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PARENTS AS PAIN KILLERS IN THE PAIN MANAGEMENT OF PRETERM INFANTS

by

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To the families who participated in this study

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ABSTRACT

The aim of this study was to develop a new pain management method called facilitated tucking by parents (FTP) to alleviate procedural pain in preterm infants in the Neonatal Intensive Care Unit (NICU). In two randomized controlled crossover trials, the effectiveness of FTP was compared to a non-pharmacological evidence-based practice (oral glucose), a pharmacological method (intravenous oxycodone) and a placebo (oral water) or control care in the context of heel lance and endotracheal or pharyngeal suctioning. In addition, the short-term adverse effects (desaturation, bradycardia) and the prolonged effects of pain management on sleep were measured. The gestational age of the infants was a median of 28 weeks (n=20) in Study I and a mean of 28 $^{1/7}$ (n=20) in Study II. The primary outcome measure for procedural pain was the Premature infant pain profile (PIPP). After interventions, sleep structure was analysed from 13-hour polysomnographic recordings. In the third study, the mothers (n = 23) who had used FTP from 2-4 weeks in the NICU were interviewed using the Clinical interview for parents of high-risk infants with additional questions related to the infants' pain care.

During heel lance, the PIPP scores were significantly lower with oral glucose (mean 4.85 ± 1.73, p≤0.001) and FTP (mean 5.20 ± 1.70, p=0.004) when compared to the placebo (mean 7.05 ± 2.16). During pharyngeal suctioning, the scores were lower with oral glucose (mean 11.05 ± 2.31, p=0.014) and FTP (mean 11.25 ± 2.47, p=0.034) compared to the placebo (mean 12.40 ± 2.06). Opioid equalled placebo during both procedures. Significantly more short-term adverse effects were related to the administration of oral glucose (21.3%) and oral water (12.5%) compared to opioid (5%) or FTP (5%). Oxycodone treatment altered the sleep structure by significantly decreasing the amount of REM sleep. The FTP was positively perceived by all participating parents. In the mothers, three different styles of involvement in pain care were identified. The differences found in the involvement of pain care were related to maternal attachment and NICU-related stress of the mothers.

The FTP was preferable to oral glucose and intravenous oxycodone when efficacy, safety and family issues were considered in treating short-term procedural pain in preterm infants.

Keywords: preterm infant, pain management, sleep, parenting, NICU

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TIIVISTELMÄ

Tutkimuksen tarkoituksena oli kehittää uusi kivunlievitysmenetelmä, Vanhempien käsikapalo, keskoslasten kivunhoitoon vastasyntyneiden teho-osastolla. Vanhempien käsikapalon tehokkuutta verrattiin kahdessa satunnaistetussa kontrolloidussa crossover-tutkimusasetelmassa ei-lääkkeelliseen näyttöön perustuvaan hoitoon (P.O. glukoosiliuos), lääkkeelliseen menetelmään (I.V. oksikodoni) ja lumeeseen (P.O. vesi) tai kontrolli hoitoon kantapääpiston ja hengitysteiden imemisen aikana. Lisäksi mitattiin kivunhoidon lyhytaikaisia sivuvaikutuksia (hapetuksen- ja pulssinlasku) ja pidempiaikaisia vaikutuksia uneen. Tutkittujen lasten ikä oli 28 raskausviikkoa (n = 20) ja 28 $^{1/7}$ (n = 20). Toimenpidekipua arvioitiin Premature Infant Pain Profile (PIPP) -kipumittarilla. Interventioiden jälkeen unen rakenne analysoitiin 13 tunnin polysomnografia-rekisteröinneistä. Viimeisessä vaiheessa haastateltiin äitejä (n = 23), jotka olivat käyttäneet vanhempien käsikapaloa 2–4 viikkoa vastasyntyneiden teho-osastolla, strukturoidulla the Clinical Interview for Parents of High-Risk Infants -haastattelulla, johon oli lisätty kysymyksiä lapsen kivunhoidosta.

Kantapääpiston aikana PIPP–pisteet olivat merkitsevästi matalampia P.O. glukoosiliuoksella (ka 4,85 ± 1,73, p ≤ 0,001) ja vanhempien käsikapalolla (ka 5,20 ± 1,70, p = 0,004) verrattuna lumeeseen (ka 7,05 ± 2,16). Hengitysteiden imemisen yhteydessä PIPP–pisteet olivat matalampia P.O. glukoosiliuoksella (ka 11,05 ± 2,31, p = 0,014) ja vanhempien käsikapalolla (ka 11,25 ± 2,47, p = 0,034) verrattuna lumeeseen (ka 12,40 ± 2,06). Oksikodonin teho oli verrattavissa lumeeseen kummankin toimenpiteen aikana. P.O. glukoosiliuoksen (21,3 %) ja lumeen (12,5 %) annosteluun liittyi merkittävästi enemmän lyhytaikaisia sivuvaikutuksia verrattuna oksikodoniin (5 %) tai vanhempien käsikapaloon (5 %). Oksikodoni muutti keskoslasten unen rakennetta vähentämällä merkittävästi aktiivisen unen määrää verrattuna muihin hoitoihin. Vanhemmat suhtautuivat positiivisesti käsikapalon käyttöön. Äitien osallistuminen kivunhoitoon voitiin jaotella kolmeen eri tyylin, jotka selittyivät äidin kiintymyksen tunteilla ja lapsen tehohoitoon liittyvällä stressillä.

Vanhempien käsikapalo on suositeltavampi lyhyen toimenpidekivunlievittäjä kuin P.O. glukoosiliuos tai I.V. oksikodoni, kun tehokkuus, turvallisuus ja perhe otetaan huomioon.

Avainsanat: keskoslapsi, kivunhoito, uni, vanhemmuus, vastasyntyneiden teho-osasto

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

BPD	Bronchopulmonary dysplasia
CP	Cerebral palsy
CLIP	the Clinical interview for the parents of high risk infants
cPVL	Cystic periventricular leukomalacia
DC	Developmental care
ECG	Electrocardiogram
EEG	Electroencelogram
EMG	Electromyogram
ELBW	Extremely low-birth-weight infants
FTP	Facilitated tucking by parents
GA	Gestational age
IVH	Intraventricular haemorrhages
KC	Kangaroo care
MT	Movement time
NEC	Necrotizing enterocolitis
NFCS	Neonatal facial coding scale
NICU	Neonatal intensive care unit
NIPS	Neonatal infant pain scale
NREM	Non-rapid eye movement
PCA	Post-conceptional age
PDA	Patent ductus arteriosus
PIPP	Premature infant pain profile
PNA	Postnatal age
REM	Rapid eye movement
RDS	Respiratory distress syndrome
VLBW	Very low-birth-weight

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text with Roman numerals I – IV.

I. Axelin A, Salanterä S & Lehtonen L. 2006 “Facilitated tucking by parents” in pain management of preterm infants – a randomized crossover trial. Early Human Development, 82(4), 241–247.

II. Axelin A, Salanterä S, Kirjavainen J & Lehtonen L. 2009. Oral glucose and parental holding preferable to opioid in pain management in preterm infants. The Clinical Journal of Pain, 25(2), 138–145.

III. Axelin A, Kirjavainen J, Salanterä S & Lehtonen L. 2010. Effects of pain management on sleep in preterm infants. European Journal of Pain, 14(7), 752–758. Epub 2009, Dec 16.

IV. Axelin A, Lehtonen L, Pelander T & Salanterä S. 2010. Mothers’ different styles of involvement in preterm infant pain care. The Journal of Obstetric, Gynecologic and Neonatal Nursing, 39(4), 415-424.

1. INTRODUCTION

The starting point for this study lies in the caring culture and pain management of preterm infants in 2000. Back then, I was working as a nurse in a Neonatal intensive care unit (NICU). It was not exceptional to see a mother crying outside the patient room while the crying infant inside the room was subjected to painful procedures. I was puzzled why the mother and infant were separated from each other during this stressful situation. The answers to this dilemma have offered a ten year trip into nursing research for me, but I was not the first person focusing my interest on the pain of preterm infants.

Just 25 years ago, it was commonly believed that preterm infants were not capable of sensing pain due to their immature nervous system. One initiator of research was Jill Lawson, who fought for her son Jeffrey’s right to analgesia during Patent ductus arteriosus (PDA) surgery. Jeffrey Lawson died following surgery without analgesia (McGrath & Unruh 2007). At the same time revolutionary research was conducted, showing fentanyl analgesia during PDA surgery improved preterm infants’ outcomes remarkably (Anand et al. 1987). Since then, the idea of preterm infants’ inability to sense pain has receded to active research in the area, and evidence-based practice has developed in the pain care of preterm infants. Along the way, however, research into the role of the parents in the pain care of preterm infants has not received the attention it deserves. Clearly a more distinct role in the pain care of preterm infants could be assigned to parents and they have also expressed a wish to actively participate in this area of preterm infant care.

The best possible foundation for the healthy life of a preterm infant in the NICU is provided through high quality care and closeness to the parents. Untreated procedural pain and the often consequential separation from the parents are still risk factors for developmental problems in the intensive care of preterm infants. Separation during painful procedures is also a factor which prevents parents from protecting their infant from the harmful effects of pain. Active parental participation in pain care could improve the quality of preterm infant care during the first few weeks or months of life, while providing better infant pain management in NICU and preparing the parents for life after discharge. By developing a tool enabling parental participation in pain management we may prevent separation and unite the family in an occasion when the preterm infant needs the parents to help regulate stress and pain.

Procedural pain in preterm infants is a global problem in nursing care. Preterm infants suffer from untreated pain no matter which country they live in. It is also probable that many of these infants have the underused resource of comfort – the parents – right next to them. An effective, safe and easy to use pain management method enabling parental participation in the pain care of preterm infants could provide tangible improvements in the pain care of preterm infants throughout the world.

2. REVIEW OF THE LITERATURE

The aim of this literature review was to gain a comprehensive picture of pain care of preterm infants from its early years in 1985 to March 2010. In addition to pain care, the family aspect in the care of preterm infants was examined in literature from 2000 to March 2010. The linking of these two perspectives gave an understanding on how these two issues relate in conducted and potential future research. The final literature review consisted of three major sections. In the first part, the nature of neonatal intensive care was looked at from the context of the family. In the second part, the procedural pain of preterm infants in the NICU environment was reviewed. The third part, of parental participation in the pain care of preterm infants, was covered based on the scarce literature available.

It is notable that the studies especially concerning parents have been conducted primarily in North America and Western Europe which are societies with high financial resources and technological development. Generalizing or transferring the results to the other contexts must be done cautiously particularly with respect to factors such as traditional family roles and welfare systems vary between countries.

The reviewed literature was gained through the authors own expertise in the research of preterm infant care and especially in the field of pain care (Figure 1). Detailed searches were conducted in different databases and manually in the reference lists of the articles. The broad scope of the literature was ensured by conducting a systematic search in four databases: PubMed, Cinahl, PsychINFO and Cochrane. This systematic search covered approximately half of the articles gained through the manual searches. A total of 167 articles were included in the final literature review. In addition, during the review process 14 articles were added.

Keywords	**PubMed**	**Cinahl**	**PsycINFO**	**Cochrane**	**Inc.**
	Abstracts/ Accepted				
	Manual searches for Pain care 102 Family issues 64				166
Infant, premature [Mesh] or Premature infant* or Preterm infants* **AND** Pain [Mesh] or Pain measurement [Mesh] or Pain* (Publication date 1985-3/2010)	386/56	51/1	93/1	48/1	Covered 58/102 of pain articles New articles n=1
Infant, premature [Mesh] or Premature infant* or Preterm infants* or neonatal **AND** Intensive care units, Pediatric [Mesh] **AND** Parents [Mesh] or Parenting [Mesh] or Parent*[Ti no Ab] (Publication date 2000-3/2010)	574/24	447/4	338/4		Covered 32/64 of family articles
		Exclude Medline Records		in Cochrane Reviews	**Total:** 167 +14= **181**
Limits: only items with abstracts, Humans, English					

Figure 1. Systematic search path of the articles included.

2.1. Families in Neonatal intensive care unit (NICU)

2.1.1. Preterm infants in NICU

A preterm infant is a newborn infant born under 37 weeks of gestation. Globally the rate of preterm births is increasing. A global prevalence of preterm birth is 9.6% influencing approximately 12.9 million babies annually. The numbers of babies born prematurely are highest in Africa and Asia. The highest percentages of births born preterm occur in Africa and North America. (March of Dimes 2009.) In Finland, the number of infants born prematurely has stayed at the same level during last twenty years. In 2008, 5.7% (n=3 438) of newborns were born prematurely (National Institute of Health and Welfare 2009). This number is low compared to many Western countries, such as 12.7% in the USA in 2007 (the National Center for Health Statistics 2009), 8.1% in Canada in 2004 (Public Health Agency of Canada 2008) and 7.9% in the UK in 2008-2009 (National Health Care UK 2009). In Europe, the number of infants born prematurely in Finland is equal to those in Estonia, Latvia, Lithuania, the Slovak Republic, Ireland, France and Sweden (European Perinatal Health Report 2008). The median length of hospital stay in very-low-birth-weight (VLBW) infants (<32 weeks of gestation or a birth weight <1501 g) was 53 days in Finland between the years 2000 and 2003. Large regional differences of up to ten days were found among the different hospital districts. The length of stay decreased with increasing gestational age (GA) (Korvenranta et al. 2007).

A low GA also increases the risk of developmental problems (Hack & Fanaroff 2000). In VLBW infants, the early morbidities which are associated with long-term developmental problems were respiratory distress syndrome (RDS) 74%, bronchopulmonary dysplasia (BPD) 32%, necrotizing enterocolitis (NEC) 7%, severe intravetricular haemorrhages (IVH) 9% and cystic periventricular leukomalacia (cPVL) 3% (Vermont-Oxford Network 2008). In the more fragile population of extremely low-birth-weight (ELBW) infants (birth weight <1000 g) born in Finland in 1999-2000, the incidence of morbidities were RDS 83%, BPD 49%, NEC 4%, severe IVH 17% (Tommiska et al. 2007). However, the majority (66.2%) of very preterm infants (<32 weeks of gestation) born in 2000-2003 survived without any long-term morbidities. In the remaining infants, the morbidities related to prematurity, which were over presented compared to healthy term infants, were obstructive airway disease 20%, other ophthalmologic problems 13.4%, Cerebral Palsy (CP) 6.1%, visual disturbances or blindness 3.8%, seizures 3.0% and hearing loss 2.5% (Korvenranta et al. 2009). At five years of age, the average development and behaviour of these children and their health related quality of life scores were less optimal than for healthy term infants as rated by their parents, although the majority scored comparably to the controls (Rautava et al. 2009, 2010). The latest regional study from Finland shows that the cognitive development of VLBW infants was within the normal range (Munck et al. 2010). The differences in the outcomes of very preterm infants can result, for example, from differences in populations and the environment and from differences in care practices, such as the length of ventilator treatment (Walsh et al. 2005), the efficacy in sepsis prevention (Stoll et al. 2004) and levels of pain exposure (Grunau et al. 2009).

The progress in modifying the NICU environment to support neurological development in preterm infants has been vast during the last few decades. One contribution of nursing care to these improvements is developmental care (DC). The concept of developmental care can be applied in a variety of ways. One method of implementing a comprehensive program of DC is through the Newborn individualized developmental care and assessment program (NIDCAP). In DC, the care giving to preterm infants is adapted according to their behavioural signs and the physical environment is enhanced, for example with reduced lighting, lower noise levels, supportive handling and positioning. Reduced light and noise levels in order to save an infant's energy for coping with painful procedures are a recommendable environmental strategy for pain management (Franck & Lawhon 1998). Active parental participation in the care of preterm infants and a well-planned discharge are also essential parts of the DC protocol. In preterm infants, DC has been shown to decrease the duration of ventilator treatment, to lead to earlier complete feeding and to improve neurodevelopmental outcomes (Als 1986, Als et al. 1986, 1994, Westrup et al. 2002) or at least to have no negative impacts on VLBW infants (Westrup et al. 2000). However, the sample sizes in these studies were small. In the Cochrane review 2006, the authors concluded that there was evidence of limited benefits and no major harmful effects of DC (Symington & Pinelli 2006). The latest adequately powered studies leave us with the same controversial results (Maguire et al. 2009, Peters et al. 2009) which can be partly explained by the challenges in designing randomized controlled trials on this widely used complex intervention and its main focus being on the infant and not on the parents.

Developmental care is also related to shorter sleep latency, diminished sleep stage changes and increased total sleeping time compared to routine care (Bertelle et al. 2005) but it did not increase the proportion of quiet sleep (Westrup et al. 2002) or improve sleep maturation (Ariagno et al. 2007). The goal of clustered nursing care is also to secure longer periods of uninterrupted sleep for preterm infants. Sleep is one essential and easily disturbed element affecting the brain development of preterm infants in the NICU environment. Brain development mainly takes place during sleep, since these infants spend little time awake (Mirmiran et al. 2003, Peirano et al. 2003, Peirano and Algarin, 2007). Sleep state differentiation is present after approximately 25 weeks of gestation when traditionally three different sleep states (active or rapid eye movement (REM) sleep, indeterminate sleep and quiet or non-rapid eye movement (NREM) sleep) can be distinguished (Scher et al. 2005). Whether indeterminate sleep is really a specific sleep state in preterm infants can be questioned. Rapid eye movement sleep is considered as an inducer of brain development during the neonatal period (Roffwarg et al. 1966, Marks et al. 1995). On the other hand, information acquired during wakefulness is further processed during NREM sleep (Siapas & Wilson 1998, Euston et al. 2007). Sleep has an important role in synaptic remodelling (Kavanau 1994, Liu et al. 2010).

In addition to gentle nursing care and sleep, parents' closeness and touch are prerequisites for the optimal development of preterm infants. Kangaroo care (KC) is the most studied and effective single intervention improving the development of preterm infants with parents' proximity. In KC, a parent holds the infant on the chest, offering skin-to-skin contact. The systematic use of this method has been shown to have several positive physiological and behavioural effects for the development of preterm infants by improving sleep, breast feeding, growth and early-interaction. It has also had a positive impact on neurobehavioural development and psychosocial factors (Feldman et al. 2002, Conde-Agudelo & Belizán 2003, Hake-Brooks & Anderson 2008, Ludington-Hoe, 2008).

Despite the advantages in neonatal care the number of invasive painful procedures has stayed at the same level over the past ten years. The exposure is on average ten or more painful procedures per day during intensive care; furthermore, appropriate pain management is often lacking (Johnston et al. 1997, Simons et al. 2003a, Carbajal et al. 2008). In addition, the youngest preterm infants undergo the most painful procedures at the time of their active cortical development. This abnormal sensory input at the time of rapid neurological development puts them under the greatest risk for developmental problems (Grunau et al. 2009). Surprisingly, we know very little about how pain affects preterm infants' day-rhythm including sleep. Pain causes agitation (Porter et al. 1999) and painful procedures increase active waking and sleep-wake transitions compared to control interventions (Brandon et al. 1999).

2.1.2. Parents in NICU

Preterm birth is a challenging situation for the parents due to the interrupted development in parenthood and worry for the sick infant. This situation causes emotional distress to both parents, although the mothers seem to adjust more poorly being more anxious, hostile, and depressed than fathers (Doering et al. 1999). In mothers, the emotional bond to the newborn preterm infant can be unfinished at the time of admission to the NICU. The mother has to bond with her sick infant in an unexpected environment after birth (Aagaard & Hall 2008). Being a mother of an infant in the NICU has been described as a process of growth from being an outsider to an engaged parent. During this process, knowing the infant leads to a greater and infant-driven involvement in care (Heermann et al. 2005). The mother's readiness to participate in her preterm infant's care is closely tied to the other elements of motherhood in the NICU environment. During pregnancy, maternal attachment to the foetus increases simultaneously with foetal development.

