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# NEONATAL STRESS AND PAIN: MUCH TO GAIN

PURSUING COMFORT AMIDST  
PREMATURE STRESS EXPOSURE



Naomi Meesters



# **NEONATAL STRESS AND PAIN: MUCH TO GAIN**

Pursuing comfort amidst premature stress exposure

Naomi J. Meesters

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## **Neonatale stress en pijn: de weg naar verbetering**

Streven naar comfort tijdens vroegtijdige blootstelling aan stress

### **NEONATAL STRESS AND PAIN: MUCH TO GAIN**

Pursuing comfort amidst premature stress exposure

#### **Proefschrift**

ter verkrijging van de graad van doctor aan de  
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# Chapter I



General introduction

## **GENERAL INTRODUCTION**

Until birth, infants in the uterus are mostly protected from the outside world. However, what if, for various and often unknown reasons, an infant is born significantly earlier than expected? The protection from external influences is then prematurely disrupted – and admission to the Neonatal Intensive Care Unit (NICU) is inevitable. Here, infants receive life-saving treatment, but will also face many challenges because this treatment is inseparably linked to repetitive and ongoing painful and stressful interventions and situations. Moreover, the admission is not only stressful for the infant but also for the entire family. As NICU clinicians, we can play a crucial role in protecting these vulnerable infants and their parents from pain and stress. For one thing, these infants rely on us when it comes to recognizing and assessing the levels of pain and stress. But the question is, are we able to accurately determine the level of pain in the vulnerable NICU population? And consequently, what can we do to adequately treat pain and to prevent its negative consequences? Moreover, where should our focus lie to reduce the stress associated with the NICU admission for these families?

### **PRETERM BIRTH & NICU ADMISSION**

The World Health Organization estimates that approximately 15 million infants are born prematurely (before 37 weeks of gestation) each year.<sup>1</sup> Globally, complications of preterm birth are the leading cause of death among children under five years of age. In the Netherlands, 11,350 infants were born before 37 weeks of gestation in 2021, of which 1807 (16%) below 32 weeks and 251 (2%) below 26 weeks.<sup>2</sup> Between 2011 and 2017, the survival rates for infants born with a gestational age of 24 or 25 weeks were 34% and 59%, respectively.<sup>3</sup> Nevertheless, the impact of premature birth continues after discharge from the NICU for those who survive.

### **THE IMPACT OF PRETERM BIRTH**

Dutch single-center follow-up data of children born very prematurely (gestational age <30 weeks) between 1990 and 2011 reveal that at the ages of 2,5 and 8 years, mild neurodevelopmental impairment (NDI) was observed in 31%,36%, and 30%, respectively, and moderate-to-severe NDI in 15%,9%, and 9% of them.<sup>4</sup> In a French cohort, the authors concluded that only 10% of the infants born with a gestational age of 24 weeks survived without any neurodevelopmental disabilities at five years of age.<sup>5</sup> However, the same study highlighted that even

among infants born at 28 weeks of gestation, only 40% of the children did not encounter any neurodevelopmental disabilities. Additionally, even children born extremely prematurely without any NDI diagnosis may still have substantial medical needs after discharge due to other morbidities.<sup>6</sup> While NDI is often used as an outcome measure and encompasses major disabilities, less severe but more prevalent issues related to the physical and mental well-being of the child, such as nutritional status and increased internalizing or externalizing behavior, might have an even greater impact on their quality of life.<sup>7</sup> Children and adolescents born extremely preterm still had significantly lower health-related quality of life compared to term born children.<sup>8,9</sup> During a crucial period of rapid brain growth and development after preterm birth, the exposure to pain might play an important role in this long-term impact of preterm birth.<sup>10</sup>

## THE IMPACT OF PAIN

The global awareness that newborns can experience pain began in 1987 when Anand et al. demonstrated that preterm infants who underwent surgery for patent ductus arteriosus and received analgesics during surgery experienced significantly fewer complications than those who did not receive analgesics.<sup>11</sup> Today, many studies have highlighted the negative impact of pain during the NICU stay on neurodevelopment, somatosensory functioning, and pain response later in life.<sup>12</sup>

From the moment it became clear that infants can experience and suffer from pain, NICU clinicians also acknowledged the importance of pain management. However, without a valid way to assess pain, it is impossible to treat pain appropriately. Therefore, pain assessment is an essential first step in pain management. While pain in general is defined as a subjective experience, infants rely on others to assess their pain intensity. Since the 1980s, more than 40 observational measurement instruments have been developed to help NICU clinicians in determining the level of pain in infants.<sup>13</sup> The extent to which these instruments are validated varies greatly, and each instrument has its own strengths and limitations.<sup>14,15</sup> Accurately evaluating the validity and reliability of these instruments can provide insight into these strengths and limitations and is therefore necessary in order to select the optimal instrument.

In 2001, infants at the NICU of the Erasmus MC Sophia Children's Hospital were exposed to a mean of 14 painful procedures per day. Eight years later, this exposure was reduced to 11 painful procedures per day after implementing clinical pharmacological and non-pharmacological pain

guidelines.<sup>16,17</sup> It is important to keep exploring ways to prevent exposure to pain and to focus on treatment options for pain that cannot be prevented. Even before considering the pharmacological treatment of pain, non-pharmacological pain-reducing interventions play a very important role at the NICU. Examples of evidence-based non-pharmacological interventions are skin-to-skin care, non-nutritive sucking, and facilitated tucking.<sup>18,19</sup> Although many studies have demonstrated the pain-reducing effect of administering sucrose to infants before a painful procedure, some practical considerations regarding this administration, e.g., the optimal waiting time before starting the painful procedure, remain unclear.<sup>20</sup>

### **THE IMPACT OF STRESS**

Over the past decade, our focus has shifted from pain to stress as a broader concept in order to disentangle the impact of preterm birth.<sup>21-23</sup> The exposure to pain in the NICU is often discussed together with exposure to stress because it is challenging to distinguish pain from stress in these infants.<sup>24,25</sup> Infants show a comparable neurophysiological response to both tactile and noxious stimuli up until 35-37 weeks gestational age.<sup>24</sup> Since exposure to pain is always considered stressful, the many painful procedures related to NICU treatment, along with the experience of prolonged, persistent, or chronic pain are important causes of stress for these infants.<sup>16</sup> However, even procedures that are not typically considered painful, such as diaper changes, can cause variable amounts of stress in infants admitted to the NICU.<sup>26</sup> Next to the stressors related to NICU treatment, these infants are exposed to physical stressors, such as light and noise, and psychological stress, for example due to separation from their parents.<sup>27</sup>

The exposure to stress in preterm infants during the neonatal period, whether related to acute procedures (e.g., heelstick procedures) or prolonged interventions (e.g., having an endotracheal tube), is significantly associated with impaired neurobehavioral outcomes at term-equivalent age.<sup>22</sup> Distinguishing between pain and stress might be important particularly to effectively apply comforting strategies. Yet, both focusing on relieving pain and stress may be key in improving outcome after preterm birth.

### **THE IMPACT ON PARENTS**

NICU admission not only impacts the infants themselves but also the parents, as it is a very stressful period for families. This stressful period

can result in parental acute and/or post-traumatic stress disorder, depression and anxiety, which often co-occur.<sup>28,29</sup> Studies often primarily focus on the mothers' wellbeing and may not include fathers.<sup>28,30</sup> It was highlighted that the hospital admission of the infant was significantly associated with worse physical health-related quality of life at two months after childbirth in a large Dutch cohort of more than 4300 mothers.<sup>31</sup>

Understanding the most important causes of stress may provide opportunities to prevent these negative outcomes. The two most commonly mentioned sources of stress for parents are parental role adjustment and the child's appearance.<sup>28</sup> The level of stress that parents experience during NICU admission, for example when their baby seemed to be in pain or looks sad, is associated with posttraumatic stress symptoms in the parents.<sup>32</sup>

Given the previous findings, focusing on the assessment, treatment, and prevention of both pain and stress in infants admitted to the NICU may offer opportunities to reduce the negative consequences related to preterm birth for both children and their parents.

### **OVERALL RESEARCH QUESTION**

What methods can be applied to accurately determine the levels of pain and stress in infants during NICU admission, and how to pursue comfort for all preterm infants?

## GENERAL OBJECTIVES

This thesis is divided into three parts, with each part addressing specific research questions:

### ***PART I – Pain assessment***

- Do current behavioral pain measurement instruments validly measure the effect of pain-reducing interventions in infants?
- Is the COMFORTneo scale a valid and reliable instrument to measure prolonged pain at the NICU?
- Can existing pain measurement tools assess pain and comfort levels in extremely preterm infants?

### ***PART II – Pain treatment***

- Is the time interval between sucrose administration and a heelstick procedure correlated with pain scores?
- To what extent are infants exposed to pain and analgesic treatment before and after NEC-related surgery?

### ***PART III – Stress exposure***

- How can we determine the daily stress exposure of very preterm infants during the first 28 days of life?
- What factors contribute to the daily stress exposure of very preterm infants during the first 28 days of life?
- What has been the impact of COVID-19 –related visitation restrictions at the NICU on parents' exposure to stress?

## OUTLINE OF THIS THESIS

The outline of this thesis is shown in Figure 1.

**PART I** focuses on assessing pain in (premature) NICU patients. We systematically reviewed the validity of existing pain measurement instruments for infants in **chapter 2**. **Chapter 3** describes the further validation of the COMFORTneo scale, designed to assess prolonged pain in NICU patients. **Chapter 4** evaluates the differences in behavioral and physiological pain indicators in situations with varying levels of comfort for extremely preterm infants.

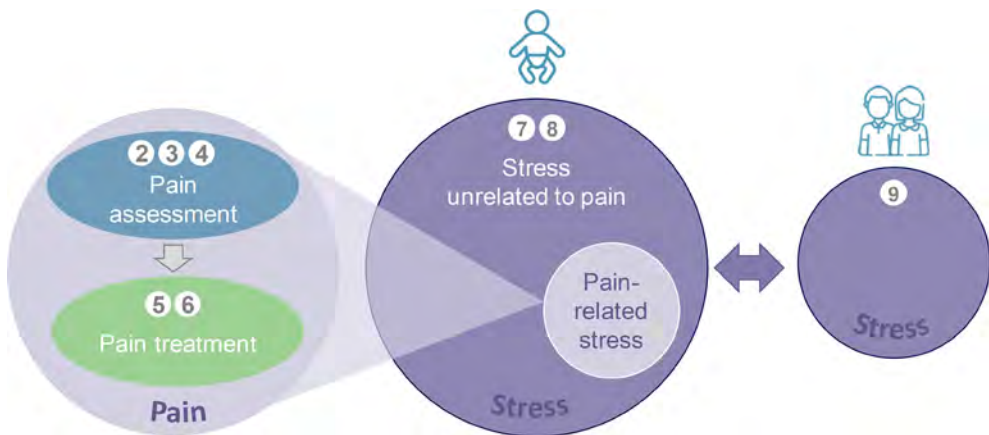
**PART II** applies appropriate pain measurement instruments to assess the effects of pain treatment. In **chapter 5**, we explored the correlation between the time-interval after sucrose administration and pain related

to heelstick procedures. **Chapter 6** describes pharmacological pain treatment before and after NEC-related surgery on the guidance of the COMFORTneo scale.

