive care patients, as a volunteer study suggested that taking paracetamol four grams daily could result in elevated alanine aminotransferase (ALT) plasma levels in a substantial proportion of healthy volunteers. As such, it is possible that this problem can be more prevalent for intensive care patients due to concomitant usage of drugs that may affect the liver and impaired perfusion of the liver. Therefore, in **Chapter 9**, we studied the incidence of ALT elevations after short-term use of paracetamol four grams daily in 93 consecutive patients after cardiac surgery. Postoperative ALT-levels of >1x upper limit of normal (ULN) was observed in 17% (n=16), and 4% (n=4) exceeded >3x ULN. These four patients all had right ventricular failure or cardiogenic shock during the postoperative period. Thus, the incidence of significant ALT elevations after using daily paracetamol as an analgesic agent for cardiac surgery, at a dose of four grams per day, was low and most likely to complications after surgery. Our results, albeit still very limited, provided some reassurance about the safety of paracetamol four grams daily, as a supplementary analgesic agent for adult patients undergoing cardiac surgery.

MAIN CONCLUSIONS AND PERSPECTIVES

In this thesis, we focused on pain assessment, pain management at rest and during painful procedures, and the efficacy and safety of morphine and paracetamol.

In conclusion, we significantly improved the pain management in the intensive care unit. More specifically, we were able to reduce pain levels which are substantially lower compared to other studies. However, despite the efforts for pain management at rest and during painful procedures, one part of the patients still experience unacceptable pain levels during their intensive care stay.

More research is needed to identify objective parameters which may be used for pain measurement in case the patient is not able to report pain. Furthermore, there is a need of identifying the high risk patient for unacceptable pain scores during painful procedures, thereby including pharmacogenetics, potentially in the preoperative evaluation. In this way, individual pain treatment regimens can be implemented, and studies can be designed to identify the real contribution of genetics in the individual patient. These high risk patients may potentially benefit from another pain treatment during painful procedures, in which procedural sedation may be useful in the anxious patient. At last, the results of pharmacokinetic study, in which the glucuronidation capacity and elimination of morphine and M3G was studied, can be used to develop more individualized dosing regimens.



Pain Still Hurts

SUMMARY IN DUTCH

INTRODUCTIE

Pijn op de intensive care is een veel voorkomend probleem, waarbij 63-77% van de patiënten pijn rapporteert. De behandeling van pijn vormt daarom een essentieel onderdeel van de zorg voor intensive care patiënten. Adequate pijnbehandeling versnelt het fysiologisch herstel en verminderd stress, waardoor de morbiditeit en mortaliteit afneemt. Daarnaast draagt adequate pijnbehandeling bij aan de dagelijkse standaard patiëntenzorg en is dan ook één van de kwaliteitsindicatoren in de Nederlandse ziekenhuizen. Ook werd het belang van een goede pijnbehandeling groter, naar aanleiding van het nieuwe standpunt met betrekking tot de ideale diepte van sedatie, die is gewijzigd van diepe sedatie in combinatie met spierrelaxantia naar lichte sedatie.

Adequate pijnbehandeling kan alleen maar worden bereikt door het gebruik van effectieve methoden om pijn te herkennen, te evalueren en te monitoren. Het is daarbij noodzakelijk kennis te hebben van de meest geschikte pijnschalen, en inzicht te hebben in welke behandelaar pijn zou moeten meten indien de patiënt niet in staat is te communiceren. Echter, pijnmeting in intensive care patiënten is gecompliceerd als gevolg van onderliggende morbiditeit en verminderd bewustzijn, waardoor de pijnscore van de patiënt mogelijk ontbreekt.

Wat betreft analgetica vormen morfine en paracetamol de hoeksteen van de pijnbehandeling op de intensive care. Hoewel beide analgetica veel gebruikt worden en al uitgebreid onderzocht zijn, de optimale dosering van deze analgetica wat betreft effectiviteit en veiligheid is nog niet bekend, waarbij in het bijzonder morfine gekarakteriseerd wordt door een grote inter-individuele variabiliteit in analgetisch effect.