Ideally, the mother's physical, biological, cognitive and emotional changes during pregnancy enable her to create an emotionally secure and safe environment for her baby (Cohen & Slade 2000). Preterm birth and the consequential separation between mother and infant immediately after birth interfere with this process (Latva et al. 2008). In addition, the possible inability to fulfil the maternal role in the restrictive intensive care environment (Miles et al. 1991) and the related stress (Singer et al. 1999, Franck et al. 2005a) impose further challenges on the mother.

In fathers, the experience of having a preterm infant has the same elements as for mothers. The research concerning fathers, however, is more sparse. The major way in which fathers have described the situation is having a sense of lack of control (Arockiasamy et al. 2008.) The NICU admission is also a psychologically demanding experience for the fathers and they suffer NICU-related stress (Franck et al. 2005a, Turan et al. 2008). Fathers are worried about their infants' condition and the observation that nurses are not always emotionally involved in the care of preterm infants. However, fathers can keep their emotions hidden in order to maintain their strength within and outside the family (Pohlman 2009).

Many of the fathers see that their role is to support their wives since according to them mothers have to put up with even more stressful things (Arockiasamy et al. 2008.) Similarly, mothers often rely on the fathers to take the role of infants' advocate. Men are somewhat outsiders from the daily experience of mothering in the nursery. This more neutral position helps in avoiding potential conflicts with nurses which can affect infant care (Fenwick et al. 2001). Fathers themselves have also agreed on this protective role in the family. They have described activities such as working, getting away from the NICU and exercising in order to maintain a sense of control. These activities are aimed outside of the NICU, supporting fathers' experience in needing more support from health care professionals (Arockiasamy et al. 2008). Fathers have ranked support, information and assurance needs as less important than mothers did. However, differences in comfort and proximity needs have not been found (Ward 2001).

Accordingly, parents need unique support in relation to their personal needs and their new role in the family. In these circumstances, health care professionals responsible for the care of sick preterm infants have a central and obligatory role in answering parents' information needs (De Rouck & Leyes 2009) and in supporting the bonding between parents and their infant in this unexpected environment. Nurses have a unique opportunity to help parents experience meaningful parenthood in NICU settings. They can facilitate or hinder this process of growth to parenthood by giving the mother opportunities to be the primary caregiver or by excluding her from the infant's care, respectively (Fenwick et al. 2001, Wigert et al. 2006)

2.1.3. Parenting in NICU

Parenting in the NICU can be supported by many nursing interventions in order to avoid separation and secure the growth process in parenthood. The first requirement is free visiting times for parents. Infrequent visits by mothers are associated with later behavioural and emotional problems in preterm infants (Latva et al. 2004). Fathers visit less frequently in the NICU than mothers (Franck & Spencer 2003, Latva et al. 2004). The longer duration of a visit predicts the parents' engagement in care giving activities (Franck & Spencer 2003). The lack of daily visits and a short duration of visits by the mother can be a sign of the mother feeling like an outsider in the NICU. The frequency of visits can also be explained by practical issues such as the distance between home and hospital or country-specific welfare benefits. In addition to the frequency of visits, nurses can also focus on the quality of visits. Parents have to feel welcome and enjoy their stay in this environment.

Developmental care and family-centred care aim to positively influence this shortcoming in the technical and stressful NICU environment. Developmental care has succeeded in allowing mothers to feel closer to their infants, but they can also have higher levels of anxiety, possibly due to the stronger bond with their infant. However, the exact interventions for parents are not clearly defined (Kleberg et al. 2007.) Results referring to the ineffectiveness of DC on parental outcomes are available in the literature (van der Pal et al. 2007). In Sweden, the latest study on family-centred care showed that by making it possible for parents to stay 24 hours a day next to their preterm infant from admission to discharge reduced the length of stay by five days (Örtenstrand et al. 2010). This result suggests that it is worth increasing parental presence in the NICU. The constant closeness and availability of parents can further optimize the development of preterm infants. This kind of model of family-centred care is available in quite a few countries in Europe and it is more common in northern Europe (Greisen et al. 2009), whereas there is a need for short-term and more easily available interventions. In addition, all parents need education and support in order to be able to take care of their preterm infant.

Educational-behavioural intervention programs aim to increase parental sensitivity towards the preterm infant and through this help the parents to engage more sensitively and more actively in the care of their child. Nurse-delivered audiotape information and activity books in four phases or eight daily one-hour sessions in the NICU followed by four home visits have been shown to improve the mental health outcomes of parents (Kareseen et al. 2006), enhance parent-infant interactions and reduce both the length of stay in hospitals and the costs related to preterm birth (Melnyk et al. 2006, 2008, 2009). Both the abovementioned programs helped parents to see their infants' signs of distress and further taught them to respond appropriately to those cues. This is a useful parenting skill as preterm infants are likely to be under stress and pain many times a day during their NICU stay.

2.2. Procedural pain in preterm infants

The International Association for the Study of Pain (IASP) defines pain “as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” An important addition for preterm infants was made to this definition in the 1990s. It now says that “the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment.” (IASP 1994). This addition recognized humans incapable of self-report, such as preterm infants and their ability to feel pain (Anand & Craig 1996). The IASP definition of pain also highlights that an individual learns the meaning of the word pain through her or his own experience related to injury in early life (IASP 1994). Even the youngest preterm infants have a neurological readiness to sense pain. Importantly, infants less than 32 weeks gestation lack the ability to modulate pain with descending pathways. This may lead to even greater pain (Beggs & Fitzgerald 2007.) Every painful stimulus is significant and has the potential for a negative impact on the development of preterm infants.

The duration of pain can vary from short-term procedural pain to prolonged pain such as a consequence of ventilator treatment or surgery. In procedural pain, the source of potential or actual tissue damage is the short-term pain induced by the medical or nursing care of preterm infants. These procedures constitute the most prominent source of pain for this population as preterm infants are exposed to dozens of painful procedures during their NICU stay (Johnston et al. 1997, Simons et al. 2003a, Carbajal et al. 2008). The most common painful procedures are suctioning of airways and heel lances. The suctioning procedures can constitute 52-64% of pain exposure and heel lancing 7-20% depending on the practices in the unit. Unfortunately, many of these procedures are still performed without appropriate pain management (Simmons et al. 2003a, Carbajal et al. 2008) since only 0.7-30% of the procedures were managed with some non-pharmacological or pharmacological pain management method (Carbajal et al. 2008).

Earlier research has focused on pain caused by heel lancing. It is understandably widely used in pain research as it can be largely standardized. However, suctioning is an even more common and unpleasant procedure and is the cause of severe pain, according to the nurses performing it (Simmons et al. 2003a). The lack of information regarding suctioning procedure in pain research studying different pain management methods is evident as only a few studies can be found which focused on the treatment of suction-related pain (Anand et al. 2004, Saarenmaa et al. 1997).

2.2.1. Assessment of pain

Reliable pain assessment was one of the first challenges in the pain research of preterm infants, and this challenge still exists today. In the pain sensation of preterm infant, sensory-discriminative (intensity) and affective-motivational (unpleasantness) dimensions are emphasized whereas the cognitive-evaluative dimension is not as evolved as in adults due to the cognitive development phase of infants (Melzack & Casey 1968), although pain or pain behaviours cause reaction at the cortical level (Bartocci et al. 2006, Slater et al. 2006). The pain sensation in preterm infants is not fixed but has individual differences (Johnston & Stevens 1996). The effectiveness of pain assessment in clinical practice can be questioned (Franck & Bruce 2009), but an objective outcome measure is needed in research. There are over 40 pain assessment tools available for infants and many controversies still exist concerning the pain assessment of preterm infants (Ranger et al. 2007).

The first uni-dimensional pain assessment tool, the Neonatal Facial Coding Scale (NFCS) (Grunau et al. 1987), and the multi-dimensional assessment tools, the Neonatal Infant Pain Scale (NIPS) (Lawrence et al. 1993) and the Preterm Infant Pain Profile (PIPP) (Stevens et al. 1996), developed for acute pain 15 to 20 years ago are still relevant today. It is considered that a tool combining behavioural and physiological parameters offers a more reliable estimate of pain than uni-dimensional tools. However, the correlations between behavioural and physiological measures across studies and situations are low (r=0.3) (Barr 1996). These same parameters also react to normal nursing care such as changing nappies (Holsti et al. 2005a). In addition, pain reduction only on the behavioural not physiological responses may leave preterm infants vulnerable to adverse effects of pain on the developing brain, in particular to the stress hormone system (Holsti & Grunau 2010). Combining these two components of pain in multi-dimensional pain assessment tool hinders their separate evaluation.

The background variables of an infant such as GA, behavioural state and medical condition further interfere with accurate assessment by altering the behaviour of the infant (Stevens et al. 1996, Slater et al. 2009). Different solutions have been made to resolve these challenges, for example, in the PIPP the background variables are integrated in the assessment tool (Stevens et al. 1996, Ballantyre et al. 1999). The behavioural components of the PIPP have correlated well with cortical reaction during pain (0.70), but the addition of the physiological parameters or background variables did not add anything to the relationship (Slater et al. 2008) suggesting that the cortical activity represents evoked response to the procedure. Over the 15 years of use, the PIPP has shown good reliability and validity across studies (Stevens et al. 2010a). There is little consensus over the outcome measures concerning pain (Leslie & Marlow 2006). However, the PIPP and the NFCS are the most widely used acute pain assessment tools in research.

2.2.2. Management of pain

Procedural pain can be managed by both pharmacological and non-pharmacological means. Opiates and, more precisely, morphine are the first and most studied pharmacological option. Research on other analgesic medications is scarce (Durrmeyer et al. 2010). The effectiveness of different non-pharmacological pain management methods has been widely studied. However, the only systematic research approach and cumulative evidence is available for oral sucrose (Stevens et al. 2010b), which was in some cases considered as a pharmacological method. Research on other non-pharmacological methods is inconsistent and more scattered (Franck 2002, Cignacco et al. 2007). In addition, there are no studies available describing the benefits of non-pharmacological methods such as time, costs and ease of implementing these interventions in clinical practice. The main concern in research related to pain management seems to be the inadequate knowledge of safety issues, since studies mainly focused on the effectiveness of different methods.

Pharmacological pain management

Pharmacological pain management with opioids have been proven the most effective pain alleviation method reducing both behavioural and physiological responses of procedural pain experienced by preterm infants during suctioning (Anand et al. 2004, Saarenmaa et al. 1997). Opioids like fentanyl (Anand et al. 1987), morphine (Anand et al. 1999), alfentanil (Saarenmaa et al. 1997) and oxycodone are the most studied and most used (Debillon et al. 2002, Simons et al. 2003a) pharmacological methods. The fact that the effectiveness of these methods is as relevant as that of non-pharmacological options is often ignored. There is some evidence suggesting inconsistence in the effectiveness of morphine during heel lance and suctioning (Scott et al. 1999, Simons et al. 2003b, Carbajal et al. 2005) even though they are routinely used in procedural pain management (Anand et al. 2004, Anand & Hall 2006). Furthermore, morphine treatment has been suggested to be associated with a longer duration of mechanical ventilation (Bhandari et al. 2005), a delay in the time of initiation and attainment of full enteral feeding (Menon et al. 2007) and hypotension (Hall et al. 2005). In addition, the administration of opioids during nasal continuous positive airway pressure (CPAP) treatment may not be the optimal solution as the number of apneas, desaturation and clinically significant respiratory suppression events have been found to increase after opioid treatment in vulnerable infants (Taddio et al. 2009). Opioids have also been shown to increase electro-encephalogram (EEG) discontinuity in preterm infants (Bell et al. 1993, Nguyen The Tich et al. 2003), suggesting that drug-related changes must be accounted for when interpreting EEG monitoring.

Morphine infusion has not resulted in brain complications such as IVH, PVL and increased mortality when compared to placebo. However, these neurological complications were more prevalent if open-label morphine was administered in addition to infusion (Anand et al. 2004). A greater exposure to intravenous morphine has not been able to prevent alterations in the stress response of ELBW infants (Grunau et al. 2007). In conclusion, the risk versus benefit ratio needs to be considered very carefully when administrating analgesics for preterm infants due to their potential adverse effects on brain development. Alternative options should be explored.

The use of paracetamol in preterm infants is a much less studied pharmacological option. However, the available evidence is negative as a single orally administered high dose of paracetamol did not provide adequate analgesia for procedural pain caused by heel lance in preterm infants (Badiee & Torcan 2009). The evidence for term infants is the same (Shah et al. 1998). Pharmacological treatments other than opioids cannot be routinely recommended for treating procedural pain in infants considering the current evidence (Durrmeyer et al. 2010).

Local anaesthetic cream (tetracaine) alone did not provide analgesia but together with morphine it was found to be superior to morphine alone in preterm infants undergoing central line placement. However, morphine caused respiratory depression and tetracaine caused erythema in 30% of the infants (Taddio et al. 2006). In term infants, local lidocaine-prilocaine 5% cream (EMLA®) has been less effective in reducing pain during venepuncture compared to oral glucose (Gradin et al. 2002). Oral sucrose has also been shown to be more effective during subcutaneous injections compared to EMLA. However, oral sucrose and EMLA together have a synergistic effect which is more effective than either alone (Mucignat et al. 2004). EMLA may diminish the pain from venipuncture, arterial puncture and percutaneous venous catheter placement in preterm infants. However, efficacy data for these procedures is limited. EMLA does not diminish the pain from heel lancing in preterm infants which may be explained by painful squeezing during blood collection. As far as safety is concerned, it is known that a single administration of local anaesthetic cream does not cause methemoglobinemia (Taddio et al. 1998.) It seems that local anaesthetics have synergistic effects with other treatments. However, it must be kept in mind that local anaesthesia creams must be applied at least 30 minutes before the procedure, depending on the preparation.

Non-pharmacological pain management methods

In non-pharmacological pain management the idea is to reduce preterm infant's pain and stress by improving the regulatory and coping abilities of the infant (Franck & Lawhon 2000). The mechanisms of these interventions are mainly still unknown. One assumption is that non-pharmacological methods activate the gate control mechanism (Melzack & Wall 1965). The effects of sucrose and pacifiers are thought to be mediated by both endogenous opioid and non-opioid systems (Blass & Shah 1995, Blass & Watt 1999) although not all of the evidence supports this view (Gradin & Schollin 2005). Oxytocin released for example by non-noxious sensory stimulation (Uvnäs-Moberg et al. 1993) may also have an anti-nociceptive effect (Lundeberg et al. 1994, Petersson et al. 1996). Pain alleviation can also occur by the presence of a comforting person and touch (Diego et al. 2007) diverting attention.

Oral sucrose (Stevens et al. 2010b) and glucose (Carbajal et al. 2002) are the most widely studied treatments and have been proven to be effective and comparable (Okan et al. 2007) despite different constitutions. The pain reduction effect of sucrose is mainly seen in behavioural responses (Stevens et al. 2010b, Holsti & Grunau 2010). The sweet solutions alleviate procedural pain during heel lance (Gibbins et al. 2002, Okan et al. 2007), venepuncture (Gaspardo et al. 2008), subcutaneous injection (Mucignat et al. 2004) and nasogastric tube insertion (McCullough et al. 2008). During eye examination alleviating (Gal et al. 2005) as well as neutral results (Stevens et al. 2010) are available. Despite reduction in the PIPP scores, the pain intensity has remained relatively high (Sun X et al. 2010). The optimal dose of sweet solution has been impossible to identify since the dose range of 0.05 ml to 0.5 ml of 24% sucrose solution has been proven to be effective. The greatest analgesic effect occurs when sucrose is administered approximately two minutes prior to a painful procedure (Stevens et al. 2010b.) A study by Johnston et al. (1999) suggests that repeated dosing at two minute intervals further decreases pain compared to single dosing. The effectiveness has also been shown to endure over time by frequent administration (Stevens et al. 2005).

In a recent Cochrane review, no major short-term adverse effects were found related to the administration of single doses of oral sucrose. However, adverse effects were only reported in 12 out of 44 studies and more studies are needed on vulnerable preterm infants (Stevens et al. 2010b). There are some uncertainties related to the long-term adverse effects of oral sucrose, such as weaker self-regulatory behaviours and delayed motor development at term, when compared to preterm infants treated with a placebo (Johnston et al. 2002), therefore possible adverse effects related to the long-term use of oral sweet solutions require further investigation (Holsti & Grunau 2010).

The pacifier is one of the first studied non-pharmacological methods and was proven to effectively decrease behavioural and physiological distress at some extent in preterm infants during heel lance (Field & Goldson 1984, Stevens et al. 1999, Corbo et al. 2000). The benefit of using a pacifier is that it can easily be combined with the use of an oral sweet solution. This synergistic effect is found to further decrease pain compared to the sweet solution or pacifier alone (Stevens et al. 1999, Gibbins et al. 2002). However, synergistic effect requires frequent and intense sucking, which is sometimes absent in preterm infants (Blass & Watt 1999, Carbajal et al. 2002).

Research concerning other non-pharmacological options is scarce and inconsistent. There is reasonable evidence available to suggest that methods utilizing physical contact such as kangaroo care (KC), breastfeeding and facilitated tucking alleviate pain in preterm infants (Cignacco et al. 2007, Leslie & Marlow 2006, Golianu et al. 2007). These methods offer touch and proximity to preterm infants and involve or have the potential to involve the parents in pain management. Implementation of these methods in clinical practice requires new paradigms of care expecting increased focused attention, empathy from staff and avoidance of separation between parents and infants (Anand & Hall 2008).

Kangaroo care is an effective pain alleviation method for preterm infants during heel lance (Ludington-Hoe et al. 2005, Cong et al. 2009, Cambell-Yeo 2010). Pain reduction has been more consistent in behavioural than in physiological parameters (Johnston et al. 2003, Castral et al. 2008). Although research concerning this method is quite recent, a Cochrane review including fourteen studies is to be published soon. Skin-to-skin contact before a painful procedure varied in studies from two minutes to three hours. However, in 11 out of 14 studies the duration of skin-to-skin contact was under 30 minutes (Cambell-Yeo 2010). This indicates that this method is quite achievable in the NICU environment if pain management is carefully prearranged. However, KC is not easy to apply several times during one day unless the infant is in kangaroo mother care (KMC), involving 24-hour skin-to-skin contact.

Breastfeeding adds two potential components of pain alleviation to KC; milk and sucking. It has been shown to alleviate both behavioural and physiological components of procedural pain in term infants when compared holding, positioning, pacifier, placebo or no intervention. The administration of a sweet solution had a similar effectiveness as breastfeeding for reducing pain (Shah et al. 2006, Leite et al. 2009.) In one study, the effect of breastfeeding has even exceeded the effect of oral sucrose when administered on the third postnatal day (Codipietro et al. 2008). The recent study suggests that the effect of intervention is related to duration, dosing and sucking frequency (Leite et al. 2009). However, all of these studies were done with term infants. This is understandable due to the challenges of breastfeeding in preterm infants. Despite future research should pay more attention to this patient group. In preterm infants, 1 ml of breast milk administered via a syringe was not shown to alleviate pain (Skogsdal et al. 1997.) This might be explained by missing additive effects such as suckling and the proximity of the mother. However, 5 ml of breast milk administered via a syringe has alleviated pain in term infants (Upadhyay et al. 2004) suggesting more studies with variation in timing and dosing are needed.