The focus of **PART III** expands to stress exposure for premature NICU patients and their parents. **Chapter 7** described the development a cumulative score to quantify the daily stress exposure in very preterm infants. **Chapter 8** discusses cumulative stress exposure and its risk factors in a national cohort of very preterm infants. **Chapter 9** describes the impact of COVID-19 –related restrictions regarding the presence of parents and other family members at the NICU on parents' wellbeing.

**Chapter 10** places the main findings in a broader perspective, discussing future perspectives. **Chapter 11** provides a summary of this thesis in both English and Dutch.

**Figure 1 - Thesis overview**



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# PART I

Pain  
assessment



# Chapter 2

Do pain measurement instruments detect the effect of pain-reducing interventions in neonates?  
A systematic review on responsiveness

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## **ABSTRACT**

The effectiveness of pain-reducing interventions in newborns can only be determined if pain measurement instruments are responsive; i.e. able to detect a decrease in pain intensity after the pain-reducing intervention. This review assesses the methodological quality of studies on this measurement property – the responsiveness. We searched the literature published until January 2018 for validation studies of pain measurement instruments focusing on responsiveness to pain-reducing treatment in neonates. Methodological quality of the included studies was rated using the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist. Nine studies were included involving 10 pain measurement instruments. These studies differed with respect to the population, setting and type of pain-reducing intervention. In all studies, pain scores were significantly lower after a pain-reducing intervention and the instrument used was therefore considered responsive. We rated four studies as having poor methodological quality, five as fair quality and none as good quality. In conclusion, the responsiveness was studied for only ten of the 43 existing pain measurement instruments for the use in neonates. As this is an important property of a pain instrument, more research on this topic is needed, with attention for blinding and formulating a specific hypothesis before start of data collection.

## INTRODUCTION

Worldwide, more than 15 million children a year are born prematurely and this number is rising.<sup>1</sup> In the NICU setting they are at risk of acute pain; one study reported a mean number of 11.4 painful procedures per day during the first 14 day.<sup>2</sup> They are also at risk of prolonged or chronic pain from, for example, skin conditions, gastro-intestinal conditions, inflammation and the aftermath of surgery.<sup>3, 4</sup>

From the moment it became clear that neonates are capable of experiencing pain - in the late 1980s - some 40 pain measurement instruments for the use in neonates have been developed.<sup>5</sup> While the Premature Infant Pain Profile (PIPP) is one of the best known instruments to measure acute pain, the Échelle Douleur Inconfort Nouveau-Né (EDIN) and COMFORTneo are two of the instruments developed to measure prolonged pain.<sup>6-8</sup> The American Association of Pediatrics recommends to consistently use validated instruments to assess the need for pain management throughout a neonate's hospitalization.<sup>9</sup> The quality of such an instrument is largely determined by its clinimetric properties.<sup>5, 10</sup> One of these properties is responsiveness. Its definition varies in the literature; in some sources it is defined as the ability to detect a change in general, also called "sensitivity to change".<sup>11</sup> In this definition, the change could be of any magnitude. Other definitions add that this change should be clinically important.<sup>11</sup> A third group of definitions consider an instrument responsive only if score change reflects a real change in the construct to be measured.<sup>11</sup>

The Consensus-based Standard for the selection of health Measurement Instruments (COSMIN) guidelines adhere to the latter definition: "the ability of an instrument to detect change over time in the construct to be measured".<sup>12</sup> Because there is no gold standard for the measurement of pain in neonates a construct approach is recommended according to these guidelines and hypothesis testing is the correct way to determine responsiveness.<sup>12, 13</sup> The hypotheses should be based on the expected mean difference between the changes in scores before and after an intervention in groups or the expected correlation between the changes in scores of the studied instrument compared to an instrument of which the responsiveness has been established.

Pain-reducing interventions are necessary to prevent detrimental effects on brain development and developmental outcomes.<sup>14-17</sup> Analgesia or sedation could be necessary to adequately treat prolonged pain. A European cohort study showed that this was the case for 34% of the

NICU patients.<sup>18</sup> The consistent use of a pain measurement instrument is important to guide pain-reducing treatment – either pharmacological or non-pharmacological. and the instrument therefore should be able to detect real changes in pain intensity. With respect to the measurement of pain in infants, the responsiveness of an instrument is based on either the infant's reaction to a painful intervention or the infant's reaction to a pain-reducing intervention.<sup>19</sup> It is clinically important to evaluate patients' pain intensity and the appropriate pain-reducing intervention should be decided based on this evaluation.

Because NICU patients are frequently exposed to pain and because neonates respond to pain differently than do older infants,<sup>20</sup> we wanted to know if the current pain measurement instruments are validly measuring the effect of pain-reducing interventions in neonates. We therefore performed a systematic review of the literature, focusing on this measurement property.

## **METHODS**

### ***Inclusion- and exclusion criteria***

Eligible for inclusion were original validation studies evaluating the responsiveness of pain measurement instruments in neonates, defined as newborns up to a postnatal age of 28 days. If the postnatal age was not specifically described, articles using the concept "neonates" were also considered eligible for inclusion. A study was included only if the study population at least partially consisted of neonates. Studies in which interventions were pharmacologic, non-pharmacologic or both were included.

The definition of responsiveness for this review was adapted from the COSMIN definition as follows: "The ability of an instrument to detect changes in pain intensity over time after a pain-reducing intervention". The selected studies did not always apply this definition but did evaluate responsiveness. All studies had a longitudinal aspect and evaluated the change in pain score before and after a pain-reducing intervention within the same patient. Because efficacy trials designed to evaluate the effect of interventions with the use of validated pain measurement instruments serve a different purpose from that of validation studies, we excluded these trials.

Only validation studies of which a full text version was published were included. The pain had to be assessed in a hospital. The year of publication

was considered to be irrelevant for this research question; therefore there were no restrictions with respect to the publication date. Articles published in other languages than Dutch or English were excluded. The English-language abstracts of articles published in other languages than Dutch or English were screened to determine their possible eligibility.

### **Search strategy**

The electronic bibliographic databases EMBASE, MEDLINE, Web of Science, Scopus, Cochrane, Cinahl, PsychINFO and google scholar were searched until January 2018 by a biomedical information specialist (WB) from the Erasmus University Medical Center Medical Library.

Search terms used were combinations of the following words:

- Neonates: "newborn" or "neonat\*" or "premature" or "preverbal" or "0-year-old" or "young children" or "baby" or "low birthweight"
- Validation: "valid\*" or "sensitivity to change" or "responsiveness" or "psychometric\*"
- Pain: "pain" or "distress" or "comfort"
- Measurement: "scale" or "score" or "measurement" or "profile"

Complete search strategies are included in appendix 1.

We also searched the literature to determine the number of instruments published until January 2018. We included the instruments mentioned in the systematic reviews on pain assessment in neonates of Cong et al., Stevens et al. and Duhn et al.<sup>5, 10, 21</sup> that met our inclusion criteria, as well as the ones additionally found in the database for this review. Furthermore, we hand-searched the reference lists of the articles for additional relevant articles.

### **Selection of articles**

References of the different databases were combined and duplicates were removed. Two reviewers (MvD and NM) selected potentially eligible articles based on title and abstract. Articles of which the title and abstract made clear that the study did not meet the inclusion criteria were excluded. The full texts of the remaining studies, if available, were read and assessed on eligibility: first, whether the study population met the inclusion criteria and second, whether a change in the pain score before and after a pain-reducing intervention was analyzed. Also, the reference lists of these studies were manually searched to identify other potentially eligible studies. If the two independent reviewers did not agree on inclusion, a third reviewer (CT) was consulted and whose verdict was accepted.

### ***Data extraction***

Information on the measurement instrument, study department, study population and intervention was extracted for each study. The specific method used to calculate responsiveness and the number of measurements, the time interval between the pain reducing intervention and the assessment of pain, the (blinding of the) observers and the statistical analysis were described. Methodological quality was the primary outcome and described together with the results of the studies, as the degree to which pain scores were lower after the intervention served as secondary outcome.

### ***Quality assessment***

The COSMIN group, an international multidisciplinary team of experts, reached consensus on taxonomy, terminology and definitions of measurement properties following an international Delphi study in 2010<sup>22</sup> Three different quality domains are described, namely reliability, validity and responsiveness. The accompanying critical appraisal tool, the COSMIN checklist, guides the evaluation of the methodological quality of studies on measurement properties.<sup>23</sup> For systematic reviews, a scoring system has been developed to obtain an overall quality rating of the different COSMIN items.<sup>24</sup> Four response options (excellent, good, fair, poor) are defined for each item. The lowest rating of any item determines the quality score for each measurement property. For the evaluation of the included studies in this review we used only the items referring to the quality of determining the responsiveness. These items and the accompanying scoring system have been described by Mokkink et al.<sup>23</sup> The total scores before and after a pain reducing intervention were compared using Cohen's d. If the mean and standard deviation were absent, we took the median to represent the mean and calculated the standard deviation by multiplying the IQR by 0.741. The effect size was considered small at Cohens' d of 0.20, medium at 0.50, and large at 0.80.<sup>25</sup>

## **RESULTS**

The search strategy yielded 1915 citations. After having removed duplicates, we screened the titles and abstracts of 811 citations on eligibility. Thirty-seven articles were written in another language than English or Dutch, but all those studies would also have been excluded based on the English abstract. Thirty-three full texts were read, of which nine validation studies met all the inclusion and exclusion criteria and

were included in this review (figure 1). After having consulted a third reviewer (CT) for two studies, the two reviewers agreed on all studies. One study was excluded because no data was provided about the change in scores.<sup>26</sup> Checking the reference lists did not result in additional studies to include.

