FACING PAIN
IN INFANCY AND CHILDHOOD

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FACING PAIN
IN INFANCY AND CHILDHOOD

Het gezicht van pijn
op de kinderleeftijd

Proefschrift

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	Prof.dr. J. Passchier
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	Prof.dr. H. Huijer Abu-Saad
	Prof.dr. H.M. Koot

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Chapter 1

Introduction

1.1 Introduction

Pain is a significant part of growing up. It is a powerful stimulus that drives primitive survival behaviour and teaches children to avoid harm and danger. The most common sources of pain in children are the everyday incidents, averaging one incident per child every three hours [1]. Fortunately, few of these incidents result in serious injury and the pain associated with them is typically of short duration. When staying in a hospital, children, especially (premature) neonates, often experience pain as well. In this situation the most common sources of pain, apart from surgical intervention, are invasive procedures, some for investigation and some for treatment.

Pain during hospitalisation serves no purpose at all. For example, if pain is not adequately treated, it progressively increases responses of spinal dorsal horn neurons, a phenomenon that is called "wind-up". Large doses of opioids are then needed to suppress the established hyperexcitability, which could have been prevented by small doses given pre-emptively, i.e. before pain appears [2]. This hyperexcitability is most easily evoked in premature neonates [3]. Pain also causes physiologic stress, which in its turn may lead to metabolic instability, and finally may increase the risk of morbidity and mortality [4,5]. Because of greater body surface and energy needs, yet smaller reserves of protein, carbohydrate and fat, metabolic stability is more difficult to maintain in (premature) neonates than in older children [6]. Inadequately treated pain may also lead to behavioural problems at home [7,8], which may last 2 to 4 weeks longer than the duration of pain itself [9]. Finally, research findings suggest that pain exposure during early infancy results in a permanently altered neural circuitry, altered pain sensitivity, and probably also in behavioural sequelae [10-12].

Till the end of the 1980s the treatment of medically induced pain in children received little attention. Intramuscular administration of opioids on an if-necessary basis was the most common method of postoperative pain treatment, despite its demonstrated ineffectiveness [13], and the fear it raises in children [14]. Even more disturbing was the generally accepted notion that neonates could not feel pain and did not have any memory pertaining to painful stimuli [15]. In line with this notion less than 20% of the clinicians administered (systemic) opioids in neonates and infants following major surgery [16].

The last decade has seen rapid changes in this malpractice of undertreatment and misconception. It is now generally acknowledged that even neonates can feel pain [17-20]. Many instruments have been developed to assess pain in neonates, infants, and children [21,22] and a variety of analgesics, methods of administration, and protocols are applicable to neonates, infants, and children [23].

It is striking, therefore, that after more than 10 years of progress the attitude towards the management of procedural pain has not changed fundamentally [24-26]. Procedures such as heel stick, arterial and venipuncture, or tracheal suction are consistently performed without analgesia [24,27]. Most cynically, the children with the greatest risk of wind-up, metabolic instability, and of long-term sequelae are most intensively subjected to these procedures [28]. Lack of time to administer drugs during emergency procedures, the risk/benefit ratio of administering drugs for very brief procedures, or fear for adverse consequences are common rationales put forward to justify the failure to administer adequate pain relief [24].

Another striking finding is that the majority of the children in day care surgery suffer pain, most pronouncedly following circumcision [24,29] and (adeno)tonsillectomy [9]. Yet, clinicians as well as nurses describe these procedures as very painful and traumatic [24,30]. Fear of side effects of the analgesics used, or lacking the skills to apply local or regional anaesthesia might be explanations [29]. Incorrect assumptions about the pharmacokinetic aspects of analgesics could also explain the high incidence of pain after minor surgery.

In contrast, postoperative pain following major surgery appears to be treated consistently [27], primarily with opioids. Analgesic potency without a ceiling effect and maintenance of homeostatic stability even in critically ill neonates may explain this popularity. At present, recommended analgesic regimens have been defined which are based on the philosophy of pre-emptive analgesia rather than on the if-necessary approach [23,31]. The dilemma, however, is that there is inter-individual as well as intra-individual variability in pain relief and analgesic needs [32-35]. Therefore, opioid dosages have to be adjusted according to the individual requirements. This can be achieved when opioid requirements are adjusted according to valid assessment of pain or when children participate in their own pain management program.

In summary, the elimination and amelioration of medical induced pain is still capable of improvement. This can be achieved either by means of improving the

methods of pain assessment or by studying the efficacy of analgesic drugs, topics which are both addressed in this thesis.
When studying pain in children, careful consideration must be given to the continuing process of maturation and development, both in the biological and the psychological dimensions of pain. For example, the transmission of pain differs between neonates and older children, the metabolism of medication varies with age, and the perception and understanding of pain depends on the children's cognitive development. The latter also restricts the applicability of pain assessment methods.

1.2 Scope of this thesis

This thesis focuses on how medically induced pain in children can be treated, evaluated, and on whether the administration of analgesics prevents neonates and infants from developing long-term sequelae. Various age groups were studied. The chapters 2 to 4 comprise studies in neonates and infants into the sensitivity and specificity of the face for the assessment of pain and into the development of long-term sequelae. The chapters 5 to 7 describe studies in older children and adolescents evaluating various analgesic techniques for a variety of surgical interventions.

1.2.1 Neonates and infants

As neonates and infants are not able to tell if they are in pain, they have to rely on the knowledge and skills of nurses and clinicians. According to nurses and parents the most specific measure to assess the condition of the infant is the face. Chapter 2, therefore, reviews the literature to determine whether this is true or not. As this measure is not validated for the assessment of postoperative pain, its validity for this purpose is assessed in chapter 3. Chapter 4 uses the face to assess whether the use of judicious analgesia has profound effects by reducing the vulnerability of children to develop long-term alterations in pain sensitivity.

1.2.2 Children

In this section pain is not assessed by means of facial expression but by other validated pain-related indices. This because nurses responsible for the evaluation of pain were not trained in analysing facial responses, and because self-report is considered the gold standard in older children.

Adequate pain relief during circumcision can be provided either by local or regional anaesthesia, or the administration of opioids. These techniques, however, are not preferred by many clinicians as local and regional anaesthetic techniques require special skills and opioids are known for their side effects. To gain clinical acceptability, alternative analgesic strategies have to meet two criteria, i.e. easy to administer and few side effects. Whether application of EMLA cream can replace the difficult, highly skilled regional anaesthesia techniques is examined in chapter 5. Paracetamol and diclofanac are the most commonly used analgesics for (adeno)tonsillectomy. Both are given pre-emptively, but there is no consensus about dose, time of administration and efficacy. Chapter 6, therefore, reviews all available papers on this subject to find out which of these two drugs should be preferred, not only from an efficacy point of view but also from that of side effects. Theoretically, pain management is optimal when, apart from pre-emptive analgesia, the children are allowed to self administer analgesics whenever necessary. Patient controlled analgesia (PCA) is a technique that satisfies these criteria. The efficacy of this technique in comparison with continuous infusion of morphine is examined in chapter 7.

1.3.3 General discussion and summary

Chapter 8 is the general discussion. In this part the results from the previous chapters are discussed in the light of developments within the field of pain assessment in children. Suggestions for further research are given.

Part one

Measurement and long-term effects of pain

Chapter 2

The value of the face to assess pain: a literature review

2.1 Abstract

Background Neonates and infants lack the ability to report their pain and thus rely on nurses and clinicians skills to determine whether they are in pain or not.
Objective To review the literature reporting on the sensitivity and specificity of the face for pain assessment.
Design Systematic review.
Methods A MEDLINE and PSYCLIT search from 1966 through 2000 was carried out. Language restrictions were not applied.
Results There are two coding systems to objectively code facial movements in neonates and infants: the Neonatal Facial Coding System and the Maximum Discriminative Facial Movement Coding System. The first was used in 34 of the 38 original studies found. In general, facial movements have only been studied in relation to acute pain, using needle pain as the gold standard painful event.
Conclusion The facial response to acute pain has good sensitivity and specificity, and is characterised by a constellation of seven well-defined facial actions that are different from expressions associated with anger, fear, or sadness.

2.2 Introduction

Pain is a subjective phenomenon and for that reason cannot be simply measured and quantified, especially not in children. The gold standard of measuring pain should be what one reports about one's experience, but infants and young children lack this ability. It is generally acknowledged that in this age group the non-verbal bio-behavioural alterations by pain constitute the infantile forms of self-report [36]. These alterations include: 1) cardiorespiratory responses, 2) neurochemical secretions such as adrenaline and noradrenaline, 3) paralinguistic vocalisations in the form of crying, screaming or moaning, 4) behavioural reactions including reflexive withdrawal of torso and limbs or purposeful action designed to ward off injury or to palliate pain, and 5) facial expression [37]. A broad range of need states and situations can also provoke most of these bio-behavioural alterations. Fatigue, hunger, discomfort from being soiled, pain, and other states of distress overlap in their behavioural manifestations [38]. The low specificity of most indices necessitates isolating those bio-behavioural responses within the complex of ongoing flow of children's activities that have limited signal-to-noise ratio.
Several lines of evidence indicate that facial activity is particularly valuable for pain assessment. Facial activity serves primarily as a source of communication to others who may provide help [39]. It allows parents and other adults to differentiate between positive and negative emotions, motivational states, and cognitive states [40-42]. Several emotional facial expressions have a universal meaning, regardless of the culture in which one is raised [43,44]. These expressions differ from the facial response to pain, which also has unique characteristics [45-47]. Finally, infants' facial responses to pain contribute more to adult judgements of the severity of pain than does crying [46,48].
The importance of the face has been acknowledged as all multidimensional pain assessment instruments have included the face (see Table 2.1). However, there is no consensus on what the face looks like when infants suffer pain. Descriptions range from a negative or marked contorted face to grimacing or frown, a withdrawn or disinterested face with quivering chin and clenched jaws and so forth. Moreover, most of these descriptions are not made operational and in general we do not know what to look at.

Table 2.1 **Descriptions of the facial expression items included in multidimensional pain assessment instruments for infants**

Instrument	Description
Post Operative Pain Score [104]	0 = marked constant facial expression of pain; 1 = less marked intermittent facial expression of pain; 2 = calm relaxed face
CRIES [105]	0 = no facial expression; 1 = grimace; 2 = grimace/grunt
Scale for Use in New-borns [106]	0 = totally relaxed face, no tone or expression; 1 = reduced facial tone or expression; 2 = normal, neutral, no tension; 3 = increased tension, furrowed brow; 4 = contortion, grimace, vigorous cry
COMFORT scale [107,118]	1 = facial muscles totally relaxed; 2 = facial muscles normal; 3 = tension evident in some facial muscles; 4 = tension evident throughout facial muscles; 5 = facial muscles contorted and grimacing
Toddler–Preschooler Postoperative Pain Scale [108]	0 = relaxed face, smiling; 1 = wry mouth; 2 = grimace (mouth and eyes)
Riley Infant Pain Scale [109]	0 = neutral face, smiling; 1 = frowning, grimacing; 2 = clenched teeth; 3 = full cry expression
Nursing Assessment of Pain Intensity [109]	0 = smiling; 1 = neutral face; 2 = frowning, grimacing; 3 = clenched teeth
FLACC [110]	0 = no particular expression or smile; 1 = occasional grimace or frown, withdrawn, disinterested; 2 = frequent to constant quivering of the chin, clenched jaw
Mills Toddler Pain Index [111]	Facial expressions may occur: frowning (grimacing); clenched jaw; "O " mouth (with movement, crying); fear (widened eyes), serious/sad; or flinching

Liverpool Infant Distress Score [112]	0 = eyes closed or relaxed; 1 = eyelids remain closed but face slightly screwed up with lines around mouth, eyes and brow; 2 = attentive, receptive expression, paying interest to environment; 3 = eyes partly closed with lines around, mild furrowing of brow, face slightly contorted into frown expression, chin quiver; 4 = moderately furrowed brow, eyes closed and screwed up tightly causing many lines around eyes, nostrils sharp and flaring, lips tightly held, jutting lower lip; 5 = expression held practically all the time without relief
Modified Infant Pain Scale [113]	Facial expressions (brow bulge, open lips, chin quiver, stretch mouth vertical, stretch mouth horizontal, naso-labial furrow, eye squeeze): 0 = marked; 1 = less marked; 2 = calm
Neonatal Infant Pain Scale [114]	0 = restful face, neutral expression; 1 = tight facial muscles, furrowed brow, chin, jaw (i.e. negative facial expression, nose, mouth, and brow)
Modified Behavioural Pain Scale [115]	0 = definite positive expression; 1 = neutral expression; 2 = slightly negative expression (e.g. grimace); 3 = definite negative expression (i.e. furrowed brows, eyes closed tightly)
Premature Infant Pain Profile [116]	Brow bulge; eye squeeze; naso-labial furrow: each facial action is scored for its presence: 0 = not present, i.e. 0-9% of time; 1 = minimum present, i.e. 10-39% of time; 2 = moderate present, i.e. 40-69% of time; 3 = maximum present, i.e. ≥70% of time
Early Verbal Pediatric Pain Scale [117]	0 = relaxed facial expression; 2 = grimacing (brows drawn together, eyes partially closed, squinting); 4 = severe grimace (brows lowered, tightly drawn together, eyes tightly closed)

This led us to review the following topics regarding the sensitivity and specificity of the face as a means to communicate pain. 1) Which facial actions consistently accompany pain in neonates and infants? 2) Are there individual differences in the appearance of these facial actions? 3) Are these facial actions sensitive to change? 4) Does the occurrence of these facial actions vary across several modalities of pain (e.g. acute vs. postoperative pain)? And 5) do these facial actions discriminate between pain and emotional states or distress?

2.3 Methods

We aimed to identify all publications on facial expression of pain in infants. A MEDLINE and PSYCLIT literature search from 1966 through 2000 was conducted. The keywords used were pain, facial expression, infants and children. Language restrictions were not applied. After collecting the articles, all listed references were checked for additional relevant articles or books.

2.4 Results

2.4.1 Search

This search resulted in a total of 38 original studies. These had been published in the following journals: Pain 11 times; [47,49-58], Pediatrics 4; [59-62], Developmental Psychology 3; [63-65], Journal of Pediatric Psychology 3; [66-68], Archives of Diseases in Childhood 3; [69-71], and other journals 15 times [72-84]. One original study was included in a book [85].

A noticeable finding is that two distinct anatomy based facial coding systems are available that can be used in neonates and infants to describe changes in the face: the Neonatal Facial Coding System (NFCS) and the Maximally Discriminative Facial Movement Coding System (MAX). The NFCS is most accepted as 34 of the 38 studies used this system.

The NFCS [49,50] has been adapted from the Facial Action Coding System [86] and identifies action units representing discrete facial movements. These facial movements are derived from knowledge of the facial muscles that underlie skin movements. This system comprises ten well defined facial actions, i.e. brow bulge, eye squeeze, naso-labial furrow, open lips, horizontal and vertical mouth stretch, taut tongue, lip purse, chin quiver, and tongue protrusion (see Table 2.2).

The NFCS can be applied using fine graded video analysis [49,50] as well as in real time at the bedside [56,57,69,76].

The MAX was initially developed to determine which muscles are responsible for various facial movements, i.e. appearance changes (ACs), involved in discomfort/pain, and eight universal emotions, i.e. anger, fear, sadness, disgust, contempt, interest, joy, and surprise. These ACs are served by three separate branches of the facial nerve and by three relatively independent sets of muscles in three regions of the face: the Forehead/Eyebrows/ Nasal root (FEN) region, Eye/Nose/Cheek root (ENC) region, and the Mouth/Lips/Chin root (MLC) region. The FEN region has 6 ACs, the ENC region 7 ACs, and the MLC has 17 ACs. Combinations of these ACs represent the presence of discomfort/pain or one of the fundamental emotions [63,64,85]. Using fine graded video analysis, coders have to identify the offset and onset time of each AC.

Table 2.2 Definitions of the facial actions

Facial actions	
Brow bulge	Bulging, creasing, and vertical furrows above and between brows occurring as a result of the lowering and drawing together of the eyebrows.
Eye squeeze	Squeezing or bulging of the eyelids. Bulging of the fatty pads about the infant's eyes pronounced.
Naso-labial furrow	Primarily manifested by pulling upwards and furrow deepening of the naso-labial furrow.
Open lips	Any separation of the lips.
Horizontal mouth stretch	Distinct horizontal pull at the corners of the mouth.
Vertical mouth stretch	Characterised by tautness at the lip corners (vertical) coupled with a pronounced downward pull of the jaw.
Taut tongue	A raised, cupped tongue with sharp tensed edges.
Tongue protrusion	Tongue visible between the lips extending beyond the mouth.
Lip purse	The lips appear as an "oo" sound is being produced.
Chin quiver	An obvious high-frequency, up-down motion of the lower jaw.

2.4.2 Facial actions accompanying pain

Only nine studies report which of the ten facial actions appear or increase in intensity as a reaction to various modalities of acute pain. All studies identified the presence of brow bulge, squeezing of the eyes, naso-labial furrow, open lips and taut tongue when children were in pain [47,49,50,52,53,55,66,80]. Seven studies identified vertical mouth stretch as a pain-related facial action [47,49,50,52,55,66],

five identified horizontal mouth stretch [47,52,55,66], and two identified chin quiver [49,50]. In term-born infants tongue protruding was only observed in situations of discomfort but not during pain [49]. In preterm neonates at 32 weeks gestation, however, this facial action was observed in about 18% of the infants following lancing of the heel and in 25% during squeeze [56]. Lip purse has not been identified as a pain-related facial action.

Six studies have examined whether these facial actions are interrelated or act independently. High correlations ($r > 0.78$) between brow bulge, eye squeeze, and naso-labial furrow suggest that these facial actions occur simultaneously when pain is present [50,67]. The correlation between these three facial actions and open lips, vertical mouth stretch, and taut tongue was moderate to low ($r = .14 - .50$) [50]. Principal component analysis yields the same findings as reported above [47,53,55,66]. Brow bulge, eye squeeze, naso-labial furrow, open lips, horizontal and vertical mouth stretch, and taut tongue loaded on one dimension; with the upper facial actions having higher factor loadings than the lower facial actions. These findings suggest that these facial actions form a facial composite of pain, and that the upper facial actions are the necessary components with the other features recruited thereafter, contingent upon the severity and specific sources of pain [47]. An example of this composite is presented in Figure 2.1a. This expression is similar to the one defined by the MAX, i.e. lowered and bulged brows, bulge and/or vertical furrows between the brows, eyes tightly closed and an angular and squarish mouth, though sometimes the mouth is wide open with the lips stretched tightly [87]. Moreover, this composite is the same as found in adults suffering from pain [46,88,89]. It thus appears that this expression has a universal meaning and is independent of cultural learning processes, thereby supporting Darwin's [90] claim that some facial expressions are innate responses with an evolutionary history that originally had survival value for mankind.

2.4.3. Individual differences

Substantial variation within the facial expression has been observed which appears to be related to the behavioural state, i.e. sleeping or awake prior to a noxious event, and to the gestational age of the infant as well as to previous pain exposure.

Behavioural state

According to Prechtl, neonates and infants display prolonged and characteristic episodes of stable behaviour during the day. These episodes represent distinct and qualitative different modes of overall neural activity. Five distinct behavioural states can be distinguished, ranging from quiet sleep to alert crying [91].

It is not clear whether the reactivity of the facial pain expression is dependent on the behavioural state. Grunau and Craig [50] found no association between behavioural state and the number of infants responding with brow bulge, eye squeeze, naso-labial furrow, or open lips following heelstick. The occurrence of taut tongue and vertical stretch mouth, however, was significantly related to behavioural state. The proportion of children responding with taut tongue and vertical mouth stretch was the largest in infants who were quiet awake prior heelstick; 85% and 55%, respectively, and the smallest for infants in quiet sleep; 57% and 22%, respectively. Findings by Stevens et al. [52] in preterm neonates suggest that the appearance of facial actions depend on the behavioural state. The proportion of time that brow bulge, eye squeeze and naso-labial furrow were present following heelstick was 64%, 55%, and 63%, respectively, in those who slept quietly prior to heelstick, and 91%, 74%, and 92%, respectively, in the active awake.

Age

Premature neonates respond to pain with the same facial actions as term-born babies do. However, the vigour of facial activity to noxious stimuli in premature neonates is significantly less than in term-born neonates [47,51,92]. Moreover, premature neonates may react to procedural pain with tongue protrusion [56], in contrast to term-born infants [49]. They also display more horizontal mouth stretch than neonates, who tend to react with vertical mouth stretch and taut tongue [49,50,52,92]. This difference in mouth stretch might be based on immaturity of the prematurely born neonate, as only soft tissue is involved in horizontal mouth stretch, whereas mandibular action as well as soft tissue are involved in vertical mouth stretch [51].

Using the MAX, some investigators [63,64,85] have demonstrated that after needle penetration the occurrence of the pain expression decreases with age, whereas the anger expression increases. Besides pain and anger, infants also display sadness as a

reaction to needle penetration. The occurrence of this latter expression seems to be independent of age.
Using the NFCS, others have demonstrated that 4-month-old infants display less facial reactivity to noxious stimuli than 2-month-old infants do [51,53], but also less when compared with facial reactivity at the ages from six to eighteen months [53].

Early pain exposure
Findings suggest that perinatal pain exposure, particularly when no adequate analgesia is given, alters the vigour of the facial reaction to subsequent pain [59,75], as well as its expression in later childhood [82,93-95]. For example, Grunau et al. [75] reported that the facial actions were more extreme in infants who had experienced more stressful deliveries. Moreover, the duration of brow bulge, eye squeeze and naso-labial furrow to subsequent routine immunisation in circumcised infants was significantly greater compared with non-circumcised infants [82]. Others [59], by contrast, found that preterm infants of 28 weeks gestation age who had spent 4 weeks in a NICU and who had suffered a greater number of noxious procedures were less mature in their facial pain response than premature neonates of 32 weeks gestation age. In this study, the less mature facial responsiveness was associated with a higher number of painful procedures previously undergone.

2.4.4 Ability to detect change
To detect whether the facial reaction is sensitive to changes in pain severity, the NFCS facial actions were combined into a single index pain score. These indices were determined by summating the duration of the facial actions during the observation period.
(Preterm) neonates and infants who are exposed to noxious stimuli display significantly more facial activity than when exposed to non-noxious stimuli, for example when subjected to rubbing the thigh or applying a non-noxious stimulus to the heel [47,49,50,52-54,59,60,66,68,74,77,79,92].
Neonates display less facial activity when undergoing venipuncture instead of heelstick, but more when compared with neonates exposed to non-noxious stimuli [62]. Facial activity during venipuncture is diminished when EMLA cream is pre-emptively applied [78]. Neonates, on contrary, who had received EMLA before circumcision displayed three times greater facial activity during surgery than before

at baseline [72,83]. This latter finding suggests that EMLA is contraindicated for this procedure as demonstrated by others [96,97]. Scott et al. [80] demonstrated that preterm neonates who receive morphine display significantly less facial activity during heelstick compared with a placebo group.

2.4.5 Different pain modalities

There are no data on whether the facial actions described above also occur when (premature) neonates and infants experience subacute or longer lasting pain, e.g. postoperative pain or pain due to neonatal illness such as necrotizing entrocolitis, meningitis, or osteomyelitis. In contrast to acute short enduring pain, subacute pain has an inflammatory cytochemical or paracrine basis initiating or continuing the pain [98]. The pain may not be obvious to observers and the response may be subtler and not continuously present.

2.4.6 Discrimination between pain, emotional states and distress

Pain versus emotional states

As early as 1872, Darwin [90] pointed out that various facial expressions have a universal meaning, regardless of the culture in which people are raised. Thorough work of Izard et al. [99] and Ekman et al. [43,44] confirms Darwin's observations. They demonstrated that a total of six facial expressions, i.e. the expression of anger, fear, sadness, disgust, shame, interest, joy and surprise seem to have a universal meaning. Some have argued that the expressions associated with interest and shame also have a universal meaning [99]. Others, on the contrary, believe that the position of the head provides clues for distinguishing these emotions [86]. Each of these expressions is clearly distinguished from the expression of pain. The core expression of anger is almost the same as that of pain, although in anger the eyes are narrowed instead of tightly closed. Fear is characterised by lifted brows and wide open eyes while the mouth is slightly opened, and sadness by raised and medially pulled brows, narrowed eyes, with the corners of the mouth drawn downward and slightly outward [87] (see Figure 2.1). These emotional expressions have also been observed in neonates and infants and can be distinguished from the pain expression as described earlier [63,65,85]. Like the facial display of pain and anger the expressions of interest, joy, and disgust can be identified at birth; sadness in 2-month-old, surprise in 4-month-old, and fear in 7-month-old infants [63,64].

Pain versus distress

In one study [73] a considerable overlap was found in facial actions between infants who suffered from colic pain (Wessel's colic infants) and healthy controls who cried before and after feeding. Before feeding, brow bulge and taut tongue were observed to appear slightly longer in infants who cried due to abdominal cramps, compared with crying healthy controls; i.e. brow bulge was present 118 vs. 110 seconds, respectively, and taut tongue was present for about 70 vs. 42 seconds, respectively. With respect to eye squeeze and naso-labial furrow no significant differences were found between both groups. These facial actions may also appear during distress, i.e. following heel rub [50], warming of the foot [52,92], sham heelstick [77], and following the provocation of the withdrawal reflex by application of Von Frey hairs [84]. However, their occurrence is much shorter when the infant is in discomfort than when in pain [56,92].