If given the right support, such as touch, infants can develop behaviours helping them to cope better with the stresses of extrauterine life. One potential method using both touch and position is facilitated tucking (Corff et al. 1995, Huang et al. 2004, Ward-Larsson et al. 2004). In facilitated tucking, a nurse holds the infant in the side-lying, flexed foetal-type position. This posture supports the infant body, which may increase the infant's ability to cope with pain. Adding simultaneous skin contact to postural support may also result in a synergistic effect of pain control. Earlier crossover studies showed that facilitated tucking alleviated pain during heel lance (Corff et al. 1995, Huang et al. 2004) and after endotracheal suctioning (Ward-Larson et al. 2004) in preterm infants. Facilitated tucking has also been found to reduce sleep disruption time and sleep stage changes during a 15-minute post-heel-lance period compared to a normal nursing routine without tucking (Corff et al. 1995). It is not always possible to evaluate if pain reduction appears in behavioural or physiological parameters (Huang et al. 2004, Ward-Larson et al. 2004). In one study, the increase in heart rate during heel lance has been comparable to that during no treatment (Corff et al. 1995). In these studies, the pain management was applied by a nurse but the method can easily be adapted to the parents. Facilitated tucking could be a new, easily and frequently applied family-centred approach for parents to use in the NICU.

2.2.3. Consequences of pain

It is necessary that caregivers understand the consequences of neonatal pain so that they understand the importance of treating it appropriately (Anand & Hall 2007). The immediate adverse effects of pain are changes in behavioural and physiological stability, such as crying, agitation (Porter et al. 1999), increased blood pressure, heart rate, respiratory rate and desaturation episodes (Lawrence et al. 1993), and changes in intracranial pressure (Bartocci et al. 2006). Fluctuations in blood pressure, especially during the first week of life, predispose these infants to IVHs (Volpe 1995).

Recurrent pain exposure is associated with increased pain behaviours and sensitization in the area of tissue damage such as the heel (Fitzgerald et al. 1989, Andrews & Fitzgerald 1994, Abdulkader et al. 2008), whereas prolonged exposure has lead to dampened pain behaviours in preterm infants (Johnston & Stevens 1996). Pain also modulates the responses to non-painful stimuli and vice versa. Pain before clustered nursing care has been found to dampen self-regulatory behaviours and induce behavioural reactions comparable to pain reactions during this non-painful event (Holsti et al. 2005b). On the other hand, a tactile stimulus before heel lance resulted in an increased pain response (Porter et al. 1998). These alterations can be explained by central sensitization, in which the central nervous system becomes sensitized to a stimulus (Fitzegerald et al. 1988, 1989, Andrews & Fitzgerald 1994).

Stress markers, such as the levels of cortisol, were also shown to be altered due to pain in preterm infants in the NICU, and still at the corrected age of 18 months. The high number of painful procedures was significantly correlated with alterations in the endocrine stress response system, putting preterm infants at risk of adverse effects on brain development (Grunau et al. 2005, 2006, 2007). These alterations occur when the systems involved in maintaining homeostasis, such as the hypothalamic-pituitary-adrenal axis, the immune system and the autonomic nervous system, remain elevated over time, leading to increased ongoing stress. Accordingly, pain and stress from several sources can have additive or synergistic effects. Pain and stress can interfere with the development of hippocampal region (Grunau et al. 2006) which is important for cognitive functions such as long-term memory.

The long-term consequences of neonatal pain include alterations in sensory processing and non-optimal neurological development. Very low-birth-weight infants were shown to have a lower pain sensitivity than full-term controls at one month of age (Grunau & Craig 1994). Neonatal care and surgery are associated with persistent changes in sensory processing, such as a decreased sensitivity to thermal modalities due to localized tissue injury and centrally mediated alterations in nociceptive pathways (Hermann et al. 2006, Walker et al. 2009). The most severe deleterious finding was the association between high pain exposure and cognitive and sensomotoric delay at 18 months in very preterm infants (Grunau et al. 2009).

The long-term consequences of pain are further modified by interaction within the infants' family. It was shown that neonatal experience with repeated pain exposure, poor maternal sensitivity to child cues, and child avoidance of proximity at the age of three years have predicted somatization in extremely preterm infants (birth weight <1000g) (Grunau et al. 1994). Furthermore, low parenting stress in the mother positively modulates the deleterious effects of pain on cognition of preterm infants (Grunau et al. 2009, Tu et al. 2007). These findings suggest that parents have an important and understudied role in modulating pain-related adverse effects in preterm infants. On the other hand, the influence of infant pain on the parents is another similarly ignored side effect. Franck et al. (2004, 2005) showed that it causes psychological stress to the parents. Infant pain seems to have a two-way influence within the family and this interaction needs further research.

2.3. Parental participation in the pain care of preterm infants

When asked, parents expressed a wish to get more involved in the pain care of their preterm infants (Franck et al. 2004, 2005b). Several reasons were given for participation, such as the lack of sensitivity of the staff regarding infant pain, the parental protective role and the fact that participation in pain care alleviates their own pain-related stress (Gale et al. 2004). Rationales for active parental participation were also retrieved from research into the needs of infants in relation to pain care. Preterm infants are exposed to a considerable amount of untreated pain during their NICU stay (Carbajal et al. 2008.) This untreated pain has harmful effects on the development of preterm infants (Grunau et al. 2009) which could be reduced by optimal parenting (Grunau et al. 2009, Tu et al. 2007).

2.3.1. Experiences of parents in pain care

Parents are aware of infant pain in the NICU (Franck et al. 2001) and it is a source of stress for them (Franck et al. 2004, Gale et al. 2004). In the qualitative study by Gale et al. (2004), this stress was related to the inability to fulfil a parental role such as protecting and comforting the baby. Parents were also worried about the consequences of pain on the later development of their infant. However, support and information from nurses, as well as active involvement in pain care, were factors which relieved the parents' infant pain-related stress (Gale et al. 2004.) The concerns of parents related to the harmful consequences of pain in their infants were confirmed in the quantitative approach by Franck et al. (2004). Over all, the parents were satisfied with the pain care, however, all their information needs were not met during their NICU stay. Information on pain care increased parents' awareness of infant pain and its management. The majority of parents would have preferred a more active role in the pain care of their infants. Parents who were more stressed and rated their infant's pain higher appreciated being absent during painful procedures. In addition, it was shown that parental stress was predicted by the concerns of parents related to infant pain (Franck et al. 2004).

Every third parent was found to be concerned about the effects of infant pain on their mutual relationship with their infant. Some parents also said that they were not totally satisfied with the actions of staff in relation to their infant's pain. According to some of the parents, it was thought that the staff could give more information and be more sensitive to the parents' wishes: some wanted to participate as much as possible, some needed encouragement and some wished to withdraw during painful procedures or pain (Franck et al. 2005b). The parents in this study were from the same sample as those in the 2004 study by Franck et al. It is not known in-depth how active participation in the pain management of preterm infants is experienced by parents. Consequently, there is no knowledge of the factors which could explain the different attitudes of parents to participation. The stress resulting from the NICU environment or from infant pain may help to explain this variation to some extent. Studying the process of actively involving parents in the pain care of preterm infants could give a deeper understanding of the matter.

2.3.2 The potential in parents for pain management

Mothers have instinctively comforted their offspring as a means of survival of the species throughout human history (Johnston et al. 2007). It was only the technical NICU environment that separated families from the care of their infants in its early years, although this was done with good intentions, such as the prevention of infection. The increased awareness of the harmful effects of separating parents from their preterm infant and good outcomes related to parental participation (Feldman et al. 2002, Melnyk et al. 2006) have changed the methods of care towards a more family-centred approach. The pain care of preterm infants is perhaps one of the last areas of care where the resources and potential of parents are not fully recognized and used. Studies with kangaroo care have shown that parents are capable and willing to alleviate their preterm infants' procedural pain (Cambell-Yeo et al. 2010). In addition, parents have been found to be equally effective at carrying out complex sensorial saturation pain management procedures as nurses during heel lance (Bellieni et al. 2007).

If the presence of parents in the NICU is to be increased (Örtenstrand et al. 2010), and if the role of primary caregiver is to be given to them, it is essential to know what kind of support they need during infant pain and stress so that they are able to support optimal development of their preterm infants. The frequent but soothable crying and the consequential holding of a preterm infant have been positively related to the quality of mother-infant interactions (Korja et al. 2008), suggesting that skill in sensitively responding to infant stress cues can have a positive effect on development of the preterm infant. It is also possible that if parent-infant interactions during stressful and painful procedures are not supported, long-term negative effects can result (Grunau et al. 2004, 2009). The unidentifiable and underused potential in parents to protect their preterm infants from harm are factors which encourage their active involvement in the pain management of preterm infants in the NICU.

2.3.3. Barriers to parental participation in pain management

In general, parents are more willing to take responsibility for the care of their infants than nurses and neonatologists previously thought. Both parents and healthcare professionals see that parents can alleviate infant pain, although this is not yet routinely practiced in clinical work (Nyqvist & Engvall 2009.) Very little is known about the factors which limit active parental participation in the pain care of preterm infants.

One barrier preventing parents from carrying out their protective role is their absence when the infants are exposed to pain (Gale et al. 2004, Franck et al. 2005b). This could be a consequence of their infrequent visits to the NICU or of the nurses deliberately performing painful procedures outside parent visiting times. An explanation for the nurses working this way could be that they are afraid that the infant pain is too much for parents to see and manage. In one study, only 64% of nurses were willing to recommend kangaroo care for pain management, even though it is known to alleviate pain. Their main concern was that they would stress the mothers by using kangaroo care as a pain management method (Cambell-Yeo 2010).

Parents need more information and a means of detecting and alleviating the pain of their preterm infants (Franck et al. 2001). Parents' expectations of pain care could also be taken into account more carefully**.** Active parental participation in the pain care of preterm infants presumes an open communication and active guidance from NICU staff (Gale et al. 2004, Franck et al. 2004, 2005b). In addition, it is challenging for parents to offer their infant 30-minute kangaroo care before six painful procedures in a day. Breast feeding also has limitations due to preterm infants' inability to actively suck when sick and so young. Clinical practice is missing pain management methods which enable the frequent participation of parents in the pain care of preterm infants.

2.4. Gaps in the knowledge of current literature

Parents need education and support when the family encounters an unexpected preterm birth. This situation puts the parents and the preterm infant at risk of separation. In the NICU environment, it is crucial to engage parents in the care of their preterm infants as early, extensively and sensitively as possible in order to safeguard the optimal development of preterm infants. Infant pain is one situation which often leads to the separation of parents and their infant. Preterm infants are subjected to dozens of untreated painful procedures during their NICU stay. Earlier findings suggest that parents have an important and understudied role in alleviating infant pain and modulating its adverse effects. On the other hand, the influence of infant pain on the parents is another adverse effect which is often overlooked although it is known to cause psychological stress to parents. Infant pain seems to have a two-way influence within the family and this interaction needs further research.

Although infant procedural pain can be effectively treated by pharmacological and non-pharmacological means, very little is known about the short-term and prolonged effects of these methods in preterm infants. In addition, to the best of our knowledge, opioids and non-pharmacological pain management methods have not been compared to each other in any previous study. The pain management of preterm infants is also in need of new and easily applied methods which the parents can use since they want to participate more actively in pain care and they have the potential to modulate the deleterious effects of pain on the later development of their infants. The next step in research could be to develop a new, effective, safe and feasible pain management method for parents to use and to study its influence within the family.

3. AIMS AND HYPOTHESES OF THE STUDY

The aim of this study was to examine whether pain management using facilitated tucking by parents (FTP) is an effective and safe treatment for procedural pain in preterm infants, and whether it is accepted by their parents.

The detailed research questions and the hypotheses or research tasks of the study were:

1) Does FTP alleviate procedural pain in preterm infants?
   a) We hypothesized that FTP is an effective pain management method compared to control care (the nurse was allowed to talk to and pat the infant) during endotracheal or pharyngeal suctioning in preterm infants (Study I).
   b) We hypothesized that non-pharmacological methods (FTP, oral glucose) are equally effective as a pharmacological method (intravenous oxycodone) and more effective than a placebo (oral water) in pain management during heel lancing and pharyngeal suctioning in very preterm infants (Study II).

2) Does FTP during painful procedures compromise physiological stability in preterm infants?
   a) We hypothesized that preterm infants calm down significantly faster with pain management (FTP) than without pain management after endotracheal/pharyngeal suctioning (Study I).
   b) We hypothesized that short-term adverse effects related to the administration of FTP do not differ from those with oral glucose or intravenous oxycodone in very preterm infants (Study II).
   c) We hypothesized that sleep structure in very preterm infants is different after painful procedures accompanied by FTP or other pain management methods (oral glucose or intravenous oxycodone) compared to painful procedures without pain management (oral water as placebo) (Study III).

3) How do parents accept their active role in the pain care of their preterm infants using FTP?
   a) Description of parents' perceptions of FTP (Study I).
   b) Description of mothers' involvement in the pain care of their preterm infants by using FTP (Study IV).

4. MATERIAL AND METHODS

The answers to the research questions were researched using three different study designs (Figure 2).

Research questions	Study design	Participants
1) Does FTP alleviate procedural pain in preterm infants?	RCT, crossover design (Study I, 2003-2004) RCT, crossover design (Study II, 2005-2007)	Preterm infants born < 37 weeks of GA, n=20 Preterm infants born ≤ 31 weeks of GA, n=20
2) Does FTP during painful procedures compromise physiological stability in preterm infants?	RCT, crossover design (Study I, 2003-2004) RCT, crossover design (Study III, 2005-2007)	Preterm infants born < 37 weeks of GA, n=20 Preterm infants born ≤ 31 weeks of GA, n=18
3) How do parents accept their active role in the pain care of their preterm infants with FTP?	Post-intervention survey (Study I, 2003-2004) Post-intervention CLIP interview (Study IV, 2008-2009)	Parents, who used FTP in Study I, n=20 Mothers of preterm infants (32-34 GA), who used FTP during infants' hospital stay, n=23

Expected outcome: Recommendation whether FTP can or cannot be implemented in the pain management of preterm infants in clinical practice

Figure 2. Three research questions, study designs and participants.

4.1. Experimental intervention of Facilitated tucking by parents (FTP)

In this study, the effective pain alleviation method of facilitated tucking applied by the nurses (Corff et al. 1995) was adapted for the parents use. In tucking, a parent holds the infant by her or his hands in a side-lying, flexed foetal-type position, offering support and skin contact (Figures 3 and 4). The parent's hands have to be warm and the hold needs to be firm before, during and after the painful procedure. It takes from one to two minutes for the infant to adapt and relax under the new sensorial stimulation; therefore, it is recommended that tucking is applied at least two minutes before the painful stimulus. Parents need very detailed education in how to hold the infant in advance. During the painful procedure the nurse can provide support by encouraging the parent to keep holding firmly.

Figures 3 and 4. In facilitated tucking by parents, a parent holds the infant in the side-lying, flexed foetal-type position. The support by the parent's hands can be offered mostly to the infant's middle and lower-body (Figure 3) or to the upper-body (Figure 4) depending on which way the most skin-to-skin contact and support is available for the infant.

The effect of FTP could be based on the infant's supported position which promotes sleep (Modricin-Talbot et al. 2003) and physiological stability (Grenier et al. 2003). Physiological stability in preterm infants can also be supported by touch (Harrison et al. 2000), skin-to-skin contact (Feldman et al. 2002) and massage (Hernandez-Reif et al. 2007). This has been suggested to be mediated through increased parasympathetic activity (Diego et al. 2007, 2009) during relaxed state. Touch is the earliest sensory modality which develops at 9-12 weeks of GA. The analgesic effect of touch may also be mediated through oxytocinergic mechanisms (Uvnäs-Moberg et al. 1993). In addition, C-fibres mediate both pain and sensorial stimulation in the preterm period, therefore, these two sensations can potentially override each other (Beggs & Fitzgerald 2007).

4.2. Study subjects

Participants (Study I)

During a ten-month period in 2003-2004, 20 preterm infants and one parent of each infant participated in this study in the NICU at the Turku University Hospital. The criteria for inclusion were ≤ 37 completed weeks of GA at birth, no major congenital anomalies, a need for regular endotracheal or pharyngeal suctioning and no analgesics for four hours before the procedure. Parents of five preterm infants refused participation. Reasons were the stress caused by the sick preterm infant (n=4) and a fear that the study could cause more pain for their child (n=1).

The sample size for this prospective randomized crossover study (Study I) was calculated using the primary outcome of pain response measured by NIPS (Lawrence et al. 1993). Using data from prior studies (Blauer & Gerstmann 1998, Hudson-Barr et al. 2002), a reduction of 2 points in the NIPS scores during a painful procedure was considered clinically significant. The calculation for the sample size was performed using a Wilcoxon rank sum test with 80% power, a significance level of 0.05 and SD 2.5. A sample size of 20 preterm infants was required.

Altogether 20 preterm infants (Table 1) and one parent of each child took part in the study. Six of the infants were girls and four were boys. Most of the infants (15/20) did not have any IVH, three had IVH grade I, one had IVH grade III and one had IVH grade IV. Almost every infant (17/20) needed a CPAP device for respiratory support; two infants were on a ventilator during the study and one had just been extubated.

Table 1. Characteristics of the study infants in Study I.

Characteristics	Median	Range
GA at birth (weeks)	28	(24-33)
PNA (days)	15	(6-37)
Birth weight (g)	950 g	(690-1920)
Prior suctioning	65	(24-235)

Three fathers and seventeen mothers participated in the study. The median age of the parent was 28 years old (range from 18 to 38 years). The parents had 0 to 3 older children and one family had previously had another child in a NICU. Thirteen parents visited their child several times a day, six visited once a day, and the remaining parent visited less than once a day. Every parent had some experience in the care of their preterm infant before the study.

Participants (Studies II and III)

During the two-year period from 2005–2007, all infants up to the GA of 31 $^{0/7}$ weeks at birth, who were cared for at the NICU of the Turku University Hospital, were eligible for participation in the study. The exclusion criteria were 1) no need for nasal CPAP, or no need for regular blood sampling and pharyngeal suctioning at post-conceptional age (PCA) below 32 weeks, 2) a major congenital anomaly, 3) IVH > II in an ultrasound examination before the study or cystic PVL in magnetic resonance imaging later at term age, 4) pain or sedative medication six hours before the study and 5) unstable health condition at the time of the study according to the attending neonatologist. Twelve of the families who were approached for consent refused to participate (35%). Thus, a total of 22 preterm infants and their parents participated in this study, which was performed when the infants were at PCA of 28 to 32 weeks. The drop-out analysis showed no differences in GA or birth weight between the study infants and the infants who did not participate. The participant flow is illustrated in Figure 5.

The sample size for this prospective randomized crossover study (Study II) was based on a clinically significant three-point reduction of pain in the PIPP scores (Stevens et al. 1996) during a painful procedure with pain management compared to a placebo. The calculation was performed using a paired t-test with 85% power, a significance level of 0.05 and SD 3.53 (Stevens et al. 1999). A sample size of 19 preterm infants was required. Due to the lack of previous studies, the sample size calculation for sleep variables in Study III was not possible. In a post-hoc power analysis, a sample size of 18 infants had the power to demonstrate an 8.0% to 9.6% difference in total sleep time and a 12.1% to 12.5% difference in REM sleep proportion after oral glucose or FTP compared to the placebo during the post-intervention hour. The calculation was performed using the paired t-test with 85% power, a significance level of 0.05, a 0.25 correlation between measurements and SD 9.3-11.1 for total sleep time and SD 12.35-14.45 for the REM sleep proportion.