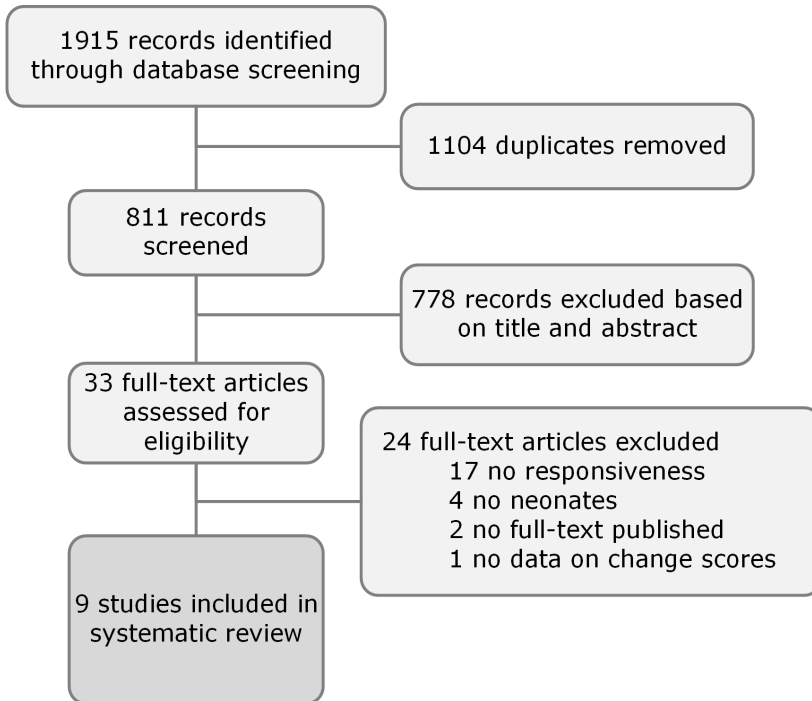
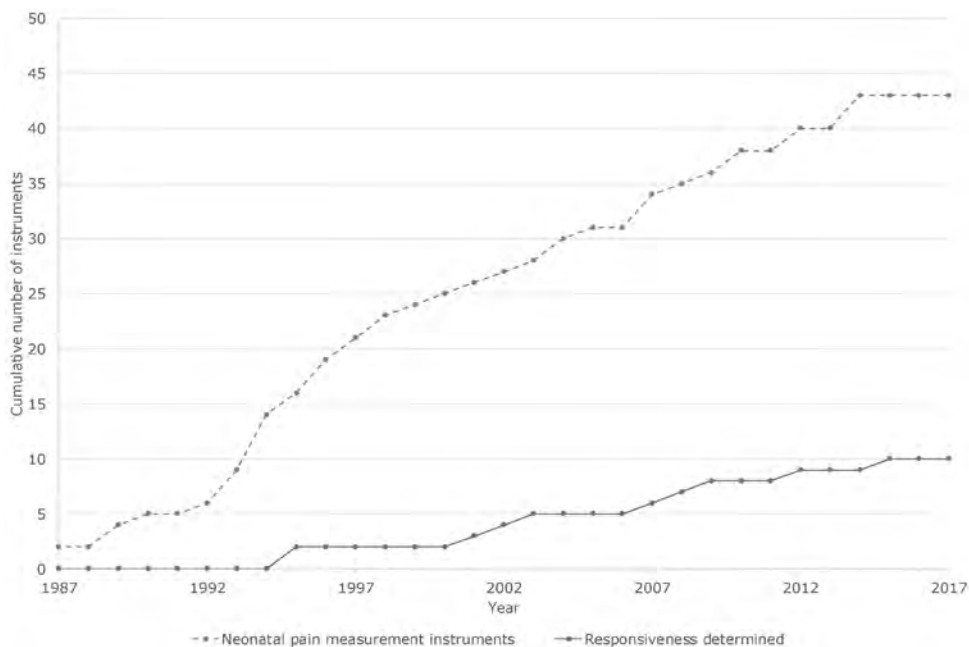


Figure 1 - Flowchart

### Study description

Next to the 35 instruments that were included in the three reviews and met our inclusion criteria reviews,<sup>5, 10, 21</sup> the search strategy yielded another 8 instruments (see appendix 2). The responsiveness was evaluated for 10 of these 43 instruments (Figure 2). Table 1 gives an overview of the nine included studies that studied the responsiveness of 10 different pain measurement instruments. Five of these studies included only neonates,<sup>7, 8, 27-29</sup> of which the EDIN study only included premature infants.<sup>7</sup> The four other studies included not only neonates but also older children.<sup>30-33</sup> One study did not describe the postnatal age range but was not excluded because one quarter of the children were younger than 0.1 years.<sup>33</sup> Four studies only focused on the postoperative period.<sup>27-29, 32</sup> The EDIN study concerned

preterm born neonates diagnosed with respiratory distress syndrome and assigned an EDIN score of 7 or higher before the pain-reducing intervention.<sup>7</sup> In the four other studies, the source of the pain was not mentioned.<sup>8, 30, 31, 33</sup>



**Figure 2 - Evaluation of responsiveness in neonatal pain measurement instruments**

**Table 1 - Study description**

Author, year	Instrument	Department	Population	Intervention
Krechel et al. 1995	CRIES Secondary: OPS	NICU/PICU	Postoperative infants N = 24 At birth: Mean gestational age 36 weeks (27-40 weeks) During participation: Mean gestational age 44 weeks (32-60 weeks)	Administration of analgesics.
Debillon et al. 2001	EDIN	NICU	Preterm infants admitted for respiratory distress syndrome (RDS) N = 40 (for responsiveness) Age unknown	Intravenous fentanyl at a dose of 1 mcg/kg/h after an initial bolus of 1 mcg/kg.
Horgan et al. 2002	LIDS	Surgical unit	Postoperative neonates N = 11 Postnatal age unknown	Administration of paracetamol PRN and a caudal block for two infants.

Manworren et al. 2003	FLACC	PICU PACU Surgical/ trauma Hematology/ oncology Infant unit	Infants less than 3 years of age N = 147 Postnatal age 1 day to 34 months	Prescribed analgesics on a PRN basis.
Ramelet et al. 2007	MAPS	PICU	Postoperative children N = 20 Postnatal age: 4 days to 31 months (median 7.5 months)	Administration of rescue analgesia: a standardized dose of intravenous morphine (50- 100mcg/kg).
Hummel et al. 2008	N-PASS	NICU	Intubated and/or postoperative neonates N = 46 Gestational age: 23 to 40 weeks Postnatal age: 0 to 100 days	Administration of analgesics and/or sedatives.
Van Dijk et al. 2009	COMFORT- neo	NICU	Neonates N = 76 Scores N = 110 Gestational age 24.6 to 42.6 weeks (total population) Postnatal age unknown	Administration of analgesics, sedatives or a non- pharmacological intervention
Fournier- Charriere et al 2012	EVENDOL	Pediatric accident and emergency department (AED)	Infants N = 101 (3 intervention groups) Age: between birth and 83 months	Administration of analgesics.
Boerlage et al. 2015	COMFORT behaviour	PICU	Infants N = 180 Median age 0.4 years (IQR 0.1 to 2 years)	Administration of analgesics/ sedatives

CRIES: Crying; Requires increased oxygen administration; Increased vital signs;  
 Expression; Sleeplessness; OPS: Observational Pain Scale; EDIN: Echelle Douleur  
 Inconfort Nouveau-Né; LIDS: Liverpool Infant Distress Score; FLACC: Face, Legs, Activity,  
 Cry, Consolability scale; MAPS: Multidimensional Assessment Pain Scale; N-PASS: Neonatal  
 Pain, Agitation and Sedation Scale; EVENDOL: Evaluation Child Pain  
 NICU = Neonatal Intensive Care Unit; PICU = Pediatric Intensive Care Unit; PACU = Post  
 Anesthesia Care Unit

In all but one study the intervention consisted of pharmacological analgesic treatment. Only the study on the responsiveness of the COMFORTneo scale also included non-pharmacological interventions in the analysis.<sup>8</sup> Dosing of the analgesics was described in only two studies, on the EDIN and MAPS.<sup>7, 32</sup> In the remaining six studies the evaluated intervention was the administration of analgesics and/or sedatives, but dosing was not specified.<sup>27-31, 33</sup>

### ***Study quality***

Table 2 describes the methods used for determining the responsiveness of the pain measurement instrument, the results, and the quality score according to the COSMIN checklist. The quality of five studies was rated as poor for the following reasons.

In three of these studies the sample size was smaller than 30,<sup>27, 29, 32</sup> and thus are of poor methodological quality according to the COSMIN checklist.<sup>24</sup> In two of these studies the required power had not been calculated;<sup>27, 29</sup> in the MAPS study, the sample size was calculated for the interrater reliability instead of the responsiveness.<sup>32</sup> Regarding the LIDS, only the p-value of the difference was reported and no additional information was given.<sup>27</sup> The article on the COMFORTneo did not describe the time between the two assessments and for another pain instrument, the EVENDOL, the statistical analysis used was not clearly described.<sup>8, 30</sup>

The quality of the four other studies was rated as fair. Figure 3 shows the complete assessment of all nine studies. Because of the lack of a gold standard, items 15 to 17 need not be assessed [24].

### ***Missing items***

Six studies only used paired pain assessments, both before and after the intervention, and did not describe missing assessments.<sup>7, 8, 27, 28, 31, 32</sup> Items 1 and 2 of the COSMIN checklist were considered not applicable for these studies. In the study on the COMFORT behavior scale, the pain scores were retrieved retrospectively and the authors specified the number of lacking re-assessments.<sup>33</sup> In the EVENDOL study the number of pain scores after the intervention was lower than that before the intervention in two different situations (in rest and during mobilization), but the reason was not described.<sup>30</sup> The authors of the study on the OPS and CRIES stated they included all infants admitted to the NICU and that each was assessed hourly with both pain scales; the reason why there were more OPS-scores (N=77) than CRIES-scores (N=74) is unclear.<sup>29</sup>

Table 2 - Used (statistical) methods and quality of the studies

Instrument	Methods	Observer	Statistics	Results	Quality
CRIES, OPS [24]	Pain score at time of analgesic administration and the hour immediately following the administration	Nurses	Wilcoxon Signed Rank test	Significantly lower CRIES score after analgesic administration with a mean decline of 3.0 units ( $p < 0.0001$ , $n = 74$ ) Significantly lower OPS score after analgesic administration with a mean decline of 3.4 units ( $p < 0.0001$ , $n = 77$ )	Poor
EDIN [12]	EDIN scores before and eight hours after intravenous fentanyl	Nurses	Paired T-test	Significantly lower pain scores after than before analgesia ((4.7 (2.1) vs. 9.2 (1.7); mean (SD): $p < 0.0001$ )  Mean difference of 4.4 points between before and after intervention (95% CI 3.6 to 5.2)	Fair
LIDS [22]	Observations each hour for the first six hours post-delivery, than at 18, 19, 24, 25, 42 and 43 hours post-delivery  Administration of analgesia after the observations were complete	Researcher, blinded	Paired T-test comparing scores immediately before and immediately following analgesia	Significant lower score after the administration of analgesia ( $p = 0.004$ )	Poor
FLACC [26]	- Time 1: Before start of analgesia - Time 2: 10 minutes (intravenous) or 30 minutes (oral) after administration of analgesia - Time 3: 30 minutes (intravenous) or 60 minutes (oral) after administration of analgesia	Nurses	One-way ANOVA	Significantly different pain scores between the three time points ( $p < 0.001$ )  The mean [95% CI] score for time point 1 was significantly higher (7.03 [6.66-7.41]) than those on time point 2 and 3 (2.05 [2.68-2.43] and 0.74 [0.48-1.00] respectively)	Fair