In dit proefschrift werd de meest optimale methode voor het meten van pijn bij intensive care patiënten onderzocht. Er zijn verschillende pijnschalen geëvalueerd. Tevens is geïdentificeerd welke behandelaar pijn zou moeten meten, indien de patiënt zelf hiertoe niet in staat is. Als tweede hadden we als doel het pijnbeleid te verbeteren tijdens rust en tijdens onvermijdelijke routine procedures bij patiënten na hartchirurgie. Daarbij hebben we de invloed van genetica op pijngevoeligheid onderzocht, en hebben we getracht voorspellers te vinden voor het ontwikkelen van chronische thoracale pijn bij deze patiënten. Tevens was een deel van het onderzoek gericht op de farmacokinetiek van morfine in intensive care patiënten, waarvoor een populatie farmacokinetisch model ontwikkeld werd. Tot slot werd de veiligheid van paracetamol in postoperatieve patiënten na hartchirurgie geëvalueerd.

PIJNMETING IN INTENSIVE CARE PATIËNTEN

Er zijn diverse pijnschalen beschikbaar, maar het is nog onduidelijk in hoeverre ze betrouwbaar kunnen worden toegepast bij de diverse patiëntenpopulatie op de intensive care. Verder

is het van belang te weten welke hulpverlener (verpleegkundige, arts of consultant) pijn kan scoren, indien de patiënt niet in staat is te communiceren.

In **hoofdstuk 2** werden in een prospectieve studie de visual analoge scale (VAS). De numeric rating scale (NRS) en de behavioral pain scale (BPS) vergeleken. Tevens werden de pijnscores die gerapporteerd werden door intensive care patiënten vergeleken met de pijnscores gerapporteerd door de verschillende waarnemers.

Tot nu toe waren de VAS en de NRS alleen gevalideerd voor acute pijn, maar niet voor pijnmeting bij intensive care patiënten. Bovendien was de BPS alleen gevalideerd voor pijnmeting in gesedeerde en beademde patiënten, en is deze pijnschaal nog niet geaccepteerd voor dagelijks gebruik. Deze studie toonde aan dat intensive care patiënten die kunnen communiceren, zelf de pijn moeten aangeven met behulp van de NRS. Bij gesedeerde patiënten zou de verpleegkundige die betrokken is bij de dagelijkse verzorging de pijn van de patiënt moeten scoren met behulp van de BPS in combinatie met de NRS. Hoewel de verschillende pijnschalen een hoge betrouwbaarheid vertonen, werd de pijn regelmatig onderschat door de verpleegkundige, vooral indien de patiënt hoge NRS waarden (≥4) rapporteerde.

Naast wakkere, communicatieve patiënten en gesedeerde patiënten, kan er nog een derde groep patiënten worden geïdentificeerd, namelijk de *conscious sedated* patiënten. Tegenwoordig wordt ernaar gestreefd om waar mogelijk sedatie te beperken tot een lichte bewustzijnsdaling. Dit is in overeenstemming met het nieuwe standpunt, waaruit bleek dat beademde patiënten baat hebben bij de dagelijkse onderbreking van sedativa. Deze *conscious sedated* patiënten zijn aanspreekbaar, maar zelfrapportage met behulp van de NRS of VRS-4 kan ingewikkeld of onbetrouwbaar zijn, als gevolg van hun tijdelijk beperkte capaciteit voor abstractie en concentratie, en een gebrek aan bevattingsvermogen.

Daarom is in **hoofdstuk 3** het gebruik van de behavioral pain scale (BPS) bij *conscious sedated* patiënten vergeleken met het gebruik van de BPS in diep gesedeerde patiënten voor wie de pijnschaal is ontwikkeld. Bovendien werd in *conscious sedated* patiënten de combinatie van de BPS en de verbal rating scale (VRS-4) geëvalueerd. In een prospectieve observationele studie met 80 kritisch zieke volwassen intensive care patiënten, bleek de BPS een waardevol instrument voor het meten van pijn tijdens pijnlijke procedures wanneer patiënten *conscious sedated* waren. Samenvattend kan de BPS worden beschouwd als een brug tussen de observationele schaal die wordt gescoord door verpleegkundige en de VRS-4 gerapporteerd door de intensive care patiënt.

