NEONATAL PAIN
Out of Sight, Out of Mind?

Proefschrift

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List of Abbreviations

AGA	Appropriate for Gestational Age
AHP	Analytic hierarchy process
CDC	Consensus Development Conference
CI	Confidence Interval
CL	Clearance
CP	Chronic Pain
CPAP	Continuous Positive Airway Pressure
CPT	Cold Pressor Test
ECG	Electrocardiography
EEG	Electroencephalography
EDIN	Échelle Douleur Inconfort Nouveau-Né
HPLC	High-Performance Liquid Chromatography
HR	Hazard Ratio
IASP	International Association for the Study of Pain
IPPV	Intermittent Positive Pressure Ventilation
IQ	Intelligence Quotient
IQR	Interquartile range
i.v.	Intravenous
IVH	Intraventricular Hemorrhage
MRI	Magnetic Resonance Imaging
NEC	Necrotizing Enterocolitis
NGT	Nominal Group Technique
NICU	Neonatal Intensive Care Unit
NIRS	Near Infrared Spectroscopy
N-PASS	Neonatal Pain, Agitation and Sedation Scale
NRS	Numerical Rating Scale
NVK	Nederlandse Vereniging Kindergeneeskunde
PCQ	Pain Coping Questionnaire
PICU	Pediatric Intensive Care Unit
PIPP	Premature Infant Pain Profile
PMA	Post Menstrual Age
POPS	Project On Preterm and Small for gestational age infants
PTH	Pain Threshold
PTO	Pain Tolerance
SD	Standard Deviation
SGA	Small for Gestational Age
SPSS	Statistical Package for the Social Sciences
UV	Ultraviolet
VAS	Visual Analogue Scale

CHAPTER 1

Introduction and Outline of the Thesis

Pain in the Newborn, an Introduction

Pain in the newborn has received much scientific attention since the 1980's. However, pain in early human life has been recognized since ancient times. The first descriptions of infant and child pain can be found in the era of the Egyptian pharaohs. The boy-pharaoh Tutankhamun, who died in adolescence, probably suffered from juvenile aseptic bone necrosis[1], a disease associated with severe joint pain. Wear and tear on walking aids found in his tomb suggest Tutankhamun suffered from this condition maybe during a considerable part of childhood.[1] An indication that the boy-pharaoh's pain was treated was found in the discovery of fruits of Zizyphis spina-christi, Christ's thorn Jujube, in his tomb.[1] This herbal pain medicine is still in use today in Africa, the Middle East and Asia and its analgesic properties have been described in animal studies.[2]
Translations of ancient Egyptian papyrus, images and inscriptions provide evidence that Egyptian physicians, alongside incantations and methods to drive away evil gods and demons, treated pain or distress in a way we would today consider more appropriate. On a piece of papyrus, probably written in 1550 BC, a recipe can be found to treat young infants with excessive crying. The recipe is believed to originate from the 34th century BC. It describes a mixture of "pods of a poppy plant", most likely opium, and dirt from flies that had to be scraped of the wall.[3] With current day knowledge it should be clear which of the ingredients is responsible for the analgesic properties of the mixture.

Eleven-hundred years later, Hippocrates described a disease in children, characterized by pain in the head and neck, accompanied in some by seizures and sometimes quickly fatal.[4] Hippocrates also wrote about a disease with pain in the belly, especially in children, most of whom died.[5] He even describes a symptom of pain, tachypnea. Furthermore, he distinguishes acute pain, for instance of the ear, from prolonged pain that accompanied a disease most likely to be meningitis.[5,6]

Aulus Cornelius Celsus, an encyclopaedist who lived under the reign of Rome's first emperor Augustus and his adoptive son and successor Tiberius, mentions in his works painful ulcers and pustules in children. The treatment would be exercise and diminishing foods. Nursing women should be treated the same, especially when the baby was affected.[7] In this respect, Celsus can be regarded as the first author that describes pain in newborns specifically.
Soranus of Ephesus, a Greek physician from the first and second century AD practicing in Alexandria and Rome, wrote the first textbook on obstetrics and gynaecology. In his 'Gynecology', a note on assessment of the newborn emphasizes the importance of assessing sensitivity "by pressing the fingers against the surface of the body, for it is natural to suffer pain from everything that pricks or squeezes".[8]

In the 17th century a Dutch physician, Steven Blankaart, wrote the first Dutch Textbook on Pediatrics. In his *"Verhandelinge van de opvoedinge en ziekten der Kinderen" ("Memoirs of the upbringing and diseases of children"),* Blankaart described the causes and symptoms of belly pain in breastfed toddlers. His advice was to treat the pain with salt water or a sip of anise brandy.[9]

In summary, several ancient sources already acknowledged pain in newborns and children, and even provide advice for treatment. In contrast, studies from the beginning of the previous century suggested that newborns were not capable of feeling pain. In 1941, Myrtle McGraw summarized 2008 longitudinal observations regarding sensory-motor reactions to pin-prick stimulation.[10] The author suggested that the lack of response to pin-prick in some newborns indicated undeveloped pain pathways.[10] During development the response to pin-prick became more clear in this group of infants, that was followed up from birth to the age of four years.[10] In this time age the common assumption was that newborns could not feel pain.
The emerging evidence that newborns have well developed physioanatomical and neurochemical systems necessary to mount physiological responses to pain was analyzed and summarized in 1987.[11] Anand suggested in his landmark paper that the reaction to nociception may constitute a psychological stress response.[11] Recent evidence shows that preterm infants with a gestational age of as little as 25 weeks indeed activate the anterior cingulate cortex in response to painful stimuli, possibly indicating awareness of pain.[12] Bellieni takes this even a step further and advocates that newborns can suffer.[13]

The Concept of Pain in the Newborn

The mounting evidence that newborns and preterm infants born near the limits of viability are capable of pain perception has lead to the publication of numerous papers on this topic. However, research has mainly focused on acute and procedural pain. The concept of acute pain has been described, other types of pain still lack fundamental understanding.[14] Acute pain occurs as a consequence of nociceptive events and is limited in time.[15] Examples are the pain associated with heel lance, suctioning procedures, placement of nasogastric tubes and venipuncture. Newborns admitted to Neonatal Intensive Care Units (NICU) are subjected to a mean of 11-14 of such painful procedures every day.[16-19] Other types of pain identifiable in newborns are the prolonged pain associated with surgery and disease states such as necrotizing enterocolitis and epidermolysis bullosa. Often, this type of pain and acute pain are difficult to disentangle.[14] In the adult, the distinction between acute and chronic pain has been suggested to depend on the time domain and intensity of underlying pathology.[15] The need for research on ongoing, prolonged and chronic pain in the newborn has been stressed before.[20]

Assessment of Pain in the Newborn

Since pain is a subjective emotion and newborns are not able to express their pain verbally, healthcare workers have to rely on other means to assess whether a newborn is in pain. This proves nothing less than challenging. Research on assessment of pain has lead to the development of over 40 pain measures.[21] Several behavioral, physiological and (bio)behavioral indicators of neonatal pain as well as modifying factors such as gestational age, have been identified and have found their way into these pain measures. Only one of these measures, the French Échelle Douleur Inconfort Nouveau-Né (EDIN), has been developed specifically for prolonged pain.[22] Three pain measures that were developed for acute or procedural pain have been tested in situations of prolonged or chronic pain, such as surgery and mechanical ventilation.[23-25] These situations, however, were often chosen on subjective grounds and are not based on sound theoretical or observational arguments.

Recent evidence suggests that the foundation of most pain measures: changes in facial expressions and autonomic activity during pain, do not always relate to cortical evoked potentials.[26] This raises questions regarding the sensitivity and specificity of the pain measures that are currently used. Multi modal assessment of pain using simultaneous electroencephalography (EEG), near infrared spectroscopy (NIRS), electrocardiography (ECG) and video analysis seems promising[27], but is only useful for research purposes. Pain-specific events in EEG or NIRS have yet to be identified.[28] In addition, EEG patterns in preterm infants change during maturation, showing lower frequencies predominantly early in gestation and higher frequencies with increasing post menstrual age.[29] Furthermore, EEG patterns may be influenced by pharmacotherapy and co-morbidity such as intraventricular hemorrhage, stroke, asphyxia and meningitis.

Treatment of Newborn Pain

Controversies regarding newborn pain management exist. Clinicians lack sufficient evidence to safely treat pain in the newborn and are confronted with the short term side-effects of analgesics. Administration of opioids in the absence of pain may even have an adverse effect on neurodevelopment.[30] In addition, the efficacy of available analgesics has yet to be proven, and as noted, it is difficult to assess pain or the effect of treatment in the newborn. These factors may explain the observation that newborn pain is still undertreated. In a French study in 13 NICU's only 20% of painful procedures were performed with analgesics.[31]
While in one study continuous morphine during mechanical ventilation decreased pain scores significantly, the clinical importance of this effect is debatable, since effect size is too small to conclude that pain is treated adequately.[32] To put it simply: a five-point difference on a given pain scale may be statistically significant, but if both the pain score before and after the intervention are within the same range indicating 'pain' or 'no pain', the clinical relevance is very limited.

Routine administration of morphine in ventilated newborns did not provide adequate analgesia for acute procedural pain in two other studies.[33,34] Furthermore, opioids are shown to have undesirable side effects such as hypotension[35], respiratory depression[36] and gastro-intestinal depression.[37]
Paracetamol has been in use in pediatric and adult medicine for decades and, in these populations, is safe when dosed and administered correctly. In neonatology, paracetamol rectally and orally are used widely. However, data regarding the efficacy of these compounds is conflicting. Several papers showed that in term and preterm infants paracetamol rectally or orally did not decrease pain scores during heel stick.[38-43] In a recent study the prophylactic use of rectal paracetamol in term born infants born after an assisted vaginal delivery was even associated with higher pain scores during heel stick procedures on day 3 or 4.[43] Furthermore, the concomitant use of paracetamol and opioids did not lead to decreased use of opioids after major surgery in young infants.[44] Questions remain regarding the efficacy of rectal and oral paracetamol, the type of pain that can be treated with paracetamol and efficacious dosing regimens. In infants in whom it is not possible to give paracetamol orally, the intravenous option might provide an attractive treatment option. Data on the pharmacokinetics of paracetamol intravenously are emerging, but are unknown in very preterm infants < 32 weeks.

Consequences of Newborn Pain

Several papers address the short and long-term consequences of pain in the newborn. Animal studies suggest factors such as underdeveloped myelination, slower synaptic transmission, the larger cutaneous receptive fields for nociception and decreased inhibitory control lead to greater vulnerability of the preterm infant.[45] In addition, pain experience is more diffuse in the newborn than in the adult.[45] These factors may lead to the hyperalgesia and central sensitization noted in infants with repetitive painful procedures, as detected by facial action and crying.[46] Animal studies further suggest that repetitive pain leads to increased apoptosis in the developing brain, an effect that is only partially influenced by morphine.[30] In human preterm infants, cumulative neonatal pain is associated with reduced white matter and subcortical gray matter, decreased frontal and parietal brain width, altered magnetic resonance imaging (MRI) diffusion and functional connectivity in the temporal lobes, and abnormalities in motor behavior on neurobehavioral examination at term equivalent age.[47,48] In a cohort of preterm infants born after 24-32 weeks gestation, neonatal pain-related stress was associated with thinner cortex in multiple regions at school age.[49]
Neonatal pain may contribute to altered neurocognitive development. In a cohort of 7 year old ex-premature infants alterations in the spectral structure of spontaneous cortical oscillatory activity was demonstrated.[50] Cumulative neonatal pain was associated with changes in background cortical rhythmicity, specifically in preterm infants born with a gestational age of 24-28 weeks. These changes were negatively correlated with visual-perceptual abilities at school-age.[50]

Preterm infants born with a mean gestational age of 31 weeks, compared to term born peers showed hypersensitivity at the age of 12-18 years.[51] In contrast, a recent study suggests that ex-preterm infants aged 18 years do not differ with their healthy peers in terms of pain experience and pain response (as measured by a standardized Cold Pressor Task).[52]
Although anatomical and physiological changes have been well documented and provide data on marked consequences of pain in early life, there is only sparse data on the influence of early pain on the growing child or young adult in daily life.

Aims of the Thesis and Research Questions

The first aim of this thesis is to investigate the concept of chronic pain in the newborn by developing a concept of chronic pain in the dimensions of definition, etiology and diagnostic determinants. To address this goal we first determine the most valid research method **(Chapter 2)**. Second, we use the most valid study design to find answers on three questions **(Chapter 3)**: (1) What is the definition of chronic pain in the newborn?, (2) Which are the etiologic determinants? and (3) Which are the diagnostic determinants?
Since there are methodological issues with statistical approaches in qualitative and mixed method research designs we tried to identify alternative methods to analyze the data we collected with our research method. Especially regarding the interpretation of the term 'consensus' in a group of experts, there is no consensus in literature. In **Chapter 4** we evaluate a mathematical method to reach consensus in a group of experts.

The second aim of this thesis is to investigate a novel method to treat neonatal pain in extremely preterm infants. Since the use of opioids is associated with side effects and efficacy has yet to be determined we investigated paracetamol, an over the counter medicine in the Netherlands which has been in use in pediatrics for decades. In **Chapter 5** we describe a case series of preterm infants that received paracetamol intravenously. This retrospective observational study has lead to the following research questions: (1) What are the pharmacokinetic properties of paracetamol intravenously in preterm infants below 32 weeks' gestation? and (2) Is intravenous administration of paracetamol in these infants safe? We address these questions in **Chapter 6**.

The third aim of the thesis is to determine if pain in the neonatal period leads to altered pain response and pain behavior later in life. Since there are no databases that provide insight in the direct relation between cumulative neonatal pain and altered pain response and pain related behavior in later life we look at estimates of neonatal disease severity. The hypothesis is that with gestational age and birth weight, and presence or absence of complications of prematurity such as necrotizing enterocolitis, sepsis and intraventricular hemorrhage, the prevalence of cumulative neonatal pain varies.

It has been shown that the number of neonatal skinbreaking procedures as a marker of cumulative neonatal pain was significantly correlated with illness severity on day 1, gestational age, and days of mechanical ventilation.[53] We address the following research questions: (1) Do perinatal factors such as gestational age, birth weight and estimates of neonatal disease severity in preterm infants lead to altered pain coping behavior later in life? **(Chapter 7)**; (2) Do perinatal factors such as gestational age, birth weight and estimates of neonatal disease severity in preterm infants lead to altered pain threshold, tolerance and intensity later in life? **(Chapter 8)**

In **Chapter 9** we summarize and discuss the findings of our research. We provide recommendations for future research aiming at conceptualizing and treating pain in the newborn, thus preventing possible long term effects of pain in the newborn.

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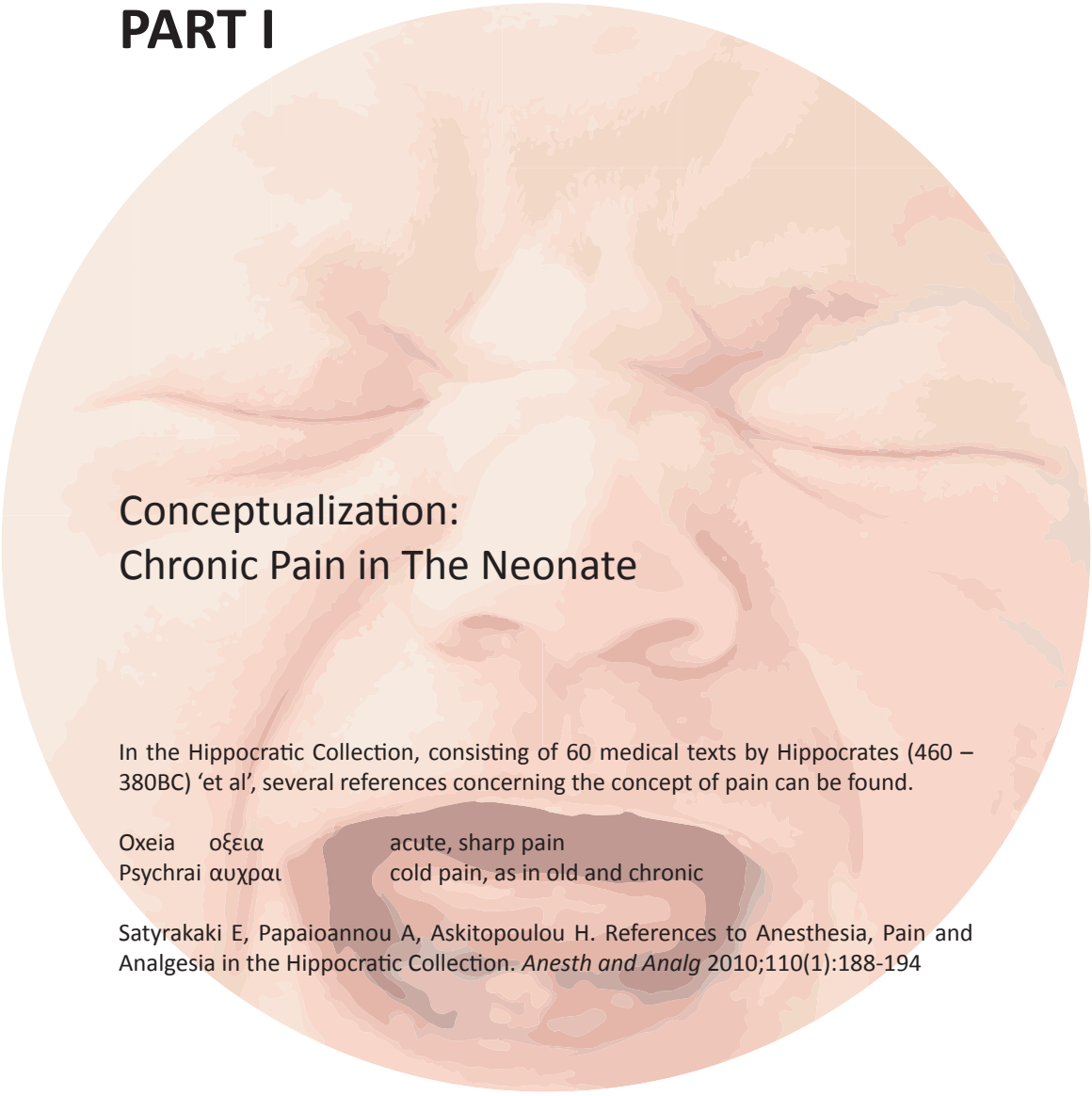
PART I



Conceptualization:
Chronic Pain in The Neonate

In the Hippocratic Collection, consisting of 60 medical texts by Hippocrates (460 – 380BC) 'et al', several references concerning the concept of pain can be found.

Oxeia	οξεια	acute, sharp pain
Psychrai	αυχραι	cold pain, as in old and chronic

Satyrakaki E, Papaioannou A, Askitopoulou H. References to Anesthesia, Pain and Analgesia in the Hippocratic Collection. *Anesth and Analg* 2010;110(1):188-194

CHAPTER 2

Chronic pain in the neonate: a research design connecting Ancient Delphi to the modern 'Dutch Polder'.

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ABSTRACT

Introduction

To date research on neonatal pain has focused mainly on acute or procedural pain. It is recognized that prolonged or chronic pain exists in this age group. Studies on this subject fail to provide a clear description of chronic pain in the neonate.

Objectives

To identify the most appropriate consensus building method in order to answer three research questions concerning the definition of chronic pain in the neonate, the etiology, and the clinical signs and symptoms.

Methodology

We performed a literature search with regards to the methodology of the Delphi method, the Nominal Group Technique and the Consensus Development Conference.

Results

We found only sparse data reviewing the Nominal Group technique and the Consensus Development Method. More data was found for the Delphi Method.

Discussion

We chose to design a Delphi survey in the light of our research questions. Main arguments were the ability to include experts from all over the globe, and the low probability of introducing bias.

Conclusion

All three methods have strong and weak points. A major criterion should be the validity of the design. However, conclusions on validity are hampered by the marginal amount of papers found for two of the three designs.

Key points

1. Delphi, Consensus Development Conference and Nominal Group Technique all have weak and strong attributes.
2. Based on these attributes researchers can choose the appropriate design in the light of their research questions.
3. There is a need for research on the validity of CDC and NGT.
4. There is a need to define “expertise” for research designs relying on experts.

INTRODUCTION

Until well into the second half of the previous century the general assumption was that neonates and preterm infants were unable to experience pain, due to immaturity of the nervous system. As a consequence analgesia was thought to be unnecessary. Since Anand published his landmark paper entitled "Pain and its effects in the human neonate and fetus" in 1987[1], research has shown that neonates and even preterm infants are fully capable of feeling pain. Repeated pain in preterm infants is even suggested to induce altered pain response later in life, although causality has not been proven.[2]

Several definitions of pain exist, the most widely used being the definition by the International Association for the Study of Pain (IASP): "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. 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. Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life".[3]

The first part of the definition is readily applicable to hospitalized neonates, since skin breaking procedures are performed on a regular basis. The definition also recognizes that pain is a subjective experience: experiences reported as pain should be considered pain. However, since neonates are unable to report pain themselves they have to rely on parents or caregivers to assess pain. This knowledge has led to a myriad of pain assessment tools, as shown by Stevens et al.[4] Most of these tools aim to assess procedural pain, some aim to assess prolonged postoperative pain. Interestingly, given the suggestion that repeated pain may alter pain response, indicators that are used in procedural pain scales are also used in prolonged pain scales.[4]

Different types of pain exist, the most commonly known are acute and chronic pain. Turk and Okifuji presented an overview of these different types of pain and apart from chronic and acute pain they identified 14 different types of pain.[5] Stevens identified 3 types of pain in neonates and infants: acute procedural pain, acute prolonged pain and chronic pain.[4] Although the concept of acute-procedural pain in the neonate is established and well understood, knowledge is limited on prolonged or chronic pain. The general assumption is that infants may experience chronic pain.[6] No working definitions for chronic pain in neonates exist and there is no valid assessment tool.[4]

Chronic pain in the adult has been described as a chronologic pain state for a duration of 3 or 6 months.[5] Another definition states that chronic pain is pain extending beyond the expected healing time.[5] Turk and Okifuji state that psychological factors are part of the pathophysiology of chronic pain.[5] They propose a model in which time and physical pathology are interrelated, leading to the following definition: "chronic pain is usually elicited by an injury but may be perpetuated by factors that are both pathogenetically and physically remote from the originating cause. Chronic pain extends for a long period of time, representing low levels of underlying pathology that does not explain the presence and extent of pain, or both".[5]

Turk and Okifuji suggest that environmental and affective factors interact with the tissue damage and that, especially in early life, processing of noxious information may be altered.
When one applies these definitions chronic pain cannot be established in neonates, since the neonatal period extends only to the first 28 days of life. The preterm neonate presents an even greater problem as they are subjected to repeated painful procedures each day. In these infants it not only is difficult to define the beginning of a persistent pain state but also to define "a normal expected healing time". Finally, especially during an intensive care period, several sources of pathology or interventions such as sepsis, necrotizing enterocolitis, surgical procedures and so on, may interact with the advent or persistence of the pain state.
Pillai Riddell et al, using personal and group-interviews in a cohort of NICU clinicians, attempted to define chronic pain in infancy.[6] Although clinicians were convinced chronic pain in infants admitted to a NICU or PICU exists, it proved impossible to clearly define the concept in terms of duration of pain, endpoint and etiology.

As mentioned before, the literature suggests that repeated pain may alter pain response. If this is the case indicators that are used in procedural pain assessment tools might not be applicable to others types of pain. To our knowledge only five studies looked at indicators of prolonged (mostly post-operative) or chronic pain in neonates.
In 2001 the development of the Echelle Douleur Inconfort Nouveau-Né (EDIN), was described.[7] EDIN relies on facial expression, which is also used in acute pain assessment tools, movement, sleep and consolability. To our knowledge there is no data on the practical use of EDIN. EDIN has moderate to substantial interrater reliability, and established intrarater, construct and content validity.[4] The applicability of EDIN in the extreme preterm infant is being questioned because the indicators 'quality of contact with nurses' and 'quality of sleep' might be difficult to assess.[8]
The NEOPAIN trial offered an opportunity to look at indicators for persistent pain.[9] Facial expressions of pain, high activity levels, poor response to routine care, and poor ventilator synchronicity were identified as possible markers for persistent pain in preterm infants. The Boyle study did not look at psychometric properties of these indicators. Hummel et al looked at N-PASS as a possible tool for measuring acute-prolonged pain and sedation levels.[10] In this study, interestingly, a high correlation was found with the Premature Infant Pain Profile, an assessment tool for procedural pain. Observers were not blinded as N-PASS was evaluated in a clinical setting. Recently, van Dijk et al published a paper in which an adapted COMFORT scale was applied in neonates with prolonged pain.[8] The authors established good interrater reliability, concurrent validity and good sensitivity to change. They also showed that the COMFORTNeo scale is significantly lower in neonates receiving opioids, paracetamol, benzodiazapines or a non-pharmacological intervention. The authors note that pain and distress may occur simultaneously and may be interrelated, making correct assessment of the two concepts a challenging task.

Also recently, Pillai Ridell et al looked at the level of agreement in a cohort of clinicians regarding 7 groups of possible indicators of chronic pain in infancy.[6] In these groups of indicators 2 out of 20 indicators reached an agreement level of 53 and 51%, all others had an agreement level of less than 31%. Interestingly, the level of disagreement for most indicators was between 0 and 7%. As a conclusion the 'inability to settle' and 'hyporeactivity' were identified as indicators with the highest level of agreement.
None of the mentioned studies provide a definition of prolonged or chronic pain in this age group. In addition, in none of these studies a rationale for the etiology of prolonged or chronic pain is given. Data on the applicability of known indicators for acute pain in situations of prolonged or chronic pain begins to emerge.

This leads to three research questions: what is the definition of chronic pain, which are the sources of chronic pain and which signs and symptoms can be used to diagnose chronic pain? The only work to date that addressed these research questions is the earlier mentioned study by Pillai Ridell et al. This study resulted in a wealth of data, however it failed to provide a clear description of the concept of chronic pain in infancy.
The researchers used semi-structured individual or group interviews to collect statements from a cohort of clinicians on the definition, etiology and symptoms of chronic pain. Data were then analyzed by the research team, leading to quantification of the level of agreement (agree, disagree or ambivalent) in the cohort of participants. The authors state that the participants had different notions of chronic pain and its key constructs. On a few aspects there was a high level of agreement, but within the cohort there were controversies regarding the duration of pain before it could be called 'chronic', some of the supposed causes of pain and the possible signs and symptoms. Since the participants were only interviewed and had no opportunity to discuss their statements this was not a true consensus building method.
Our hypothesis is that a consensus building research method might aid in answering the three research questions and resolve the current controversies. In literature we identified three commonly used formal consensus methods: the Delphi method, the Consensus Development Conference (CDC) and Nominal Group Technique (NGT).

OBJECTIVE

The objective of this paper is to identify the most appropriate consensus building method to answer the three research questions related to chronic pain in neonates: how to define chronic pain in the neonate, what is the etiology, and which are the clinical signs and symptoms.
The Delphi method relies on a panel of experts.[11] The experts answer questionnaires in several rounds. After each round, a facilitator provides an anonymous summary of the experts' opinions. Hence, experts are encouraged to revise their earlier answers in light of the opinion of the group. The variability of the answers decreases and the group will converge towards consensus. The process is stopped after a pre-defined stop criterion (e.g. number of rounds, achievement of consensus).
An example of this method is a study by the British Association of Chartered

Physiotherapists.[12] This group aimed at reaching consensus on physiotherapy in asymptomatic children with cystic fibrosis. The Delphi method resulted in consensus on 18 statements, forming the basis for a nationwide clinical guideline.
The NGT is a structured variation of group discussion methods. After presenting an open-ended question the panelists write down their opinions. Second, every member of the group gives one opinion to the facilitator, who organizes the opinions. The group then clarifies and discusses each opinion. Next, all members anonymously rate the opinions. Finally, the ranked opinions are discussed again and re-rated, leading to a final statement.[13] Using NGT an Australian study identified psychological factors influencing breastfeeding duration in a cohort of mothers who breastfed and clinicians.[14]
The CDC aims at rendering consensus statements based on a systematic literature review, presentations by experts and input from invited panelists and an audience.[15] These conferences usually start with a plenary session during which the state of science is presented by invited experts.[16] Next, the panelists and audience are allowed to comment on the presentations and ask for clarification. In the next step the panel tries to reach consensus and drafts a statement paper, usually in an all-night session. The final step gives the panelists the opportunity to comment on the statement paper and endorse it. In the Nordic countries in 2008 a two day CDC was organized in order to reach consensus on the management of undescended testes. The CDC resulted in a number of unanimous conclusions regarding the best treatment options, based on which a consensus statement was drafted and published.[17]

METHODOLOGY

We performed a literature search to identify the strong and weak points of the Delphi method, the Nominal Group Technique and the Consensus Development Conference. We searched in the databases of Pubmed, SUMSearch and EMBASE/Ovid using three search strings: “Delphi AND methodology”, “Nominal group technique AND methodology” and “Consensus conference AND methodology”. We limited our search to English written papers, published from 2000 to the current time.
We reviewed the three methods with regards to quality of information, risk of introducing bias, anonymity, composition of the cohort, risk of loss to follow-up, geographic limitations, costs, time-investment, flexibility and validity of the design.

RESULTS

Our search resulted in 263 full papers on the Delphi technique, 15 papers on NGT and 406 papers on CDC. Analysis of the 263 titles found regarding the Delphi method resulted in 9 papers focusing on the methodology itself. Regarding the NGT method we were able to identify 1 paper. None of the titles found with regards to CDC actually reviewed the method. Cross references yielded 3 papers reviewing the methodology of NGT and CDC. These papers were published well before the year 2000 but we decided to include them as they were the only sources of information we could find.

Figure 1 shows the process leading to the results of our literature search.

