General discussion

GENERAL DISCUSSION

In this general discussion, from an overall view, we will discuss the main findings of this PhD thesis, set out the limitations of the studies executed and discuss implications of the present findings both for research as well as for clinical practice.

The content of this PhD thesis covers two settings: the pre- and postoperative setting.

Regarding the preoperative setting, the aims of this thesis were:

1. to explore associations between children's emotional/behavioral problems, as assessed with the Child Behavior Checklist (CBCL), and their anxiety during induction of anesthesia, when undergoing elective day-care surgery;

2. to validate a new, easy-to-use anxiety assessment tool during induction of anesthesia;

3. to evaluate the usefulness of an audio-visual aid to decrease parental state anxiety.

Considering the postoperative setting, this thesis focused on associations between children's emotional/behavioral problems and: 1. emergence delirium (ED) at awakening; 2. changes in sensory processing as assessed with the Infant/Toddler Sensory Profile ($ITSP_{6-36}$) two weeks after surgery for circumcision; 3. pain at home after adenotonsillectomy.

Following this line of thought, the next sections will discuss the findings of this thesis: first focusing on the period prior to surgery, then on the period after surgery.

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

In the first study (chapter 2) we focused on the association between children's pre-existing emotional/behavioral problems and their state anxiety during induction. In 401 children admitted for day-care surgery, we examined whether the scores on the CBCL[1,2] – a well-validated parent report assessing emotional/behavioral problems during the 6 months prior to surgery – were associated with anxiety during induction, as assessed by trained research nurses using the modified Yale Preoperative Anxiety Scale (mYPAS)[3]. Our main findings showed that internalizing problems prior to surgery were significantly associated with anxiety at induction, as were the child's state anxiety on admission in the

hospital, the child's age and the level of parental education (PE). Externalizing problems were not associated with anxiety at induction. Similar results were obtained by Fortier *et al.*[4] in a pilot study with adolescents, showing that internalizing problems as assessed by the CBCL were predictive for anxious behavior during induction.

It is interesting to compare our findings to those of Davidson *et al.*[5], who aimed to assess risk factors for anxiety at induction, using a cohort study of 1,224 children aged 3 – 12 years. Their analysis identified younger age, behavioral problems during previous health care attendance, duration of the procedure and parental anxiety as risk factors for anxiety during induction of anesthesia. They also studied the influence of pre-existing emotional/behavioral problems. To measure emotional/behavioral problems, they did not use the CBCL, but instead a question that the parents had to answer with a simple 'yes' or 'no'. In contrast to our results and those of Fortier *et al*., Davidson *et al.* did not find evidence for an effect of pre-existing emotional/behavioral problems on the child's anxiety during induction. The discrepant results may be explained by the different assessment tools used. The method of Davidson *et al.* has not been psychometrically established so far. Furthermore, our model explained 33% of the variance in the children's anxiety at induction, whereas that of Davidson *et al.* explained only 5.3%.

In literature, children's behavior in the direct preoperative period has been reported to be associated with children's state anxiety at induction[6-10]. In our study anxious behavior on admission in the holding area (measured with the mYPAS by independent research nurses) was strongly associated with anxiety at induction. This indicates that the use of a preoperative screening tool may give valuable information to anesthesiologists, since this can create an opportunity to attune the preparation of children during induction of anesthesia to their psychological needs.

Our results showed that the younger the age of the child, the higher the risk for anxiety at induction. This is indeed in line with previous findings[5,11]. However, assessing children's state anxiety during induction is a complex matter; older children and adolescents may show socially desirable behavior and may be inhibited to express themselves openly. This is one of the reasons why it has been recommended to use the parent report CBCL[4], because a screening tool regarding preoperative emotional/behavioral problems seems more suited as a screening tool than state anxiety scores on the mYPAS provided by health care workers (nurses, anesthesiologists).