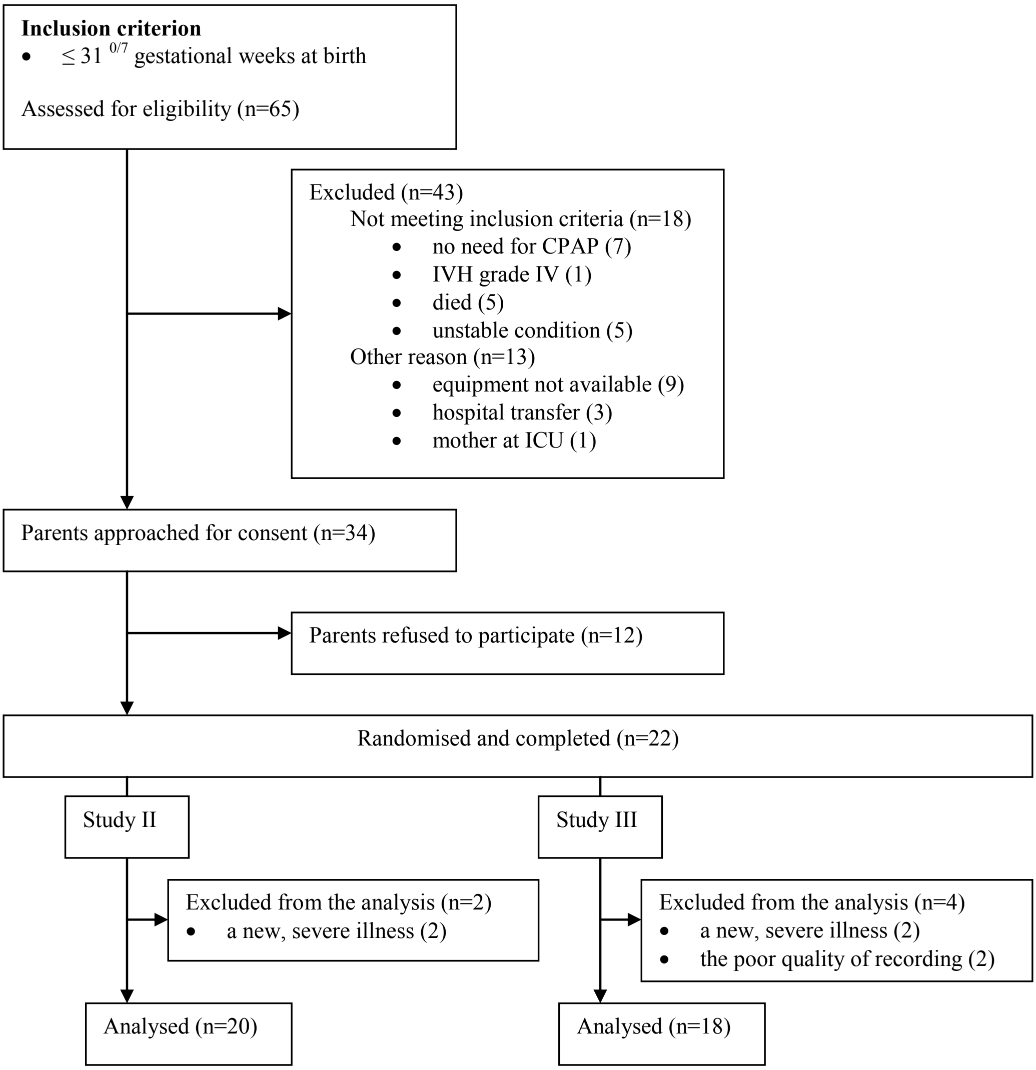

Figure 5. Participant flow to Study II and Study III.

The study sample for Studies II and III comprised of 22 preterm infants (Figure 5). In Study II, two recordings were discarded and in Study III four recordings were discarded. Only one infant had IVH (grade II). Half of the infants were on theophylline treatment

(6 mg/kg/day). The characteristics of the study infants are described in more detail in Table 2.

Table 2. Characteristics of the study infants in Study II and Study III.

	Study II (n=20)		Study III (n=18)	
Characteristics	**Mean**	**(SD)**	**Mean**	**(SD)**
Female/male	8/12		7/11	
GA at birth (weeks)	$28^{1/7}$	(2.3)	$28^{1/7}$	(2.3)
PNA (days)	16	(12)	16	(12)
Birth weight (g)	1123	(327)	1140	(332)
5 min Apgar (median, range)	7	(2-9)	7	(2-9)
Prior painful procedures	121	(109)	122	(115)
Prior suctioning	56	(64)	56	(68)
Prior heel lance	42	(35)	42	(37)
Prior oxycodone doses	20	(30)	20	(32)
Prior acetaminophen doses	3	(6)	3	(6)

Participants (Study IV)

Mothers whose preterm infants were born between 32 and 34 weeks of gestation and were cared for in the NICU were eligible to participate in this study. Exclusion criteria were: 1) mother's inability to participate in infant care on the third post-partum day, 2) mother's native language being other than Finnish or Swedish, 3) planned hospital transfer of an infant before discharge and 4) an infant with a life-threatening illness. Twenty-nine families were approached for participation, of whom six refused. The reasons mentioned for refusal were stressful situation for the family and unwillingness to be recorded by video during the interview. Informed written consent was obtained from both parents of each infant. After providing the parents with written and verbal information on the second or third post-partum day, the parents were given one day to consider their participation in the study.

Twenty-three mothers (n=23) participated in the study. Six of them had twins. The mean age of the mothers was 31 years old and the mean length of education after the nine years of elementary school was six years. Only five of them had a previous child or children. Every mother participated in the care of her preterm infant at least twice a day. Preterm infants of these mothers were relatively healthy. Their mean gestational age was $32^{6/7}$ weeks and the mean birth weight was 1960 g. Only 6 out of 29 infants had been on a ventilator for a mean of two days. The mean number of painful procedures was three per day per infant during the first two weeks of life.

4.3. Study designs, procedures and data collection

Study I

By using a prospective randomized crossover design (Figure 6), each preterm infant and parent was to undergo endotracheal or pharyngeal suctioning for clinical purposes using either FTP or control care within a period of no longer than two days. The order of conditions was randomized by an outside assistant. In the FTP condition, the parent had been taught the procedure in advance. The FTP was used during the entire suctioning procedure and after until the infant calmed down. In control care, the nurse was allowed to talk to and pat the infant. There were no other procedures for at least an hour before the study procedures. The incubator was covered with a blanket and the infant's position was supported by nesting. During endotracheal or pharyngeal suctioning, each infant was laid on their right side. If used, the nasal CPAP device was removed just before the procedure.

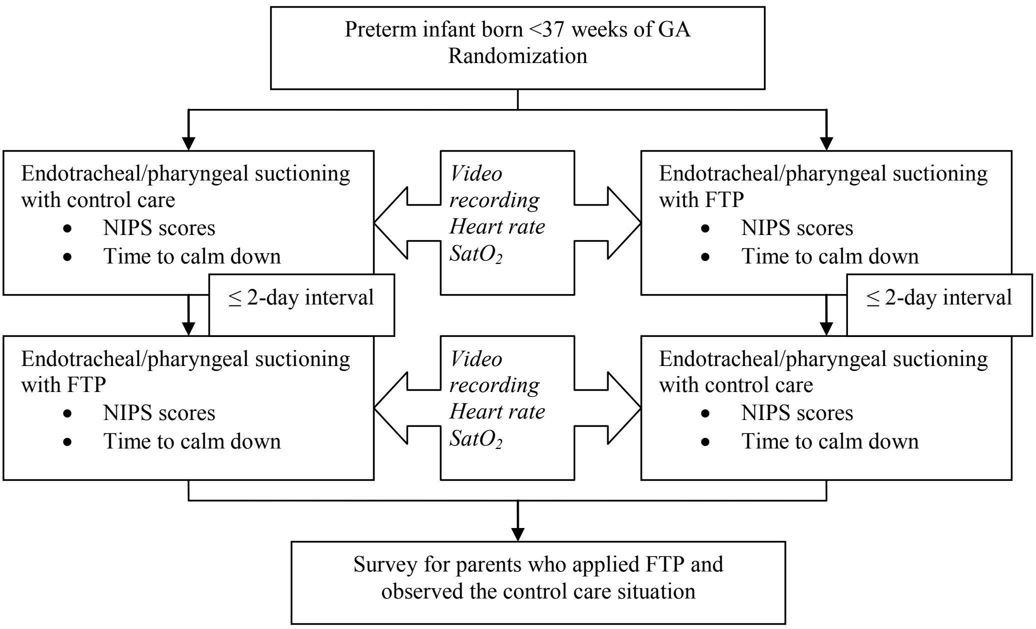

Figure 6. Intervention and measurement protocol in Study I.

Baseline video recording was started two minutes before the suctioning procedure. After two minutes, a nurse applied saline to both nostrils and suctioned the throat and mouth of the infant and the endotracheal tube of the intubated patients. Video recording continued for at least a minute or until the infant had calmed down. In addition, the parents were asked during recording if the infant's arms or legs were tense or struggling to support visual analyses of the tapes. The parents were given a questionnaire after both conditions.

Background data concerning the infant was collected from the patient records. This information included gender, birth weight, GA at birth, postnatal age, respiratory support, possible IVH and the number of earlier endotracheal or pharyngeal suctionings. The parents were given a separate questionnaire inquiring their gender, age, number of older children, possible previous experiences in an NICU, how often they visited the NICU and how many times they had taken part in the child's care before the study.

Heart rate and oxygen saturation data were gathered from the bedside monitors. Hewlett Packard 60 S and Philips IntelliVue Neonatal B.05.67 monitors recorded the parameters in one minute intervals. The heart rate was computed by averaging the 12 most recent beats-per-minute values and oxygen saturation was recorded at the end of each minute.

Studies II and III

A prospective randomized placebo-controlled crossover design was used for both Studies II and III (Figure 7). The study design was adapted to the routine, daily care of preterm infants in this NICU. All infants were lying sideways in an incubator or on a warmer table with the temperature adapted to maintain the normal 37 °C body temperature. The electrodes for sleep recording were fitted between 11:00 and 11:25 a.m. The 13-hour study protocol was always carried out between 1:00 p.m. and 2:10 a.m. Beginning at 2:00 p.m., each infant underwent four 25-minute nursing care periods at three-hour intervals. The resting period (2 h 35 min) between care giving periods was prearranged to be calm and included reduced lighting and limiting of disturbing factors around the infant's bed. During the rest period, the infants were on nasal CPAP, which was removed just before nursing care. The nursing care periods were standardized by having one dedicated research nurse performing the same care routines in the same order for the same duration across the different care periods, thus maximizing comparability. In these periods, the structured care protocol included blood pressure measurement, heel lance, diaper change, temperature measurement, sensor replacement, pharyngeal suctioning, positioning and the beginning of feeding via a nasogastric tube.

Standardized phases of the heel lance procedure included a baseline period (30 seconds), a heel warming period (4 minutes), one heel lance and two squeezes, and a rest period (30 seconds). The lancet used was a Medlance® (SelefaTrade, Ozorków, Poland). The phases during pharyngeal suctioning were as follows: a baseline period (30 seconds), a preparation period (4 minutes), suctioning, and a rest period (30 seconds). During suctioning, the research nurse inserted 0.2 ml saline into both nostrils and suctioned the throat and the mouth of the infant using a Nelaton catheter® No 6 (Unomedical, Denmark). The infants were re-positioned on the right side during the preparation period. This position was supported by nesting or FTP during the procedures.

The following pain management methods were used: 1) Facilitated tucking by parents: using their hands, the parent held the infant in a side-lying, flexed, foetal-type position, offering support and skin contact. The parent had been taught the procedure in advance. The method was applied before the heel lance and pharyngeal suctioning, and continued until the infant had calmed down; 2) Oral glucose: the infants were given 0.2 ml of 24% glucose on the tip of their tongue using a 1 ml syringe, two minutes before and just immediately before the heel lance and pharyngeal suctioning; 3) Placebo (oral water): the infants were given 0.2 ml of sterile water in the same way as the oral glucose; and 4) Opioid (oxycodone): the infants were given an intravenous dose of 0.05 mg/kg of oxycodone hydrochloride 10 minutes before the last nursing care period (Oxanest® 10 mg/ml solution for injection, Leiras Oy, Turku, Finland). The heel lance was conducted 15 minutes later and the pharyngeal suctioning 25 minutes after the administration of the opioid.

The opioid treatment was always administered before the last nursing care period to exclude a carry-over effect. The order of the other three interventions was randomized by a study assistant. The researcher (AA) opened a closed envelope, which contained the randomized order, and delivered the syringes of glucose, opioid and water to the research nurse accordingly. Other members of the study group were blinded to the order of glucose and water.

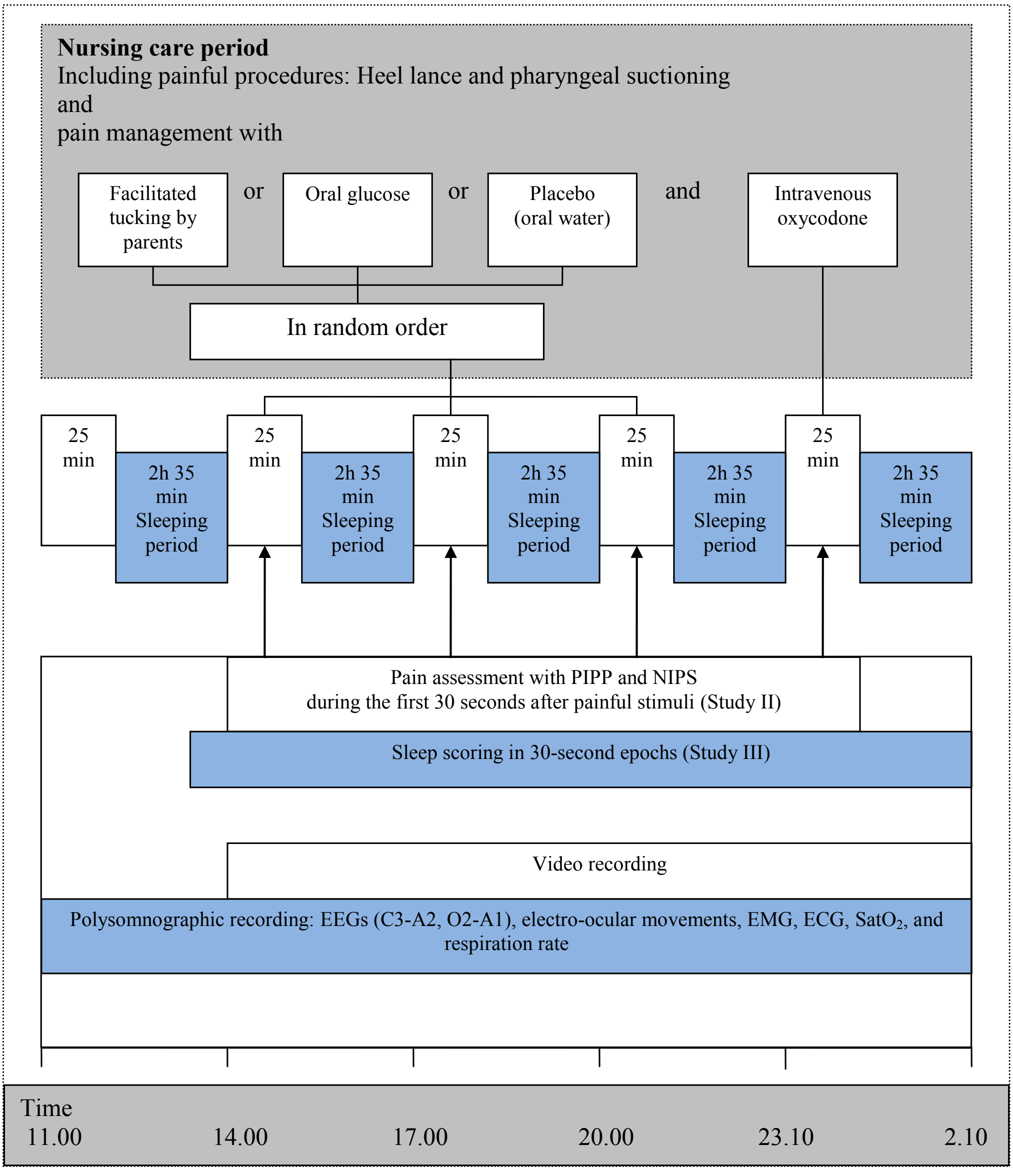

Figure 7. Intervention and measurement protocol in Studies II and III.

Background data concerning the infant were collected from patient records. This information included gender, GA at birth, postnatal age (PNA), birth weight, Apgar scores at 1 and 5 minutes age, possible IVH, possible cystic PVL at term age, possible theophylline treatment, the number of earlier painful procedures and previously given analgesics. Painful procedures that were recorded included intubation, extubation, endotracheal/pharyngeal suctioning, intravenous or arterial line insertion, heel lance, removal of tube/i.v.-line fixation and nasogastric tube insertion. Short-term adverse effects after different pain management methods included desaturation ($SatO_2$ <85) and/or bradycardia (heart rate <100). The occurrence of adverse effects was observed immediately after the administration of different pain managements. The study protocol was not continued until it was certain that the infant's condition was stable after the administration of pain management.

The behavioural data for pain assessment and sleep analysis was collected by video recording using a camera providing a full view of the infant's face and body from above. There was a concern that the FTP itself could have an effect on NIPS parameters such as the movement of arms and legs by restraining movements and by blocking the view for accurate assessment of movements of the extremities. Therefore, during FTP the parents were asked if the infant's arms or legs were tense or struggling to support visual analyses of the tapes. Video recording was started five minutes before the 12-hour study protocol. A Panasonic NV-DX100® was used and the video was captured on a laptop hard disk using PinacleStudio® 8.2 software (Pinnacle Systems, California, USA), (Figure 7).

The physiological parameters for pain assessment and polysomnographic sleep recording were measured using an EMBLA® sleep recording polygraph and were analysed using Somnologica3 ® software (Medcare, Reykjavik, Iceland). The following signals were recorded: two EEGs (C3-A2, O2-A1), electro-ocular movements, chin-electromyogram (EMG), electrocardiogram (ECG), oxygen saturation, and respiration rate. Eye movements were detected with a small piezo electrode placed on the upper eyelid. Disposable Neuroline® electrodes (Ambu, Ølstykke, Denmark) were used to measure all other signals. The respiration rate was detected from respiratory movements measured by thoracic impedancemetry (Hewlett-Packard 26CT, California, USA). The ECG electrodes were placed on the lower part of the thorax and the sampling rate was 100 Hz. For oxygen saturation, the sampling rate was 1 Hz and for all other signals it was 200 Hz. During recording, possible external and behavioural events were indicated by online marking.

Study IV

The study NICU has a family-centred care philosophy which aims for parental competence in infant care prior to discharge. Parents are encouraged to actively participate in the care of their infants immediately after birth. The responsibility for care is gradually shifted from the nurses to the parents during the hospital stay. The nursing interventions that promote this transition include, for example, free visiting times for parents, regular kangaroo care and the primary nursing care model. However, before the year 2008 it was not a common practice for parents to participate in their infants' pain care in the study NICU. In order to understand whether parents were willing to participate in this area of care, FTP was introduced for parents and nurses. The implications of this new practice were evaluated from the mothers' point of view.