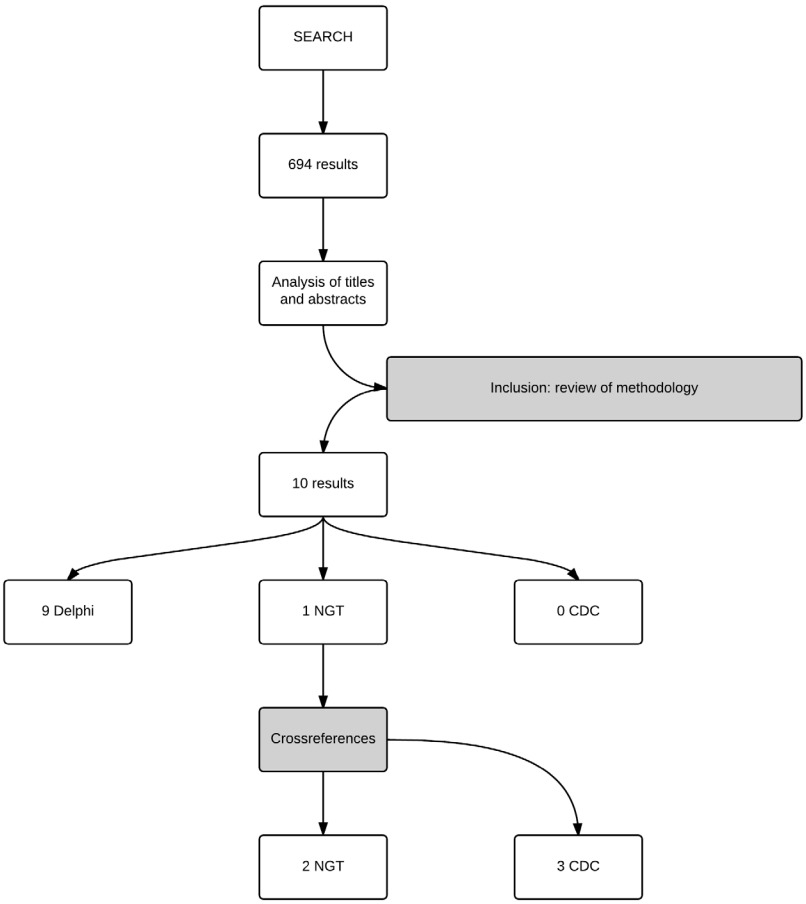

***Figure 1**: the literature search*

Quality of information

A major point of critique on the Delphi method is that the quality of information is influenced by the inability of experts to interact.[11,13] Because of this, the reasons for disagreement cannot be explored thoroughly. NGT provides the opportunity to elaborate on views in group sessions.[13,18] It is suggested that the response to the open-ended question(s) in the NGT should show saturation of data.[13] A major critique concerning the CDC lies in the preconference preparation. Often it is unclear how and to what extent the information panelists receive to prepare for the meeting has been selected, analyzed and synthesized.[19,20] The quality of information may be influenced by the time the research methods take. With the Delphi method there is no time limit, however the longer the process takes, the greater the loss to follow-up. For CDC it is reported that there is a considerable time pressure during the actual meeting to deliver results.[19] Furthermore, because of this time pressure the panelists receive prepared recommendations or questions regarding the focus of the meeting. This process is likely to influence the composition of the experts and panelists.[19]

Bias

Al three methods contain the possibility of introducing bias, mainly in selecting experts.[11,19,20] Random sampling in both NGT and CDC is difficult to achieve since experts are asked for a considerable commitment.[13,19]

Face to face contact in both NGT and CDC can lead to bias.[19] By means of discussion those with a deviant opinion could be influenced to conform themselves to the groups opinion.[13,18] Herein lies an important role for the moderator of both the NGT and CDC meeting. Allen advocates for moderators that are experienced in managing group processes for NGT.[13] In Delphi, bias can be introduced when the researcher categorizes and summarizes the answers from open-ended questions.[11] This is also true for NGT.

In CDC bias may be introduced due to several factors: selection of experts as well as panelists, selection of preconference literature or research questions and the lack of formal decision making procedures.[19] The relevance of the over-night drafting of the consensus statement should not go unnoticed. Panelists may get tired, influencing the consensus building process.[19]

Anonymity

Anonimity is reported to have advantages like an equal weight of opinions and prevention of bias due to participants knowing each others identitities.[11] Furthermore anonymity facilitates expression of opinions without pressure of influential panel members.[11] In both NGT and CDC experts meet face-to-face. In Delphi studies experts do not necessarily meet in a physical environment. Anonymity may not be guaranteed since the researcher may know the names of the experts, and experts can be aware of each others participation through personal contacts. Therefore there is no guarantee that the expression of views are anonymous. In NGT valuing the statements is anonymous.[18] In CDC there is no anonymity at all.[19]

Composition of the cohort

All three methods use experts. One of the main questions valid for all 3 methods is: Who is the expert? Baker and Keeney elaborate on the definition of 'the expert', heterogeneity of the panels and the panel size in Delphi designs.[11,21] Delphi, NGT and CDC do not differ in this respect. Some problems regarding the selection of participants might be overcome using participants from other populations in follow-up studies.[18] In selecting participants for Delphi and NGT care has to be taken to prevent domination of particular interests or opinions.[18]

Delphi studies have been carried out with numbers of experts ranging from a few to more than a thousand.

In NGT usually 9 to 12 experts participate.[13,18] Such a cohort is manageable while allowing for a broad range of views.[13] In CDC the panel usually consists of 9-18 members[19], a number for which no rationale could be found. How the panelists are selected often remains unclear, but the panel generally consists of both scientists and lay-members.[19] A panel chair is selected, often based on leadership capabilities and stature.[19] Often it is unclear how the experts that present information to the panel and audience have been selected.[19,20] The size of the audience varies from 150-1000.[19] The audience often attends only to observe the proceedings, but may also ask questions.[19]

Risk of loss to follow-up

Risk of loss to follow-up in Delphi studies is related to the size of the questionnaires or the time experts need to participate. With every round response has been shown to decline.[11] One main advantage of both the NGT and the CDC is that invited experts commit themselves to participate during the meeting, reducing loss to follow-up.[13]

Geographic limitations

Delphi uses questionnaires which can easily be distributed via e-mail or internet. With this technique there are no geographic boundaries.[13] In theory, both NGT and CDC also are not influenced by geographic boundaries, however both NGT and CDC usually use experts from just 1 country.

Costs

Depending on the composition of the panel in NGT and CDC there are costs for travel, a meeting venue, locum cover and overnight stay.[13] Costs for a CDC are estimated at $ 90.000 in the United States.[20] Since the clinical implementation of recommendations drafted with a CDC is variable there are doubts whether the costs are justifiable.[20] Delphi costs depend on the way the questionnaire is distributed. Email distribution is costless, making Delphi probably the cheapest method of the three.

Time-investment

Both in NGT and Delphi the process can be very time-consuming.[13] With both designs the researcher has to analyze, summarize and categorize the data generated in round 1. For the experts the first round with both designs is probably equally time-consuming, as they are only asked to answer open-ended questions. Round 2 of NGT and Delphi are also comparable, as in both designs this phase yields statistical

data on the level of agreement and disagreement. For the experts this phase will be comparable for both designs. Delphi proceeds with a third round, whereas in NGT in the next phase the actual meeting of experts takes place. For both experts and researcher this phase in NGT is time-consuming. Time investment in Delphi for this phase is comparable to round 2.
In CDC the time investment can be divided in a preparation phase, in which invited experts are asked to prepare a presentation.[19] Next, some of them are asked to prepare a presentation. Usually the actual meeting takes 2 to 3 days.[19] For both experts and researcher this constitutes a considerable time-investment. In literature no comparison could be found on this subject, evaluating the three methods.

Flexibility of the design
NGT an CDC have a fairly rigid design. This may enhance the validity of the design. Delphi has been used in numerous variations and has been shown to be a flexible design.[11] The researcher can, for instance, decide if an extra round is necessary to further explore opinions.

Validity of the design
The validity of consensus building methods has been questioned, mainly because of lack of defining expertise, viewing the methods as means to facilitate group communication as opposed to sound research and the insecurity that the results of the methods provide the truth.[18] In literature numerous variants on the original Delphi design can be found, weakening its validity. The validity of the method has also been questioned, for example because of the inability of experts to discuss issues.[11,18]
There is no consensus on the number of rounds and the number of experts.
Validity of the CDC depends mainly on the credibility of experts as well as panelists.[19,20]
Validity is further influenced by lack of defining consensus, which is true for all three methods.[11,19]
Table 1 provides an overview of the strong and weak points of the 3 methods.

Research Method	Delphi	CDC	NGT
Quality of information[11,13,18-20]	+/-	+/-	+
Bias[11,13,18-20]	+/-	+/-	+/-
Anonimity[18,19]	+	-	-
Composition of the cohort[11,13,18-21]	+	+/-	+/-
Loss to follow up[11,13]	-	+	+
Geographically limited[13]	+	-	-
Costs[13,20]	+	--	-
Time consuming[13,19]	+/-	+/-	+/-
Flexible design[11]	+	-	-
Validity[11,18-20]	+/-	+/-	No data

Table 1: *strong and weak points of the Delphi Survey (Delphi), Consensus Development Conference (CDC) and Nominal Group Technique (NGT). +: strong attribute; -: weak attribute; +/-: neither strong nor weak*

DISCUSSION

After analysis of the designs we chose the Delphi method based on the following arguments.
The main argument to choose Delphi as research method is (quasi-)anonymity and equality of the experts, ensuring that every expert can express an opinion freely without being impressed or overruled by another expert. Furthermore the technique is suitable for an international and heterogeneous panel, since the research questions can be distributed via email or website. This facilitates cultural and professional differences regarding pain to be taken into account. Regarding our research questions we found this to be important as there are known cultural, ethnical and professional differences in the interpretation of pain. The method is relatively inexpensive as opposed to CDC and NGT.

CONCLUSION

All three consensus building methods have strong and weak attributes. This study provided us with some major insight with regards to enhancing validity of the Delphi design. Consensus should be clearly defined, the rationale for the selection and composition of the cohort should be clarified.
In Dutch politics the "Poldermodel" is a term that is used to describe consensus policy in economics. The verb "polderen" means "(a frequently slow process of) decision making using consensus". With all three consensus building methods the question remains if consensus equals the correct answer, or the truth. Results of such a study only provides the state of science or even the state of mind amongst a certain group of experts, chosen on certain grounds by the researcher. However, these methods might be the best way, a "Polder –solution", or a compromise, to gather information and produce working hypotheses on a subject with limited knowledge base. These hypotheses should then be tested in the real world.

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Chapter 3

Chronic Pain in the Newborn: Toward a Definition.

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ABSTRACT

Objective

Chronic pain is poorly addressed in neonatal pain research. We aimed at contributing to define the concept of chronic pain in the newborn.

Method

We designed a web-based, three round Delphi survey. We invited an international panel of experts (health care providers) in the fields of neonatology and neonatal pain to participate.

Results

In the first round, participants (n=189) answered three open-ended questions: (1) define chronic pain in your own words, (2) what are the possible causes and (3) which signs and symptoms are used to diagnose chronic pain? The answers were categorized and summarized into 437 statements, which were valued by the participants (n= 189) on a 5-point Likert scale. In the second round, the remaining participants (n=72) were asked to reflect on 65 selected statements with a mode or median ≥ 4 or mean ≥ 3.75. These threshold values provided the opprtunity to reach consensus in the following round. In the third round, the remaining participants (n=33) were provided with the group and individual responses. This process resulted in 23 statements with mode, mean and median of ≥ 4, on which the participants reached consensus.

Discussion

Although several etiologic factors were defined, no useful diagnostic criterion could be identified. The survey resulted in a description of chronic pain in the newborn. Identifying chronic pain is clinically relevant because it interferes with growth, prolongs hospitalization, leads to altered pain perception, and impairs cognitive and behavioral development.

INTRODUCTION

There is no uniform definition of chronic pain (CP). The International Association for the Study of Pain (IASP) defined CP in adults as pain that persists beyond the expected healing time (3-6 mo) after an injury.[1] Applying this time criterion to the newborn will exclude any newborn who is in pain from birth up to the age of 3 months from having CP. Hence, a specific time criterion may not be applicable in the newborn. Turk and Okifuji propose a model in which acute and CP are represented by the dimensions time and level of pathology. A short period of pain with high physical pathology in this model reflects acute pain, while a longer duration in the presence of low physical pathology represents CP.[2] To the best of our knowledge there is no scientific literature reviewing the validity of this adult concept in newborns.

As in adults, the American Pain Society defines CP in children as persistent and recurrent pain, lasting longer than 3 months. Most common CP conditions in pediatrics are associated with musculoskeletal pain, headache and abdominal pain.[3] However, the younger the age, the more difficult it is to define duration, type, character or source of pain. Preschool children report any pain often as 'tummy pain'.[4] In general, toddlers and newborns show a generalized response to acute pain, consisting of changes in facial expression, crying, splaying of fingers and toes and flexion or extension of limbs. Extremely premature infant are unable to display gross motor responses, and may react to acute pain with only increase of heart rate or oxygen desaturation. These non-specific symptoms have found their way into numerous pain assessment tools, developed mostly for acute pain.[5] Acute pain occurs routinely in the neonatal intensive care unit (NICU). Newborns admitted to the NICU are subjected to approximately 16 painful events per day.[6-8] However, no data is available for CP conditions as a consequence of repeated (acute) pain events. Furthermore, 'expected healing time' in infants with conditions that are perceived as being painful, such as necrotizing enterocolitis (NEC) or pneumothorax is difficult to define. Although acute and procedural pain in the newborn are well studied, to the best of our knowledge only 5 papers address prolonged or chronic neonatal pain.

In 2001 a pain scale for prolonged pain, the Echelle Douleur Inconfort Nouveau-Né (EDIN), was developed.[9] The authors defined prolonged pain as pain lasting several hours or days. They identified sources for prolonged pain such as mechanical ventilation, NEC and the period after patent ductus arteriosus ligation. Video observations of behavioral indicators of pain (facial activity, body movements, quality of sleep, quality of contact with nurses and consolability) were assessed by a panel of experts. The EDIN pain scale showed acceptable interrater reliability and high internal consistency. EDIN scores in two extreme situations (pain and no pain) were compared and showed a significant difference between these 2 conditions, presumably indicating construct validity.

Pillai Riddell and colleagues performed qualitative research among clinicians in an attempt to define CP in infancy. The researchers conducted a series of interviews leading to 6 possible indicators for CP: inability to settle, social withdrawal, constant grimacing, tense body, hyporeactions or hyperreactions to acute pain and dysregulated sleep or feeding patterns.[10]

Some of these indicators show resemblance to the indicators incorporated in the EDIN scale. No definition could be extracted from the results of this study. Although participants reached consensus that CP in infancy exists, there was no consensus on the definition. Aspects that were identified were duration of the pain, expected healing time or endpoint, and repetitive exposure to acute pain as a source. Some participants in this study stated that if something is considered CP in the adult or verbal child, it also should be considered CP in infancy. None of these aspects reached consensus.[10]

The NEOPAIN trial offered an opportunity to look at indicators for persistent pain associated with mechanical ventilation and neonatal intensive care.[11] In this study, no definition for persistent pain was provided. Ancillary NEOPAIN study suggested 4 clinical signs most frequently associated with persistent pain in preterm newborns ≤ 32 weeks of gestation: facial expressions of pain, high activity levels, poor response to handling, and poor ventilator synchronicity.[12]

The Neonatal Pain, Agitation, and Sedation Scale (N-PASS), an assessment tool for acute pain, was tested in situations of ongoing or acute-prolonged pain, associated with mechanical ventilation and the post operative state.[13] The authors define CP as "a pathological pain state without apparent biological value that has persisted beyond the normal tissue healing time, usually 3 months". However, it is unclear on what data this definition was based. The authors were able to show beginning validity of the N-PASS as a tool to assess ongoing pain and sedation.

Recently, van Dijk et al[14] published a study in which they validated an adapted COMFORT scale for application in newborns with prolonged pain. Again, in this study no definition for prolonged pain was given. The authors point out that it is difficult to differentiate between pain states, distress or even the combination of the 2. No rationale could be distracted from the paper for etiologic factors as prolonged ventilation and necrotizing enterocolitis. Although the authors postulated that the COMFORT Neo was a promising tool, they also speculated that prolonged pain may lead to marginal signs of distress due to low energy reserves of preterm infants. This could mean cut-off points that are currently used in pain scales to discriminate pain from no pain are possibly not valid for ongoing, prolonged or CP.

In summary, although 5 papers address types of pain other than acute pain, a sound conceptual framework for "ongoing pain", "persistent pain", "prolonged pain" or "CP" in newborns is lacking and cannot be extracted from these papers or from existing adult and pediatric literature. There is no fundamental understanding of the sources of these types of pain. Facial activity and grimacing, identified as indicator for prolonged or persistent pain is also used in assessment tools for acute pain. Other indicators, such as response to handling or social interaction are difficult to assess in preterm infants.

Although the gaps in knowledge concerning types of pain other than acute or procedural were recognized years ago,[15] and important progress has been made since, subsequent research did not lead to a thorough understanding of the concept of CP in the newborn. The need for further research in the field of types of pain other than acute was emphasized in a report from an international expert panel in 2006.[16]

These conclusions lead to three open-ended questions: (1) *What is the definition of CP in the newborn?, (2) What are the causes of CP in the newborn? and (3) Which signs and symptoms can we use to diagnose CP in the newborn?*
Qualitative research aims at the development of ideas to understand a certain phenomenon and is appropriate to answer the first question above.[17] Question 2 and 3 are descriptive and explanatory in nature, and quantitative research is suitable for these research purposes.[17] Several study designs address these different purposes, and there are several designs that incorporate both qualitative and quantitative aspects (multi method research). In this paper we present the results of the Delphi survey seeking to define CP in the newborn.

METHODS

Previously we reported on the results of a literature study with regards to the methodology of consensus building methods.[18] We found only sparse data reviewing the methodology of the Nominal Group Technique and the Consensus Development Conference. More data were found with regard to the Delphi method. A critical appraisal of the methodology resulted in strong and weak points for all 3 methods. A major criterion should be the validity of the design. However, conclusions on validity are hampered by the marginal amount of papers found for 2 of the 3 designs.
We designed a Delphi survey to be carried out in a heterogeneous panel, consisting of different nationalities, professions and cultural backgrounds. The main argument to choose the Delphi technique was the low probability of introducing bias as a result of interaction of experts.
The literature is not uniform regarding the selection of an expert panel.[19] Some advocate the use of highly trained and competent participants within a specialized area of knowledge.[20] However, there is no consensus on what 'highly trained and competent' should be. Knowledge does not necessarily equal expertise.[21] Inviting only renowned 'experts' limits the available sample size and possibly introduces bias (experimental or scientific knowledge may be distant from clinical practice).[21] Inclusion of patients or users of health care services, despite a lack of years of experience, may yield important new views. However, including patients may decrease validity of the results because of personal experience and unfamiliarity with medical terminology. We have selected our expert panel using the aid proposed by Baker et al.[21] We defined 'expert' as a health care provider working in the field of neonatal care or a parent who had a newborn in NICU. A general definition of 'the expert' aids in generating new ideas or insights in an unexplored field. To obtain a general view we aimed at a heterogeneous sample. We defined knowledge as having personal experience with newborns in pain. We did not quantify a necessary level of knowledge as there is no evidence on what constitutes sufficient knowledge, nor how to measure this. Moreover, a certain predetermined level of knowledge may exclude those with new and fresh ideas. Experience was defined in the same manner as knowledge. We included representatives of our patients. We believe that parents have an excellent notion on how their baby's feel. However, we are aware that parents opinions may be biased by personal experience.

The panel was recruited by extracting email addresses from papers published by experts in the field of neonatal pain. Secretariats from several neonatologist and parental organizations were contacted and asked to send the invitation to their members. We announced the survey on international fora. Members of the Dutch National Study group for Pain in Neonatal Intensive Care Units and the members of the Dutch Association for Pediatrics were asked to participate **(Table 1)**. Contact data of these groups were readily available. In our invitational e-mail we stimulated potential participants to forward the mail to neonatal health care providers in their pain network.

TABLE 1. Sources of Participants

Group	Source
Personal emails	Extracted from original papers
Centre for pediatric pain research	Pediatric pain mailing list
General neonatal practitioners	99NICU.org
General pediatric practitioners	Dutch Association for Pediatrics
Arabic neonatologists	Arab Neonatology Forum
Spanish neonatologists	Spanish Society for Neonatology
Dutch neonatal nurses	Dutch National Studygroup for Pain in NICU's
New Zealand neonatal nurses	New Zealand Association of Neonatal Nurses
Parents	Dutch Association for Parents of NICU patients (VOC-Vereniging Ouders van Couveuse-kinderen), and Parents of Premature Babies (Preemie-L)

Table 1. *The table provides an overview of the sources that were contacted for the recruitment of participants. NICU indicates neonatal intensive care units.*

An online survey was designed to facilitate easy participation. Participants needed to register with their email address and were asked to answer 3 open ended questions: (1) *what is the definition of CP in the newborn*, (2) *what are the signs and symptoms, and* (3) *what are the causes of CP in the newborn*. The answers were deidentified, categorized and summarized into statements. The researcher did not alter the original participants' answers and was blinded to which answers were given by which participant. An automated email was then sent to the participants, asking them to rate the statements on a 5-point Likert scale.[22] Value 1 of the scale represented total disagreement, value 5 represented total agreement. The data that resulted from this second round were analyzed. In the third round, participants were provided with the group's response, given as mean values and range for each remaining statement, as well as their own values from round 2. They were asked to reflect on their own value for each statement in the light of the group's opinion. In this third round it was possible for participants to change their original values from round 2.

Statistical analysis

The statistical method applied in a Delphi survey should detect the rate of consensus and aid in the process of reaching consensus. As we use the ordinal Likert scale, the statistical measures of choice are measures of central tendencies, such as mode and median. However, mean and standard deviation might also generate insight in the importance of the statements for the total group of experts.[22,23] As the results of the second round became available, use of mode and median alone would yield a third round of 329 statements (mode or median ≥ 4) or 199 statements (mode and median ≥ 4) respectively. Therefore, we added the statistical measure mean to the analysis. We assumed a cut-off point of 3.75 for round 2, which reflects a fair amount of agreement, while limiting the number of statements to be valued in round 3 to prevent further loss to follow-up. For the final analysis, however, we used the predefined cut-off point as a mean ≥ 4.

RESULTS

Our strategy resulted in the initial participation of 189 experts. Demographic data for the participants are listed in **figures 1** and **2**.

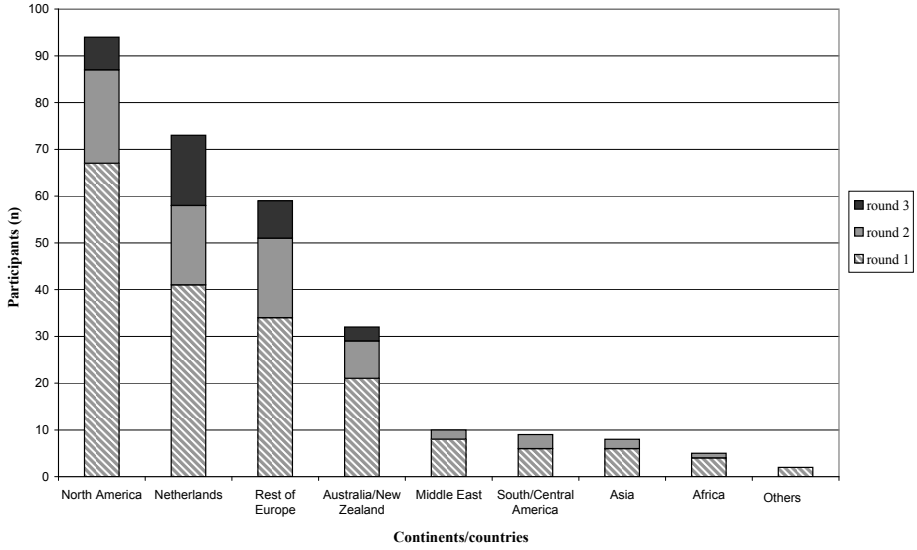

***Figure 1**: countries of origin from the participants, given as numbers, across the 3 rounds of the survey.*

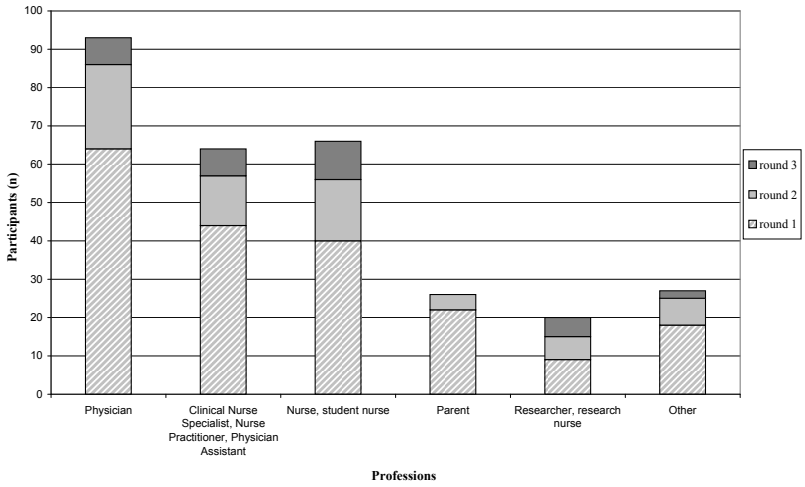

***Figure 2**: professions of the participants, given as numbers, across the 3 rounds of the survey.*

The answers on the open ended questions resulted in 3 categories and 12 subcategories with a total of 437 statements **(Table 2)**.

TABLE 2. Categories, subcategories and Numbers of Statements

Categories	Subcategories	Statements (n)
Definition	Definition	34
	Etiology	29
	Miscellaneous	47
	Intensity	4
Etiology	Disease related	69
	Miscellaneous	28
	Procedure related	52
	Environment related	13
Signs&Symptoms	Behavioral	97
	Hormonal	6
	Physiological	27
	Miscellaneous	31
Total		437

***Table 2**: This table provides an overview of the number of statements in the 3 main categories, resulting from round 1 of the survey.*

Round 2 resulted in a loss to follow up of 117 participants, with 72 participants remaining in the survey. After analyzing the results, 65 statements (15%) with a mean value of 3.75 remained for further evaluation in round 3. Statements from the subcategories "physiological" and "hormonal" in the category "signs & symptoms" were below the cut-off value of 3.75 and therefore excluded for further evaluation. Round 3 yielded a drop out of 39 participants, with 33 participants (17% of the initial participants) completing the survey. Of the originally participating 9 geographic regions only 4 completed the survey. None of the participating parents completed round 3, and the drop-out rates were 89% for the physicians, 84% for nurse practitioners (including clinical nurse specialists and physician assistants), 75% for the nurses, and 45% for researchers. **Table 3** shows the final results, with 32 statements attaining both median and mode values of ≥ 4 and mean values of ≥ 4. This table also provides information about the changes in values for the statements between rounds 2 and 3. The subcategories "environment related" and "procedure related" in the category "etiology" did not meet the cut-off criteria and were excluded for final analysis. The same is true for all subcategories in the category "signs & symptoms" except for the subcategory "miscellaneous". On the basis of our data we hypothesize the following theoretical framework on CP in the newborn.

Category definition.
CP can often not be associated with a specific cause. It has no obvious end point in sight and is no longer proximate to an event or procedure. CP may alter perception causing non-noxious events to be perceived as painful, leading to a CP response. It depletes stress hormones, increases energy consumption, therefore interferes with growth. As a consequence, CP may likely prolong hospitalization and worsen or add to existing neonatal morbidities.

Category etiology.
Etiologic factors included epidermolysis bullosa, which showed the highest rate of consensus, followed by inadequate pain management and the skin breakdown in staphylococcal scalded skin syndrome. (Septic) arthritis, tissue ischemia and necrosis, nerve lesions, skin damage (alcohol burns), and daily episodes of continuous or recurrent pain sensations were also mentioned as possible causes for CP.

Category Signs and Symptoms.
Diagnostic factors specific to CP could not be identified.

TABLE 3. Results of the Delphi Survey Across Rounds 2 and 3

		Round 2				Round 3				Likert Value		
		Mean	Mode	Median	SD	Mean	Mode	Median	SD	1	2	3
Definition												
1	Chronic pain in the newborn may lead to a state where any interaction/procedure that is happening to the infant is perceived as painful.	3.85	4	4	0.88	4.33	4	4	0.55	0	0	1
2	Chronic pain may likely prolong hospitalization, worsening or adding to the existing morbidities.	4.11	4	4	0.91	4.17	4	4	0.65	0	0	4
3	Pain that occurs over a period of time, that is ongoing and has no obvious end point in sight.	4.14	4	4	0.99	4.13	4	4	0.98	1	2	1
4	Both recurrent and long lasting pain may become chronic.	4.00	4	4	0.82	4.13	4	4	0.78	1	0	1
5	Chronic pain depletes stress hormones and increases energy consumption therefore interfering with growth.	3.94	4	4	0.99	4.10	4	4	0.92	1	0	5
6	It can be anywhere in the body depending on the reason for the pain.	3.77	4	4	0.81	4.07	4	4	0.75	1	0	1
7	Poorly controlled acute pain may lead to hyperalgesia, altered pain perception, and possibly a predilection to chronic pain states.	4.02	4	4	0.77	4.03	4	4	0.81	1	0	2
8	Pain that is ongoing, no longer proximate to a procedure or event.	3.88	4	4	1.09	4.03	4	4	0.69	0	1	4
9	A painful event may also alter perception causing events that normally would be tolerate to be perceived as painful, leading to a chronic (longer duration) pain response.	4.04	4	4	0.85	4.03	4	4	0.67	0	0	6
Etiology												
10	Epidermolysis bullosa	4.33	5	4	0.82	4.21	5	4	1.01	1	1	3
11	Inadequate pain management	4.15	4	4	0.92	4.17	4	4	0.80	1	0	1
12	Longstanding under-treated or ignored acute pain	4.23	4	4	0.77	4.11	4	4	0.88	1	1	0
13	Scalded skin syndrome skin breakdown.	4.18	4	4	0.84	4.10	4	4	0.93	1	1	2
14	This pain often cannot be associated with a specific etiology but might well be from a combination of things.	3.83	4	4	0.97	4.07	4	4	0.37	0	0	1
15	Arthritis	3.98	4	4	0.81	4.03	4	4	1.02	1	2	2
16	Daily continuous or intermittent episodes of painful sensations in the newborn	4.05	4	4	0.87	4.00	4	4	0.69	0	1	4
17	Nerve lesions.	3.93	4	4	0.82	4.00	4	4	0.80	1	2	0
18	Tissue ischaemia.	3.87	4	4	0.91	4.00	4	4	0.87	1	1	2
19	Tissue necrosis	3.97	4	4	0.79	4.00	5	4	1.13	1	3	3
20	Skin damage, eg alcohol burns	4.15	4	4	0.79	4.00	4	4	1.07	1	3	1
Signs & symptoms												
21	Signs maybe be none, or very non-specific.	3.80	4	4	1.03	4.24	4	4	0.83	1	0	1
22	Treatment should be based on signs of relief or comfort.	3.85	4	4	0.96	4.07	4	4	0.61	0	1	1
23	There are different thresholds of this type of pain and every baby reacts differently.	3.80	4	4	0.96	4.03	4	4	0.72	0	1	4

***Table 3**: This table provides an overview of the statistical values of the statements that were selected for analysis across rounds 2 and 3 of the survey. In the columns with heading "Round 2" the values the statements reached in round 2 can be found. The columns with heading "Round 3" represent the values resulting from round 3. The differences between these colums reflect the tendency toward consensus for each statement. For round 3 the frequency of the Likert-value 1, 2 or 3 is given for all statements.*

DISCUSSION

Our study yielded interesting statements regarding the definition of CP in the newborn. However, it is unclear whether these statements can be applied to "ongoing pain", "persistent pain", or "prolonged pain".[12] Some statements are in line with the definitions for CP in the adult. Turk and Okifuji postulate that acute and CP may differ in the dimensions of time and degree of pathology. In their conceptualization of CP Turk and Okifuji state that CP "may be elicited by an injury or disease but is likely to be perpetuated by factors that are both pathogenically and physically remote from the originating cause".[2] Our data suggest that the same is true for the newborn. Ample evidence shows that, especially in early life, the brain is modified by experience and may alter the way noxious information is processed.[24-26] This concern was also raised by our participants.