MAPS [32]	Pain score before an IV morphine bolus and 15, 30 and 60 minutes after A mean score per time point was calculated per patient for up to three doses	Trained clinical nurse	Friedman test	80% pain scores before and 30% pain scores after intervention $\geq 4$  Decrease of 5 points in median pain score after intervention ( $p < 0.001$ )	Poor
N-PASS [23]	Pain score before and 1 hour after administration of analgesia	Trained nurses	Wilcoxon signed rank	Significantly lower pain score after the analgesic intervention (4.86 (3.38) vs. 1.81 (1.53); mean (SD); $p < 0.001$ )	Fair
COMFORT neo [41]	Pain score before and after a pain or distress reducing intervention	Nurses	Paired T-test	Significantly lower pain score after the pain or distress reducing intervention (19.8 (3.8) vs. 12.0 (3.4); mean (SD); $p < 0.001$ )	Poor
EVENDOL [15]	Pain score in 4 different situations: - Before an intervention at rest - Before an intervention during mobilization - After analgesic treatment at rest - After analgesic treatment during movement	Triage nurse	Unknown	Lower pain scores after the administration of nalbuphine/morphine, codeine and acetaminophen during rest (9 to 3, 7 to 0 and 3 to 0, respectively) and during movement (13 to 6, 11 to 4 and 7 to 3, respectively)	Poor
COMFORT behaviour [6]	Pain scores before and after the start of analgesics or sedatives	Nurses	- Paired T-test - Multilevel regression analysis - Hypothesis 1: a decrease of 5 points after an intervention is clinically relevant - Hypothesis 2: A decrease of the pain score to below 17 is considered responsive	Significantly lower pain score after the intervention (20.0 (3.7) vs. 14.1 (4.7); mean (SD); $p < 0.001$ ) - 63% of the pain scores decreased at least 5 points after the intervention - 74% of the pain scores was below 17 after the intervention - A mean decrease of the pain score of 5.97 points after the intervention ( $p < 0.001$ )	Fair

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Overall
CRIES, OPS	2	3	4	1	1	2	2	3	2	2	○	○	3	3	4
EDIN	○	○	3	1	1	1	2	3	2	2	○	○	3	3	3
LIDS	○	○	4	1	1	2	2	3	2	2	○	○	1	3	4
FLACC	○	○	1	1	1	2	2	3	2	2	○	○	3	3	3
MAPS	○	○	4	1	1	1	2	1	1	2	○	○	3	3	4
N-PASS	○	○	3	1	1	2	2	1	2	1	○	○	3	3	3
COMFORTneo	○	○	1	1	4	2	2	3	2	2	○	○	3	3	4
EVENDOL	2	3	1	1	1	2	2	3	2	2	○	○	3	4	4
COMFORT behavior	1	2	1	1	1	2	2	1	1	1	○	○	3	1	3

**Figure 3 - COSMIN checklist quality scores for responsiveness**

1 Excellent; 2 Good; 3 Fair; 4 Poor; ○ Not applicable

Items 1 to 14: see study Mokkink et al. for complete description<sup>23</sup>

Short description:

- |                             |                                              |
|-----------------------------|----------------------------------------------|
| 1: Percentage missing items | 8: Hypotheses formulated                     |
| 2: Handling missing items   | 9: Direction of change in hypotheses         |
| 3: Sample size              | 10: Absolute or relative magnitude of change |
| 4: Longitudinal design      | 11: Description comparator instrument        |
| 5: Time interval            | 12: Properties comparator instrument         |
| 6: Description intervention | 13: Important flaws design or method         |
| 7: Change in patients       | 14: Adequate design and statistical methods  |

### **Hypothesis formulation**

All studies hypothesized that the mean group score after a pain-reducing intervention would be lower than that before the intervention. In two studies the size of the expected absolute or relative difference was predefined.<sup>28, 33</sup> For the NPASS, the power analysis was based on an expected difference of 1.2 points, but the authors did not support this with evidence.<sup>28</sup> An expected difference of five points for the COMFORT behavior scale was based on a previous study and the authors also aimed for a COMFORT behavior score below 17, which is taken to be the cutoff value for treatment.<sup>33</sup>

### **Blinding**

Only in the LIDS study, pain scores were assigned bedside by nurses who were not aware of the situation – before or after the intervention.<sup>27</sup>

### ***Timing***

Responsiveness was based on two<sup>7, 8, 28, 29, 33</sup> or more<sup>27, 30-32</sup> pain scores per patient. The time interval between the before and after assessments varied between studies, from one hour<sup>28, 29</sup> to eight hours<sup>7</sup>. In three studies with multiple pain scores, the time interval between assessments was pre-defined but increased between the assessments.<sup>27, 31, 32</sup> The EVENDOL was scored two times in two different situations, whereby the time interval was specified.<sup>30</sup>

### ***Analysis***

All nine studies tested the significance of the difference between the score before and after a pain-reducing intervention. In the EVENDOL study it was not described which test was used,<sup>30</sup> the eight other studies used a paired t-test, one-way ANOVA or the equivalent non-parametric tests. In six studies either the mean difference per patient was calculated<sup>7, 29</sup> or mean scores before and after the intervention were presented.<sup>8, 28, 30, 31</sup> The studies on the MAPS and COMFORT behavior scale presented also the number of scores above (MAPS) or below (COMFORT behavior) a certain value.<sup>32, 33</sup> Regarding the LIDS, only the p-value and actual scores are presented.<sup>27</sup>

### ***Responsiveness***

All studies found significant decreases of the scores after the intervention. With respect to the a priori formulated hypotheses, after the intervention 63% of the COMFORT behavior scores had decreased at least 5 points and 74% of the pain scores were below 17.<sup>33</sup> While the mean difference for the N-PASS was not calculated in the study, the difference between the scores before and after the intervention was 3.0 points.<sup>28</sup> It was concluded for all included pain measurement instruments that they were responsive.

Table 3 shows the calculated Cohen's d for eight measurement instruments. For seven instruments the difference between before and after intervention scores was large and for one instrument (LIDS) medium. It was not possible to calculate the effect size for the CRIES and OPS, because only the mean decline was presented.

**Table 3 - Change scores expressed as effect size**

Instrument	ES
CRIES, OPS <sup>24</sup>	-
LIDS <sup>22</sup>	0.53
N-PASS <sup>23</sup>	1.16
COMFORT behaviour <sup>6</sup>	1.39
EVEN <sup>30*</sup>	1.59 Rest
	1.49 Mobilization
COMFORTneo <sup>41</sup>	2.16
FLACC <sup>31</sup>	2.18
EDIN <sup>7</sup>	2.36
MAPS <sup>32*#</sup>	2.43

ES = effect size, small at Cohens' d of 0.20, medium at 0.50, and large at 0.80.

#Multiple assessments were performed, effect size was calculated for the last assessment before and the first assessment after the intervention.

\* Recalculated using median and IQR. However, it should be noted that the boxplots in both studies showed that pain scores were not normally distributed and therefore the effect size should be interpreted with caution.

## DISCUSSION

Despite the enormous increase in neonatal pain and pain assessment research, very little is still known about the responsiveness of pain measurement instruments. This review evaluated the property of neonatal pain measurements to detect changes after a pain-reducing intervention as well as the quality of the studies evaluating this measurement property. While the responsiveness of the neonatal pain measurement instruments included in this review proved satisfactory, the quality of the studies in question as judged by the COSMIN checklist was only poor to fair. Responsiveness to treatment is an important clinimetric property of pain measurement instruments in general.<sup>5, 34</sup> This review points out some important issues to improve future research on this measurement property.

Poor quality of the validation studies was primarily due to the lack of clearly formulated a priori hypotheses. Because no high quality evidence on the responsiveness of pain measurement instruments in neonates was found, formulating hypotheses in future studies on the correlation between change in scores on another instrument is currently not appropriate.

Hypotheses should be based on the expected mean difference between the changes in scores before and after an intervention. Only in the study on the COMFORT behavior scale the expected mean difference was explicitly stated in the hypothesis.<sup>33</sup> In the N-PASS study, this was reflected in the power analysis.<sup>28</sup> Another option would be to aim for a score below the cut-off score for pain, as in the study on the COMFORT behavior scale.<sup>33</sup> In that case it is also necessary to determine the expected size of the change, for example expressed as the percentage of scores below this value after the intervention. None of the included studies formulated hypotheses on the expected effect size or the mean difference between two groups whose change scores are expected to differ in change. With respect to the eight instruments in the current study for which Cohen's *d* could be calculated, only for the LIDS the Cohen's *d* was below 0.80. However, according to the COSMIN checklist, this calculation should always be compared with that stated in a priori hypothesis. Seven of the included studies determined the responsiveness by calculating *p*-values for the differences between the scores without the formulation of any hypothesis.<sup>7, 8, 27, 29-32</sup> This means that only the statistical significance of the difference is calculated, but not the relevance of the change score for clinical practice. According to the COSMIN checklist, this is not a correct method if not combined with a beforehand formulated hypothesis. Furthermore, the *p*-value is also dependent on the standard deviation of the change and the sample size.

Another problem is the risk of bias when the assessor is not blinded to the situation – before or after the intervention. Blinding is notably difficult in this type of study design. It seems impossible to blind assessors and adhere to a fixed time interval after the intervention if pain is assessed at the bedside. Still, in one study assessors could be blinded for the situation.<sup>27</sup> In this study the time interval between the intervention and pain assessment varied greatly, however. A possible solution for blinding is having assessors assign pain scores afterwards when watching video recordings of the child.<sup>33</sup> These recordings will be randomized for the before and after the intervention situation and will typically not reveal any patient identification. This practice may also result in more consistent and objective pain scores.<sup>35</sup>

For the N-PASS, on the other hand, the authors deliberately chose not to do this because their goal was to develop a measurement instrument usable in daily practice.<sup>28</sup> Moreover, it is not easy to obtain high-quality footage of premature neonates lying in an incubator, especially those with the lowest

gestational age: it is relatively dark, the incubator's surface is reflective, the face is partly covered by fixation material for respiratory support and sometimes a pacifier. Three previous studies used videotapes to validate pain measurement instruments in extremely premature neonates.<sup>36-38</sup> In two of these, however, these neonates were filmed at a postconceptional age of 32 weeks.<sup>36, 38</sup> and the third only included neonates whose face was well visible because they were not intubated or on non-invasive ventilation<sup>37</sup> Pain needs to be assessed in NICU patients of all ages and in all circumstances. Therefore, the question remains if it is possible to reliably assess pain using videotapes in all premature neonates.

The evaluation of the responsiveness of all the included instruments focused on prolonged pain treated primarily by analgesics and sedatives. The definition of responsiveness suggests that a change over time must occur. With respect to a change in pain after pain reducing interventions, this definition seems to be inseparably linked to a prolonged aspect of pain. Validation studies that focus on acute pain measurement instruments, such as the PIPP,<sup>6</sup> often evaluate the responsiveness by comparing the pain score during a painful intervention to the baseline pain score or a score during a non-painful intervention. These studies were excluded because the concept of responsiveness to pain differs from the concept of responsiveness to a pain reducing intervention.