The study intervention included written and verbal information for both parents regarding how to alleviate infants' pain with FTP. The tucking procedure was also practiced with the parents during the third post-partum day. Special attention was paid to the firmness of the hold and to having warm hands during the tucking. It was hoped that the parents would use FTP every time the infant was in pain or stress, according to their own opinions. Every nurse in the NICU (n=76) received the same education personally from the main researcher (AA) before the beginning of the study. New nurses were educated in the use of FTP during their orientation period. Parents were encouraged to consult with the nurses about the FTP procedure as needed. Within a few days, the researcher ensured that the parents had understood the procedure.

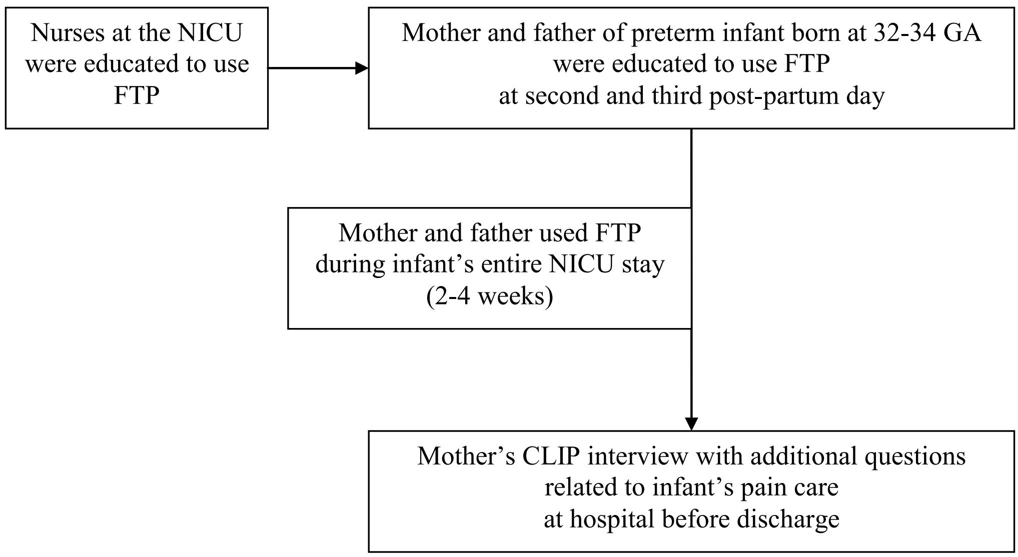

Figure 8. Intervention and measurement protocol in Study IV.

The mothers were interviewed before their infants' discharge after they had used FTP for two to four weeks. The interviews were conducted by one researcher (AA) in an undisturbed room during a one-year period in 2008–2009. All the interviews were videotaped. The interview technique was practiced with three mothers. These pilot interviews were assessed and discussed with a psychologist experienced in the use of the clinical interview for parents of high-risk infants (CLIP). After the discussions, some minor revisions, such as minimizing prompting, were made to the interview technique. The interviews lasted from half an hour to one and a half hours depending on how forthcoming the mother was. Data saturation was obvious after nineteen interviews since no obviously new issues related to FTP or infant pain care were identified. The last four interviews were conducted to ensure saturation.

4.4. Measurements and data analysis

4.4.1. Pain assessment (Studies I and II)

The primary outcome was procedural pain assessed by PIPP (Stevens et al. 1996) (Study II) and NIPS (Lawrence et al. 1993) (Studies I and II).

The PIPP is a 7-indicator, 4-point composite pain scale which consists of three behavioural facial action-based indicators (brow bulge, eye squeeze and nasolabial furrow) and two physiological indicators (heart rate, oxygen saturation). Gestational age and behavioural state are accounted for and modify the given scores. The PIPP scores vary between 0 and 21. A higher total score indicates more intensive pain. The PIPP has been shown to have a good construct validity and moderate internal consistency (0.59-0.74). The inter-rater reliability (0.93-0.96) and the intra-rater reliability (0.94-0.98) of PIPP are excellent (Ballantyre et al. 1999, Stevens et al. 1996). The concurrent validity between the PIPP and the NIPS scale was established ($r_s = 0.44$, $p<0.001$) (Simons et al. 2003b).

The NIPS quantifies the level of pain on a scale from zero to seven based on five behavioural characteristics: facial expressions, crying, movements of arms and legs and the state of arousal. In addition, the breathing pattern is used as a physiological parameter. A higher total score indicates more intensive pain. The instrument has a good construct validity, inter-rater reliability (0.92-0.97) and internal consistency (Cronbach`s alfa 0.87) (Lawrence et al. 1993).

In Study I, the videotapes were analysed by using NIPS in one minute sections. This way, it was possible to assess the infant’s pain at baseline and both during and after suctioning. The highest NIPS score during suctioning was used to represent the maximum pain during the procedure. Two independent scorers rated the NIPS scores from videotapes during both procedures. The peer observer was blinded to the order of the conditions. Inter-rater reliability between scorers was good (Kappa coefficient 0.927).

In Study II, the videotapes and the physiological data were analysed by using PIPP and NIPS. The first 30 seconds after skin puncture and after the suctioning catheter was put in the infant’s mouth were used to represent the pain during the procedure. The duration of the total procedure (heel lance and two squeezes) never exceed 30 seconds in any case. The 30 seconds of suctioning represented the first invasive painful seconds. The duration of suctioning varied between procedures but lasted always at least 30 seconds.

Pain assessment was scored by two independent scorers. Inter-rater reliability between these two observers measured with Kappa coefficient was 0.968 with NIPS and 0.986 with PIPP. The peer observer was blinded to oral glucose and oral water. Another observer also scored a randomly chosen 20% of the periods in which oral glucose, oral water or oxycodone were applied. This peer observer was blinded to all three interventions. Inter-rater reliability between the main scorer and this observer was 0.890 with NIPS and 0.949 with PIPP.

4.4.2. Measurement of short-term adverse effects (Studies I and II)

In Study I, the moments when the parent first placed the infant into the tucking position and when they released it were measured with NIPS in order to detect a potential change in the scores caused by the procedure. In Study II, the number of pain management interventions complicated by bradycardia and desaturation were calculated.

4.4.3. Analysis of behavioural state and sleep (Studies I and III)

In Study I, the time taken for the infant to return to a calm behavioural state i.e. the time interval between the end of the suctioning and reaching the NIPS score of 1 or below was recorded.

In Study III, the 13-hour sleep recordings were scored in 30-second epochs. Infant state was scored as REM sleep, NREM sleep, awake, movement time (MT) or nursing care according to the modified criteria of Lamblin et al. (Lamblin et al. 1999). The criteria for *REM sleep* included continuous or semi-discontinuous EEG, rapid eye movements, irregular breathing, no or only short phases of muscle activity in the EMG and body movements. The criteria for the other sleep states were as follows: *NREM sleep*: discontinuous or semi-discontinuous EEG, no rapid eye movements, regular breathing rate, EMG activity, no or sparse body movements; most of the sleep epochs which did not meet the criteria for REM sleep were scored as NREM sleep; *Awake*: epoch full of muscle activity and movement artefacts or EMG activity; *MT*: epoch in which the state was impossible to score due to signal distortions caused by body movements; *Nursing care*: the period between the start and end of marking points, indicating a nursing care period during recording.

Latency to sleep was determined as the time between the end of the nursing care period, which was noted during online recordings, and the first sleep stage. For the onset of sleep, the first sleep stage was determined as the first four epochs of the same sleep stage after latency to sleep. The total sleep time included REM sleep, NREM sleep and MT. Arousal was defined as one epoch in the awake state, and awakening as more than one epoch of the awake state. In the final statistical analysis, arousals were included in awakenings. The epochs of awakenings were included and the epochs of MT were ignored in the number of sleep stage shifts.

The sleep periods one hour before and after the nursing care periods were scored; the first scorer (JK) was blinded to the infants' pain management during the first three nursing care periods and scored the sleep recordings without visual data from the video recordings; the second independent scorer (AA) scored the infants' behaviour based on polysomnographic and video recordings. The video recordings were also used to identify the signal artefacts. For the final data the two scoring sessions were compared and any discrepancies were resolved by a consensus. The other parts of the sleep recordings were scored by one scorer (AA). This data is shown in a graph (Figure 9) but were not used in the statistical analysis.

4.4.4. Survey (Study I)

The parents completed a questionnaire developed for this study which inquired their experiences in participating in the pain management of their child. They were asked whether they preferred active participation or passive observation during the suctioning procedure. In addition, they were asked to write down explanations for their responses in their own words.

4.4.5. CLIP interview (Study IV)

The clinical interview for parents of high-risk infants (CLIP) (Meyer et al. 1993) was used to understand the mothers' experiences of infant pain care in a broader context. The CLIP is a semi-structured clinical interview which assesses early adaptation to parenthood and to the NICU environment. It is designed to elicit the parent's story of the pregnancy, birth, relationship with the infant, feelings as a parent, reactions to the NICU environment and staff, and expectations about the future. Additional questions related to infant pain care and FTP were integrated into the CLIP. In these questions, the mother was asked to describe a situation when her infant was in pain and to specify her feelings and actions in relation to it. The mothers were also asked about their experiences of using FTP and its feasibility.

4.4. Statistical analysis (Studies I, II and III)

Study I

For the statistical analysis a 2 × 2 crossover design was used to test for differences between the procedures (Jones & Kenward 1989). In cases where there was an absence of carry-over effect, these analyses were performed using a two-sample t-test or Wilcoxon rank sum test. A chi-square test and a two-sample t-test were used to detect possible group differences. Multiple testing was taken into account by using the Bonferroni method. Correlations between the variables were studied using Spearman's correlation coefficient (r_s). The duration of suctioning was used as a covariate in the analysis. Inter-rater reliability between the researcher and a peer observer was examined with the Kappa coefficient (Studies I and IV).

Studies II and III

Drop-out analyses were performed in order to exclude systematic differences in gender (chi-square), age and birth weight (Mann-Whitney U-test) between drop outs and participants. Non-parametric methods were used where age and birth weight were not normally distributed (Studies II and III).

Linear mixed models were used to model the differences between the interventions in PIPP values (Study II) and the other continuous variables (Study III). The subject was used as a random effect in the linear mixed model. The restricted maximum likelihood estimation method was used. In addition, the amount of REM sleep 30 and 60 minutes before treatment was compared to the amount of REM sleep 30 and 60 minutes after treatment using a mixed model without treatment or period effects.

The distribution of the latency to sleep was positively skewed. Before the data analysis, it was grouped into 30-second intervals up to 90 seconds and after that into one group. In addition, the NIPS values were divided into three categories for logistic models; (1) 0-2 no pain/mild pain, (2) 3-4 moderate pain and (3) 5-7 severe pain. Cumulative logistic regression was used to analyse differences between the treatment groups in NIPS values (Study II) and the latency to sleep (Study III). Binomial logistic regression was used to analyse differences between the intervention groups in the first sleep stage (Study III). The generalized estimation equation estimation was used to account for correlations between the repeated measurements in these analyses.

The carry-over effects were considered in the analysis but the effects were not statistically significant in any case, so in the final analysis the carry-over effect was removed from the model. The period effect was also removed from the model in order to estimate differences between oxycodone and the other interventions. With the period effect in the model, it was not possible to estimate differences between the other groups compared to oxycodone, because it was only used in the last period. All the other differences were taken from the model with the period effect included.

In Study III, cubic splines were used to create a smooth graph of the relationships between time after interventions and the percentage of infants in REM sleep.

In all studies, p-values <0.05 were considered statistically significant. The statistical analyses were performed using the SAS System for Windows (SAS Institute Inc, Cary, NC).

4.6. Qualitative data analyses (Studies I and IV)

In Study I, the parents' written explanations as to why they preferred active (n=19) or passive (n=1) participation were inductively categorized into themes such as the infant's pain was alleviated, important role in the care of infant and parent's stress during painful procedure, for example. After categorization, the themes were quantified by counting the parents supporting each category (Burns & Groove 2005)

The mothers' interviews were analysed in three phases: 1) inductively with cross-case analysis (Miles & Huberman 1994), 2) deductively with a coding scheme by Keren et al. (2003) and 3) by drawing the two earlier analyses together.

In the first phase, the inductive cross-case analysis started by transcribing verbatim sections of the mothers' interviews concerning the use of FTP and infant pain care. Then cross-case analysis was used for a descriptive approach (what and how) and an explanatory approach (why). The descriptive approach showed that all the mothers regarded FTP as a positive tool and had used it. The explanatory approach revealed that the mothers' use of FTP was based on different reasons and that it had different meanings for them. Therefore, it was decided to create a typology from the mothers' different ways of being involved in infant pain care with FTP. Themes which emerged during the interviews such as "primary caregiver in pain management", "the efficacy of FTP" and "nurses' role in FTP usage" were recognized by a variable-oriented strategy. The descriptions of themes were based on patterns that appeared in the data (Patton 1990). Using the conceptually ordered display, we analysed which interviews shared similar characteristics and how the content of themes differed across them. The mothers' experiences concerning infant pain care were organized according to the use of FTP and their explanations for its use. The result of the first phase was a typology of three different styles of the mothers' involvement in preterm infant pain care with FTP. To confirm the credibility of cross-case analysis, the data of seven mothers were given to another researcher (SS) who was able to identify the involvement styles of the mothers. In addition, all of the data and the cross-case analysis were introduced to this researcher and she was able to confirm the analysis with some suggestions. The final analysis is a consensus of the views of these two researchers (AA & SS).

In the second phase, with deductive coding, the data were viewed again from the perspective of single cases. One researcher (AA) coded the separate CLIP interviews from video recordings according to the coding scheme developed by Keren et al. (2003). The coding scheme included the following twenty items: 1) fear of loss of the infant, 2) first reaction to pregnancy, 3) was the pregnancy planned, 4) the course of pregnancy, 5) the timing of "pregnancy feeling real", 6) readiness for delivery, 7) fear of loss of the infant or herself during labour, 8) first feelings towards the baby, 9) present feelings towards the baby, 10) the feeling of mutual recognition, 11) parental self-image, 12) reaction to staff, 13) reaction to NICU setting, 14) reaction to lack of control over baby, 15) support system, 16) foreseen future for the baby, 17) readiness for discharge, and mother's general characteristics during interview; 18) affect, 19) organization and 20) the richness of the content. Each item had two to four options. The coding manual was obtained from Dr Keren. Double-coding was conducted on seven interviews (TP) and the inter-rater reliability between coders on all items was 0.79 (Kappa coefficient).

In the third phase, the two earlier analyses were drawn together. The typology of the mothers' three different styles of involvement formed in the first phase was used to examine whether some of the twenty deductively coded CLIP items were typical for the different involvement styles. To understand possible patterns of CLIP items in relation to typology, a typology-based case-ordered descriptive matrix was generated for the CLIP items (Miles & Huberman 1994). At the left side of this matrix was the mother who represented the strongest characteristics of externalized involvement and at the other end was the mother with the strongest elements of internalized involvement. The following six out of twenty CLIP items varied systematically across the three involvement styles: 1) the timing of "pregnancy feeling real", 2) first feelings towards the baby, 3) present feelings towards the baby, 4) the feeling of mutual recognition, 5) reaction to staff and 6) NICU setting. These items were used to make interpretations about the nature of motherhood and adaptation to the NICU environment in relation to involvement in pain care with FTP.

In our typology, maternal attachment was apparent in all styles of involvement but it varied between the different styles. Maternal attachment was defined as the mother's bond towards the infant consisting of behavioural and emotional dimensions. The behavioural dimension included providing protection and care for the infant (George & Solomon 2008). The emotional dimension consisted of the mother's special affectionate bond with the infant and having the infant on her mind (Stern 1998).

4.7. Research ethics

All the study protocols received a favourable statement by the Joint Commission on Ethics of Hospital District of Southwest Finland and were approved by the Turku University Hospital. Written informed consent was obtained from both parents of each infant in every study. The infants were at least five days old when consent was requested to give the parents some time to adapt to the preterm birth (Studies I, II and III). In Study IV, consent was requested on the second or third post-partum day to enable the parents to actively participate in the pain care of their preterm infant as early as possible. After providing the parents with written and verbal information, they were given one day to consider their participation in the study (for all studies).

In the study design for Studies II and III, a placebo was used and all painful procedures of the protocol were not needed each time for clinical purposes. The infants were exposed to two or three extra painful procedures. A placebo-controlled trial is ethically acceptable in cases when only minor harm is caused to the subject or when the methodology is sound (World medical association 2008). The benefit in this study was a strong methodology and the number of infants exposed to possible harms of the study was small. In this study, additional heel lances were considered as a minor harm to the infant. This decision was based on careful evaluation of research ethics (Axelin & Salanterä 2008) and infant safety when conducting pain research with preterm infants. The parents were informed very thoroughly about the use of a placebo and the possible additional heel lancing procedures included in our standardized study design. A relatively high refusal rate of 35% occurred due to parental concern over the additional pain that the study included (n=4) and the infant's already stressful situation (n=8).

Our research protocol raised ethical questions due to the use of a placebo and additional pain. According to the Declaration of Helsinki, a new method should be tested against the best current methods. However, based on our current knowledge it was impossible to name the best evidence-based method as safety issues have not yet been studied sufficiently. It is possible that in future studies the placebo will prove to be safer than our currently used pain management methods. When conducting a randomized trial, it is important to decide what the primary outcome is to be (Tomlinson & Detsky 2010): the effectiveness or the safety of studied intervention.

On the other hand, considering current knowledge on the harmful effects of untreated pain in preterm infants (Grunau et al. 2009), the future design of studies which cause even minor pain to infants can be questioned. The use of a placebo should be considered carefully (Bellieni et al. 2010), although optimal pain management in preterm infants is not known (Taddio et al. 2009). The challenge for the future is to develop sensitive pain assessment tools capable of detecting differences between effective pain management methods. The absence of a placebo would increase sample sizes and expose more infants to the possible risks of clinical studies.

5. RESULTS

5.1. The efficacy of FTP in the alleviation of procedural pain (I, II)

Heel lance

During heel lance, the PIPP scores were significantly lower with oral glucose and FTP when compared to the placebo. The effect of oxycodone did not differ from that of the placebo. The NIPS score classification indicated less pain with FTP and oxycodone, but not with oral glucose, when compared to the placebo (Table 3.). The NIPS scores correlated with the PIPP scores during heel lance (r = 0.7, p<0.0001).

Endotracheal or pharyngeal suctioning

During pharyngeal suctioning, the PIPP scores were significantly lower with oral glucose and FTP when compared to the placebo. The effect of oxycodone did not differ from that of the placebo. The NIPS score classification indicated less pain with FTP when compared to the placebo or control care. The effects of oral glucose and oxycodone did not differ from that of the placebo (Table 3). The NIPS scores did not correlate strongly with the PIPP scores (r = 0.2, p=0.06). In Study I, no statistically significant differences in heart rate or oxygen saturation were found between FTP and control care.

The mean duration of suctioning was 85 seconds (SD 40 seconds) during FTP and 102 seconds (SD 63 seconds) during control care. However, FTP had a statistically significant effect on NIPS scores when the duration of suctioning was included as a covariate (p<0.001). The duration of suctioning partly explained the NIPS scores (p=0.023) (Study I).

Table 3. PIPP and NIPS score distributions during heel lance and endotracheal/pharyngeal suctioning with different interventions.