Impaired postnatal growth is likely to have great impact on later life. Known effects are the development of a short stature, and also altered insulin sensitivity and blood pressure.[27] The long term effects of repetitive or prolonged pain have been associated with impaired cognition,[24,28-31] short-term memory,[30,32] altered pain thresholds,[33-36] attention deficit disorder,[37-39] abnormal visual-motor coordination and visual-perceptual difficulties,[31,32,40] and impaired executive functions.[41]

Our results suggest that CP is not approximate to an event and has no clear endpoint in sight. This is in agreement with others.[13] In our study no consensus could be reached on a quantitative time criterion in the definition of CP, although the terms "ongoing pain", "prolonged pain", and "persistent pain" may be applied to different phases in the chronicity of neonatal pain. Although in the Pillai-Ridell study a time criterion was considered important, no consensus was reached on how to define this criterion.[10]

The etiological factors showed a remarkable high amount of disease states as opposed to interventions. That may be good news, since only a limited number of patients admitted to the NICU will be subject to these diseases. However, inadequate pain management as a risk factor concerns all patients given the number of invasive procedures on a daily basis.[6-8] Surprisingly, some of the etiologic factors identified in the first round, such as the postoperative state, NEC or prolonged ventilation during NICU admission, that were used in previous studies, failed to reach consensus in round 2 and 3 of our study. This may be due to the use of different terminology: there is a risk of inadequate pain management in postoperative infants or infants with NEC. Pillai-Ridell et al[10] also failed to show consensus amongst health care providers concerning etiologic factors such as NEC. As suggested by other researchers, prolonged ventilation may be associated with stress and pain; however, research failed to show a beneficial effect of continuous morphine analgesia.[42,43] This leaves questions such as: are we measuring pain adequately, or, is morphine an adequate analgesic for the type of pain/stress supposed to be associated with mechanical ventilation.

Similar to others, our study was unable to identify specific diagnostic determinants.[10] In other words, to date there is no way to determine whether or not a newborn is experiencing a CP state. Signs and symptoms may be non-specific or dependant on

the stage of pain.[10] If this is true, it renders current pain assessment tools unsuitable for the measurement of chronic neonatal pain. However, the COMFORT Neo scale in newborns shows promising results in the assessment of prolonged pain.[14] Internal consistency was shown to be good, although item correlation varied among the 5 diagnostic criterions from the COMFORT Neo scale and depends on the newborn being mechanically ventilated or not.[14] Hence, although several papers identified possible diagnostic determinants of prolonged or CP, based on our results it is doubtful whether a valid or practically useful instrument can be developed using the parameters commonly assessed in neonatal pain scales. Novel techniques, perhaps using neuroimaging or neurophysiological approaches, or methods for measuring pain thresholds in newborns, may offer promising avenues for the future assessment of CP in the newborn.[44,45]

Methodological limitations

As with any Delphi survey bias may have been introduced. We had only partial control over the experts that participated and did not define their "expertise" to avoid selection bias. This has the potential effect of not including experts as defined by academic competencies. A second and opposite potential effect is that healthcare workers that are not acknowledged as true experts but may have valuable insight, novel ideas, or new data were able to participate. We therefore did not ask for demographic data such as years of experience in neonatal care or years of experience as a pain specialist. This choice has led to a heterogeneous panel of participants with the possible advantage of obtaining an unbiased, broad view of a concept that is not well understood.[20]

The advantage to use Internet-based recruitment is the potential participations of a variety of professionals over all continents. A disadvantage of the methodology is that the potential pool size of recruitment is unknown.

There is no literature to support the use of a specific number or ranger of number of experts. Panels range from 10 to a few thousand participants, but the number is typically < 50.[46] In homogenous panels, a number of 10 to 15 would be sufficient, in a heterogeneous panel more participants are needed.[20] Therefore it is difficult to assess the impact of a large panel such as ours on the results.

We did not alter the answers on the questions in round 1, thus preventing bias to be introduced at this stage. This has led to a large number of items, which might explain the loss to follow up among busy professionals with multiple competing priorities. The results of our study may not reflect a global expert opinion, as only 4 out of 9 regions were represented in round 3. Parents contributed only in rounds 1 and 2, none of the parents completed the study. The drop-out rate among professions ranged from 45% (researchers) to 89% (physicians) during the Delphi survey. To guarantee anonymity and unbiased processing of the data, it was not possible to correlate statements of professions between the first rounds and the final analysis.

Although likely to have an effect,[19] there is only sparse scientific data that further explores the consequences of large numbers of drop-outs on the results obtained using the Delphi technique.[47] A firm conclusion about how the drop-out rate affected our results cannot be drawn from these data.

Bias may be introduced by our definition of consensus and the statistical methods used in this study. The method of choice for ordinal scales is using mode and median. Because the data were skewed the use of mean and standard deviation is theoretically incorrect. However the use of these measures did provide some discrimination between the statements, leading to a third round that was not too laborious.
Finally, the Delphi survey itself as a research method includes potential bias such that experts may be pushed toward consensus since this is the desired outcome of the method, thereby compromising their own opinion. To our knowledge no review on the research method focused on this aspect. However, this aspect is common for all consensus building methods.

CONCLUSION:

In summary, our Delphi survey provides data leading to a description of CP in the newborn. We identified several components of the concept CP, comparable to previous work in the adult and pediatric population. This study does not support the inclusion of a time criterion in the definition. Inadequate pain management is a risk factor for CP, supporting the hypothesis that every newborn subjected to neonatal intensive care may be at risk to develop a CP state. This underlines the need for meticulous pain assessment and management Our data suggest that pain assessment tools developed specifically to assess acute pain may be inappropriate for the assessment of CP. Our hypothetical framework is open for discussion and future research using different study designs will be necessary to strengthen or reject our hypothesis.

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Chapter 4

A consensus model for Delphi processes with linguistic terms and its application to chronic pain in neonates definition.

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ABSTRACT

This paper proposes a new model of consensus based on linguistic terms to be implemented in Delphi processes. The model of consensus involves qualitative reasoning techniques and is based on the concept of entropy. The proposed model has the ability to reach consensus automatically without the need for either a moderator or a final interaction among panelists. In addition, it permits panelists to answer with different levels of precision depending on their knowledge on each question. The model defined has been used to establish the relevant features for the definition of a type of chronic disease. A real-case application conducted in the Department of Neonatology of Máxima Medical Center in The Netherlands is presented. This application considers the opinions of stakeholders of neonate health-care in order to reach a final consensual definition of chronic pain in neonates.

1. INTRODUCTION

Delphi technique is a well-known group decision-making method involving a structured interaction among a panel of experts or stakeholders, which anonymously tries to reach consensus on the significant features of a certain topic.[1] Since its introduction in the 1960s, it has been used to attain convergence of expert opinion in a variety of fields of knowledge such as program planning, needs assessment, policy determination and resource utilization.[2-5]

The Delphi method has proved to have some functional advantages over other consensus-building methods, such as brainstorming, dialectical inquiry and nominal group.[1,4-7] The moderator in these group decision-making techniques conducts the group communication and consensus processes through several rounds. However handling uncertainty and linguistic terms in group assessments is one of the main problems of this type of methods.

To handle the uncertainty and linguistic information inherent to human consensus processes, many group decision-making techniques have been developed and are available in the academic literature.[7-12] In [13] a review of consensus models in a fuzzy environment can be found. There is, nowadays, a wide range of areas of application for these methods, from managerial to medical or engineering.[14-17] In particular, some fuzzy Delphi approaches have been proposed to deal with uncertainty and linguistic information.[18-20] Although, through these approaches, participants use a set of ordered linguistic labels, they are unable to use different levels of precision in their assessments. In addition, these fuzzy Delphi approaches share with original Delphi technique the absence of a definition of a degree of consensus. These have been considered as significant drawbacks by Delphi technique users.

The new approach to the Delphi method developed in this paper, not only includes the use of linguistic information, with different levels of precision, but also computes a degree of consensus in each round of the Delphi process. It permits each participant to utilize linguistic terms that reflect more adequately the level of uncertainty intrinsic to his evaluation, and to be dynamically aware of their agreement in each round.

To this end, the new Delphi approach is based on qualitative reasoning techniques.[21] Participants' assessments through linguistic terms are considered qualitative labels in an absolute order-of-magnitude qualitative space.[22] Different levels of precision are used to reflect the distinctions required by evaluators' reasoning processes. Techniques based on order-of-magnitude qualitative reasoning have provided theoretical models that permit operating in conditions of insufficient or non-numerical data.[21] One of the advantages of qualitative reasoning is its ability to tackle problems in such a way that the principle of relevance is preserved, i.e., each variable involved in a real problem is valued with the level of precision required.

The paper comprises six sections. Section 2 introduces the main features of Delphi processes. The theoretical framework for this new approach is then presented in Section 3. In Section 4 the new approach for Delphi processes, based on a group consensus measure with linguistic terms is explained. A real case example in the health-care sector is presented in Section 5 to show the performance of this new approach. Finally, the main conclusions and lines of future research are discussed in Section 6.

2. DELPHI PROCESSES: OVERVIEW AND KEY POINTS

Dalkey and Helmer and the Rand Corporation developed the Delphi technique in 1963.[3] This technique is usually used for determining the set of possible alternatives, finding implicit assumptions conducting to different judgments, exploring new solutions for a specific problem, or reaching consensus about a specific topic from a panel of experts or stakeholders.

A Delphi process is generally designed through 3 to 4 rounds of questions. In the first round, in order to gather panelists' opinions, open-ended questions are used. The results of this first round are classified into statements which are then valued by the panelists in a second round. In the consecutive rounds the panelists are showed the values of the total panel and are asked to re-assess their own values in the light of the group's opinion. Frequently, this type of iteration leads to a consensus on the group of significant statements.

The main weaknesses or limitations on the Delphi method are the absence of a definition of a degree of consensus, the difficulty of dealing with the uncertainty involved in panelists' opinions, and the way in which some opinions are suppressed during the consensus process.

Several fuzzy Delphi approaches have been developed in the literature to solve these issues. The application of fuzzy theory to the Delphi method by means of linguistic variables was initially introduced in [20]. A fuzzy Delphi method considering pessimistic, moderate and optimistic assessments of experts via triangular fuzzy numbers was introduced in [23]. Using triangular fuzzy numbers to model the experts' judgments, in [24] consensus is reached in only one round thanks to the implementation of the max-min fuzzy Delphi method and a new Delphi method via fuzzy integration. After reviewing the previous fuzzy Delphi works, a new approach using fuzzy statistics is proposed in [18]. An application of fuzzy Delphi Method to obtain the critical factors of the regenerative technologies by using fuzzy AHP to find the importance degree of each factor is introduced in [25]. A web based consensus support system for group decision making problems and incomplete preferences was introduced in [8]. The method is similar to Delphi technique but it does not rely on the use of questionnaires and the moderator tasks can be replaced. An extension of the recent literature and an implementation of fuzzy Delphi for the adjustment of statistical forecast can be found in [19]. This study presents a fuzzy Delphi adjustment process to improve accuracy and introduced an empirical study to illustrate its performance.

A new approach for Delphi processes is proposed in this paper. It is based on a definition of a degree of consensus that can be used when experts' answers (as from round 2) are given with linguistic terms. Linguistic terms are handled by means of order-of-magnitude qualitative reasoning techniques. [22,26] offer a detailed application of these methods to group decision-making and consensual processes.

3. ORDER-OF-MAGNITUDE REASONING FRAMEWORK

In this section, we briefly review the basic concepts of the qualitative absolute order-of-magnitude model which will be used in the next sections.[21,22,27] This paper relies on the use of linguistic terms based on this model. This allows the imprecision involved in panelists' opinions in Delphi processes to be managed. The qualitative absolute order-of-magnitude model of granularity n considers a finite set of *basic* qualitative labels, $\mathbb{S}_n^* = \{ B_1 , \dots , B_n \}$ which is totally ordered: $B_1 < \dots < B_n$.[22,27,28]
In general, each basic qualitative label corresponds to a linguistic term, for instance for $n = 5$: B_1 = "Strongly disagree" B_2 ="Disagree" B_3 = "Neither agree nor disagree" B_4 = "Agree" B_5 ="Strongly agree".
The *complete universe of description* for the absolute order-of-magnitude space with granularity n, is the set $\mathbb{S}_n$:

$$\mathbb{S}_n = \mathbb{S}_n^* \cup \{[B_i, B_j] \,|B_i, B_j \in \mathbb{S}_n^*, i < j\},$$

where the *non-basic* label $[B_i, B_j]$ with $i < j$ is defined as the set $\{ B_i , B_{i+1},\dots,B_j \}$ whereas $[B_i ,B_i] = B_i$.[22,27]
Following with the above-mentioned set of $n = 5$ linguistic terms, the nonbasic label $[B_1 , B_2]$ represents the linguistic term ["Strongly disagree", "Disagree"]. The linguistic term "Unknown" is represented by ["Strongly disagree", "Strongly agree"], i.e., $[B_1 ,B_5]$. This least precise qualitative label is denoted by the symbol ?, i.e., in $\mathbb{S}_n$, $[B_1, B_n] \equiv \alpha$. This structure permits working with all different levels of precision from the basic labels $B_1, \dots , B_n$ to the ? label (see **Figure 1**).

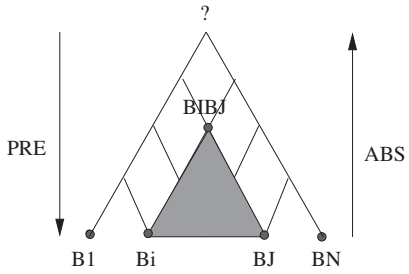


***Fig 1**. The complete universe of description $\mathbb{S}_n$.*[22]

In addition, we also review the concept of extended measure in $\mathbb{S}_n$ and the connex union and intersection operations introduced in [22]:
A normalized measure μ is considered in the set of basic qualitative labels, μ $\mathbb{S}_n^*$: $\rightarrow [0, 1]$ such that $\sum_{B_i \in \mathbb{S}_n^*} \mu(B_i) = 1$. This measure is directly extended to $\mathbb{S}_n$ by defining μ $([B_i , B_j]) = \sum_{k=i}^{j} \mu(B_k)$.
In order to define the degree of consensus among a set of panelists' opinions, the connex union and the intersection between qualitative labels are also considered.[22]
Given two qualitative labels $[B_{i_1},B_{j_1}],[B_{i_2},B_{j_2}] \in \mathbb{S}_n$, their connex union is the label $[B_{i_1},B_{j_1}] \sqcup [B_{i_2},B_{j_2}] = [B_{\min(i_1,i_2)},B_{\max(j_1,j_2)}]$. When $[B_{i_1},B_{j_1}] \cap [B_{i_2},B_{j_2}] \neq \emptyset$, their intersection is the qualitative label $[B_{i_1},B_{j_1}] \cap [B_{i_2},B_{j_2}] = [B_{\max(i_1,i_2)},B_{\min(j_1,j_2)}]$.

Finally, an *iterative relaxation process* is initiated in order to reach a nonempty intersection among the set of qualitative labels when this intersection is initially empty (see a detailed explanation in [22]). The iterative relaxation process is done by means of a dive function Φ which makes an immersion in a space with a greater granularity (with more levels of precision).
Considering $\mathbb{S}_n$ with basic labels $\mathbb{S}_n^* = \{B_1, \ldots, B_n\}$ as the initial space with granularity n, and a space $\mathbb{S}_{n+1}$ with granularity $n+1$, with basic labels $\mathbb{S}_{n+1}^* = \{B'_1, \ldots, B'_{n+1}\}$ the *dive function*[22] is the map:

$$\phi : \mathbb{S}_n \to \mathbb{S}_{n+1},$$

such that, $\phi(B_i) = [B'_i, B'_{i+1}]$ for any basic label $B_i \in \mathbb{S}_n$ and,
$\phi([B_i, B_j]) = \bigcup_{k=i}^{j} \phi_0(B_k) = [B'_i, B'_{j+1}]$ for any non-basic label.

This relaxation process is performed iteratively as many times as necessary in order to get a non-empty intersection. When this process is iterated over time, in each iteration a new measure μ' is computed. For instance, in the first iteration the new measure μ' can be obtained applying the next formulas for the basic labels:

$$\begin{aligned}
\mu'(B'_1) &= \frac{1}{2}\mu(B_1), \\
\mu'(B'_i) &= \frac{1}{2}(\mu(B_{i-1}) + \mu(B_i)), \quad i = 2, \ldots, n \\
\mu'(B'_{n+1}) &= \frac{1}{2}\mu(B_n),
\end{aligned}$$

and the following for non-basic labels:

$$\mu'([B'_i, B'_{j+1}]) = \sum_{k=i}^{j} \mu'(B'_k), \quad \forall i, j = 1, \ldots, n.$$

In the next section, computations in Examples 1 and 3 illustrate this iterative relaxation process and the computation of the new measure μ'.

4. A NEW APPROACH FOR DELPHI PROCESSES

The new approach for Delphi processes involves the measure of consensus among panelists with respect to each statement in several rounds. For this reason, a degree of consensus is defined to order the statements in view of the opinions given by a panel of participants through a Delphi survey. Panelists opinions are expressed using a set of linguistic terms with various levels of precision as introduced in Section 3.

4.1. Measuring Consensus among Panelists

Let us consider a panel of m stakeholders and a set of statements Λ to be assessed from the second round on of the Delphi process. The new approach of Delphi processes proposed in this paper involves the notion of entropy of a qualitative label, defined in $\mathbb{S}_n$ as a measure of the information provided by the qualitative labels in

$\mathbb{S}_n$, inspired from the Shannon entropy concept in information theory.

Definition 1. The entropy of a qualitative label $Q \in \mathbb{S}_n$ is defined as:

$$H(Q) = -\log_2(\mu(Q))$$

where μ is the considered normalized measure in the set of basic qualitative labels.

Note that Definition 1 is obtained by considering a restriction of the entropy definition introduced in [22]. In this paper, we consider the entropy of each qualitative label in $\mathbb{S}_n$, instead of considering the entropy of a qualitative description of a set over $\mathbb{S}_n$. The reason is that, in the proposed approach for Delphi processes, the concept of entropy of each qualitative label in $\mathbb{S}_n$ is needed to define the degree of consensus among panelists with respect to each statement.
Once the notion of entropy of a qualitative label has been defined, the definition of the degree of consensus of the set of panelists with respect to a statement $a \in \Lambda$ is introduced as a quotient of entropies as follows:

Definition 2. Given m qualitative labels $Q_1, \cdots, Q_m \in \mathbb{S}_n$, associated to the assessments of m panelists for a given statement a, such that $\cap_{j=1}^{m} Q_j \neq \emptyset$, the *degree of consensus* with respect to a, is:

$$\kappa(Q_1, \cdots, Q_m) = \frac{H(\sqcup_{j=1}^{m} Q_j)}{H(\cap_{j=1}^{m} Q_j))} = \frac{\log_2(\mu(\sqcup_{j=1}^{m} Q_j))}{\log_2(\mu(\cap_{j=1}^{m} Q_j))}$$

If the intersection of all Q_j the is empty then the *iterative relaxation process* mentioned in Section 3 is performed in order to reach a non-empty intersection.
Note that in the case that panelists only use basic qualitative labels, the condition is $\cap_{j=1}^{m} Q_j \neq \emptyset$ only fulfilled when all the panelists' opinions are the same and then the degree of consensus is 1; otherwise, a lower degree of consensus is obtained.
Next example illustrates how the diving function and the updating measure together with the proposed degree of consensus are computed.

Example 1. Let us consider the statement *a = "Almost continuous pain longer than few hours"* and a set of three panelists $\mathbb{E} = \{e_1, e_2, e_3\}$ consisting of a nurse e_1, a doctor e_2 and a mother e_3. Let us assume that the assessments of the three panelists with respect to *a* are represented by three qualitative labels defined as:

$$Q_1(a) = [B_1, B_2],\ Q_2(a) = B_3,\ Q_3(a) = B_2$$

using the meaning of basic labels $B_1, \ldots, B_5$ given at the beginning of Section 3. Finally, let us define $\mu(B_i)=1/5,\ i = 1, \ldots, 5$.
Note that there is not consensus among the panelists' assessments because $Q_1(a) \cap Q_2(a) \cap Q_3(a) = [B_1, B_2] \cap B_3 \cap B_2 = \emptyset$.

For this reason, the dive function must be applied once, obtaining a non-empty intersection: $\phi(Q_1(a)) \cap \phi(Q_2(a)) \cap \phi(Q_3(a)) = [B'_1, B'_3] \cap [B'_3, B'_4] \cap [B'_2, B'_3] = B'_3 \neq \emptyset$ and a new measure μ' in S_6^* given by:

$$\begin{aligned}
\mu'(B'_1) &= \frac{1}{2}\mu(B_1) = \frac{1}{10};\\
\mu'(B'_i) &= \frac{1}{2}(\mu(B_{i-1}) + \mu(B_i)) = \frac{1}{5}, \quad i = 2, \ldots, 5;\\
\mu'(B'_6) &= \frac{1}{2}\mu(B_n) = \frac{1}{10}.
\end{aligned}$$

Then, since $\sqcup_{k=1}^{3}\phi(Q_i(a)) = [B'_1, B'_3] \sqcup [B'_3, B'_4] \sqcup [B'_2, B'_3] = [B'_1, B'_4]$ and $\cap_{k=1}^{3}\phi(Q_i(a)) = [B'_1, B'_3] \cap [B'_3, B'_4] \cap [B'_2, B'_3] = B'_3$ the degree of consensus is:

$$\begin{aligned}
\kappa(Q_1, Q_2, Q_3) = \quad & \frac{H(\sqcup_{k=1}^{3}\phi(Q_i(a)))}{H(\cap_{k=1}^{3}\phi(Q_i(a))))} = \frac{H([B'_1, B'_4])}{H(B'_3)} = \\
& = \frac{\log_2 7/10}{\log_2 1/5} = 0.22
\end{aligned}$$

This value of $\kappa(Q_1, Q_2, Q_3)$ suggests a low level of consensus among panelists, consistent with intuition. Next examples present results when different statements and initial panelists' assessments are considered.

Example 2. Analogously to Example 1, let us consider now the statement b = "The pain often cannot be associated with a specific etiology but might well from a combination of things" and assume that the assessments of the three panelists with respect to b are represented by: $Q_1(b) = [B_1, B_2], Q_2(b) = [B_1, B_2], Q_3(b) = B_2$ using the same meaning of basic labels B_1, ..., B_5 given at the beginning of Section 3 and the same measure μ as in the above example. In this case there is consensus among the panelists' assessments because $Q_1(b) \cap Q_2(b) \cap Q_3(b) = B_2$. Then, since $\sqcup_{k=1}^{3}(Q_i(b)) = [B_1, B_2]$ and $\cap_{k=1}^{3}(Q_i(b)) = B_2$ the degree of consensus is:

$$\begin{aligned}
\kappa(Q_1, Q_2, Q_3) \quad & = \frac{H(\sqcup_{k=1}^{3}(Q_i(b)))}{H(\cap_{k=1}^{3}(Q_i(b))))} = \frac{H([B_1, B_2])}{H(B_2)} = \\
& = \frac{\log_2 2/5}{\log_2 1/5} = 0.57.
\end{aligned}$$

This value of $\kappa(Q_1, Q_2, Q_3)$ suggests a greater level of consensus among panelists, consistent with intuition. Finally, let us consider the extreme case in which two panelists opinions are "strongly disagree" and "strongly agree".

Example 3. Let us consider now the statement c = "Daily continuous or intermittent episodes of painful sensations in the newborn" and assume that the assessments of the three panelists with respect to c are represented $Q_1(c) = B_1$, $Q_2(c) = B_1$, $Q_3(c) = B_5$ by: using the same meaning of basic labels and the same measure as above. Obviously, there is not consensus among the panelists' assessments and the dive function must be applied four times in order to obtain a non-empty intersection: $(\phi_4 \circ \phi_3 \circ \phi_2 \circ \phi_1)(Q_1(c)) \cap (\phi_4 \circ \phi_3 \circ \phi_2 \circ \phi_1)(Q_2(c)) \cap (\phi_4 \circ \phi_3 \circ \phi_2 \circ \phi_1)(Q_3(c)) = [B_1'''', B_5''''] \cap [B_1'''', B_5''''] \cap [B_5'''', B_9''''] = B_5''''$. Then, since $\sqcup_{k=1}^{3} \phi^{(4)}(Q_i(c)) = [B_1'''', B_9''''] = \alpha$ and $\cap_{k=1}^{3} \phi^{(4)}(Q_i(c)) = B_5''''$

computing their values through the updating measure μ'''' the degree of consensus is:

$$\kappa(Q_1, Q_2, Q_3) = \frac{H([B_1'''', B_9''''])}{H(B_5'''')} = \\ = \frac{\log_2 1}{\log_2 16/80} = 0.$$

In this extreme case in which two panelists' opinions are "strongly disagree" and "strongly agree", the degree of consensus is 0. When the connex union of the initial panelists opinions is the qualitative label ?, the degree of consensus will be 0. For this reason, in real cases applications, outliers will be removed for statements in which panelists extremely disagree.

4.2. The Proposed Approach for Delphi Processes

The new approach for Delphi processes, enables the handling of imprecise information given by evaluators. The proposed approach is based on the degree of consensus introduced in the previous subsection. The degree of consensus allows the ranking and selection of statements. As a result, it has the capacity to obtain consensus automatically without the need for an interaction between participants.
Analyzing the results obtained in Examples 1, 2 and 3 in the previous subsection, it can be seen that qualitative labels with different levels of precision are simultaneously handled to compute the degree of consensus presented. A comparison of the results obtained using the degree of consensus proposed in this paper in Examples 1, 2 and 3 together with the classic statistical parameters that would be used in classic Delphi is presented in **Table 1**.

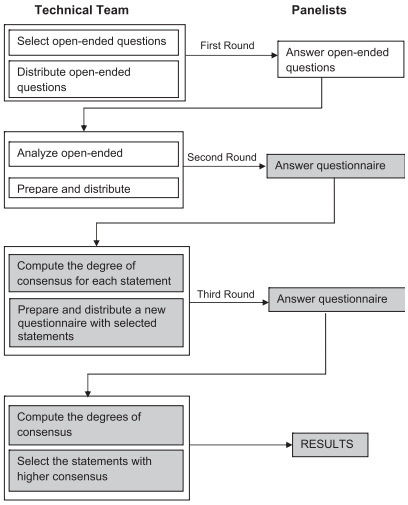
	Panelists assessments			Degree of consensus k	Mean μ	Standard Deviation SD
	Q_1	Q_2	Q_3			
Ex1 (a)	$[B_1, B_2]$	B_3	B_2	0.22	2.17	0.62
Ex2 (b)	$[B_1, B_2]$	$[B_1, B_2]$	B_2	0.57	1.67	0.24
Ex3 (c)	B_1	B_1	B_5	0	2.33	1.89

Table 1. *Results examples 1, 2 and 3*

In addition, the comparison of the outputs produced by the proposed degree of consensus with the classic statistical parameters shows that the new measurement is more consistent with human intuition on consensus. Note that even in the cases where the panelists opinions have initially no intersection, we are able to compute a measure of consensus. The proposed methodology takes into account the necessary effort that would be needed to reach consensus.

Let us consider the new approach for a Delphi process consisting of three rounds. A scheme for the proposed approach is shown in **Figure 2**, where the differences between the proposed approach and the classic Delphi are shadowed.

Figure 2: the new scheme of the Delphi process



First, note that the qualitative absolute order-of-magnitude model presented in Section 3 is used in the interaction with the panelists in rounds 2 and 3. When panelists answer the corresponding questionnaires, they can assess statements using linguistic terms with different levels of precision. In addition, the measure of

consensus presented in Subsection 4.1 is applied in the way the degree of consensus is computed after rounds 2 and 3, and in the final selection of statements. The proposed consensus scheme allows us to detect statements for which most participants are in consensus, and then, to rank them accordingly to their importance.

5. A REAL CASE APPLICATION TO CHRONIC PAIN IN NEONATES DEFINITION

Nowadays there is a lack of an adequate definition of chronic pain in the newborn period. Research has shown that pain in the newborn period has consequences later in life, such as altered behavior, increased pain sensitivity and decreased function of the immune system.[29-31] To date neonatal pain research has mainly focused on acute and procedural pain. Only little is known about other types of pain that are common in the adult, for instance prolonged or chronic pain. Although a small number of studies suggest that chronic pain does exist in the newborn[32-34], there is no consensus on the definition, etiology is unknown and there are no specific diagnostic determinants. An adequate definition of chronic pain in the newborn period, stating the significant features consensuated by stakeholders of neonate health-care, would enable to design the appropriate treatment.

This section focuses on the definition of chronic pain in neonates. An analysis of the opinions given by doctors, nurses and other stakeholders is conducted by implementing the proposed new approach for Delphi processes in order to select the specific diagnostic determinants for the definition of chronic pain in the newborn period.

A web-based, three round Delphi survey was performed to provide a definition, the etiology and the specific diagnostic determinants of chronic pain in the newborn. The survey, considering the three mentioned aspects, was carried out by the Department of Neonatology of the Máxima Medical Center, Eindhoven Area in The Netherlands. An international panel of experts in the field of neonatology and neonatal pain was invited to participate: health-care providers (doctors and nurses) and parents. The introduced methodology was applied to find a consensus among panelists with respect to the definition of chronic pain in the newborn considering the panelists' responses. A definition of chronic pain in neonates was obtained by using the proposed model. This real case example shows the potential and benefits of the presented methodology.

5.1. Data description

In the first round, participants (n = 189) answered the open-ended question define chronic pain in own words. The answers were classified and summarized into 114 statements, which were valued by the participants (n = 189) on a 5-point Likert scale. In the second round the remaining participants (n = 72) were asked to reflect on a selection of 25 statements with a mode or median ≥ 4 or mean ≥ 3.75. These threshold values were used to provide the opportunity to easily reach consensus

in the following round. In the third and last round the remaining participants (n = 33) were provided with the values of the total panel responses and their individual response and were asked to re-assess their own values in the light of the group's opinion. **Table 2** shows participants' regions of origin and participants' profiles respectively.