Next, our study showed that children of parents with a high educational level were less anxious at induction than children from parents with a lower education level (in research parental education is often used as indicator for socio-economic status[12]). A

possible explanation for our finding is that in general children of parents of a lower socio-economic status tend to have more emotional/behavioral problems[13,14]. In addition, another possible explanation might be that highly educated parents may have more facilities to provide their children with specific informative tools for psychological preparation, which could be anxiety-reducing for their children.

In contrast to the extensive study by Davidson *et al*. and earlier studies[5,11,14,15], our study found that parental state anxiety was not an independent risk factor for children's anxiety at induction. To measure parental state anxiety at admission both Davidson *et al*. and our research team used the Spielberger's State Trait Anxiety Inventory (STAI)[16], which is considered the *Gold Standard*. However, we used the STAI in our regression model whereas Davidson *et al*. used the parents' scores on a global Visual Analogue Scale just after induction in their regression model. This may explain the discrepancy between our results and those of Davidson *et al*. Apart from all this, we do support their view that the overall child-parental interaction is much broader than *only* parental anxiety during induction and that 'the relationship between the child's and the parent's anxiety is probably complex with bidirectional influences'. This may also explain the equivocal findings reported in the literature regarding the impact of parental anxiety on the children's anxiety at induction.

Another relevant finding of our study was that parents of younger children compared to those of older children had higher levels of state anxiety during induction. Furthermore, in comparison to mothers, fathers revealed less state anxiety during induction than mothers, although no difference in trait anxiety between fathers and mothers was found. Both findings are in line with a previous study[17].

Considering our main outcomes above, we recommend to introduce psychological screening (by means of the CBCL) in perioperative care, together with an assessment of the child's anxiety in the direct preoperative period using the structured mYPAS (by trained nurses).

Several methods exist to measure children's anxiety. Chapter 3 presents the results of our study into the validity of the newly developed Visual Analogue Scale during induction (VAS-I) to assess anxiety in children. This instrument was meant to be completed by the child's parents. This has the advantage that the parents will feel that they are involved in the medical procedure and taking care for their child, which might consequently have a beneficial effect on parental knowledge[18], as to providing medical care and providing adequate pain medication for their children at home. It also fits well with the philosophy of Family-centered Pediatric Perioperative Care[10].

The VAS-I was developed with the aim of measuring anxiety during induction, considering that children's state anxiety increases during the entire preoperative period and peaks during induction[10,11]. This is the moment when children exhibit more overt anxious behavior. Therefore, the induction of anesthesia can be considered the best time to assess the child's state anxiety. One earlier study demonstrated that preoperative VAS child anxiety assessments in the holding area by accompanying mothers were inaccurate predictors of their child's anxiety during induction[19].

Only two assessment tools[7] are currently available to assess the child's state anxiety in the perioperative period. The mYPAS, regarded as the *Gold Standard* in research[3], is a well-validated and reliable tool but needs training of the raters and is time-consuming. Therefore it may not be feasible to use the mYPAS in a busy clinical setting. The second scale, the Induction Compliance Checklist (ICC)[20] can be used as a measure for the child's anxiety during induction of anesthesia (chapter 4). The ICC has excellent inter-and intra-observer reliability but its validity has never been established. A further disadvantage is that both scales cannot be used by parents. More recently developed tools like the Pediatric Anesthesia Behavior score[21] and the Children's Perioperative Multidimensional Anxiety Scale (CPMAS)[22] neither include an evaluation by the parents. The VAS-I scale, proposed and investigated in our present study, has the advantage that it can be used in children across a broad age-range (1 – 16 years), including nonverbal children (i.e., infants or toddlers who are too young to speak). Previous research has been much more limited in using a narrower age-range (7 – 16 years)[23].