Pain management	**Heel lance** PIPP score Mean (SD) Study II	NIPS score Median (Q_{25}-Q_{75})	**Endotracheal/** PIPP score- Mean (SD)	**pharyngeal suctioning** NIPS score Median (Q_{25}-Q_{75})	Study I
FTP	5.20 (1.70)**	2 (1-3)***	11.25 (2.47) *	3 (2-3)***	3 (2-3)***
Oral glucose	4.85 (1.73)***	3 (2-3)	11.05 (2.31) *	4 (3-4)	
I.V. oxycodone	6.80 (2.31)	3 (2-3) *	11.85 (2.80)	4 (3-4)	
Placebo (oral water)	7.05 (2.16)	4 (3-5)	12.40 (2.06)	4 (3-4)	
Control care					5 (4-6)

There was a statistically significant difference between the intervention and placebo and the intervention and no treatment; p<0.05*, p<0.01**, p<0.001***. FTP = Facilitated tucking by parents

5.2. The adverse effects of pain and pain management (I, II, III)

5.2.1. Short-term adverse effects (I, II)

The NIPS scores were assessed when the parent first placed the infant into the tucking position and when they released it to detect possible stress caused by the parents' touch. The NIPS scores were 0 in 19/20 of cases and 1 in the remaining case (Study I).

The number of patients exposed to adverse effects such as desaturation and bradycardia related to the administration of the different pain management methods was higher with oral glucose (n=11/20) and oral water (n=8/20) when compared to oxycodone (n=1/20) or FTP (n=1/20). The swallowing of glucose or water often disturbed the breathing pattern of the infants. One infant needed additional nursing care during two administrations. The infant recovered in a few seconds by tickling her foot and providing oxygen supplementation (Study II).

5.2.2. Effect on behavioural state and sleep (I, III)

Effect on behavioural state

The infants calmed down (NIPS score ≤1) more quickly after FTP compared to control care. It took a mean of 5 seconds for an infant to calm down after FTP and a mean of 17 seconds after control care (p=0.024) (Study I).

Latency to sleep and sleep onset

Most of the infants were already asleep at the end of the nursing care period. Thus, the median sleep latency was 0 sec (Q_{25}-Q_{75} 0-0 sec) and did not differ significantly between the pain management interventions. There was a trend to shorter sleep latency after FTP when compared to placebo (to fall asleep in a shorter time OR 4.3, 95% CI 0.93-20.05, p=0.062). After oxycodone, sleep onset was NREM sleep more frequently than for all other interventions: oxycodone vs. FTP (OR 5.0, 95% CI 0.96-26.11, p=0.056), oxycodone vs. oral glucose (OR 8.0, 95% CI 1.41-45.41, p=0.019) and oxycodone vs. placebo (OR 17.0, 95% CI 2.29-126.16, p=0.006) (Table 4).

Sleep structure during the post-intervention hour

The first post-intervention hour seemed to be unique in terms of sleep structure after all interventions. The mean amount of REM sleep was higher before (72.2%) than after (50.6%) the nursing care period in a 30-minute period (p<0.001) and 70.4% vs. 59.3%, respectively, in a 60-minute period (p<0.001). The proportion of REM sleep changed from an initial 72.1% (SD 23.9) to 51.0% (SD 15.8), 37.6% (SD 16.5), 48.9% (SD 25.0), 70.4% (SD 19.6) and 75.5% (SD 21.0) during the subsequent 10-minute periods. The percentages of infants in REM sleep during the 2.5-hour periods are shown in Figure 9. The sleep structure during the hour before nursing care did not differ between the interventions. In that time period, the infants were awake 17.0% (SD 12.2) of the time. The total percentage sleep time was 83.0% (SD 12.2), and this was divided as follows: REM sleep 70.4% (SD 14.2), NREM sleep 29.1% (SD 14.2) and MT 0.6% (SD 0.1). The mean number of sleep stage shifts was 23.2 (SD 7.3) and the mean number of awakenings was 8.4 (SD 3.7).

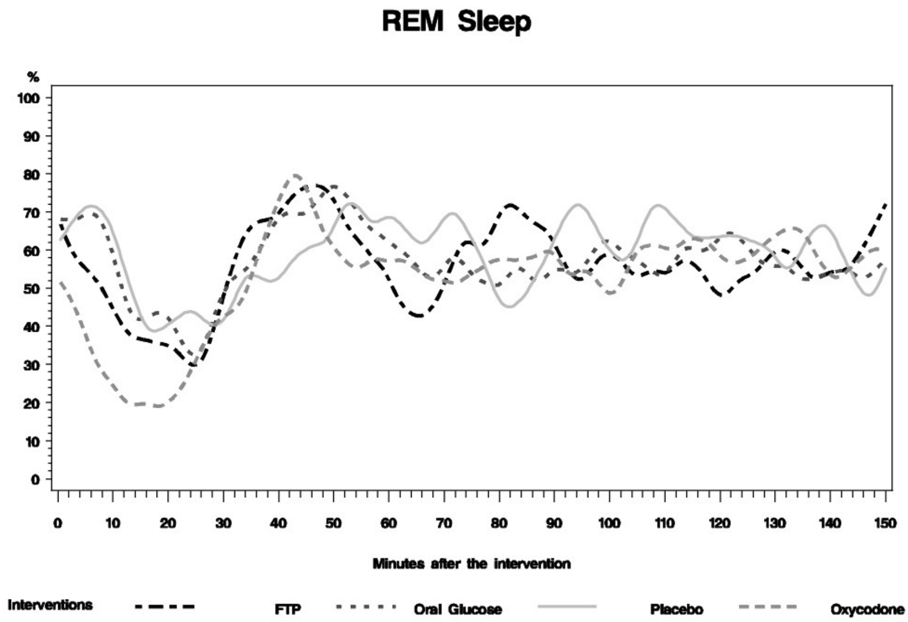

Figure 9. The percentages of infants in REM sleep in 30-second epochs after the four pain management interventions during 2.5 post-intervention hours. (Axelin et al. 2010a)

Effects of the interventions on sleep structure

There was an intervention effect on sleep structure in that oxycodone significantly decreased the amount of REM sleep. The amount of REM sleep was lower after oxycodone compared to FTP (-13.6%, 95% CI -20.9% to -6.3%, p=0.004), oral glucose (-16.4%, 95% CI -23.6% to -9.1%, p<0.001) or placebo (-14.9%, 95% CI -22.2 to -7.7%, p<0.001) during the first hour after nursing care. Consequently, the amount of NREM sleep increased after oxycodone compared to FTP (13.8%, 95% CI 6.6-21.1%, p<0.001), oral glucose (16.5%, 95% CI 9.2-23.7%, p<0.001) or placebo (15.1%, 95% CI 7.9-22.4%, p<0.001) during the same time period. In addition, after oxycodone the longest NREM period was significantly longer than after FTP (p=0.020) or oral glucose (p=0.011) and the number of NREM periods was significantly higher compared to the placebo (p=0.019). No differences were seen in the proportion of awake periods between the interventions although there was a trend for less time awake after oxycodone (oxycodone vs. placebo p=0.070, and oxycodone vs. FTP p=0.075). The characteristics of the infants' sleep structure during the first post-intervention hour are shown in more detail in Table 4.

Table 4. The characteristics of sleep structure during the first post-intervention hour. The mean (SD) is presented unless otherwise indicated. (Axelin et al. 2010a)

Sleep characteristics		Pain management method			
		FTP	Oral glucose	Placebo	Oxycodone
Latency to sleep (s), median (range)		0 (0-1620)	0 (0-480)	0 (0-900)	0 (0-120)
Sleep at onset	REM	83%	89%	94%	50%
	NREM	17%	11%*	6%**	50%
Wakefulness	(%)	10.1 (12.9)	8.6 (9.3)	10.2 (9.3)	4.7 (4.2)
	(min)	6.1 (7.7)	5.2 (5.6)	6.2 (5.9)	2.8 (2.5)
Total sleep time	(%)	89.9 (12.9)	91.4 (9.3)	89.8 (9.3)	95.3 (4.2)
	(min)	53.9 (7.7)	54.8 (5.6)	53.8 (5.9)	57.2 (2.5)
REM sleep proportion	(%)	61.6 (11.9)**	64.4 (12.8)***	62.9 (16.1)***	48.0 (14.9)
	(min)	32.9 (6.5)	34.9 (5.4)	33.6 (8.0)	27.3 (8.4)
NREM sleep proportion	(%)	37.7 (11.6)***	35.1 (12.9)***	36.4 (16.1)***	51.6 (15.0)
	(min)	20.7 (7.9)	19.6 (7.6)	19.9 (9.3)	29.6 (9.3)
MT proportion	(%)	0.6 (1.0)	0.6 (1.5)	0.6 (1.3)	0.4 (0.9)
	(min)	0.3 (0.6)	0.3 (0.9)	0.3 (0.7)	0.2 (0.5)
Awakenings (n)		5.1 (3.5)	5.3 (3.4)	4.3 (3.6)	3.6 (3.2)
Sleep stage shifts (n)		16.2 (6.0)	16.3 (5.2)	13.9 (6.0)	14.8 (6.9)
REM sleep periods (n)		7.7 (2.8)	7.7 (2.5)	6.7 (2.7)	6.4 (2.7)
Length of REM periods (min)		4.8 (1.8)	5.2 (2.7)	5.6 (2.3)	4.9 (2.5)
Length of the longest period (min)		11.6 (5.1)	12.2 (6.7)	12.5 (5.9)	11.0 (5.6)
NREM sleep periods (n)		4.8 (2.3)	5.1 (3.8)	3.6 (1.5)*	5.7 (3.2)
Length of NREM periods (min)		6.2 (5.2)	5.4 (4.0)	5.8 (2.4)	6.5 (3.5)
Length of the longest period (min)		12.3 (6.7)*	11.8 (7.6)*	14.1 (7.3)	17.4 (7.0)

There was a statistically significant difference between the intervention and oxycodone; p<0.05*, p<0.01**, p<0.001***. FTP = Facilitated tucking by parents, REM = Rapid eye-movement sleep, NREM = Non-rapid eye movement sleep, MT = Movement time.

5.3. Parental participation in pain care using FTP (I, IV)

5.3.1. Acceptance of FTP among parents (I)

All but one of the parents (19/20) preferred participation in their own preterm infant's pain care with FTP during the pharyngeal/endotracheal suctioning when compared to passive observation. In the written responses some of the parents (n=5) expressed that they felt uncomfortable in these situations. Despite feeling uncomfortable they wanted to participate and help their child during the painful procedure. The parents felt that they had an important role in the care of their child (n=13), since they could comfort him or her. They felt that their child was calmer (n=7), in less pain (n=6), was more secure (n=10) and calmed down more quickly (n=4) when FTP was used. The FTP did not only decrease the infant's pain, but according to some parents (n=4), helped them cope better with their own stress as well.

5.3.2. Mothers' different styles of involvement in the pain care of preterm infant using FTP (IV)

The FTP was perceived positively and was used by all participating mothers. Overall, the mothers did not express any negative issues about FTP. However, they thought that the nurses could use the method more actively. The mothers were surprised that not all nurses systematically used or offered FTP for parents to use.

We were able to identify three different styles of involvement in preterm infants' pain care with FTP. This typology formed a continuum from external to random and finally to internalized involvement. Variation between the different involvement styles seemed to be explained by increasing maternal attachment and the level of the mother's NICU-related stress. In external involvement, mothers had a strong behavioural dimension in their actions in relation to their infants, whereas in random involvement the emotional dimension was emphasized more. In internalized involvement both these dimensions were clearly recognizable (Figure 10). One mother implied that it may be possible to move along on this typology continuum with the help of FTP. In her case, FTP seemed to facilitate her bonding with her infant. The mother had previously had a weak behavioural connection with her infant immediately after birth. The use of FTP made her recognize that she was able to help her infant during painful procedures. Participation also made her feel better and increased her maternal attachment as she felt that she and her infant needed each other.

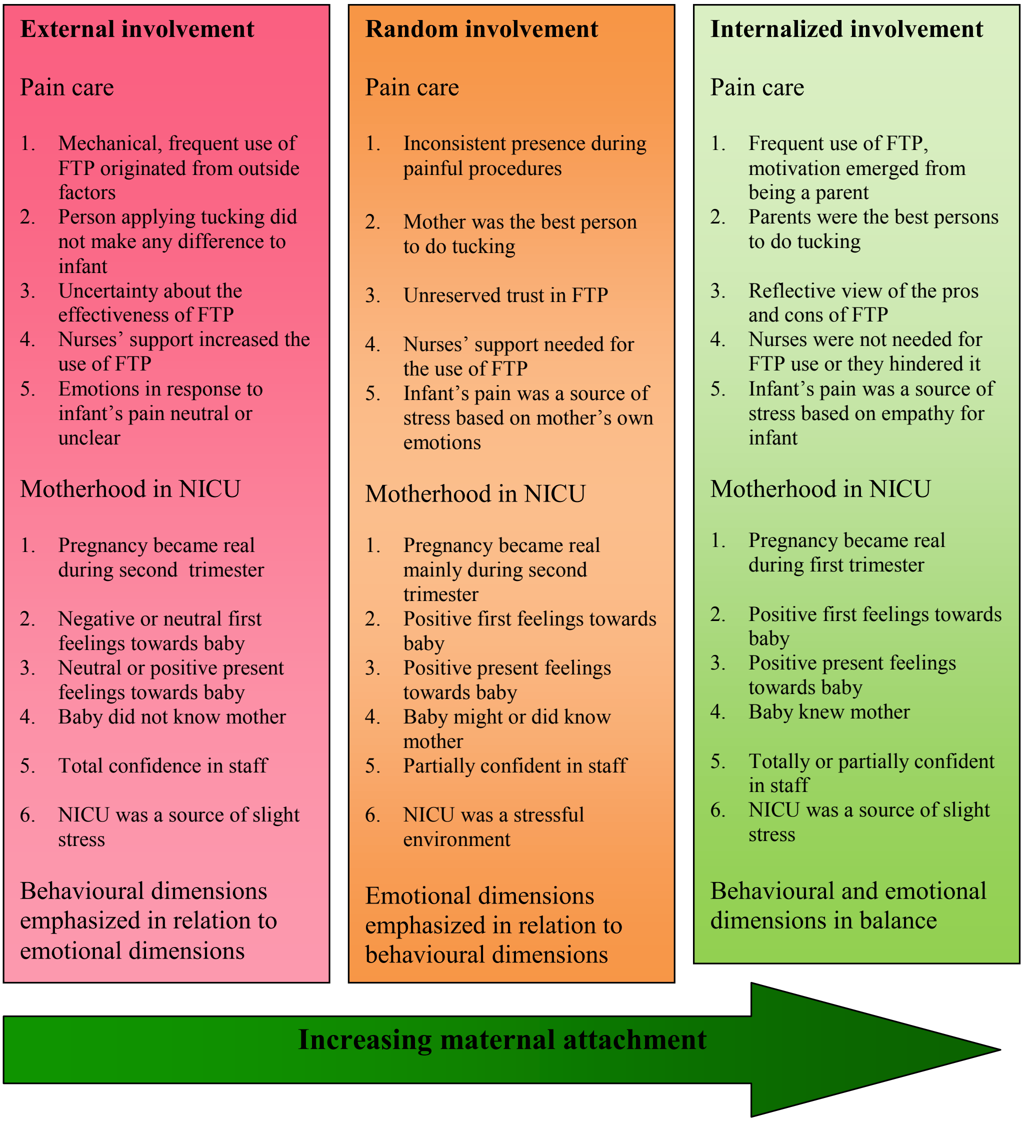

Figure 10. Typology of mothers' three different ways of being involved in infant pain care with facilitated tucking by parents. (Axelin et al. 2010b)
FTP = Facilitated tucking by parents, NICU = Neonatal intensive care unit

Pain care

Mothers with external and internalized involvement used FTP frequently (Figure 10). In the former, the use was mechanical and seemed to be based on the fact that it had been taught to the mothers and recommended for use. In the latter, both parents used tucking due to its effectiveness. Mothers with random involvement found infant pain and the NICU environment stressful themselves and their participation in pain management was minimal. The view that the mother was the best person to apply tucking was shared in random and internalized involvement, whereas mothers with external involvement still thought themselves strangers to the infant and therefore did not see their uniqueness in applying tucking. All the mothers wanted to participate in their infant's pain care. However, the mothers with external or random involvement were willing to withdraw from painful situations if they found it too stressful.

Opinions of the effectiveness of tucking and the emotions in response to infant pain varied according to mothers' ability to recognize the infants' signs of pain. Increasing confidence on own interpretations of infant pain and a greater involvement in pain care resulted in a more realistic view on the effectiveness of FTP. The mothers with internalized involvement regarded FTP most positively. They stated that pain alleviation with FTP made their infants feel more secure, and it supported infant development by offering a feeling of security. Mothers recognized that FTP helped them by giving them an opportunity to bond with their infants and by supporting parenting in the NICU. Infant pain was a source of stress for mothers with random and internalized involvement. However, the primary reason for stress differed between these two styles of involvement. In random involvement, the mothers' anxiety caused stress, whereas in internalized involvement the stress was related to the mothers' empathy for the infant.

The actions of the nurses positively influenced the use of FTP in mothers with external or random involvement. Their support made these mothers increasingly use FTP, reinforced their trust in its effectiveness and helped them understand their importance in their infants' pain care. In contrast, in mothers with internalized involvement the nurses were neutral bystanders or even had a negative influence on the mothers' experiences. These mothers wanted to protect their infants from pain and did not need encouragement from the nurses to do that. They thought that the nurses could have supported their use of FTP more actively and that they were sometimes even a barrier to parental involvement in infant pain care.

Motherhood in the NICU

The state of motherhood in the participating mothers was at different phases according to their style of involvement (Figure 10). The time when pregnancy became real to the mother and the feelings towards the baby had a role in their motherhood in the NICU. The strong maternal attachment in internalized involvement led to greater emotionally and physically oriented involvement in pain care. The mothers with external involvement acquainted their infant with physical contact and they were often available for infant pain care. The mothers with random involvement found the NICU environment stressful and they were not physically available for infant pain care as often. However, they were very much emotionally involved with their infants.