2.5 Discussion

The reviewed literature shows that when in pain, neonates and infants react with brow bulge, eye squeeze, naso-labial furrow, and open lips. Other facial movements such as mouth stretch and taut tongue may occur as well, probably providing information about the severity of pain. These pain-related facial actions are sensitive to change, demonstrated by comparing noxious stimuli with non-noxious stimuli but also following the administration of analgesics. Moreover, they form a constellation of pain that can be distinguished from the facial expressions associated with emotional states such as anger, sadness, or fear. These pain-related facial actions have also been observed in infants who suffer from distress due to hunger or discomfort.

In this review we found that facial reactivity to a standardised pain stimulus is subjected to inter and intra-individual differences such as behavioural state, gestational age, and previous pain experiences. For example, the facial response to noxious procedures is greater in term-born neonates than in neonates born at premature age. Moreover, this response is more vigorous in term-born neonates who have a history of pain exposure, but less vigorous in premature-born neonates with a comparable history. These findings, however, are in contrast with findings demonstrating that pain thresholds increase with increasing gestational age and that premature neonates and term-born neonates with a history of pain have lower pain thresholds than neonates without any history of pain [3,11].

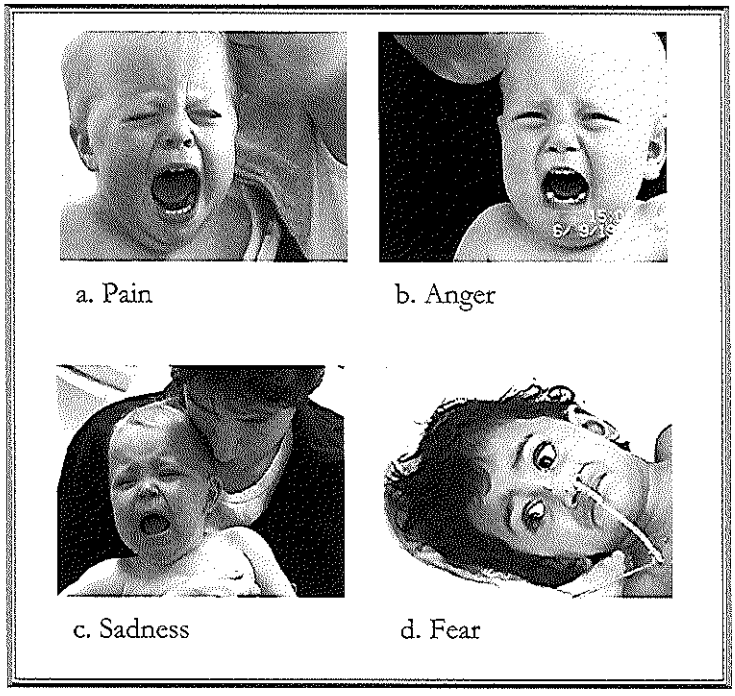


Figure 2.1 **Facial expressions of pain, anger, sadness, and fear**

It thus appears that the vigour and richness of the facial response should be interpreted in relation to some characteristics of the child such as gestational age, and history of perinatal pain exposure.

In none of the 38 publications, facial activity was studied in situations of subacute pain. Whether the face is sensitive and specific enough for the assessment of subacute, longer-lasting pain such as postoperative pain or pain associated with neonatal illness is not known. This, however, is a more challenging complex question and of greater clinical importance than short, acute pain. The responses to subacute pain may be subtler. Infants may not display their pain continuously but may tend to go in a passive state to conserve their energy [59,100], as animals do when they cannot escape from a threat or stress (e.g. severe traumatic injury or repeated defeat in social encounters) [101]. Moreover, many of these infants have a history of frequent pain exposure [102], which might lead to hypersensitivity or allodynia [103]. In the end they may be too exhausted to communicate their pain. Sedatives may further influence the infant's ability to communicate pain. Further studies should explore whether infants use the same facial actions in situations of subacute pain as well as their sensitivity and specificity in these situations.

The constellation of facial actions that emerges from the literature is the same as Darwin [90] described more than a century ago. Darwin, however, defined this face as the face of suffering caused by pain, distress, and hunger. Darwin's observations still hold true. Recent studies have only led to refinements, i.e. the vigour and richness of the pain expression as well as tongue movements allow us to discern pain from discomfort, but not pain from hunger.

As mentioned in the introduction, the variety of descriptions of the pain face in the multidimensional pain assessment instruments led us to undertake this review. These descriptions seem to be based on a-priori data without any reference to empirical data. Most instruments do not define which facial actions are involved in the facial display of pain or grimace [104-108]. This raises questions such as what is a pain face or when does a grimace appears. These vague descriptions increase subjectivity and may reduce reliability of the observation. Other instruments misinterpret what should be observed. For example clenched jaw is mentioned in four instruments [109-111], while others include chin quiver as a pain-related facial action [110,112,113]. In this review we did not find any evidence that clenched jaw or chin quiver can be regarded as pain-related facial actions. In another instrument [111] fear was included as a possible reaction to pain. To date fear has not been

observed as a common reaction to pain, unlike anger and sadness [64]. Hence, it would be more appropriate to include an objectively described facial response based on empirical findings, such as reviewed in this paper.
In conclusion: the sensitivity and specificity of the infant's facial response to pain was reviewed in this paper. In general the available data demonstrate that the infant's face is remarkably plastic. The facial response to pain has good sensitivity and is characterised by a constellation of seven well-defined facial actions. This constellation can be distinguished from the facial expressions associated with emotional states such as anger, fear or sadness. In comparison with other pain indices, the specificity of the facial actions is relatively high, although it remains difficult to discriminate between pain and distress due to discomfort.

Chapter 3

The value of the Neonatal Facial Coding System for assessing postoperative pain in infants

J.W.B. Peters, H.J. Duivenvoorden, R.V.E. Grunau, J. de Boer, M.J. van Druenen, D. Tibboel, H.M. Koot
Submitted

3.1 Abstract

Background The validity of the Neonatal Facial Coding System (NFCS) has not been established yet for postoperative pain assessment.

Objective To compare postoperative pain responses assessed by the NFCS with those assessed by several valid pain-related indices. Secondly, to examine whether all ten NFCS facial actions are necessary for valid assessment of postoperative pain.

Design Prospective observational study

Methods Thirty-seven children (0–18 months old) undergoing major abdominal or thoracic surgery were included. The children's facial, behavioural (COMFORT 'behaviour' and VAS) and physiological (blood pressure and heart rate) responses were assessed eight times during the first 24 hours. Catecholamine and morphine plasma concentrations were also determined. Random Regression Analysis served to assess the association between NFCS and the other pain indices. Multidimensional scaling was carried out to examine whether some facial actions could be combined.

Results All ten facial actions were combined into a single index of pain. This index significantly associated with COMFORT 'behaviour', VAS, and with heart rate and blood pressure, but not with the catecholamine, morphine, and M6G plasma concentrations. Multidimensional scaling revealed that brow bulge, eye squeeze, naso-labial furrow, horizontal mouth stretch and taut tongue could be combined into a single measure of pain. The remaining five facial actions were not interrelated. Also this single measure significantly associated with COMFORT 'behaviour', VAS, and with heart rate and blood pressure, but not with the catecholamine, morphine, and M6G plasma concentrations.

Conclusion The same facial actions that characterise acute pain are also valid indicators of postoperative pain. This study confirms previous findings demonstrating good reliability of the NFCS. The reduction of the NFCS to five facial actions appears to increase the specificity for pain assessment without reducing the sensitivity and validity for detecting changes in pain.

3.2 Introduction

Since the landmark publications of Anand et al. [4,119], which demonstrated the adverse effects of untreated pain in neonates undergoing surgery, pain assessment in infants and young children has received great interest. Assessment of infant pain is challenging; because self-report is not available the presence of pain is inferred. While pain assessment during acute pain-related procedures has been characterised extensively, the measurement of subacute pain, such as postoperative pain or pain associated with neonatal illness (e.g. necrotizing entrocolitis, meningitis or osteomyelitis), is even more complicated and has barely begun to be addressed in infants. In the postoperative period for example, the manifestation of observable behaviours by infants in pain may not be obvious, may be diminished [59] or even not (continuously) present [120]. Moreover, sedatives may alter the ability to express pain.

At present, of all non-verbal pain indicators the facial response to pain appears to be the most specific for the expression of acute pain. Not only do facial responses differentiate pain/distress from other emotion states [63,64], for caregivers they are also more consistent than, for example, cry [121] and even more salient than cry [48]. Furthermore, following noxious procedures facial activity explains more variance than cry, body movements, or heart rate do [55,67].

Studies on the infant's facial response to pain have mainly used the Neonatal Facial Coding System (NFCS) [49,50,122]. This is an anatomy-based measure in which ten discrete facial actions are coded as present or not. Of these, seven are typically associated with acute pain: i.e. brow bulge, eye squeeze, naso-labial furrow, open lips, horizontal mouth stretch, vertical mouth stretch, and taut tongue. Chin quiver is less frequent, and lip purse never occurs during pain. The tenth facial action, tongue protrusion, has been found to be counterindicative of pain in term-born infants [49] but controversially was related to pain in preterm infants at 32 weeks gestation [56]. The NFCS has been validated for premature neonates [47,52,54,57], term-born neonates [49,50] as well as for older infants up to 18 months of age [53]. This instrument is sensitive to acute pain because it discriminates between noxious (e.g. heel stick) and non-noxious stimuli (e.g. heel swab) [47,56,77] and also between infants receiving sucrose or morphine and controls during invasive procedures [25,71,76,80].

Some investigators suggest that of the ten facial actions described only three, i.e. brow bulge, eye squeeze, and naso-labial furrow, will suffice for valid pain observation [59,77,82,116]. The rationale for using only this subset of facial actions is that these are the most frequently observed in neonates and infants undergoing painful procedures and that each can distinguish between acute pain and non-pain states [54,66]. In contrast, Grunau et al. [56] argued against reducing the number of facial actions because those facial actions that are not universally observed may provide important information, e.g. about individual differences in pain experience. Furthermore, in case of subacute or chronic pain, subtle signs of ongoing discomfort might be missed if only the most common facial actions in response to acute procedural pain are assessed. The importance of evaluating the facial actions across development and in different situations has been underscored by the finding that tongue protrusion is associated with acute pain in preterm neonates younger than 33 weeks of gestation [56] but not in term-born infants [49].

It has not yet been established whether the NFCS is of clinical value for assessing pain in infants after major surgery. Determining the presence and severity of pain in the postoperative period is problematic, because of its subjective nature and the lack of gold standards. The present study has two main aims. The first aim was to compare responses obtained by using the NFCS with those obtained by using a modified version of the COMFORT-scale (COMFORT 'behaviour' scale) [107,118], the Visual Analogue Scale (VAS), as well as a number of bio-physiological pain indicators (i.e. heart rate, blood pressure, and catecholamine plasma concentrations), and morphine plasma concentrations. The second aim was to examine whether all ten facial actions included in the NFCS are necessary for valid assessment of postoperative pain in infants. To this aim a subset of facial actions was derived through multidimensional scaling. This subset was validated by comparing reactivity with COMFORT 'behaviour', VAS, bio-physiological responses as well as with morphine plasma concentrations. Additionally, this study addressed possible age, sex, and mechanical ventilation effects, as well as time trend effects and effects of method of morphine administration.

3.3 Materials and Methods

3.3.1 Design

This prospective, observational study is part of a larger, pre-stratified double-blind randomised clinical trial assessing the efficacy of continuous morphine administration and intermittent morphine administration after major surgery in neonates and young children up to 3 years of age [123].

The inclusion criteria of the main trial were: I) neonates aged ≤ 4 weeks with a gestational age ≥ 35 weeks and a body weight ≥1500 grams; II) and infants with a corrected postnatal age of at least 5 weeks up to 3 years; III) admitted to the ICU after thoracic or abdominal surgery. Patients were excluded if they 1) had received preoperative morphine or other opioids, 2) were given sedative drugs or muscle relaxants, 3) had hepatic or renal dysfunction, 4) neurologic damage, 5) altered muscle tone, or 6) preoperative anaemia (hematocrit less than 30%). The hospital's medical-ethical committee approved the trial and parental consent was obtained.

The infants were pre-stratified into three age groups because age differences in behavioural and physiological reactivity were expected to be of relevance, i.e. neonates, ≤ 4 weeks old; young infants, 5 weeks to 6 months old; and infants, ≥ 6 months old, respectively.

Anaesthesia was standardised for all patients. After the induction of anaesthesia an arterial line was placed from which blood samples were drawn for measurement of catecholamines and morphine plasma concentrations.

After the operation all patients received morphine until they were pain free, defined as VAS < 4. For postoperative analgesia the patients received either a continuous morphine infusion 10 mcg.kg.h^{-1} or intermittently morphine 30 mcg.kg^{-1} every 3 hours (IM). In case of inadequate analgesia, defined as VAS ≥ 4, patients received additional morphine (intravenous bolus dose 10 mcg.kg^{-1}).

The NFCS and video-recordings were added to the main clinical trial as new elements. Data generated by the main clinical trial, such as COMFORT 'behaviour' scale and VAS scores as well as bio-physiological data and morphine plasma concentrations were, also used in this additional study.

3.3.2 Subjects

All children who participated in the larger clinical trial in the period between 28-06-97 and 11-08-98 and who were younger than 18 months were included in this study.

The background characteristics of these 37 children are presented in Table 3.1. Most children (76%) were younger than 6 months and most often had undergone an abdominal operation (73%) for a variety of reasons, mostly closure of entero- or colo-stoma (24%). Postoperative mechanical ventilation was necessary in 43% of the children for at least 24 hours and in 8% of the children for 12 to 24 hours.

Table 3.1 Background characteristics

	Number of infants	%
Age group		
- Neonates (0 – 4 weeks)	11	30
- Young infants (4 weeks – 6 months)	17	46
- Infants (6 – 18 months)	9	24
Sex		
- Male	19	51
- Female	18	49
Surgery		
- Abdominal high/low	27	73
- Thoracic (with or without abdominal)	9	24
- Superficial	1	3
Surgical procedures		
- Stoma closure	9	24
- Miscellaneous (diaphragmatic paresis, tumour, teratoma cyst, choledochal atresia, M Hirschsprung)	6	16
- Tracheo-oesophagal atresia	4	11
- Lobectomy	4	11
- Septic gastro-intestinal (intussusception, perforation, ileus)	4	11
- Intestinal atresia/malrotation	3	8
- Congenital diaphragmatic hernia	3	8
- Gastroschisis	1	3
- Nephrectomy	1	3
- Nissen fundoplication	1	3
- Colon interposition	1	3
Postoperative mechanical ventilation		
- None	18	49
- 12 – 24 hours	3	8
- > 24 hours	16	43

3.3.3 Assessment measures

The NFCS was used to provide detailed descriptions of facial activity. This anatomy based coding system focuses on changes in 10 discrete facial actions: i.e. brow bulge, eye-squeeze, nasolabial furrow, open lips, horizontal mouth stretch, vertical mouth stretch, taut tongue, lip purse, chin quiver, and tongue protrusion.

To compare facial activity with changes in pain-related indicators, the facial actions were combined into a single index score of facial activity (NFCS_total). This index was determined by summating the duration of the observed facial actions and dividing the sum by 10. As the observation periods lasted 120 seconds, each facial action could in theory be present for a maximum of 120 seconds. The index could thus range from 0 to 120.

The COMFORT 'behaviour' scale [118] is an adaptation of the original COMFORT scale [107], adding the item 'crying', and removing the physiological items 'heart rate' and 'mean arterial blood' pressure. It thus comprises seven behavioural items, i.e. Alertness, Calmness, Muscle tone, Physical movement, Facial tension, Respiratory behaviour, and Crying. The item Respiratory behaviour is scored only in ventilated patients, Crying in non-ventilated patients. The resulting six items are scored on a 5-point scale, ranging from 1 to 5, so the total score can range from 6 to 30. The COMFORT 'behaviour' scale is reliable and valid for the postoperative pain situation [118]. In the main clinical trial, and thus also in this sub-study, COMFORT 'behaviour' ratings were obtained from trained nurses.

The observational Visual Analogue Scale (VAS) is a horizontal continuous 10-cm line with the anchors 'no-pain' at the left side and 'extreme pain' at the right side. Nurses are asked to indicate on this line the extent to which they think the patient is in pain. Concurrent validity with other postoperative pain measures has been shown [124,125].

Heart rate and mean arterial blood pressure were measured with the Hewlett Packard Component Monitoring System (Böblingen, Germany). The raw data were used to calculate the mean and variability (i.e. standard deviation) of heart rate (HR_mean and HR_var, respectively) and mean arterial blood pressure (BP_mean and BP_var, respectively), for each observational period. Concurrent validity of these physiological indicators has been established with the COMFORT 'behaviour' scale [126].

Catecholamine plasma concentrations of adrenaline and nor-adrenaline were measured by HPLC using fluorometric detection [123].

Plasma concentrations of morphine and its metabolite M6G were assessed using the fluorometric immuno assay method.

3.3.4 Procedures

Procedure: measurements

All study subjects were observed by nurses for 120 seconds on admission to the intensive care unit, and every 3 hours, up to 24 hours postoperatively. During these bedside observations a nurse registered the patient's heart rate and mean arterial blood pressure every 20 seconds; then at the end of the observation period the COMFORT 'behaviour" and VAS scores were assigned.
At the same times, except 15 hours after surgery, continuous video recording was carried out for 120 seconds and providing a full view of the patient's face.
Arterial blood samples for catecholamine and morphine plasma concentrations were taken at the end of surgery, and at 6, 12 plus 24 hours postoperatively.

Video analysis

NFCS coding was carried using video analysis by one primary coder [author JWBP] and one reliable coder [co-author MvD] who both were not aware of the data of the main clinical trial. For each observation period separate video playbacks were used to code each facial action for presence or absence. Computer keyboard entries marked the onset and offset of each facial movement. The beginning of each observation period coincided when nurses started with COMFORT 'behaviour' observations and lasted 120 seconds.

Apparatus

A VHS colour camera (Hitachi VM-S7200E) was used. A copy was made of each videotape and a Vertical Interval Time Code was added (Adrienne Electronics Corporation; Las Vegas, USA). This means that each frame of the video recording was marked with a unique format (Hours: Minutes: Seconds: Frames) enabling selection and coding of specific sections of the videotape. A Videotape Analysis System was used which included: a computer with a Vertical Time Code Reader (16-bits ISA-board), the Observer 3.0 Base Package for Windows and the Observer 4.0 Software Package for video analysis (Noldus: Wageningen, The Netherlands), a video cassette recorder (Panasonic AG 5700) with remote control, stop action and slow motion feedback, and a 50 Hertz monitor.

3.3.5 Reliability

Inter-observer reliability for the NFCS was assessed by using a random selection of 10 video recordings in which the children displayed facial movements. Inter-

observer reliability was calculated for each facial action in accordance with the conservative Facial Action Coding System reliability formula [50,66]. The agreement ranged from 0.84 for vertical mouth stretch to 1.0 for open lips. Nurses were trained in using the COMFORT 'behaviour' scale until they reached the criteria for inter-observer reliability, i.e. when linearly weighted Cohen's kappa for each item exceeded 0.40 [118].

3.3.6 Data analysis

To estimate the association between NFCS scores and COMFORT 'behaviour' and VAS scores, as well as with bio-physiological pain indices and morphine plasma concentrations, Random Regression Modelling (error covariance = unstructured) for continuous data [127] was carried out with SAS 6.12 for Windows. The following covariates were included in all analyses: (linear) time trend, morphine administration condition (CM and IM), age, sex, and mechanical ventilation (yes, no). With respect to age, two dummy variables were created: neonates (yes/no) and young infants (yes/no). Each random regression model incorporated random intercepts and random time slopes.

To obtain a subset of facial actions, Multidimensional Scaling with phi-square measure was carried out with SPSS 9.0 for Windows. Distances ≥1.0 between stimuli co-ordinates were regarded as substantial. Each observational event of 120 seconds was divided into 24 intervals of five-seconds in which the coder identified whether each separate facial action occurred.

To assess whether NFCS-facial activity scores were affected by age, sex, or spontaneous versus mechanical ventilation, Random Regression Analysis was carried out repeatedly with one of these three variables dropped each time [128].

To achieve normal distributions, log transformations (natural logarithm) were carried out on VAS, HR_var, BP_var, adrenaline, and noradrenaline, morphine plus M6G.

3.4 Results

A total of 273 observations were performed. The median values for NFCS_total and the other pain-related behavioural and physiological indices of all these observations are presented in Table 3.2. The median NFCS-total score was highest

in the young infants; with a maximum score of 63.5. The median values for VAS, COMFORT 'behaviour', HR_var, and BP_var were also the highest in the young infants, compared with neonates and infants.

Table 3.2 Median (range) values of the pain-related indicators

	I Neonates Median(range)		II Young infants Median(range)		III Infants Median(range)		Statistical differences
NFCS_total	12	0-38.4	12.5	0-63.5	12	0-46.5	I<II*
VAS	1.3	0.2-6.6	2.5	0.2-9.5	1.3	0.1-6.5	I < II‡; III<II‡
COMFORT 'behaviour'	13.8	6.0-25.0	16.8	6.0-28.0	13.8	7.0-23.0	I < II‡; III<II*
HR_mean	144	113-185	155	110-206	159	104-193	-
BP_mean	52	37-77	78	56-130	80	52-115	I < II‡; II<III‡
HR_var	3.5	0.6-24.5	6.3	0.8-22.4	4.7	0.6-20.8	I < II†; III<II*
BP_var	1.6	0-6.4	3	0.4-14.6	2.4	0.6-9.6	I < II†; III<II*; I<III*
Adrenaline	23	1-378	140	9-1463	336	16-2046	I < II†; II<III†; I<III*
Noradrenaline	313	103-2091	431	106-1425	420	173-950	-
Morphine	21.6	0-218.0	13.2	1.0-109.0	4.7	0-98	-
M6G	18.0	0-85.0	9.0	0-52.0	4.5	0-17.4	-

Notes: Differences between the three age groups were compared using the summary measurement approach. For testing overall differences the non-parametric Kruskal-Wallis test was performed. Mann-Whitney U test was used to assess pairwise differences.
$p < .05$; †$p < .01$; ‡$p < .001$.

3.4.1 Performance of NFCS_total

NFCS_total was significantly ($p < .01$) associated with VAS and COMFORT 'behaviour' scores and also with HR_mean, BP_mean, HR_var, and BP_var (see Table 3.3). No significant associations were found between the NFCS_total scores and adrenaline, noradrenaline, morphine, and M6G plasma concentrations.
The significant associations are depicted in Figure 3.1; only significant estimates (i.e. NFCS_total and covariates) are included (see Table 3.3). This figure shows that when NFCS_total increased from zero to maximum activity score (i.e. from 0 to 60, see Table 3.2), the increase in VAS scores ranged between 1.3 to 4.1. The latter increase was influenced by two factors: the time of postoperative pain assessment and the need for mechanical ventilation. COMFORT 'behaviour' scores increased with 11 points, HR_mean with 35 beats, and BP_mean with 20 mmHg. With respect to HR_var the increase was 2.3 and for BP_var the increase ranged between 4.2 to 7.9. This latter increase was influenced by the age of the children and need for mechanical ventilation. Figure 3.1 further indicates that VAS scores in the early postoperative period were higher than 24 hours after surgery and were

lower in mechanically ventilated, compared with spontaneous breathing children. HR_mean was lowest in neonates. BP_mean and BP_var, were lower in neonates compared with young infants and were also lower in mechanically ventilated children.

3.4.2 Complexity of facial actions structure

Application of Multidimensional Scaling revealed a four-dimensional configuration. Five of the ten facial actions had similar properties and could be grouped together, i.e. brow bulge, eye squeeze, naso-labial furrow, horizontal mouth stretch, and taut tongue. The other facial actions were not interrelated. The five related facial actions were combined into a single index of pain (NFCS_subset). This pain score was determined by summating the duration (total seconds) of the observed five facial actions and dividing the sum by 5. The other facial actions were considered to be independent. For each independent facial action the duration was used as a facial activity score.

These NFCS facial activity scores are presented in Table 3.4. Young infants showed higher NFCS_subset scores than both the neonates and older infants. The median NFCS_subset score for the young infants was 2.4 with a maximum score of 98.7, for the neonates and young infants the median scores were 0.7 and 0, respectively, with maximum scores of 49.4 and 69.0, respectively.