In chapter 3 we present preliminary evidence regarding the validity of the VAS-I tool. To our knowledge, global, brief anxiety rating scales have not been validated before for use during induction of anesthesia in children. As to concurrent validity, our findings showed strong correlations between the VAS-I and mYPAS. For construct validity it is important that an assessment tool (in this case the VAS-I) is sensitive to known group differences. It was hypothesized that VAS-I ratings of parents and anesthesiologists would be higher in younger children (1.5 – 5 years) than in older children (6 – 16 years) and higher in high-anxious parents than in low-anxious parents. Consistent with these hypotheses, our results showed that: 1) the VAS-I scores of both parents and anesthesiologists were higher for younger children than for older children; 2) VAS-I scores were higher for children of high-anxious parents than for children of low-anxious parents. This latter result was not only found while considering the VAS-I scores of the parents (in this case, 'shared informant bias' possibly played a role, as the parents rated both their own and their child's anxiety), but also while looking at the VAS-I scores of the anesthesiologists. Moreover, parent ratings (VAS-IP) were significantly higher than the anesthesiologists' ratings (VAS-IA). This is in line with our findings described in chapter 4, also showing

that the parental VAS-I anxiety assessment scores were higher than anesthesiologists' ratings. Finally, in our study optimal cut-offs were identified for the VAS-IP (37 mm) and VAS-IA (30 mm) in order to identify anxious children as identified by the mYPAS (cut-off value ≥ 30) during induction.

Considering our findings, the VAS-I provides an opportunity to incorporate anxiety assessment and management in a busy daily perioperative clinical practice. Parents can easily complete it and it requires no training. Our evidence-based cut-off points will need to be confirmed in future research. If the VAS-I is further validated, than more children at risk for perioperative anxiety can be detected. Also, the use of the VAS-I could be instructive for parents to pay extra attention to anxiety. It should be explained to parents that children with higher state anxiety during induction are at risk for more postoperative pain[23,24].

So far, this discussion has mainly focused on the child's anxiety. However, more attention should also be devoted to the parents' anxiety. After all, parents accompanying their child during induction of anesthesia tend to become very anxious[15,25,26]. Their state anxiety increases towards the anesthetic induction, when their child will lose consciousness and parents will be separated from their child after induction[17,25,26]. Chapter 4 presents the results of a randomized controlled trial (RCT) into the effects of an audio visual aid (AVA) to reduce the accompanying parents' anxiety during the induction of anesthesia of their child. In this trial, the level of parental state anxiety increased during the entire period in the operating theatre up to the moment of the child's induction, in both intervention and control groups. From a psychological point of view this seems natural and logical considering the precarious situation of the child. Our results are in line with previous findings, showing increases in parental heartrate and skin conductance[26,27] during induction of anesthesia of their child. Although parents may become very anxious, they can be very motivated to be present during the induction and our findings showed that parents strongly believe their presence is very useful for their child. This is consistent with earlier studies[17,25]. Surprisingly, in our study parents from both the control and the AVA intervention group were equally satisfied about the procedure and the information received. It should be mentioned that besides the AVA in the intervention group, both groups also received extended general written information[28].

Although, as said above, parental state anxiety increased in both groups, this increase was significantly less in the intervention group, indicating that AVA seems a useful tool in preparing parents. This finding is in accordance with earlier findings in literature[29-32]. However, two more recent studies[33,34] could not show a beneficial effect of visual aids on parental state anxiety. Still, one of these studies found that a preoperative video DVD

could enhance parents' participation on how to actively support their child and also had a positive effect on the child postoperative pain (children aged 3 – 10 years) during one-day surgery[33], while the other study demonstrated an improved parental self-efficacy about their role in the OR[34].

In addition, our results showed no differences in child's state anxiety at induction (as rated by the parents and the anesthesiologists using the VAS-I) between the AVA and control group. Put otherwise, the small but significant favorable effect of the AVA on parental state anxiety was not paralleled by a favorable effect on the child's state anxiety during induction, which is in line with the two above-mentioned studies[33,34].

In conclusion, our study showed that AVA had a favorable influence on parental state anxiety. Therefore it can be recommended to use AVA for preparing parents towards anesthesia of their child. Unfortunately, AVA had no beneficial effect on the child's anxiety. In a sense, this is not surprising because, as already mentioned, there are probably complex bidirectional influences in the relationship between the child's and the parent's anxiety. Next to that, even if parental anxiety decreases, it is still the child who has to face the realistic danger of surgery. From an evolutionary survival perspective, it is logical and natural that anxiety increases in the face of acute realistic, imminent danger. To reduce the children's state anxiety we recommend to develop additional interventions, specifically targeted at the child's anxiety (see the section 'Implications and recommendation for future research' below).