This is not the first review that found that studies on the responsiveness of pain measurement instruments lack quality. A review on the responsiveness of the FLACC concluded that 18 out of the 20 included studies had a poor or fair methodological quality.<sup>19</sup> In 2011, Angst criticized the COSMIN initiative and suggested it should be possible to use more traditional ways to determine the responsiveness.<sup>39</sup> He raised the question of how to deal with existing literature if the methods used in those studies are considered inappropriate. The authors of the COSMIN checklist responded that the guidelines are not meant to question previous studies, but rather to help researchers to improve studies on measurement properties.<sup>40</sup> We believe this is also how the results of the current review should be interpreted. Next to this, NICU personnel should keep in mind that high-quality research on the responsiveness of pain measurement instruments is lacking. They use these instruments in clinical practice and should always consult other professionals if they feel an assessment does not correspond to their clinical judgement.

In the past few years research efforts have focused on more objective measures to assess pain in neonates, such as heart rate variability,<sup>41</sup>

skin conductance,<sup>5, 42</sup> and “brain-oriented” approaches such as near-infrared spectroscopy (NIRS) and electroencephalography (EEG).<sup>5, 42, 43</sup> A multimodal approach, possibly automated, has been suggested to improve pain assessment.<sup>44, 45</sup> By comparing noxious-evoked activity during a venipuncture with topical local anesthetic to a venipuncture without this anesthetic, Hartley et al. concluded that their EEG template was sensitive to analgesic modulation.<sup>43</sup> It is important that future validation studies on these physiological pain indicators also include the responsiveness. More evidence is needed before these indicators can be reliably implemented in clinical practice.<sup>5</sup>

It is possible that unpublished data is available on other pain measurement instruments, resulting in publication bias. As none of the measurement instruments was addressed more than once, data pooling was not possible. Also, the included studies are heterogeneous with a large variation in study population, setting and type of intervention, which prevents comparison of the measure of responsiveness of the included pain measurement instruments. Finally, this review concentrates on only one measurement property and therefore is not suitable for determining the optimal measurement instrument to assess pain in neonates.

We may have missed relevant publications in other languages than English and Dutch, although none of the English-language abstracts of studies in other languages met our inclusion and exclusion criteria. Furthermore, we excluded all studies not designed to evaluate the clinimetric properties. These included efficacy trials in which the effect of a pain reducing intervention in neonates was evaluated with the use of a pain measurement instrument. For these trials, the instrument’s responsiveness should have been ascertained first. The studies on the COMFORT behavior, FLACC, MAPS and EVENDOL also included children beyond the neonatal age. In these studies, subgroup analysis of the data on neonates was not performed; it is not known, therefore, whether these instruments are more or less responsive in this specific population.

There is an urgent need for pain measurement instruments that could tell whether a pain-reducing intervention has the desired effect in newborns. This is the first review that describes the quality of validation studies on neonatal pain measurement instruments that included responsiveness as a measurement property. We found that for only 10 out of the 43 existing instruments the change in pain intensity in neonates after a pain-reducing intervention has been studied. Methodological quality of the studies in question was found to be poor to fair. Therefore, and because alternative

methods to assess pain in clinical practice are lacking, more research on this topic is needed, with more attention to blinding and formulating a specific hypothesis before start of data collection.

## APPENDIX 1

### *Embase.com*

('pain measurement'/exp OR 'pain assessment'/exp OR ((pain/exp OR comfort/de) AND ('rating scale'/exp OR 'scoring system'/exp OR 'clinical assessment tool'/exp OR 'facial expression'/exp OR 'monitoring device'/de )) OR ((pain\* OR comfort\*) NEAR/6 (measure\* OR assess\* OR scale\* OR Profile OR validit\* OR score\* OR quantif\* OR rating OR intensit\* OR monitor\*)):ab,ti) AND (newborn/de OR prematurity/exp OR 'newborn intensive care'/exp OR 'low birth weight'/exp OR 'newborn period'/exp OR 'gestational age'/exp OR 'newborn care'/exp OR 'newborn disease'/de OR 'newborn surgery'/de OR baby/de OR (newborn\* OR (new\* NEXT/1 born\*) OR neonat\* OR (prematu\* NEAR/3 (infant\* OR child\*)) OR preterm\* OR nicu OR nicus OR 'low birth weight' OR 'low birthweight' OR lbw OR elbw OR vlbw OR 'gestational age' OR baby OR babies OR (0 NEAR/3 year\* NEXT/1 old\*) OR (first\* NEXT/2 month\* NEXT/2 life)):ab,ti) AND ('validation study'/exp OR 'validation process'/exp OR validity/exp OR psychometry/de OR 'internal consistency'/de OR (validat\* OR validit\* OR psychometr\* OR responsiv\* OR (sensitivit\* NEAR/3 change\*)):ab,ti)

### *Medline ovid*

("pain measurement"/ OR ((exp pain/ ) AND ("facial expression"/ )) OR ((pain\* OR comfort\*) ADJ6 (measure\* OR assess\* OR scale\* OR Profile OR validit\* OR score\* OR quantif\* OR rating OR intensit\* OR monitor\*)).ab,ti.) AND (exp "Infant, Newborn"/ OR "Intensive Care Units, Neonatal"/ OR "Intensive Care, Neonatal"/ OR "gestational age"/ OR (newborn\* OR (new\* ADJ born\*) OR neonat\* OR (prematu\* ADJ3 (infant\* OR child\*)) OR preterm\* OR nicu OR nicus OR "low birth weight" OR "low birthweight" OR lbw OR elbw OR vlbw OR "gestational age" OR baby OR babies OR (0 ADJ3 year\* ADJ old\*) OR (first\* ADJ2 month\* ADJ2 life)).ab,ti.) AND ("validation study"/ OR "Validation Studies as Topic"/ OR Psychometrics/ OR (validat\* OR validit\* OR psychometr\* OR responsiv\* OR (sensitivit\* ADJ3 change\*)).ab,ti.)

### *psycINFO ovid*

("pain measurement"/ OR ((exp pain/ ) AND ("facial expressions"/ OR "Rating Scales"/ )) OR ((pain\* OR comfort\*) ADJ6 (measure\* OR assess\* OR scale\* OR Profile OR validit\* OR score\* OR quantif\* OR rating OR intensit\* OR monitor\*)).ab,ti.) AND (120.ag. OR "Neonatal Intensive Care"/ OR (newborn\* OR (new\* ADJ born\*) OR neonat\* OR (prematu\* ADJ3 (infant\* OR child\*)) OR preterm\* OR nicu OR nicus OR "low birth weight" OR "low birthweight" OR lbw OR elbw OR vlbw OR "gestational age" OR baby OR babies OR (0 ADJ3 year\* ADJ old\*) OR (first\* ADJ2 month\* ADJ2 life)).ab,ti.) AND ("Test Validity"/ OR Psychometrics/ OR (validat\* OR validit\* OR psychometr\* OR responsiv\* OR (sensitivit\* ADJ3 change\*)).ab,ti.)

*Cinahl ebsco*

(MH "pain measurement+" OR ((MH pain+ ) AND (MH "facial expression+" )) OR ((pain\* OR comfort\*) N5 (measure\* OR assess\* OR scale\* OR Profile OR validit\* OR score\* OR quantif\* OR rating OR intensit\* OR monitor\*)) AND (MH "Infant, Newborn+" OR MH "Intensive Care Units, Neonatal+" OR MH "Intensive Care, Neonatal+" OR MH "gestational age+" OR (newborn\* OR (new\* N1 born\*) OR neonat\* OR (prematu\* N2 (infant\* OR child\*)) OR preterm\* OR nicu OR nicus OR "low birth weight" OR "low birthweight" OR lbw OR elbw OR vlbw OR "gestational age" OR baby OR babies OR (0 N2 year\* N1 old\*) OR (first\* N2 month\* N2 life))) AND (MH "validation studies+" OR MH Psychometrics+ OR (validat\* OR validit\* OR psychometr\* OR responsiv\* OR (sensitivit\* N2 change\*)))

*Cochrane*

((pain\* OR comfort\*) NEAR/6 (measure\* OR assess\* OR scale\* OR Profile OR validit\* OR score\* OR quantif\* OR rating OR intensit\* OR monitor\*)):ab,ti AND ((newborn\* OR (new\* NEXT/1 born\*) OR neonat\* OR (prematu\* NEAR/3 (infant\* OR child\*)) OR preterm\* OR nicu OR nicus OR 'low birth weight' OR 'low birthweight' OR lbw OR elbw OR vlbw OR 'gestational age' ORoreiorien baby OR babies OR (0 NEAR/3 year\* NEXT/1 old\*) OR (first\* NEXT/2 month\* NEXT/2 life)):ab,ti) AND ((validat\* OR validit\* OR psychometr\* OR responsiv\* OR (sensitivit\* NEAR/3 change\*)):ab,ti)

*Web-of-science*

TS=(((pain\* OR comfort\*) NEAR/5 (measure\* OR assess\* OR scale\* OR Profile OR validit\* OR score\* OR quantif\* OR rating OR intensit\* OR monitor\*)) AND ((newborn\* OR (new\* NEAR/1 born\*) OR neonat\* OR (prematu\* NEAR/2 (infant\* OR child\*)) OR preterm\* OR nicu OR nicus OR "low birth weight" OR "low birthweight" OR lbw OR elbw OR vlbw OR "gestational age" OR baby OR babies OR (0 NEAR/2 year\* NEAR/1 old\*) OR (first\* NEAR/2 month\* NEAR/2 life))) AND ((validat\* OR validit\* OR psychometr\* OR responsiv\* OR (sensitivit\* NEAR/2 change\*))))

*Scopus*

TITLE-ABS-KEY((((pain\* OR comfort\*) W/5 (measure\* OR assess\* OR scale\* OR Profile OR validit\* OR score\* OR quantif\* OR rating OR intensit\* OR monitor\*))) AND ((newborn\* OR (new\* W/1 born\*) OR neonat\* OR (prematu\* W/2 (infant\* OR child\*)) OR preterm\* OR nicu OR nicus OR "low birth weight" OR "low birthweight" OR lbw OR elbw OR vlbw OR "gestational age" OR baby OR babies OR (0 W/2 year\* W/1 old\*) OR (first\* W/2 month\* W/2 life))) AND ((validat\* OR validit\* OR psychometr\* OR responsiv\* OR (sensitivit\* W/2 change\*))))

*Pubmed publisher*

("pain measurement"[mh] OR ((pain[mh] ) AND ("facial expression"[mh] )) OR ((pain\*[tiab] OR comfort\*[tiab])) AND (measure\*[tiab] OR assess\*[tiab] OR scale\*[tiab] OR Profile