PIJN MANAGEMENT IN INTENSIVE CARE PATIËNTEN NA HARTCHIRURGIE

Om de pijn in rust bij intensive care patiënten na hartchirurgie te verbeteren, werd in **hoofdstuk 4** het effect van een pijnmanagement programma geëvalueerd, dat bestond uit (1) een pijneducatie programma voor artsen en verpleegkundigen, (2) de introductie van

systematische pijnmeting en registratie, en (3) de optimalisatie van het analgeticaprotocol. In deze prospectieve tweefase studie werden de pijnscores die werden gerapporteerd door patiënten na hartchirurgie voor en na de implementatie van het pijnmanagement programma vergeleken. Het programma bleek succesvol in het voorkomen van onacceptabele pijn (NRS≥4) tijdens het intensive care verblijf (OR 2.54 [95%CI 1.22 - 5.65], *P*=0.01). In verdere verbetering van pijnmanagement, zou de focus moeten liggen op de het individualiseren van de pijnmedicatie en procedurele pijn, omdat nog steeds een deel van de patiënten onacceptabele pijn ervaart. Daarom werd er een pijntitratieprotocol ingevoerd, dat bestond uit vier gram paracetamol per dag en een continue morfine infuus, waarbij de dosering werd aangepast op basis van de pijnscores. In hoofdstuk 5, waarin procedurele pijn geëvalueerd werd, werden alle patiënten behandeld volgens dit pijntitratieprotocol. In deze studie populatie werd een lage incidentie van pijn bij rust (16%) waargenomen, vergeleken met de situatie dat alleen een pijnmanagement programma geïmplementeerd was (Chapter 4).

Om de incidentie onacceptabele pijn verder te reduceren, werd in **hoofdstuk 5** de effectiviteit van een intraveneuze bolus morfine 2.5 versus 7.5 mg geëvalueerd voor de preventie van procedure gerelateerde pijn bij patiënten na hartchirurgie. In een prospectieve, dubbelblinde gerandomiseerde studie werden alle patiënten behandeld volgens het pijntitratie protocol voor pijn bij rust. Op de eerste postoperatieve dag werden patiënten gerandomiseerd naar een intraveneuze bolus morfine van 2.5 of 7.5 mg voor het ondergaan van een pijnlijke interventie (draaien van de patiënt, of het verwijderen van thorax drains). Deze studie toonde aan dat patiënten die adequaat behandeld worden volgens het pijntitratie protocol, een lage incidentie voor pijn tijdens een pijnlijke interventie hebben (NRS≥4; 25%). In deze context is een intraveneuze bolus morfine 2.5 mg voldoende voor de pijnverlichting tijdens een pijnlijke interventie.

Ondanks adequate behandeling ervaart nog steeds een deel van de patiënten (25%) onacceptabele pijn tijdens een pijnlijke procedure. Het is bekend dat pijn tussen patiënten sterk kan verschillen, die deels verklaard kan worden door verschillen in patiëntkarakteristieken, zoals geslacht en angst. Daarnaast zijn er enkele genen in verband gebracht met verschillen in pijngevoeligheid van patiënten. In **hoofdstuk 6** onderzochten we de invloed van het catechol-O-methyltransferase (*COMT)* Val158Met polymorfisme op de pijngevoeligheid in 117 intensive care patiënten na hartchirurgie. Deze patiënten werden behandeld met morfine, en ondergingen een onvermijdelijke pijnlijke procedure op de eerste postoperatieve dag. Patienten die drager waren van het Met-allel, hadden hogere gemiddelde pijnscores gedurende de meetperiode, vergeleken met patiënten met het Val/Val genotype. Tevens rapporteerden Met/Met patiënten hogere gemiddelde pijnscores vergeleken met Val/Met patiënten en Val/Val patiënten. In de Met/Met patiënten was de toename van de NRS scores ten opzichte van de baseline NRS significant en klinisch relevant. Tot nu toe was alleen in experimentele studies met gezonde vrijwilligers aangetoond dat het *COMT* Val158Met polymorfisme de pijn gevoeligheid beïnvloedt. Onze resultaten kunnen deze associatie bevestigen bij patiënten

na hartchirurgie die reeds met morfine behandeld werden. Hierbij zijn Met-allele dragers gevoeliger voor procedure gerelateerde pijn en pijn in het algemeen. Patiënten die het Met-allele dragen, zouden daarom baat kunnen hebben bij een andere pijnbehandeling, waarbij analgetica toegepast worden die niet afhankelijk zijn van endogeen enkephalinen en de μ-receptor dichtheid.