Region	**n**	**%**	**Profile**	**n**
Europe	75	39.7	Physician	64
North America	69	36.5	Nurse Specialist/ Practitioner,	
Australia/New Zealand	21	11.1	Physician Assistant	44
Middle East	8	4.2	Nursing staff	40
South/Central America	6	3.2	Parent	22
Asia	6	3.2	Reseracher	9
Africa	4	2.1	Others	10
Total	189	100	*Total*	189

***Table 2**: Distribution of panelists' regions profiles*

5.2. Experimental results

A comparison between the results of the classic Delphi methodology and the new approach presented in this paper has been conducted taking into account the assessments given by participants in the third round about the selected 25 statements. It should be noted that using the classic Delphi methodology those statements with mode, mean and median ≥ 4 simultaneously were selected, resulting in 12 statements. On the other hand, the approach presented in this paper was applied to select the most consensual statements among the obtained 25 statements. The iterative relaxation process explained in Section 4 was applied resulting in 7 statements, in which the participants reached a degree of consensus over 0.20 (see **Table 3**).

Note that, in Table 3, numbers in bold correspond to those statements selected either by the classic method or the new approach. In addition, shaded rows indicate the 5 statements selected by both methods.

	Classical Delphi				New approach
Statements	Mode	Median	Mean	SD	Degree of Consensus
Chronic pain in the newborn may lead to a state where any interaction/procedure that is happening to the infant is perceived as painful.	**4**	**4**	**4.22**	0.55	**0.37**
Chronic pain may likely prolong hospitalization, worsening or adding to the existing morbidities.	**4**	**4**	**4.17**	0.65	**0.37**
Both recurrent and long lasting pain may become chronic.	**4**	**4**	**4.13**	0.78	0.09
Pain that occurs over a period of time, which is ongoing and has no obvious end point in site.	**4**	**4**	**4.13**	0.98	0.09
Chronic pain depletes stress hormones and increases energy consumption therefore interfering with growth.	**4**	**4**	**4.1**	0.92	0.09
Treatment should be based on signs of relief or comfort.	**4**	**4**	**4.1**	0.61	**0.37**
It can be anywhere in the body depending on the reason for the pain.	**4**	**4**	**4.07**	0.74	0.09
This pain often cannot be associated with a specific etiology but might well be from a combination of things.	**4**	**4**	**4.07**	0.37	**0.98**
Pain that is ongoing, no longer proximate to a procedure or event.	**4**	**4**	**4.03**	0.69	0.09
A painful event may also alter perception causing events that normally would be tolerate to be perceived as painful, leading to a chronic (longer duration) pain response.	**4**	**4**	**4.03**	0.72	**0.37**
Poorly controlled acute pain may lead to hyperalgesia, altered pain perception, and possibly a predilection to chronic pain states.	**4**	**4**	**4.01**	0.85	0.09
Daily continuous or intermittent episodes of painful sensations in the newborn.	**4**	**4**	**4**	0.69	0.09
Pain lasting more than 1 week that does not fall under the category of acute pain.	4	3	3.79	0.90	**0.24**
Pain lasting hours or days.	4	3	3.99	0.94	**0.24**

Table 3: *Obtained results*

The coincidences and divergences between results of both methods over all the 25 statements are shown in **Table 4**. The new approach proposed in this paper agreed with classic Delphi in 68% of the statements: 20% of the statements were selected by both methods, whereas 48% were not. Two statements were selected using the new method whereas they were not selected by classic Delphi.

	Selected by first method	Not selected by first method
Selected by second method	20%	8%
Not selected by second method	24%	48%

Table 4*: Comparison table*

These two statements suggest to incorporate a time variable in the definition of chronic pain. However, using classic Delphi method, no time variable was selected. On the other hand, seven statements among those selected by classic Delphi were not selected by the new approach. These seven statements express more than one concept each and, according to health-care providers, this could be quite confusing

for the panelists. This confusion is captured by the proposed approach. In the group of statements that were selected by both methods, in general, those with high mean values and post hoc calculated small standard deviation show a high level of agreement (degree of consensus) using the new method.
In this example, stakeholders were forced to value statements using a 5-point Likert scale predefined values when they might have wanted to rate them less precisely. This is why, even if we could have dealt with that imprecision with the proposed methodology, we applied it assuming that all the estimations were given by basic labels.

6. CONCLUSIONS

The method proposed in this paper, based on a measure of consensus, offers a technique to synthesize a group of stakeholders' opinions through a Delphi survey. Participants use a set of linguistic labels associated to an order-of-magnitude model to express their evaluations. With this method the group is able to reach consensus automatically without needing neither a moderator nor any interaction between the participants. Moreover, this approach does not need prior normalization to handle imprecise information given by the experts.
There are three main advantages to this approach. First, the different degrees of strictness of the experts' opinions are taken into account. Second, there is no need to compute an average value of ordinal data. And third, this method accommodates "unknown values" by using the label "?" defined in the absolute order-of-magnitude qualitative model.
The proposed method has been used to reach a consensus on the definition of chronic pain in neonates. In addition, a comparison of the results obtained with a statistical study has been performed. The result is a 60% congruence between traditional statistics and this new approach.
Three main lines of future research are being considered. First, from a theoretical perspective, the introduction of machine learning techniques will be explored. This will allow us to update information and landmarks for the selection of statements in each round. Second, a web-based software device for Delphi processes, based on the concepts introduced in this paper is being developed. It will be capable to collect and synthesize opinions expressed with different levels of precision simultaneously. Third, in regard to the real case study presented in this paper, the nature of the 40% difference between both methods will be analyzed and cut-off points will be validated.
To conclude, let us remark that the theory introduced in this paper has a wide domain of potential application in knowledge management, including consumer ratings in marketing research and evaluation or accreditation processes in human resources studies.

Acknowledgement
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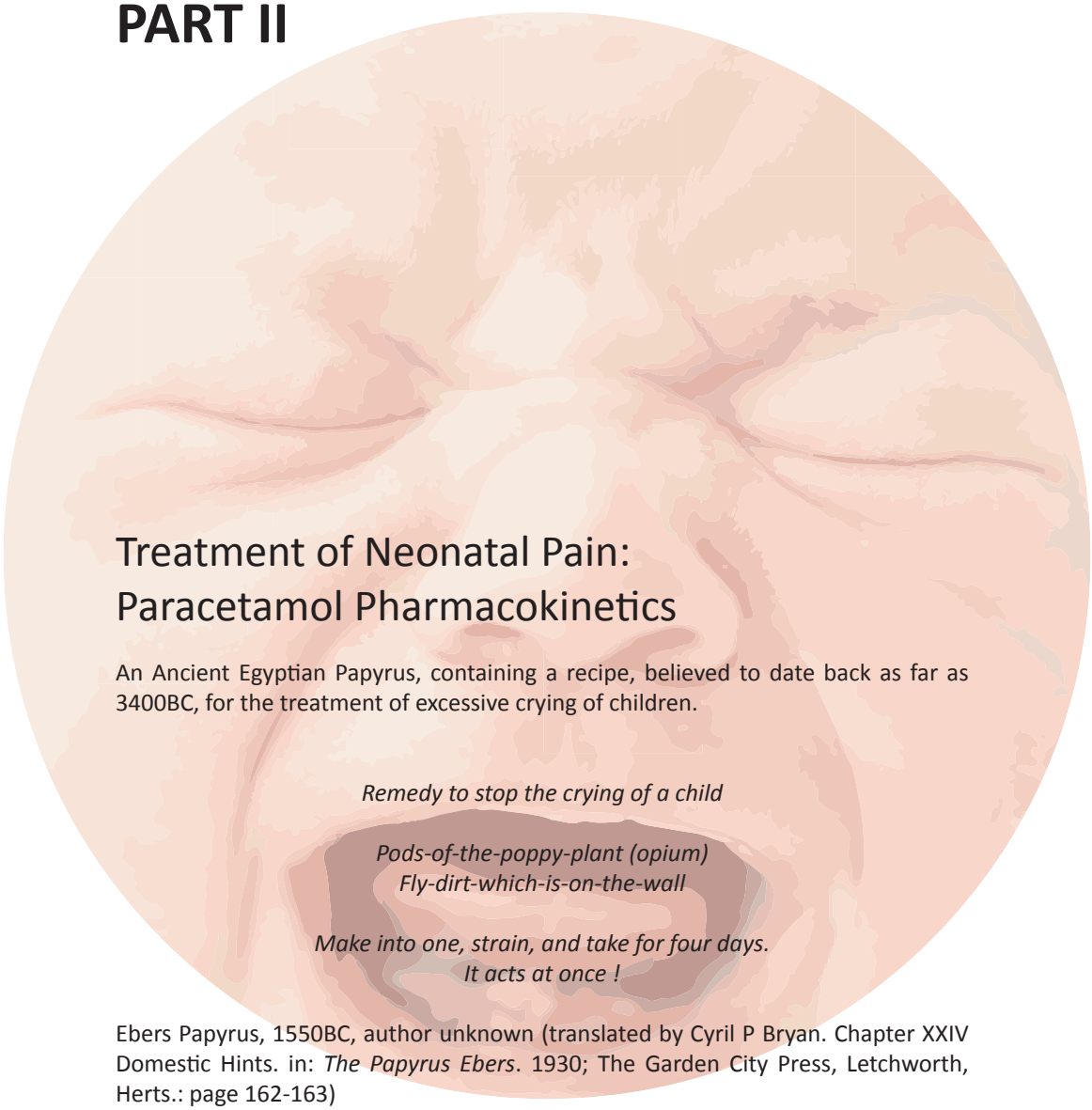
PART II



Treatment of Neonatal Pain: Paracetamol Pharmacokinetics

An Ancient Egyptian Papyrus, containing a recipe, believed to date back as far as 3400BC, for the treatment of excessive crying of children.

Remedy to stop the crying of a child

Pods-of-the-poppy-plant (opium)
Fly-dirt-which-is-on-the-wall

Make into one, strain, and take for four days.
It acts at once !

Ebers Papyrus, 1550BC, author unknown (translated by Cyril P Bryan. Chapter XXIV Domestic Hints. in: *The Papyrus Ebers*. 1930; The Garden City Press, Letchworth, Herts.: page 162-163)

Chapter 5

Paracetamol serum concentrations in preterm infants treated with paracetamol intravenously: a case series.

C. van Ganzewinkel, T. Mohns, R. van Lingen, L. Derijks and P. Andriessen

Journal of Medical Case Reports 2012; 6: 1

ABSTRACT

Introduction

Until now, studies on paracetamol given intravenously have mainly been performed with the pro-drug propacetamol or with paracetamol in preterm infants above 32 weeks of gestation. Studies in these infants indicate that intravenous paracetamol is tolerated well, however studies on the efficacy of paracetamol intravenously are lacking. Furthermore, there are no pharmacokinetic data on the administration of multiple doses of paracetamol in preterm infants with a gestational age below 32 weeks.

Case presentation

We present a case series of 9 caucasian preterm infants, 6 males and 3 females, with a mean gestational age of 28.6 weeks (range 25.9 – 31.6 weeks). Case 1, a female with a gestational age of 25 weeks and 6 days, presented with necrotizing enterocolitis. In the second case, a female infant with a gestational age of 26 weeks and 2 days presented with hematoma. In case 3, a female infant with a gestation of 26 weeks and 1 day developed intraventricular hemorrhage. In case 4 a male infant with a gestational age of 31 weeks and 4 days presented with pain after vacuum delivery. Case 5, a female infant born after a gestation of 29 weeks and 6 days presented with hematoma. In case 6 a male infant with a gestation of 30 weeks and 6 days presented with hematoma. In case 7 a male infant, born with a gestational age of 30 weeks and 6 days presented with caput succedaneum and hematoma. In case 8 a male infant, born after a gestation of 28 weeks and 4 days developed abdominal distention. Finally, case 9, a female infant, born with a gestational age of 27 weeks and 3 days presented with hematoma. These infants were treated with paracetamol 15 mg/kg every 6 hours intravenously. Serum concentrations and aspartate transaminase were determined after prolonged administration. Pain scores were assessed using the Premature Infant Pain Profile.

Conclusion

Paracetamol serum concentrations ranged from 8 to 64 mg/L after 8 to 12 doses of paracetamol intravenously. Adequate analgesia was obtained in 7 infants. During paracetamol therapy the median serum level of aspartate transaminase was 20 U/l (range 12-186 U/l).This case series indicates that prolonged administration of paracetamol intravenously in preterm infants with a gestational age of less than 32 weeks is tolerated well in the first days after birth. However, in the absence of proper pharmacokinetic data in this age group we cannot advocate the use of paracetamol intravenously.

INTRODUCTION

Pain management in the newborn is limited by the availability of only few analgesics. The use of opiates in newborns is limited because of relevant clinical side effects. Alternatively, paracetamol is a well-known analgesic in children without significant side effects. There are only limited data on the use of paracetamol in the newborn. The first drafts of the evidence-based guideline regarding pain management in children of the Dutch Pediatric Society supported the intravenous (i.v.) administration of paracetamol (15 mg/kg every 6 hours) in infants. In advance of the guideline we introduced i.v. administration of paracetamol to preterm infants in our neonatal intensive care unit to reduce the use of opiates. As a safety precaution we determined serum levels of paracetamol and aspartate transaminase in infants with i.v. paracetamol.
After the release of the final version of the nationwide evidence-based guideline on pain assessment and management in children, it became clear that the guideline restricted i.v. administration of paracetamol to term infants after the first month.[1] After the release of the final guideline we discontinued the local policy of i.v. administration of paracetamol in preterm infants. The Institutional Review Board/ Independent Ethics Committee was informed afterwards and concluded that the presented data were obtained legally according the Dutch Law on Medical Research with Humans (WMO).

Though the case series of nine is achieved in an unusual manner, we consider the data on paracetamol levels in preterm infants below 32 weeks of gestation as relevant information for future clinical studies.

CASE PRESENTATION

Case 1

A Caucasian female infant was admitted to our NICU after a gestation of 25 weeks and 6 days. Although delivery started in the hospital the 1 minute apgar score is not available because no health care provider was present at the time of birth. The 5 minute apgar score was 6, birth weight was 890 grams (p50-75). During the third week of life she developed necrotizing enterocolitis grade 1 according to Bell's criteria. She received 15 mg/kg paracetamol i.v. every 6 hours, with a total of 4 doses. Co-medication were antibiotics and ranitidine. Pain score, as measured with the Premature Infant Pain Profile (PIPP) decreased from 10 to 8 (12 or more reflects moderate to severe pain). After 24 hours paracetamol was discontinued because of low PIPP scores. The paracetamol serum level was determined 4 hours after the last dose and showed to be 24 mg/L.

Case 2

A Caucasian female infant, born with a gestational age of 26 weeks and 2 days, was admitted to our NICU with respiratory failure. She was intubated shortly after delivery. Apgar scores were 1 and 5 after 1 and 5 minutes respectively. Birth weight was 680 grams (p5-10). Because of hematoma she received 15 mg/kg paracetamol i.v. every 6 hours. Therapy was started 4 hours after birth, she received a total of 6 doses. Pain scores decreased from 10 to 9 only. Co-medication were antibiotics and caffeine. Paracetamol serum level, which was determined 3 hours after the last dose, was 29 mg/L.

Case 3

A Caucasian female infant was admitted to our NICU after a gestation of 26 weeks and 1 day. Shortly after birth she developed respiratory failure and was intubated. Apgar scores were 1 and 5 after 1 and 5 minutes respectively, birth weight was 800 grams (p25-50). She developed a grade 3 intra-ventricular hemorrhage for which morphine was started. Further co-medication were antibiotics. In an attempt to stop morphine, paracetamol was started, in a dose of 15 mg/kg every 6 hours. Pain scores were below 6 during morphine and remained so during paracetamol mono-therapy. She received 6 doses of paracetamol and the serum level was determined 20 hours after the last dose. The serum level was 12 mg/L.

Case 4

A Caucasian male infant, born with a gestational age of 31 weeks and 4 days, was admitted to our NICU after vacuum delivery. Apgar scores were 8 and 9 after 1 and 5 minutes respectively, birth weight was 1600 grams (p25-50). He received 15 mg/kg paracetamol i.v. every 6 hours for a total of 8 doses. Pain scores decreased from 14 before start of therapy to 9 during therapy. The paracetamol serum level was determined 10 hours after the last dose and was 25 mg/L.

Case 5

A Caucasian female infant, born after a gestation of 29 weeks and 6 days, was admitted to our NICU with hematoma due to traumatic birth and breach delivery. After birth she received cardiopulmonary resuscitation because of apnea and bradycardia. Apgar scores were 1 and 6 after 1 and 5 minutes respectively. Birth weight was 1300 grams (p25). Diagnosed with hematoma she received 15 mg/kg of i.v. paracetamol every 6 hours starting 5 hours after birth. She received a total of 9 doses of paracetamol, the serum level was determined 1 hour after the last dose and showed to be 46 mg/L. Thirty hours later the serum level was determined again and showed to be < 5 mg/L. Co-medication consisted of antibiotics and caffeine. Pain scores decreased from 16 before start of paracetamol to 9 during therapy.

Case 6

A male Caucasian infant was admitted to our NICU after a gestation of 30 weeks and 6 days. Birth took place in a peripheral hospital and was complicated by breech presentation and forceps delivery. Apgar scores were 2 and 7 after 1 and 5 minutes respectively. Birth weight was 1480 grams (p25). In the first hours of life he developed respiratory failure and was intubated. The infant showed extensive hematoma for which 15 mg/kg paracetamol i.v. every 6 hours was started. He received a total of 10 doses and 3 hours after the last dose we obtained a blood sample which showed a paracetamol serum level of 64 mg/L. Co-medication were antibiotics and caffeine. Pain scores decreased from 10 before therapy to 6 during therapy.

Case 7

A Caucasian male infant, born with a gestational age of 30 weeks and 6 days, was admitted to our NICU after an uneventful preterm delivery. The apgar scores were 9 and 10 after 1 and 5 minutes respectively, birth weight was 1755 gram (p50-75). He was diagnosed with caput succedaneum and also had a small hematoma on one of the upper limbs. Due to high pain scores he received 15 mg/kg of i.v. paracetamol every 6 hours starting 2 hours after birth. He received a total of 11 doses of paracetamol, the serum level was determined 4 hours after the last dose and showed to be 37 mg/L. He received no co-medication. Pain scores decreased from 14 before start of paracetamol to 7 during analgesic therapy.

Case 8

A Caucasian male infant, born after a gestation of 28 weeks and 4 days, was admitted to our NICU with respiratory failure due to respiratory distress syndrome. Apgar scores were 4 and 8 after 1 and 5 minutes respectively, birth weight was 860 grams (p25-50). He developed severe abdominal distention on the second day of life and received 15 mg/kg paracetamol i.v. every 6 hours, for a total of 14 doses. There were no radiological signs of necrotizing enterocolitis and his condition improved over the next few days. Co-medication were antibiotics and caffeine. Serum level of paracetamol was taken 5 hours after the last dose, and was 8 mg/L. Pain scores decreased from 14 before starting paracetamol to 3 during therapy.

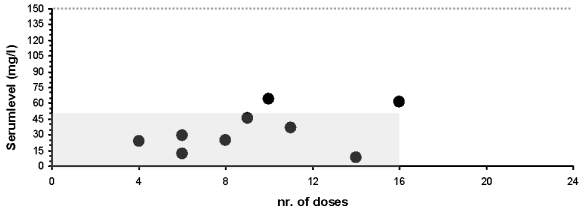
Case 9

A Caucasian female infant, born with a gestational age of 27 weeks and 3 days was admitted to our NICU after preterm rupture of membranes and an uncomplicated delivery. Apgar scores were 6 and 9 after 1 and 5 minutes respectively, birth weight was 990 gram (p50). Due to hematoma and subsequent high pain scores (14) paracetamol 15 mg/kg of i.v. paracetamol every 6 hours was prescribed. She received a total of 17 doses. Due to inadequate analgesic effect 10µg/kg/h morphine was started during paracetamol therapy. The paracetamol serum level, determined 7 hours after the last dose, was 61 mg/L.
Table 1 summarizes the clinical data of the nine infants.

Case	Gestational age (wk)	Birth weight (g)	Duration of therapy (hr)	Start therapy (hr after birth)	Interval last dose-blood sample (hr)	Serum concentration (mg/l)
1	25.9	890	24	408	4	24
2	26.4	680	36	4	3	29
3	26.1	800	36	72	20	12
4	31.6	1600	48	1	10	25
5	29.9	1300	54	5	1	46
6	30.9	1480	60	1	3	64
7	30.9	1755	66	2	4	37
8	28.6	860	84	37	5	8
9	27.4	990	102	1	7	61

***Table 1**: Clinical data of the nine infants*

Figure 1 shows the paracetamol serum concentrations of the nine infants, related to the number of doses.



***Legend figure 1**: In 7 infants the serum levels of paracetamol (the black dots) are < 50 mg/l (grey area), the upper margin value found by Palmer for infants > 32 weeks of gestation.[2] The highest serum concentration (64 mg/l) was far below 150 mg/l (indicated by the dotted grey horizontal line), which has been reported as a toxic value in children.[3]*

DISCUSSION

We administered i.v. paracetamol in a dose not supported by literature. The dose we used in preterm infants of less than 32 weeks gestation is being used in term infants, and is not a result of miscalculation due to the differences in formulations of propacetamol and paracetamol.[4]

Until now, most studies on i.v. paracetamol have been performed with propacetamol in preterm infants above 32 weeks of gestation. Propacetamol is a pro-drug of paracetamol and is hydrolyzed by plasma esterases after i.v. administration such that 1 g of propacetamol is hydrolyzed to 0.5 g of paracetamol.[4-6] To our knowledge this is the first report of paracetamol concentration data in preterm infants below 32 weeks of gestation, in whom multiple dose i.v. paracetamol (Perfalgan®) was administered for non-surgical analgesia in the first hours after birth.

This case series indicates that in preterm infants below 32 weeks i.v. paracetamol is tolerated well. In 7 infants we found serum concentrations below 50 mg/l, the upper margin value reported by Palmer.[2] In 2 subjects serum values were around 60 mg/l. During paracetamol therapy we found no indications for liver failure.

Although the therapeutic window for paracetamol in children is assumed to be 10-20 mg/l, there is no consensus on dosage regimens for i.v. administration of paracetamol in infants.[7] Allegaert, using propacetamol, suggests a maintenance dose of 20 mg/kg every 12 hours for infants below 31 weeks gestational age after a loading dose of 30 mg/kg propacetamol.[4] Using this dose, Allegaert was not able to show significant analgesic effect.[5] However, with a maintenance dose of 12.5 mg/kg every 6 hours Allegaert showed analgesic effects.[6] Autret suggests a maximum of 7.5 mg/kg every 6 hours after a loading dose of 15 mg/kg propacetamol in newborns for antipyretic effects.[8] Autret did not study the analgesic effect. In term newborns, de la Pintière describes a maintenance dose of i.v. propacetamol of 120 mg/kg/day, equivalent to paracetamol 60 mg/kg/day.[9]

Limited data is available concerning the pharmacokinetics of propacetamol and paracetamol.[2,5,6,10] Both Allegaert and Palmer found serum levels of paracetamol between < 6 and 50 mg/l, after a single dose of propacetamol and multiple doses of i.v. paracetamol, respectively. Note that Palmer included preterm infants above 32 weeks of gestation.[2] In a letter to the editor, Bartocci et al report their Stockholm experience of postoperative analgesia with i.v. morphine and paracetamol (maintenance dose 7.5 mg/kg every 8 hours) in newborns with a postconceptional age between 25 and 42 weeks.[11] From the letter, however, it is unclear at what postnatal age paracetamol is given and no paracetamol concentration data are shown.

Several cases report accidentally given overdoses of propacetamol or paracetamol. Two doses of approximately 300 mg/kg propacetamol (equivalent to 150 mg/kg paracetamol) at a 6 hour interval given to a term baby, resulted in a serum level of 166 mg/l without signs or symptoms of liver failure.[9] Two infants born prematurely after maternal overdose of paracetamol had serum concentrations of 76 and 260 mg/l respectively, without apparent adverse effects.[12,13] A paracetamol overdose in a preterm infant resulted in a serum concentration of 121 mg/l.[14]

Recently, Bristol-Myers Squibb Pharmaceuticals Ltd issued a letter with drug safety information concerning accidental overdose in 23 world wide cases. All were infants younger than 1 year, 1 of whom died. Scope of the letter was a raising concern on the possible confusion in prescribing ml/kg instead of mg/kg, leading to a tenfold overdose.[15] The letter does not provide information on serum levels or liver functions in these cases.

CONCLUSION

This case series is no formal pharmacokinetic study. Obviously, the small sample size and the single serum concentration limit a pharmacokinetic interpretation of paracetamol therapy in preterm infants. Still, this case series of nine very preterm infants indicates that paracetamol administration in a maintenance dose of 15 mg/kg/day every 6 hours results in paracetamol concentrations that are in the range of others.[2,5,10] It suggests that i.v. paracetamol is tolerated well in the first hours after birth in very preterm infants. However, since proper pharmacokinetic data in this age group is still lacking, we cannot advocate the use of paracetamol intravenously based on our observations. It is obvious that future studies should target determination of dosing regimens to achieve maximum analgesic effect (efficacy) without adverse effects (tolerance) in newborns in the first 4 weeks after birth.

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Chapter 6

Multiple intravenous doses of paracetamol result in a predictable pharmacokinetic profile in very preterm infants.

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ABSTRACT

Aim

The therapeutic options available to treat neonatal pain are limited and one alternative for non-opioid systemic treatment is paracetamol. However, pharmacokinetic data from prolonged administration of intravenous paracetamol in neonates are limited. The aim of this study was to present pharmacokinetics after multiple dose of intravenous paracetamol in very preterm infants of less than 32 weeks' gestation.

Methods

Fifteen very preterm infants received five, six-hourly doses of intravenous paracetamol (7.5 mg/kg). Blood samples were taken to measure paracetamol, glutathione and hepatic function, together with urine samples for paracetamol metabolites.

Results

A two-compartment pharmacokinetic model gave the best fit for all individual patients and resulted in a predictable pharmacokinetic profile. The estimated pharmacokinetic population parameters were volume of distribution 0.764 ± 0.225 l · kg-1, elimination rate constant (k_e) 0.117 ± 0.091 h^{-1} and inter compartment rate constants k_{12} 0.607 ± 0.734 h^{-1} and k_{21} 1.105 ± 0.762 h^{-1}.

Conclusion

Our study found that multiple doses of intravenous paracetamol resulted in a predictable pharmacokinetic profile in very preterm infants. Increases in postmenstrual age and weight were associated with increased clearance. No evidence of hepatotoxicity was found.

Key notes

- There are limited therapeutic options available to treat neonatal pain and this study presents pharmacokinetics after multiple dose of intravenous paracetamol in very preterm infants.
- Fifteen infants received five, six-hourly doses of intravenous paracetamol (7.5 mg/kg) and blood and urine samples were taken.
- The treatment resulted in a predictable pharmacokinetic profile: increases in postmenstrual age and weight were associated with increased clearance and no hepatotoxicity was found.

INTRODUCTION

The therapeutic options to treat neonatal pain are limited. Data are conflicting on the efficacy of opioids. In ventilated preterm neonates morphine does not lead to significant differences in pain scores compared with placebo.[1,2] Furthermore, opioids are associated with serious short-term side effects such as hypotension, a decrease in intestinal motility, respiratory depression, tolerance and withdrawal symptoms.[1,3-5] Concerns have recently been raised regarding the effects of morphine exposure in the neonatal period on long-term cognitive development. At 5 years of age, a visual analysis IQ subtest showed significant lower scores in a cohort of neonates who had received morphine in the first 28 days of life.[6] However, this effect was not noted at the age of 8-9 years.[7]

An alternative for nonopioid systemic treatment of neonatal pain is paracetamol, which can be administered orally, rectally and intravenously. Enteral administration in preterm infants is limited as oral or orogastric medication can only be administered when feeds are tolerated well. In addition, the minimum amount of enteral feeding to safely administer drugs through this route is not known. Studies on the efficacy of rectal paracetamol show conflicting results. Pharmacokinetic data show that absorption of rectal paracetamol is unpredictable in preterm infants born at > 32 weeks' gestation.[8,9] In contrast, the absorption of a single dose paracetamol in preterm infants < 32 weeks' gestation results in therapeutic analgesic concentrations in the majority of cases.[10]

Recently, the intravenous form of paracetamol (Perfalgan®, Bristol-Myers Squibb B.V., Utrecht, the Netherlands) has become available in the Netherlands. An intravenous formulation of the pro-drug propacetamol is also available. Intravenous propacetamol is hydrolyzed by plasma esterases such that 1 g of propacetamol is hydrolyzed to 0.5 g of paracetamol.[11-13] Data concerning the pharmacokinetics of propacetamol and paracetamol are emerging.[12-15] The available studies have focused on the use of intravenous propacetamol or paracetamol in preterm infants > 32 weeks' gestation[11-13,15], not in very preterm infants < 32 weeks' gestation.

There is great variability in the dosage regimens for intravenous administration of paracetamol in newborns.[8] Allegaert, using propacetamol, evaluated the analgesic effect of a maintenance dose of 20 mg/kg 12-hourly for infants < 31 weeks' gestation after a loading dose of 20 mg/kg.[11] Using this dose, Allegaert was not able to show significant analgesic effect.[12] However, with a maintenance dose of 12.5 mg/kg 6-hourly Allegaert showed analgesic effects.[13] For its antipyretic effects, Autret suggested a maximum of 7.5 mg/kg 6-hourly after a loading dose of 15 mg/kg propacetamol in neonates, but did not study analgesic effect.[16] In term newborns, de la Pintière describes a maintenance dose of intravenous propacetamol of 120 mg/kg/day,[17] equivalent to paracetamol 60 mg/kg/day.[11] In the Palmer study 10 mg/kg of paracetamol at 6-h intervals is suggested for preterm infants.[15] Because the available data at the time of implementation of our study suggested that clearance may be inversely correlated to gestational age[12], we chose a dose of 7.5 mg/kg six-hourly for the very preterm infant.

Our primary objective was to study the pharmacokinetics of multiple doses

intravenous paracetamol in very preterm infants below 32 weeks' gestation. We aimed to determine a time-paracetamol serum concentration profile and obtaining population pharmacokinetic estimates of clearance and volume of distribution. Furthermore we looked at covariate effects on pharmacokinetics. Our secondary objective was to study the safety of intravenous paracetamol (measured by liver enzymes and paracetamol associated metabolites).

METHODS

The study was reviewed and approved by the Dutch Central Committee on Research involving Human Subjects (registration number NL27531.015.11). The Institutional Review Board of Máxima Medical Centre also approved the study. Written informed consent was obtained from the parents of each infant. Eligible subjects were preterm infants < 32 weeks' gestation with an arterial catheter in situ for intensive care management and requiring analgesia. No arterial catheters were inserted nor remained longer in place because of the study. Demographics were recorded, including gestational age, postmenstrual age (gestational age + postnatal age), Apgar score, birth weight, weight at the day of inclusion, diuresis and indication for analgesia. Subjects with signs or symptoms of perinatal asphyxia (two or more of the following items: 5-min Apgar score < 5; umbilical pH < 7.0; need of advanced resuscitation after delivery > 10 min; signs of encephalopathy), a recent intubation < 12 h before inclusion; alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) > 50 IU and the use of phenobarbital, sedatives and muscle relaxants were excluded.