OR validit\*[tiab] OR score\*[tiab] OR quantif\*[tiab] OR rating OR intensit\*[tiab] OR monitor\*[tiab])) AND ("Infant, Newborn"[mh] OR "Intensive Care Units, Neonatal"[mh] OR "Intensive Care, Neonatal"[mh] OR "gestational age"[mh] OR (newborn\*[tiab] OR (new born\*[tiab] OR newly born\*[tiab]) OR neonat\*[tiab] OR (prematu\*[tiab] AND (infant\*[tiab] OR child\*[tiab])) OR preterm\*[tiab] OR nicu OR nicus OR "low birth weight" OR "low birthweight" OR lbw OR elbw OR vlbw OR "gestational age" OR baby OR babies )) AND ("validation study"[mh] OR "Validation Studies as Topic"[mh] OR Psychometrics[mh] OR (validat\*[tiab] OR validit\*[tiab] OR psychometr\*[tiab] OR responsiv\*[tiab] OR (sensitivit\*[tiab] AND change\*[tiab]))) AND publisher[sb]

### Google scholar

"pain|comfort measurement|assessment|scale|validity|score"

newborn|neonate|neonatal|prematurity infant|infants|nicu|nicus

validation|validity|psychometry|responsiveness|responsivity|"sensitivity to change"

## APPENDIX 2

Year	Author	Scale	Type*	Resp**	Comments
1987	Grunau	NFCS	1	○	
1990	Stevens	NAPI	1	○	Validated in neonates by Schade et al., 1996
1993	Craig	IBCS	1	○	
1993	Lawrence	NIPS	1	○	
1994	Hodgkinson	PAT	1	○	
1995	Krechel	CRIES	1	●	
1996	Sparshot	DSVNI	1	○	
1996	Horgan	LIDS	1	●	
1996	Stevens	PIPP	1	○	
1997	Carbajal	DAN or APN	1	○	
1998	Blauer	SUN	1	○	
2001	Debillon	EDIN	1	●	
2002	Hudson-Barr	PAIN	1	○	
2003	Marceau	NNICUPAT	1	○	
2004	Cignacco	BPSN	1	○	
2007	Bellieni	ABC	1	○	
2007	Holsti	BIIP	1	○	
2008	Hummel	NPASS	1	●	
2009	van Dijk	COMFORTneo	1	●	
2010	Hand	COVERS	1	○	
2010	Milesi	FANS	1	○	

2012	Liaw	PASPI	1	○	
2014	Lundquist	ALPS	1	○	
2014	Pollki	NIAPAS	1	○	
2014	Gibbins	PIPP-R	1	○	
1987	Hannalah	OPS	2	●	Validated in neonates by Krechel et al., 1995
1989	Barrier	POPS or CSS	2	○	Validated in neonates by Schade et al., 1996
1992	Ambuel	COMFORT	2	○	
1996	Schade	RIPS	2	○	Validated in neonates by Schade et al., 1996
1997	Merkel	FLACC	2	●	Validated in neonates by Manworren et al., 2003
2000	Buttner	CHIPPS	2	○	
2004	Suominen	CAAS	2	○	
2005	Ista	COMFORT-B	2	●	
2007	Ramelet	MAPS	2	●	
	Fournier-Charriere	EVENDOL	2	●	
2012	Bell	NPAS	3	○	
1994	Pokela	BPS	3	○	
1995	Friedrichs	NPAT	3	○	
1998	Guinsberg	MPCS	3	○	
1989	Johnson	PAIN	4	○	
1994	Lin	IPEC	4	○	
1994	Wielenga	WOPP	4	○	
1999	Jorgensen	PIPA	4	○	

\* Type of pain measurement instrument

1: Validated neonatal pain measurement instrument

2: Infant/pediatric pain measurement instrument, validated in neonates

3: Pain measurement instrument used in neonates, not validated

4: Pain measurement instrument used in neonates, no full text published

\*\* Responsiveness determined ○ No / ● Yes

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# Chapter 3

COMFORTneo scale: a reliable and valid instrument to measure prolonged pain in neonates?

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## **ABSTRACT**

### ***Objective***

We studied the reliability and validity of the COMFORTneo scale, designed to measure neonatal prolonged pain.

### ***Study design***

This prospective observational study evaluated four clinimetric properties of the COMFORTneo scale from NICU nurses' assessments of neonates' pain. Intra-rater reliability was determined from three video fragments at two time points. Inter-rater reliability and construct validity were determined in five neonates per nurse with the COMFORTneo and numeric rating scales (NRS) for pain and distress. Pain scores using N-PASS were correlated with COMFORTneo scores to further evaluate construct validity.

### ***Result***

Intra-rater reliability: Twenty-two nurses assessed pain twice with an intraclass correlation coefficient (ICC) of 0.70. Inter-rater reliability: The ICC for 310 COMFORTneo scores together with 62 nurses was 0.93. Construct validity: Correlation between COMFORTneo and NRS pain, distress and N-PASS was 0.34, 0.72 and 0.70, respectively.

### ***Conclusion***

The COMFORTneo can be used to reliably and validly assess pain in NICU patients.

## INTRODUCTION

Experiencing pain negatively impacts a premature infant's development with respect to cognitive, motor, behavioral and neurological outcome.<sup>1-6</sup> Neonatal Intensive Care Unit (NICU) nurses consider the prevention and reduction of pain and stress in NICU patients the most important research priority.<sup>7</sup> The accurate assessment of pain in these patients is essential to accomplish adequate pain management.<sup>8</sup> The use of self-report is the first choice in assessing pain in pediatric and adult patients, but this is impossible in neonates.<sup>9, 10</sup> Because of the lack of a gold standard, the assessment of pain remains a difficult aspect of neonatal care.<sup>11</sup> The application of a measurement instrument to quantify pain is considered the best alternative. Nowadays, more than 40 measurement instruments have been developed to assess pain in neonates.<sup>8, 12</sup> These instruments primarily use behavioral observations to quantify the level of pain, sometimes combined with physiological aspects and contextual information such as gestational age. Despite the large number of observational pain measurement instruments, more research focusing on the reliability, validity, clinical utility and applicability of these instruments is necessary in order to ensure that pain is assessed adequately.

According to the framework provided by Anand in 2017, neonatal pain can be divided into either acute (episodic or recurrent) or prolonged, persistent and chronic pain depending primarily on the onset and duration of pain.<sup>13</sup> Most pain measurement instruments focus on the assessment of acute pain related to procedures, for example heel sticks and venipunctures.<sup>11</sup>

More attention for the assessment of prolonged pain, unrelated to procedures, is needed in NICU patients. A survey study from 2017 in 18 European countries showed that prolonged pain was assessed at least once during the NICU stay in 32% of the patients, with daily assessment occurring in only 10% of all neonates.<sup>14</sup> This is worrying because a lack of assessment impedes sufficient treatment.<sup>15</sup> One of the instruments that has been developed specifically to assess prolonged pain is the COMFORTneo scale (supplementary file 1). This instrument was introduced in 2004 at the NICU of the Sophia Children's Hospital. In 2009 the first validation study was published and concluded that the instrument showed preliminary reliability and validity for the evaluation of prolonged pain.<sup>16</sup> Nowadays, an increasing number of NICUs worldwide use the COMFORTneo scale either in clinical practice or for research purposes.<sup>17-21</sup>

The validation of an instrument is a continuous process; it is never fully complete.<sup>22</sup> For one, knowledge regarding the measurement of pain in NICU patients is evolving and this strengthens the possibilities to validate a pain measurement instrument.<sup>22</sup> Since a gold standard for pain assessment, self-reporting, is unavailable for infants, this further complicates the validation process.<sup>23</sup>

The original COMFORTneo validation study already mentioned possibilities to strengthen the evaluation of the instrument's measurement properties.<sup>16</sup> While the same nurse assessed Numeric Rating Scores (NRS) for pain and distress and the COMFORTneo, this should ideally be assessed by different caregivers to minimize observer bias. The Neonatal Pain, Agitation and Sedation Scale (N-PASS) was not yet published during the first validation study, but nowadays has been validated to assess prolonged pain in neonates.<sup>24</sup> Van Dijk et al. mentioned that both the N-PASS and the COMFORTneo should be assessed by two independent assessors at the same time to confirm the construct validity.<sup>16</sup> Lastly, the intra-rater reliability was not determined during the first study. Therefore, our study aimed to further evaluate the reliability and validity of the COMFORTneo scale as an instrument to measure prolonged pain at the NICU.

## **SUBJECTS AND METHODS**

### ***Design***

This prospective validation study addressed four measurement properties: inter-rater and intra-rater reliability, concurrent validity and construct validity.

### ***Patients and setting***

Data collection was conducted from November 2015 until April 2016 in the level 3 neonatal intensive care unit (NICU) of the Erasmus MC – Sophia, Rotterdam, the Netherlands. Approximately 100 NICU nurses are employed at this NICU. There were no exclusion criteria for patients or nurses, as in clinical practice the COMFORTneo is also applied by all nurses and to all preterm and term patients. The nurses only assessed the pain of each infant once, but different nurses could observe the same patient. The neonates could be observed any time of the day, but all observations were made during rest while the patients were not disturbed. Both nurses (depending on their presence and availability during their shift) and patients (depending on practical reasons such as the absence of parents) were selected based on convenience sampling.

## **Measurement instruments**

### *COMFORTneo*

The COMFORTneo consists of 7 behavioral items (alertness, calmness/agitation, respiratory response, crying, body movement, facial tension and muscle tone), of which 6 items should be scored (respiratory response or crying depends on the presence of invasive ventilation).<sup>16</sup> In order to score these items the neonate is observed for two minutes. Each item has a score range of 1 to 5 and the total score ranges from 6 to 30. A score of 14 and higher is considered a sign of distress and pain. A score below 9 suggests that it might be possible to decrease the opioid or sedative dose. All NICU nurses are trained to apply the COMFORTneo when they start working at the NICU because the COMFORTneo is part of our standard of care. They are at least vocational or bachelor trained nurses with a certified NICU specialization or are in training of this NICU specialization. The COMFORTneo training starts with a presentation focusing on pain in NICU patients and the COMFORTneo scale as an assessment tool. After this presentation, they are asked to assess pain using the COMFORTneo score in 10 NICU patients together with a qualified nurse that has already completed the training, independently. If the linearly weighted Cohen's kappa is lower than 0.65, the 10 paired assessments are repeated after discussing the differences until the agreement exceeds 0.65.

### *NRS pain and NRS distress*

NRS scores range from 0 (no pain) to 10 (worst pain possible) with cut-off scores set at 4 or higher for both pain and distress. In clinical practice, NICU nursing staff are trained to always apply the COMFORTneo and NRS scores simultaneously.

### *N-PASS*

The N-PASS consists of 5 items with scores ranging from -2 to 2; four behavioral items (crying/irritability, behavior state, facial expression, extremities tone) and one item for vital signs (changes in heart rate, respiratory rate, blood pressure and oxygen saturation). Pain is scored from 0 to 2 for each behavioral and physiological criterion, total pain score will be between 0 (no pain) and 10 (pain/agitation). Sedation is scored from -2 to 0 and total sedation score ranges from -10 to 0. Additionally, a correction for gestational age is applied (+3 if <28 weeks, +2 if 28-31 weeks, +1 if 32-35 weeks). The goal of pain treatment is an N-PASS score of 3 or less. The N-PASS was validated in 2008 for prolonged pain and in 2010 for acute pain.<sup>24, 25</sup>

## Data collection

We repeated the evaluation of the inter-rater reliability more than 10 years after the introduction of the COMFORTneo and added an evaluation of the intra-rater reliability. Next to this, we asked different raters to independently apply the COMFORTneo and either NRS or N-PASS scores to determine the construct validity in the present study. The institutional ethical review board waived the need for approval because this is an observational study and data were analysed anonymously (MEC-2014-547).