Naast postoperatieve acute pijn, is de ontwikkeling van chronische thoracale pijn na hartchirurgie een serieus probleem. Afhankelijk van de definitie van chronische pijn, worden incidenties tussen de 11 en 56% gerapporteerd. Het doel in **hoofdstuk 7** was voorspellers te identificeren voor het ontstaan van chronische pijn na hartchirurgie via sternotomie. Er werd een follow-up studie uitgevoerd, met de 120 patiënten die tevens aan de gerandomiseerde studie deelnamen. Hierbij bleek één jaar na de ingreep, 20% van de 90 responders chronisch thoracale pijn te rapporteren. Naast een leeftijd onder de 69 jaar en een body mass index (BMI) boven de 28 kg/m^2, bleek intra-operatief gebruik van remifentanil een onafhankelijke voorspeller te zijn voor het ontwikkelen van chronische thoracale pijn. Deze relatie was doseringsafhankelijk. Om deze bevindingen te bevestigen zijn gerandomiseerde trials noodzakelijk, die het gebruik van intra-operatief remifentanil in relatie tot chronische pijn evalueren.

MORFINE EN PARACETAMOL GEBRUIK BIJ INTENSIVE CARE PATIËNTEN

Morfine en paracetamol zijn veel gebruikte analgetica voor de behandeling van matige tot ernstige (postoperatieve) pijn in de intensive care. Hoewel beide analgetica al decennia lang gebruikt worden en uitgebreid zijn onderzocht, zijn er nog vragen over de effectiviteit en veiligheid van morfine en paracetamol. Het klinisch gebruik van morfine wordt gekenmerkt door een grote inter-individuele variabiliteit in analgetisch effect. Dit kan gedeeltelijk worden verklaard door verschillen in de farmacokinetiek van morfine als gevolg van de variabiliteit in de gezondheidstoestand, de hepatische metabole capaciteit en de renale klaring van een patiënt, met name als het intensive care patiënten betreft. Morfine wordt voornamelijk gemetaboliseerd in de lever via glucuronidering door fase II metabolisme enzym UDP-glucuronosyltransferase (UGT) 2B7 in twee metabolieten; morfine-3-glucuronide (M3G) en morfine-6-glucuronide (M6G). Beide metabolieten en de onveranderde morfine worden uitgescheiden via de nieren. Tot nu toe is de farmacokinetiek van morfine nog niet gekwantificeerd in intensive care patiënten. Daarom werd bij deze patiënten in **hoofdstuk 8** de glucuronidering en eliminatieklaring van morfine geëvalueerd, en vergeleken met gezonde vrijwilligers. Het populatie farmacokinetisch model omvatte 135 intensive care patiënten (117 patiënten na hartchirurgie en 18 kritisch zieke patiënten), die een continue intraveneus morfine infuus kregen toegediend, waarbij de dosering morfine werd aangepast op basis van de pijn. Hier werd data van een eerdere publicatie aan toegevoegd; deze omvatte 20 gezonde vrijwilligers die een intraveneuze bolus morfine ontvingen, gevolgd door een 1-uur

durend morfine infuus. Het bleek dat de glucuronideringsklaring van morfine naar M3G en eliminatieklaring van M3G in intensive care patiënten significant was afgenomen met respectievelijk 17% en 81%, in vergelijking met gezonde vrijwilligers. Bovendien werd het serum creatinine concentratie geïdentificeerd als een covariaat voor zowel de eliminatieklaring van M3G binnen de groep van intensive care patiënten, als voor niet-M3G klaring van morfine bij zowel de intensive care patiënten en gezonde vrijwilligers. Als gevolg hiervan kunnen aanzienlijk verhoogde M3G concentraties worden verwacht in intensive care patiënten, die nog meer uitgesproken zullen zijn bij verhoogde creatinine concentraties. Gezien de potentiële anti-nociceptieve en hyperalgetische activiteit van M3G, kan deze bevinding klinisch relevant zijn. Indien morfine wordt toegepast bij deze patiëntenpopulatie moet hiermee rekening worden gehouden, vooral wanneer morfine infusies langdurig worden toegepast.