Measurements:
After enrolment in the study, the infants received 7.5 mg/kg six-hourly for a total number of five doses. After administration of the first dose, blood was sampled to determine paracetamol serum levels at t=0.5, t=1, t=3 and t=6 h, respectively. In addition, blood was sampled 1 h after the fifth dose (t = 31 h). Six hours after the first dose and 1 h after the fifth dose, glutathione levels were measured. Also, 1 h after the fifth dose, serum alanine aminotransferase, aspartate aminotransferase and (unconjugated) bilirubin were tested. After the first and the fifth dose of paracetamol, urine was collected to determine paracetamol and associated metabolites.

Analytic procedures:
Paracetamol serum levels were measured in the laboratory of the Department of Clinical Pharmacy, Máxima Medical Centre, Veldhoven, The Netherlands. Serum paracetamol was separated by reversed-phase high-performance liquid chromatography (HPLC) and quantified using ultraviolet (UV) detection. The lower limit of quantification was 0.015 mg/L, the concentration range was 0.5-20.0 mg/L, recovery was 89% and the linear correlation coefficient was 0.9998. Paracetamol, paracetamol glucuronide and paracetamol sulphate in urine were determined by an alternative HPLC method with UV detection. For paracetamol, paracetamol glucuronide and paracetamol sulphate, respectively, the lower limits of quantification were 0.015, 0.021 and 0.021 mg/L, the concentration ranges were 0.3-40 mg/L, 2.3-

300 mg/L and 6.3-450 mg/L, recovery was 100% and the linear correlation coefficients were 0.9999, 0.9999 and 1.000. Urine paracetamol metabolites were expressed in mg/l. The glucuronide/sulphate ratios were calculated after conversion into molar weight (paracetamol glucuronide, M 328 mg/mmol; paracetamol sulphate, M 230 mg/mmol).[18]
Glutathione was analyzed using a fluorometric assay. Both alanine aminotransferase and aspartate aminotransferase were analyzed with pyridoxal phosphate activation. Unconjugated bilirubin was analyzed using the colorimetric endpoint assay according to Jendrassik and Grof.

Pharmacokinetic modeling:
Population parameters estimates were obtained using MW/Pharm© Computer Aided Therapeutic Drug Monitoring version 3.81 (Mediware, Groningen, The Netherlands).[19] Mw/Pharm© supports several kinetic models, including one-, two- and three-compartment kinetics and nonlinear elimination kinetics. The software package takes into account individual patient characteristics (gestational age, birth weight, sex en creatinine) for prediction of the time-concentration profile. The KinPop module of the program uses an iterative two-stage Bayesian fitting and calculates means, medians, and standard deviation (SD) of the pharmacokinetic parameters.[20,21] Before the actual modeling starts, rough estimates of the model parameters and their (SD) are entered from basic pharmacokinetics of paracetamol in adults. In the first stage of modeling, the software calculates individual pharmacokinetic parameters ± SD that best fit the actual plasma measurements for every patient. The previously entered estimates are used as starting point. In the second stage, all individual values are pooled resulting in (1) a population mean for every parameter, (2) a covariance matrix with values for interparameter associations and (3) an estimate of the residual standard deviation. Then, the cycle is repeated using the newly found population values as starting point. The calculation is finished when the new population values and the residual standard deviation are similar to the values from the previous cycle. The parameter estimation is supported by a graphical presentation of the medication history of each individual patient with time-concentration points and fitting curves of initial parameter estimation and after Bayesian fitting, respectively. The model output comprises the estimates volume of distribution (V), elimination rate constant (k_e) and inter compartment rate constants k_{12} and k_{21}. V is expressed as L/kg. The rate constants are expressed as per hour. Clearance (CL) can easily be derived by multiplying V and k_e and is expressed as L/h/kg. In case of multiple compartment modeling the model also shows predictive drug concentrations in the peripheral compartment.
The relationship between clearance and unconjugated bilirubin was explored by correcting the unconjugated bilirubin at t = 31 h for birth weight category. For each patient the unconjugated bilirubin was expressed as a percentage of the phototherapy limit (birth weight < 1000 g: 100 µmol/L; 1000-1250 g: 150 µmol/L; 1250-1500 g: 190 µmol/L; 1500-2000 g: 220 µmol/L; > 2000 g: 240 µmol/L). This approach was chosen to reflect normal postnatal variation in unconjugated bilirubin with birth weight.

Statistical analysis:
For parameters with a normal distribution, results are presented as mean (SD), otherwise results are presented as median (inter quartile range, IQR). Comparisons were made by Student t-test or Mann-Whitney U-test, respectively. The influence of gestational age, postmenstrual age, (birth)weight and the corrected percentage of unconjugated bilirubin on the pharmacokinetic parameters was studied using linear regression analysis and Pearson correlation coefficient (r). Non parametric data were log-transformed before linear regression analysis. SPSS 19.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A p value < 0.05 was considered statistically significant.

RESULTS

During the study period (October 2011-November 2012) 24 preterm infants below 32 weeks' gestation were eligible for pain management. Fifteen infants were included in the study. The demographic data of these infants are summarized in **Table 1**. All infants were included in the first 2 days of life, except for one case (postnatal age of 7 days). Nine infants were excluded because of having no pain (n = 3), perinatal asphyxia (n = 2), elevated liver enzymes (n = 2), no arterial catheter (n = 1) or no informed consent was obtained (n = 1).

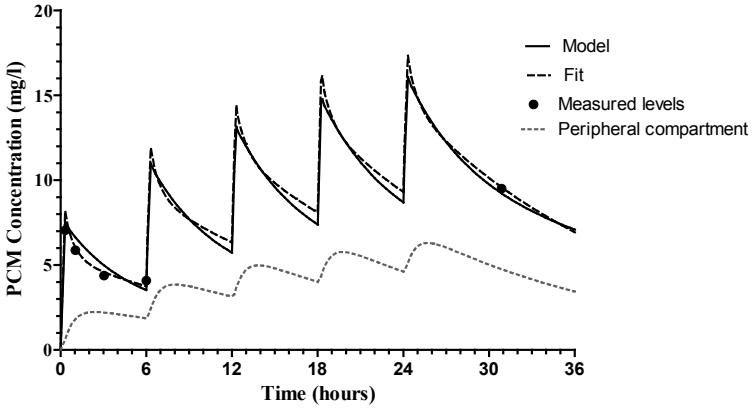
Table 1: Demographics

Gestational age (weeks)	28.1 + 2.3
Postmenstrual age at inclusion (weeks)	28.3 + 2.3
Antenatal steroids	13 (87%)
Birth weight (g)	1205 + 415
Weight at inclusion (g)	1207 + 414
1-min Apgar	7 [5-7]
5-min Apgar	7 [6-7]
Female: male	7:8
Indication analgesia	
• Hematoma	11
• Skin lesion	4
• Caput succedaneum	4
• NEC	1

Legend: *Neonatal patient characteristics of the study population. Values are expressed as mean + SD, median [IQR] or numbers. NEC, necrotizing enterocolitis.*

In general, paracetamol levels did not exceed 20 mg/L at any time point. The median paracetamol level at steady state (t = 31 h) was 10 mg/L [IQR, 7-13]. Individual serum paracetamol levels were fitted to obtain individual pharmacokinetic parameters. A two-compartment model was superior to the one- or three-compartment models, showing less Bayesian iterations for curve fitting and smaller standard deviation of the estimates. The model fitting curve of a representative patient is shown in **Figure 1.** The population parameters of the model are shown in **Table 2**.

Figure 1: Predicted time-concentration of paracetamol concentration



Legend: *Plasma concentration profile in a preterm infant of 30 weeks' gestation, following a dosing schedule of 7.5 mg/kg intravenously six-hourly for a total of five doses. The time-concentration points of paracetamol at 0.5, 1, 3, 6 and 31 hour(s) are indicated by bold dots. The figure shows the predicted plasma concentration profile using initial parameters estimates (solid line) and after Bayesian fitting (broken line). The predicted paracetamol concentration in the peripheral compartment (V2) is illustrated by the dotted grey line.*

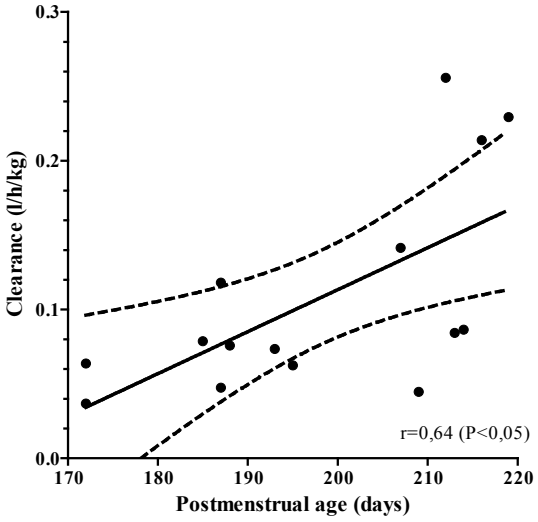
Table 2: Population pharmacokinetic model parameters

Pharmacokinetic estimate	Mean + standard deviation
V (L/kg)	0.764 + 0.225
k_e (h^{-1})	0.117 + 0.091
k_{12} (h^{-1})	0.607 + 0.734
k_{21}(h^{-1})	1.105 + 0.762

Legend: *The model output comprises the pharmacokinetic estimates volume of distribution (V), elimination rate constant k_e and inter compartment rate constants k_{12} and k_{21}.*

Clearance correlated with postmenstrual age (r = 0.64) and birth weight (r = 0.67), respectively. **Figure 2** illustrates CL as a function of postmenstrual age.

Figure 2: The relationship between PMA and CL.



Legend: *The relationship between postmenstrual age (expressed in days) and clearance (CL, L/h/kg). The solid line indicates the linear fit (r=0.64, P < 0.05) and the dotted lines represent the 95% confidence interval range.*

Unconjugated bilirubin - corrected for birth weight and postnatal age - after five doses of paracetamol was not correlated with CL. We found no alanine aminotransferase or aspartate aminotransferase levels above 50 U/L. No relationships between plasma glutathione, urine glucuronide, urine sulphate or glucuronide/sulphate ratio and postmenstrual age or weight were found. The plasma glutathione did not change after five doses of paracetamol. Urine glucuronide and sulphate increased significantly after five doses of paracetamol ($p < 0.01$), but their molar ratio did not change after five doses of paracetamol. The paracetamol-associated metabolites are shown in **Table 3**.

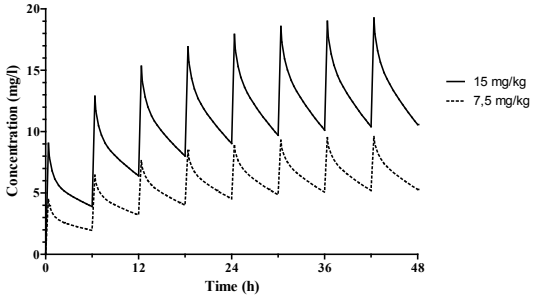
Table 3: Glutathione and paracetamol associated metabolites

Metabolites	
Plasma glutathione (µmol/L), t=6 h	786 [648-890]
Plasma glutathione (µmol/L), t=31 h	668 [549-811]
Urine paracetamol glucuronide (mg/L), t=6 h	6 [2-14]
Urine paracetamol glucuronide (mg/L), t=31 h	22 [13-43]
Urine paracetamol sulphate (mg/L), t=6 h	60 [35-72]
Urine paracetamol sulphate (mg/L), t=31 h	244 [199-378]
Urine glucuronide: sulphate ratio, t=6 h	0.10 [0.03-0.20]
Urine glucuronide: sulphate ratio, t=31 h	0.08 [0.04-0.11]

Legend: *Values are expressed as median and IQR.*

Figure 3 shows the predicted time-concentration profiles of intravenous paracetamol administration at a regular interval of 6 h for two dose regimens, 7.5 and 15 mg/kg. Steady state was achieved at approximately 24 hours after the first dose with a peak concentration of approximately 20 mg/L and a trough concentration of approximately 10 mg/L after six-hourly dosing of 15 mg/kg. The lower dose (7.5 mg/kg) achieved half of these values.

Figure 3: Predicted paracetamol concentration with two dose regimens.



Legend: *Predicted time-concentration profiles in very preterm infants with two regular six-hourly dosing paracetamol regimens of 7.5 and 15 mg/kg, respectively*

DISCUSSION

Pharmacokinetic data and the impact of covariate information on intravenous paracetamol in neonates are limited. The available studies include single administration of paracetamol (or propacetamol) or multiple doses in neonates, with only a minor representation of very preterm infants < 32 weeks' gestation.[12,13,15,22] To our best knowledge, this is the first study to investigate pharmacokinetics after

multiple doses of paracetamol intravenously in very preterm infants < 32 weeks' gestation.
Paracetamol administered intravenously in the very preterm infant < 32 weeks' gestation resulted in a predictable pharmacokinetic profile. Using an iterative Bayesian approach, a two-compartment model showed that steady state was achieved after five doses of paracetamol with a median paracetamol level of approximately 10 mg/L. Although no target effect concentration is available for neonates, 10 mg/L is comparable to the target effect concentration reported in children after tonsillectomy.[23] In our study, clearance and volume of distribution was 0.090 L/h/kg (6.28 L/h per 70 kg body weight) and 0.764 L/kg (53.5 L per 70 kg body weight), respectively. Our data of clearance are in line with the results in preterm (0.116 L/h/kg)[12], near-term (0.148 L/h/kg)[15] and term infants (0.170 L/h/kg)[12,15]. Likewise, the data of volume of distribution are comparable with the results in preterm (0.61 L/kg) and term infants (0.64 L/kg).[12]
We found significant relationships between paracetamol clearance and postmenstrual age and weight, respectively. These observations are in line with data from studies in infants > 32 weeks' gestation.[14,15] Moreover, size (described by weight) may be the major covariate contributing to paracetamol clearance variance in neonates.[22]

Validation of a pharmacokinetic model is an important part of building an optimal dosing strategy. Pharmacokinetic population parameters derived from a training set may be applied on independent data to confirm adequate accuracy of the individual pharmacokinetic parameters. In a previously reported case series of nine infants < 32 weeks' gestation, we used a two-fold higher maintenance dose of 15 mg/kg at 6-h interval. This resulted in a median serum paracetamol level of 29 mg/L (IQR, 24-46 mg/l) and adequate pain management in the majority of cases.[24] The serum paracetamol data from the case series study (validation set) were correctly predicted using the pharmacokinetic population parameters of the present study (training set). The dosing regimens used in clinical practice vary from the manufacturers' recommendations and varies between studies. The Palmer study provided a predicted time-concentration profile for preterm and term equivalent neonates with dosing regimens of 7.5 mg/kg six-hourly and 15 mg/kg six-hourly, respectively.[15] The predicted time-concentration points from that study are comparable with the predicted profile of our study in very preterm infants (Figure 3). The internal validation of the case series with a two-fold maintenance dose supports this even more. In a recent paper, a loading dose of 20 mg/kg, followed by maintenance doses of 10 mg/kg at 6-h interval is suggested for infants within the range of 32-44 postmenstrual weeks.[22] Future research should target at determining a dose-effect relationship in very preterm infants.

Paracetamol associated hepatotoxicity is dependent on the balance between the capacity of safe elimination pathways of conjugation, safe binding to glutathione and forming of a harmful highly reactive arylating metabolite N-acetyl-p-benzoquinone imine by the CYP3A4 enzyme.[25] The balance of these processes in neonates is unknown. Paracetamol is metabolized by both sulphate and glucuronide conjugation.

Urine paracetamol glucuronide and sulphate increased from t = 6 to 31 h, indicating adequate conjugation in very preterm infants. The glucuronide/sulphate ratio of 0.08 after five doses of intravenous paracetamol is comparable with the results of rectally administered single dose paracetamol to preterm infants 28-32 weeks' gestation.[10] In near-term and term infants ratios of 0.27-0.34 are reported.[10,18] This indicates that maturation is important in conjugation. Through cytochrome P450 metabolism, glutathione binds paracetamol metabolites into nontoxic metabolites, and depletion of glutathione is potentially hepatotoxic. We observed no decrease in plasma levels of glutathione after five doses of paracetamol, indicating that prolonged intravenous administration of paracetamol 7.5 mg/kg did not have a significant effect on the glutathione storage in very preterm infants. Unlike others, we did not find a relation between high unconjugated bilirubin and clearance.[15,22] An explanation could be that our patients were recruited very early in life (14 patients within 2 days after birth) and bilirubin levels were not very high.

Methodological limitations:
Although the population size is small, the Bayesian approach is generally accepted to calculate pharmacokinetic population data. Several software programs are available for pharmacokinetic modeling, of which the NON-linear Mixed Effect Modeling (NONMEM) is well known.[26] We chose for Mw/Pharm© as a modeling program because of availability and broad experience with this easy-to-interpret software package. Our study group focused on relatively stable preterm infants without a history of asphyxia or liver dysfunction. We cannot exclude that paracetamol pharmacokinetics is different in sick asphyxiated preterm infants. Although conjugation and glutathione storage seem appropriate in very preterm infants, we did not study the formation of paracetamol associated arylating metabolites.

CONCLUSION

Our study contributes to the available pharmacokinetic data of paracetamol in neonates. Multiple intravenous administration of paracetamol in the very preterm infant results in a predictable pharmacokinetic profile. Prolonged administration of paracetamol 7.5 mg/kg six-hourly was not associated with impaired hepatic conjugation or glutathione depletion. Caution is warranted since safety data on the prolonged administration of paracetamol exceeding five doses in very preterm infants is still lacking.

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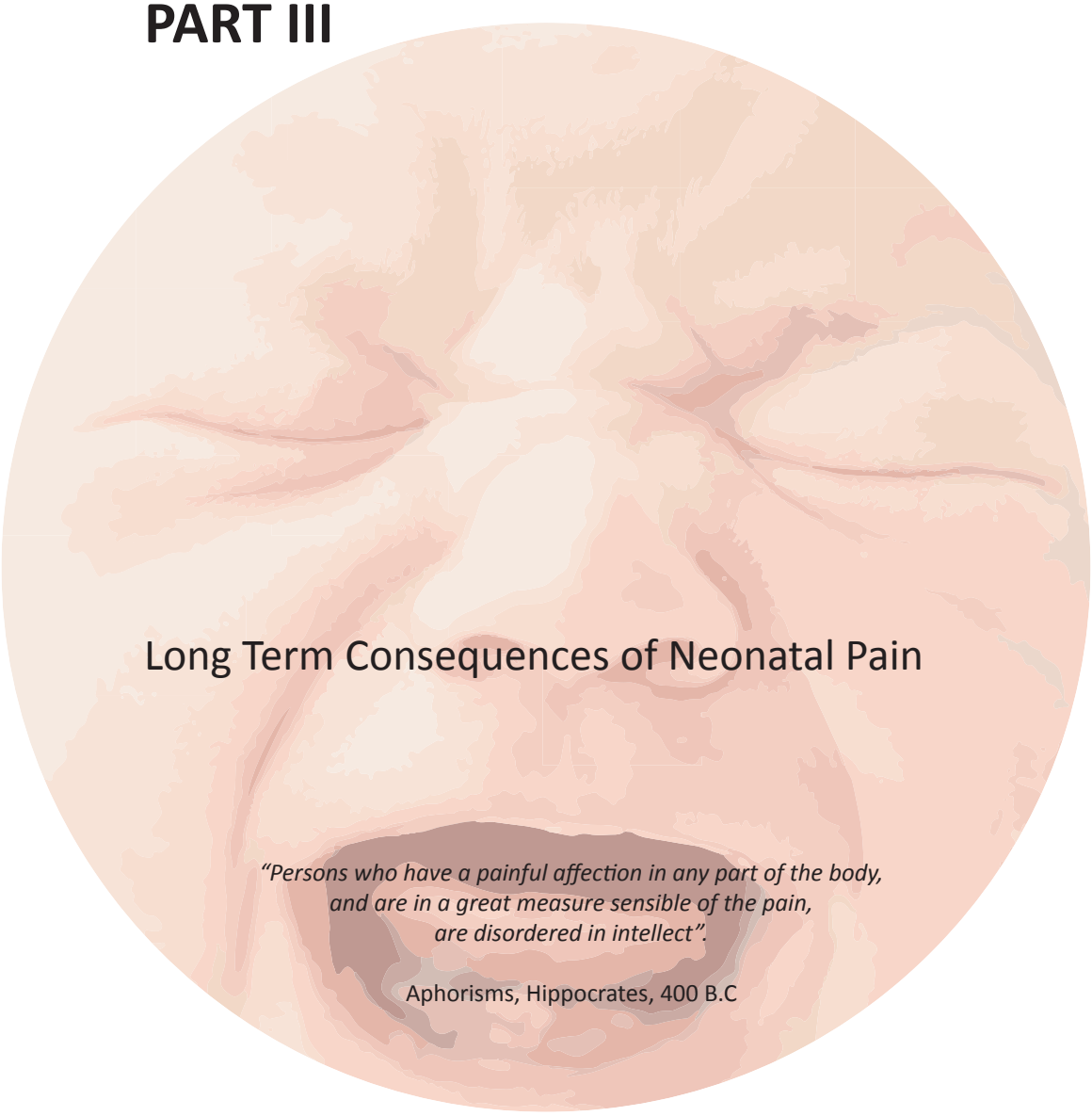
PART III



Long Term Consequences of Neonatal Pain

"Persons who have a painful affection in any part of the body,
and are in a great measure sensible of the pain,
are disordered in intellect".

Aphorisms, Hippocrates, 400 B.C

Chapter 7

Pain coping strategies: neonatal intensive care unit survivors in adolescence.

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ABSTRACT

Background

Data on long-term consequences of preterm birth on pain coping later in life are limited.

Aim

To assess whether gestational age, birth weight and neonatal disease severity have effect on pain coping style in adolescents born preterm or with low birth weight.

Study Design

Observational, longitudinal study (Project On Preterm and SGA-infants, POPS-19).

Subjects

We analyzed data of 537 adolescents at the age of 19 years, who were born at a gestational age < 32 weeks or with a birth weight < 1500 g.

Outcome measures

Participants completed the pain coping questionnaire (PCQ) that assesses pain coping strategies in three higher-order factors: approach ("to deal with pain"), problem-focused avoidance ("to disengage from pain") and emotion-focused avoidance ("expression of pain"). Furthermore, their pain coping effectiveness, pain controllability and emotional reactions to pain were assessed. All participants completed an IQ test.

Results:

Univariate analysis showed no significant correlation between length of stay, sepsis and necrotizing enterocolitis and any of the higher-order factors. Approach was only correlated with IQ. Problem-focused avoidance was, in the multiple regression analysis (including gestational age, IVH and IQ), only correlated with IQ. For emotion-focused avoidance (including birth weight, SGA, IVH, respiratory support and IQ) three independent predictors remained: IVH was positively correlated, while respiratory support and IQ were negatively correlated with emotion-focused avoidance.

Conclusions:

Early neonatal characteristics and neonatal disease severity have limited effect on pain coping style in adolescence. Higher IQ was associated with the use of adaptive coping strategies, while maladaptive strategies were used less.

INTRODUCTION

The perception of pain and the response to pain reflect complex interactions of biological, psychological and social factors.[1] Biological factors may be influenced by complications of prematurity such as intraventricular hemorrhage and developmental problems specific to the vulnerable immature brain such as delayed myelination or reduced brain volume.[2,3] Long-term follow-up shows that adolescents born very preterm or with very low birth weight have internalizing behavioral problems.[4,5] Internalizing behavioral problems may have great impact on perception of physical pain. Psychological and social factors may be moderated by the cognitive capacity of the developing child, parental education and parental employment.[6]

Psychological adjustment to pain is closely related to pain coping strategies.[7] In adolescents with a variety of pain conditions, pain coping strategy influences pain sensitivity, symptoms of depression, and somatic symptoms, while maladjustment may lead to disability.[8] Therefore, identifying pain coping strategies may be clinically relevant. The Pain Coping Questionnaire (PCQ) is a validated measure for children and adolescents.[7] The PCQ assesses both adaptive and maladaptive pain coping strategies. Information seeking, problem solving, seeking social support, cognitive distraction and behavioral distraction reflect adaptive pain coping strategies. Additionally, positive self-statement or optimism is suggested to positively influence pain coping.[9] In contrast, internalizing/catastrophizing is a maladaptive coping mechanism associated with inward behavior, anxiety and depression.[10,11] Externalizing behavior is characterized by aggression, hyperactivity, antisocial behavior and delinquency.[11] It is suggested that pain controllability and emotion controllability leads to more use of adaptive coping strategies and less use of maladaptive strategies.[7]

While the effect of preterm birth on behavioral outcome in children is known, no data exist on pain coping strategies in adolescents born preterm. To the best of our knowledge, only two published studies provide important information on pain coping strategies in ex-preterm school children. One study showed differences in coping styles between 43 preterm born children (< 26 weeks gestation) and 44 term born controls at the age of 11 years.[12] In general, preterm born children sought social support more often than term born controls. Information seeking was reported to be employed more often in a subgroup of 12 preterm born children exposed to major surgery or other major procedures (e.g. chest drains) during their NICU stay.[12] In a second study in 9 to 14 year old children, 19 preterm born children tended to catastrophize more often than 20 healthy term born controls.[13]

Using the database of the Collaborative Project on Preterm and Small for Gestational Age Infants in the Netherlands (POPS-1983), we aimed to identify neonatal characteristics that may influence pain coping style in adolescence. We hypothesized that neonatal characteristics, and variables reflecting neonatal disease severity in preterm or low birth weight infants influence pain coping style in later life. Secondly, we examined the relationship between pain coping style and deficits in academic

achievements as reported previously.[4] Finally, we examined how pain coping style in ex-preterm born adolescents compare to healthy children and adolescents in the general population.

PATIENTS AND METHODS

Subjects

The POPS project, a nation-wide follow-up program that studies the effects of prematurity and low birth weight on later outcome, comprised 94% (n=1338) of all babies born alive in the Netherlands in 1983 with a gestational age less than 32 weeks or with a birth weight < 1500 g.[14] From the original cohort, 379 (28%) did not survive to the age of 19 years. The remaining 959 (72%) were eligible for the present study.

Procedure

At the age of 19 years, survivors were invited to participate in an extensive follow-up program, including assessment of pain coping mechanisms with the PCQ. Furthermore, pain-coping effectiveness, pain and emotion controllability and emotional reactions to pain were assessed. The medical ethics review boards of all participating medical centers approved the study protocol. The participating centers were all 10 NICU's in the Netherlands. Details on the logistics, response rate and selective non-response bias have been reported previously.[15]

Questionnaires

Several studies have used the PCQ in healthy children up to the age of 18 years and in children with pain related morbidity.[16-19] The PCQ comprises 39 coping items categorized in eight subscales and may be presented as three higher-order factors.[7] The approach factor measures direct attempts to deal with the pain and the use of active methods to regulate feelings when in pain; it comprises information seeking (4 items), problem solving (5 items), seeking social support (5 items), and positive self-statements (5 items) subscales. The problem-focused avoidance factor measures attempts to disengage from the pain; it includes positive self-statements (5 items) , behavioral distraction (5 items), and cognitive distraction (5 items) subscales. The emotion-focused avoidance factor measures strategies in which emotions are freely expressed and strategies that reflect a lack of effort to regulate feelings when in pain; it comprises externalizing (5 items) and internalizing/catastrophizing (5 items) subscales.[7] Participants were asked to indicate the frequency (1 = never, 2 = hardly ever, 3 = sometimes, 4 = often, 5 = very often) with which they used the 39 coping items in response to the prompt, *'When I am hurt or in pain for a few hours or days, I …'.*
Pain coping effectiveness was tested by rating seven items (e.g. *'I handled the pain*

well') on a 5-point Likert scale (1 = totally disagree, 5 = totally agree).[7] Participants rated two questions indicative of pain and emotion controllability on a 5-point scale (1 = never, 5 = very often) as well: *'how often do you feel you can do something to change the pain'* and *'when in pain, how often can you do something about how you feel'*.[7] Emotional reactions to pain were assessed by rating on a 4-point scale (1 = not at all, 4 = really) the reactions happy, sad, angry, agitated, calm, afraid and nervous/worried to hours or days of pain.[7] Happy and calm were reverse coded. Scores of the tests for pain coping effectiveness, pain and emotion controllability and emotional reactions to pain were averaged to provide three composite values.

Intelligence (IQ)

Intelligence at 19 years of age was assessed with the computerized version of the Multicultural Capacity Test–Intermediate Level developed by Bleichrodt[20] and was used as a proxy for academic achievement. This standardized intelligence test measures intellectual and cognitive capacity and skills of individuals with secondary education. It derives an IQ with a mean of 100 and a standard deviation of 15 in a normal Dutch sample.

Background characteristics

The demographic data of gestational age, birth weight, gender, small-for-gestational age (SGA, birth weight less than the 10th centile for gestational age, gender and parity[21]) were extracted from the database. Length-of-stay, necrotizing enterocolitis (NEC, grade I – III according to Walsh and Kliegmann[22]), sepsis (defined as positive blood culture[23]) and intraventricular hemorrhage (IVH, grade I – IV according to Papile[24]) were also extracted as estimates of neonatal disease severity. Since no control group was available, we searched the PubMed database for studies using PCQ with the search string "pain coping questionnaire" AND "healthy", and filtered for "adolescents 13-18 years" OR "young adults 19-24 years".

Statistical analysis

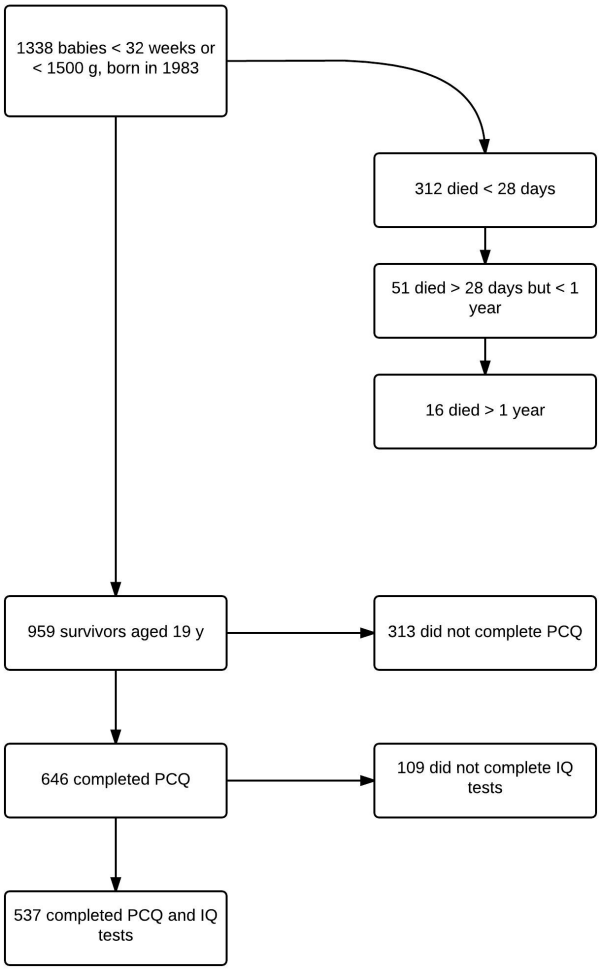
Group comparisons of continuous data were analyzed with the Student t-test if normally distributed and the Mann-Whitney U-test if not normally distributed. Group comparisons of categorical data were analyzed with the Pearson Chi square test. For each participant we averaged the items of each subscale of the PCQ and calculated the mean and standard deviation for the three higher-order factors.
The Pearson correlation coefficient was calculated to estimate correlations between the three higher-order factors and the adolescents appraisals of pain controllability, coping effectiveness and emotional distress. Linear regression analysis was used to estimate the effect of neonatal characteristics and adolescent IQ on the three higher-order factors and presented as regression coefficient (B) with 95% CI. Multiple linear regression analysis was applied to assess the independent effects of variables on the higher-order factors, including only the variables that were significantly associated

with the outcome in the univariate analysis.
We checked for normal distribution of residuals and collinearity.
Statistical difference was assumed if p-value < 0.05. Data were analyzed with the SPSS v19.0.0 software program (IBM, New York).