PERIOD AFTER SURGERY: EMERGENCE DELIRIUM, SENSORY PROCESSING CHANGES, POSTOPERATIVE PAIN AT HOME AND SLEEP PROBLEMS

In chapter 2 we examined the possible predictive power of parent reported pre-existing emotional/behavioral problems in children for Emergence Delirium (ED) at awakening from anesthesia as assessed by nurses with the well validated PAED scale. This was done in a sample of 343 children undergoing elective day-care surgery. So far, this topic had not been investigated thoroughly. An earlier study of 521 children aged 3 – 7 years, using a temperament scale, demonstrated a univariate association between children's temperament (low adaptability) and ED[35]. In the multivariate analysis, only Ear Nose Throat (ENT) surgery, time to awakening and the use of isoflurane as inhalational anesthetic appeared to be independent risk factors for ED. Furthermore, in other studies state anxiety in children was demonstrated to be associated with ED[24,36-38].

In line with earlier findings, we demonstrated in our final multivariate model that the child's age and its first experience with anesthesia were independently associated with ED. We did not find an association between pre-existing emotional/behavioral problems and ED (on PAED scores), nor between child's state anxiety and ED. As already mentioned, this last finding is in contrast with earlier studies[24,36-38].

Several reasons might explain why we did not find an association between pre-existing emotional/behavioral problems and ED. In general, it is clear that ED is a very complex phenomenon, influenced by psychological, medical and social putative risk factors[39-41]. Related to this, the assessment of ED at awakening from anesthesia (like the assessment of all behaviors in children awakening from anesthesia) remains challenging[37,42-44]. ED can be measured, but all instruments available for this purpose have their limitations. For example, it is difficult to distinguish ED from pain due to overlaps between the PAED scale and pain assessment tools[42,43,45]. In this respect, a recent retrospective analysis of observational studies posed that making no eye contact and unawareness of the surroundings characterized ED in children, whereas crying, abnormal facial expression, and inconsolability indicated pain[45].

However, there were several strengths to the approach that we used. The present study assessed ED with a validated tool and in the final analysis, children with moderate and severe pain were excluded to control for the confounding influence of postoperative pain. Furthermore, we considered ED as psychological construct on a continuum (using continuous scores) rather than dichotomizing it into two categories (by using a cut-off score: ED yes or no). This may be considered an advantage, as dichotomization results in loss of information. Apart from that, it is still a matter of debate which cut-off value should actually be used to dichotomize ED[46].

In chapter 5 we studied changes in sensory processing after anesthesia in toddlers. This is a clinically relevant issue, because changes in sensory processing influence the toddlers' arousal, attention, affect and behavioral actions. Consequently changes in sensory processing can contribute to postoperative behavioral changes.

Sensory processing after anesthesia and its relation to emotional/behavioral problems is an unexplored field. In a group of 45 boys aged between 18 – 30 months, circumcised for religious reasons, we studied pre- to postoperative changes in sensory processing, using the ITSP[47,48], and we investigated if preoperative children's emotional/behavioral problems were associated with these sensory processing changes. To the best of our knowledge, this is the first study to look at changes in sensory processing following pediatric anesthesia, using a structured instrument to assess sensory processing.

Significant changes were found on low registration, sensation avoiding and low threshold and on auditory and tactile processing, which can be considered clinically relevant: our study showed that following surgery children reacted less sensitively to sensory input (e.g. less alert detection of auditory/tactile information). Changes in sensory processing might give rise to under-responsive behavior. Such behavior could be interpreted as withdrawn or passive, which seems consistent with earlier findings showing that apathy and withdrawal besides separation anxiety are common in children after having undergone surgery[49,50]. This increase of under-responsive behavior could affect the toddlers' daily social functioning. This is an unexplored domain and should be unraveled further in future research.

