General Introduction
One of the important aims of pediatric anesthesia is to shepherd each child through the surgical procedure with the least possible mental and physical stress. Since its emergence in the 1940's, the field of pediatric anesthesia has reached a high level of sophistication, with many novel anesthetic agents, locoregional techniques and patient monitoring tools that have been developed. Over the past two decades, the interest in the child’s perioperative behavior (anxiety, emergence delirium, postoperative behavioral changes) within the field of pediatric anesthesia has increased considerably. Correspondingly, the relevance of identifying vulnerable children, who are at elevated risk for such problems is beyond dispute. What seems to be lacking still, however, is research into psychological aspects in this field, such as the influence of pre-existing emotional/behavioral problems on the child’s perioperative behavior. Children’s emotional/behavioral problems that are already present before induction of anesthesia might have a considerable impact on the child’s psychological and somatic recovery and also on postoperative pain. Therefore, in this thesis emotional/behavioral problems will be studied as clinically relevant factors for the medical treatment of children being operated upon.

In the past decades, an increasing body of information was accumulated about children's perioperative behavior. Preoperative anxiety in children was shown to be associated with emergence delirium, negative postoperative behavior changes and sleeping problems. Incidences up to 75% of children with significant anxiety at induction of anesthesia have been reported. The incidence of emergence delirium in children varies between 2 - 80%, depending on the used assessment procedures and the diagnostic criteria. Also negative postoperative behavior changes (such as separation anxiety, general anxiety, eating disturbances, apathy/withdrawal, sleep anxiety and aggression towards authority) are commonly seen in children after surgery with reported percentages between 24% and 73%.

Moreover increased perioperative anxiety is also associated with neuroendocrine changes (e.g. higher serum levels of cortisol, adrenocorticotropic hormone, epinephrine, natural killer cell activity). This interferes with wound healing and is related to postoperative immunosuppression.

Additionally, it is well established that increased children's preoperative anxiety is associated with higher postoperative pain scores. Furthermore, postoperative pain at home
is often underestimated and undertreated in children with reported incidences of significant pain up to more than 50% the first days after surgery. A negative maladaptive perioperative experience might also interfere with future medical contacts, in the sense of anxious reactions to hospital equipment, medical procedures or non-adherence to medical (follow-up) consultations or treatment.

Finally, the child’s state anxiety will challenge the social and communicative skills of the whole anesthesia team.

**Preoperative preparation of children**

Nowadays, when preparing children for a surgical procedure, a lot of attention is paid to preventing and alleviating preoperative anxiety during induction of anesthesia. Still, more than 75% of children are very anxious at induction, notwithstanding pharmacological treatments that are available to reduce anxiety, including midazolam, clonidine, and dexmedetomidine. Of note, children do not necessarily need premedication or they (especially toddlers) may even react adversely to it.

Many non-pharmacological interventions have been developed to reduce children’s preoperative anxiety such as streamed video clips, cartoon distraction, computer preparation, web-based preparation, music therapy, clown doctors, and parental presence at induction. Also extensive psychological-behavioral programs (including: distraction, video modelling, education, involving and coaching of parents, no excessive parental reassurance of the child, exposure /shaping of the child using an induction mask and support by a psychologist) have proven their efficacy. Recently, researchers stated that shaping/exposure by using an induction mask and distraction by parents significantly reduced the child’s anxiety at induction. So, parental presence appeared to be helpful. A recent Cochrane report, however, showed that parental presence at induction was not useful in reducing children’s anxiety at induction of anesthesia. Nowadays, also modern tools such as virtual reality are available to reduce children’s anxiety. However, their efficacy has to be established.

Considering the above, more attention should be paid to identification of children at risk for perioperative emotional/behavioral problems in order to optimize children’s preparation for surgery. Preparation of children towards a surgical intervention under anesthesia is a very complex matter.

In the remainder of this chapter we will make a distinction between:
• the period prior to the induction of anesthesia, focusing on preoperative anxiety;
• the period after surgery, focusing on emergence delirium, postoperative behavioral
changes and sleep problems and postoperative pain at home.

Hereafter, the overall aim and the outline of the thesis will be described.

A. PERIOD PRIOR TO THE INDUCTION OF ANESTHESIA: PREOPERATIVE
ANXIETY IN CHILDREN AND PARENTAL INVOLVEMENT

Children’s preoperative anxiety and distress behavior was studied by Chorney et al. They filmed children during their walk from the holding area towards the operating theatre and during induction of anesthesia. In a majority of children the following behaviors were observed: 1) crying or screaming (28.1 %); 2) verbal and nonverbal resistance (53.6 %); 3) negative verbal emotional expressions (8.6 %). Acute distress behavior is especially seen in very young children (less than 3 years old). In comparison to adults, children show higher levels of preoperative anxiety and express their anxiety in a very marked or explicit behavioral sense. Unlike adults, children often try to escape the anesthetic induction in up to 30% of cases. The child’s state anxiety peaks at induction and steadily declines in the postoperative period.