Wat betreft de veiligheid van het gebruik van paracetamol in intensive care patiënten is nog veel discussie, waardoor artsen en apothekers terughoudend zijn bij het gebruik van paracetamol bij deze patiënten. Dit als gevolg van een vrijwilliger studie, die suggereerde dat het gebruik van 4 gram paracetamol per dag kan leiden tot verhoogde alanine aminotransferase (ALT) plasma concentraties in een aanzienlijk deel van de gezonde vrijwilligers. Dit probleem kan ernstiger zijn bij intensive care patiënten, die meerdere geneesmiddelen gebruiken die de lever aandoen, waarbij tevens sprake kan zijn van een verminderde perfusie van de lever. Daarom hebben we in **hoofdstuk 9** de incidentie van ALT stijgingen geëvalueerd bij 93 patiënten na hartchirurgie, die kortdurend 4 gram paracetamol per dag gebruikten. Postoperatieve ALT stijgingen van meer dan één keer de Upper Limit of Normal (ULN) en drie keer de ULN werden waargenomen bij respectievelijk 17% (n=16) en 4% (n=4) van de patiënten. Deze vier patiënten hadden rechter ventrikel falen of een cardiogene shock tijdens de postoperatieve periode. Bij kortdurend paracetamolgebruik blijkt de incidentie van een significante ALT-stijging zeer laag te zijn, waarbij deze stijgingen zeer waarschijnlijk het gevolg waren van complicaties na hartchirurgie. Onze resultaten geven, zij het nog steeds zeer beperkt, enige geruststelling over de veiligheid van 4 gram paracetamol per dag, indien deze toegepast wordt als analgeticum voor volwassen patiënten na hartchirurgie.