Interestingly, pre- to postoperative sensory processing changes were associated with pre-existing emotional/behavioral problems. As already noted above, changes in sensory processing and postoperative behavior changes are different though clinically related concepts. For this reason it is worthwhile to mention the results of Fortier *et al*.[50], which showed that internalizing problems were associated with maladaptive postoperative behavior. Fortier's study was the first to investigate pre-existing emotional/behavioral problems, assessed by the CBCL, as predictors for maladaptive postoperative behavior. Noteworthy, earlier studies already demonstrated that children with more internalizing problems tend to have more behavior inhibition[51]. In general, these children tend to be more calm and withdrawn. Further research is needed to unravel these complex patterns.

We investigated whether pre- to postoperative changes in sensory processing were related to postoperative pain because pain is a strong risk factor of postoperative problematic behavior[52,53]. We did not, however, find such a relationship. This may be due to the religious reasons for the circumcision and also to of the relative small study sample. In our study almost 50% of the children had moderate to serious pain on day one postoperatively, which is conform previous findings[54,55]. Only 40% of the parents did adhere to the prescribed medication for their child and this is line with previous findings[56-58]. The modest adherence to pain medication may be explained by the fact that the children underwent circumcision for religious reasons[59], which may have contributed to both parental pain assessment and their attitude towards the child's pain medication.

Finally, in this study the child's state anxiety (assessed with the VAS-I) was not associated with changes in sensory processing. The relation between sensory processing, anxiety and pain needs to be investigated further, using larger samples with more serious procedures (requiring longer anesthesia) and more long-term follow-up assessments.

Next to emergence delirium and sensory processing changes, pain was one of the post-operative/anesthesia outcomes that this thesis was interested in. In chapter 7, we studied postoperative pain at home and sleep problems in children who had undergone surgery. An observational study was performed in 160 children aged 1.5 – 5 years undergoing adenotonsillectomy, to evaluate postoperative pain levels and sleep problems at home and to test whether emotional/behavioral problems were predictive for postoperative pain up to three days after surgery. Of the participating children, 50% had moderate to severe pain and this is consistent with previous research[56,60]. Only 25.2% of parents adhered to the prescribed pain medication for their child at home. Previous findings also showed that compliance with prescribed pain medication following surgery was suboptimal[56,60]. Both findings closely resemble our results obtained in the group of boys who were circumcised, as described in chapter 5.

In our study of children who underwent adenotonsillectomy, pre-existing internalizing problems and parental need for information were associated with higher children's pain scores at home during the first postoperative three days. A plausible explanation for the relationship we found may be that children with more internalizing problems are more anxious, which has been shown to be related to higher pain scores[23,24]. These children also react more emotionally and have more somatic complaints which may further explain their vulnerability. In contrast, another study with a relatively small sample (n = 43) of children undergoing tonsillectomy found no association between preoperative CBCL scores (internalizing/externalizing and total emotional/behavioral problems) and postoperative pain[61]. At present, there is still insufficient good-quality evidence to draw strong conclusions about the influence of pre-existing internalizing problems on postoperative pain. Although not specifically related to postoperative pain, it could be interesting in this context to mention that previous studies associated higher levels of internalizing problems with recurrent abdominal pain[62] and headache in children[63].

Parents reported close to 40% postoperative sleep problems for children at home, which is consistent with previous findings in large sample of 241 children undergoing adenotonsillectomy[24]. This study showed that anxious children had a higher incidence of postoperative sleep problems. Importantly, the relationship between pre-existing emotional/behavioral problems and postoperative sleep problems in children needs to be investigated further.

A higher parental need for information as assessed with the APAIS was associated with higher postoperative pain scores in their children. Reasons for this association are speculative, but a potential explanation may be found in the parent's anxiety. That is, parental need for information was related to higher parental state anxiety (which is consistent

with the literature[64,65]) and parental state anxiety was (univariately) associated with the child's postoperative pain scores (which also fits with earlier findings[11,66]).