### Before starting the validation study

The principal investigator (PI; NM) was trained before the start of the study by assessing pain using the COMFORTneo score and the N-PASS during ten paired observations for each scale together with a pain expert (MvD). Linearly weighted Cohen's kappa for the PI compared to the pain expert after ten paired scores with the COMFORTneo score and the N-PASS was 0.92 and 0.95, respectively.

Figure 1 shows a flow chart of the study design.

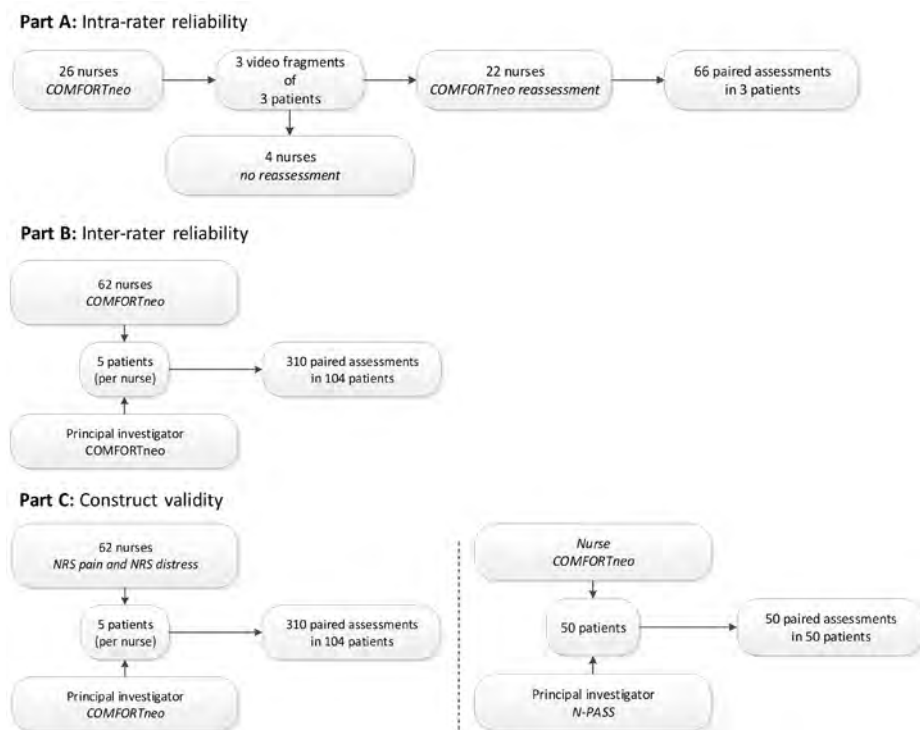


Figure 1 - Study design

### *Intra-rater reliability (Part A)*

Three video fragments lasting exactly two minutes were selected by the PI (NM) based on 1) different gestational ages of the neonates (one neonate with a gestational age below 28 weeks, one between 28 and 32 weeks and one older than 32 weeks) and 2) different pain levels. This selection was made since the instrument should measure pain reliably in patients with different gestational ages and pain levels. The video fragments were to be shown twice at a four-week interval to at least twenty NICU nurses. The NICU nurses were invited to rate the fragments during a coffee break depending on their availability without discussing the observations with each other. During the first time nurses were not informed that they would be asked to observe and assess the video fragments a second time.

### *Inter-rater reliability (Part B)*

Each nurse that participated in part B of this study assessed pain at the bedside together with but independently of the principal investigator in five patients using the COMFORTneo. During the assessment, these patients were lying in the incubator and not exposed to any procedure.

### *Construct validity (Part C)*

During the simultaneous observations with the PI to evaluate the inter-rater reliability, the nurses also scored the NRS pain and NRS distress.

During the last part of this study, after observing a neonate bedside for two minutes, the principal investigator (NM) applied the N-PASS to assess pain while a trained NICU nurse simultaneously applied the COMFORTneo scale. A total of 50 different neonates were scored, resulting in 50 combined assessments.

### **Data analysis**

Patient characteristics and other data are presented as mean (standard deviation, SD) in case of normally distributed variables or median (interquartile range, IQR) in case of non-normally distributed variables for continuous variables and as percentages for categorical variables. In case of a skewed distribution or small sample size, non-parametric statistics were used (detailed below). All statistical tests used a two-sided significance level of 0.05. Data were analyzed in IBM SPSS Statistics for Windows, version 25, Armonk, NY: IBM Corp. Measurement properties were calculated according to the Consensus-based Standard for the selection of health Measurement Instrument (COSMIN) guidelines.<sup>26</sup>

### *Intra-rater reliability (Part A)*

The intraclass correlation coefficient (ICC, 95% CI) was used to calculate intra-rater reliability for all the COMFORTneo total scores and each video fragment separately (two-way mixed effects model, absolute agreement for single measures). An ICC value of 0.70 is considered acceptable.<sup>27</sup>

### *Inter-rater reliability (Part B)*

The ICC was used to determine the inter-rater reliability for the COMFORTneo total scores (two-way mixed effects model, absolute agreement for single measures). An ICC value of 0.70 is considered acceptable. Due to the complex design with repeated measurements of both nurses and patients, the calculation of a valid confidence interval was not considered feasible. Because this analysis was not adjusted for the repeated measurements within the same patient, we also calculated the ICC (95% CI) for the first paired pain assessment in each patient.

### *Construct validity (Part B & C)*

The correlation between the NRS pain and distress scores from the nurses and the COMFORTneo scores from the PI was calculated with the Spearman rank order correlation coefficient. The correlation coefficients were calculated over all observations, without adjustment for repeated measurements. Due to the complex design with repeated measurements of both nurses and patients, the calculation of a valid confidence interval was not considered feasible. Because of the non-normal distribution, the Spearman rank correlation coefficient (95% CI) was also used to determine the correlation between the COMFORTneo score from the nurses and the N-PASS score from the PI.

We formulated hypotheses regarding these correlations a priori - according to the COSMIN guidelines -, namely that the correlation between the COMFORTneo and the NRS pain score and N-PASS respectively should be at least 0.60.<sup>28</sup>

## **RESULTS**

Table 1 shows the patient characteristics of all 130 neonates that were observed once or multiple times during the 426 paired pain scores for the different study parts. Gestational age ranged from 24<sup>+0</sup> to 41<sup>+3</sup> and postnatal age from 0 to 125 days. If neonates were observed more than once, the mean postnatal age was calculated and used to determine the median postnatal age for all 130 neonates.

**Table 1 - Patient characteristics of all assessed patients (N=130)**

Variable	N (%)	Median (IQR)
Boys/girls	72 (55%) / 58 (44%)	
Gestational age (weeks+days)		29 <sup>+4</sup> (27 <sup>+3</sup> to 35 <sup>+0</sup> )
Postnatal age (days)		8 (3 to 22)
Invasive ventilation; yes/no	75 (17.6%) / 351 (82.4%)	

***Intra-rater reliability (Part A)***

Twenty-two nurses assessed all three video fragments twice with a range of four to 10 weeks between the two observation days. Four nurses never reassessed the video fragments after the first assessment and therefore were excluded. For fragment 1, 2 and 3 respectively, the median of the mean COMFORTneo scores was 14.5, 13.5 and 18.3. The systematic difference between the first and second assessment was close to zero (mean difference -0.23) and comparable for each of the three video fragments (mean difference -0.27, 0.09 and -0.50 for fragment 1, 2 and 3, respectively).

The ICC of all 66 paired COMFORTneo scores between the first and second observation was 0.70 (95% CI 0.55 to 0.80;  $p < 0.001$ ).

***Inter-rater reliability (Part B)***

Sixty-two nurses participated in Part B of the study. The median COMFORTneo score was 12 (IQR 10 to 14) for the nurses and 12 (IQR 10 to 14) for the PI. The ICC of all 310 paired COMFORTneo scores (62 nurses x 5 assessments) versus the scores of the PI was 0.93. Figure 2 shows the correlation between the paired COMFORTneo scores. Pain could be assessed in these neonates multiple times by different nurses. After selecting only the first paired COMFORTneo score for each individual patient, the ICC for those 104 COMFORTneo scores was 0.96 (95% CI 0.94 to 0.97).

***Construct validity – NRS (Part C)***

The 62 nurses also rated the level of pain and distress using the NRS for all 310 paired assessments with the PI (applying the COMFORTneo). The median COMFORTneo score, NRS pain and NRS distress of the PI for these observations was 12 (IQR 10 to 14), 0 (IQR 0 to 0) and 0 (IQR 0 to 1), respectively. In 178 assessments (57.4%) no pain or distress was suspected (NRS 0) by the nurses. The NRS pain and/or NRS distress was rated 4 or higher by the nurses during 28 observations (9.0%).

The Spearman rank correlation coefficient between the 310 COMFORTneo scores assessed by the PI and the NRS pain and NRS distress assessed by the nurses was 0.34 and 0.72, respectively (Figure 3a and 3b). When selecting only the first paired assessment for each individual patient, the Spearman rank correlation coefficient was 0.37 (95% CI 0.21 to 0.49) and 0.73 (95% CI 0.62 to 0.81), respectively.