Table 3.4 Median (range) values of the six indices of facial activity derived from Multidimensional Scaling

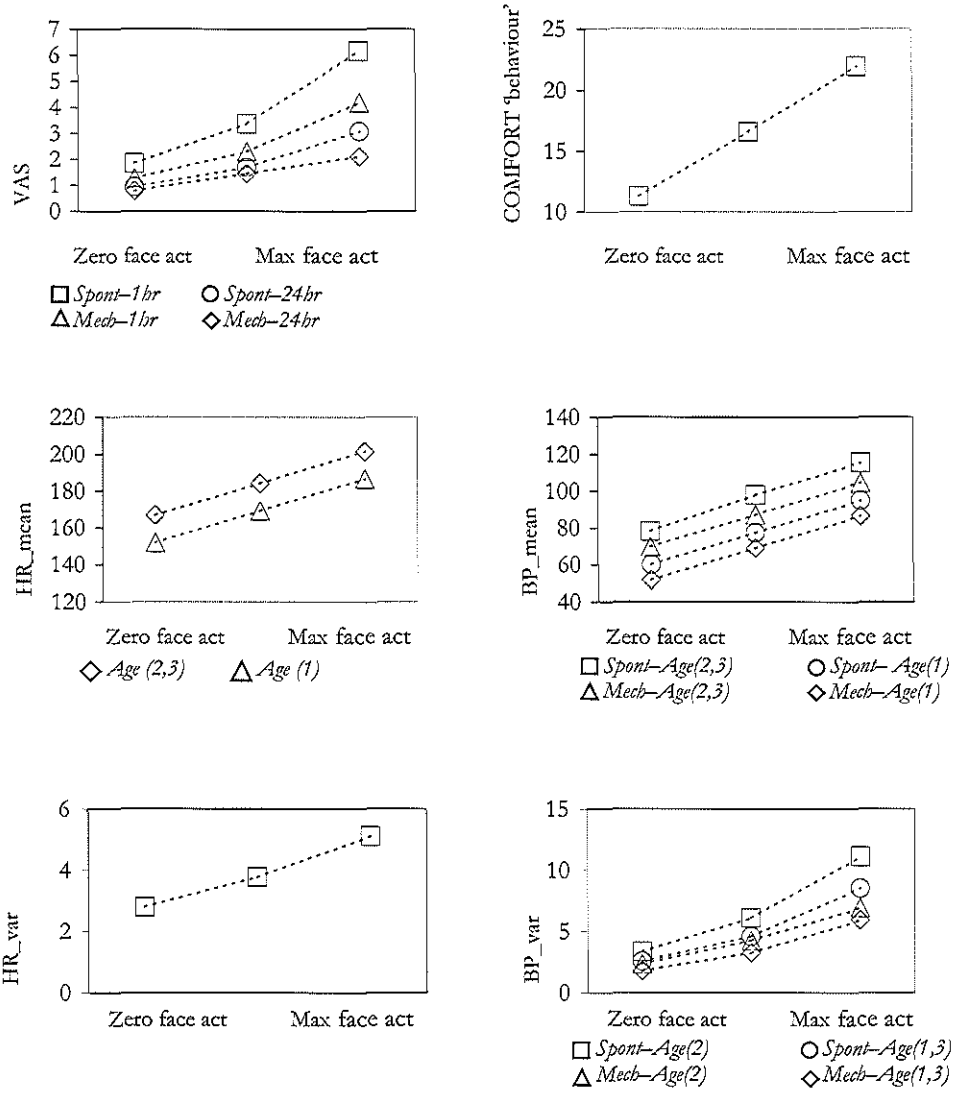
	I Neonates		II Young infants		III Infants		Significant differences
	Median	(range)	Median	(range)	Median	(range)	
Subset $_{BB, ES, NLF, HMS, TT}$	0.7	0-49.4	2.4	0-98.7	0	0-69.0	III<II*
VMS	0	-	0	0-32.7	0	-	I<II; III<II*
TP	0	0-2.3	0	0-38.0	0	0-1.2	I<II*
LP	0	0-1.5	0	0-73.3	0	-	I<II*; III<II*
CQ	0	0-5.4	0	0-63.1	0	0-11.1	I<III†; III<II†
OL	114.5	0-120	109.0	0-120	120	0-120	-

*Notes: Differences between the three age groups were compared using the summary measurement approach. For testing overall differences the non-parametric Kruskal-Wallis test was performed. Mann-Whitney U test was used to assess pairwise differences. BB: brow bulge; ES: eye squeeze; NLF: naso-labial furrow; OL: open lips; HMS: horizontal mouth stretch; VMS: vertical mouth stretch; TT: taut tongue; TP: tongue protruding; LP: lip purse; CQ: chin quiver. * $p < .05$; † $p < .01$; ‡ $p < .001$.*

Table 3.3 Summary of Random Regression Analyses on pain indicators by NFCS_total plus covariates

	ß	$SE_ß$	df	p	ß	$SE_ß$	df	p
	LN(VAS)				COMFORT 'behaviour'			
Intercept	-.11	.47	32	.82	11.21	2.26	32	.00
NFCS-total	.02	.00	166	.00	.18	.02	167	.00
Time	-.03	.01	36	.00	-.13	.04	36	.73
Condition	-.10	.16	166	.53	-.15	.69	167	.83
Neonates	.32	.26	166	.22	.87	1.11	167	.44
Young infants	.34	.20	166	.09	1.11	.86	167	.20
Sex	-.11	.08	166	.19	-.47	.89	167	.50
Ventilation	.38	.19	166	.05	1.51	.84	167	.07
	HR_mean				BP_mean			
Intercept	166.88	13.57	32	.00	61.32	8.69	32	.00
NFCS-total	.58	.07	167	.00	.33	.05	152	.00
Time	-.00	.15	36	.99	.13	.10	36	.19
Condition	-2.57	4.43	167	.56	.00	2.87	152	.99
Neonates	-14.99	6.87	167	.03	-18.15	4.43	152	.00
Young infants	-10.24	5.54	167	.07	-1.01	3.59	152	.78
Sex	-7.66	4.42	167	.09	-4.50	2.87	152	.12
Ventilation	-3.04	4.65	167	.52	8.40	2.94	152	.01
	LN(HR_var)				LN(BP_var)			
Intercept	1.03	.51	32	.05	.22	.33	32	.52
NFCS-total	.01	.00	167	.01	.02	.00	149	.00
Time	.00	.01	36	.93	.00	.01	35	.84
Condition	.03	.16	167	.86	-.02	.10	149	.83
Neonates	-.01	.25	167	.96	-.03	.16	149	.85
Young infants	.25	.20	167	.21	.27	.12	149	.03
Sex	-.17	.16	167	.27	-.10	.10	149	.34
Ventilation	.35	.18	167	.06	.36	.12	149	.00

Notes: Time: time postoperative in hours, range 0–24 hours; Condition: method of morphine administration CM/IM, coded as 1 and 2, respectively; Neonates and Young infants entered as dummy variable no/yes, coded as 0 and 1, respectively; Sex: boys and girls, coded as 1 and 2, respectively; Ventilation: mechanical ventilation versus spontaneous ventilation, coded as 1 and 2, respectively.



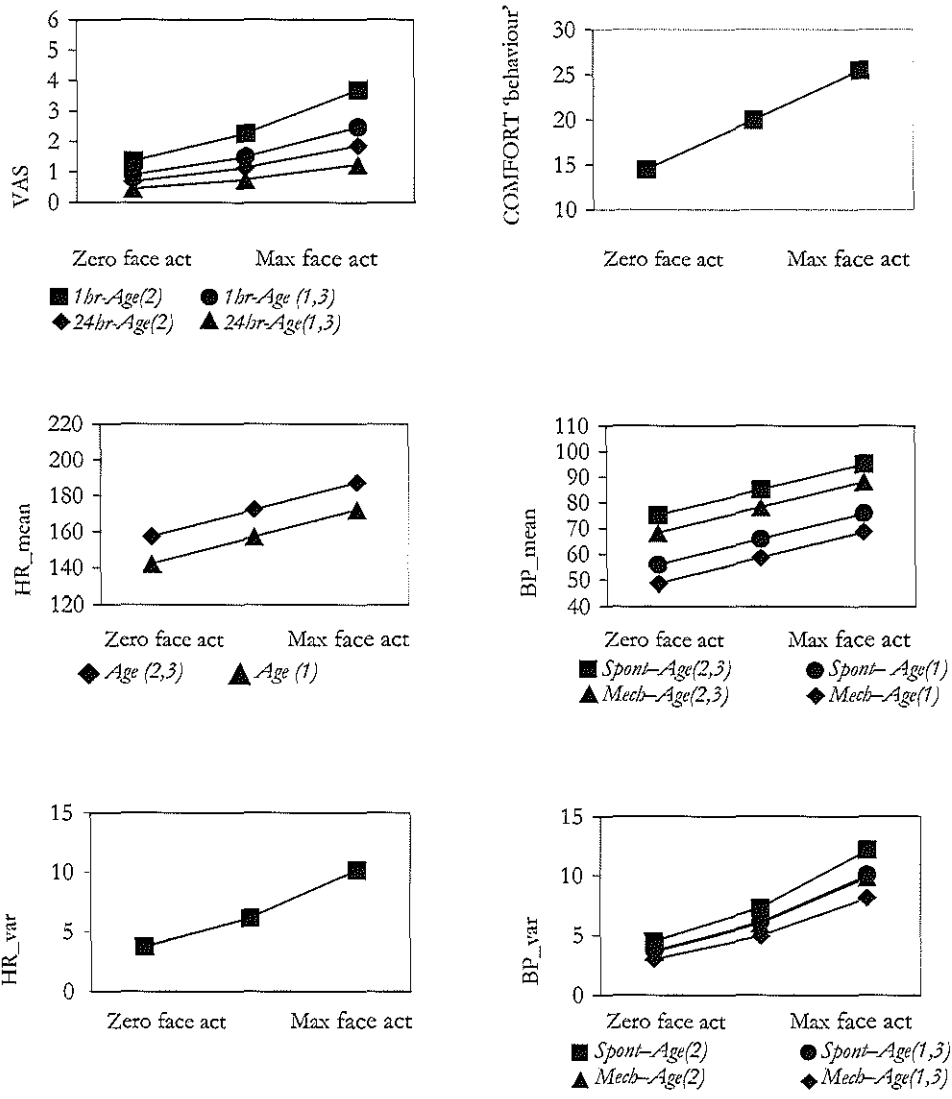
Notes: Only significant estimates (i.e. NFCS_total and covariates) were included (see Table 3.3). Zero face act: NFCS_total score equals 0; Max face act: NFCS_total score equals 60; Spont: spontaneous breathing; Mech: mechanical ventilation, 1 hr: 1 hour after surgery; 24 hr: 24 hours after surgery; age(1): neonates; age(2): young infants; age(3): infants.

Figure 3.1 **Relations between NFCS_total and other pain indicators within the first 24 hours postoperative**

Table 3.5 Summary of Random Regression Analyses on pain indicators by NFCS_subset and independent facial actions plus covariates

	ß	$SE_ß$	df	p	ß	$SE_ß$	df	p
	LN(VAS)				COMFORT 'behaviour'			
Intercept	-.06	.51	32	.90	14.5	1.92	32	.00
Subset $_{BB, ES, NLF, HMS, TT}$	.01	.00	164	.00	.11	.01	165	.00
CQ	-.01	.00	164	.06	-.04	.02	165	.02
OL	.00	.00	164	.02				
Time	-.03	.01	36	.00	-.03	.03	165	.32
Condition	-.09	.16	164	.58	-.56	.63	36	.37
Neonates	.34	.26	164	.20	.19	1.02	165	.85
Young infants	.41	.20	164	.05	1.21	.80	165	.13
Sex	-.12	.08	164	.16	-.21	.32	165	.51
Ventilation	.36	.19	164	.06	.59	.77	165	.45
	HR_mean				BP_mean			
Intercept	157.29	12.81	32	.00	61.06	7.58	32	.00
Subset $_{BB, ES, NLF, HMS, TT}$	.30	.04	166	.00	.20	.03	151	.00
VMS					.38	.20	151	.05
OL	.05	.02	166	.01				
Time	-.03	.15	36	.84	.10	.10	36	.31
Condition	2.76	4.48	166	.54	-.78	2.74	151	.78
Neonates	-15.15	6.95	166	.03	-19.59	4.26	151	.00
Young infants	-9.70	5.59	166	.08	-1.44	3.43	152	.67
Sex	-3.79	2.23	166	.09	-2.06	1.38	151	.14
Ventilation	-3.51	4.72	166	.46	7.19	2.87	151	.01
	LN(HR_var)				LN(BP_var)			
Intercept	1.32	.37	32	.00	.89	.20	32	.00
Subset $_{BB, ES, NLF, HMS, TT}$	.01	.00	166	.01	.01	.00	149	.00
TP	.02	.00	166	.06				
Time	-.00	.01	36	.85	.00	.00	35	.95
Condition	.00	.12	166	.99	-.03	.07	149	.63
Neonates	-.05	.20	166	.81	-.05	.11	149	.67
Young infants	.17	.16	166	.28	.19	.08	149	.03
Sex	-.06	.06	166	.32	-.03	.03	149	.40
Ventilation	.24	.14	166	.09	.21	.08	149	.01

Notes: Time: time postoperative in hours, range 0–24 hours; Condition: method of morphine administration CM/IM, coded as 1 and 2, respectively; Neonates and Young infants entered as dummy variable no/yes, coded as 0 and 1, respectively; Sex: boys and girls, coded as 1 and 2, respectively; Ventilation: mechanical ventilation versus spontaneous ventilation, coded as 1 and 2, respectively.



Notes: Only significant estimates (i.e. NFCS_subset and covariates) were included (see Table 3.5). Zero face act: NFCS_subset score equals 0; Max face act: NFCS_subset score equals 100; Spont: spontaneous breathing; Mech: mechanical ventilation, 1 hr: 1 hour after surgery; 24 hr: 24 hours after surgery; age(1): neonates; age(2): young infants; age(3): infants.

Figure 3.2 **Relation between NFCS_subset and other pain indicators within the first 24 hours postoperative**

The young infants were the only ones who displayed vertical mouth stretch; they also had the highest scores on tongue protrusion, lip purse, and chin quiver. Open lips appears to have a low specificity for pain because this facial action was present during most of the observations and did not differ between neonates, young infants, and infants. To assess whether the NFCS_subset or any individual facial action was related to changes in other pain-related indicators, all indices were entered into Random Regression Analysis. To obtain only the relevant indices, stepwise backward elimination (one by one) was carried out (p-out was set at $p > 0.10$; see Table 3.5).

Of these indices only NFCS_subset significantly estimated VAS, COMFORT 'behaviour' HR_mean, BP_mean, HR_var, and BP_var, respectively. In addition, open lips was related with VAS ($p = .02$) and also with HR_mean ($p = .01$). Vertical mouth stretch was related with BP_mean ($p = .05$). In contrast, chin quiver was negatively related to COMFORT 'behaviour' ($p = .02$). Adrenaline, noradrenaline, morphine, and M6G plasma concentrations were not related to either the NFCS_subset or any of the independent facial actions.

Figure 3.2 demonstrates that the association between NFCS_subset and VAS, COMFORT 'behaviour', HR_mean, BP_mean, HR_var, and BP_var equals that of NFCS_total. For example, when facial activity increased from zero to maximum activity (i.e. from 0 to 99, see Table 3.4), the predicted increase in VAS scores ranged between 0.7 to 2.3. The time of postoperative pain assessment and age of the children influenced this latter increase. COMFORT 'behaviour' scores increased with 11 points, HR_mean with 30 beats, and BP_mean with 20 mmHg. HR_var increased with 6.4 and the increase in BP_var ranged between 5.7 to 7.6. This latter increase was influenced by the age of the children and need for mechanical ventilation.

Furthermore, VAS scores were higher in the early postoperative period than 24 hours after surgery, and were higher in young infants compared with neonates and infants. HR_mean was lowest in neonates. With regard to BP_mean and BP_var, both physiological indices were lowest in neonates and in mechanically ventilated children.

3.4.3 Sensitivity of facial activity in pain and no-pain situations

In 48 of the 273 observations, a VAS score ≥ 4 was assigned. Random Regression Analysis shows that NFCS-total scores and NFCS-subset scores were significantly greater when the subjects were judged to be in pain ($p < .01$) (see Figure 3.3).

The difference in mean facial activity scores in no-pain and pain situations was the highest for the NFCS_subset pain index, compared with NFCS_total, 19.1 and 9.9, respectively.

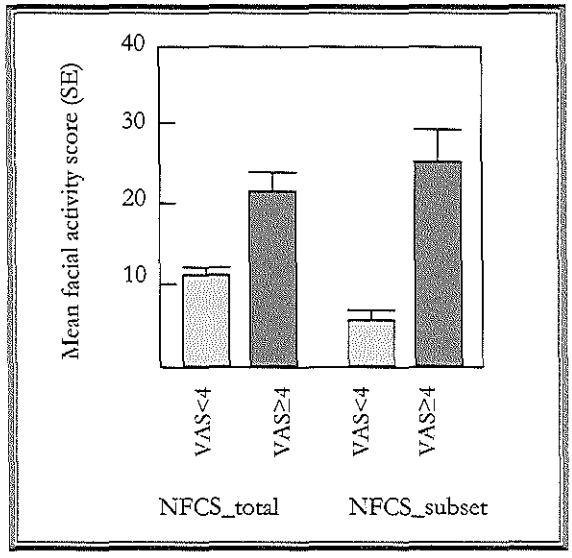


Figure 3.3 Error bars (SE) of facial activity stratified by pain level VAS

3.4.4 Confounding

The estimates of both NFCS_total and NFCS_subset did not change when age, sex or mechanical ventilation was eliminated from the analysis, indicating that the presence and vigour of NFCS facial activity does not depend on age, sex, or mechanical ventilation.

3.4.5 NFCS_total versus NFCS_subset

To examine whether NFCS_subset provided better estimates of the pain-related indicators than NFCS_total, or vice versa, the models of NFCS_total and NFCS_subset were compared by means of the difference in -2 Residual Log Likelihood ratio taking into account the degrees of freedom [129]. No significant differences were found between the models. Thus reducing the NFCS to five facial actions does not lead to a significant worse modelfit, pleading for reducing the NFCS to the content of the NFCS_subset.

3.5 Discussion

We found that the NFCS was sensitive to changes in postoperative pain, and was associated with other behavioural and physiological indicators of pain in neonates and infants following major abdominal or thoracic surgery. Without unfavourable consequences for its sensitivity, the original NFCS can be reduced to a subset of five facial actions, i.e. brow bulge, eye squeeze, naso-labial furrow, horizontal mouth stretch, and taut tongue. These five facial actions are similar to those observed most frequently in acute pain situations. No adjustments have to be made for age, sex, or mechanical ventilation.

Our analyses show that these five facial actions carry the bulk of information and are consistent across acute and postoperative pain situations in infancy. Reducing the NFCS to five facial actions has several advantages, including a reduction in training time, workload, and thereby in coding costs. Moreover, only facial actions that are relevant for pain have to be taken into account. It has been suggested that dropping certain facial actions may increase the risk of missing subtle signs of ongoing discomfort [56]. However, our data show that these extra facial actions do not supply extra information. Open lips was only associated with VAS and HR_mean, probably because of low specificity. Others have also reported this low specificity [116,130]. Chin quiver was found to be negatively related with increasing COMFORT 'behaviour' scores, suggesting no sensitivity and specificity for pain. Lip purse was not associated with any of the pain-related indicators, consistent with previous studies in which it was dropped due to low occurrence [47,49,66]. The role of vertical mouth stretch in pain assessment is not clear yet. In (premature) neonates this facial action has been associated with acute pain, although the sensitivity is small compared with the upper facial actions [47,50,52,56,66,116], which is also the case in healthy term-born neonates [49,50]. For infants aged 2 to 28 months, horizontal mouth stretch as well as vertical mouth stretch were eliminated from the NFCS because of infrequent occurrence [53]. Some studies in adults found vertical stretching of the mouth during pain [131,132] whereas others did not [45,133]. The lower facial actions are more likely to occur during severe pain [45,89,134] or are associated with the clinical syndrome being investigated [131]. In our study the incidence of severe pain was low, which may explain why vertical mouth stretch occurred less frequently than the other five facial actions did.

To gain clinical acceptability of the subset of five facial actions, the validity and clinical utility for postoperative pain should be elucidated. In this study, content validity is established by the fact that brow bulge, eye squeeze, naso-labial furrow, horizontal mouth stretch, and taut tongue together form a facial display of pain. This finding is supported by many commonalties between this configuration and those widely accepted as indices of acute pain in neonates and infants [50,66,134], of postoperative pain in children aged 1 to 6 years [130], and of acute or chronic pain in adults [131-133]. Independent of age, open lips was defined to be part of the configuration. This may be explained by the fact that in these studies the configuration was assessed using only the data following an acute procedure, whereas in our study all observational periods were used.

Concurrent validity of the NFCS was evaluated from the perspective that pain is a multidimensional construct [135]. Strong relationships were found between NFCS_total, NFCS_subset, and COMFORT 'behaviour' scale. Changes in facial activity were paralleled by changes in HR_mean and BP_mean as well as in HR_var and BP_var, and are thus likely to reflect changes in pain. Some other findings were unexpected.

First, independent of (the vigour of) facial activity, VAS scores decreased over time and were lower in mechanically ventilated than in spontaneous breathing children. This raises the question whether VAS scores completed by nurses are valid measures of pain severity [136]. Our findings suggest that nurses, apart from overt behaviour, take into account additional information when assigning VAS scores. It has been demonstrated that nurses use deductive and inductive reasoning to assess whether the infant is in pain. Also characteristics and diagnosis of the infant are taken into account [137-139]. Thus VAS scores may not reflect solely the severity of pain but rather include nurses' confidence that an infant is in pain.

Second, neonates normally have higher resting heart rates than infants have. In this study, however, the opposite was found. Morphine may be responsible as this drug is believed to produce dose dependent bradycardia caused by central stimulation of the vagal nucleus in the medulla. In this study neonates received the same amounts of morphine as (young)infants did, but due to lower clearance and longer elimination half-life [140] the neonates had the highest morphine and M6G plasma concentrations.

Third, no association was found between facial responsiveness and stress hormone concentrations. Others support this observation [141,142]. Facial reactivity and

catecholamine responses appear to have different levels of sensitivity and specificity for pain assessment. Both are blunted by appropriate pain relief [4,76,80,143, 144]. Catecholamine plasma concentrations, however, may be subject to many influences other than pain [145,146] and pain-related behaviours are not always displayed when in pain [120,147,148]. The absence of pain-related behaviour does not imply absence of high catecholamine concentrations elevated by pain [144]. Thus, facial activity and catecholamine responses appear to be relatively independent indices of infants' reactivity to pain.

Construct validity is the most difficult and challenging task in instrument development. The difference in facial activity between pain and non-pain states was greater for NFCS_subset than NFCS_total, suggesting that NFCS_subset is a more specific measure for postoperative pain. In this study we did not examine whether facial activity decreased after the administration of analgesics. Guinsburg et al. [76] did so and demonstrated that morphine decreases NFCS scores in mechanically ventilated premature neonates less than 33 weeks gestational age, as did Scott et al. [80] in neonates 24 to 39 weeks who were undergoing noxious procedures.

A burning question concerns the added value of the NFCS. In contrast with other mainly multidimensional pain assessment instruments the NFCS is very detailed and the facial actions are well defined. The facial configuration of pain can be distinguished from emotional states such as anger, fear, or sadness [63]. In contrast with the other behavioural measures, the child need not be disturbed, for example taking off the blanket, as the face is normally visible. Apart from fine graded video analysis, there is evidence that the NFCS can be used in real time at the bedside [56,57,76], with high inter-observer reliability. Moreover, our findings demonstrate that sex, age, or mechanical ventilation does not affect facial activity. The NFCS facial actions are well defined, in contrast to the global and vague definitions of facial activity and other pain-related behaviours in most of the multidimensional pain assessment instruments. We are aware that the NFCS only includes overt facial movements, while many multidimensional pain assessment instruments, apart from overt behaviours, also include physiological pain indices. However, in two studies the authors concluded that in the postoperative period physiological measures do not add extra information to the behavioural findings and for that reason can be dropped from the instrument [113,118]. For these reasons we suggest that the NFCS may be a good alternative.

In summary, this is the first study demonstrating that the same facial actions that characterise acute pain are also valid indicators of postoperative pain. Content and current validity for the postoperative period were established as well as a first phase of construct validity. This study confirms previous findings demonstrating good reliability of the NFCS. Reducing the NFCS to five facial actions appears to increase the specificity for pain assessment without reducing the sensitivity and validity for detecting changes in pain.

Chapter 4

Major surgery within the first three months of life and subsequent bio-behavioural pain responses to immunisation at later age: a case comparison study

J.W.B. Peters, H.M. Koot, J. de Boer, J. Passchier, J.M. Bueno-de-Mesquita, F.M. de Jong, H.J. Duivenvoorden, D. Tibboel
Submitted

4.1 Abstract

Background Pain exposure during early infancy alters the pain perception beyond infancy into childhood.

Objective To examine if major surgery within the first three months of life in combination with pre-emptive analgesia, alters infants' pain responses to immunisation at toddler's age. Secondly, so assess whether these alterations are greater in toddlers with a larger number of negative hospital experiences.

Design Case comparison study

Methods Two groups of 50 toddlers each were compared: index and control group. All index toddlers had participated within the first three months of their life in a random clinical trial evaluating the efficacy of pre-emptive morphine administration for postoperative analgesia. The control group consisted of matched controls. Pain reactions were recorded at routine immunisation at either 14 months (MMR immunisation) or 3 years and 9 months (DTT immunisation) of age. Outcome measures were facial reaction, coded by the Maximum Discriminative Facial Movement Coding System, heart rate, and cortisol saliva concentration. Negative hospital experiences included: number of operations requiring morphine postoperatively, cumulative TISS scores, and 1) number of days mechanically ventilated, 2) length of stay in ICU, or 3) total hospitalisation days.

Results No differences were found between the index and control group in the facial display of pain, anger, or sadness, or in heart rate, and cortisol concentrations. Intra-group analyses of the index group showed that following MMR the number of operations and total TISS score correlated positively with the facial responsiveness, r =.72 and .61, respectively. Conversely, the number of operations, total TISS score, days of mechanical ventilation, and length of ICU stay correlated negatively with heart rate responses, r = -.58 to -.76. No effect was seen after DTT immunisation.