CONCLUSIONS OF THIS PhD PROJECT

Previous evidence had already shown that perioperative anxiety was probably associated with ED, postoperative maladaptive behavior and higher postoperative pain intensity scores[36].

The present thesis provided additional evidence that pre-existing emotional/behavioral problems (as assessed by the CBCL) during the six months prior to surgery were associated with the child's preoperative state anxiety, ED, changes in sensory processing and postoperative pain at home. More specifically, the studies of the present thesis show that:

1. children's preoperative internalizing problems as assessed by the accompanying parent at admission prior to surgery are associated with children's state anxiety at induction as assessed by the mYPAS;
2. children's preoperative externalizing problems are associated with ED assessed by the PAED scale, whereas internalizing problems are not;
3. children's preoperative total emotional/behavioral problems are associated with pre- to postoperative changes in sensory processing;
4. after adenotonsillectomy children's preoperative internalizing problems are associated with postoperative pain intensity scores as assessed with the PPPM during the first three days at home.

Our findings show evidence that preoperative screening with a standardized tool such as the CBCL helps us focus on children at risk for perioperative maladaptive psychological and physical outcomes (such as anxiety, ED, sensory processing changes and pain) in order to improve perioperative health care management. This should lead to a more individualized approach in preoperative preparation of children based on their specific vulnerability and could also support health care workers to pay more attention to children at risk.

This thesis also presented preliminary data supporting the validity of a VAS-I to be completed by parents and anesthesiologists, in order to assess children's anxiety during induction of anesthesia. It is important to have an easy-to-use tool, which requires no training and can be quickly completed. This allows parents to be involved and become aware of their child's anxiety level and vulnerability.

We concluded that an Audio Visual Aid (AVA), shown to parents immediately prior to their child's anesthetic induction, reduced parental state anxiety. Considering the fact that parents become very anxious during the anesthetic induction of their child, it is essential that the whole preparation should not only be directed towards the child, but also towards the accompanying parents. If the parents' anxiety can be reduced, this will strengthen their ability to cope with their own feelings as well as with their child's feelings of anxiety during induction. However, in our study the AVA did not influence the child's state anxiety and compliance during induction. Therefore, we recommend that, when psychologically preparing the parents, specific psycho-education is provided to them offering (communication) tools and strategies on how to decrease children's anxiety and how to cope with the stressful situation.

In conclusion, our studies contribute to understanding children's perioperative behavior and parents' involvement in their child's preparation and anxiety management.

STRENGTHS AND LIMITATIONS

The studies presented in this thesis have several strengths. Firstly, they include relatively large prospective observational cohorts varying from 70 to 401 children in several age groups ranging from 1.5 years up to 16 years which enhances generalizability.

Secondly, further strengths are that throughout the studies we made use of international well-validated assessment tools like the CBCL[1,2], $ITSP_{6\text{-}36}$[47], mYPAS[3], ICC[20], PAED[67] scale, Spielberger's STAI[16], APAIS[64], PPPM[68,69] and the FLACC[70] scale among others, at well-defined time-points. The two latter pain scales are in fact recommended by Core Outcome Domains and Measures for Pediatric Acute and Chronic/Recurrent Pain Clinical Trials (PedIMMPACT)[71], which also strongly advocates assessment of sleep problems. Apart from the validated state anxiety assessment tools (mYPAS and ICC) in children, we provided some evidence for the validity of a new global general state anxiety assessment tool, the VAS-I.

There are several limitations to this study that need to be mentioned. In our study groups all children underwent minor day-care surgery and did not receive any premedication, all anesthetic inductions were performed by inhalation, and the studies were performed in a single center. There was also an overrepresentation of parents with low education status.

It also should be kept in mind that there are a few limitations concerning some of the scales that we used. The mYPAS might not be suited for the use in very young children (≤ 2 years), nor for adolescents (> 12 years) whereas the ICC rather assesses the child's compliance during induction[8,20,72].