5.4. Summary of the results

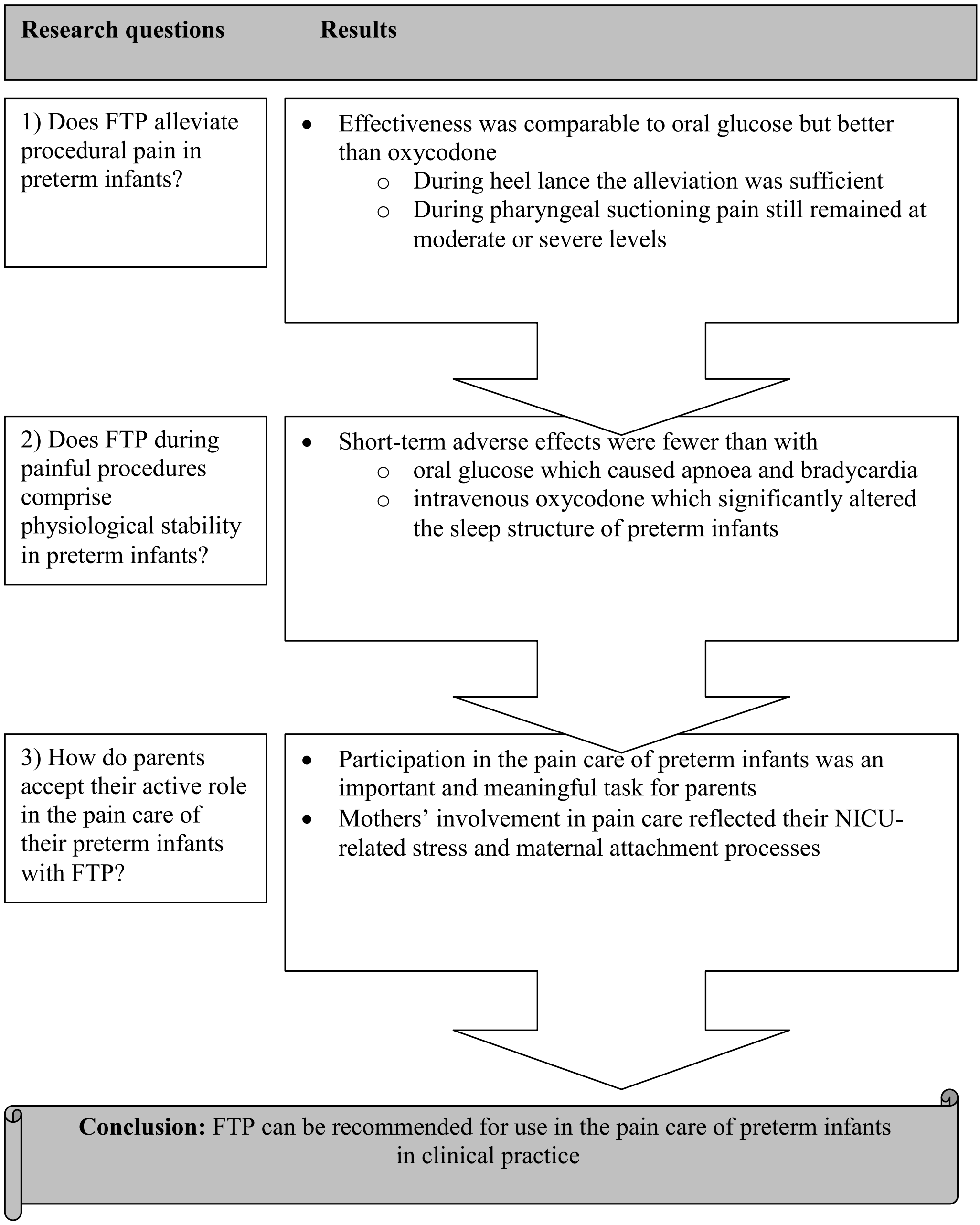

Figure 11. Summary of the results.

6. DISCUSSION

6.1. The efficacy of FTP in the alleviation of procedural pain

In this study, FTP alleviated the procedural pain of preterm infants. During heel lance procedure, the pain relief provided by FTP was sufficient. However, during pharyngeal suctioning the preterm infants still suffered from moderate pain similar to that observed with oral glucose. The FTP is a feasible, non-pharmacological pain management method with a level of effectiveness comparable to the most studied evidence-based practice, oral sweet solutions. Intravenous oxycodone did not offer measurable pain relief from short-term procedural pain.

FTP

This study demonstrated that FTP is equally effective as oral glucose when only pain alleviation is considered. These two methods were comparable in effectiveness during heel lance and pharyngeal suctioning procedures and exceeded the effect of the opioid, which equalled the effect of the placebo. Two reviews available on facilitated tucking, including our Study I, also suggest that it would be beneficial to use this method during procedural pain (van Brakel et al. 2008, Obeidat et al. 2009). Comparing our pain scores to earlier studies is difficult due to the different pain measures used (Corff et al. 1995). Where comparable, the PIPP scores during heel lance with facilitated tucking indicated moderate pain (Huang et al. 2004) whereas in our study they indicated mild pain during the same procedure. A possible explanation for this could be the longer duration of blood collection after heel lance in the former study. In the same study, swaddling was found to be equally effective as facilitated tucking (Huang et al. 2004). However, swaddling does not offer proximity of the parents to the infant. In the study by Ward-Larsson et al. (2004), the pain intensity measured immediately after endotracheal suctioning was lower than the pain measured during suctioning in our study. The different assessment points may explain this difference as pain intensity decreases when a painful stimulus ends.

Factors influencing the effectiveness of FTP may include the duration of a painful procedure and firmness of the hold which is difficult to objectively assess. Variations in the length of suctioning time had an effect on pain during FTP in Study I. In Study II, the duration of heel lance was only 30 seconds. The effectiveness of FTP should also be tested with painful stimuli of a longer duration and under different contexts, such as the insertion of an intravenous line and eye examinations. The other important observation which possibly influences the effectiveness of FTP is education of the parents. They need accurate education in advance and possibly further support during painful procedures in order to maintain a firm hold. In our study, the effectiveness of the parents hold was measured in a controlled environment. In addition, the research nurse supported the parents by encouraging them to keep their hold firm.

Oral glucose

The effect of oral glucose was comparable to earlier findings indicating sufficient pain relief during heel lance (Stevens et al. 2010b), although the pain intensity was lower across all of the interventions in our data. In the Cochrane review, the PIPP scores indicated moderate pain compared to no pain or mild pain in our study. The short duration of the heel lance procedure in our study probably explains this difference. A review on the effectiveness of oral glucose during procedural pain is also available and includes our Study II. The PIPP scores after oral glucose were significantly lower compared to oral water or no treatment during heel lance. Surprisingly, the results were not conclusive with other pain measures. (Hogan et al. 2010.) A plausible explanation for this is the smaller number of studies available on the effectiveness of oral glucose in preterm infants.

The current study is the first one to study the effectiveness of oral sweet solutions in the context of pharyngeal suctioning. Due to the benefits of oral glucose observed during the painful procedures in this study further research is needed to cover a large group of painful situations. However, oral glucose did not offer adequate pain relief during pharyngeal suctioning with high pain intensity. The possible benefit of repeated dosing is impossible to verify with our data as comparisons to single dosing were not available. Therefore, more studies like Johnston et al. (1999) are needed in order to compare dosing intervals.

Intravenous oxycodone

The opioid offered poor procedural pain relief in both painful procedures, as was also shown in earlier studies (Simmons et al. 2003b, Carbajal et al. 2005). However, this finding is surprising since opioids are the most frequently administered pain medications to very preterm infants (Debillon et al. 2002, Simons et al. 2003b) and have offered pain relief during endotracheal suctioning, measured by modified NIPS, heart rate and respiratory rate (Saarenmaa et al. 1996, Anand et al. 2004). The possible reasons for its ineffectiveness in the current study could be a lower dose compared to earlier studies with observed effectiveness of morphine (Anand et al. 1999, 2004), scarce knowledge of the pharmacodynamics of oxycodone (Lugo & Kern 2004, Kokki et al. 2004) and individual differences in the effectiveness of opioids due to the variation in amount of specific opioid receptors in preterm infants (Nandi & Fitzgerald 2005). It must also be considered that opioids might not function in the context of short-term procedural pain.

The dose used was adopted from recommended morphine doses for neonates (Anand et al. 2001). Using the minimum recommended dose we were nearly able to avoid short-term adverse effects such as compromised breathing in spontaneously breathing infants (Bellu et al. 2005, Taddio et al. 2009). Higher doses might be needed in order to gain optimal pain relief but the trade-off would be an increased risk of adverse effects. In our study design, the oxycodone period was always the last one to avoid a carry-over effect. This might have resulted in a consequent stimulus overload for the infants in our study protocol, although a carry-over effect was not found in our design. We conclude that the benefit vs. harm ratio of opiods might be lower compared to non-pharmacological pain management methods such as FTP and oral sweet solutions. This view is supported by the latest recommendations for pain management in preterm infants since non-pharmacological methods are considered as the first-line treatment for procedural pain relief due to controversies over opioid use (Durrmeyer et al. 2010).

Effectiveness according to the painful procedure

The strength in this study was that it not only compared different pain management methods but also two different painful procedures with different pain durations and intensities. Pharyngeal suctioning induced scores of pain intensity on the PIPP scale 5 points higher than the heel lance procedure. In our study, pain alleviation was adequate during heel lance with FTP and oral glucose. The pain responses caused by pharyngeal suctioning were not alleviated enough by any of the studied methods. However, the response to FTP and oral glucose in some infants was considered clinically significant (3-point decrease) when measured with the PIPP. There is an urgent need for effective pain alleviation methods for this procedure, which causes moderate to severe pain, as it is the most common painful stimulus in preterm infants (Simons et al. 2003a, Carbajal et al. 2008). As synergies between compatible pain alleviation methods may lead to highly effective pain management during the heel lance procedure (Johnston et al. 1999, Bellieni et al. 2002), this could also be a solution in the context of suctioning procedures. As well as developing methods of care which lead to less pain exposure, such as the avoidance of unnecessary suctioning, should continue to be developed.

Indirect management of pain

The indirect management of pain refers to the avoidance of painful procedures (Franck & Lawhon 2000). Studies aiming to decrease pain exposure in preterm infants are rare. One reported example of this approach is the successful implementation of early nCPAP and early extubation policies in a NICU. This change resulted in less invasive respiratory support and was associated with fewer painful procedures and less pain medication. This study also showed that both painful procedures and pain medication are treatment related rather than markers of an underlying illness and it was suggested that painful procedures and related medications may be a mechanism mediating the harmful effects of ventilator treatment (Axelin et al. 2009).

In addition, different techniques of performing painful procedures have effects on pain intensity in term and preterm infants. The differences in heel lance equipment have influenced the success of this procedure, the damage caused by sampling and pain (Harpin & Rutter 1983, Vertanen et al. 2001, Shah et al. 2003). It is also evident that venepuncture is less painful than heel lancing in blood sampling (Shah & Ohlsson 2007). In future research, it would be optimal to concentrate on non-invasive treatment strategies which reduce pain-provoking situations in order to avoid both pain and the potentially deleterious effects of its treatment.

The role of pain assessment

The fact that oxygen saturation and heart rate measures did not show a reaction to pain in Study I was possibly due to infrequent sampling as the other study concerning facilitated tucking have shown a faster return to baseline heart rate compared to no treatment (Corff et al. 1995). However, physiological parameters do not react specifically to pain (Craig et al. 1993, Stevens at al. 1992) and the correlation between behavioural and physiological measures across studies and situations is low (Barr 1999). The other concern was that behavioural-based NIPS might not be an ideal measure of pain during FTP as the method itself could affect NIPS parameters concerning the movements of the arms and legs by restraining these movements.

In Study II, the goal was to overcome the above-mentioned limitations by using the multi-dimensional PIPP measurement tool together with NIPS. In addition, a frequent sampling of physiological parameters was added to the measurements. One limitation of PIPP is that it includes behavioural state at the baseline as a modifier of the score. It assumes that deep sleep dampens pain expression and, therefore, scores are increased by 3 points for the pre-procedure deep sleep state. Because of this, it was not possible to measure the infants' reactions to painful stimuli. This differs from other measures, such as the Behavioural Indicators of Infant Pain (BIIP), which consider wakefulness or crying during procedures as indicators of pain (Holsti & Grunau 2007). Such measures could be used to measure pain reactions from baseline scores to post-procedure scores. These varying approaches for integrating baseline behavioural states in pain measurement reflect the controversies about this issue. Our study does not provide information about the components of pain the pain treatment influenced as we used multi-dimensional pain assessment tools. We did not analyze the physiological and behavioural components of pain in PIPP separately in our Study II since we decided to use PIPP in the way it has been validated. In future studies, it would be advisable select tools that measure these responses separately to ensure that infant pain does not leave under treated.

The use of two different pain measurement tools at the same time points was undertaken in order to gain more reliable estimates of pain and to increase understanding about these tools. The PIPP score, our main outcome measure, showed oral glucose to be more effective than FTP, but with the NIPS scores the reverse was observed. The PIPP was more sensitive in finding differences between the effects of the treatments and differences in intensity between the procedures. However, it seemed to be insensitive at low levels of pain as it did not detect pain in 20% of the heel lance procedures with placebo, as was also reported previously (Johnston et al. 1999, Slater et al. 2009). The NIPS scores indicated pain in every painful procedure but they did not distinguish different intensities between pharyngeal suctioning and heel lance. On the other hand, the NIPS emphasized the effects of the opioid and FTP during pharyngeal suctioning because it measures the behaviour of infants. This could imply a more sedative than analgesic effect of FTP. We regarded the PIPP score as our main outcome since we focused on post-stimuli, high-pain situations.

The BIIP has the potential to become a more reliable pain assessment tool in future research. With the BIIP physiological and behavioural parameters are kept separate at the scoring phase. This enables the parameters in which a pain response is evident to be distinguished. In addition, the behavioural state is taken into account as a response, not as a modifier. This solution is supported by Slater et al. (2006) who showed that infants who are awake have larger cortical responses to noxious stimulation than sleeping infants. This is contradictory to the structure of PIPP in which sleeping infants are assumed to feel pain as equally as awaking infants. Furthermore, BIIP uses more pain specific and developmentally relevant motor cues such as finger splays and fisting in measuring pain behaviours. The BIIP has already been tested and shown to be a reliable and valid tool for measuring acute pain in preterm infants (Holsti & Grunau 2007a, 2008). However, it can also be argued that current pain assessment tools only observe generalized reactions instead of pain specific activation in the nervous system of preterm infants. A couple of new possibilities available for pain assessment are the galvanic skin response and near infrared spectroscopy. These two methods have been shown to be able to differentiate touch from pain and have correlated well with PIPP scores (Bartocci et al. 2006, Eriksson et al. 2008). On the contrary, quantitative analysis of cortical brain activity by EEG has not proven to be a useful measure of acute pain in infants in a clinical context (Norman et al. 2008). The feasibility of these techniques at bedside is still questionable. Simple behavioural based assessment tools are the state of art in clinical practice.

One of the weaknesses in pain research in general and in the results of this study relates to our superficial knowledge about pain and its manifestation, leaving open to debate which parameters are the most appropriate for use in estimating the impact of painful procedures.

6.2. The adverse effects of pain and pain management

6.2.1. Short-term adverse effects

Our study provided strong support for the use of FTP since this new method was found to be effective in both of the painful situations studied without significant short-term side effects. With oral glucose, the short-term adverse effects were evident in half of the infants. Therefore, FTP is not just equal, but preferable to oral glucose and intravenous oxycodone when both efficacy and safety are considered. The only observed short-term adverse effect related to FTP was the obstruction to breathing when the head of an infant was tucked too close to her chest. This potential complication has to be kept in mind when teaching the method to parents. Intravenous oxycodone also caused short-term adverse effects to one child. The dose of oxycodone used in this study was too low to alleviate pain, however, the breathing in one infant became superficial leading to desaturation. This adverse effect is likely to be more common with higher doses, creating a risk of decreased breathing effort (Bellu et al. 2005, Taddio et al. 2009).

Adverse effects were common with oral glucose since half of the study population had these side-effects during our four administrations. Therefore, it is very likely that almost every infant will suffer pain management-related adverse effects when treated repetitively with oral sweet solutions during their NICU stay. The high frequency adverse effects can be explained by repeated dosing, low GA and PCA, and the fragile health of the infants. We chose to use repeated dosing based on previous studies which showed better response rates to repeated doses without reporting any adverse effects (Johnston et al. 1999, Gormally et al. 2001). In previous studies the range of adverse effects varied from 0% to13% (Stevens et al. 1999, Carbajal et al. 2002). However, infants below 32 weeks of gestation tend to experienced more adverse events compared to more mature preterm infants (Gibbins et al. 2003). It is also questionable whether adverse effects have been evaluated and reported accurately in earlier studies. Only twelve of the forty-four studies reported adverse effects and five of these observed minor short-term adverse effects. In addition, the authors of one review addressed the need for further studies with fragile preterm infants (Stevens et al. 2010b). The cause of desaturation or bradycardia after the infant had been administered glucose is likely to be a vagal response or a change in breathing pattern. Our findings emphasized the need for alternative non-pharmacological pain management methods, especially in very preterm infants susceptible to breathing instabilities. Furthermore, special attention should be paid in the dosing procedure.

6.2.2. Effect on sleep

The infants calmed down faster after a painful procedure with FTP compared to control care. However, our hypothesis that pain management protects sleep compared to a placebo in preterm infants was not supported by our data. Regardless of the intervention, the clustered nursing care was found to cause sleep deprivation which resulted in a reduction of REM sleep. In addition, this study demonstrated that intravenous oxycodone significantly decreased the amount of REM sleep compared to non-pharmacological pain management and the placebo, suggesting that opioids have a strong effect on the sleep structure of preterm infants.

FTP

In this study, FTP did not alter sleep structure compared to the placebo, which therefore supports the safety of using FTP in clinical practice. Based on earlier research, it could be assumed that FTP is developmentally beneficial for a preterm infant by helping the infant to cope better with stress. This was supported by our finding that infants calmed down faster after FTP compared to no treatment. Furthermore, there was a trend towards a shorter latency to fall asleep after FTP compared to the placebo. Previous research showed that developmental care, including hand swaddling, reduced stress behaviour and induced shorter sleep latencies compared to routine care without support (Als 1986, Bertelle et al. 2005).

Kangaroo care, another touch-based non-pharmacological pain management method, was found to induce more deep sleep during an extremely short 2-minute follow up period compared to no treatment (Castral et al. 2008). Kangaroo care not related to pain was found to induce more NREM sleep and less REM sleep compared to control infants in an incubator (Ludington-Hoe et al. 2006, Messmer at al. 1997). Frequent kangaroo care from 32 weeks of gestation improved sleep state organization around term age by increasing NREM sleep and alert wakefulness, and by improving the sleep-wake cycles compared to control infants (Feldman et al. 2002, Feldman & Eidelman 2003). Gentle human touch applied for a 10-minute period has also been shown to induce more NREM sleep (Harrison et al. 2000, Modrcin-Talbot et al. 2003). It was thought that the short period of skin-to-skin contact during FTP does not have such a distinctive effect as longer contact during kangaroo care. The future challenges related to the long-term effects of FTP are to study its effectiveness in repeated dosing, the possible effects on later development in preterm infants and parent-infant relationships.

Oral glucose

As with FTP, oral glucose did not have prolonged effects on the sleep structure of the preterm infants, which supports the use and safety of this method. Other evidence of the effects of oral glucose on sleep is scarce, although oral sucrose was found to decrease periods awake compared to oral water in a 30-minute recovery period after heel lance in preterm infants (Gaspardo et al. 2008). However, the systematic use of oral sucrose did not promote physiological stability as measured by heart rate variability and salivary cortisol compared to oral water in a one-week follow-up in preterm infants (Boyer et al. 2004). More research about the possible beneficial effects of oral sweet solutions on stress after immediate pain and about the risks related to long-term adverse effects is needed (Johnston et al. 2002, Fitzgerald 2009, Taddio et al. 2009, Holsti & Grunau 2010).

Protection of sleep by pain management

Our hypothesis that effective non-pharmacological pain management protects sleep in preterm infants was not supported by our data. The sleep period after effective pain alleviation (oral glucose or FTP) did not differ from the sleep period after the placebo during our one-hour follow-up period.

The analgesic effect of sucrose has been questioned as it did not prevent hyperalgesia occurring after five painful procedures (Taddio et al. 2009). Neither did it affect painful procedure related brain activity (Slater et al. 2010). Despite this the PIPP scores decreased during the painful procedures in both studies (Taddio et al. 2009, Slater et al. 2010). Based on this finding it has been suggested that sweet solutions are primarily sedative, not analgesic (Fitzgerald 2009). Our missing effect of oral glucose and FTP on sleep may be similarly explained by their primarily short-term sedative not analgesic effects.