Conclusion Major surgery in combination with pre-emptive analgesia within the first months of life does not alter pain responses to subsequent pain exposure in childhood. Exposure to (non-)noxious procedures during hospitalisation influences the pain responses for a prolonged period. These, however, diminish after a prolonged period of non-exposure.

4.2 Introduction

It has been well established that the nociceptive pathways, (sub)cortical centres, and neurochemical systems necessary for pain perception and transmission are intact and functional from an early stage of foetal development [149]. However, in new-borns this neural system is still very immature and requires time to mature into childhood. Experimental data suggest that during this "critical period of immaturity" alterations in normally occurring activity patterns, e.g. due to frequent pain exposure, make this system more susceptible to perturbation than at any other time of life [10,11,150,151].

New-borns admitted to neonatal ICUs will be exposed to noxious interventions associated with life-saving high technology care [28]. In (premature) neonates this results in a decreased pain threshold [103,152], and a prolonged period of sensory hypersensitivity [153,154]. These decreases in pain threshold coincide with clinically significant bio-behavioural changes in pain reaction, i.e. in facial reaction, cardiovascular response, and saliva cortisol response [59,75,155-157].

Emerging evidence suggests that these bio-behavioural changes will persist after discharge from the hospital. At corrected ages of 4 and 8 months premature infants born with extreme low birth weight (ELBW) show less facial activity but higher heart rate in response to subsequent pain than term-born infants do [60,158]. This effect is most pronounced in infants who seemed to be sicker at birth, stayed longer in the NICU, experienced more painful procedures, and received greater amounts of morphine [60]. Parents' reports suggest that ELBW neonates at 18 months corrected age are less reactive to everyday pain than term-born toddlers [94]. At the age of 8-10 years, ELBW children rated pictures of medical events as more painful than pictures of psychosocial pain events, unlike term-born peers [159]. In this latter study it was found that, apart from pain sensitivity, also the affective aspects of the pain experience were altered. At the age of 12 to 16 years, however, no significant differences on a pain questionnaire could be demonstrated between ELBW and term-born adolescents [160].

The few reports on healthy, full-term infants' responses to pain over time also suggest prolonged increased pain sensitivity as a consequence of early pain experience. Circumcision without any form of analgesia increased the infants' bio-behavioural pain responses to subsequent immunisation at the age of 4 to 6 months [82,93]. Also, stressful conditions at birth, i.e. assisted delivery versus elective

caesarean section, were associated with increased salivary cortisol responses to immunisation at 2 and 6 months of age [161,162].
At present, the effects of major surgery on the immature nervous system and subsequent pain response in childhood are unknown. In contrast with a decade ago, neonates now receive pre-emptive analgesia for postoperative pain relief [16]. Experiments in animals suggest that appropriate doses of morphine may prevent the development of altered pain sensitivity [10]. In humans, however, it is not known whether effective dosages of morphine diminish the iatrogenic effects of pain.
This is why we set up a case comparison study to answer the question: does major surgery within the first three months of life, under the condition of pre-emptive analgesia, alters the pain responses to immunisation at toddler's age?
We also were interested whether the number of negative hospital experiences during infancy alters pain responses to immunisation at toddler's age. For example, infants born with congenital abnormalities often undergo more than one surgical intervention and are hospitalised for a long period during which they are subjected to many noxious procedures. In contrast with pain following major surgery, many noxious procedures are still carried out without any form of analgesia [25].

4.3. Methods

4.3.1 Design

A prospective case comparison study in a number of community health care centres in the Netherlands was undertaken. This study includes part of a cohort of (young) children who have participated in a large double blind randomised clinical trial, which was carried out in the ICU of the Sophia Children's Hospital, the Netherlands, between April 1996 to August 1999. The aim of the larger trial was to assess the efficacy of pre-emptive continuous versus intermittent morphine administration following major abdominal or thoracic surgery, e.g. stoma closure diaphragmatic paresis, teratoma cyst, choledochal atresia, or M. Hirschsprung. Additional postoperative analgesics were given when nurses assigned Visual Analogue Scale scores $\geq$ 4 cm [123].

4.3.2 Subjects

All children who have participated in this larger trial are prospectively being followed. Those who had to receive either their routine Measles, Mumps, and Rubella (MMR) or Diphtheria, Tetanus, and Trivalent polio (DTT) immunisation between January 1998 to July 2000 and who had participated within the first three months of their life in the larger trial were included in this underlying case comparison study (index children). The immunisation was given at each toddler's own community health care centre.

At each centre matched control toddlers were selected. The match variables were community health care paediatrician and type of immunisation. Inclusion criteria for these matched controls were no history of abdominal or thoracic surgery and undergoing either MMR or DTT immunisation. To prevent selection bias, the toddler closest in time to the immunisation of the index child was selected. When parents refused consent, the toddler next in time was selected.

Exclusion criteria for the index as well as the control group were 1) mental retardation, 2) deafness, 3) blindness, and 4) overt signs of illness at the day of immunisation. The Medical Ethical Committee of this hospital approved this study and informed parental consent was obtained.

According to routine schedules for immunisation in infancy and childhood, the MMR was given at the age of 14 months and the DTT at the age of 3 years and 9 months.

4.3.3 Assessment measures

Alterations in pain responses were assessed from a bio-behavioural perspective. The behavioural responses to immunisation were assessed by the Maximum Discriminative Facial Movement Coding System (MAX) [63,64]. This coding system was selected to assess whether early pain experiences alter pain sensitivity and/or the affective aspects of the pain experience [159]. The MAX is an anatomy based facial coding system that focuses on facial movements (appearance changes (AC)). These ACs are served by three separate branches of the facial nerve and by three relatively independent sets of muscles in three regions of the face: the Forehead/Eyebrows/ Nasal root (FEN region), Eye/Nose/Cheek root (ENC region), and the Mouth/Lips/Chin root (MLC region). The FEN region has 6 ACs, the ENC region 7 ACs, and the MLC has 17 ACs.

Combinations of these ACs represent the presence of pain/distress or discrete emotions, e.g. anger, sadness, or fear [87].
Heart rate (HR) and salivary cortisol concentration were the bio-physiological pain indicators. HR was registered by a pulse oximeter (Ohmeda Biox 3700, Ohmeda, Boulder, Colorado, USA). Cortisol in saliva was assessed using a coated tube radio immuno assay method (Diagnostic Products Corporation, Los Angeles, USA) [163].
Negative hospital experiences were understood to be: total number of minor surgical procedures (i.e. not requiring morphine for postoperative analgesia), major operations (i.e. requiring morphine postoperatively), (N)ICU related procedures as evaluated by the Therapeutic Intervention Scoring System (TISS) [164], total days mechanically ventilated, length of stay in the (N)ICU, and length of hospital stay. TISS is a well-established and validated parameter that can be regarded as a measure of the care and treatment given to a patient [164-166]. TISS scores are daily calculated by the nurses. For this study for each patient all TISS scores were summed up into an index of illness.

4.3.4 Procedures and apparatus

Immunisation

The child was placed in the parent's lap. The parent was instructed to hold the child in a tight hug. The paediatrician, according to a protocol standardised for all participating community health care centres (see Figure 4.1), then gave the immunisation. The protocol did not allow for (non-)pharmacological pain interventions such as EMLA, distraction, or given the toddler control over the situation [167], i.e. choosing the limb and moment of immunisation.

Data sampling

The facial response to immunisation was recorded by an 8 mm video camera (Hitachi VM-H90E). This camera was handheld to get a close up of at least two thirds of the children's face. A same type of camera was put on a tripod to record i.a. the display of the pulse oximeter (see Figure 4.1). To get an impression of each toddler's neutral face, video recordings lasting at least 60 seconds were made before immunisation.

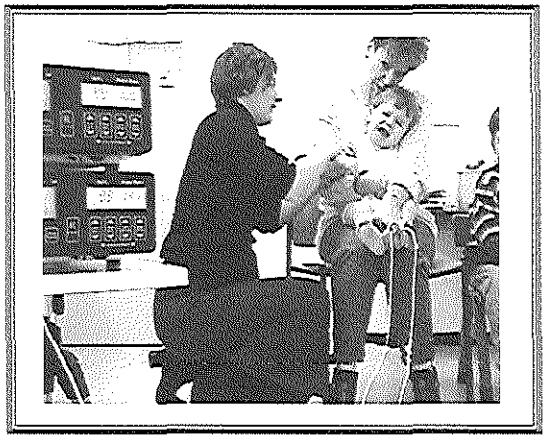


Figure 4.1 Standard immunisation procedure

Two saliva samples were taken, one before and one 20 to 30 minutes after immunisation [156,168]. To stimulate saliva flow, 0.3 ml of a citric acid solution (1.5%) was administered orally. The saliva was sampled with a cotton-bar on which a nonwoven swab was fixed. At least 0.5 ml. of saliva was collected during a maximum period of 5 minutes. After swabbing, saliva was squeezed from the nonwoven swab in a syringe and stored in a vial at -20°C. A duplicate analysis of cortisol was done in each saliva sample. To avoid inter-assay variation, samples of one individual were analysed in the same assay.

Video analysis

MAX and HR were coded by one of the two coders [author JWBP or co-author JBdeM]. With respect to the MAX, video playbacks were used to code separately the brow, eye and mouth regions of the face. One specific code was given for each AC. Coding of the face spanned the period from needle insertion up to 60 seconds thereafter. Several measures as a reaction to immunisation were created: 1) sensory reaction, i.e. duration of pain/distress expression, 2) affective reactions, i.e. duration of anger, sadness, or fear expression, and 3) overall facial response, i.e. duration of sensory plus affective reactions.

Heart rate data were coded from the videotapes on a second by second basis starting from 60 seconds before to 60 seconds after immunisation. These data were used to calculate baseline heart rate (HR_base; i.e. mean heart rate during 30 seconds preceding needle insertion), heart rate after immunisation (HR_mean; i.e. mean heart rate of the 60 seconds after immunisation), and heart rate response (HR_change; i.e. HR_mean minus HR_base).

Apparatus

To mark onset and offset of the ACs in a chronological order and to register heart rate response with exact one second intervals, a copy was made of each videotape and a Vertical Interval Time Code was added (Adrienne Electronics Corporation; Las Vegas, USA). This means that each video frame (picture) was marked with a unique format frame (Hours: Minutes: Seconds: Frames) enabling selection and coding of various segments of the tape. A Videotape Analysis System was used which included: a computer with a Vertical Time Code Reader (16-bits ISA-board), the Observer 3.0 Base Package for windows and the Observer 4.0 Software Package for video analysis (Noldus: Wageningen, The Netherlands), a video

cassette recorder (Panasonic AG 5700) with remote control and stop action and slow motion feedback, and a 50 Hertz monitor.

4.3.5 Reliability training

Inter-observer reliability had previously been obtained by using the MAX manual and training videotape. Each coder independently coded the training tape. Inter-observer reliability was assessed with the master code and was computed following Izard's [87] indications in the MAX manual: agreements / (agreements + disagreements). Reliability was above the required 80%, i.e. 86% and 88% for the two coders.

4.3.6 Data analysis

The facial responses were analysed with the Mann Whitney U-test because of highly skewed data. Multiple linear regression analyses were used to assess differences in heart rates and cortisol concentrations. These analyses were adjusted for MMR or DTT immunisation and with respect to the cortisol data also for circadian rhythm; i.e. time of immunisation. To achieve normal distributions, log transformations (natural log) were carried out on the variables cortisol concentrations after immunisation and changes in cortisol concentrations. Missing values were replaced by predicted mean matching method [169]. Spearman rank correlation was used to assess the association between negative hospital experiences and pain responses.

4.4 Results

Both the index and control group consisted of 50 children, distributed over 44 community health care centres. Thus six centres were visited twice. Patient characteristics are presented in Table 4.1. Overall, 28 children received MMR and 72 the DTT immunisation. Sex did not differ significantly between the index and control group.

With respect to the index group the majority of children had undergone only one major and one minor surgical procedure. The median number of days of hospitalisation and (N)ICU stay was 42 and 13 days, respectively, and the median total TISS score was 115.

With respect to the control group 16 toddlers had stayed in a hospital and 7 of them had undergone minor surgery, mainly because of birth circumstances, e.g.

forceps delivery or vacuum extraction and day care surgery such as adenotomy or myringotomy. The control children were at least 1 year and 6 months old when undergoing these minor surgical procedures.

Table 4.1 Background characteristics		
	Index	Control
Immunisation		
- MMR	14	14
- DTT	36	36
Sex		
- Male	28	23
- Female	22	27
Negative hospital experiences		
- Surgery		
Major surgery§	1 (1-6)	
Minor surgery§§	1 (0-14)	#
- Days hospitalised	42 (5-248)	##
- Days at (N)ICU	13 (2-248)	
- Total TISS score	115 (24-2079)	
- Days mechanically ventilated	2 (0-26)	

Notes: §: opioids were administered for postoperative pain relief; §§: no opioids were administered for postoperative pain relief; #: 7 children had undergone minor surgical procedures, i.e. adenotomy or myringotomy; ##: 16 children had stayed in a hospital; median number of days of hospitalisation was 2, ranging from 1 to 14.

4.4.1 Differences in painfulness between MMR and DTT immunisation

First we assessed whether the two immunisations differed in painfulness. The proportion of toddlers reacting with a pain expression to MMR was greater than that reacting to DTT, 89% and 33%, respectively. Anger and sadness were also more prominently present in the MMR group. In addition, the times of occurrence of each of these facial expressions as well as those of the overall facial response were longer following MMR than following DTT immunisation (see Figure 4.2 and Table 4.2). Because MMR evoked greater pain responses than DTT immunisation we decided to stratify to type of immunisation.

4.4.2 Differences between index and control group

The index and control group did not differ with regard to the presence of pain/distress, sadness or anger expression. Moreover, no differences were found in the overall facial response (see Figure 4.2).

HR_base and HR_mean values are presented in Figure 4.3. No differences in HR_base before immunisation were found between the index and the control group. As expected, HR_base was significantly ($p < .01$) lower in children of the DTT group. Following immunisation, HR_mean was similar between the index and control group. Again this value was significantly lower ($p < .01$) in children of the DTT group. No difference was found in HR_change between the index and control group.

Table 4.2 Number of subjects showing the pain/distress and emotional facial expressions

	MMR (n = 28)	DTT (n = 72)
Pain/distress	25 (89%)	24 (33%)
Sadness	20 (71%)	33 (46%)
Anger	23 (82%)	36 (50%)
Fear	2 (7%)	1 (1%)

Cortisol concentration before immunisation did not differ between the index and control group. No difference was found between the index and control group in the amount of change in cortisol concentration before and after immunisation. Children in the DTT group had lower cortisol concentrations ($p = .02$) than those in the MMR group (see Figure 4.4). After immunisation, no difference in cortisol concentration was found between the index and control group. Again the DTT group had significant lower ($p = .04$) cortisol concentrations.

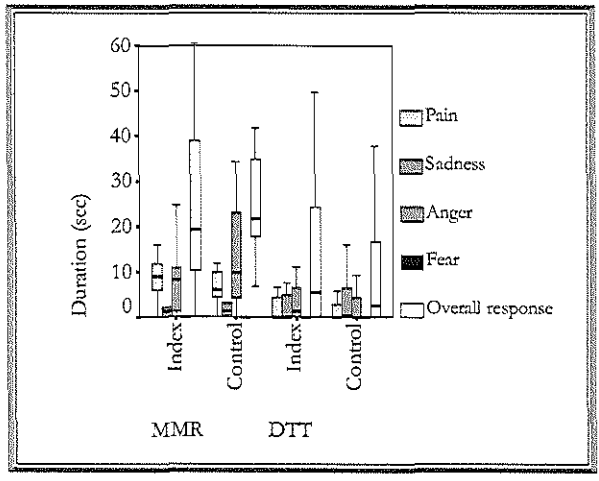


Figure 4.2 Duration of the several displays of pain

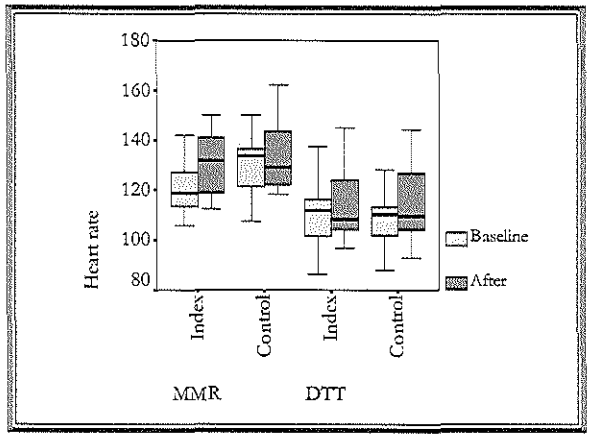


Figure 4.3 Heart rates at baseline and post-immunisation

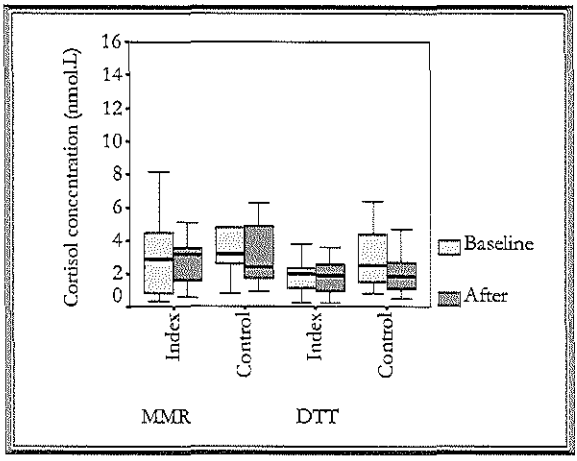


Figure 4.4 Salivary cortisol responses to immunisation

4.4.3 Effects of negative hospital experiences

Significant Spearman rank correlation coefficients between measures of pain sensitivity and negative hospital experiences are presented in Table 4.3. For the index children receiving MMR a greater number of operations and higher total TISS score were associated with increased facial pain/distress and overall facial response. Length of hospital stay, total TISS score, number of operations and days of mechanical ventilation were negatively associated with HR_mean. Total number of operations and length of stay at the (N)ICU were also negatively related with HR_change. No association was found between the other pain measures and number of negative hospital experiences.

For the control children who received MMR, no correlations were found between pain indices and number of days hospitalised or number of minor surgical procedures. For the control children receiving the DTT, only HR_mean was negatively associated with number of minor surgical procedures. Heart rate before immunisation was also negatively associated with number of minor surgical procedures.

Table 4.3 Significant Spearman rank correlations between measures of negative hospital experiences and pain sensitivity indicators

		Pain/distress expression		Total facial activity		HR_base		HR_mean		HR_change	
		MMR	DTT	MMR	DTT	MMR	DTT	MMR	DTT	MMR	DTT
Index group	Major surgery	r = .72 p <.01		r = .66 p = .01				r = -.69 p <.01		r = -.76 p <.01	
	Minor surgery										
	Days hospitalised							r = -.70 p <.01			
	Days at (N)ICU									r = -.64 p = .01	
	Total TISS score	r = .61 p = .02						r = -.58 p = .03			
	Days mechanically ventilated							r = -.63 p = .02			
Control group	Minor surgery						r = -.39 p = .04		r = -.38 p = .04		
	Days hospitalised										

4.5 Discussion

We found that major surgery in combination with pre-emptive morphine administration within the first three months of life does not alter the behavioural and physiological pain response to intrusive immunisation, neither at the age of 14 months, nor at the age of 3 years and 9 months. However, in the index group negative hospital experiences, as evidenced by higher number of major surgical procedures and a higher total TISS score, were positively associated with greater facial pain but with a reduced heart rate response to immunisation at the age of 14 months but not at 3 years and 9 months of age.

Experimental studies in animals have demonstrated that nociception during a distinct period of life changes the neuroanatomical architecture as well as pain sensitivity [150,151,170]. It has been suggested that these alterations may be maximal in rat pups at 6 to 9 days after birth [11]; after 14 days there is still an effect, but less pronounced [150]. The central nervous system (CNS) of a 7-day-old rat functions like that of a full term human neonate, and that of a 14-day-old rat corresponds to that of an infant 1 year of age [149]. The specific mechanisms by which these alterations in neuroanatomy and pain sensitivity are induced have not fully been established. It is assumed that activation of the N-methyl-D-aspartic acid receptor ion-complex produces an increase in intracellular calcium and other second messengers, which stimulate protein kinases and new gene expression [10,11,171]. We therefore theorised that major surgery in early infancy induces structural alterations in children's central neural processing of painful stimuli [82,93].

In this study, however, no differences in pain responsiveness were found between the index and control group. This suggests that appropriate and standardised analgesic protocols following major surgery prevent the development of alterations in pain sensitivity. Others, on the contrary, have found that pre-emptive analgesia, i.e. EMLA before neonatal circumcision, does not prevent infants from developing increased pain sensitivity [83]. EMLA, however, has only mild to moderate analgesic properties for circumcision [97,172]. Oberlander et al. [60] found that infants who had received greater amounts of morphine during their stay at the NICU were more sensitive to pain; whether judicious doses of morphine were administered is not clear. Inadequate doses of morphine (i.e. either too low or too high) also induce neuroanatomical changes, which may give the same outcome as nociception [10].

Our data show that greater numbers of negative hospital experiences alter the pain responses to immunisation at the age of 14 months but not at the age of 3 years and 9 months. A possible explanation is that the plasticity of the young infant's CNS may lead to compensation that minimises permanent changes when allowing sufficient time between previous pain exposure and subsequent pain stimulus. This was evident for the children with few negative hospital experiences receiving MMR and for all who received the DTT immunisation. Experimental studies in animals

also suggest that time "heals" as the altered pain thresholds return to normal values at adult age [170,173].

Another explanation for the absence of associations between negative hospital experiences and pain response at the age of 3 years and 9 months may be that at this age the phenomenon pain has increased in complexity. At this age, factors other than the tissue damage influence children's pain perception and hence their reaction to immunisation. These are cognitive factors such as memory for pain and cognitive development, as well as sociological factors such as family and cultural learning. [174]. A third explanation might be that, in contrast with MMR, the pain following DTT is not severe enough.

An unexpected finding was the diminution in heart rate accelerations with increasing number of negative hospital experiences. From a psychological perspective, heart rate deceleration can be regarded as a process that facilitates environmental intake; heart rate acceleration, on the contrary, filters irrelevant stimuli out that have distraction-value for the performance of internalised cognitive elaboration [175]. From this perspective, it thus appears that with increasing number of negative hospital experiences children become less effective in filtering nociceptive input. On the other hand, the less vigorous acceleration in heart rates can also be regarded as an adaptive response of the body as it reduces, among other things, overall oxygen consumption.

It is obvious that for ethical reasons we were limited in the selection of a representative and standardised pain stimulus. One may question whether immunisation is a valid intervention to assess long-term sequelae. For example, the area of the body to which the immunisation is applied is not the same as the area of perinatal pain exposure. In other studies, however, this intervention was effective to demonstrate alterations in pain response [93,161,162]. A possible explanation for these latter findings is that neuroanatomical changes of the CNS due to nociception are not only restricted to the dorsal horn but also extend to higher levels of brain development [11].

Experimental studies in animals show that repetitive neonatal pain, apart from alterations in pain thresholds, may lead to vulnerability to stress disorders and anxiety-mediated adult behaviour [170]. Grunau et al. [159] found that in former ELBW born children the duration of NICU stay after 8 to 10 years was related to small increases in pain affect ratings in recreational and daily living settings, but not for medical and psychological pain. We, therefore, investigated whether major

surgery or negative hospital experiences would alter the affective dimension of the pain experience. Anxiety was found in three children, of which two had a history of major surgery. However, this emotion was fleeting, as the maximum time of occurrence was no more than two seconds. Moreover, no differences in occurrence were found between the index and control group with respect to the other affective pain reactions, such as anger and sadness. Neither was there a relation between these emotions and number of negative hospital experiences.

In summary, this is the first clinical study demonstrating that major surgery in combination with an appropriate and standardised analgesic protocol within the first months of life does not result in an altered pain response to subsequent pain exposure in childhood. However, it appears that chronic exposure to (non-)noxious stimuli during hospitalisation contributes to an altered pain response. The inherent plasticity of the young infants' CNS after a prolonged period of non-exposure may lead to compensation that diminishes this long-term effect. Whether in humans structural neuroanatomical alterations are still apparent after a prolonged period is not known, but it seems highly likely. New achievements in neuroimagining such as MRI [176] or contrast PET scan [177] might give new clues to answer these intriguing questions.

Part two

Management of pain

Chapter 5

Pre and postoperative application of EMLA cream is not a suitable replacement for caudal block in children undergoing circumcision: a randomised controlled trial

J.W.B. Peters, A.E.E. Meursing, D. Tibboel
Submitted

5.1 Abstract

Background Many boys suffer pain following circumcision even when performed in the hospital.

Objective To evaluate the efficacy of EMLA cream for analgesia in children undergoing circumcision compared with a caudal block and placebo.

Design Random clinical trial.

Methods Sixty-four boys aged 1 to 12 years scheduled for elective circumcision in day care. Circumcision was carried out under standardised general anaesthesia. The efficacy of pre as well as postoperative application of EMLA was compared with that of caudal block, and placebo cream for peroperative as well as postoperative pain relief. Peroperative efficacy parameters were blood pressure, heart rate, respiratory rate, and inspiratory halothane concentration. Postoperative efficacy was assessed by Visual Analogue Scale scores assigned by the nurses, three times in the first 120 minutes postoperatively, and by the patient's need for additional analgesics.