Regarding the parental PPPM assessment, parental psychological traits (such as state/trait anxiety, stress and pain catastrophizing thoughts) may have an impact on the assessment. Furthermore, it must be kept in mind that parents tend to overestimate the severity of the child's pain[73], which is why children's pain self-report would be preferred[71,73].

When analyzing ED with the PAED scale it has become clear that instead of using all the PAED scale items, maybe only those now considered as ED-specific[42,43] (*no eye contact*, *no purposeful action*, and *no awareness of surroundings*) should be used.

Furthermore, in general, when using the CBCL to obtain an assessment of the child's emotional/behavioral problems, it is often proposed to use a multi-informant approach (such as both parents, a caregiver or teacher) instead of a single informant, as was used in this thesis' studies. The CBCL was completed on the day of surgery which could have biased the parents' perception and their ratings as to the child's typical behavior.

Finally, we should also pay attention to the so-called *common method variance*[74] – the same respondent completing multiple measures. In other words, having one informant completing questionnaires (as in our studies), may have biased the obtained scores. Parents, for instance, who tend to rate higher CBCL scores might also do the same when rating the PPPM or the STAI. This might lead to inflated associations.

IMPLICATIONS AND RECOMMENDATIONS FOR CLINICAL PRACTICE

The results of this thesis underline the importance of an individualized approach and preoperative screening of children in their perioperative period. Healthcare workers should be aware of an increased vulnerability in children with higher scores on pre-existing emotional/behavioral problems. Preoperative preparation should not consist of a uniform method, rather it should be seen as an individualized program tailored in a more holistic approach[18]. In an ideal situation it would be essential to screen for psychological vulnerability, which was shown in our studies to be related to children's maladaptive perioperative and postoperative behavior (perioperative state anxiety, ED, postoperative maladaptive behavior and postoperative pain intensity). This makes it

possible to prioritize extensive behavioral preparation programs, which are effective[10,75], to the most vulnerable children.

This thesis gives additional evidence that higher emotional/behavioral CBCL problem scores are associated with difficult perioperative behavior. So the CBCL proved to be a clinically significant and useful screening tool in this context. For future clinical use, we recommend that these screenings ought to be organized in an anonymous online safe web-based connection at home.

As concerns the assessment of the child's anxiety during the perioperative period, we recommend to perform this assessment during the process of induction, the point at which the highest child state anxiety is measured during the whole perioperative period[5,11]. To this end, we propose that parents and anesthesiologists apply the user-friendly VAS-I. The information thus obtained on the child's anxiety, and consequently its vulnerability, can be discussed with the parents.

Regarding the preparation of their child towards the surgical procedure, our AVA study showed that parents should be encouraged to be involved and could benefit from receiving specific information, to reduce their state anxiety. We recommend additional tools to reduce children's preoperative anxiety, such as an innovative, age-attuned Virtual Reality Exposure[76] (see further below).

With reference to the child's pain management at home, this thesis demonstrated high pain scores in children at home[54,56,60] and insufficient parental adherence to the prescribed medication regimen[55,56]. Accordingly postoperative care should be enhanced by better follow-up consisting of clear instructions to parents and online assessment of postsurgical pain by the parents. This could be supplemented by automatic text messages that remind parents when to administer medication, by giving parents direct access to an email address for questions, and the availability of liaison nurses who can be contacted for advice.

If all these recommendations (psychological screening for the child's vulnerability, the child's anxiety assessment and parental involvement) will be adopted, it will bring us closer to the ideal of Family-centered Pediatric Perioperative Care[18]. This thesis showed that children with existing internalizing problems as well as their and their parents' level of anxiety should receive more attention from healthcare workers, who in turn also ought to realize that these individual aspects have to be incorporated into a flexible perioperative health care delivery system.

DIRECTIONS FOR FUTURE RESEARCH

Considering the above, the question remains how to fit all our recommendations into a busy clinical practice in times when economic and financial matters have become prominent in healthcare decision making. It is in this light that the following suggestions for future research should be read.