1. Child specific predictors
Several predictors of child preoperative anxiety can be identified:
1) age of the child: children between 1-5 years are more at risk;
2) low level of cognitive development;
3) higher trait anxiety;
4) a passive coping style;
5) previous bad experience with medical encounters;
6) emotional/behavioral problems were found to be predictive for anxiety at induction in a small sample of adolescents;
7) parental anxiety.

2. Assessment tools for preoperative anxiety
The assessment of the child’s state anxiety remains a challenge. Kain et al. published the modified Yale Perioperative Anxiety Scale (mYPAS) which was designed for researchers to assess child’s state anxiety in the preoperative period from the holding area onwards to the induction of anesthesia. The mYPAS is a well validated tool for use in children aged between 2 – 12 years, with good to excellent psychometric characteristics. It consists of five behavioral domains: activity, emotional expressivity, state of arousal, vocalization...
and use of parents. The mYPAS can be considered nowadays as the Gold Standard to measure state anxiety at induction of anesthesia in children. However, it requires training, is time-consuming, was not devised for parental completion and is difficult to incorporate in daily practice. Another very often used tool is the Induction Compliance Checklist (ICC). This is, however, a rather limited tool; it aims to assess state anxiety at induction by observing compliance of the child. Compliance and state anxiety, however, are different concepts.

An easy-to-use tool for the assessment of preoperative anxiety is not available yet. It has been recommended that good anxiety assessment and management should be incorporated as a cornerstone of Family-centered Pediatric Perioperative Care. There is a need for an easy-to-use anxiety assessment tool, which requires no training and is suited for a broad age-range, including non-verbal young children. In order to incorporate anxiety assessment into Family-centered Pediatric Perioperative Care, it is important that not only anesthesiologists but also parents can quickly complete such a tool in a busy clinical setting. An advantage of letting parents complete a Visual Analogue Scale (VAS), is that it requires them to focus on and be aware of their children's anxiety level.

Therefore, in the present thesis, a VAS to assess perioperative anxiety in children was investigated. With the VAS we aim to assess state anxiety throughout the entire perioperative period for children from a broad age-range, including young non-verbal children.

**Perioperative parental involvement**

Not only children but also parents may find the surgery of their child a stressful experience. Parents may become very anxious when their child undergoes a surgical intervention under anesthesia. This is reflected by physiological changes such as increased heart rate, heart rate variability, blood pressure and skin conductance. Parents are also often very motivated to be present at induction. Several studies have shown that parents with a high desire to be present at the anesthesia induction of their child are very anxious. High levels of parental state and trait anxiety (situational anxiety and a more general anxiety disposition) have been identified as important risk factors for children's preoperative anxiety. Parental anxiety may even intensify the child's perioperative state anxiety. Therefore, it is of utmost importance to prepare parents to decrease parental anxiety, when they accompany their child during induction of anesthesia. Preparing parents may also increase their feeling of self-efficacy and trust in their role in the operating room. This can help to decrease their children's anxiety at induction.
B. PERIOD AFTER SURGERY: EMERGENCE DELIRIUM, POSTOPERATIVE BEHAVIORAL CHANGES, SLEEP PROBLEMS AND POSTOPERATIVE PAIN AT HOME.

Emergence delirium

1. Definition
Emergence Delirium (ED) has been defined as: *a disturbance in a child’s awareness of and attention to his or her environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyper-active motor behavior in the immediate post-anesthesia period*. The incidence of ED in children varies widely between 2 - 80%, depending on the assessment system and the anesthetic technique used. It most often occurs during awakening from anesthesia in the Post Anesthesia Care Unit (PACU). Although ED is mostly of short duration, it should not be underestimated for the following reasons: possible physical hazards for children (i.e. injury surgical wound repair), elevated anxiety in children and parents, extra workload for nurses (constant supervision) and professional feeling of guilt for the healthcare provider resulting from seeing the child agitated.

2. Predictors
The following risk factors for ED can be distinguished:
1) preschool age;
2) higher incidence for ear nose throat and eye surgery;
3) anesthesia related factors (new inhalation anesthetics: sevoflurane & desflurane give rise to a higher incidence);
4) experience of previous surgery;
5) state anxiety child / parent;
6) psychological factors in relation to the child (i.e. low adaptability to novel situations).