Results Peroperative blood pressure, respiratory rate, and inspiratory halothane concentrations were highest in those who had received placebo. Compared with the caudal block, children who had received preoperative EMLA cream had lower heart rates but higher inspiratory halothane concentrations at the end of surgery. The Visual Analogue Scale scores did not differ between the treatment methods. However, boys who received either EMLA or placebo cream were 6 and 14 times, respectively, more likely to receive rescue analgesics within the first 120 minutes postoperatively compared with the Caudal group. No differences were found in the number of children needing analgesics for the first 24 hours at home.

Conclusion EMLA cream is less effective than caudal block and thus can not be considered a suitable alternative.

5.2 Introduction

In many societies, boys are subjected to circumcision during infancy or childhood. Not only the procedure is painful, boys will suffer pain for some time thereafter [178]. Nevertheless, even when performed in a hospital many clinicians withhold appropriate pain treatment. The common reasons for this obsolete practice are "concern about adverse effects", "not familiar with the technique", and "takes too much time". Other reasons are "procedure does not warrant it", and "infants do not remember pain" [29].

To provide adequate analgesia during and after circumcision, caudal block in combination with general anaesthesia is commonly used. The alternative is Eutectic Mixture of Local Anaesthetics (EMLA), a topical anaesthetic cream containing 2.5% lidocaine and 2.5% prilocaine in water, providing efficient penetration of the local anaesthetics through the skin [72,179]. The use of EMLA cream as an anaesthetic has several advantages: the application technique is simple and does not cause a motor blockade, which takes away a major concern of parents [180]. Secondly, there is no risk of systemic toxicity or pain due to unsuccessful blockade [181].

Several studies in awake neonates have claimed efficacy and safety of EMLA cream for circumcision [72,83,182]. However, in these studies the behavioural and physiological responses during the procedure were significantly greater compared with baseline. Whether these are due to distress from being restrained or due to inadequate analgesia is not clear. Performing circumcision under general anaesthesia may exclude this confounder. No data are available about the efficacy of EMLA during circumcision under general anaesthesia.

With respect to postoperative analgesia the efficacy of topical anaesthesia has been claimed in two studies [183,184] but contradicted by others [185].

The aim of this study was to assess whether application of EMLA cream could adequately replace a caudal block for circumcision.

5.3 Methods

5.3.1 Design

A randomised placebo controlled trial was carried out. Sixty-four boys aged 1 to 12 years with American Society of Anaesthesiologists (ASA) status 1 to 2 [186] and scheduled for elective circumcision in day care surgery were included. Exclusion criteria were a known allergy for local anaesthetics, neurological disorders,

methaemoglobinaemia, a clinically obvious phimosis, and the use of sulphonamides. The Medical Ethical Committee of this hospital approved the study. Parents were informed of the purpose of the trial and their written informed consent was obtained.

5.3.2 Assessment measures

Peroperative analgesia was assessed by cardiorespiratory responses to surgery, i.e. systolic and diastolic blood pressure (SBP and DBP, respectively), heart rate (HR), respiratory rate (RR), and inspiratory halothane concentration. These parameters were recorded at induction of anaesthesia, at incision, and at 2, 5, and 10 minutes thereafter.

The Visual Analogue Scale (VAS) was used to assess differences in postoperative analgesia. The VAS is a horizontal continuous 10-cm line with the anchors 'no-pain' at the left side and 'extreme pain' at the right side. Nurses were asked by placing a mark on this line to estimate the extent to which the child was in pain. The reliability and validity of the VAS for pain assessment has been established [124,125]. The VAS forms the commonly used pain assessment instrument in our clinic.

The number of children receiving rescue analgesics within the first 120 minutes after surgery also served to assess the efficacy of postoperative analgesia.

5.3.3 Study medication

Four different packages were prepared i.e. 1) EMLA pre- and postoperatively (group EE); 2) placebo cream pre- and postoperatively (Caudal group); 3) EMLA preoperatively and placebo cream postoperatively (group EP); or 4) placebo cream preoperatively and EMLA postoperatively (group PE). These packages were provided by ASTRA (Södertälje, Sweden) and contained two tubes of sterile cream marked as either 'preoperative' or 'postoperative' and a sealed envelope which contained an instruction to apply caudal block or not. The EMLA tubes contained a five-gram dose of EMLA cream; the placebo tubes were identical to the EMLA tubes and contained cosmetically identical Miglyil R 012 oil. A computer-generated randomisation was used to randomise these packages; the randomisation code was broken after inclusion of all study children.

5.3.4 Procedure

The patients were allocated to a study package in order of their appearance. Forty-five minutes before circumcision the cream marked 'preoperative' was applied to both the external and internal surfaces of the foreskin of the penis and covered with an occlusive dressing, i.e. a finger condom.

Anaesthesia was completely standardised. Induction of anaesthesia was achieved with intravenous thiopentone 5 $mg.kg^{-1}$ or diprivan 3 to 4 $mg.kg^{-1}$, or by inhalation of halothane in a O_2/N_2O (2:1) mixture followed by maintenance via a face mask with O_2/N_2O (2:1) and halothane. After removal of the cream, any local skin reactions were recorded. The anaesthesiologist opened the envelope to find out whether a caudal block had to be given. Caudal block with bupivacaine 0.25%, 2 $mg.kg^{-1}$ was given to children in the Caudal group only; in all other patients only iodine tincture was applied to the skin at the coccygeal bone. Halothane was continued at 1 MAC (corrected for age), in O_2/N_2O (1:2) by facemask. Incision was carried out after a 15-minute pause. After incision, halothane was decreased in steps of 0.5% every minute as long as SBP, DBP, or HR did not change. Halothane was increased in steps of 0.5% every 30 seconds in case of inadequate anaesthesia, defined as an increase in HR and/or increase in SBP or DBP > 10%, or in case of involuntary movements. All children were anaesthetised by the same anaesthesiologist.

After surgery, the cream marked 'postoperative' was applied to the wound and covered with a bandage.

VAS scores were assigned at arrival at the day care unit, and 60 and 120 minutes after surgery. Alfentanil 10 to 20 $mcg.kg^{-1}$ iv plus paracetamol 30 to 50 $mg.kg^{-1}$ rectally was used as rescue analgesics and administered at nurses' VAS scores ≥ 4 cm. Muscle weakness, vomiting, duration of procedure, and time of urination were recorded.

At discharge all children received a prescription of paracetamol suppositories (90 $mg.kg.day^{-1}$) for the next three days. The day after the operation, parents were asked by telephone about presence of pain, need for pain relief, urination pattern, and any incidence of vomiting.

5.3.5 Data analysis

The summary measurement approach [187] was used in this study, taking the mean cardiorespiratory responses and nurses' VAS scores of each child as outcome variables. Differences across groups were tested using linear regression analysis for

the continuous variables; with age as covariate. In each analysis the Caudal group served as the reference group. The Kruskal-Wallis Test and the Mann Whitney U Test were used in case of highly skewed data. Odds-ratios (95% confidence intervals) were calculated to assess differences in the number of children needing additional analgesics postoperatively.
Before start of this study, sample size had been calculated from pilot data in other children (n = 15) who had received caudal block before circumcision (the gold standard group in this study). The mean SBP at incision was 93, with a standard deviation of 7. To estimate the sample size, the effect size approach was used [188]. An increase of > 10% of the mean was defined as a clinical significant difference, yielding an effect size of 1.3. Using an alpha of 0.05 and a beta of 0.05 yields a sample size of 16 for each group.

5.4 Results

At baseline the four groups were comparable with respect to age and weight. (Table 5.1). Two patients from group EP and two from the Caudal group were excluded from analysis because of unscheduled additional surgery (n = 2), the development of laryngeal spasm at induction (n = 1), and breakfast prior to induction (n = 1).

Table 5.1 Background characteristics

	Group EE n=16	Group EP n = 14	Group PE n = 16	Caudal group n = 14
Age (years)	3 (1-8)	4 (1-10)	4 (1-10)	3 (1-12)
Weight (kg)	16 (10-30)	17.5 (11-37)	16 (9-36)	13.5 (10-59)

Note: Values are median (range).

5.4.1 Peroperative efficacy

Logarithmic transformations were carried out on diastolic blood pressures as well as on inspiratory halothane concentrations. No differences were found between group EE, EP, and the Caudal group in mean systolic and diastolic blood pressures, and respiratory rates (see Table 5.2). However, in groups EE and EP the mean heart rate responses were significantly lower than those in the Caudal group (p = .01 and .04, respectively).
Children who had received placebo (group PE) had significantly greater systolic and diastolic blood pressures, and respiratory responses to circumcision than those in the caudal group (p = .01; .01, and .04, respectively). The mean heart rate responses did not differ between these two groups.

Five and ten minutes after incision, the halothane concentrations were significantly greater in group PE compared with the caudal group (p = .01 and .01, respectively). Ten minutes after incision, children in group EE and PE needed also significantly more halothane than the caudal group (p = .01 and .04, respectively; see Table 5.2).

Table 5.2 **Mean cardiorespiratory responses and inspiratory halothane concentrations during circumcision**

	SBP	Log(DBP)	HR	RR	log (Halothane at 5 min)	log (Halothane at 10 min)
				β (SE)		
Intercept	90.6 (2.6)	1.62 (0.02)	124.1 (4.5)	42.3 (3.4)	.55 (.21)	.03 (.04)
Group EE	-3.6 (2.9)	0.02 (0.03)	-13.1 (4.9)	-1.4 (3.8)	.13 (.23)	.13 (.04)
Group EP	-1.1 (2.9)	0.03 (0.02)	-10.8 (5.0)	1.0 (3.9)	.03 (.24)	.09 (.04)
Group PE	8.2 (2.8)	0.07 (0.02)	5.3 (4.9)	7.9 (3.8)	.54 (.23)	.11 (.04)

Notes: Groups EE, EP and PE were entered as dummy variables in the regression analysis. The regression coefficients in this table are dispersions from the mean cardiorespiratory responses and the mean inspiratory halothane of the Caudal group. Intercept equals the values of the Caudal group.

5.4.2 Postoperative efficacy evaluation

The first 120 minutes after surgery no differences were found between the four groups in mean VAS scores (i.e. scores assessed at arrival at the day care unit, and at 60 and 120 minutes after surgery). However, during this first 120 minutes, rescue analgesics were administered to 8/16, 10/14 and 7/14 of the children of group EE, EP and PE, respectively, compared with 2/14 of the Caudal group. The odds-ratio for rescue analgesics between group EE and the Caudal group was .17 (95% CI: .028 – .997); between group PE and the Caudal group .17 (95% CI: .027 – 1.036). When comparing all EMLA treated children (i.e. group EE plus PE) with those of the Caudal group, the odds-ratio for rescue analgesics was .17 (95% CI .032 – .877). The odds-ratio between the placebo group and the Caudal group was .067 (95% CI: .010 – .443). These findings demonstrate that children who had received EMLA or placebo were 6 and 14 times, respectively, more likely to receive additional analgesics postoperatively, compared with the Caudal group (see Figure 5.1).

No differences were found in the numbers of children needing analgesics at home, i.e. 5/13, 7/11, 6/11 and 5/12 in group EE, EP, PE, and the Caudal group, respectively.

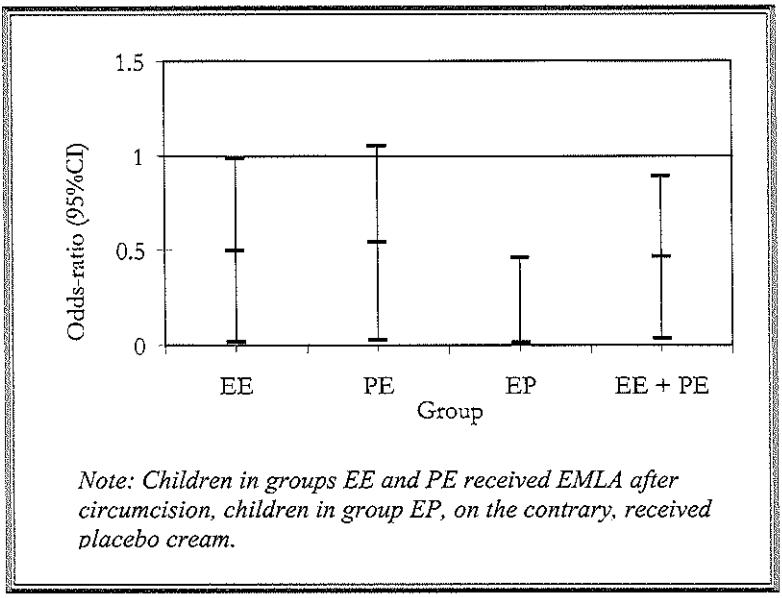


Figure 5.1 Odds-ratios (95% CI) for the need of additional analgesics

5.4.3 Side effects

None of the children had clinical signs of methaemoglobinaemia. One child in each group vomited postoperatively. No urinary retention was observed. Five patients in the Caudal group had clinical signs of muscle weakness as revealed by the anaesthesiologist.

5.5 Discussion

We found that EMLA cream has mild analgesic properties. However, it appears to be insufficient when used alone, because higher halothane concentrations were recorded at the end of circumcision compared with the caudal block. Furthermore, children who had received EMLA for postoperative analgesia were 6 times more likely to receive rescue analgesia during the first two hours following surgery. These findings thus indicate that EMLA is not a suitable analgesic to replace caudal block. A surprising finding was that children in the Caudal group had significantly higher heart rates during circumcision compared with both EMLA groups. We doubt whether this is due to intra-operative stress, because systolic and diastolic blood pressures and respiratory rates did not significantly differ between these groups. Although this is very uncommon observation in this age group, we assume that the

administration of bupivacaine had caused vasodilatation, which was compensated for by an increase in heart rate.

Recently published guidelines suggest that regional anaesthesia and EMLA are both appropriate and effective techniques for circumcision [190,191]. In many cultures, however, circumcision is carried out in neonates or children who are awake. Our findings show that EMLA alone is not completely effective for circumcision, as additional pain relief was necessary to diminish peroperative stress. Others demonstrated that regional and local anaesthesia in awake neonates is more effective than EMLA alone [96,189]. Furthermore, Benini et al. [192] showed that EMLA is only effective for about one third of the circumcision time span. It thus appears that EMLA does not penetrate deeply enough to be very effective during circumcision and that it is contra-indicated when used in neonates or children who are awake.

The efficacy of lidocaine as a topical anaesthetic for postoperative analgesia following circumcision was demonstrated by Tree-Trakarn et al. [183,184]. They found that lidocaine spray (10 to 20 mg), ointment (25 to 50 mg), or jelly (10 to 20 mg) produced similar pain relief as morphine (0.2 $mg.kg^{-1}$) or dorsal penile nerve block. Moreover, also the duration of pain relief did not differ between these techniques. Apart from lidocaine, EMLA contains also prilocaine. As this drug has a faster onset time than lidocaine, we expected that EMLA would be effective directly after application. Nevertheless, EMLA was found to be ineffective for postoperative pain relief compared with caudal block. Lee [185], who compared a two-gram dose of EMLA cream with dorsal penile nerve block, reported similar findings. It could be argued that lidocaine may have induced vasodilatation [193] and subsequent may have increased systemic absorption of the local anaesthetics from the mucosa [194]. This, however, cannot explain both our and Lee's findings as Lee applied similar doses of lidocaine as Tree-Trakarn did, i.e. 50 mg. The ineffectiveness of EMLA for postoperative pain relief may also be due to the fact that both in our and in Lee's study the wound was covered with a bandage. This may have increased the absorption of water from the EMLA cream and thereby decreased penetration into the skin. In the lidocaine studies, on the contrary, either the wound was left open or covered with petroleum jelly and surgical gauze. When the wound is left open, lidocaine jelly forms a thin film of coating over the wound which is similar to protective plastic wound coating [183].

We found that 40 to 60% of the children needed analgesics at home, independent of the analgesic technique used. This problem has been described before by Knight et al. [178], who found that following circumcision about 85% of the children needed additional analgesics for at least 36 hours. Others suggest that this need may even last four days [184]. Inadequate analgesia on the day of surgery may cause behavioural problems which may last up to 3 to 4 weeks, in many cases longer than the pain itself [7,9]. Neonates who suffer pain from circumcision develop an increased pain sensitivity which persists several months after the event [82,93]. It is important, therefore, that analgesia should be continued at home and not stopped at discharge from the hospital.

With respect to circumcision, topical anaesthesia in the form of EMLA applied pre and/or postoperatively can not be considered a suitable replacement for a caudal block.

Chapter 6

Postoperative pain management in children following (adeno)tonsillectomy: efficacy, pharmacokinetics and safety of paracetamol and diclofenac

Based on:
J.W.B. Peters, A.G. Vulto, R. Grobbee, A.E.E. Meursing
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6.1 Abstract

Background There is doubt about the optimal analgesic regimen for postoperative pain management following (adeno)tonsillectomy.

Objective To assess efficacy of paracetamol (acetaminophen) and diclofenac in children aged 3 to 12 years for postoperative pain relief following (adeno)tonsillectomy. Pharmacokinetics and adverse effects of the two agents are also addressed.

Design Systematic review.

Methods A MEDLINE search from 1966 through 1998 was carried out. Language restrictions were not applied.

Results In general, systematic and practise-based research on these drugs for this indication is scarce.

Conclusion Paracetamol 20 $mg.kg^{-1}$ administered orally, 60 minutes preoperatively, and diclofenac 2 $mg.kg^{-1}$ administered rectally at induction seem to achieve satisfactory pain relief in the majority of children during the first few hours postoperatively.

6.2 Introduction

(Adeno)Tonsillectomy ((A)TE) is one of the most common otolaryngologic surgical procedures performed in children, and is routinely done in an ambulatory setting [195]. Both children and physicians describe (A)TE as very painful and traumatic [30].

Following (A)TE, the patient has an open pharyngeal wound that after 24 hours is covered with a granulation membrane, which is replaced by peripheral mucosa within 3 weeks [196]. The child's crying, associated with increased vascular congestion of the head and neck, may segregate the granulation membrane with subsequent bleeding. Furthermore, untreated throat pain may prevent the child from drinking, thereby increasing dehydration risk. It is believed that adequate postoperative pain relief will reduce such sequelae and promote the child's well being.

Analgesics commonly used after (A)TE include opioids, local anaesthetics and nonsteroidal anti-inflammatory drugs (NSAIDs); opioids and local anaesthetics, however, carry the potential risk of (severe) complications. For instance, vomiting, as enhanced in the use of opioids, may induce bleeding. Inhibited laryngeal reflex mechanisms, such as occur with the use of local anaesthetics, may increase aspiration risk. It is our experience that with the commonly recommended NSAID dosages pain relief is inadequate, since many children are still in pain and restless and uncooperative after surgery. This, therefore, was the incentive for reviewing the rationale behind recommended doses of the different analgesics, and this paper reviews the literature from this perspective.

It was observed that the literature contains predominantly studies on paracetamol, diclofenac and ketorolac. Ketorolac is not included in the present review because a significant increase in the incidence of postoperative haemorrhage has recently been reported in children receiving ketorolac before and after (A)TE [197-199], thus precluding its use for this indication. Therefore, this review concentrates on paracetamol and diclofenac, with particular focus on efficacy, pharmacokinetics and tolerability.

6.3 Methods

We aimed to identify all primary published, randomised, clinical trials focusing on pain in post-tonsillectomy in children. A MEDLINE literature search from 1966 through 1998 was conducted. No language restrictions were applied. The keywords

were: (postoperative) pain, tonsillectomy and child(ren) aged 3 to 12 years. After collecting the articles, all the listed references were checked for additional relevant articles.

6.4 Results

This search resulted in a total of 11 original studies. Three had been published in Anaesthesia; [200-202], two in Paediatric Anaesthesia; [203,204], and five in other journals [205-209]. One original study was published in a thesis [210]. Variation in doses, routes, times of administration, and methods of pain assessment prevented meta-analysis.

6.4.1 Efficacy

Paracetamol

Paracetamol is a *p*-aminophenyl derivative that was first introduced into clinical medicine in 1893 as an antipyretic agent. Later, the drug was also used as a mild to moderate analgesic, probably because of its capacity to inhibit the nociceptive response in the central nervous system (CNS) [211].

The therapeutic plasma concentration was defined as 10 to 20 $mg.L^{-1}$ [212]. Whether a dose of 10 to 20 $mg.kg^{-1}$ in children, shown to be effective in reducing fever [213-215], provides sufficient pain relief is not clear. Findings in children following (A)TE have shown variable results. In one study [205], a dose of 10 $mg.kg^{-1}$, administered rectally at the end of the operation, failed to provide sufficient pain relief because 37 of the 42 children experienced pain and needed additional opioids. This finding was corroborated by Gaudreault et al. [206], who concluded that administration of even 20 $mg.kg^{-1}$ paracetamol rectally at the induction of anaesthesia did not prevent immediate postoperative pain, i.e. all 12 children receiving paracetamol needed supplemental doses of opioids.

In three other studies, therefore, higher rectal doses of up to 30 to 50 $mg.kg^{-1}$ were given. However, immediate postoperative pain could not be prevented [207], most children required additional opioids postoperatively [208], or reported too much pain [210]. Even the combination of rectal paracetamol 30 to 50 $mg.kg^{-1}$ with intramuscular fentanyl 1 $mcg.kg^{-1}$ did not improve pain relief [210]. Recent findings [203,216] have demonstrated that not only the timing of administration but also the chosen route may be critical. Mather and Peutrell [203] administered a dose of 20

mg.kg^{-1} paracetamol orally 60 minutes before induction. These authors concluded that a single preoperative dose of paracetamol provides satisfactory pain relief in the majority of children: only nine of their 24 patients needed additional postoperative morphine.
Pharmacokinetic studies have shown that paracetamol 20 mg.kg^{-1} orally provides higher plasma concentrations within a shorter period than a dose of 35 mg.kg^{-1} rectally (see Table 6.1). It thus is reasonable to assume that Mather and Peutrell's findings may have contributed to higher plasma concentrations. Anderson et al. support this hypothesis [209], demonstrating that pain relief after TE was superior when plasma concentrations exceeded 14 mg.L^{-1}. In this study 100 children were randomly assigned to 40 mg.kg^{-1} paracetamol either orally 40 minutes preoperatively or rectally after induction of anaesthesia. Although the authors used double the oral dose that Mather and Peutrell administered, rescue opioids remained necessary in 10 of the 50 children who had received paracetamol elixir compared with 23 of the 50 children of the rectal group.
These efficacy results have to be carefully interpreted as only four studies used validated measurement instruments to assess pain [207-210]. In the other studies rescue opioids were given based on subjective judgement of the nurses. Additionally, in none of these cited studies adequate doses of opioids were pre-emptively administered to prevent children from suffering pain during surgery; only nitrous oxide and inhalation anaesthetics were given. Such suffering can cause "wind-up" and may consequently influence the effectiveness of postoperative pain relief. Therefore, at the induction of anaesthesia opioids should be administered to provide adequate prevention or suppression of pain during surgery and the early recovery period.

Diclofenac

Diclofenac belongs to the phenylacetic acid derivatives and was specifically developed as an anti-inflammatory agent. In contrast to paracetamol, this agent inhibits the prostaglandin synthesis in peripheral tissues, although some of its analgesic action may also be elicited within the CNS [217]. Diclofenac was introduced into clinical medicine in 1970; its efficacy for postoperative TE pain was established in 1984 in adults receiving diclofenac 1 to 3 mg.kg^{-1} rectally after surgery [218].

Watters et al. [200], however, found that diclofenac (1 $mg.kg^{-1}$) administered at induction provided inadequate pain relief in a majority of children, i.e. 52% (i.e. 13 out of 25) needed rescue analgesics at awakening. A lower incidence in the use of rescue analgesics was found by Thiagarajan et al. [201]. In this study, 183 children received, at induction, either diclofenac (1 $mg.kg^{-1}$) intramuscularly or papaveretum (0.2 $mg.kg^{-1}$) intramuscularly; the incidence of rescue opioids was 25 and 16%, respectively. In comparison, Bone and Fell [202], in 60 children, administered at induction either a higher dose of diclofenac (2 $mg.kg^{-1}$ rectally) or a similar dose of papaveretum (0.2 $mg.kg^{-1}$ intramuscularly). Rescue analgesics were not necessary in any of the children at awakening. This finding was corroborated by Mendham and Mather [204], i.e. none of the 25 children who had received diclofenac (1 $mg.kg^{-1}$ rectally) at induction needed rescue opioids at recovery.

These efficacy results are difficult to interpret because study findings were divergent. This might be attributed to the fact that the rescue opioids were given at the discretion of the nursing staff, rather than on guidance of reliable and validated pain measurement tools.

Sufficient pain relief was provided in the majority of the children, although peroperatively no opioids were given in either of the studies. Nevertheless, the combination of diclofenac (1 $mg.kg^{-1}$ rectally) plus fentanyl (0.75 $mcg.kg^{-1}$ intravenously) at induction provides an overall better postoperative pain relief, compared with diclofenac (1 $mg.kg^{-1}$ rectally) alone [204].

6.4.2 Pharmacokinetics

There is generally a relationship between plasma concentrations and effect with considerable intra-individual variation in both kinetics and dynamics. In order to understand the analgesic efficacy and duration of an administered drug, it is useful to study its pharmacokinetics and pharmacodynamic relationships. Relevant data are limited and some information needs to be inferred from research in adults.