The other possible reason for the lack of stronger protection of sleep by non-pharmacological interventions is sleep deprivation. Similarly to routine nursing care, the care periods in the study were long, with the infants being kept awake for about 25 minutes. Sleep deprivation induces more NREM at sleep onset and also increases the amount of NREM sleep in term infants (Thomas et al. 1996, Anders & Roffwarg 1973). Our data consistently showed more NREM sleep in preterm infants during the first hour after the clustered nursing care periods than before the next nursing care period. This important finding suggests that the possible effects of non-pharmacological pain management on sleep could be counteracted by sleep deprivation. Holsti et al. (2005b, 2006, 2007b) showed that clustered care increased stress responses and dampened self-regulatory behaviours after pain, which is likely to cause sleep deprivation. We can speculate that the interventions could have protected sleep more effectively after isolated procedural pain than in between nursing care periods. Our study, however, simulates clinical practice in neonatal intensive care where the trend is to cluster care and procedures in one session to provide the infant longer resting intervals.

Whether our sample size was large enough to accurately show the effects on sleep can be questioned. In post-hoc power analysis, our sample size was large enough to find an average of 10% difference in the total sleep time and in the proportions of REM sleep. To find more subtle differences, new studies are needed to explore the effects of procedural pain on preterm infants' sleep. It would also be advisable to add the control episode without pain in future study designs in order to understand whether a single painful procedure has an effect on sleep in preterm infants in the context of care episodes.

Developmental care has the potential to improve sleep in these infants as it has been shown to increase total sleep time, however, the proportions of REM and NREM sleep have remained unchanged when compared to control care (Bertelle et al. 2005, Westrup et al. 2002). The other potentially better caring environment for preterm infants might be the chest of the parents since continuous skin-to-skin contact was found to improve the quality of sleep in preterm infants (Feldman et al. 2002, Feldman & Eidelman 2003).

Intravenous oxycodone

Earlier studies have shown that ventilated preterm and term infants receiving opioids spend more time asleep and less time in agitated states (Porter et al. 1999, Anand et al. 1999). Our study showed that opioids induced more NREM sleep at the cost of REM sleep and periods awake. This effect may not be desirable since the reduction in REM sleep may be harmful due to the importance of REM sleep on brain maturation. Oxycodone decreased the amount of REM sleep by 10% during the first post-intervention hour compared to non-pharmacological interventions and the placebo. In addition, in half of the cases the sleep onset was non-physiological NREM sleep (Curzi-Dascalova et al. 1988). Similarly to our findings, a sulfentanil bolus in preterm infants induced a discontinuous EEG pattern and REM sleep disappeared in all infants (Nguyen The Tich et al. 2003). One limitation of our study was the fixed order for oxycodone as the last intervention to avoid its carry-over effect. It can be speculated that this partly explains the increased amount of NREM sleep. We found that the infants' sleep structure had already stabilized 60 minutes before the next nursing care period.

Animal studies suggest that the harmful effects of REM sleep reduction are considerable. In newborn rats, the pharmacological suppression of REM sleep resulted in behavioural, anatomical and biochemical alterations. Behavioural effects included reduced exploratory behaviour and learning difficulties (Mirmiran et al. 1981), attention problems, anxiety and sleep disturbances (Mirmiran 1986). In addition, REM sleep deprivation has been shown to reduce brain mass (Mirmiran 1986, Morrissey et al. 2004). The results of these studies should be interpreted cautiously because of multiple effects of these drugs on the developing brain (Peirano et al. 2003). It is significant that even mild REM sleep deprivation – which may be comparable to the clinical situation – induced by waking up rats immediately after REM sleep onset – interfered with hippocampal development and subsequent memory function (Morrissey et al. 2004, Lopez et al. 2008, Guzman-Marin et al., 2008). Rapid eye movement sleep also plays a critical role in visual development, which is altered by REM sleep deprivation in cats (Marks et al. 1999). Rapid eye movement sleep deprivation also prevented the compensatory effects of environmental enrichment on cortical maturation, suggesting decreased brain plasticity (Mirmiran et al. 1981). These results emphasize the importance of REM sleep on neurological maturation in rats. In addition to proportions of sleep states, the cyclicity of sleep may be equally important factor as the proportions of sleep do not rule out fragmentation. This provides a reason for investigating sleep protection and disturbing factors in humans.

One strength of our study was the 3-hour recording of sleep states. Previous studies on pain management have rarely exceeded a 10-minute follow-up, reflecting the tradition of studying only immediate effects of pain management related to procedural pain. Sleep structure has the potential to be a more objective measure of the prolonged effects of pain and its management than the existing pain assessment tools. This method could also be applied to study post-operative pain in preterm infants as opioids are the treatment of choice in post-operative pain. Amplitude-integrated EEG has given a new feasible tool to measure long-term sleep.

6.3. Parental participation in pain management using FTP

Parents' participation in the pain care of preterm infants is understudied despite their importance in this context (Pillai Riddel & Chambers 2007). This is surprising since it was the mother of a preterm infant who turned our focus towards the pain of preterm infants by fighting for her son's right to analgesia during surgery 25 years ago. We can ask why parents have not been exposed to infant pain in the NICU since with healthy infants it is natural for the mother to comfort her child during stress and pain. Is it the unwillingness of parents or our caring culture which separates parents from their infants in these situations? This is the first study which actively involved parents in the pain care of preterm infants over a period of weeks and which described the mothers' experiences of this involvement.

6.3.1. Acceptance of FTP among parents

Our study gives support to earlier reports which suggested that parents want to get involved in the pain care of their preterm infants (Franck et al. 2005b, Gale et al. 2004). Active participation with FTP was accepted without reservation by all participating parents, except one mother. Facilitated tucking by parents provides a new feasible tool for supporting parents in stressful NICU environments to develop their parenting skills and to bond with their sick infant.

During painful procedures the parents were able to interpret the infants' cues of stress or comfort. In addition, some parents mentioned that participation relieved their own infant pain-related stress. Observing and helping an infant in a stressful situation could support the parents, the infant and their sensitive interactions since parenting skills are easily compromised in NICU settings (Muller-Nix et al. 2004). Interventions such as parental information and guidance for active participation in care have improved the well being of parents, their relationships with the infants and infant behaviour (Kaareseen et al. 2006, Melnyk et al. 2006). Active participation in pain management with FTP has the potential to reduce parental stress related to infant pain (Franck et al. 2005b) and to further increase the positive feedback on parenting skills.

6.3.2. Mothers' different styles of involvement in the pain care of preterm infants using FTP

The possibility of alleviating infant pain and stress with FTP was a meaningful part of parenting for mothers in the NICU environment. However, the level of involvement in pain care differed according to the mother and her experiences before and during NICU admission.

Our typology concerning the mothers' different styles of involvement in the pain care of preterm infants with FTP reflects the process of growth to motherhood in the NICU environment (Heermann et al. 2005). In our study, the mothers were at different phases of this process as not all of the mothers had reached both emotional and behavioural competence in motherhood at the time of discharge. Readiness for motherhood has been linked to more optimal mother-infant interactions in the NICU compared to mothers with maternal rejection (Keren et al. 2003). This was also seen in our study as the mothers with internalized involvement seemed to handle pain care well, whereas mothers with random involvement compromised their involvement possibly due to NICU-related stress. The mothers with external involvement had some elements of maternal rejection, although they actively participated in pain care. The differences in involvement in pain care can be explained not only by the NICU environment but equally by the mother's early adaptation to parenthood during pregnancy. This understanding of the role of maternal attachment in relation to infant pain care gives more depth to our understanding of mothers' experiences (Franck et al. 2004, Franck et al. 2005b, Gale et al. 2004).

The primary caregiver-infant relationship during the first year of life is often seen as the primary context for the early acquisition of distress regulation. One existing model explaining the caregiver's involvement in infant pain care is the sociocommunication model of pain. In this model the caregiver-infant relationship has a central role. Pain expression by the infant triggers the caregiver to give proximity and care according to the caregiver's interpretations. (Pillai Riddell & Chambers 2007.) The closeness and sensitivity to an infant's cues helps the caregiver to regulate infant distress (Figure 12). This theory of the caregiver's response to an infant's stress cues had some limitations in the NICU environment. In our study, the caring culture did not always support parental involvement. In addition, mothers under stress or with unfinished maternal attachment were not fully able to participate in pain care. Separation during a painful procedure can therefore result from the caring culture or the mother's personal background. This prevents her from giving closeness, being sensitive to the infant's cues and regulating the infant's distress in the NICU environment (Figure 12). Facilitated tucking by parents can serve as an intervention tool for nurses to actively involve parents in pain care, which consequently prevents parent-infant separation during painful procedures and supports the distress regulation of the preterm infant within the family (Figure 12.)

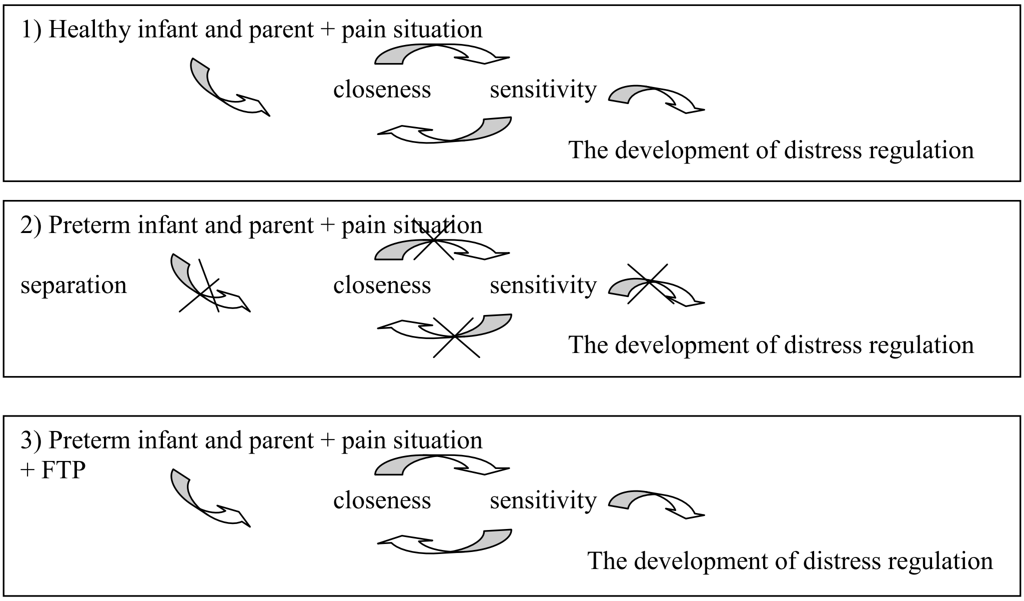

Figure 12. The proposed model of distress regulation between parent and infant during short-term procedural pain: 1) healthy infant and parent, 2) preterm infant and parent and 3) preterm infant and parent with FTP. FTP = Facilitated tucking by parents

Our typology suggests that involving the mother in pain care is one important step in supporting motherhood in the NICU. After involvement of the mother, the next step could be to teach her to recognize her infant's cues in these situations. Facilitated interaction supports the mother's competence and helps her to understand the infant by increasing sensitivity. This competence-creating circle (Figure 12) may supports synchrony in mother-infant interactions during stressful situations and could have positive effects on the development of distress regulation in preterm infants. In different involvement styles, this process of participation in pain care should be adapted according to the mother's situation.

Mothers with an external involvement style may need practical reinforcement when participating in infant pain care. While maternal attachment is still developing (Cohen

& Slade 2000) some mothers do not yet experience their infants like their own children (Bialoskurski et al. 1999). Nurses can help the mothers interpret the infant's cues and provide a closer relationship with the infant by other nursing interventions such as kangaroo care (Feldman et al. 2002) and developmental care (Als et al. 2003).

Mothers with a random involvement style could particularly benefit from the reduction of NICU-related stress. The psychological stress related to preterm birth interferes with attachment (Kaaresen et al. 2006), maternal sensitivity to infant cues (Zelkowitz et al. 2007) and mother-infant interactions (Muller-Nix et al. 2004). In other words, the process required for internalized involvement in infant pain care is threatened when the mother is under stress. Participation in infant care should also include less intense situations such as holding and kangaroo care since infant pain can be too much for these mothers (Franck et al. 2005b). The withdrawal of a mother from pain care should be accepted (Franck et al. 2005b). Learning to interpret infant cues and participation in pain care could reduce mothers' stress as shown in our Study I. Active support by nurses is a necessity for these mothers to participate in infant pain care. A mother's strong emotional bond with her infant is a strength which nurses should be able to use to support the mother-infant relationship.

Mothers with an internal involvement style are at risk of being left alone in the NICU as they seem to handle motherhood well. Infant pain and NICU admission are also likely to be stressful to these mothers (Aagaard & Hall 2008). A strong maternal attachment helps them to adapt faster to this new environment for their infants' benefit (Heermann et al. 2005). Despite knowing their infants best, these mothers cannot intuitively know good practices in the NICU. Providing knowledge of good pain care practices is therefore the responsibility of nurses (Franck et al. 2005b). In addition, nurses need to be sensitive to the experiences and opinions of parents and allow them to be the primary caregivers in pain care. There is a possibility of mismatch in the perception of infant pain between parents and staff (Gale et al. 2004). In our study, this was reflected in the mothers' comments that nurses can be a barrier to their use of FTP. There might be a setting for a conflict if empowering parents happens before family-driven values are established among staff. Therefore, it is important to focus on changing the unit culture when supporting parental empowerment.

In our qualitative Study IV, FTP catalysed mothers' participation in the pain care of preterm infants. Our study can be questioned in terms of credibility, dependability and transferability (Graneheim & Lundman, 2004). The credibility of our results is supported by our rich data which can connect the participation of mothers in infant pain care with the wider context of motherhood in the NICU. However, the decision to use the CLIP interview as a framework could have limited our opportunities to bring up new issues related to this participation. The cross-case approach gave us a more general understanding of generic phenomena that occurred across the cases. To increase the reliability of data interpretation, parallel coders were used in the different phases of the analysis. The dependability of our results was at risk in the multi-phased analyses. However, the process between data collection and analysis was short. The first general view of the data was not taken until nineteen interviews had been conducted so that the focus of observation did not narrow too early. The transferability of our results is diminished by the fact that our sample represents a white, well-educated population with average incomes and relatively healthy preterm infants. In addition, the caring culture in the NICU was family-centred, which limits transferability of the results to less family-centred caring cultures.

7. IMPLEMENTATION AND FUTURE RESEARCH

This study gave rationales to implement FTP in clinical practice. The future challenge is to implement FTP in different caring cultures in order to increase the family-centered care and limit separation between parent and infant during infant pain in NICU. The systematic use of FTP requires further research on its feasibility as embedding intervention into clinical practice is challenging. This was seen in our study as the mothers' different styles of involvement. Differences were also seen in how different nurses implemented FTP. This is notable as they were all educated systematically in the use of FTP.

The effects of implementation of FTP can be considered from three different perspectives (Figure 13.). From the perspective of infant, the pain management will probably improve as the short-term procedural pain will become treated more often as also the parent is managing it with this safe method. In addition, it is the primary caregiver who regulates her distress during pain. The parental involvement widens the perspective to the family. In this context, FTP can prevent separation between infant and parent during pain and have different effects within family. However, new questions arise such as: Are some procedures too invasive for parents to participate or how much nurses can encourage parents to participation without being too aggressive and possibly cause anxiety to them. The answers to these questions will differ according to mother but are also related to the third perspective; caring culture in NICU. We could assume that in Nordic countries the implementation of FTP is different than in southern Europe due to the phase of family-centered care in NICUs (Greisen et al. 2009). In some NICUs, FTP can be a good initiator to parental participation in pain care. However, some units for example in Sweden may feel that FTP is not necessary anymore as preterm infants are already cared in parent's chest while in KMC.

The same three main aspects can also be seen in the future research (Figure 13):

1) The effectiveness of FTP needs to be studied during different painful procedures with different durations and intensities. In addition, the effectiveness of FTP under repetitive use is not known. The synergist effect of FTP and other pain management methods such as oral glucose could offer better pain relief than each of them alone. The possible long term consequences of FTP on the later development of preterm infants are also worth studying. The possible protective effect of effective non-pharmacological pain management on sleep should be measured in isolation of clustered nursing care in future studies.

2) The influence of FTP on the development of parent-infant relationship is other interesting perspective for research as it prevents the separation within family

during infant pain. Active parental participation in pain care could for example effect on parents' stress, sensitivity to infant's cues or growth process to parenthood. Based on our study we also have only very limited knowledge of father's role in the pain care of preterm infant.

3) The effect of FTP on the development of family-centered pain care in different caring cultures is the important perspective in future feasibility studies. The role of nurse in facilitating parent's participation in pain care needs to be understood more deeply. The pain care of preterm infant always expects interaction between parent and nurse in NICU. The factors that nurse herself and caring culture bring to this situation and their influence on parent needs to be studied further. This study also suggests that mothers with different styles of involvement could benefit from different kind of nursing interventions. Developing a tool for nurses to identify mothers with different styles of involvement and tailored interventions for them would also benefit clinical practice.

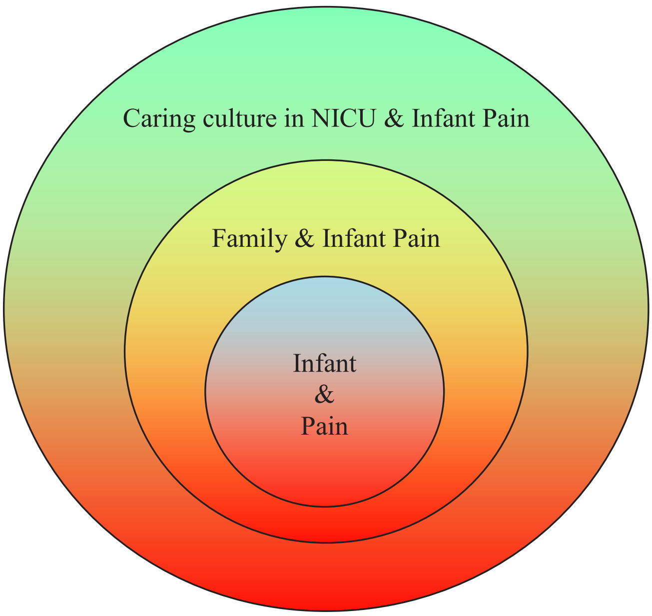

Figure 13. Three different aspects can be considered in the implementation and future research of facilitated tucking by parents.

8. CONCLUSIONS

This study showed that FTP was preferable to oral glucose and intravenous oxycodone when efficacy, safety and family issues were considered in treating short-term procedural pain in preterm infants. Oral glucose, although effective, was related to a high amount of short-term adverse effects. The effect of opioids was equal to that of the placebo and there were further concerns that it decreased the amount of REM sleep in this fragile patient population, thereby potentially interfering with brain maturation. These results address the need to carefully balance effective pain management and its potential adverse effects.

This study also showed that in a stressful and painful NICU environment, parents are willing and capable of alleviating pain in preterm infants using FTP. However, the type of involvement in pain management is dependent on the mother and her experiences before and during NICU admission. Nurses need to consider maternal factors when involving mothers in the pain care of preterm infants. In conclusion, FTP as a safe and effective pain management method can be recommended for use in the pain care of preterm infants in clinical practice.

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