In the previous section, we emphasized the value of preoperative psychological screening of children scheduled for surgery. Considering our findings and the psychometric qualities of the CBCL, with availability of translations and normative data for different countries (which is useful for patients from different ethnic minorities), we recommend the CBCL for this purpose. Since the CBCL takes about 15 minutes to complete, it can be useful to provide the questionnaire via a secured internet site to parents and also its parallel version for teenagers, the Youth Self Report, for youth aged 11 – 17 years. If this is not feasible, we consider it worthwhile to investigate the usefulness of the Brief Problem Monitor[77], a short form of the CBCL (19 items only) to screen for emotional/behavioral problems[78]. Further research could also pave the way to establish specific cut-off values for the CBCL to distinguish between vulnerable and less vulnerable children prior to surgery, which would make the CBCL more clinically applicable.

In this thesis we recommended the VAS-I as a tool to assess children's anxiety during induction. We provided preliminary evidence on the validity of this instrument. However, further research is needed to establish the psychometric properties of the VAS-I more extensively.

Future investigation should also be directed towards the efficacy of integrating anxiety management into clinical practice and towards the improvement of pain management for children at home. Interventions to improve parental pain medication adherence should be developed and tested on their efficacy.

Furthermore, we consider it relevant to examine a possible association between pre-existing child's emotional/behavioral problems and persistent postsurgical pain. In this study, pain measurements were restricted to up to 10 days after surgery. It has been recognized that children who undergo a surgical procedure are at risk of developing posttraumatic stress symptoms[79] and chronic pain[80,81]. This is, however, still an understudied area. There is evidence to suggest that preoperative pain[82,83], postoperative pain intensity[83-85], child pain coping efficacy[86] and parental pain catastrophizing thoughts[87,88] are predictors of persistent postsurgical pain in children. However, the impact of chil-

dren's pre-existing emotional/behavioral problems on persistent postsurgical pain has not been studied so far.

According to the results presented in this thesis, an AVA seems to be a useful tool to reduce parents' anxiety as to their child's surgery. Future research should focus on developing innovative tools for preparing children and parents for surgery, such as online videos/games[89,90] or web-based interventions[90-92]. Certainly worth mentioning here is a new preparation tool, namely Virtual Reality Exposure. In an ongoing study[76] at the Erasmus MC-Sophia, the perioperative process is simulated by means of an interactive Virtual Reality tool. Using Virtual Reality Exposure may reduce anxiety surrounding surgery, and enhance coping mechanisms and self-efficacy of both child and parent. Other tools like chat groups and skype sessions guided by and under supervision of trained and experienced hospital staff may also facilitate the psychological preparation of children and their parents and should be further investigated.

Postoperative maladaptive behavior is still very common. For example, a study by Power and co-workers[53], using a cohort of children aged 2 – 12 years who underwent general surgery, urology or ear, nose and throat surgery, documented that up to 80% of the children exhibited problematic behavior. In most cases, postoperative maladaptive behavior is examined by using the Post Hospitalization Behavior Questionnaire[93], of which the validity and reliability is questionable[94]. In this context, the ITSP might break new grounds in perceiving how changes in sensory processing influence postoperative behavior in toddlers and children. This should be investigated using larger, multicenter samples, using different age ranges and more serious types of surgery. Longitudinal studies with a longer-term follow-up are necessary (e.g. to study bidirectional relationships between parameters over time).

As a final thought, this dissertation was necessarily limited in scope. It did not focus on the influence of characteristics such as the child's temperament, the quality of parent-child attachment (in families from different cultures), nor the child's intelligence on peri- and postoperative behavior. To our knowledge, this has not yet been studied before. Nor did this study consider the behavior of healthcare workers (nurses and anesthesiologists). This is a delicate issue, because certain specific behaviors (for example, reassuring comments, empathy, apologies, and criticism) might actually increase stress/anxiety in the child and parent[95,96]. To avoid possibly anxiety-inducing behaviors, more attention should be given to training and collaboration of healthcare workers (for example to promote more distracting behavior, humor, and nonprocedural talk)[95,97]. It is our opinion that all these issues should be further explored in studies covering psychological aspects of anesthesia in children.

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