Paracetamol

Bioavailability of paracetamol in children is not known. In adults, the oral bioavailability of paracetamol increases with increasing dose [219,220], being 63% after a dose of 7 $mg.kg^{-1}$ and 88% after a dose of 14 and 28 $mg.kg^{-1}$ [219]. Bioavailability of rectally administered paracetamol is, in contrast, not dose-

dependent [221], and is less than after oral administration, ranging from 40 to 93% [221,222].

Because of the poor solubility of paracetamol, the rate of uptake with the rectal route is lower and shows a wider variation compared with the oral route. Moolenaar et al. [221,222] showed that this might be due to various aspects of the formulation. The bioavailability of rectally administered aqueous suspensions ≥ 10 ml, in contrast to suppositories [222], is similar to that found after oral administration, but decreases with decreasing volume of the suspension [221]. For suppositories, the particle size, volume and the nature of the excipient may all have an impact on the pharmacokinetics [213,214,221-224]. For example, bioavailability from lipophilic-based suppositories is greater than that from hydrophilic-based suppositories [213,214]. Moreover, bioavailability from lipophilic-based suppositories increases with finer paracetamol particles as well as with increasing suppository size [221].

In children, the peak plasma concentration (C_{max}) following the administration of paracetamol elixir appears between 30 and 60 minutes [215,220,225-228]. The C_{max} after 12 mg.kg^{-1} paracetamol elixir was 15 mg.L^{-1} [220,225,228]. High plasma concentrations were reached after administration of 20 mg.kg^{-1} paracetamol elixir; 19.6 mg.L^{-1} and 16.5 mg.L^{-1} at 60 and 240 minutes, respectively. When administered rectally, C_{max} is reached after 100 to 180 minutes [206,213,216,227,229,230], which is lower and more erratic. The reported C_{max} after administration of a rectal paracetamol solution of 20 mg.kg^{-1} was 11 mg.L^{-1} [206,230], and with suppositories of 40 to 45 mg.kg^{-1}, it was 13 to 17 mg.L^{-1} [216,231]. Table 6.1 provides an overview of these pharmacokinetic findings.

Plasma protein binding of paracetamol does not occur when therapeutic doses are administered, i.e. when plasma concentrations remain below 60 mg.L^{-1} [232,233]. Paracetamol distributes well through the body, as is reflected by the hypothetical volume of distribution (V_d), which is about 0.7 to 1 L.kg^{-1} in children [220,234,235].

Inactivation of paracetamol occurs through hepatic metabolism and subsequent renal excretion. Only 5 to 10% is excreted in the urine as the parent compound [236,237]. The major pathways of inactivation are sulphation, glucuronidation, and oxidation.

Table 6.1 Paediatric pharmacokinetic studies on paracetamol

Authors	No. of patients	Route	Formulation	Dose ($mg.kg^{-1}$)	T_{max} (min)	C_{max} ($mg.L^{-1}$)	T½ß (min)
Gaudreault et al. [206]	20	rectal	Liquid solution	20	Mean 120	Mean 10.9 SD 1.7	
Cullen et al. [213]	28	rectal	Hydrophilic suppository	Range 15-20	Mean 120	Mean 7.7	
	10	rectal	Lipophilic suppository	Range 15-20	Mean 120	Mean 9.6	
Windorfer & Vogel [215]	12	oral	Elixir	5	Mean 30	Mean 3.7 SD 1.1	
	12	oral	Elixir	10	Mean 30	Mean 11.9 SD 2.5	
	12	oral	Elixir	20	Mean 30	Mean 19.7 SD 4.6	
Anderson et al. [216]	20	rectal	Polythidine glycol base contained in glycogelatine capsules	40	Mean 137 SD 72	Mean 17 SD 7.2	
Wilson et al. [220]	10	oral	Tylenol elixir	9	Mean 42 SD 25.2	Mean 9.3 SD 3.9	Mean 184
	8	oral	Tylenol elixir	12	Mean 33 SD 18.7	Mean 14.6 SD 9.0	Mean 149
Nahata et al. [225]	6	oral	Tylenol elixir	Range 12-14		Range 9.9-19.6	
	4	oral	Tylenol elixir	Range 22-27		Range 18.4-40.1	
Walson et al. [226]	40	oral	Tylenol elixir	10	Mean 54	Mean 6.8 SD 2.2	

Hopkins et al. 1990 [227]	5	oral	Calpol elixir	Mean 14.5 CI 13.9-15.1	Mean 114 CI 75-153	Mean 10.5 CI 9.0-12.0	Mean 138 CI 108-168
	9	rectal	Triglyceride suppository	Mean 15.3 CI 13.0-17.6	Mean 153 CI 77-229	Mean 5.3 CI 2.0-8.6	Mean 156 CI 84-228
Kelley et al. [228]	18	oral	Tylenol elixir	Mean 11.6 SD 0.7	Mean 27	Mean 12.3	
Kollöfel et al. [230]	4	rectal	Propylene/water solution	20	Mean 96	Mean 11.7	
Montgomery et al. [231]	10	rectal	Abenol suppository	45	Mean 180	Mean 13 SD 6	
Birmingham et al. [287]	9	rectal	Hydrogenated vegetable oil base	10	Mean 107 Range 30-120	Mean 5.5 Range 3.5-8.7	
	9	rectal	Hydrogenated vegetable oil base	20	Mean 288 Range 150-480	Mean 8.8 Range 4.1-13.6	
	10	rectal	Hydrogenated vegetable oil base	30	Mean 210 Range 120-300	Mean 14.2 Range 7.5-22.7	

Notes: T_{max}*: time to maximum concentration,*
C_{max}*: maximum plasma concentration,*
$T½\beta$*: elimination half-life,*
SD: standard deviation,
CI: 95% confidence interval

The capacity for sulphation and oxidation appears to be larger in children than in adolescents and adults; both metabolise paracetamol mainly via glucuronidation [236-239]. The overall rate of elimination in children is similar to that in adults [236]. The reported elimination half-life ($t_{½\beta}$) ranges from 1.2 to 2.9 hours [220,225,227,228,240], for both the oral and the rectal route [227]. The clearance is about 5 to 6.6 ml.min.kg^{-1} [220,234].

Diclofenac

Bioavailability of diclofenac after oral or rectal administration is unknown.
In contrast to paracetamol, diclofenac is soluble and therefore rapidly absorbed. In adults, time to maximum concentration (T_{max}) after rectal administration varies from 30 to 60 minutes [241-243]. In children, however, T_{max} and C_{max} are not known after rectal administration. The T_{max} and C_{max}, after intramuscular administration of 1 mg.kg^{-1}, are reported to be between 15 to 45 minutes [244] and 4 nmol.g^{-1}, respectively [244]. This C_{max} is considerably lower than the C_{max} reported in adults (6 nmol.g^{-1}) who had received the same intramuscular dose [244]. With oral administration a similar trend is seen. After oral administration of 1.5 mg.kg^{-1}, the C_{max} was 1.6 mg.L^{-1} [245], while in adults this C_{max} was obtained following administration of 0.8 mg.kg^{-1} [246,247]. This age-related discrepancy in plasma concentration is reflected by a 5-fold higher (0.9 L.kg^{-1}) V_d in children [248] compared with adults (0.17 L.kg^{-1}) [246].
In adults diclofenac is highly protein bound (>99%) [242,243]; the amount of plasma protein binding in children is unknown. Furthermore, in adults 80% of the diclofenac is metabolised [241,242] and is excreted in the form of glucuronide and sulphate metabolites, 65% in urine and for 35% in bile [241,242]. It has been suggested that the renal elimination in children is similar to that found in adults [245]; evidence for this is lacking. The $t_{½\beta}$ in children is reported to be 78 minutes [248], the same as in adults [247,249]. Systemic clearance (CL) in children (7.7 ml.min.kg^{-1}) is twice as high as in adults [244,248].
The greater V_d and CL in children could be due to a lesser degree of protein binding than in adults [250,251]. Because only the unbound drug can cross the blood-brain barrier [243], a lower protein binding in children increases CNS

penetration, thereby possibly inhibiting the nociceptive neurotransmission in the CNS.

6.4.3 Safety

In order to determine whether paracetamol and diclofenac are safe to administer after (A)TE, the nature and frequency of adverse effects have to be taken into account.

Paracetamol

The adverse effects of paracetamol are uncommon at therapeutic doses [252], defined in children as a maximum of 90 mg.kg.day^{-1}, in four to six doses [253,254]. Elevated aspartate transaminase serum values (SGOT), consistent with hepatotoxicity, have been reported after ingestion of > 150 mg.kg^{-1} within 1 day [255-257]. Symptoms include vomiting, anorexia, and epigastric pain. Hepathic encephalopathy may develop, leading to coma and death. Paracetamol plasma concentrations associated with hepatotoxicity are usually > 200 mg.L^{-1} at 4 hours and > 50 mg.L^{-1} at 12 hours after ingestion [255,256].

Hepatotoxicity is rare when therapeutic doses are administered. There have been a total of ten published cases of children diagnosed with hepatotoxic effects following the administration of < 90 mg.kg.day^{-1} for 1 day to 1 week [258,259]. This raises the question whether paracetamol was the sole cause of the observed hepatotoxic reaction [260]. Nearly all these children were febrile and were probably malnourished. According to Heubi et al. [258], reductions in caloric or protein intake combined with multiple doses of paracetamol might lead to reduced amounts of sulphated and glucuronate metabolites. However, paracetamol-associated hepatic failure and extrahepatic organ dysfunction might also be responsible [261].

Paracetamol-induced hepatotoxicity results from accumulation of a reactive intermediate: *N*-acetyl-*p*-benzoquinone (NAPQI). At therapeutic doses, paracetamol is mainly metabolised by sulphation and glucuronidation, whereas the mixed-function oxidase system (cytochrome P450) inactivates small amounts of paracetamol to NAPQI. Normally, NAPQI is detoxified by conjugation with glutathione. In case of (acute) overdose, the sulphation and glucuronidation pathways may get saturated, subsequently increasing the metabolism through the oxidation pathway. If this is not matched by a sufficient supply of glutathione,

NAPQI will bind to hepatocellular proteins thereby causing oxidative stress [262], eventually leading to liver necrosis.
This process can be rectified with the drug *N*-acetylcysteine (NAC), which replenishes glutathione stores, providing a glutathione substitute and slightly enhancing disposition by non-toxic sulphate conjugation [255,263]. The outcome of NAC treatment, however, depends on the paracetamol plasma concentrations and the time interval between paracetamol ingestion and the institution of antidote therapy [264-267].

Paracetamol overdose in children ≤ 12 years of age has a distinctly different pattern than that in adults, i.e. a lesser degree of hepatotoxicity and minor increases in SGOT levels were found in children compared with adults following overdose [233,256,264,268].

Rumack [256] calculated that adolescents and adults were six times more likely to develop SGOT level > 1000 $IU.L^{-1}$ following NAC treatment compared with children ≤ 6 years of age. In another prospective study [268], a total of 2231 children ≤ 12 years and 2637 adults, admitted to a poison control centre for paracetamol overdosage, were evaluated. The adults had considerably more serious consequences from paracetamol exposure than the children did. While prolonged, severe or life-threatening effects were found in 0.3% of the children, in adults this incidence was 5.2%. None of the children died, whereas 10 deaths were reported in the adult population.
One might argue that the lower incidence in children results from differences between the time course of paracetamol ingestion and NAC therapy or from higher toxic plasma levels in adolescents and adults; however, this seems not to be the case. In children ≤ 6 years old, with plasma concentrations > 200 $mg.L^{-1}$ at 4 hours and 50 $mg.L^{-1}$ at 12 hours after ingestion, only 5.5% (i.e. 3 out of 55) developed SGOT levels > 1000 $IU.L^{-1}$. The children with abnormal SGOT levels received NAC treatment > 16 hours after paracetamol ingestion [256]. In adolescents and adults, with plasma concentrations ranging from 200 to 300 $mg.L^{-1}$ at 4 hours and 50 to 75 $mg.L^{-1}$ at 12 hours after ingestion, SGOT levels > 1000 $IU.L^{-1}$ occurred in 11% of those who received NAC therapy within 10 hours after overdose. When NAC therapy was instituted within 10 to 16 or 16 to 24 hours after paracetamol ingestion, 29% and 62%, respectively, developed hepatotoxicity reactions [267,269].

Experiments in mice and rats revealed similar age-related differences. Several possible explanations for these differences have been put forward, e.g. differences in microsomal protein binding [270] or a more rapid glutathione (re)synthesis in the younger animals [271-273] compared with adult animals [270]. The extrapolation of these findings to humans is not simple, because mice and rats differ in the severity of paracetamol-induced hepatic necrosis and the extent of hepatic glutathione depletion [274].

In summary, paracetamol administered in therapeutic doses is a well-tolerated analgesic. Moolenaar's findings [221] from comparing different volumes of paracetamol suspensions, provide indirect evidence that rectal absorption is prolonged but complete. Moreover, a lower bioavailability was associated with a significantly higher ratio of free paracetamol/paracetamol-glucuronide, such as after rectal administration, partly as a result of increased first-pass metabolism. It is unknown whether this first-pass metabolism contributes to glutathione-store depletion.

Diclofenac

Current guidelines recommend a maximum diclofenac dose of 2 to 3 $mg.kg.day^{-1}$ [275]. With this dose, mild and transient adverse effects occur in 30% of adults and adolescents [218,276,277]; this is in the same range as adverse effects on placebo [218,276]. No data are available in children. In clinical practice there is some concern whether or not diclofenac increases the incidence of primary (< 24 hours postoperative) and secondary bleeding (> 24 h postoperative), because prolonged skin bleeding times [278,279] have been reported. Diclofenac inhibits the enzyme cycle-oxygenase, an enzyme essential in platelets for the production of thromboxane A_2, which is an important mediator of platelet aggregation and vasoconstriction. These are processes constituting the primary haemostatic response to vessel injury [278].

Postoperative haemorrhage following (A)TE occurs more frequently in adults than in children and adolescents [280]. Chronic infection of the tonsil may be responsible. Comparison among studies in children, reporting various frequencies of postoperative bleeding, is difficult due to the indistinctness of what is regarded as serious postoperative bleeding. Secondly, findings were not differentiated for

either TE or (A)TE [281-283], although the incidence of postoperative haemorrhage following (A)TE doubles that of TE alone [281].
The reported frequencies of serious primary bleeding in children following TE and (A)TE, requiring operative arrest for haemorrhage, vary between 0 to 0.9% [198,280] and 0 to 2.7%, respectively [199,208,284,285]. The incidence of secondary bleeding, demanding reoperation, was found to vary between 0.9 to 2.5% [198,280] and 0 to 1.03%, respectively [199,284]. These incidence rates comprise only those children who did not receive NSAIDs.
There are three publications involving children that provide incidence figures regarding primary and secondary bleeding after the administration of diclofenac. Thiagarajan et al. [201] in 183 randomised children, found no increased incidence in primary bleeding; only 1% of those who had received diclofenac (1.0 $mg.kg^{-1}$ intramuscularly) at induction had to return to the operating theatre, compared with 2% of those who had received papaveretum (2 $mg.kg^{-1}$ intravenously). In a more recent study [204], primary haemorrhage occurred in 5% (i.e. 3 of 58) of the children who had received diclofenac (1.0 $mg.kg^{-1}$ rectally) at induction compared with 3.2% (2 of 63) who had received tenoxicam (0.4 $mg.kg^{-1}$ intravenously) at induction. Tewary and Curry [286] reviewed 363 records; 232 children underwent (A)TE and 131 had adenotomy alone. All children received 25 mg diclofenac rectally at induction. Primary bleeding was reported in 1.6% (i.e. six of 232) of the patients; four of these patients needed to return to the operating theatre. Between the second and the eighth postoperative day, 1.3% (i.e. four of 232) of the children returned to the hospital with bleeding.

6.5 Discussion

Postoperative pain management (efficacy, pharmacokinetics and tolerability) in children after (A)TE was reviewed in this paper. In general, available data on pain medication for this indication are scarce. The published trials were essentially limited to two drugs: paracetamol and diclofenac. The question is whether it is possible to make a well-founded choice between these two options.
Postoperative pain relief is desirable both from the point of prevention of postoperative complications and the patients' favourable recovery and well being. Adequate pain relief can be achieved with both drugs in most children. As children are required to have an empty stomach at induction, the oral route may be disadvantageous.

To reach adequate pain relief, paracetamol has to be administered orally at least 60 minutes before the procedure in order to obtain adequate plasma concentrations. This may give rise to some residue in the stomach at the time of induction of anaesthesia. When administered rectally, paracetamol should be administered about 3 hours before surgery because of the slower absorption from suppositories; this can be impractical. Diclofenac, however, is rapidly absorbed from the rectum: suppositories can be inserted at induction of anaesthesia, allowing for adequate pain relief once the procedure is over and anaesthesia is terminated.
For paracetamol, findings suggest that adequate pain relief can be obtained with plasma concentrations > 14 $mg.L^{-1}$ [209]. To obtain such plasma concentrations, paracetamol doses of at least 20 $mg.kg^{-1}$ orally [215,225] or > 40 $mg.kg^{-1}$ rectally [209,216] are necessary. However, more data regarding plasma concentration in relation to pain score and anaesthetic technique are required. An initial rectal dose of 40 $mg.kg^{-1}$ is almost half the recommended daily maximum dose of 90 $mg.kg.day^{-1}$, which means there is little room for supplementary doses when the plasma concentration declines after the first dose and pain returns; supplementation of other drugs such as diclofenac may be necessary.
There is, however, evidence that for the short-term use a maximum daily dose not exceeding 150 $mg.kg^{-1}$ may be acceptable, with little risk of developing hepatotoxicity. Unfortunately, the evidence for the efficacious and safe use of paracetamol for this procedure at such dose is not conclusive.
Pharmacokinetic studies on diclofenac in children are scarce; therefore we have to draw conclusions from efficacy studies only. From those studies, 1 to 2 $mg.kg^{-1}$ administered rectally or intramuscularly at induction apparently seems to provide a satisfactory course postoperatively, although the scientific rigor of the published trials is disappointing. Because of some inhibitory effect on platelet aggregation, the major concern when using diclofenac as a postoperative analgesic is the risk of primary and secondary bleeding. Published evidence regarding this adverse effect suggests that there may be a tendency towards a higher bleeding risk. The practical relevance for this indication and these patients is not clear and needs further study.
In conclusion, the available data suggest that adequate postoperative pain relief can be achieved with rectal administration of diclofenac at induction of anaesthesia; the same cannot be said for paracetamol. The timing of a rectal dose of paracetamol is bound to lead to some failures. In addition, the required dose is relatively high,

leaving little scope for additional doses when the analgesic effect diminishes. The risk for developing liver toxicity in some predisposed patients cannot be excluded [257-259].

When the possibility of a small increase in the risk of postoperative bleeding seems of minor clinical significance, rectal diclofenac in a dose of 2 $mg.kg^{-1}$ at induction of anaesthesia appears a better choice for postoperative pain relief after (A)TE in children.

Chapter 7

Patient controlled analgesia in children and adolescents: a randomised controlled trial

Based on:
J.W.B. Peters, I.E.N.G. Bandell Hoekstra, H. Huijer Abu-Saad, N.J. Bouwmeester, A.E.E. Meursing, D. Tibboel
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7.1. Abstract

Background There are no data about the efficacy of Patient Controlled Analgesia (PCA) when a background infusion is added, in comparison with continuous infusion of morphine (CM) only.

Objective To assess the efficacy of PCA (background infusion of 15 mcg.kg.h^{-1} and bolus doses of 15 mcg.kg^{-1} with a lockout interval of 10 minutes) with that of continuous infusion of morphine (20 to 40 mcg.kg.h^{-1}; CM) in terms of pain relief, morphine needs and side effects.

Design Stratified randomised clinical trial.

Methods Forty-seven children aged 5 to 18 years undergoing major elective lower/upper abdominal or spinal surgery were allocated. The magnitude of surgery was assessed by the Severity of Surgical Stress scoring system (SSS). Differences in postoperative pain were determined by children's self-report on the Visual Analogue Scale every three hours up to the second day postoperatively. Side effects compatible with morphine were recorded.

Results No differences were found in pain scores between both groups. However, morphine intake in the PCA group was significantly higher than in the CM group. Moreover, greater morphine intake was associated with higher SSS scores, independent of the technique of administration. Despite a greater morphine intake in the PCA group side effects did not differ between both groups.

Conclusion PCA with a background infusion and CM only provide similar, moderate pain relief. Research is indicated to find out why children do not use the PCA device to diminish their pain.

7.2 Introduction

Patient Controlled Analgesia (PCA) and continuous infusion of morphine (CM) are well-established methods of relieving postoperative pain in children [13,35,288]. Theoretically, PCA meets the prerequisites for effective pain relief, i.e. the opioid dosage is adjusted to the individual requirements and plasma concentrations are maintained at a constant level [289]. This technique can be applied with or without a continuous background infusion (BI).
Studies in children comparing PCA without a BI (PCA-BI) with CM only reported divergent results. In one study PCA reduced the morphine intake without decreasing pain relief [290]. Others demonstrated that PCA increased the morphine needs but also improved pain relief in 9 to 15-year-old children but not in children aged between 5 and 8 years [34,291]. Further evidence indicates that pain relief [35] and sleeping patterns [292] improve when a BI is added to PCA. At present, there are no studies in children that have compared PCA plus a BI (PCA+BI) with CM. We hypothesised that postoperative pain scores on the Visual Analogue Scale of children who receive PCA+BI would be 15 mm lower than those of children treated with CM. Secondly, morphine intake of children receiving PCA+BI does not exceed 25% of the morphine intake of children receiving CM only.

7.3 Methods

7.3.1 Design

A randomised controlled clinical trial was performed. The inclusion criteria were age 5 to 18 years, physical status ASA 1 or 2 [186], and hospitalised for elective lower/upper abdominal or spinal surgery. Postoperatively the children remained in a normal or medium care environment. Developmental retardation, caudal or regional blockade, and inability to feel pain in the area of operation (e.g. meningomyelocele) were the exclusion criteria. The Medical Ethical Committee of this hospital approved this study. Written parental informed consent was obtained before the patients were entered into the study.

7.3.2 Assessment measures

The Severity of Surgical Stress scoring system (SSS) was used to assess the magnitude of the surgical stress. This system takes into account seven factors that contribute to the stress of surgical trauma [119]: blood loss, superficial dissection, visceral trauma, site and duration of surgery, associated stress factors, and cardiac surgery. In this study, SSS scores tend to be relatively low, because cardiac surgery was not included.

The Visual Analogue Scale (VAS) was used to assess differences in postoperative pain. The VAS is a horizontal continuous 10-cm line with the anchor 'no-pain' at the left side and 'extreme pain' at the right side. The children were supposed to put a mark on this line indicating the extent of pain. This scale has proven to be adequately understood by 5-year-old children, and has satisfactory supportive data on validity [293]. The children assigned VAS scores hourly for the first four hours and next once every three hours, except when asleep. Total registration period was the day of surgery and the first two days thereafter.

Morphine intake of the PCA group was registered by the PCA pump, and for the CM group by the nurses' registration on medication charts.

Side effects such as nausea, vomiting, urinary retention requiring bladder catheterization, slow and/or superficial breathing, and itching were assessed and registered by a nurse, every three hours.

7.3.3 Procedure

The day before surgery, children were instructed by one of the first two authors how to use the VAS and the PCA device.

Preoperatively midazolam was administered on an if-necessary basis. Peroperative anaesthesia was standardised; fentanyl was the only analgesic administered. At the end of the operation children were randomly assigned to either PCA+BI or CM. Before randomisation all children were stratified into three age groups (5 and 6, 7 to 11, and 12 to 18 years), based on Piaget's stages of cognitive development [294]. To guarantee equal group sizes, random permuted blocks of four patients' assignment were used [295].

After surgery the anaesthesiologist completed the SSS score system. All patients received morphine until they were pain free. Thereafter, PCA or CM was started. The PCA pump (Graseby 3300®, Watford, UK) was adjusted for bolus doses of 15 mcg.kg^{-1}, with a lockout interval of ten minutes. The BI was set at 15 mcg.kg.h^{-1}. This BI dose represents 50% of average hourly requirements of children receiving PCA for postoperative pain [35,292]. The CM device (Brown perfusor®, Melsungen, Germany) was set between 20 and 40 mcg.kg.h^{-1}, which has been proven to be effective in children [288].

A consultant paediatric anaesthetist visited the patients every morning to check whether the technique was working satisfactorily and to readjust the BI or CM amounts according to the child's pain reports and general condition. PCA bolus dose amounts and the lockout interval were not changed during the study.

7.3.4 Data analyses

The Mann Whitney U-test was used to compare the demographic data and SSS scores between both groups. The serial measurement data, i.e. pain scores and morphine intake, were analysed using the summary measurement approach [187] and stepwise multiple linear regression analysis. For the purpose of the analyses, intervention was coded as 1 for PCA+BI and 2 for CM.

Power analysis was based on the comparison of two independent means [296]. A mean difference of 15 mm was defined as clinically relevant. It was expected that 95% of the mean reported pain scores would range between 0 and 80 mm, resulting in a standard deviation of 20 mm. One-sided testing with an alpha of 0.05 and a beta of 0.20 yielded a sample size of 44 patients. To correct for dropouts it was decided to include at least one more patient in each group.

7.4 Results

Patients' data are presented in Table 7.1. Forty-seven children were included, 24 of them received PCA+BI and 23 CM. Most of them (57%) were between 7 and 11 years of age. There were no significant differences between the groups for age, weight, sex or ethnic background. Surgery was performed for a wide variety of indications, mostly laparotomy of the upper abdomen (n=14), laparotomy of the lower abdomen (n=11), and lumbotomy (n=9) (see Table 7.2).