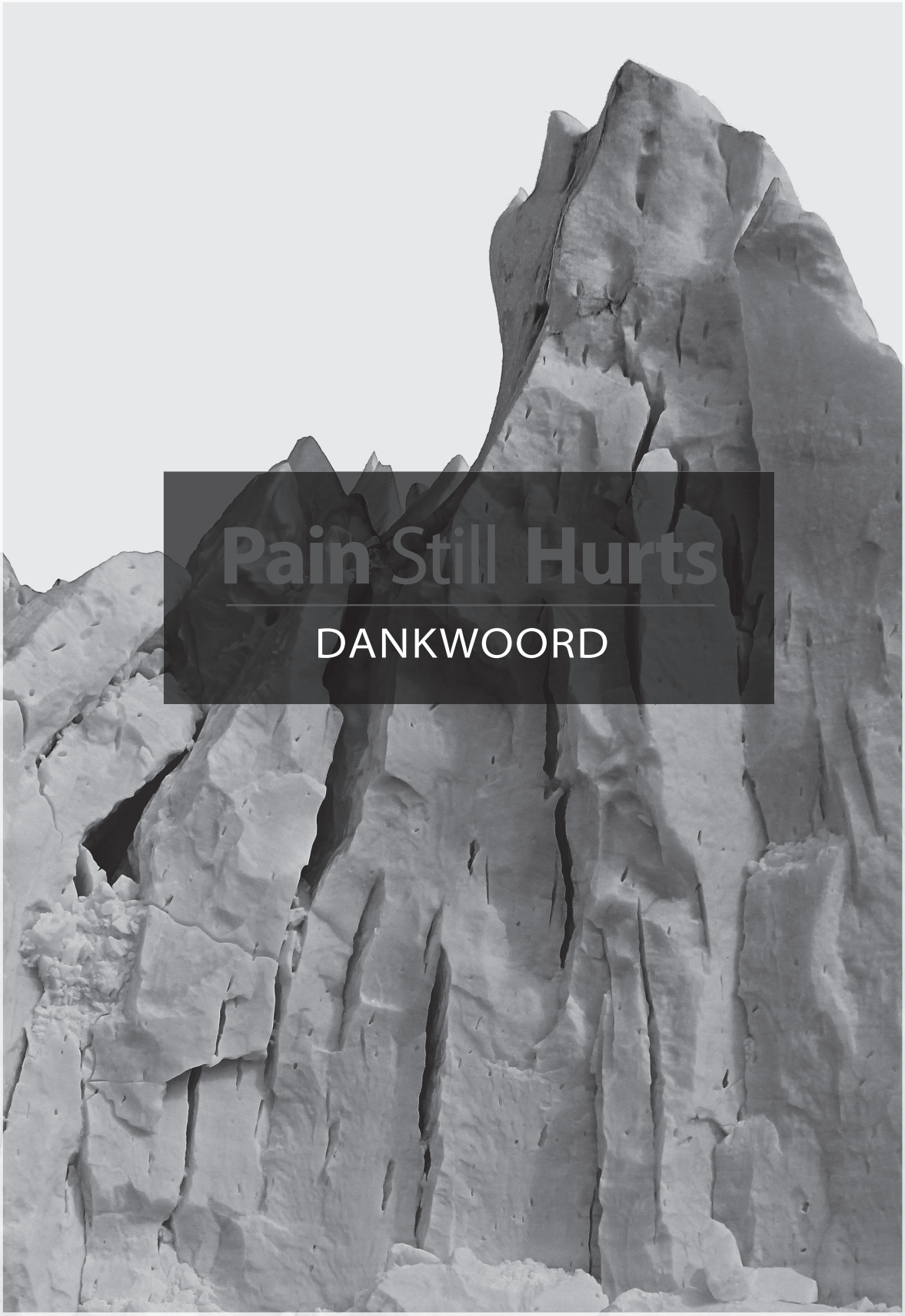
BELANGRIJKSTE CONCLUSIES EN AANBEVELINGEN

In dit proefschrift hebben we ons gericht op pijnmeting, pijnbestrijding in rust en tijdens pijnlijke procedures, en de effectiviteit en veiligheid van paracetamol en morfine.

De pijnbehandeling voor patiënten op de intensive care is significant verbeterd, en is de incidentie van onacceptabele pijn tijdens een verblijf op de intensive care lager vergeleken met andere studies die eenzelfde patiëntenpopulatie evalueerden.

Echter, ondanks onze inspanningen om de pijnbehandeling te verbeteren, heeft nog steeds een deel van de patiënten onaanvaardbaar veel pijn tijdens een intensive care

verblijf. In dit kader is er meer onderzoek nodig om objectieve parameters te identificeren die gebruikt kunnen worden als pijnmeetinstrument indien de patiënt niet in staat pijn te rapporteren. Bovendien moet er onderzoek worden gedaan naar het identificeren van hoog risico patiënten voor het ontwikkelen van pijn tijdens onvermijdelijke routine procedures. In de toekomst kan farmacogenetica hierbij een grotere rol gaan spelen, waarbij het genetica profiel mogelijk bij in de preoperatieve setting geëvalueerd kan worden. Op deze manier kan de pijnbehandeling geïndividualiseerd worden en kunnen studies ontwikkeld worden die de werkelijke bijdrage van genetica in de individuele patiënt kunnen bestuderen. Verder kunnen hoogrisico patiënten baat hebben bij een andere behandeling dan opiaten tijdens pijnlijke procedures, waarbij wij suggereren dat procedurele sedatie nuttig kan zijn bij de angstige patiënt. Tenslotte kunnen de resultaten van de farmacokinetische studie, waarin de glucuronidatie en de eliminatie van morfine en M3G onderzocht werden, gebruikt worden voor het ontwikkelen van geïndividualiseerde doseerschema's van morfine in intensive care patiënten.