Furthermore, it should be stated that some of the predictors which contribute to preoperative anxiety are the same for ED, which implies that there may be a common underlying psychological cause.

3. Assessment tools
Sikich et al published the Pediatric Anesthesia Emergence Delirium scale (PAED), a well validated scale with good intra-observer reliability, internal consistency and with a cut-off value to establish ED. Nevertheless, it is extremely complicated to assess behavior...
during awakening from anesthesia, since anxiety, pain, discomfort and ED are interrelated and can easily be confused\textsuperscript{60,61}.

\textbf{Postoperative behavioral changes and sleep problems}

Undergoing anesthesia and surgery can have a profound impact on the psychological well-being of the child, with negative postoperative behavioral changes and changes in sleep pattern (problems falling asleep, staying asleep and waking up crying) as a consequence\textsuperscript{5,6,11,62,63}. Among the changes that may occur in children after undergoing anesthesia are changes in sensory processing. Sensory processing is how children perceive, modulate and self-regulate sensory information (auditory, visual, tactile, vestibular and oral) and how it might influence their behavior (attention, arousal, affect and action). Therefore in this thesis we studied sensory processing.

In previous research the following predictors were found to be associated with maladaptive postoperative behavioral functioning at home
1) preoperative state anxiety, distress\textsuperscript{1,4-6,60};
2) younger age\textsuperscript{6};
3) inhibited temperament\textsuperscript{64,65};
4) pre-existing internalizing problems (anxious/depressed and somatic problems) and quality of previous medical contacts\textsuperscript{2,6,11,65};
5) parental factors such as parental state/trait anxiety, cultural aspects, socio-economic status and level of education\textsuperscript{6,11,62,66}.

However, to the best of our knowledge, changes in sensory processing have not been investigated in this context before. Therefore, we investigated pre- to postoperative changes in sensory processing, since insight in these changes might be a useful contribution to explain observed postoperative behavioral changes.

To evaluate the sensory processing skills of young children we used the Infant Toddler Sensory Profile (ITSP 6-36)\textsuperscript{67}. It assesses different aspects of sensory processing skills and modulating sensory input of toddlers and covers 5 processing sections: 1. auditory; 2. visual; 3. tactile; 4. vestibular; 5. oral sensory.

Furthermore, sleep problems in children in pain conditions often occurs after surgery. However, sleep problems have not been thoroughly investigated despite the fact that they are very common\textsuperscript{5,63,68}. There is no wide variety of validated assessment tools regarding the assessment of postoperative sleep problems in children\textsuperscript{68}. Therefore, in our
study we used some of the questions of the Posthospitalization Behavior Questionnaire (PHBQ) related to sleep problems.

Pain after surgery at home

1. Prevalence of postoperative pain in children
Significant postoperative pain has been reported to occur in up to 80% of all children. A possible explanation for this phenomenon is that nowadays pediatric surgery is often performed on a day-case basis. Consequently, parents become responsible for their child’s pain management at home. Research shows that postoperative pain management by parents for children at home is often insufficient.

2. Predictors of postoperative pain in children
Parents are quite capable to recognize their child’s pain. However, several predictors influence parental pain management of their child and children’s postoperative pain at home such as:
- parental personality characteristics;
- parental anxiety;
- parental level of education;
- cultural factors;
- parental misconceptions.

Parents can have the following misconceptions about pain medication:
1) 52% believe that analgesics are addictive;
2) 73% have concerns about side effects;
3) 37% even believe that analgesics work better the less often children receive them.

Parents often do not expect that their child can have a persistent level of pain.

Among child-related factors influencing children’s postoperative pain are:
- children’s higher levels of preoperative anxiety;
- children’s postoperative pain anxiety;
- children’s refusal to take the medication.

Finally, ineffective medication and hospital related organizational system factors, such as insufficient information at discharge and poor communication from health care professionals, may contribute to children’s postoperative pain.
3. Assessment tools
As far as we know, the only well validated assessment tool for parents to rate their children's pain at home is the Parents’ Postoperative Pain Measure (PPPM)\textsuperscript{79}, developed for children aged from 1 to 12 years. The PPPM has been recommended\textsuperscript{68} and it is proven that the PPPM has a good specificity (80%) and sensitivity (88%) to detect children with postoperative pain\textsuperscript{79}.

RATIONALE

As outlined in the previous sections, several aspects of children's perioperative behavior have been studied so far: preoperative situational state anxiety, ED, postoperative maladaptive behavior changes and pain. Important associations between these variables were found, showing that the child’s state anxiety at induction might be related to ED, postoperative pain and negative postoperative behavioral changes\textsuperscript{4}.