RESULTS

Out of the 959 survivors in the POPS data set, 646 (67%) survivors completed the PCQ questionnaire, and 537 (56%) participants completed IQ testing (**Figure 1**).

Figure 1: selection of participants



Legend: *selection of participants*

Table 1 shows the characteristics of the participants who completed both the PCQ and IQ tests and of those who did not complete the PCQ. There were statistically significant differences in gender and IQ between these groups.

Table 1: demographic data of the POPS-19 cohort.

Variables	Survivors with PCQ and IQ N=537	Survivors without PCQ N=313	*p*-value
gestational age (weeks)	31.0 ± 2.5	30.1 ± 2.7	0.38
birth weight (g)	1307 ± 303	1313 ± 252	0.97
gender (female)	296 (55%)	110 (35%)	< 0.001
small-for-gestational age	207 (39%)	118 (38%)	0.82
necrotizing enterocolitis	33 (6%)	16 (5%)	0.53
sepsis	178 (33%)	116 (37%)	0.26
intraventricular hemorrhage	86 (16%)	52 (17%)	0.82
respiratory support (CPAP/IPPV)	263 (51%)	155 (49%)	0.9
In hospital length-of-stay (days)	63 [49-80]	62 [49-79]	0.41
IQ at 19 years of age	101 ± 15	86 ± 11[#]	< 0.001

Legend: *categorical data are expressed as numbers (percentage) and continuous data are expressed as mean ± SD or median [inter quartile range]. # Only 25 subjects without PCO completed IQ tests.For categorical data p-value was calculated with Chi square, for normally distributed continuous data p-value was calculated with Student-T test, for non-normally distributed continuous data (in hospital length-of-stay) Mann-Whitney-U test. Continuous Positive Airway Pressure (CPAP), Intermittent Positive Pressure ventilation (IPPV); intelligence quotient (IQ).*

The Pubmed search identified 21 papers, of which four were of potential interest. Three of these papers referred to a wide age range between 8-18 years. As age may influence coping strategy, we excluded these papers. The only paper referring to healthy adolescents, aged 13-18, presents data of PCQ higher-order scales.[7]

Table 2 shows the means and CI for the higher-order scales. We observed no differences between our cohort and healthy adolescents in approach and problem-focused avoidance. In contrast, emotion-focused avoidance in our study group showed significantly lower values than healthy adolescents.

Table 2. Higher order factors of the PCQ: POPS-19 study population and healthy controls.

(n=537 ex-preterms)	This study (n=144 healthy) age 19	Reid 7 age 13-18
Approach	2.7 [2.65;2.75]	2.8 [2.70;2.90]
Problem focused avoidance	2.9 [2.84;2.96]	2.9 [2.79;3.01]
Emotion focused avoidance	1.6 [1.55;1.65]	2.5 [2.37;2.63]

Legend: *The subscale results are expressed as mean [95%CI]. The 95% confidence intervals were calculated as mean ± 1.96*SD/√n.*

The three higher-order factors were correlated with the adolescents appraisals of pain controllability, self-rated coping effectiveness and emotional distress in the expected directions. Approach and problem-focused avoidance were both positively correlated to pain coping effectiveness ($r = 0.10$, p 0.02 and $r = 0.28$, $p < 0.001$, respectively) and pain controllability ($r = 0.49$, $p < 0.001$ and $r = 0.25$, $p < 0.001$, respectively). Emotion-focused avoidance was negatively correlated with pain coping effectiveness ($r = -0.31$, $p < 0.001$) and positively with emotional reactions ($r = 0.62$, $p < 0.001$).

Table 3 summarizes the significant correlations between neonatal characteristics and PCQ higher-order factors. No significant correlations were found between in hospital length of stay, sepsis and NEC and any of the higher-order factors. Gestational age was positively correlated with problem-focused avoidance, while birth weight and respiratory support were negatively correlated with emotion-focused avoidance. SGA infants used more emotion-focused avoidance than their AGA peers. IVH was correlated with a decrease in problem-focused avoidance and increase in emotion-focused avoidance, respectively. We found a positive correlation between IQ and the higher-order factors approach and problem-focused avoidance. In contrast, IQ was negatively correlated with emotion-focused avoidance.

Table 3. Pain Coping Questionnaire results in infants < 32 weeks' of gestation or < 1500g with complete IQ tests (n=537): Univariate Linear Regression Analysis.

	Approach	Problem focused avoidance	Emotion focused avoidance
Gestational age (weeks)	0.01 [-0.12;0.32]	0.02 [0.00;0.05]*	0.01 [-0.01;0.02]
Birth weight (kg)	0.01 [-0.18;0.19]	-0.01 [-0.21;0.19]	-0.09 [-0.19;-0.00]*
SGA vs AGA	0.07 [-0.04;0.18]	0.11 [-0.01;0.23]	0.06 [0.01;0.12]*
IVH vs no IVH	-0.08 [-0.23;0.07]	-0.18[-0.34;-0.02]*	0.15 [0.02;0.29]*
Respiratory support vs no respiratory support	-0.02 [-0.13;0.09]	0.01 [-0.11;0.13]	-0.11 [-0.12;-0.01]*
Intelligence (per IQ point)	0.01 [0.00;0.01]***	0.01 [0.00;0.01]***	-0.01 [-0.01;-0.00]***

Legend: *regression coefficients (B) from linear regression with [95% CI] are shown. Level of significance: p-value <0.05 *, p-value <0.01 **, p-value <0.005 ***. Appropriate-for-gestational age (AGA); small-for-gestational age (SGA); intraventricular hemorrhage (IVH); intelligence quotient (IQ).*

Multiple regression analysis was applied for problem-focused avoidance and emotion-focused avoidance, respectively. For problem-focused avoidance, including gestational age, IVH and IQ in the model, only IQ remained an independent predictor. For emotion-focused avoidance, including birth weight, SGA, IVH, respiratory support and IQ in the model, three independent predictors remained: IVH was positively correlated, while respiratory support and IQ were negatively correlated with emotion-focused avoidance (**Table 4**).

Table 4. Pain Coping Questionnaire results in infants < 32 weeks' of gestation or < 1500g with complete IQ tests (n=537): Multiple Regression Analysis.

	Problem focused avoidance	Emotion focused avoidance
Gestational age (weeks)	0.02 [-0.01;0.05]	n/a
Birth weight (kg)	n/a	-0.04 [-0.15;0.06]
SGA vs AGA	n/a	0.03 [-0.03;0.1]
IVH vs no IVH	-0.12 [-0.29;0.05]	0.1 [0.02;0.17]*
Respiratory Support vs no respiratory support	n/a	-0.08 [-0.13;-0.02]*
Intelligence (per IQ point)	0.01 [0.00;0.01]***	-0.01 [-0.01;-0.00]**

Legend: *partial regression coefficients with [95% CI] are shown. Level of significance: p-value <0.05 *, p-value <0.01 **, p-value <0.005 ***. intraventricular hemorrhage (IVH); intelligence quotient (IQ); not applicable (n/a).*

DISCUSSION

Our results indicate that gestational age and birth weight do not affect pain coping strategy in adolescents. Furthermore, neonatal complications have limited effect on coping style in adolescence. After adjustment for several neonatal characteristics, IQ is positively correlated with an adaptive coping style. Remarkably, in ex-preterm adolescents we observed lower scores for emotion-focused avoidance than in healthy adolescents. Pain coping effectiveness and pain controllability were positively correlated with the use of adaptive coping strategies, which is consistent with findings in both healthy school children and adolescents and children with chronic pain states.[7]

We hypothesized that estimates of neonatal disease severity (e.g. NEC, IVH, sepsis), may reflect cumulative neonatal pain exposure and influence pain coping strategy in later life. However, with the exception of IVH and respiratory support, we could not identify any relation between neonatal disease severity and pain coping style in adolescence.

Earlier findings showed severity of illness on the first day after birth, morphine exposure, gestational age and days on mechanical ventilation were significantly correlated with cumulative neonatal pain.[25] After correcting for gestational age, mechanical ventilation and morphine use, a higher number of skin-breaking procedures predicted lower cognitive and motor development at eight and 18 months corrected age.[25] The authors did not find a significant relation between gestational age and cognitive development. In contrast, a recent review summarized the relationship between cognitive function and gestational age.[26] In this review the author showed that a lower gestational age is associated with an increased risk for cognitive impairment. Cognitive function results from a complex interplay between genetic, medical, social and environmental factors.[26] Social and environmental factors may become more important with increasing age, while adverse neonatal experiences such as pain and stress may become less important. This effect has already been demonstrated in a 5-year follow-up study in very low birth weight infants which showed that during development cognitive outcome improves with parental education and caregiver employment.[6]

It is suggested that cognitive deficits may mediate mental health symptoms in extremely preterm infants with neurodevelopmental problems.[27] In the POPS cohort, the prevalence of neurodevelopmental problems was found to be stable throughout childhood and into adolescence. Approximately 13% survivors experienced moderate to severe cognitive or neurosensory problems.[28] As children get older, they are more capable of applying cognitive coping strategies with new painful situations.[29] Our results showed that with increasing IQ, adaptive coping strategies were used more frequently while the maladaptive coping style of emotion-focused avoidance was used less often. The effect may appear small, but considering the normal range of IQ (85-115) the maximum difference of 30 x 0.01 = 0.3 on a 1-5 Likert scale may be clinically relevant. Although cognitive function does not depend on intelligence alone, the explanation for the lack of emotion-focused avoidance may be that our cohort had a normal IQ. However, this does not explain our finding that ex preterms

use even less emotion-focused avoidance than healthy peers. The lack of use of maladaptive pain coping style in our cohort is in line with the results from a study in 11 year old NICU survivors that showed only a limited increase in adaptive pain coping strategies compared to healthy controls.[12] A smaller study in 19 NICU survivors showed more internalizing/catastrophizing, but in this study an adapted version of the PCQ was used.[13]
We found a positive correlation between IVH and emotion-focused avoidance. IVH grade 3-4 and posthemorrhagic hydrocephalus are associated with adverse neurodevelopmental outcome in the extreme preterm infant.[30] Unfortunately, the POPS database did not specify the grade of IVH or hydrocephalus. Therefore, the observed correlation may underestimate the effect of severe IVH on pain coping style in adolescence.

Methodological limitations

The POPS database originates from 1983. During the conceptualization of the POPS program the choice was made not to include neonatal pain events in the database. Therefore we extracted basic demographics from the POPS database as a proxy of disease severity, with the aim to identify variables that may be related to neonatal pain exposure.[25]

Inherent to long-term follow-up, our study may be biased by selection of NICU survivors with a relatively favorable outcome. Severely handicapped survivors are possibly reflective of the group with the severest neonatal disease, and they did not engage in IQ testing. The mean IQ in our cohort may also be a result of selection bias: completion of both IQ testing and the PCQ depend on cognitive skills. A previous report on selection bias in the POPS cohort showed that in responders gender, race, maternal age, socio-economic status and maternal educational level were possible confounding factors. Non responders were associated with low maternal educational level, low socio-economic status, special education and severe handicaps.[15]

This population based follow-up study did not include a control group. We were able to identify one study with the PCQ in healthy adolescents, however this cohort comprised adolescents from 13 to 18 years. The comparison of the two cohorts may be biased by the effect that coping strategy may change with age. Our analysis did not allow for covariate adjustment and therefore may have been confounded by population differences.

However, a major strength of our study is the size and population-based characterization of the cohort. Yet, extrapolation of our findings to current time is challenging. Neonatal pain assessment and management has greatly improved since the first reports from the 1980's following evidence that perioperative analgesia results in increased survival and lower morbidity.[31]

CONCLUSION

In general, early neonatal characteristics or complications in very preterm or low birth weight infants have limited effect on pain coping style in adolescence. However, higher IQ is associated with the use of adaptive coping style, while maladaptive coping strategies were used less. Though our results may have been influenced by selection bias and the lack of age-matched healthy controls, we speculate that in early life biological and medical factors may moderate behavioral pain and stress response, while in later life intelligence, in addition to psychological, social and environmental factors modulate children's pain coping style.

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Chapter 8

Pain threshold, tolerance and intensity in adolescents born very preterm or with low birth weight.

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Submitted

ABSTRACT

Background

Data on long-term consequences of neonatal pain is limited.

Objective

To assess whether perinatal factors (gestational age, birth weight, estimates of neonatal disease severity) and pain coping strategy are associated with altered pain threshold, pain tolerance and pain intensity in adolescents born preterm.

Methods

We analysed data from the Collaborative Project on Preterm and Small for Gestational Age Infants in the Netherlands (POPS), comprising 94% of all newborns with a gestational age < 32 weeks or birth weight < 1500 grams born in 1983. Out of 959 survivors, 506 adolescents at the age of 19 performed a standardized cold pressor test (hand immersion in ice water) to assess pain threshold, tolerance and intensity. Among these, 412 completed a pain coping questionnaire.

Results

In a univariate analysis, female gender and NEC were associated with lower pain tolerance, indicated by decreased 'survival' to 180s in ice water (females 19% vs males 29%, NEC 7% vs no NEC 25%). Female gender was associated with higher pain intensity (mean difference 0.58; 95% CI 0.21;0.95) and lower pain threshold (Log Rank p 0.007). In a multivariate Cox regression analyses, externalizing pain behavior was significantly associated with lower pain threshold (hazard ratio 1.24; 95%CI 1.06;1.45) and pain tolerance (hazard ratio 1.41; 95%CI 1.15;1.72).

Conclusion

NEC was associated with altered pain response in adolescents born preterm. This finding underlines the importance of adequate analgesia in newborns with NEC. In adolescence, externalizing pain coping strategy was associated with lower pain threshold, pain tolerance and higher pain intensity.

INTRODUCTION

Despite the increasing awareness regarding pain and pain management in the neonatal intensive care unit (NICU), preterm infants are subjected to 11-14 painful procedures every day.[1,2] Repeated procedural pain and stress in neonatal life have been associated with long-term effects on pain response and pain behavior.[3] Pain response and behavior are mainly determined by pain threshold, pain tolerance, and pain sensitivity. Pain threshold is defined as the minimum intensity of an external stimulus that is perceived as painful.[4] Pain tolerance is the maximum level of pain that a subject is able to tolerate, whereas pain sensitivity range is defined by the difference between pain threshold and pain tolerance.[4]

Pain threshold, tolerance and sensitivity have been studied in NICU survivors.[5-8] However, results vary among studies. While in two studies a decrease in thermal sensitivity in NICU survivors when compared to healthy term controls was found,[5,6] others have shown an increase.[7,8] Pain intensity in children born preterm, subjected to cold pressor tests (CPT), was found to be similar to healthy controls.[8]

Internalizing pain coping strategies have been associated with lower pain tolerance[9], but in a more recent study no such association was found.[10]

Altered pain responses in NICU survivors may be mediated by pain experiences in the neonatal period. The Collaborative Project on Preterm and Small for Gestational Age Infants in the Netherlands (POPS-1983) is a national follow-up study on the effects of preterm birth or growth restriction on later outcome in childhood and adolescence. In this large population-based cohort, we examined at the age of 19 years pain threshold, tolerance, and intensity using the CPT. We hypothesized that key neonatal demographic variables and estimates of disease severity would be associated with altered pain response and behavior in later life in children born preterm or with very low birth weight. Furthermore, we were interested if pain response was influenced by pain coping strategies.

METHODS

Subjects

The Collaborative Project on Preterm and Small for Gestational Age Infants in the Netherlands (POPS-1983) cohort comprised 94% (n=1338) of all babies born alive in the Netherlands in 1983 with a gestational age below 32 weeks or a birth weight < 1500 g.[11]

Procedure

At the age of 19 years, 959 survivors were invited to participate in an extensive follow-up program, including assessment of pain threshold, tolerance and intensity with a standardized CPT. All medical ethics review boards of the participating medical centers approved the study protocol. All subjects provided written informed consent to participate in the study. Details, logistics and response rate have been reported previously.[12]

For the CPT, a cooling box was filled with water and ice-cubes. As small differences in water temperature might contribute to conflicting results[13], we included in our analysis only tests in which water temperature remained stable between 4-6°C during the test. During the test, the subject was asked to verbally mark the beginning of the first painful sensation (pain threshold T1, expressed in s). Pain tolerance was defined as the moment the subject removed the arm from the water (T2, expressed in s). After 180s the test was discontinued, a ceiling time that is recommended in pediatric populations.[14] During immersion every subject was asked to grade the pain with the Numerical Rating Scale (NRS) at pain threshold (NRS1) and pain tolerance (NRS2). NRS is scored on a 0 to 10 point scale, 0 indicating no pain and 10 indicating the most intense pain imaginable.[15,16]

Background characteristics

Basic demographic data were extracted from the POPS database. We selected the following neonatal variables as estimates of disease severity: necrotizing enterocolitis (NEC, stages ≥ 2 according to Bell's criteria[17]), sepsis (defined as positive blood culture[18]), intraventricular hemorrhage (IVH, all grades, according to Papile[19]), respiratory support (need for CPAP and/or mechanical ventilation) and length of NICU stay.

Pain Coping Questionnaire (PCQ)

The PCQ is a validated instrument to assess pain coping strategy in adolescents.[20] The PCQ comprises 39 coping items categorized across eight subscales. The subscales externalizing and internalizing were used to assess the association of pain coping strategy on pain behavior.

Statistical analysis

For normally distributed data, mean and standard deviation (SD) were calculated, otherwise median and interquartile range (IQR) were calculated. Differences between the cohort with complete CPT and PCQ test and POPS participants without CPT within the specified temperature range were calculated with the chi-square test for dichotomous data and with the Student-t test or Mann-Whitney U test for normal and non-normal continuous data, respectively.

We tested the internal consistency of the subscales of the PCQ by calculating Cronbach's alpha. Data were analyzed with the SPSS v19.0.0 software program (IBM, New York). A two-sided p-value < 0.05 was considered statistically significant in all analysis.

Pain threshold and tolerance analysis

For subjects with early withdrawal (i.e. hand withdrawal before the ceiling time of 180s), the median and IQR for time spent in ice water (i.e. 'survival time') was calculated for demographic subgroups. Kaplan-Meier analysis was used to calculate differences in these survival times across dichotomous demographic subgroups and statistical significance was tested using the log-rank test. For continuous variables we calculated hazard ratios with 95% confidence intervals using a univariate Cox regression model. Subsequently, variables that were significantly associated with pain threshold and tolerance in univariate analyses were included in multiple Cox regression models to identify factors that were independently associated with pain threshold and pain tolerance.

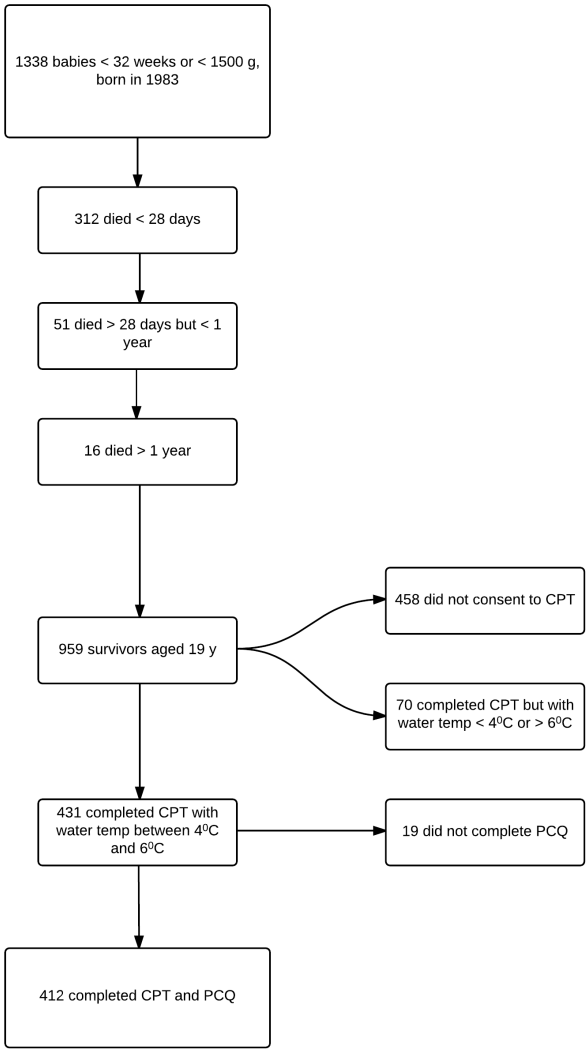
Pain intensity analysis

Associations between neonatal demographic variables, estimates of disease severity and NRS scores at pain threshold and pain tolerance were tested with Student t- test for dichotomous predictors, and linear regression otherwise. Variables significantly associated with higher NRS scores were included in a multiple linear regression model to test for their independent associations with pain intensity.

RESULTS

Of the 959 survivors in the POPS data set, 431 (45%) underwent a CPT in water with a temperature ranging from 4 to 6 degrees Celsius (figure 1). Mean (SD) age of study participants was 19.3 (0.2) years. In total 412 candidates completed both CPT and PCQ testing (**figure 1**). Cronbach's alpha for the internalizing and externalizing subscales was 0.83 and 0.79 respectively, indicating good internal consistency.

Figure 1: flowchart depicting recruitment of the cohort



Legend: *Cold Pressor Test (CPT), Pain Coping Questionnaire (PCQ)*

Demographics

Table 1 summarizes the demographic and disease severity characteristics of the candidates that completed the CPT and PCQ (n=412), compared to survivors within the POPS dataset without CPT or with a CPT with temperatures < 4 or > 6 degrees Celsius before and/or after the test.

Table 1: Demographic data of the POPS-19 cohort

Variables	Participants with complete CPT between 4 – 6^0 C and PCQ tests (n=412)	Participants without CPT or with CPT but water temperature < 4 or > 6^0 C (n=528)	*p* value
gestational age (weeks)	31.1 ± 2.5	31.0 + 2.6	0.74
birth weight (g)	1299 ± 301	1327 + 268	0.14
gender (female)	228 (55%)	225 (43%)	<0.001
small-for-gestational age	168 (41%)	182 (35%)	0.047
necrotizing enterocolitis	30 (7%)	23 (4%)	0.054
clinical sepsis	134 (33%)	156(34%)	0.33
intraventricular hemorrhage	63 (15%)	86 (19%)	0.68
respiratory support	208 (51%)	220 (47%)	0.007
length-of-stay (days)	63 [49-79]	61 [49-78]	0.79

Legend: *Characteristics of POPS participants with and without CPT with a water temperature between 4 – 6^0C. Categorical data are expressed as numbers (percentage), normally distributed continuous data are expressed as mean (SD), non-normally distributed data as median [interquartile range]. Chi square test for dichotomous variables, Student-t test or Mann-Whitney U test for normal and non-normal continuous data. Cold Pressor Test (CPT). Pain Coping Questionnaire (PCQ).*

Pain threshold and pain tolerance

Table 2 summarizes the differences in the proportion of adolescents "surviving" the ceiling time of 180s (i.e. not reaching pain threshold or tolerance before the end of the test) across the demographic subgroups. Children born SGA, females and NEC survivors had a decreased pain tolerance when compared to their AGA, male and no-NEC peers, respectively.

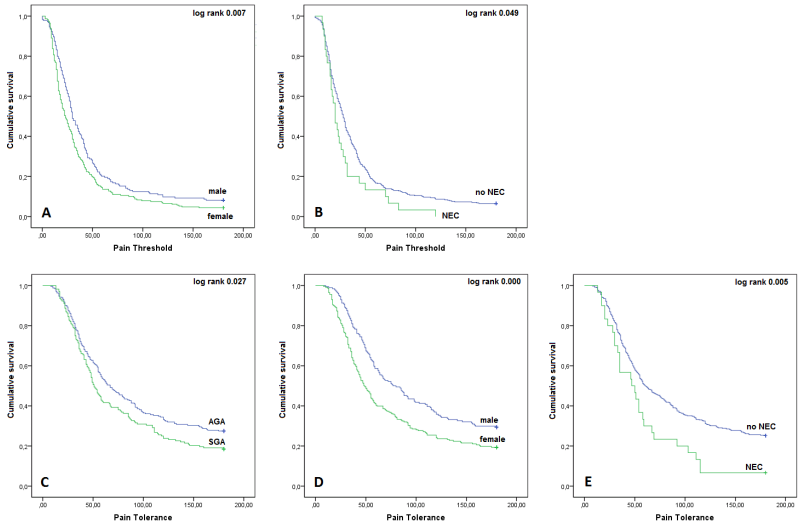
Table 2: Proportion of participants 'surviving' in ice water to the set limit of 180sec.

		T1 n/N (%)	*p* value	T2 n/N (%)	*p* value
SGA/AGA	AGA SGA	16/244 (7) 9/168 (5)	0.62	67/244 (27) 31/168 (18)	0.03
Gender	female male	10/228 (4) 15/184 (8)	0.11	44/228 (19) 54/184 (29)	0.02
NEC	no yes	25/382 (7) 0/30 (0)	0.15	96/382 (25) 2/30 (7)	0.02
Sepsis	no yes	19/278 (7) 6/134 (5)	0.35	67/278 (24) 31/134 (23)	0.83
IVH	no yes	23/349 (7) 2/63 (3)	0.29	87/349 (25) 11/63 (17)	0.20
Respiratory support	no yes	12/204 (6) 13/208 (6)	0.88	46/204 (23) 52/208 (25)	0.56

Legend: *Chi square tests on number and proportion of subjects "surviving" the ceiling time of 180s before pain threshold (T1) and pain tolerance (T2) was reached/total number of children in group (n/N). Small-for-gestational age (SGA); appropriate-for-gestational age (AGA), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH). Respiratory support comprised invasive (intubated and ventilated) and non-invasive (nasal continuous or intermittent positive airway pressure) modes.*

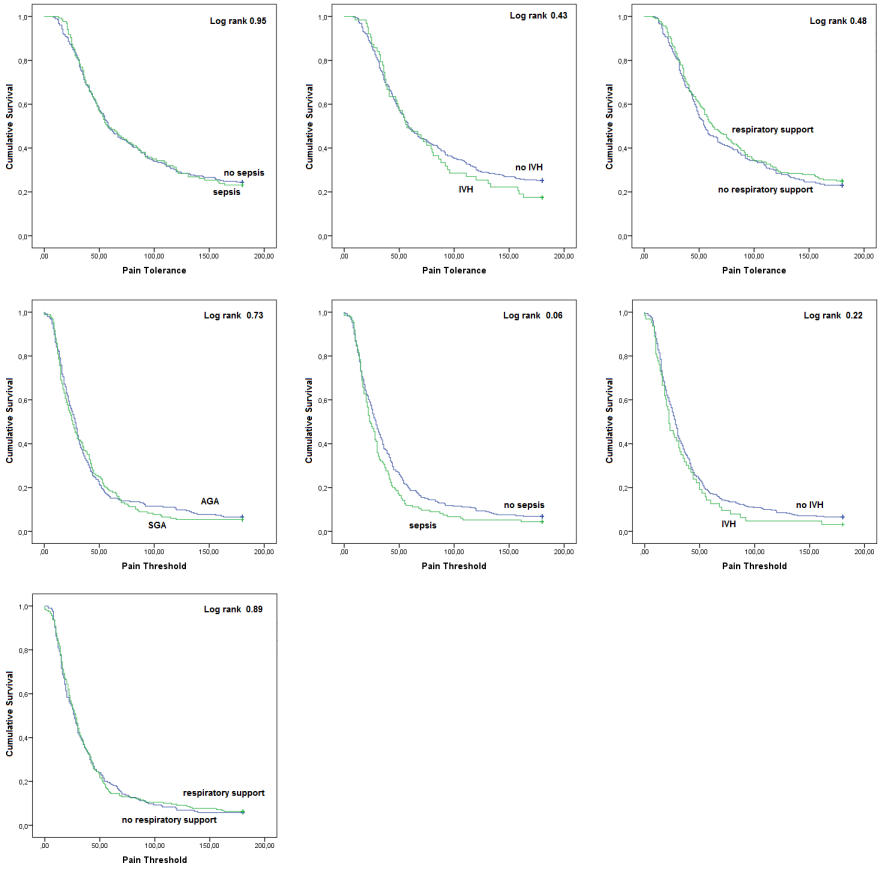
In agreement with these findings, in the univariate Kaplan-Meier analyses female gender and NEC were associated with a lower probability of surviving to 180s before reaching both pain threshold **(figure 2A and 2B)** and tolerance **(figure 2D and 2E).** In addition, SGA was associated with a decreased probability of reaching 180s without reaching pain tolerance **(figure 2C)**. Kaplan-Meier analysis for other variables showed no significant associations with either pain threshold or tolerance.

Figure 2A-E. Kaplan Meier curves for dichotomous variables associated with significant differences in survival to the ceiling time of 180s, for pain threshold and pain tolerance.



Legend: *curves show 'survival' in ice water (4 – 6^{0}C) and log rank p-values for pain threshold and pain tolerance. Appropriate for Gestational Age (AGA), Small for Gestational Age (SGA), Necrotizing Enterocolitis (NEC).*

Figure 2F. Kaplan Meier curves for dichotomous variables not associated with significant differences in survival to the ceiling time of 180s, for pain threshold and pain tolerance.



Legend: *curves show 'survival' in ice water (4 – 6^{0}C) and log rank p-values for pain threshold and pain tolerance. Appropriate for Gestational Age (AGA), Small for Gestational Age (SGA), Necrotizing Enterocolitis (NEC).*

In a univariate Cox model for continuous variables (**Table 3A)** externalizing was associated with an increased risk of reaching pain threshold before 180s. The same model showed that with increasing birth weight (per kg) the risk of reaching pain tolerance before 180s decreased. The use of internalizing and externalizing pain coping strategies were associated with an increased risk of reaching pain tolerance before 180s.