Type of surgery was equally divided between both groups. No significant differences (median (range)) in SSS or loading dose morphine amounts were found between the CM and PCA group.

Table 7.1 Background characteristics

	5 – 6 years		7 - 11 years		12 - 18 years		Ethnic background		Age (years)	Weight (kg)	Loading dose ($mcg.kg^{-1}$)	SSS
	Male	Female	Male	Female	Male	Female	Dutch	Other	Median (range)	Median (range)	Mean (SD)	Median (range)
PCA group (n = 24)	2	4	7	6	3	2	18	6	8.5 (5-16)	34 (18-71)	117 (70)	8.5 (5-14)
CM group (n=23)	3	0	7	7	1	5	19	4	9.0 (5-18)	31 (17-71)	110 (72)	8.0 (6-16)
Total	5	4	14	13	4	7	37	10				

7.4.1 Pain

The mean pain scores for each child each day (see Figure 7.1) were categorised as mild (< 3 cm), moderate (≥ 3 and < 6 cm), or severe (≥ 6 cm) [35]. On the day of surgery, PCA and CM resulted in mild pain scores in only 32% and 24% of the children, respectively. At days 1 and 2, mild pain scores were obtained in about 50% of the children of both groups (see Figure 7.1). To evaluate the overall efficacy of the PCA and CM techniques, stepwise multiple regression analysis was carried out. Intervention, morphine intake, SSS and age were entered as the predictor variables, and postoperative pain as the outcome variable. None of these variables were statistically significant predictors of reported pain intensity.

7.4.2 Morphine intake

The mean morphine intake for each day in both study groups is presented in Figure 7.2, showing that on all days the PCA group consumed more morphine than the CM group. The overall difference was assessed using multiple regression analysis. A log transformation was carried out on the morphine intake data.

Table 7.2 Distribution of surgical interventions according to expected amount of postoperative pain

Type of Surgery	PCA	CI
Major postoperative pain		
Thoracotomy	Lobectomy (2)	Lobectomy (2)
Laparotomy upper abdomen	Splenectomy (2), Adrenalectomy (1),	Splenectomy (1), Liver-cyst (1), Adrenalectomy (1)
Laparotomy lower abdomen	Gall bladder surgery (1), Bladder surgery (1), Intestinal resection (2)	Bladder surgery (1), Indiana Pouch (1), Intestinal resection (1), Stoma (1)
Other		Nephrectomy (1)
Moderate postoperative pain		
Laparotomy lower abdomen	Ureteral reimplantation (6), Uterus amputation (1)	Ureteral reimplantation (4)
Lumbotomy	Pyeloplasty (1), Partial nephrectomy (2),	Pyeloplasty (3), Partial nephrectomy (2), Elevation urethrostomy (1)
Sternum correction	Pectus excavatum correction (3)	Pectus excavatum correction (2)
Other	Open lung biopsy (1)	
Minor postoperative pain		
Laminectomy	Excision liquor cyst (1)	Excision bone tumour (1)

Note: numbers in parentheses are numbers of cases.

Stepwise multiple regression analysis was carried out. Intervention, SSS, age, and pain were entered as predictor variables. Age and pain, however, were excluded from the regression analysis because of partial F-values of 0.76 and 0.09, respectively. Hence, the final regression model contained only the variables intervention and SSS. Together they accounted for 62% of the variance; the F-value was 34.81 ($p < .01$). The final regression model can be described as: Log (Morphine intake (mcg.kg.h^{-1})) = 3.37 - 0.45 (intervention) + 0.53 (SSS). The 95% CI (p-value) for the two predictors ranged between $e^{-0.57}$ - $e^{-0.32}$ ($p < .01$) and $e^{0..3}$ - $e^{0.7}$ ($p < .01$), respectively. Thus, when controlling for SSS, the morphine intake of children with PCA+BI is about 57% greater than with CM. Moreover, morphine intake increases exponentially with increasing SSS, independent of the technique of morphine administration. No interaction was found between the independent variables.

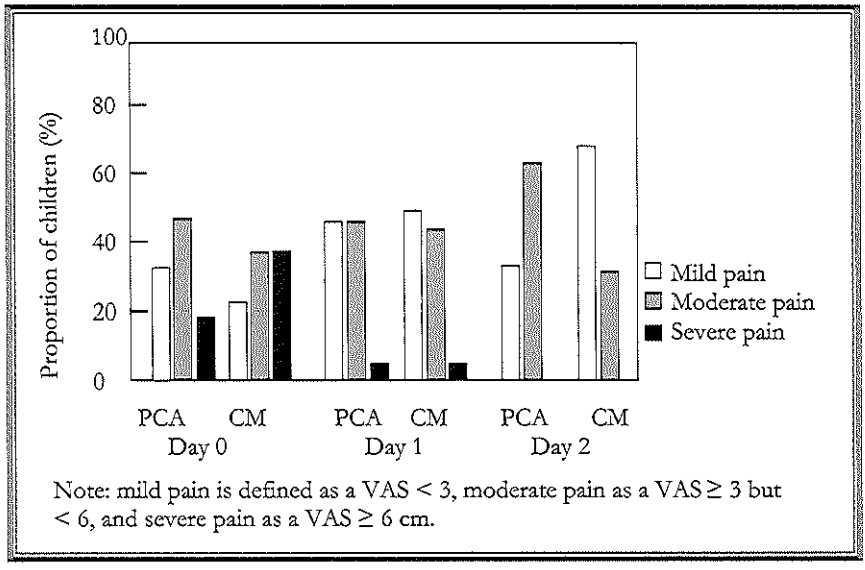

Figure 7.1 Distribution of daily mean individual pain scores

One patient, aged 5 years, receiving PCA, with an SSS of 6 and a morphine intake of 10.77 mcg.kg.h^{-1}, was omitted from statistical analysis, because of standard residual of > 3.0. In this case the BI infusion was stopped as early as day one, and PCA was stopped at day two; this trend was uncommon compared with all other cases.

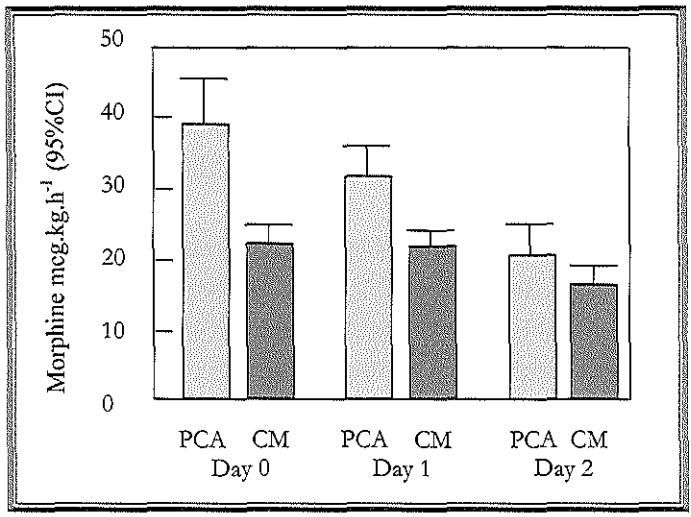

Figure 7.2 Distribution of cumulative daily morphine requirements

7.4.3 Side effects

Nausea and vomiting were noted at least once in 11 (46%) and 8 (33%) patients of the PCA group, respectively; and in 7 (30%) and 4 (17%) children of the CM group, respectively. Itching was observed in two (8%) patients of the PCA group, but in none of the CM group. Urinary retention was found once in each group (4%), and superficial breathing was noted in one (4%) patient of the PCA group. There were no statistically significant differences between the two groups for any of these side effects.

7.5 Discussion

In this study we found that while PCA+BI (15 mcg.kg.h^{-1} with bolus doses of 15 mcg.kg^{-1}) was associated with an increased morphine intake, it did not provide better pain relief than CM (20 to 40 mcg.kg.h^{-1}). Despite a greater morphine intake, PCA+BI did not increase the incidence of side effects. Moreover, morphine intake appeared to be related to the severity of surgical stress.

The incidence of mild pain was low in both groups. An explanation might be that the paediatric anaesthetist could have underestimated the severity of the postoperative pain as shown by the findings in the CM group (see Figure 7.2), i.e. although morphine doses up to 40 mcg.kg.h^{-1} could be administered, only two children received > 30 mcg.kg.h^{-1}. Findings in the PCA group suggest that most children did not use the device to diminish their pain, even when instructed to self-

administer more morphine. Similar observations have been reported in children > 5 years [35,291,297] and in adults [298,299]. It is not clear why children and adults do not self-administer morphine to diminish their pain at a level of sufficient pain relief. Perhaps the use of multimodal analgesia (e.g. addition of paracetamol or NSAIDs) might improve pain relief.

In this study, pain scores did not differ between the groups, although higher morphine amounts were used in the PCA group. We hypothesised that the higher morphine intake is related to the fact that PCA treated children used the PCA device to reduce pain caused by activity due to nursing or physiotherapy. In this study, however, pain was not assessed during activity. Additionally, psychological factors may also be held responsible. For instance, anxiety, neuroticism, depression, family environment as well as the patient's type of locus of control are related to the efficacy of postoperative pain treatment in adolescents and adults [300-305]. Further studies are indicated to assess which of these psychological factors influence effective use of PCA in children.

The use of a BI of 15 mcg.kg.h^{-1} seems to be controversial. Studies in children ≥ 6 years [306,307] and adults [308] indicate that a concurrent BI does neither reduce the frequency of self-administration of morphine nor improve pain relief. However, in a series of studies in children undergoing appendicectomy [306,307,309] a BI of 4 mcg.kg.h^{-1} with bolus doses of 20 mcg.kg^{-1}, and a lockout interval of five minutes, appeared to be the most efficacious adjustment for PCA. PCA without a BI was associated with inadequate sleeping pattern, background infusions > 4 mcg.kg.h^{-1} increased the incidence of side effects, and bolus doses of 10 mcg.kg^{-1} resulted in higher pain scores during activity. Others [35,292], however, did not observe any differences in morphine intake or side effects, when comparing PCA only with PCA+BI. In these latter studies, however, bolus doses were smaller in those receiving PCA+BI. In the present study, the BI of 15 mcg.kg.h^{-1} did not increase the incidence of side effects, compared with CM. Whether a lower BI would decrease the incidence of side effects, without altering pain relief, is not clear and needs to be further investigated.

Another significant finding in our study relates to the positive association between SSS scores and morphine intake. The SSS scoring method, however, was developed for neonates [119]. It was found that SSS scores discriminated between minor, moderate, and severe hormonal stress responses (e.g. plasma adrenaline, noradrenaline). Additionally, increasing SSS scores are associated with greater and

more prolonged changes in hormonal plasma concentrations during and after surgery [119]. In neonates, peroperative administration of opioids decreases the magnitude of stress hormone secretion and improves postoperative morbidity and mortality outcome [4,143]. In adult patients, similar hormonal stress responses and outcome values have been obtained [310,311]. For example, the release of stress hormones is lower after laparoscopic cholecystectomy than after conventional cholecystectomy. In adults the magnitude of this stress response was found to be associated with postoperative morphine requirements [310]. Hence, the neonatal stress response to surgery is the same as in adults. It seems valid, therefore, to adapt the SSS scoring system for children and adolescents. In our study, stress hormones were not determined, which calls for careful interpreting of the SSS scores and increasing morphine requirements.

In children, PCA+BI (15 mcg.kg^{-1} bolus dose + 15 mcg.kg.h^{-1}) and CM of 20 to 40 mcg.kg.h^{-1} provide similar, moderate postoperative pain relief. More studies are needed to clarify why children do not use the PCA device to relieve pain. Psychological characteristics may be involved in this effect and should be taken into account.

Part three

General discussion

Chapter 8

General discussion

8.1 Introduction

The elimination and amelioration of pain is a difficult task. It is aimed at preventing sensitisation [2], physiologic and metabolic disturbances [6], pathological complications [23,312], and long-term sequelae [11].

In children this task is even more difficult, because it is not always clear when they suffer from pain. While children of 4 years and older are able to report their pain themselves, the measurement of pain in neonates and toddlers must of necessity rely on other methods. In the very young the assessment of pain crucially depends upon either behavioural observation, or measuring of physiological indices that are not necessarily related with the pain condition [126]. We are thus often confronted with the dilemma: is pain present or not, and if so, to what degree.

Age-related differences in neurophysiology [149,313], pharmacokinetics [31,314,315], and cognition of pain [167] make the elimination and amelioration of pain even more difficult. For example, due to differences in neurophysiology sensitisation can be produced by repeated tactile stimulation in premature neonates rather than by injury as in older children, and contralateral inhibition is achieved by tactile stimulation rather than by pinch [3]. This means that stimuli that are non-noxious to adults may be perceived as pain by neonates, or may become painful because of sensitisation as a result of prolonged exposure to ICU-related stress-inducing interventions. Neonates who are being chronically exposed to ICU-related (non-)noxious procedures, may thus in fact be subjected to "chronic pain" [98].

Besides, it is not known whether the behavioural and physiological alterations in response to, for example, mechanical ventilation, endotracheal suction, or nasogastric tube insertion should be considered as consequences of either pain or stress. Stress, in this context, is defined as a disturbance in the dynamic equilibrium called homeostasis [23]. Some authors have argued that one should take care not to treat the stress responses but the pain itself, because pain and medically induced stress responses are not always interrelated [316], and the long-term effects of treatment with analgesics in the absence of pain are unknown [19]. Others, however, have expressed a contradictory opinion [144,317].

In this thesis studies are described that provide a contribution to the problem how to assess, to eliminate, and to relieve pain as well as its effects in infants and children. Evidence is given that the face is valuable for assessing whether neonates and infants are in pain. The efficacy of some pain-related interventions as well as

their benefits and consequences at the long term were studied. The validity of the various findings is discussed in the respective chapters. The aim of this general discussion is to integrate the results from the previous chapters with the developments of the last years and to provide suggestions for further research.

8.2 Measurement of pain

This thesis shows that movements in the face resulting from pain can be reliably assessed, not only by the Neonatal Facial Coding System (NFCS) but also by the Maximum Discriminative Facial Movement Coding System (MAX). These facial movements form a specific configuration that is similar for acute and subacute pain and does not change during one's life span. The latter suggests that the facial display of pain is independent of cultural learning, supporting Darwin's hypothesis that several facial expressions are innate and universal [90].

Using the NFCS we demonstrated that changes in facial activity are related with changes in VAS and COMFORT 'behaviour' scores, heart rate, and blood pressure. As expected, several facial actions could be omitted from the NFCS, as these did not contribute to its specificity. Theoretically reducing the number of facial actions increases the applicability of the NFCS.

In this thesis the clinical applicability of the NFCS was not studied, but it has been demonstrated by others who showed that facial movements can be reliably assessed in real time [56,57,76]. Coding facial movements in real time is easier than from videotape. The coder's view in real time is 3-dimensional, making movements such as bulging above and between brows, or bulging of the eyelids, more easy to detect than by 2-dimensional video analysis. Moreover, the coder can move to accommodate changes in the infant's position and the observation is not affected by extraneous factors such as recording quality, e.g. variation in lighting causing shadows. Clinical applicability, however, does not mean clinical utility, because the latter applies to the needs of the individual patient, specially to the basis for decisions regarding medical and nursing management of pain [56].

Clinical utility requires cut-off points that indicate the presence of pain and that provide a basis to adjust analgesic regimens. Theoretically, for postoperative pain the cut-off point could be an NFCS facial activity score of 25 (see chapter 3). However, if a cut-off score is taken as a signal of pain, the irony is then that those who need pain relief most urgently are left unattended. Premature neonates, for example, have a lower pain threshold and have more difficulties in maintaining

metabolic stability [6] than term-born neonates have. Their facial response to noxious stimuli, on the contrary, is less vigorous than that of term-born neonates (see chapter 2). Moreover, although premature neonates are more easily sensitised [3], they are also more often exposed to painful (non-)noxious ICU-related procedures than term-born neonates are [28]. However, in these infants frequent pain exposure diminishes the responsiveness to subsequent pain, but in term-born neonates increases the responsiveness.

The difficulty of defining an optimum cut-off point not only applies to the NFCS but to nearly all observational pain assessment instruments described up till now. Further research should clarify which influencing factors should be taken into account and whether we can adjust for them as is done for instance in the PIPP [116]. In this instrument higher scores are assigned to neonates with younger gestational ages and to those who are asleep in comparison with active-awake ones, independent of their facial activity.

The VAS is a commonly used instrument to assess the severity of pain by observation and self-report. In this thesis a VAS score ≥ 4 signalled the need of extra analgesics. This cut-off score is not empirically based, but agreed upon by clinical experts. Chapter 3 shows that nurses' VAS-scores decreased during the postoperative period, irrespective of the amount of facial activity. It thus appears that the observational VAS is not a measure of pain severity per se, but is associated with nurses' confidence whether a child is in pain or is not. Evidence shows that nurses take additional information such as health, diagnosis, or gestational age into account to assess the presence of pain [137-139]. The question is whether all their assumptions are correct. The observational VAS has the advantage of allowing nurses to adjust for contextual cues and characteristics of the child such as gestational age, pain history, etc. Its disadvantage, however, is uncertainty about the pain behaviours that were actually taken into account and how these were weighed. Combining the NFCS or other observational measures with the VAS may overcome the disadvantages of both instruments.

With regard to the VAS as a self-report measure, findings in chapter 7 show that children and adolescents report pain scores ≥ 4 points, even when they can administer additional morphine themselves by Patient Controlled Analgesia (PCA). This suggests that the VAS cut-off point of 4 is too low and that children may endure more pain before needing additional analgesics. Additionally, we must gain more understanding of what children regard as pain. Not clinical experts, but

children themselves should be asked to define cut-off points on the VAS. Using a faces-scale ranging from 0 to 6, Gauthier et al. [318] demonstrated that children wanted treatment for postoperative pain at a mean score of 3.2 (±1.2). Others [319] found a slightly lower mean treatment threshold of 2.3. While perhaps a VAS ≥ 4 is too low, it prevents the child from developing sensitisation, or physiological and metabolic disturbances, because nurses and clinicians are urged to undertake action at an early stage.

8.3 Management of pain

The attitudes towards procedural pain and minor surgery in children, especially in neonates and infants, have started to alter over the last years [16]. This has resulted in four Cochrane collaborations on neonatal analgesia [182,320-322]. In addition, two international consensus meetings to develop guidelines for routine management of procedural pain and minor surgery in neonates and infants were held recently [190]. The final result is an exhaustive list of all possible interventions (e.g. sucrose in combination with a pacifier, opioids, or local anaesthetics) that may diminish pain responses to a range of noxious procedures, such as heelstick, central line placement, chest tube insertion, or circumcision.

These guidelines aim at improving evidenced-based medicine, i.e. the "conscientious, explicit, and judicious use of current best evidence in making decisions about care of individual patients" [323]. For this reason it is not clear why interventions were suggested without any evidence of their efficacy. Moreover, no recommendations were given on preferable interventions, even when there is enough evidence to do so. For example, sucrose with a pacifier, EMLA, or regional anaesthesia were suggested for circumcision. Sucrose with swaddling reduces cry duration during circumcision but has no positive effect on postoperative cortisol levels [324]. In this thesis (see chapter 5) it was found that EMLA has some analgesic properties for circumcision, as is supported by others [72,83]. However, EMLA alone cannot be considered a suitable replacement for regional anaesthesia. Because children who had received EMLA needed higher halothane concentrations peroperatively and were more likely to receive additional analgesics in the postoperative period compared with caudal block. Others have drawn similar conclusions in awake neonates [96,325,326].

Moreover, apart from systemic analgesics and local anaesthetics, interventions such as sucrose with a pacifier or EMLA are suggested for central line placement or chest tube insertion. Whether these latter two techniques provide adequate analgesia under these conditions is not known. Theoretically, systemic analgesics can also be administered for these procedures. Multiple boluses, however, may lead to adverse side effects, because of the higher plasma concentrations achieved. With the doses adjusted to age and to the amount of pain, the risk of side effects is similar to that in older children and adults [31].

These guidelines demonstrate that clinicians and researchers measure by two standards when dealing with pain relief in infants and children. For instance, interventions that reduce screaming or cursing with about 30% [72] would be considered as unethical, inhuman, and clinically irrelevant in adults. Such interventions, however, are still advised and applied in neonates and infants. For ethical and medical considerations the same standards that are accepted as humane in adults should also be applied in children.

In chapter 3 we found that in neonates and infants pain relief is not always adequate with either continuous infusion of morphine 10 mcg.kg.h^{-1} or intermittent morphine administration 30 mcg.kg^{-1} three hourly. Some children needed additional morphine on the basis of a VAS score ≥ 4 and although NFCS, COMFORT 'behaviour' and VAS scores were relatively low at the pre-defined observation moments, high scores were occasionally measured. In children and adolescents (see chapter 7) we also found that the extent of pain relief differed between the subjects, independent of the technique of morphine administration and total amount of morphine consumption. Others have obtained similar findings [33,35,292,327,328]. It thus appears that there is gross variation in morphine needs with varying results in the efficacy of pain relief.

An explanation for this phenomenon might be that each individual has its own therapeutic analgesic plasma concentrations. Austin et al. [329] for example, demonstrated that the therapeutic analgesic plasma concentration for meperidine varied among patients, i.e. .46 $\pm$ .18 mcg.l^{-1}. Concentrations above .70 mcg.l^{-1} were calculated to provide 100% pain relief. Large variability in morphine pharmacokinetic values between children [327,330-333] is another explanation for the variation in morphine needs. Intra-individual differences in effective plasma concentrations and metabolic differences may be due to heterogeneity in pain

receptors and metabolic patterns. Perhaps DNA analysis may provide some answers.

Another explanation might be that surgical pain is often associated with inflammation [98]. Addition of NSAIDs, such as diclofenac or paracetamol, may help to improve efficacy, and decreases the risk of common side effects. In day-care surgery, high doses of paracetamol [334] and diclofenac [204] were shown to reduce morphine intake and pain scores, respectively, in older children. As found in chapter 6, paracetamol and diclofenac administered in therapeutic doses are well-tolerated analgesics; the recommended maximum daily dose is 90 $mg.kg^{-1}$ and 3 $mg.kg^{-1}$, respectively. There are no data concerning the optimum dosages and their safety following major surgery in small infants. Because data regarding pharmacokinetics, pharmacodynamics, and safety of diclofenac are lacking, this drug is contra-indicated in neonates and infants. Up till now, paracetamol has been demonstrated to be effective and safe in this age group [227,335,336].

8.4 Long-term effects

Neuroanatomy studies in experimental animals show that even a simple skin wound at birth will distort the maturation of the central nervous system, leading to permanent alterations. Nerve damage not only results in the death of sensory nerve cells, but other sensory nerve terminals sprout extensively and occupy areas normally exclusively devoted to the damaged nerve [151]. These new sprouts form inappropriate connections with spinal nerve cord cells in areas far outside their normal termination region [150,337,338], causing the nervous system to become permanently distorted. Parallel to these findings are the observations that rats develop altered pain sensitivity after perinatal pain exposure [339]. It is thought that such changes also occur in humans.

In this thesis (see chapter 4) no differences were found in bio-behavioural pain responses at immunisation between toddlers with a history of major surgery in early infancy and controls. Peroperative and postoperative surgical pain were always managed by opioids in combination with validated pain-related indices. It thus appears that judicious use of analgesics prevents the infant from developing an altered pain sensitivity. On the other hand, it could equally be argued that the inherent plasticity of the young nervous system might lead to compensation that minimises permanent change [10]. Perhaps new achievements in neuroimagining

such as MRI [176] or contrast PET scan [177] may help to disclose this phenomenon.

Findings in this thesis suggest that medically induced pain and stress cause an increase of pain sensitivity lasting beyond the period of exposure and gradually extinguishing after a long period of non-exposure. Others have demonstrated alterations in pain responses and sensitivity in former extreme low birth weight infants [60,94,158] and term-born neonates [82,93] who were exposed to pain in early infancy. These findings, however, are less convincing than those from experiments in animals are [10,151,170,340]. In this thesis as well as in those other clinical studies, alterations in pain were evaluated by bio-behavioural responses to immunisation, or by subjective parents' reports [60,82,93,94,158]. In the animal studies, however, rats were subjected to well-defined pain experiments such as the hotplate test. One may question whether immunisation is the most appropriate intervention to study alterations in pain sensitivity and perception. The stimulus may not be severe enough, or may be influenced by the paediatrician who gives the immunisation, and it does not allow comparison of differences in pain thresholds or pain tolerances. In nearly all studies bio-behavioural measures were used, these, however, do not allow to discriminate between pain sensation and affective feelings. Furthermore, when using immunisation it is very difficult to control for parent, child and doctor interaction effects.

Apart from postoperative situations, neonates and infants also receive morphine during mechanical ventilation or extracorporeal membrane oxygenation. In the latter case, however, morphine administration is aimed at reducing stress rather than pain. Experiments in animals suggest that morphine administration in the absence of pain may also mediate permanent alterations in the CNS [10,341]; these alterations are the same as those resulting from perinatal pain exposure [10]. It is not known whether this applies to humans.

Besides alterations in pain sensitivity, prolonged hospitalisation and repeated medical intervention may also lead to other long-term sequelae, such as clinically greater somatization scores [342]. Other long-term sequelae are thought to be increased anxiety, stress disorders, hyperactivity in combination with attention deficit disorder, and self-destructive disorders [343]. Anxiety disorders or alterations in pain affect, i.e. in anger or sadness reaction patterns, could not be demonstrated in this thesis. However, these emotions were only assessed directly after immunisation and not as the development of psychopathology. Further

studies are indicated to assess the effects of pain, stress, and morphine intake in early infancy.