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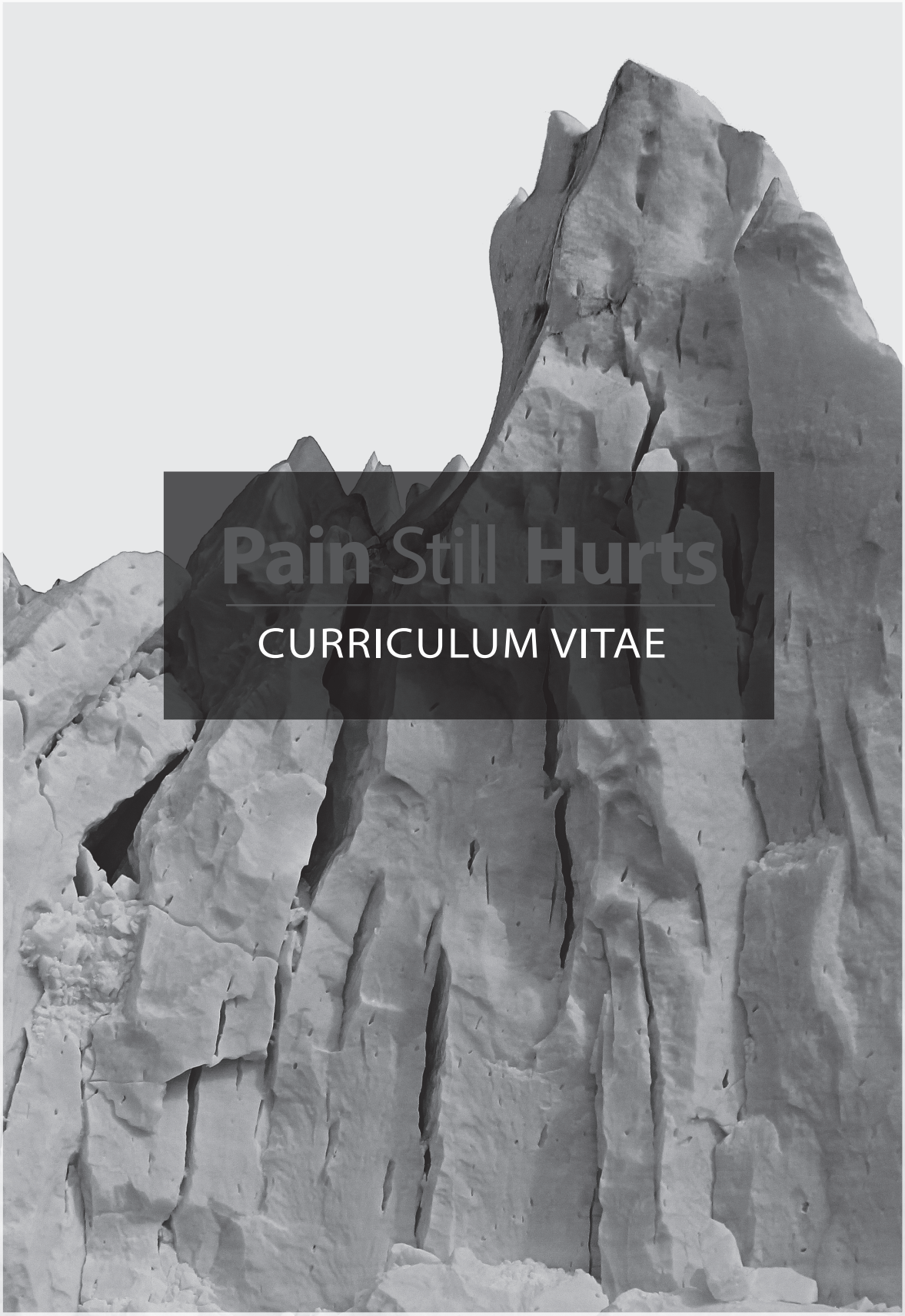

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CURRICULUM VITAE

Sabine Ahlers was born on January 14, 1982 in Sittard, the Netherlands. In 2001, she obtained her VWO diploma at the St. Janscollege in Hoensbroek. Subsequently, she studied pharmacy at the Utrecht University where she obtained her Master's Degree in Pharmacy in 2007. In 2005, she started her research project for the Master's Degree in Pharmacy at the Department of Anesthesiology, Intensive Care and Pain Management and the Department of Clinical Pharmacy of the St. Antonius Hospital, Nieuwegein (supervisors Prof. Dr. A de Boer, Dr. EPA van Dongen and Prof. Dr. CAJ Knibbe). In 2007, she entered the Department of Clinical Pharmacy in the St. Antonius Hospital, and continued the investigations, described in this thesis, in collaboration with the Sophia Children's Hospital, Erasmus Medical Centre, Rotterdam (Prof. Dr. D. Tibboel). Since 2009, she combined the PhD research with the training to become a hospital pharmacist at the Department of the Clinical Pharmacy in the St. Antonius Hospital, which will be completed in December 2013.