Table 3A. Pain threshold (T1) and pain tolerance (T2) (< 180s): univariate Cox analyses

	T1			T2		
	HR	95% CI	*p*	HR	95% CI	*p*
Birthweight (per kg)	0.92	0.66;1.28	0.60	0.58	0.39;0.84	0.005
Gestational age (weeks)	0.99	0.95;1.03	0.53	1.01	0.96;1.06	0.67
Length of stay (days)	1.00	0.98;1.00	0.68	1.00	0.99;1.01	0.32
Externalizing (per point increase)	1.28	1.09;1.49	0.002	1.52	1.29;1.79	<0.001
Internalizing (per point increase)	1.11	0.97;1.27	0.12	1.22	1.05;1.41	0.008

Legend: *pain threshold and pain tolerance, univariate Cox analysis. p - value: log rank. Hazard Ratio (HR), Confidence Interval (CI).*

Table 3B shows that, in a multiple Cox regression model female gender and the use of externalizing pain coping strategies were independently associated with lower pain threshold. Significant predictors of decreased pain tolerance included female gender, NEC and externalizing pain coping strategy.

Table 3B. Pain threshold (T1) and pain tolerance (T2) (< 180s): multivariate Cox analyses

	T1			T2		
	HR	95% CI	*p*	HR	95% CI	*p*
female vs male	1.29	1.06;1.58	0.013	1.41	1.12;1.78	0.004
SGA vs AGA	ns	ns	ns	1.20	0.93;1.52	ns
NEC vs no NEC	1.42	0.97;2.06	0.07	1.55	1.05;2.31	0.029
Birthweight (per kg)	ns	ns	ns	0.75	0.49;1.14	ns
Externalizing (per point increase)	1.24	1.06;1.45	0.007	1.41	1.15;1.72	0.001
Internalizing (per point increase)	ns	ns	ns	1.01	0.85;1.22	ns

Legend: *Pain Threshold, multivariate (adjusted model); p - value: log rank. Hazard Ratio (HR), Confidence Interval (CI), small-for-gestational-age (SGA), appropriate-for-gestational-age (AGA), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), not significant (ns)*

Pain intensity

Female gender was associated with higher NRS scores at pain threshold (mean difference 0.58, 95%CI 0.21;0.95, p 0.002) in a univariate model (**Table 4**). Increased use of externalizing pain coping strategies was associated with higher NRS at pain threshold (B 0.32, 95%CI 0.03;0.6, p 0.03) and at pain tolerance (B 0.47, 95%CI 0.11;0.83, p 0.01). Increased use of internalizing was associated with higher NRS at

pain threshold (B 0.31, 95%CI 0.05;0.56, p 0.02) but not at pain tolerance. When adjusted for gender, only externalizing was associated with an increase in NRS at pain tolerance.

Table 4: Numerical Rating Scale at pain threshold and pain tolerance: univariate analysis

	NRS Pain Threshold			NRS Pain Tolerance		
	Mean Difference	95% CI	*p*	Mean Difference	95% CI	*p*
female	0.58	0.21;0.95	0.002	0.47	0.01;0.94	0.052
SGA	-0.05	-0.43;0.34	0.82	-0.04	-0.52;0.44	0.87
NEC	0.19	-0.53;0.92	0.59	0.72	-0.18;1.61	0.12
sepsis	-0.22	-0.62;0.18	0.28	-0.09	-0.59;0.41	0.72
IVH	-0.01	-0.53;0.52	0.98	0.49	-0.16;1.14	0.14
Respiratory support	0.21	-0.17;0.58	0.26	0.27	-0.24;0.69	0.34
	B	95% CI	*p*	B	95% CI	*p*
Gestational age (weeks)	-0.02	-0.09;0.06	0.59	-0.01	-0.11;0.08	0.79
Birth weight (per kg)	-0.29	-0.91;0.34	0.37	-0.05	-0.83;0.73	0.90
Length of stay (days)	0.01	-0.01;0.01	0.38	-0.01	-0.01;0.01	0.53
Externalizing	0.32	0.03;0.6	0.03	0.47	0.11;0.83	0.01
Internalizing	0.31	0.05;0.56	0.02	0.21	-0.11;0.53	0.19

Legend: *Numerical Rating Scale (NRS) at Pain Threshold and Pain Tolerance: for dichotomous data Student t-test was performed. Shown are mean differences with confidence interval (CI) and level of significance. For continuous data linear regression coefficients with 95%CI are shown. Small-for-gestational-age (SGA), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH).*

DISCUSSION

Our data was relatively old, partly inherent to long term follow-up studies. Since pain management has greatly improved since 1983, our data may provide a benchmark for future long term follow up studies in the field of neonatal pain.

In this study, NEC was identified as an important determinant of lower pain tolerance in adolescents born preterm. Female gender and externalizing pain coping strategy were associated with lower pain threshold and pain tolerance. Higher pain intensity at pain tolerance was associated with female gender and externalizing. The use of externalizing pain coping strategy remained an independent predictor for higher pain intensity at pain tolerance when corrected for gender.

We had no exact data available on cumulative neonatal pain. Therefore we chose to assess variables that may reflect cumulative neonatal pain. We found no association between increased pain tolerance and the neonatal factors that Vederhus et al. identified in their study (days of respiratory support and cumulative pain).[8] Illness

severity on day 1 after birth, morphine exposure, gestational age and days on mechanical ventilation have been associated with cumulative neonatal pain.[21] Gestational age and the use of mechanical ventilation showed no statistically significant association with pain response in our cohort. In contrast, we found an association between pain tolerance and NEC. All participants with a history of NEC reached pain threshold before 180s, only two of them survived in ice water to 180s. The visceral pain associated with NEC may persist for days, while NEC also leads to an increase of painful interventions, up to a maximum of 18.8 times a day during five consecutive days.[22] A retrospective single center study showed that systematic pain assessment in newborns diagnosed with NEC was performed in only 30-60 percent of cases. Analgesia was used in 52-76%.[22] Therefore, inadequate pain management in these infants, which has been identified as a risk factor for the development of chronic pain states in newborns[23] may explain our observations.

Pain coping strategy has inconsistently been found to influence pain response. At the age of 11 years, children born preterm who had surgery during childhood used externalizing pain coping strategies more often than those who did not have surgery during childhood. However, pain coping strategy was not associated with altered pain tolerance in these children.[5] In another paper CPT was performed in children at the age of 12.4 years (mean; SD 2.6 years) with juvenile idiopathic arthritis.[24] Internalizing was associated with decreased pain threshold, pain tolerance and greater pain intensity.[24] We found the same associations, even when adjusted for gender. Externalizing, being a maladaptive coping strategy, may lead to a decrease in pain threshold, pain tolerance and an increase in NRS at pain tolerance. Our finding may be clinically relevant in early childhood because children born preterm tend to use maladaptive coping strategies such as externalizing and internalizing more often than reported in the general population.[25]

The gender differences we found are not in line with earlier studies. Among adolescents born preterm (n=31: 18 female, 13 male) Vederhus and colleagues showed no differences in survival to 180s between females and males.[8] In a study in 11-year-old children born preterm (n=43) no gender difference in thermal sensitivity was detected.[5] We speculate sample sizes in both studies were too small to detect a statistical difference.

Methodological limitations

The POPS database was designed as a longitudinal follow-up study in preterm infants born in 1983 and was not powered to detect statistical differences in the associations we studied. This may have influenced statistical significance of our findings. For instance, the association of NEC we found may be biased by the relatively small number of infants with NEC, as opposed to the number of infants without NEC. Likewise, demographic differences between subjects undergoing CPT (44%) and subjects without CPT (56%) may have introduced selection bias.

The NRS has been in use for self-report of childhood pain since long, despite the lack of studies investigating its validity in the pediatric population.[16] Only recently some studies addressed validity of the NRS and suggest that NRS is a valid tool to assess acute pain in children above seven or eight years.[15]

CONCLUSION

Our data suggests that necrotizing enterocolitis is associated with lower pain tolerance. Ex-preterm female adolescents have lower pain threshold, pain tolerance and report higher pain intensity when subjected to Cold Pressor testing compared to male ex-preterm adolescents. The use of externalizing pain coping strategy is an independent predictor for lower pain threshold and pain tolerance and higher pain intensity at pain tolerance.

The association between NEC and lower pain tolerance shows adequate neonatal pain assessment and pain management in NICU patients, especially those with prolonged pain, is important to prevent long term effects of neonatal pain. The association between externalizing pain coping strategy and pain behavior may be of relevance in childhood, since children born preterm are at risk to develop internalizing and externalizing behavioral problems. As a consequence they may exhibit greater pain intensity, influencing quality of life.

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Chapter 9

Summary and general discussion

This thesis studied three aspects of pain in the newborn.

1. While the concepts of acute and procedural pain have been described, the concept op chronic pain lacks fundamental understanding.
2. Treatment of neonatal pain may be important to prevent both short and long term effects of pain in early life.
3. Long term effects of neonatal pain have been study, but there has been little focus on the meaning of pain in daily life of NICU graduates.

In this chapter we will discuss the main findings of this thesis.

Part I. Conceptualization: Chronic Pain in the Neonate

In **Chapters 2, 3** and **4** we describe the development of the concept of chronic pain in the neonate. **Chapter 2** highlights the difficulties in choosing a valid study design for qualitative research aiming at the description of a phenomenon that has not well been studied before. In the research designs we studied, both strong and weak points were identified. The Nominal Group Technique (NGT), characterized by face to face meetings of an expert panel and the process of seeking consensus, has the major advantage of being able to deliberate in detail on research questions. However, experts may influence each other based on presumed authority or expertise on the subject under investigation. In addition it is a relatively expensive research method. This is especially true if the research questions at hand require multinational or multicultural input. The Consensus Development Conference (CDC) can be regarded as an expanded version of the Nominal Group Technique with the same advantages and disadvantages. Furthermore, because of its status, participants may feel pressed to deliver a result, possibly influencing the validity of the design. The Delphi technique is a relatively cheap method, ensuring anonymity and facilitating heterogeneity among experts. When performed online, global participation is easy. In addition, the design is flexible. A major disadvantage is the loss to follow up, which can be extensive and threaten validity of the results. Based upon the strong and weak points of the NGT, CDC and Delphi technique we decided to develop a Delphi questionnaire. We report the results of this questionnaire in **Chapter 3**. The Delphi study consisted of 3 rounds. In the first round the invited experts answered 3 open ended questions regarding the definition, etiology and symptoms of chronic pain in the neonate. The answers were categorized by the researcher into 437 statements. In a second round experts were asked to rate on a 5-point Likert scale whether or not they agreed with the statements. Statements with the highest degree of consensus were identified and in a second round the experts were asked to re-value these statements in the light of the groups opinion. This process was repeated in a third and final round. Consensus was reached on 23 statements, and using these statements we were able to partly describe the concept of chronic pain in the neonate. Etiological factors were identified, inadequate pain management being the most important one since all newborns are at risk for inadequate pain management.[1] A recent study highlights this finding. There are wide variations in analgesia practices in European NICU's, and structural pain assessment is performed in only 30-58% of cases, dependent on

mode of ventilation.[2]

We were not able to identify signs and symptoms specific to chronic pain. That was not surprising since decades of pain research has to date not resulted in a pain measure for acute pain with adequate sensitivity and specificity.[1] Recently, the question was raised if existing pain measures assess the emotion associated with pain sensation or only pain behavior.[3] More problems regarding pain assessment have been identified recently, most of them resulting from lack of a gold standard. Clinical feasibility of existing pain assessment tools in testing acute, prolonged and chronic pain has yet to be shown.[4] Some infants exhibit no signs of distress or pain due to energy depletion based on underlying disease.[4] Some advocate the use of video-observations and autonomic responses integrated with novel techniques such as Near Infrared Spectroscopy (NIRS), amplitude integrated electro encephalography (aEEG) or continuous measurements of changes in skin conductance.[5] Some of these techniques still have to be validated, and their clinical utility in day tot day practice may be limited due to the invasive nature of these techniques. However, integration of these techniques may result in second best pain assessment (first being self-report) and opportunity to develop a valid and clinically useful pain assessment tool.

In **Chapter 2** one of the problems with the research designs we identified was the lack of a definition of consensus. In Delphi surveys found in literature, researchers adopt (if any) different definitions of consensus.[6] However, theoretically, there always will be a problem with consensus processes, even when an expert-panel agrees 100% on an issue. For instance, it's difficult to define expertise. In addition, consensus does not necessarily equal 'the truth'. Another problem with consensus processes in study designs using Likert scales is the inability to choose values between two fixed points on such scales. This inability may reflect imprecision or uncertainty among and within participants, for instance concerning linguistic terms that are typically used in Likert scales (e.g. 'totally agree' or 'disagree').[7] To address these problems we consulted a research group at the Universitat Politècnica de Catalunya in Barcelona, Spain. This group previously designed a mathematical model to aid in consensus building research designs.[8] We describe the findings of the application of their model on our Delphi study results in **Chapter 4**. The aim of this study was to mathematically validate the findings form the Delphi survey, not to provide a definition of 'chronic pain'.

The mathematical model comprises algorithms that take into account thinking processes of participants. The model corrects for uncertainties, for instance regarding the use of linguistic terms, while computing degrees of consensus for each round. Second, the model corrects for the inability of participants to use levels of precision in their assessments. For instance, a participant may feel confident or precise to choose 'I agree' for item *x*, but may feel less confident in choosing 'I agree' or 'I totally agree' for item *y*.

The mathematical model was applied to the category 'definition' from the concept 'Chronic Pain'. For some items that showed no consensus with conventional statistical methods, the mathematical method was able to show a degree of consensus. When comparing results from the Delphi analyzed with conventional statistics and with the new mathematical model the results are the same in 68% of the statements. Both

methods alone or combined did not yield data comprehensive enough to result in a definition of 'chronic pain'. The question which method is best suited for the job remains, inherent to consensus not equaling the truth.

Recommendations

Future research should further focus on validation of the Delphi research method, especially regarding the definition and analysis of 'consensus'. The proposed mathematical method also needs further validation. With regards to the concept of chronic pain itself it will be challenging to strengthen or reject our findings. To date there are no accurate instruments to diagnose chronic pain, or identify infants that are at risk of developing prolonged or chronic pain syndromes. Follow up studies have never focused on the prevalence of chronic pain syndromes in NICU graduates. We advocate the development of a detailed follow-up program consisting of

- a database with neonatal characteristics, including pain diagnoses, pain scores and pain medication;
- longitudinal follow-up op NICU graduates with respect to pain during childhood, adolescence and early adulthood.

Part II. Treatment of Neonatal Pain: Paracetamol Pharmacokinetics

In **Chapter 5** we describe the results of a retrospective, observational study in 9 preterm infants with repeated doses of paracetamol intravenously. In preterm infants that received 15 mg/k 4 times daily we determined plasma serum concentrations because of safety issues. At the time of the study the use of paracetamol intravenously was not generally accepted in infants < 3 months post term and pharmacokinetic data was sparse. We administered paracetamol based on incomplete information in a concept pain protocol. In our cohort of preterm infants with a mean gestational age of 28 weeks no toxic plasma serum concentrations were found. The serum concentrations we found were in line with results from a study that was published in the same timeframe.[9] We found no signs of liver toxicity. Pain scores were in the normal range, as measured with the validated Premature Infant Pain Profile, version 1.[10,11] Based on these results we next designed a true pharmacokinetic study. In preterm infants with a gestational age < 32 weeks paracetamol intravenously was given in a dose of 7.5 mg/kg 4 times daily, for a maximum of 5 doses. We describe the results in **Chapter 6.** Again, we found no toxic serum concentrations and no signs of liver toxicity. We did find a very predictable pharmacokinetic profile. Serum concentrations were median 10 mg/L (interquartile range 7 - 13 mg/L). Analysis of glutathione showed non-significant differences in serum values at the start and end of the study period. This suggests a capacity of the preterm infant to synthesize glutathione or to have sufficient glutathione storage. It may also suggest that in extreme preterm infants paracetamol is predominantly metabolized by glucuronidation and sulfation, and only in part by the CYP450 system. However, we did not look at serum levels of the highly toxic metabolite NAPQI that is formed through the CYP450 system. We were not able to demonstrate a dose-effect relationship, possibly due to the preemptive

character of paracetamol administration in our study and the relatively low dose. Pain scores at the beginning of the study period were, on average, not elevated and escape medication in the form of morphine was not necessary in any of the infants. We concluded that administration of paracetamol intravenously in the given dose for a maximum of 5 doses is safe even in the extreme preterm infant.

Recommendations

Future studies should focus on finding the correct doses for adequate analgesia in pain situations that can be treated with paracetamol. Since dose-effect relationships are not established yet for all available compounds, studies should address the different administration routes of paracetamol: rectally, orally and intravenously. We should identify what types of pain can be treated with paracetamol. This may answer the underlying question whether paracetamol can be the first choice in pain management for pain resulting from vacuum delivery to the prolonged visceral pain that may exist in infants with necrotizing enterocolitis.

Part III. Long Term Consequences of Neonatal Pain

Epidemiologic studies show that neonatal pain is routine in a NICU.[12-14] Long term effects of neonatal pain have been described. An association between decreased white matter and subcortical grey matter has been found, even at school age.[15-17] At 8 and 18 months equivalent age cumulative pain has been shown to have a negative effect on neuromotor outcome.[18] Data on the sequelae of neonatal pain, in particular on pain coping and pain behavior is sparse, and it may be interesting to assess whether adverse effects of neonatal pain are sustained into adolescence. In **Chapters 7** and **8** long term effects of neonatal pain with respect to pain response and pain coping strategy in adolescence are described. We had access to a large population based follow-up database comprising 959 surviving preterm infants with a gestational age < 32 weeks or with a birth weight < 1500 grams, born in 1983 in the Netherlands (POPS-1983). In 1983 neonatal pain was not a main concern. The general opinion among health care providers was that the newborn was not capable of feeling pain. Pain management and pain assessment was not part of routine intensive care.
The POPS-1983 database did not include pain events, therefore we assumed neonatal characteristics such as gestational age, birthweight and neonatal complications such as necrotizing enterocolitis reflected cumulative neonatal pain.
Part of an extensive follow-up program at the age of 19 years was a questionnaire that provides insight in how these ex-preterm infants cope with pain in adolescence. An experimental pain test, the Cold Pressor Task, was also included in the follow-up program. Participants were asked to submerge a hand in ice water for a maximum of 3 minutes. Using this ethically accepted research method we were able to examine data concerning pain threshold, pain tolerance and pain intensity.
We describe the results of the analysis regarding pain coping strategy in **Chapter 7**.

In general, early neonatal characteristics such as gestational age, birthweight, or complications in very preterm or low birth weight infants such as necrotizing enterocolitis have limited effect on pain coping style in adolescence. However, higher IQ is associated with the use of adaptive coping style, while maladaptive coping strategies were used less. With the exception of intraventricular hemorrhage we did not find an association between estimates of disease severity, possibly reflective of cumulative neonatal pain, and pain coping style. Gestational age and birth weight were also not associated with altered pain coping strategies. In **Chapter 8** we describe the results from the cold pressor task. Adolescent females and those who had suffered from necrotizing enterocolitis were prone to early withdrawal from ice water, reflecting lower tolerance to experimental pain. Adolescents who made more use of maladaptive pain coping strategies also had lower pain tolerance. So, necrotizing enterocolitis was the only neonatal variable we identified to have an effect on experimental pain in adolescence, while factors later in life such as pain coping strategy also modulated response to experimental pain. The results of our longitudinal follow-up studies may be biased, for instance by selection of NICU graduates with a relatively favorable outcome (adolescents with a cognitive impairment may, in follow-up programs, be less likely to complete questionnaires and IQ testing). Furthermore our studies did not include healthy age-matched controls. Bias may further have been introduced by using surrogates of neonatal pain, such as presence or absence of neonatal morbidity associated with painful interventions. However, we speculate that in early life biological and medical factors may moderate behavioral pain and stress response, while in later life intelligence, in addition to psychological, social and environmental factors modulate children's pain coping style.

Recommendations

Our results suggest that adequate analgesia in newborns with necrotizing enterocolitis is important. Adequate treatment implies the availability of pain measures with sufficient sensitivity and specificity. Future research should be directed at development of pain measures that accurately assesses pain, acute, repeated as well as chronic.
The bias that may have influenced our results may be addressed by detailed recording of neonatal data as mentioned in the recommendations following part I of this thesis in a new cohort of (extremely) preterm infants and age matched controls. These data may provide the opportunity to confirm or reject an association between neonatal pain and altered pain response or pain coping strategy in later life.

Neonatal Pain: Out of Sight, Out of Mind?

In the Introduction and Outline, Hippocrates was presented as one of the ancient authors that described infant pain. Remarkably he also wrote:

"those who are used to endure pain, even if weaker and older, cope with it better than the young and strong ones, who are not used to it".[19]

If Hippocrates was right, neonatal pain should result in adequate pain coping style later in life. Maybe Hippocrates was wrong in the 4th century BC. Necrotizing enterocolitis may be associated with persistent visceral pain, and our observation that ex-preterms who suffered from this neonatal complication have lower tolerance to experimental pain suggests that long term effects of neonatal pain may extend into adolescence. In contrast, our results suggest pain coping style in adolescence is not moderated by early pain, which is in accordance with Hippocrates' statement.

Our two studies from part III of this thesis fit a hypothetical model we propose here **(Figure 1)**. This model represents the effects of neonatal pain in time.

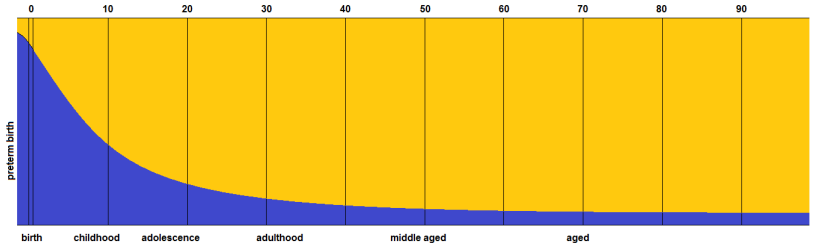


Figure 1: *hypothesis describing the association between neonatal pain experience and long term effects of neonatal pain in time. The blue curve represents the impact of long term effects of neonatal pain as time progresses. The yellow curve depicts the impact of factors such as socio-economic status, intelligence, but also pain experience later in life on subsequent pain behavior and pain coping.*

The observations that neonatal pain has long term effects in early childhood and at school age fit the model.[15-18] The importance of neonatal pain may decrease with increasing age (Out of Sight, Out of Mind?). Factors in later life, such as socio-economic status, intelligence and experiences with pain may gain importance. In this thesis we showed that IQ, as an approximate of intelligence, modulates pain coping style. In addition, pain coping style modulates pain response. Both findings fit the model, but a causal relationship between neonatal pain and long term effects on pain response and pain coping cannot be established based on our studies.

Neonatal Pain: Should we Mind?

Our hypothetical model does not imply that we should not care. First, from a humane point of view, pain that goes untreated is unacceptable. Second, if not for its long term effects, pain should be adequately managed for its detrimental short term effects, such as a worse postoperative outcome.[20] Third, we showed that ex-preterm adolescents who suffered from necrotizing enterocolitis have decreased pain tolerance. Therefore, research efforts should aim at adequate diagnosis and treatment of neonatal pain. In order to show an association (and therefore confirm or reject our hypothetical model) between neonatal pain and long term outcome we advocate the consequent and detailed documentation of painful interventions and diseases, pharmacological and non-pharmacological interventions and pain scores. These data may be useful in analysis of follow-up data. Follow up data should focus on psychological and social aspects of pain in later life. It may be more important to know how (young) children, adolescents and adults born preterm deal with pain in daily life than focus on results of experimental pain that may be statistically interesting, but provide data that on a clinical point of view may be of limited value.

For full references see Chapter 10

Chapter 10

Samenvatting en discussie

In dit proefschrift werden drie aspecten van pijn bij pasgeborenen bestudeerd:

1. de concepten 'acute-' en 'procedure-gerelateerde pijn' zijn beschreven, maar het onderscheid met het concept 'chronische pijn' is niet goed onderzocht;
2. de behandeling van pijn bij pasgeborenen kan belangrijk zijn om korte termijn en lange termijn gevolgen van pijn te voorkomen;
3. gevolgen van neonatale pijn voor de lange termijn zijn ten dele bestudeerd, maar wetenschappelijk onderzoek naar de effecten van neonatale pijn op de adolescentie is beperkt verricht.

In dit tiende hoofdstuk beschrijven we de belangrijkste bevindingen uit dit proefschrift.

Deel I. Het concept 'Chronische Pijn bij Pasgeborenen'

In de **Hoofdstukken 2, 3** en **4** beschrijven we de ontwikkeling van het concept 'Chronische Pijn bij Pasgeborenen'. **Hoofdstuk 2** belicht de moeilijkheden bij het kiezen van een geschikte onderzoeksmethode die gericht is op het beschrijven van een onbekend fenomeen. We hebben de sterke en zwakke punten van drie onderzoeksmethoden bestudeerd.
De Nominale Groep Techniek (NGT), gekenmerkt door consensusbijeenkomsten van een groep experts, heeft als belangrijk voordeel dat de onderzoeksvragen diepgaand kunnen worden besproken. Nadeel is dat experts elkaar gedurende deze bijeenkomsten kunnen beïnvloeden op basis van veronderstelde inhoudelijke autoriteit op het onderzoeksgebied. Daarnaast is het een relatief dure onderzoeksmethode, zeker als de onderzoeksvragen internationale of multiculturele inbreng vergt. De Consensus Development Conference (CDC) is te beschouwen als een uitgebreide versie van de NGT met dezelfde voor- en nadelen. Vanwege de status van de CDC kunnen deelnemers zich bovendien onder druk gezet voelen om een resultaat te leveren, wat de validiteit van de methode kan beïnvloeden. De Delphi techniek is een (relatief goedkope) onderzoeksmethode die zich kenmerkt door anonimiteit, flexibiliteit en heterogeniciteit. Als de methode online wordt toegepast is een wereldwijd publiek makkelijk bereikbaar. Een belangrijk nadeel van de Delphi methode is het afvallen van experts tussen de diverse onderzoeksronden. Het verlies aan experts is soms substantieel en kan de validiteit van de methode nadelig beïnvloeden.
Na analyse van de voor- en nadelen van deze drie onderzoeksmethoden is gekozen voor de Delphi methodiek. We bespreken de resultaten van de Delphi studie in **Hoofdstuk 3**. De Delphi studie omvatte drie onderzoekronden. In de eerste ronde werd aan experts gevraagd antwoord te geven op drie open vragen over de definitie, oorzaken en symptomen van chronische pijn bij pasgeborenen. De onderzoeker categoriseerde de gegeven antwoorden in 437 stellingen. In de tweede ronde werd aan de experts gevraagd op een 5-punts Likert schaal een waardering ('eens' – 'niet eens') te geven aan de stellingen. Stellingen met de hoogste mate van consensus werden vervolgens wederom aan de experts gepresenteerd met de vraag om op basis van het groepsgemiddelde en de eigen eerste waardering een herwaardering te

geven. Consensus werd bereikt over 23 stellingen, en met behulp van deze stellingen werd een beschrijving van het concept 'chronische pijn bij pasgeborenen' gegeven. Oorzakelijke factoren werden geïdentificeerd, waarvan inadequate pijnbehandeling de belangrijkste is, omdat alle pasgeborenen met pijn risico lopen niet goed behandeld te worden.[1] Dit risico wordt bevestigd door een recente studie waarin wordt aangetoond dat het geven van analgesie in Europese NICU's hoogst variabel is, en structurele pijnmeting wordt verricht in slechts 30-58% van de gevallen, afhankelijk van de wijze van ademhalingsondersteuning.[2]

Er werd in onze Delphi studie geen consensus bereikt over specifieke symptomen van chronische pijn. Dat was niet verrassend omdat er in de afgelopen tientallen jaren geen pijnmeetinstrument is ontwikkeld met afdoende sensitiviteit en specificiteit.[1] Recent is de vraag gesteld of de bestaande pijnmeetinstrumenten pijnbeleving meten of alleen pijngedrag.[3] Er zijn meer problemen met pijnmeting, vooral als gevolg van het ontbreken van een 'gouden standaard'. De bruikbaarheid van bestaande pijnmeetinstrumenten voor het meten van acute, langduriger of chronische pijn is nog steeds niet bewezen.[4] Dat heeft vooral te maken met het gegeven dat pasgeborenen soms te ziek zijn om symptomen van stress of pijn te tonen.[4] Sommige wetenschappers pleiten voor het gebruik van video-observaties en autonome verschijnselen (veranderingen in hartslag, bloeddruk), geïntegreerd met nieuwe technieken als Near Infrared Spectroscopy (NIRS), amplitude geïntegreerde elektro-encefalografie (aEEG) en het meten van veranderingen in huidgeleiding.[5] Deze technieken zijn echter nog niet goed gevalideerd, en de klinische toepassing in de dagelijks praktijk wordt wellicht beperkt door het invasieve karakter van deze technieken. Integratie van deze technieken zou echter in een onderzoeksetting kunnen bijdragen aan de ontwikkeling van een gevalideerd en klinisch bruikbaar pijnmeetinstrument.

In **Hoofdstuk 2** werd het ontbreken van een definitie van 'consensus' geïdentificeerd als één van de nadelen van de drie onderzoeksmethoden. In eerder gepubliceerde Delphi studies worden verschillende (of geen) definities van consensus gehanteerd.[6] Echter, in theorie is er altijd een probleem met consensus, zelfs als de experts 100% overeenstemming bereiken. Het is bijvoorbeeld lastig 'expertise' te definiëren, en 'consensus' is niet per definitie hetzelfde als 'de waarheid'. Een probleem met consensusstudies die Likert-schalen gebruiken is de onmogelijkheid om een waarde te kiezen tussen de vaste waarden op de schaal. De onmogelijkheid om dat te doen hangt samen met nauwkeurigheid en onzekerheid tussen en in experts. Een voorbeeld is het moeten kiezen tussen linguïstische termen die in Likert-schalen worden gebruikt, zoals 'totaal mee eens' of 'oneens'.[7] Deze problematiek werd onderzocht met behulp van een onderzoeksgroep van de Universitat Politècnica de Catalunya in Barcelona, Spanje. Deze groep ontwikkelde een mathematisch model wat behulpzaam kan zijn in consensusstudies.[8] We beschrijven de toepassing van dat mathematisch model op onze onderzoeksresultaten uit de Delphi studie in **Hoofdstuk 4**. Het doel van deze studie was het valideren van de resultaten uit hoofdstuk 3 met het mathematisch model, niet om chronische pijn te definiëren.