Still, there are important gaps in the current knowledge about these perioperative behaviors, gaps which provide the rationale for this study. Firstly, most studies focus on prevention or control of preoperative anxiety and do not focus on identifying vulnerable children regarding maladaptive perioperative behavior. Secondly, there is insufficient knowledge regarding children’s pre-existing emotional/behavioral problems in relation to these perioperative behaviors (anxiety, ED, changes in sensory processing) and postoperative pain. Therefore, we wanted to study these associations. Furthermore assessing pre-existing emotional/behavioral problems with an assessment tool like the CBCL might create an opportunity to tailor anxiety reducing strategies to the specific needs of each child. Thirdly, the study of changes in sensory processing might create a new opportunity for understanding postoperative behavioral changes in children.

Moreover, it would be relevant to study the overall impact of predictors of perioperative and postoperative behaviors. So far, predictors of these behaviors have mostly been studied separately.

Indeed a pilot study in adolescents\textsuperscript{43} showed that pre-existing preoperative emotional/behavioral problems were predictive for state anxiety during induction. The same authors further concluded in another study that specific child factors like pre-existing internalizing problems (anxious/depressed and somatic problems) predicted maladaptive postoperative behavior (general postoperative anxiety)\textsuperscript{65}. 
For this reason we hypothesized that pre-operative emotional/behavioral problems as assessed with the Child Behavior Checklist (CBCL)\textsuperscript{80,81}, a well validated international tool, could be associated with different aspects of perioperative behavior. Broadening our understanding of predictors of perioperative anxiety should make it possible to identify children at risk and may create an opportunity to optimize the children’s psychological preparation for surgery.

A final motivation for this study is the fact that the role of the parents in assessing and managing children’s preoperative anxiety has received scant attention. We consider it to be important that parents become aware that their child is significantly anxious and that their child will consequently be more vulnerable to postoperative maladaptive behavior and higher pain scores. So far, studies focusing on children’s preoperative anxiety mainly focused on health care professionals, without an explicit role for the parents. Parents should be involved in the preparation of their child but they should also receive adequate information (such as audiovisual aids) which in turn would lead to less parental state anxiety.

Therefore, we considered it of interest to investigate an easy-to-use tool to assess children’s state anxiety during induction of anesthesia, which can be completed by both parents and anesthesiologists without the need for training and which is also useful in the non-verbal younger age group of children.

**AIMS**

The overall aim of this thesis is to gain greater understanding of psychological aspects of anesthesia in children. The sub-aims include: 1) to examine associations between pre-existing emotional/behavioral problems in children and specific children’s peri- and postoperative behaviors; 2) to explore the validity of a new, easy-to-use anxiety assessment tool at induction of anesthesia; 3) to explore the usefulness of an audio-visual tool for decreasing parental anxiety at induction of anesthesia.

**RESEARCH QUESTIONS**

The main research questions of this thesis considering preoperative anxiety are three-fold:

1. Do preoperative emotional/behavioral problems predict anxiety during induction and ED after anesthesia in children undergoing elective day-care surgery?
2. Does the Visual Analogue Scale completed during induction of anesthesia (VAS-I) represent a valid instrument for measuring the child’s state anxiety during induction and what are optimal cut-off values on the VAS-I to distinguish between anxious and non-anxious children?

3. What is the impact of audiovisual aid (AVA) on parental state anxiety and the child’s compliance and anxiety at induction of anesthesia?

Regarding postoperative behavioral changes and postoperative pain the research questions are twofold:

1. Are there any pre- to postoperative changes in sensory processing in toddlers after pediatric anesthesia using the validated Infant/Toddler Sensory Profile (ITSP6-36) and is it possible to identify predictors of these changes?

2. What is the degree of postoperative pain and postoperative sleep problems found in children aged between 1.5 and 5 years old undergoing adenotonsillectomy and what is the influence of children’s preoperative emotional/behavioral problems on postoperative pain?

THE STRUCTURE OF THE PRESENT THESIS

In chapter 2 we examine the predictive value of the child’s emotional/behavioral problems as to their level of anxiety at induction of anesthesia and ED at awakening in the PACU. Chapter 3 provides evidence for the usefulness of a VAS to assess anxiety at induction by parents and anesthesiologists. In chapter 4 we investigate the specific influence of preoperative information towards parents, provided by means of an audio-visual tool, on parental state anxiety at induction of their child’s anesthesia. In chapter 5 we look into pre- to postoperative changes in infants’ sensory processing up to two weeks after surgery and further study the specific influence of emotional/behavioral problems on these changes. In chapter 6 we study the influence of the child’s emotional/behavioral problems on postoperative pain. Finally chapter 7 will provide a general discussion of the results of this present dissertation.
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