8.5 Overall conclusions and remaining questions

There is no uniform technique for the measurement of pain in children. Measurement techniques can be classified as self-reports, behavioural observations, or physiological measures. Self-report is regarded as the gold-standard technique in older children. A silver standard appears to be the face, because the facial reaction to pain is the same in acute and subacute pain situations and it allows to distinguish between the sensory and affective dimensions of pain, i.e. pain-related emotions such as anger or sadness. Moreover, the facial display of pain is the same for infants, children and adults.

Under certain conditions the face is worthless for the assessment of pain, for example in case of induced muscle paralysis, excessive sedation, or when the face is excessively plastered to fixate the tube. In the first two instances physiological measures may provide an outcome. The value of autonomic responses in subacute pain situations is not clear and further research is indicated.

Despite substantial evidence that pain can be reliably assessed in the clinical setting, paediatric pain is not routinely assessed in most settings [344]. Such practices lead to randomness and cannot form the basis for the current striving for evidenced-based medicine. Implementation of standardised pain assessment is a more complex activity than simply selecting an instrument. Therefore, research is indicated to define strategies for successful implementation of pain measures.

For ICU-related procedures, or following minor surgical procedures, pain management is often inadequate. When clinical care is aimed at preventing sensitisation, morbidity and long-term sequelae, current best evidence should be used in making decisions which intervention is most effective. For circumcision this means that EMLA is out of the question and is not a suitable replacement for regional anaesthesia. With respect to (adeno)tonsillectomy, paracetamol and diclofenac when given in appropriate dosages and at appropriate times appear to provide adequate pain relief following this surgical procedure in the majority of children. In our clinic a double blind, randomised clinical trial is underway to confirm the conclusions of our review and to assess which of these two analgesics provides better analgesia.

Following major abdominal or thoracic surgery, morphine dosages have to be adjusted to age-related differences in pharmacokinetics. Still the efficacy of pain

relief will be subject of intra-individual differences in pain thresholds and metabolism of analgesics. Recommended analgesic regimens therefore can only be considered as initial guidelines. The study of heterogeneity of pain receptors and metabolism patterns may provide an answer to the question which doses should be administered to a particular patient.
Pain exposure during critical developmental windows may lead to higher pain sensitivity. These appear to diminish after a prolonged period of non-exposure, but more importantly, they can be effectively prevented by the use of judicious analgesics. Further studies are indicated in which subjects are exposed to pain tests that have a high degree of standardisation, i.e. always producing similar pain, having a relation between stimulus and pain intensity, allowing repeatability with minimal temporal effects, and allowing quantification of the different qualities of pain. Integration of neuroimagining techniques such as MRI or contrast PET scan may help to increase our understanding of the long-term effects of tissue damage and pain exposure in early infancy.
While optimal management of stress-inducing procedures such as mechanical ventilation prevents the development of adverse sequelae, it is essential to ensure that the iatrogenic effects of stress are not replaced by the iatrogenic effects resulting from opioid therapy. Other aspects that have to be addressed are the effects of hospitalisation on the development of pathophysiologic disorders, such as emotional and behavioural disturbances, or somatic complaints.

In summary, in the last decade pain management has changed from an intuition-based to an evidenced-based approach. This means that current best evidence should be taken into account, not only to select initial analgesic doses but also to use well-validated pain assessment instruments. Only then we will be able to objectively evaluate the efficacy of treatment and to adjust for intra- and inter-individual differences in analgesic needs. The face is the most promising instrument to achieve this goal. Apart from the short-term effects of pain relief, clinicians should be abreast of the long-term consequences of pain exposure and use of analgesics in neonates and infants.

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Appendices

Summary

In the last decade the knowledge of and attitude towards the management of pain in hospitals have improved significantly. Nowadays, it is generally acknowledged that even neonates and young infants do feel pain and that analgesics should be given before pain appears, i.e. pre-emptively and not on an if-necessary basis when pain is already present. This prevents the development of sensitisation, physiological and metabolic disturbances, pathologic complications, and long-term (behavioural) sequelae.

After more than 10 years of progress, there are still many aspects open for improvement. This can be achieved either by means of improving the methods of pain assessment or by studying the efficacy of analgesics. Both subjects are addressed in this thesis.

The gold standard to assess the presence of pain is what one reports about one's experience. Neonates and young infants lack this ability and for this reason one has to rely on nurses' and clinicians' skills to determine whether they are in pain or not. For this purpose the sensitivity and specificity of the face as a means to communicate pain is reviewed in chapter 2. A MEDLINE and PSYCLIT search from 1966 through 2000 was carried out. It was found that there are two coding systems to objectively code facial movements in neonates and infants: the Neonatal Facial Coding System (NFCS) and the Maximum Discriminative Facial Movement Coding System (MAX). The first was used in 34 of the 38 original studies found. In general, facial movements have only been studied in relation to acute pain, using needle pain as the gold-standard painful event. The facial response to acute pain has good sensitivity and specificity and is characterised by a constellation of seven well-defined facial actions that are different from expressions associated with anger, fear or sadness. Whether the face is of value for the assessment of subacute pain, such as postoperative pain or pain associated with neonatal illnesses, is not known. Chapter 3, therefore, examines the validity of the face, as coded by the NFCS, to assess pain in the postoperative period. A prospective observational study was carried out including 37 neonates and infants. All had undergone major abdominal or thoracic surgery. The NFCS was significantly related with other pain-related indices such as nurses' observational pain scores on the Visual Analogue Scale, COMFORT 'behaviour' scores, heart rate, and blood pressure. No relations were found between NFCS and catecholamine or morphine plasma concentrations. Furthermore, multidimensional scaling revealed that five facial actions form a constellation of pain. These five appeared to predict the pain-related indices as well as the complete NFCS. Moreover, this constellation of pain is similar as the one

defined for acute pain. It was concluded that the reduction of the NFCS to five facial actions increases the specificity for pain assessment without reducing the sensitivity and validity for detecting changes in pain.

Chapter 4 examines whether the administration of pre-emptive analgesia following major surgery prevents neonates and young infants from developing altered pain sensitivity. A case comparison study was carried out. Two groups of 50 toddlers each were compared: index and control group. Characteristics of the index group were major surgery in combination with pre-emptive morphine within the first three months of life. The control group consisted of matched controls. Both groups were subjected to routine immunisation at either 14 months (MMR immunisation) or 3 years and 9 months (DTT immunisation) of age. No differences were found in facial responsiveness, heart rates, or saliva cortisol concentrations between the index and control group. Intra-group analyses of the index group showed that following MMR, children with greater number of negative hospital experiences (e.g. length of stay in the hospital, number of operations, or TISS scores) displayed greater facial activity but less acceleration in heart rates than children with few negative hospital experiences. This effect was not observed after DTT immunisation. We concluded that major surgery in combination with pre-emptive analgesia within the first months of life does not alter pain response to subsequent pain exposure in childhood. However, frequent exposure to negative hospital experiences influences the pain responses to subsequent pain. These effects, however, diminish after a prolonged period of non-exposure.

In many cultures, boys are subjected to circumcision during infancy or childhood. Not only is this procedure painful, boys will suffer pain for some time thereafter. A fair amount of clinicians do not administer analgesics, either because they fear for side effects or because they are unfamiliar with anaesthetic techniques. Chapter 5 therefore examines whether application of the topical anaesthetic EMLA cream can adequately replace caudal block for circumcision. A randomised clinical trial was carried out in 64 boys, aged 1 to 12 years, scheduled for elective circumcision in day care. In this study the efficacy of pre-operative as well as postoperative application of EMLA was compared with that of caudal block and placebo. Circumcision was carried out under standardised general anaesthesia. Those who had received placebo cream suffered most pain during circumcision. Children who had received caudal block needed less halothane during surgery than those receiving EMLA. The first 120 minutes postoperatively, boys who had been given either EMLA or placebo cream were 6 and 14 times, respectively, more likely to receive rescue

analgesics compared with the Caudal group. It was concluded that EMLA cream can not be considered a suitable replacement for caudal block.
There is still doubt about the optimal analgesic regimen for postoperative pain management following (adeno)tonsillectomy. Chapter 6, therefore, reviews the efficacy of paracetamol and diclofenac in children aged 3 to 12 years after (adeno)tonsillectomy. Pharmacokinetics and adverse effects of the two agents are also addressed. A MEDLINE search from 1966 through 1998 was carried out. In general, systematic and practise-based research on these drugs for this indication is scarce. Paracetamol 20 $mg.kg^{-1}$ administered orally 60 minutes preoperatively, paracetamol 40 $mg.kg^{-1}$ administered rectally 2 to 3 hours preoperatively, and diclofenac 2 $mg.kg^{-1}$ administered rectally at induction seem to achieve satisfactory analgesia in the majority of children during the first few hours postoperatively. Evidence shows that morphine requirements in children following major surgery are also subjected to large intra-individual differences. Patient Controlled Analgesia is a technique that meets the prerequisites for effective pain relief, i.e. the opioid dosage is adjusted to the individual requirements, and plasma concentrations are maintained at a constant level. Chapter 7 examines the efficacy of PCA (background infusion of 15 $mcg.kg.h^{-1}$ and bolus doses of 15 $mcg.kg^{-1}$ with a lockout interval of 10 minutes) with that of continuous infusion of morphine (20 to 40 $mcg.kg.h^{-1}$) in terms of pain relief, morphine needs, and side effects. A stratified randomised clinical trial was carried out. Forty-seven children aged 5 to 18 years undergoing major elective lower/upper abdominal or spinal surgery were allocated. No differences were found between both groups in pain scores as assessed by self-report using the Visual Analogue Scale. However, morphine intake in the PCA group was significantly higher than in the CM group. Greater morphine intake was also associated with higher surgical stress, independent of the technique of administration. Despite a greater morphine intake in the PCA group side effects did not differ between both groups. It was concluded that both techniques appear to provide similar pain relief when in rest. Research is indicated whether this also holds good during activity such as nursing, therapy, or playing.
Chapter 8 discusses the findings of this thesis in relation with the developments within the field of pain assessment in neonates, infants and children. Theoretical reflections are addressed and implications for further research are given.

Samenvatting

In de laatste tien jaar zijn de kennis en attitude die ten grondslag liggen aan de visie op pijn en de bestrijding daarvan bij kinderen structureel veranderd. Het wordt onderkend dat ook pasgeborenen pijn kunnen voelen en dat pijn de kans op morbiditeit en mortaliteit vergroot. Tevens is algemeen erkend dat pijnbestrijdende middelen gegeven moet worden voordat de pijn optreedt. Deze strategie, ook wel "pre-emptive analgesia" genoemd, voorkomt behalve overgevoeligheid voor pijn, ook het optreden van fysiologische en pathologische complicaties. Tevens vermindert zij de hoeveelheid pijnbestrijdende middelen en mogelijke veranderingen in de pijngevoeligheid alsmede gedragsproblemen op de lange termijn.

Na meer dan tien jaar van vooruitgang ondergaan kinderen die op de afdeling neonatologie of de intensive care liggen nog steeds veel pijnlijke procedures zonder enige vorm van pijnbestrijding, zoals de hielprik, het inbrengen van thorax drains of centrale lijnen. In veel ziekenhuizen laat de pijnbestrijding bij besnijdenis en amandelknippen te wensen over. Na grote operaties blijkt de behoefte aan morfine te variëren, tussen verschillende kinderen alsmede per kind. De vraag is dan ook hoe kan worden ingespeeld op deze verschillen in behoefte aan analgetica teneinde adequate pijnbestrijding te bewerkstelligen. Een andere vraag is of bij pasgeborenen de weefselbeschadiging die gepaard gaat met operaties, het ondergaan van pijnlijke procedures en het krijgen van pijnmedicatie consequenties hebben voor de ontwikkeling van de pijnbeleving en gevoeligheid op latere leeftijd.

Dit proefschrift behandelt onderzoek naar pijnmetingen bij pasgeborenen en baby's. Tevens wordt in dezelfde leeftijdsgroep onderzoek beschreven naar mogelijke lange termijn effecten van grote operaties op latere leeftijd. De laatste hoofdstukken betreffen studies naar de effectiviteit van enkele pijnbestrijdingsmethoden na kleine en grote operaties bij peuters, kleuters en kinderen.

Over het algemeen wordt rapportage van de patiënt zelf als de beste methode gezien om de aanwezigheid van pijn te achterhalen. Pasgeborenen en baby's kunnen dit niet, en zijn voor een goede pijnbestrijding afhankelijk van de vaardigheden van verpleegkundigen en artsen die hun gedragingen interpreteren. Onderzoek toont aan dat ouders en verzorgenden met name het gezicht gebruiken om te bepalen of pijn aanwezig is. De sensitiviteit en specificiteit hiervan wordt beschreven in hoofdstuk 2; voor dit doel werd een systematisch literatuur-onderzoek uitgevoerd. Hiervoor werden o.a. de databestanden MEDLINE en

PSYCLIT geraadpleegd. Alle beschikbare literatuur die tussen 1966 en 2000 verschenen is, werd opgenomen. In totaal werden er 38 publicaties gevonden. Er bestaan twee coderingsinstrumenten om bewegingen in het gezicht op een objectieve wijze te coderen, dit zijn de Neonatal Facial Coding System (NFCS) en de Maximum Discriminative Facial Movement Coding System (MAX). In 34 van de 38 gevonden studies werd de NFCS gebruikt. Geconcludeerd werd dat pasgeborenen en baby's bij het ondergaan van pijnlijke procedures zoals een prik, reageren met een specifieke mimiek. Deze bestaat uit gefronste wenkbrauwen, dichtgeknepen ogen, aanwezigheid van de neus-lip groef, geopende overstrekte mond en een gespannen tong. Deze mimiek verschilt met die van boosheid, angst of droefheid. Het is niet bekend of kinderen deze mimiek laten zien als de pijn langer aanhoudt.

Om deze reden is in hoofdstuk 3 een onderzoek uitgevoerd met als doel te bepalen of het gezicht een valide meetmethode is om bij pasgeborenen en baby's de aanwezigheid en mate van pijn te achterhalen gedurende de postoperatieve periode. In totaal werd dit bij 38 kinderen gedaan die allen een grote chirurgische abdominale of thoracale ingreep hadden ondergaan. De NFCS werd gebruikt om veranderingen in het gezicht te coderen. Daarnaast werden andere pijngerelateerde metingen verricht zoals COMFORT 'gedrag' en VAS, hartslag, adrenaline en noradrenaline. Morfineconcentraties in het bloed werden bepaald om te achterhalen of er een relatie is tussen hoeveelheid morfine in het bloed en mate van pijnbestrijding. Een goede samenhang werd gevonden tussen NFCS, COMFORT 'gedrag', VAS scores alsmede tussen NFCS scores, hartslag en bloeddruk. Er werd geen relatie gevonden tussen NFCS, adrenaline, noradrenaline en morfine plasma concentraties. Uit de analyses komt verder naar voren dat de mimiek voor postoperatieve pijn overeenkomt met die zoals beschreven is in hoofdstuk 2 bij pijnlijke procedures zoals een prik.

Onderzoek uitgevoerd bij de mens en bij dieren toont aan dat weefselbeschadiging en pijn in de eerste levensperiode leiden tot een veranderde pijngevoeligheid op latere leeftijd. Het doel van hoofdstuk 4 was te bepalen of het ondergaan van een grote operatie in de eerste drie maanden van het leven, in combinatie met "pre-emptive analgesia", leidt tot een veranderde pijngevoeligheid op latere leeftijd. Een tweede doel was te achterhalen of het aantal opnamedagen in een ziekenhuis en het aantal stressvolle gebeurtenissen gedurende deze opnames van invloed is op de pijngevoeligheid op latere leeftijd. In dit onderzoek werd de reactie op vaccinatie van vijftig peuters en kleuters, die in de eerste drie maanden van hun leven een

grote chirurgische ingreep hadden ondergaan, vergeleken met die van 50 gezonde op leeftijd gematchte controlekinderen. De kinderen kregen of de BMR vaccinatie op de leeftijd van 14 maanden of de DTP vaccinatie op de leeftijd van 3 jaar en 9 maanden.
Er werd geen verschil tussen beide groepen gevonden; niet in mimiek, hartslag of cortisolconcentraties. Verder kwam naar voren dat kinderen van 14 maanden oud met veel ziekenhuiservaringen, heftiger reageerden met hun mimiek maar minder heftig met een stijging in de hartslag dan kinderen van dezelfde leeftijd die relatief kort waren opgenomen. Aangenomen wordt dat kinderen met veel ziekenhuiservaringen veel pijn hebben geleden. Dit effect werd niet gezien bij kinderen van 3 jaar en 9 maanden. Dit onderzoek lijkt aan te tonen dat adequate pijnbestrijding tijdens en na een grote operatie verandering in pijngevoeligheid voorkomt. Excessieve blootstelling aan pijnlijke procedures en stress leidt tot een verhoogde pijngevoeligheid die, na een lange periode van niet blootgesteld zijn aan pijn, lijkt af te nemen.
In de hoofdstukken 5 tot en met 7 werden enkele pijnbestrijdingsmethoden op hun effectiviteit getest. In hoofdstuk 5 werd bepaald of bij besnijdenis het aanbrengen van EMLA een even goede pijnbestrijding geeft als het relatief moeilijk uit te voeren caudaal blok. EMLA is een zalf die de huid verdooft. Vierenzestig jongens van 1 tot 12 jaar namen deel aan dit onderzoek. Voor de ingreep kregen zij óf EMLA óf placebo crème, óf een caudaal blok. Behalve zij die een caudaal block hadden gekregen, kregen allen na de besnijdenis nogmaals hetzij EMLA hetzij placebo crème. De besnijdenis werd uitgevoerd onder algehele anesthesie. Zoals verwacht reageerden de jongens die placebo crème voor de ingreep hadden gekregen het heftigst op de besnijdenis. EMLA verminderde de pijn tijdens de besnijdenis, echter de effectiviteit hiervan was niet zo goed als die van het caudaal blok. Het aantal jongens dat na de ingreep extra pijnbestrijding nodig had was veel groter bij de groepen die na de besnijdenis placebo of EMLA crème hadden gekregen dan bij de groep met het caudaal blok. Geconcludeerd werd dat EMLA geen alternatief is voor het caudaal blok.
Over het algemeen geven Nederlandse artsen paracetamol tegen de pijn na amandelknippen, met wisselend resultaat. Hoofdstuk 6 heeft daarom ten doel te achterhalen welk middel in welke dosering het meest effectief is voor de pijn na amandelknippen. Een systematisch literatuuronderzoek werd uitgevoerd naar zowel de effectiviteit, farmacokinetiek als veiligheid van kleine analgetica zoals paracetamol of diclofenac die bij amandelknippen gegeven worden in Nederland.

Hiervoor werden o.a. de databestanden MEDLINE en PSYCLIT geraadpleegd. Alle literatuur die tussen 1966 en 1998 verschenen is, werd geraadpleegd. In totaal werden er 10 effectiviteitsstudies gevonden waarin paracetamol of diclofenac gegeven werd. Geconcludeerd werd dat paracetamol drank in een dosering van 20 $mg.kg^{-1}$ gegeven 60 minuten voor de ingreep, paracetamol zetpillen 40 $mg.kg^{-1}$ ingebracht 2 tot 3 uur voor de ingreep, of diclofenac zetpillen in een dosering van 2 $mg.kg^{-1}$ gegeven vlak voor de ingreep, leiden tot adequate pijnbestrijding na amandelknippen bij de meeste kinderen.
Goede pijnbestrijding heeft tot doel de hoeveelheid analgetica af te stemmen op de behoefte van de patiënt. Het meest ideale is dat de patiënt hier zelf controle over heeft, hetgeen mogelijk is met behulp van Patient Controlled Analgesia (PCA). Dit is een techniek die de patiënt zelf de mogelijkheid biedt om zichzelf kleine hoeveelheden morfine toe te dienen. PCA kan met en zonder achtergrond infuus van morfine worden toegepast. Het doel van hoofdstuk 7 was te bepalen of PCA in combinatie met een achtergrond infuus een betere pijnbestrijding geeft dan alleen een continu infuus van morfine. Zevenenveertig kinderen van 5 tot 18 jaar werden in willekeurige volgorde toegewezen aan één van deze twee methoden. De mate van pijnbestrijding was matig bij beide technieken. Kinderen die PCA hadden gekregen gebruikten veel meer morfine; dit leidde echter niet tot een hogere incidentie van bijwerkingen. Geconcludeerd werd dat meer onderzoek nodig is om te achterhalen welke factoren verantwoordelijk zijn voor het feit dat kinderen die zichzelf extra morfine kunnen toedienen toch pijn lijden.
In hoofdstuk 8 worden de bovengenoemde bevindingen in een breder verband geplaatst en besproken in het licht van ontwikkelingen op het terrein van pijnbeoordeling en -bestrijding bij kinderen. Tenslotte wordt nieuw onderzoek voorgesteld.

Curriculum vitae

Jeroen Wilhelmus Bernardus Peters werd geboren op 7 januari 1968 te Arnhem. In 1988 behaalde hij zijn VWO diploma aan het Van Lingen College in dezelfde stad. Daarna begon hij aan de HBO-Verpleegkunde opleiding te Nijmegen. Direct na afronding hiervan in 1992 begon hij met de studie Gezondheidswetenschappen aan de Rijksuniversiteit Limburg, met als specialisatie Verplegingswetenschap. Daarnaast volgde hij enkele blokken Methodologie en Statistiek. Zijn doctoraal behaalde hij in 1995.
Al tijdens deze studie werd zijn belangstelling gewekt voor het onderzoeksterrein van pijnbeoordeling en -bestrijding bij kinderen, hetgeen uitmondde in zijn doctoraalscriptie over dit onderwerp. Vanaf 1995 was hij werkzaam als wetenschappelijk medewerker bij de afdeling Kinderanesthesiologie in het Academisch Ziekenhuis Rotterdam/Sophia Kinderziekenhuis. In 1997 werd hij aangesteld bij de afdeling Kinderheelkunde van dit zelfde ziekenhuis, waar hij momenteel onderzoek verricht naar pijnbeoordeling en bestrijding bij (jonge) kinderen. Zijn aanstelling werd mede mogelijk gemaakt door subsidie van de Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO), de Sophia Stichting Wetenschappelijk Onderzoek (SSWO), de David Vervat Stichting en de Stichting Algesiologisch Instituut Rotterdam. Het onderzoekswerk waar dit proefschrift op is gebaseerd vond plaats op de afdelingen Kinderanesthesiologie en Kinderheelkunde en in samenwerking met de afdelingen Medische Psychologie en Psychotherapie van de Erasmus Universiteit Rotterdam en de afdeling Kinder- en Jeugdpsychiatrie van het Academisch Ziekenhuis Rotterdam/Sophia Kinderziekenhuis.
De auteur is getrouwd met Diana de Boer en samen hebben zij een dochter: Amber (2000).

List of abbreviations

(A)TE	(adeno)tonsillectomy
(N)ICU	(neonatal) intensive care unit
AC	appearance changes
ASA	American Society of Anesthesiologists
BB	brow bulge
BI	continuous background infusion of morphine
BP_mean	mean blood pressure
BP_var	variability in blood pressure
CI	confidence interval
CM	continuous infusion of morphine
CL	systemic clearance
C_{max}	maximum plasma concentration
CNS	central nervous system
CQ	chin quiver
DBP	diastolic blood pressure
DTT	diphtheria, tetanus, and trivalent polio immunisation
EE	application of EMLA cream pre- and postoperatively
ELBW	extremely low birth weight
EMLA	eutectic mixture of local anaesthetics
ENC	eye, nose and cheek root region
EP	application of EMLA cream preoperatively and placebo cream postoperatively
ES	eye squeeze
FEN	forehead, eyebrows, and nasal root region
HMS	horizontal mouth stretch
HR	heart rate
HR_base	mean heart rate at baseline
HR_change	difference between mean heart rate at baseline and mean heart rate during observation period
HR_mean	mean heart rate
HR_var	variability in heart rate
IM	intermittent morphine administration
LP	lip purse
MAX	maximum discriminative facial movement coding system

$mg.kg^{-1}$	microgram per kilogram
$mg.L^{-1}$	microgram per litre
MLC	mouth, lips, and chin root region
MMR	measles, mumps, and rubella immunisation
NAC	*N*-acetylcysteine
NAPQI	N-acetyl-p-benzoquinone
NFCS	neonatal facial coding system
NFCS_subset	pain score based on the duration of five facial actions
NFCS_total	pain score based on the duration of ten facial actions
NLF	naso-labial furrow
NSAID	nonsteroidal anti-inflammatory drugs
OL	open lips
PCA	patient controlled analgesia
PCA+BI	patient controlled analgesia with a continuous background infusion of morphine
PCA-BI	patient controlled analgesia without a continuous background infusion of morphine
PE	application of placebo cream preoperatively and EMLA cream postoperatively
RR	respiratory rate
SBP	systolic blood pressure
SGOT	aspartate transaminase serum values
SSS	severity of surgical stress
$T_{½ß}$	elimination half-life
TISS	therapeutic intervention scoring system
T_{max}	time to maximum concentration
TP	tongue protruding
TT	taut tongue
VAS	visual analogue scale
V_d	distribution volume
VMS	vertical mouth stretch