Het mathematisch model omvat wiskundige algoritmen die rekening houden met denkprocessen van experts. Het model corrigeert voor onzekerheden, bijvoorbeeld

tijdens het kiezen van een linguïstische term, en berekent graden van consensus in iedere ronde. Voorts corrigeert het model voor de onmogelijkheid voor experts om de mate van zekerheid in het kiezen te melden. Een voorbeeld: een expert kan zich zeer zeker voelen in de keuze voor 'mee eens' voor item x, maar kan onzeker zijn in de keuze tussen 'mee eens' en 'totaal mee eens' voor item y.
Het mathematisch model werd toegepast op de stellingen in de categorie 'definitie' uit het concept 'chronische pijn'. Voor sommige items waarover geen consensus werd bereikt met de gebruikelijke statistische methoden, kon wel consensus worden bereikt met de mathematische methode. Een vergelijking tussen de conventionele statistiek uit **Hoofdstuk 4** en het nieuwe mathematische model toonde hetzelfde resultaat in 68% van de stellingen. De vraag blijft echter welke methode nu het meest geschikt is, wellicht inherent aan het gegeven dat 'consensus' niet persé gelijk is aan 'de waarheid'.

Aanbevelingen

Vervolgonderzoek zou zich kunnen richten op verdere validatie van de Delphi methode, zeker met betrekking tot de definitie en de analyse van het begrip 'consensus'. Ook het nieuwe mathematische model moet verder worden gevalideerd. Met betrekking tot de conceptomschrijving van 'chronische pijn bij pasgeborenen' zal het lastig zijn onze bevindingen te bevestigen of weerleggen. Er zijn tot op heden geen accurate meetinstrumenten voor chronische pijn, en de identificatie van pasgeborenen die een hoog risico hebben op het ontwikkelen van chronische pijn is lastig. De neonatale follow-up heeft zich nooit structureel gericht op de prevalentie van langdurige of chronische pijn bij ex-NICU patiënten. We pleiten voor de ontwikkeling en implementatie van een gedetailleerd follow-up programma met:

- een database met neonatale karakteristieken, zoals pijndiagnoses, pijnscores en pijnmedicatie;
- longitudinale follow-up van NICU patiënten met aandacht voor pijn tijdens de kinderjaren, de adolescentie en vroege volwassenheid.

Deel II. Behandeling van Pijn bij Pasgeborenen: Farmacokinetiek van Paracetamol.

In **Hoofdstuk 5** beschrijven we de resultaten van een retrospectieve, observationele studie in 9 prematuur geboren kinderen met herhaalde doseringen paracetamol intraveneus. Bij premature kinderen die 4 maal daags 15 mg/kg paracetamol intraveneus kregen bepaalden we vanwege veiligheidsaspecten serumconcentraties. Tijdens de studieperiode was de toepassing van paracetamol intraveneus niet gebruikelijk bij kinderen met een gecorrigeerde leeftijd < 3 maanden, en er waren slechts beperkte farmacokinetische gegevens beschikbaar. Het geven van paracetamol was gebaseerd op incomplete informatie die ons bereikte gedurende de ontwikkeling van een pijnprotocol. In ons cohort prematuur geboren kinderen met een gemiddelde zwangerschapsduur van 28 weken vonden wij geen toxische serumconcentraties. De serumconcentraties die we vonden kwamen overeen met de waarden die in een studie uit diezelfde tijd werden gepresenteerd.[9] We zagen geen tekenen van levertoxiciteit. De pijnscores, gemeten met de Premature Infant Pain Profile, versie 1[10,11], waren normaal. Na deze studie volgde een farmacokinetische studie. We gaven maximaal 5 doses van 7.5 mg/kg paracetamol intraveneus, 4 maal daags, aan prematuur geboren kinderen met een zwangerschapsduur < 32 weken. De resultaten van deze studie worden beschreven in **Hoofdstuk 6**. Wederom vonden we geen toxische serumconcentraties, en geen tekenen van levertoxiciteit. De paracetamolgiften resulteerden in een voorspelbaar farmacokinetisch profiel. Serumconcentraties waren mediaan 10 mg/L (interkwartielafstand 7-13 mg/L). De analyse van glutathion toonde niet-significante verschillen in serumconcentraties bij begin en einde van de behandeling met paracetamol. Deze bevinding suggereert een capaciteit van de extreem prematuur geborene om glutathion te synthetiseren, dan wel een afdoende voorraad glutathion. De resultaten suggereren ook dat bij extreem prematuur geborenen paracetamol vooral gemetaboliseerd wordt door glucuronidering en sulfatidering, en slechts ten dele door het CYP450 systeem. We hebben echter geen data van de door het CYP450 systeem gevormde toxische metaboliet NAPQI verzameld. We waren niet in staat een dosis-effect relatie aan te tonen, mogelijk door het laagdrempelig gebruik van paracetamol in onze studiepopulatie en de relatief lage dosering. De pijnscores aan het begin van de studie waren voor alle prematuren, gemiddeld, niet verhoogd en er was geen noodzaak om in één van de gevallen morfine te starten in verband met hoge pijnscores. We concludeerden dat het geven van 5 doses paracetamol intraveneus zelfs voor extreem prematuur geboren kinderen veilig is.

Aanbevelingen

Verder onderzoek moet aantonen welke dosering paracetamol effectief is voor de verschillende indicaties. Omdat de dosis-effect relatie onbekend is voor alle vormen van paracetamol moet er gekeken worden naar zowel paracetamol oraal, rectaal als intraveneus. Vormen van pijn die adequaat met paracetamol kunnen worden behandeld moeten worden geïdentificeerd. Daarmee zou een antwoord kunnen worden gegeven op de onderliggende vraag of paracetamol effectief is voor pijn

geassocieerd met een vacuümextractie, tot de langdurige viscerale pijn die wordt geassocieerd met necrotiserende enterocolitis.

Deel III. Lange termijn gevolgen van Pijn bij Pasgeborenen

Epidemiologische studies hebben aangetoond dat pijn bij op een NICU opgenomen pasgeborenen dagelijkse routine is.[12-14] Lange termijn effecten van pijn bij pasgeborenen zijn beschreven. Zo is er een associatie met afname van witte- en subcorticale grijze stof, zelfs tot op schoolleeftijd.[15-17] Op de gecorrigeerde leeftijd van 8 en 18 maanden heeft cumulatieve neonatale pijn een negatief effect op de neuromotore ontwikkeling.[18] Er is echter weinig bekend over de effecten van neonatale pijn in de adolescentie. In de **Hoofdstukken 7** en **8** worden de lange termijn gevolgen van neonatale pijn op het gebied van pijnrespons en pijn coping strategieën beschreven. We hadden de beschikking over onderzoeksgegevens van de follow-up van 959 premature kinderen met een zwangerschapstermijn < 32 weken of een geboortegewicht < 1500 gram, geboren in 1983 in Nederland (POPS-1983 cohort). In 1983 was de heersende overtuiging dat pasgeborenen geen pijn voelden. Het diagnosticeren en behandelen van pijn behoorde niet tot de routinematige zorg. De POPS-1983 database bevat helaas geen gegevens over het aantal pijnlijke momenten, en pijnscores zijn niet beschikbaar.
Onderdeel van het uitgebreide follow-up programma op de leeftijd van 19 jaar was een enquête die inzicht gaf in de manier waarop ex-premature adolescenten omgaan met pijn. Ook een test om experimentele pijn op te wekken, de zogeheten Cold Pressor Test, maakte deel uit van het programma. Voor deze test werd aan deelnemers gevraagd een hand gedurende 3 minuten in ijswater onder te dompelen. Met behulp van deze (ethisch toegelaten) test werden data verkregen over pijndrempel, pijntolerantie en pijnintensiteit. We beschrijven de resultaten van de analyse met betrekking tot pijn coping strategieën in **Hoofdstuk 7**.

Over het algemeen hebben zwangerschapsduur, geboortegewicht en neonatale complicaties zoals necrotiserende enterocolitis bij ex prematuren < 32 weken of een geboortegewicht < 1500 gram nauwelijks effect op pijn coping stijl in de adolescentie. Met toename van intelligentie (IQ) worden adaptieve coping strategieën vaker gebruikt, en mal-adaptieve coping strategieën minder vaak. Met uitzondering van intraventriculaire bloedingen hebben wij geen associatie gevonden tussen neonatale complicaties en pijn coping strategieën. Ook zwangerschapsduur en geboortegewicht beïnvloedden in onze cohort de pijn coping stijl in de adolescentie niet.

In **Hoofdstuk 8** beschrijven we de resultaten van de cold pressor task. Ex-premature vrouwen en ex-prematuren met necrotiserende enterocolitis hadden een lagere pijntolerantie, zich uitend in vroeg terugtrekken uit koud water. Een lagere pijntolerantie was ook geassocieerd met gebruik van mal-adaptieve coping strategieën. Necrotiserende enterocolitis is daarmee de enige neonatale variabele die van invloed is op de reactie op experimentele pijnprikkels in de adolescentie.
De resultaten van onze follow-up studies kunnen zijn vertekend, bijvoorbeeld

door de selectie van ex-prematuren met een relatief gunstige ontwikkeling (ex-premature adolescenten met een cognitieve ontwikkelingsachterstand kunnen bijvoorbeeld minder goed in staat zijn mee te werken aan enquêtes en IQ tests, of zelfs niet meewerken aan dergelijke tests). Ook hadden wij niet de beschikking over een controlegroep. De resultaten kunnen verder zijn beïnvloed door het gebruik van afgeleiden van neonatale pijn, zoals de aan- en afwezigheid van neonatale complicaties die gepaard gaan met pijnlijke interventies. Ondanks deze beperkingen aan de studies speculeren we dat neonatale karakteristieken zoals zwangerschapsduur, geboortegewicht, opnameduur en neonatale complicaties zoals intraventriculaire bloedingen en sepsis bij prematuren < 32 weken of < 1500 gram weinig invloed hebben op pijn coping stijl, pijndrempel en pijntolerantie in de adolescentie. Necrotiserende enterocolitis zou hier wel effect op kunnen hebben. Factoren later in het leven, zoals IQ, hebben wel invloed op pijn coping strategieën, pijndrempel en pijntolerantie.

Aanbevelingen

Onze resultaten tonen het belang aan van goede pijnbestrijding bij pasgeborenen met necrotiserende enterocolitis. Uiteraard kan dat alleen met goede pijnmeetinstrumenten. Vervolgonderzoek moet gericht zijn op de ontwikkeling van een meetinstrument voor langduriger (wellicht chronische) pijn. Zoals in de aanbeveling van deel I beschreven kan het gedetailleerd vastleggen van data voor follow-up doeleinden inzicht geven in de mogelijke associatie tussen neonatale pijn en de betekenis van pijn voor het individu op latere leeftijd.

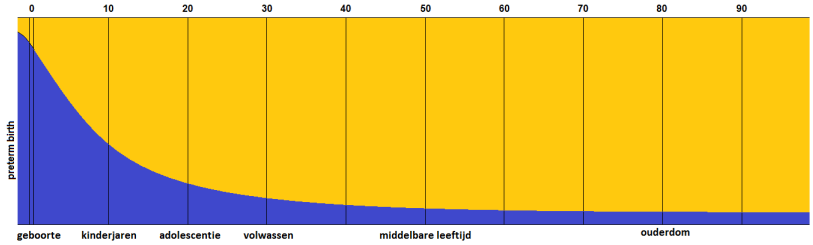
Pijn bij pasgeborenen. Uit het oog, uit het hart?

In de introductie van dit proefschrift werd Hippocrates gepresenteerd als één van de auteurs uit de klassieke oudheid die pijn bij kinderen beschreef. Daarnaast schreef hij:

"zij die gewend zijn aan het doorstaan van pijn, zelfs als zij zwakker en ouder zijn, gaan beter met pijn om dan zij die jong en sterk, en er niet aan gewend zijn".[19]

Als Hippocrates gelijk had, zou neonatale pijn moeten resulteren in adequate pijn coping strategieën op latere leeftijd. Onze bevindingen suggereren dat gebeurtenissen in de neonatale periode, zoals sepsis, opnameduur en kunstmatige ademhalingsondersteuning slechts beperkt van invloed zijn op pijnrespons en pijn coping strategieën later in het leven. Een vergelijking met gezonde a terme zuigelingen op de leeftijd van 13-18 jaar laat zien dat ex-prematuren minder mal-adaptieve pijn coping strategieën gebruiken, wat past in de stelling van Hippocrates.

De resultaten van de twee studies uit deel III uit dit proefschrift passen in een hypothetisch model (**Figuur 1**), wat de gevolgen van neonatale pijn in de tijd representeert.



***Figuur 1**. hypothetisch model met de associatie tussen neonatale pijn en lange termijn effecten daarvan in de tijd. De blauwe curve representeert de gevolgen van neonatale pijn op de lange termijn in de tijd. De gele curve representeert de gevolgen op de betekenis van pijn in het dagelijks leven van factoren als socio-economische status, intelligentie, maar ook pijnervaringen later in het leven.*

In ons model passen de aanwijzingen dat pijn en pijnervaringen vroeg in het leven 'lange' termijn effecten hebben.[15-18] Het belang van die vroege pijn zou in de loop der jaren af kunnen nemen ('uit het oog, uit het hart'). De betekenis van factoren die later in het leven een rol spelen, zoals socio-economische status, intelligentie en latere pijnervaringen, neemt daarentegen volgens dit model toe. In dit proefschrift tonen we aan dat intelligentie pijn coping strategie beïnvloed. Pijn coping strategieën beïnvloeden op hun beurt de pijnrespons. Deze observaties passen in ons model, echter een causaal verband tussen cumulatieve neonatale pijn en het verminderd vermogen om adaptieve coping strategieën te gebruiken kan op basis van onze studies niet worden vastgesteld.

Aandacht voor pijn bij pasgeborenen: is het werkelijk zo belangrijk?

Ons model impliceert niet dat we geen aandacht voor neonatale pijn hoeven te hebben. Ten eerste is onbehandelde pijn inhumaan. Ten tweede dient pijn behandeld te worden ter voorkoming van ernstige korte termijn effecten, zoals een slechtere postoperatieve uitkomst.[20] Ten derde toonden we aan dat ex-prematuren die een necrotiserende enterocolitis hebben doorgemaakt een lagere pijntolerantie hebben. Om die redenen moet onderzoek naar de diagnostiek en behandeling van pijn doorgang vinden. Om een werkelijke associatie te kunnen aantonen tussen neonatale pijn en lange termijn gevolgen van die pijn moeten we, zoals eerder in de aanbevelingen verwoord, pijnlijke interventies en aandoeningen, farmacologische en non-farmacologische interventies en pijnscores vastleggen. Deze data kan bruikbaar zijn voor de lange termijn follow-up. Die follow-up moet gericht zijn op de betekenis van pijn voor het dagelijks functioneren. Het zou van groter belang kunnen zijn om te weten hoe ex-premature kinderen, adolescenten en volwassenen met pijn in het

dagelijks leven omgaan, dan om ons te richten op de resultaten van experimentele pijn die weliswaar statistisch interessant kunnen zijn, maar beperkte waarde hebben voor de kliniek.

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Chapter 11

Appendix: Valorization

Appendix: Valorization

1. Relevance to affected patients and their families

The relevance of this thesis on pain management in neonates is best expressed by the Declaration of Montréal, developed by the International Association for the Study of Pain in the year 2010. This Declaration focuses on three issues[1]:

1. The right of all people to have access to pain management without discrimination.

2. The right of people in pain to acknowledgment of their pain and to be informed about how it can be assessed and managed.

3. The right of all people with pain to have access to appropriate assessment and treatment of the pain by adequately trained health care professionals.

Second, in a recent Delphi survey European NICU nurses identified pain and distress as having highest research priorities, indicating insufficient tools to manage neonatal pain in daily practice.[2] In this thesis we addressed these research priorities as well as the Declaration of Montréal.

Part I of this thesis showed chronic pain may exist in the neonate. In our Delphi study consensus was reached on a statement that inadequate pain management may be a risk factor for the development of chronic pain syndromes.[3] Pain in the neonate is routine. Epidemiologic studies consistently show that neonates admitted to an intensive care are subjected to 11-14 painful interventions on average every day.[4-6] A recent survey showed wide variations in pain management and pain assessment in European NICU's exist.[7] This may point to a relevant health care problem, since 15 million babies are born preterm (<37 weeks) worldwide every year.[8] Preterm born infants, accounting for 11.1% of all live births annually[8], frequently require high- or intensive care. If chronic pain in the neonate does exist, at least part of these 15 million preterm babies may be at risk. Since we have shown in an expert panel that there are no objective measures to diagnose chronic pain, this potential problem may even go unnoticed.

Part II of this thesis showed that repeated administration of paracetamol intravenously resulted in a very predictable pharmacokinetic profile in the extreme preterm infant. Furthermore, in our cohort we found no increased liver enzymes and no depletion of glutathione. To date, in literature no short term side effects of paracetamol have been reported when adequately dosed and administered.[9] Opioids have known side effects such as hypotension, decreased intestinal motility and apnea. Clinicians may be reluctant to use opioids due to concerns about these short term effects as well as long term impact on neurodevelopment.[10] Therefore, our results are relevant

such that paracetamol may be an attractive alternative for opioids when systemic analgesia is indicated. The need for identification of non opioid analgesic alternatives has been stressed before.[10] However, dose effect relationships for paracetamol have not yet been established. Types of pain or pain diagnoses for which paracetamol is the most effective treatment option have to be identified.

In part III, we have shown that in the POPS-19 cohort, with the exception of necrotizing enterocolitis, neonatal variables such as gestational age, birth weight, length of stay and sepsis in ex-preterm infants did not modulate experimental pain response or pain coping strategy in adolescence. This might be considered 'good news', however, our findings result from data analyses concerning a cohort born in 1983. Since that time era much has changed in neonatology. The boundaries of viability have shifted significantly after the successful introduction of antenatal corticosteroids and postnatal surfactant administration for respiratory distress syndrome. In the Netherlands, preterm infants born after 23-24 weeks gestation are treated nowadays. The youngest infant in our cohort was 25 weeks, and the total number of infants born with a gestational age < 26 weeks was [11]. In contrast, during a period ranging from 1 October 2010 – 1 October 2011 a total of 105 preterm infants with a gestational age of 25 weeks up to 25 weeks and 6 days were admitted to the Dutch NICU's.[11] Furthermore, 80 preterm infants of 24-25 weeks and 7 infants with a gestational age from 23-24 weeks were admitted.[11] These numbers show an almost 18 fold increase in extremely preterm infants that are subjected to intensive care, hence to painful procedures.
On the other hand, pain management has changed from virtually nothing in 1983 to pain assessment on a daily basis and the use of analgesics in infants with high pain scores or predefined pain diagnosis. If a study such as POPS were to be repeated in current time, results may be different. However, a large follow up study such as POPS is difficult and expensive to repeat. A follow up study with respect to pain may be more cost efficient. We suggest detailed digital registration of pain diagnoses, pain medication and pain scores from the neonatal period. Follow up at regular intervals up to primary school age should include items referring to pain, such as pain coping strategy, the use of analgesics and prevalence of all types of pain beyond the neonatal period. With the help of these detailed data, we may provide the opportunity to assess more in detail the possible association between neonatal pain and long term sequelae, especially in the (extreme) preterm infant.

2. Innovation

Our study on chronic pain emphasizes the need for adequate pain treatment and therefore pain assessment. The results from our expert panel suggest that to date there is no pain scale that can measure chronic pain with sufficient sensitivity and specificity. In fact, recently it was suggested that the behavioral changes that are used with current acute pain assessment tools are consistent with brainstem reflexes, not pain experience.[12] Researchers have advocated the use of integrated

measures, such as near infrared spectroscopy (NIRS), amplitude integrated electroencephalography (aEEG) and Skin Conductance measurements in conjunction with video observations and measurement of autonomic response.[12,13] Modern innovations such as unobtrusive monitoring techniques may provide opportunities for such an integration. Non invasive ECG monitoring techniques already exist.[14] Preterm infants with respiratory support often wear caps for fixation of respiratory support devices. It is a challenge to integrate NIRS and aEEG sensors in these caps while at the same time not interfering with the comfort of these infants. Automated facial detection is being developed and has shown to have 85% sensitivity and 100% specificity in resting state, while showing 100% sensitivity and specificity during painful procedures.[15] Inter-'observer' reliability between trained observers using a validated pain measure and an automated system showed a Cohen's kappa of 0.975, indicating excellent agreement.[15] An experimental version of a sock with which changes in skin conduction as a proxy for stress can be detected was developed in recent years by students of the Technical University in Eindhoven, The Netherlands. This sock, however, has not yet found its way in scientific studies. All these innovations may provide the means for non invasive, integrated measurement of signs of pain and stress.

However, the main concern may be that these methods of detecting pain only reflect part of the pain experience. Structures deep inside the brain, such as the thalamic nuclei and the limbic system, play an important role in the emotional attributes of pain.[16] NIRS and aEEG are not capable of measuring changes in cerebral oxygenation or electroencephalographic changes deep inside the brain, respectively. We do not know how well developed these structures are in the preterm infant, and if aspects such as underdeveloped myelinization in the preterm infant contribute to altered pain experience. Studies investigating the feasibility of functional Magnetic Resonance Imaging (fMRI) to detect pain signal processing in term neonates show both similarities and differences compared to adult signal processing.[17] Therefore, fMRI seems promising in detecting signal processing in deeper brain structures even in neonates. However, results are partly influenced by the sedation often needed with neonatal MRI studies.[17] On an experimental basis, integration of fMRI, aEEG, NIRS and Skin Conductance measurements may provide insight in activation of brain regions responsible for pain experience in neonates and preterm infants. This integration may further our understanding of the associations between pain behavior and emotional aspects of neonatal pain.

Software development of Electronic Patient Data Management Systems (ePDMS) should provide easy recording and analysis of pain associated events. Pain diagnoses, pain assessment scores and pain medication are available in PDMS, but these data are not integrated. For research purposes a PDMS should have the possibility to easy access these data and export them for further offline analysis. These data can be used in follow up programs to assess possible associations between neonatal pain and altered pain response, pain behavior or even increased or decreased use of Health Care resources related to pain. In the Netherlands perinatal data is being recorded by the 'Stichting Perinatale Registratie Nederland' or 'Dutch Foundation for

Perinatal Registration'. These data are predominantly being used for epidemiologic analysis, but, when extended with data on neonatal pain, could provide the necessary demographic and clinical data that are needed for research on long term effects of neonatal pain.
Follow up programs in the 10 Dutch NICU's vary, but all programs provide physical examination, psychological evaluation and physiotherapy. The follow up program is aimed at early detection of neurodevelopmental and motor developmental problems in NICU graduates. This program provides an excellent opportunity to gain insight in pain related problems at different points in time. These problems may comprise pain related complaints such as tummy pain, headache, increased or decreased pain sensitivity, use of pain medication, absence from school due to pain, and the use of adaptive or maladaptive pain coping styles. The follow up program may, in the future, be useful to help parents understand pain related problems of NICU graduates later in life, and cope with them.

3. Ultimate goal and a road map

In summary, the ultimate goal of pain research in neonates is to provide a) the means to detect pain behavior and pain experience accurately, and b) to treat pain adequately without short- and long term side effects.
In order to achieve these goals we first need to determine what signs & symptoms best reflect neonatal pain. In the innovation paragraph we highlighted possibilities to investigate signs and symptoms that reflect pain experience, rather than pain behavior. Based on these sort of data we can evaluate existing pain assessment tools or develop a feasible pain assessment tool for daily practice, in order to detect the different types of pain (acute/procedural, chronic, visceral, neuropathic and so on). In the ideal world, such a pain tool would measure continuously, simply because (preterm) neonates cannot verbally indicate they are in pain at any given point in time, or maybe to sick to give any signal at all. This calls for an automated process. Since we are still at the beginning of our understanding of true pain experience in neonates, it may well take years (if not decades) before such a process has been developed.
Pain management should be based on accurate pain measurement. It should comprise both safe and effective pharmacologic as well as non-pharmacologic therapy. While we have shown that repeated doses of paracetamol intravenously has no effect on glutathione levels or liver enzymes, we did not investigate long term adverse effects. A recent review summarized the available evidence concerning long term safety of paracetamol administration during pregnancy and early childhood. While animal studies suggest paracetamol to have adverse effects on neurodevelopment, long term follow up studies in humans only show (at best) a moderate effect in prevalence of attention deficit and hyperactivity disorders that may be explained by confounding.[18] However, a prospective clinical study combining pharmacodynamic attributes of paracetamol and long term follow up is needed. This study, again, would fit in the long term follow up programs in use today in The Netherlands. Such a study

could easily comprise other pharmacologic and non pharmacologic therapeutic options such as opioids, sucrose, facilitated tucking and kangaroo care. The effects of these therapeutic options on the developing infant has to be evaluated as part of long term follow up. We therefore advocate the development of a digital database comprising of neonatal data with respect to pain assessment and pain management, and the integration of pain related follow up data in the Dutch follow up program. This database may then provide the opportunity to answer the question whether pain and treatment of pain has adverse long term effects that cannot be explained by the many confounding factors during the development of an infant.

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Publications and presentations

Publications (chronologic order)

1. Tjeertes IF, Bastiaans DE, van Ganzewinkel CJ, Zegers SH. Neonatal anemia and hydrops fetalis after maternal mycophenolate mofetil use. J Perinatol 2007;27(1):62-4.
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4. Van Ganzewinkel CJ, Anand KJS, Andriessen P, Kramer B. Chronic pain in the newborn: Toward a Definition. The Clinical Journal Of Pain 2014;30(11):970-7.
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7. Agell N, van Ganzewinkel CJ, Sánchez M, Roselló L, Prats F, Andriessen P. A consensus model for Delphi processes with linguistic terms and its application to chronic pain in neonates definition. Applied Soft Computing 2015; 35: 942-948.
8. Van Ganzewinkel CJ, Been J, Dieleman, J; Katgert, T; Boelen-van der Loo, T; Van der Pal, S; van Dijk, M; Kramer B, Andriessen P. Pain Coping Strategies: neonatal intensive care unit survivors in adolescence. Early Human Development 2016;103:27-32

Presentations (chronologic order)

1. Premature Infant Pain Profile (PIPP); research on interobserver variability. Oral presentation. PIC 2000, Montréal.
2. Pijnbeleid, a state of the art. Oral presentation. Zorg voor de pasgeborene 2003, Utrecht.
3. Implementing pain guidelines in the Netherlands. Oral presentation. Europediatrics 2006, Barcelona.
4. Chronic pain in neonates, a Delphi Survey. Poster Europediatrics 2006, Barcelona.
5. Implementatie van pijnbeleid op een NICU. Oral presentation. Venticare 2007, Utrecht.
6. The Dutch National Studygroup for Pain in NICU's (NSPN): results of 14 years of collaboration. Oral presentation. ESPNIC 2007, Geneve.
7. A survey of the Dutch National Studygroup on Pain in NICU's : common habits and policies regarding pain. Poster ESPNIC 2007, Geneve.
8. Paracetamol serum concentrations in preterm infants treated with paracetamol intravenously, a case series of 9. Poster Europediatrics 2008, Nice.

9. Paracetamol serum concentrations in preterm infants treated with paracetamol intravenously, a case series of 9. Oral presentation. UENPS 2008, Rome.
10. Pain and Sedation: The Use of Paracetamol in the NICU. Oral presentation. EAPS 2010, Copenhagen.
11. Paracetamol bij pasgeborenen. Oral presentation. ObNeo 2010, Veldhoven.
12. Chronic pain in the neonate. Oral presentation. ObNeo 2011, Veldhoven.
13. 10 jaar onderzoek door een VS Neonatologie, een chronisch pijndossier? Oral presentation. ANP, 10 jaar cure and care, profileren en anticiperen. Veldhoven 2012.
14. Chronic pain in the newborn, a delphi survey to define the concept. Oral presentation. EAPS 2012 Istanbul.
15. Het orakel van Delphi spreekt: “Chronische pijn bij pasgeborenen bestaat niet.” Oral presentation. Vandaag is de toekomst V&VN VS congress 2012. Arnhem.
16. ‘Van Vliegenpoep en Opium tot Pasgeborenen zonder Pijn’. Oral presentation. Licht op Lucht 2015, ’s Hertogenbosch.

Curriculum vitae

Christ-jan van Ganzewinkel werd geboren op 30 mei 1965 in Gemert, in de provincie Noord-Brabant (Nederland). Hij behaalde zijn HAVO diploma in 1982 aan het Macropedius College te Gemert. Na een jaar de opleiding Verpleegkundige Psychiatrie te hebben gevolgd in Huize Padua (Handel, Noord-Brabant), behaalde Christ-jan in 1988 in het St Willibrordus ziekenhuis te Deurne zijn diploma Verpleegkunde A. Twee jaar later startte hij met de opleiding Intensive Care Neonatologie Verpleegkunde in het Sint Josephziekenhuis te Eindhoven. Na het behalen van het getuigschrift Intensive Care Neonatologie Verpleegkunde in 1991 sloot hij in 1995 zijn 2e graads Lerarenopleiding Verpleegkunde aan de Hogeschool Nijmegen met goed gevolg af. Van 1993 tot 2001 werkte Christ-jan als Senior Verpleegkundige met aandachtspunt verpleegkundige opleidingen op de NICU van het Máxima Medisch Centrum te Veldhoven. In 2003 behaalde Christ-jan zijn Master na het volgen van de opleiding Master in Advanced Nursing Practice aan de Fontys Hogeschool te Eindhoven. Vanaf 2003 werkt hij als Verpleegkundig Specialist Neonatologie op de NICU van het Vrouw-Moeder-Kind Centrum in het Máxima Medisch Centrum. Christ-jan startte zijn onderzoeksactiviteiten in 2003 in het Máxima Medisch Centrum in samenwerking met dr. Peter Andriessen van het MMC en professor dr. Boris Kramer van de Universiteit van Maastricht. In 2012 behaalde hij zijn certificaat Good Clinical Practice.
Christ-jan is getrouwd met Marianne van Erp en woont samen met haar en hun twee kinderen Lisa en Joris in Lieshout.

Christ-jan van Ganzewinkel was born on the 30th of May, 1965 in Gemert, in the province Noord-Brabant (The Netherlands). He graduated from secondary school and attained a HAVO certificate at Macropedius College, Gemert in the year 1982. Following a year of training as a psychiatric nurse at Huize Padua (Handel, Noord Brabant), Christ-jan attained his nursing degree in St Willibrordus Hospital, Deurne in 1988. Two years later he started his training as a Neonatal Intensive Care Nurse in St Joseph Hospital, Eindhoven. After completion of this course in 1991 he started and completed a course Nursing Teacher (2nd degree) at Hogeschool Nijmegen. From 1993 to 2001 he worked as a senior nurse with a special interest in nursing education at Máxima Medical Centre in Veldhoven. In 2003, Christ-jan attained his Masters degree after completion of the Master in Advanced Nursing Practice course at Hogeschool Fontys, Eindhoven. From 2003 he worked as a Neonatal Nurse Practitioner at the Department of Neonatology, Máxima Medical Center in Veldhoven. Christ-jan started his research activities in 2003 in Máxima Medical Center in cooperation with dr. Peter Andriessen from Máxima Medical Center and prof. dr. Boris Kramer from Maastricht University, Maastricht (The Netherlands). In 2012 he attained his Good Clinical Practice certificate.
Christ-jan is married to Marianne van Erp. They live in Lieshout with their children Lisa and Joris.

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