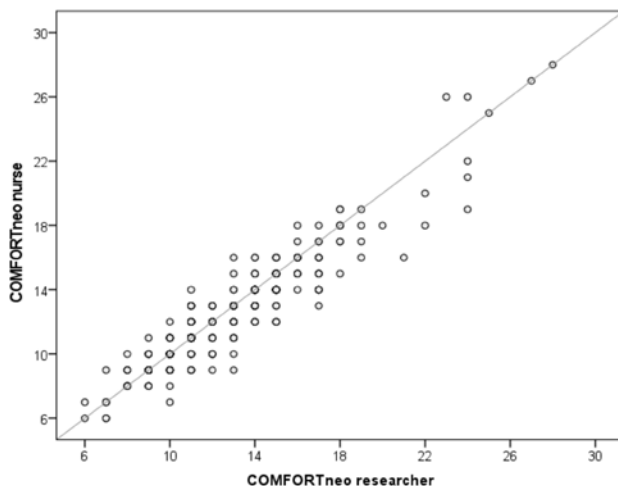


Figure 2 - Scatter plot for the COMFORTneo scores of the researcher and the nurse with the line representing perfect agreement (ICC 0.93)

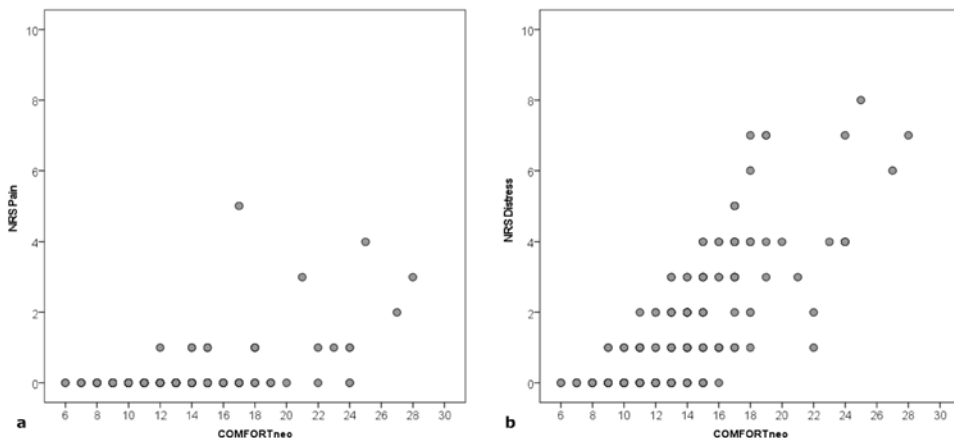


Figure 3 - Correlation between COMFORTneo score and NRS scores

3a COMFORTneo & NRS pain

3b COMFORTneo & NRS distress

### Construct validity – N-PASS (Part C)

Fifty different patients were simultaneously assessed once by both the PI applying the N-PASS and a nurse applying the COMFORTneo scale. The Spearman rank correlation coefficient between the COMFORTneo score of the nurse and the N-PASS score assessed by the PI was 0.70 (95% CI 0.52 to 0.82) and 0.75 (0.59 to 0.85) with the new correction for gestational age.

In Figure 4, pain scores are shown for the different postmenstrual age groups for which the N-PASS score was corrected. For 43 of the 50 patients (86%) the vital signs remained within normal limits (N-PASS item score 0).

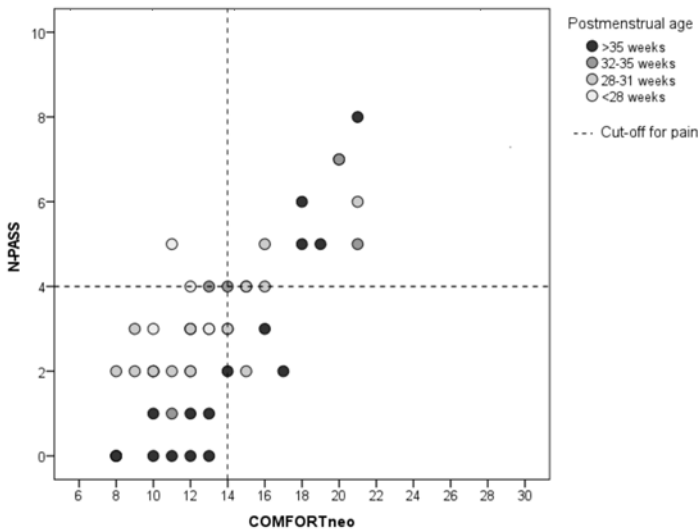


Figure 4. Correlation between COMFORTneo and N-PASS scores (N=50)

## DISCUSSION

Our study shows that the COMFORTneo is an instrument with good inter-rater reliability and acceptable intra-rater reliability and construct validity to measure prolonged pain in newborns admitted at the NICU. Our findings complement and strengthen the conclusion of the previous validation study.<sup>16</sup>

Directly after the implementation of this scale in the NICU, ten years ago, the inter-rater reliability was high with a linearly weighted Cohen's kappa of 0.79.<sup>16</sup> After using the COMFORTneo for over ten years, the

inter-rater reliability has further improved with an ICC of 0.93. A possible explanation may be the increased experience of the NICU nurses using this scale. This corresponds with the findings by Stenkjaer et al., who also found a significantly improved inter-rater reliability five years after the implementation of the COMFORTneo.<sup>18</sup>

The intra-rater reliability of the COMFORTneo was lower than expected. The ICC of 0.70 was equal to the lowest acceptable limit we set before the start of this study. The validation studies regarding other pain measurement instruments, the Neonatal Infant Acute Pain Assessment Scale (NIAPAS) and Bernese Pain Scale for Neonates (BPSN), found a higher level of agreement between the same assessors at different time points, respectively 0.99-1.00 (Pearson correlation coefficient, 2 raters) and 0.98-0.99 (Cronbach's alpha reliability, 4 raters) per rater.<sup>29, 30</sup> While the intra-rater reliability of these instruments was much better compared to our study, the lower number of raters, shorter time interval between the two assessments, and the fact that the raters were aware of the re-assessment during the first assessment of the NIAPAS and BPSN validation studies could have potentially explained these results.

Another explanation for our lower intrarater reliability could be that the environmental circumstances differed during the observations of the video fragments for the determination of the intra-rater reliability. Also, with video fragments one relies on the angle of the recording, whereas with bedside observations you can move around to have a full view of the neonate. This would mean that the intrarater reliability was influenced by environmental circumstances related to both the surroundings and the way in which the neonate is observed (i.e. bedside or video). Interestingly Black et al specifically recommend to use video recordings for research purposes in order to improve consistency.<sup>31</sup>

Regarding the construct validity, the correlation between the COMFORTneo scale and the NRS pain was lower than hypothesized. Furthermore, the correlation between the COMFORTneo and the NRS distress was higher than with the NRS pain. In our ward, the COMFORTneo is always assessed together with the numeric rating scale (NRS) for pain and distress in order to differentiate pain from distress.<sup>16</sup> In the current study few patients -fortunately - were exposed to pain ; only two of the 310 NRS pain scores were four or higher (0.6%). The lack of patients that were considered painful decreases the variation and therefore deflates the correlation. The COMFORTneo should be able to measure prolonged pain in all NICU patients in order to make it clinically applicable. It seems necessary

to validate the instrument in a population with greater variability in prolonged pain levels. It is important to determine which patients are at risk for experiencing this type of pain, but this is complicated without a clear definition. Referring to the framework presented by Anand,<sup>13</sup> Ilhan et al. recently formulated consensus-based definitions for acute episodic and chronic pain, but not for prolonged pain.<sup>32</sup> It seems like prolonged or persistent pain might be caused by painful conditions (e.g. necrotizing enterocolitis) unrelated to procedures, tissue injury (e.g. postoperative) and repeatedly experiencing painful procedures while an infant has not yet recovered from earlier procedures.<sup>13, 33</sup> It is difficult to differentiate pain from distress in neonates based on their behavior.<sup>34</sup> When applying the COMFORTneo together with these NRS scores, this may enable NICU clinicians to objectify and differentiate both pain and distress and treat accordingly.

Although there is some overlap between the COMFORTneo and the N-PASS, the most important differences between both scores are the addition of the vital parameters and the correction for gestational age in the N-PASS.<sup>35</sup> Hummel et al. chose to correct for gestational age because previous studies showed premature neonates are less able to show signs of pain than term infants.<sup>24</sup> However, in the validation studies of the N-PASS score as well as the COMFORTneo the mean pain scores were similar for each gestational age group, without adding additional points for different gestational age groups.<sup>16, 24</sup> The COMFORTneo does not include vital parameters because of the lack of evidence for a relationship with prolonged pain.<sup>16, 35</sup> The N-PASS item that assesses vital signs showed very little variability between patients in our study with 86% of the patients receiving a score of 0. Hummel et al. did not present scores per item in their N-PASS validation study, though it would be interesting to see if they found greater variability because they specifically included ventilated and/or postoperative infants that are expected to experience a higher level of prolonged pain.<sup>24</sup>

One of the strengths of the current study is the use of the Consensus-based Standard for the selection of health Measurement Instrument (COSMIN) guidelines and checklist.<sup>26</sup> Giordano et al. used this checklist to evaluate the quality of validation studies focusing on pain and sedation scales for neonatal and pediatric patients and found that the COMFORTneo was one of the seven most relevant scales for this patient population with a low risk of bias.<sup>12</sup> Another strength of our current study is that all simultaneous assessments took place with the same researcher with a high level of

agreement with the pain expert. The different COMFORTneo, N-PASS and NRS scores that were correlated were assessed independently by different assessors, which reduces the risk of bias.

This study also has some limitations. The fact that only few NICU patients were painful or distressed is reassuring but also limits this study. Still, we need to keep in mind that this is also due to our focus on prolonged pain and not on acute pain caused by heelpricks or venapunctures for example. The latter type of pain will occur more often than prolonged pain. Furthermore, in daily care doctors will prescribe pain-reducing medication as soon as a child is diagnosed with a painful condition such as necrotizing enterocolitis. This may result in low pain scores despite the condition of the child. While patients with varying gestational and postnatal age were included in our study, specific patient groups such as infants with necrotizing enterocolitis or asphyxiated infants might need additional attention in future validation studies. Next, we are not able to provide nursing characteristics. Since they were selected based on convenience sampling, however, we expect the participating nurses to be representative for the full NICU nursing staff. Furthermore we did not test responsiveness, 'the ability of an instrument to detect change over time in the construct to be measured'.<sup>22, 36</sup> Since an instrument for prolonged pain is necessary in order to evaluate the effect of pain reducing interventions, it is important to also evaluate this measurement property in a future study. Finally, our data collection was performed in 2015-2016 and the delay in publishing our finding could be considered a drawback. However, neither our policy nor our patient mix has changed in the past years and we still apply the same pain and sedation protocols as at the time of the data collection.

The behavioral response to pain might not always correspond with brain and spinal cord activity.<sup>37</sup> Physiological indicators are being studied for acute pain assessment. For example, skin conductance, heart rate variability and methods that focus on the brain such as Near-Infrared Spectroscopy (NIRS) and electroencephalography (EEG) could give information regarding the level of pain in neonates. The results of these studies are promising but more research is needed before these methods will be available to use in clinical practice and for prolonged pain.<sup>38</sup> More advanced physiological methods such as heart rate variability and NIRS could complement behavioral observations but require more testing. Assessment of pain and stress in the vulnerable NICU patients depends on the use and interpretation of observational measurement instruments

such as the COMFORTneo scale.

This validation study shows that the COMFORTneo scale has acceptable inter-rater reliability and moderate intra-rater reliability. Next to this, the COMFORTneo correlates well with the N-PASS, but less so with the NRS pain. Future validation studies should focus on neonates with prolonged painful conditions and this underlines the continuous process of validating measurement instruments. Combining the COMFORTneo score with a NRS for pain and distress might be an easy way to improve observational pain assessment in neonates until more advanced pain assessment methods become available.

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# Chapter 4

Acute pain assessment in prematurely born infants less than 29 weeks: a long way to go

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## **ABSTRACT**

### ***Objectives***

Neonates born extremely prematurely are at high risk of acute and prolonged pain. Effective treatment requires reliable pain assessment, which is currently missing. Our study explores if existing pain assessment tools and physiological indicators measure pain and comfort accurately in this population.

### ***Methods***

We prospectively collected data in 16 neonates born less than 29 weeks gestational age during three conditions: skin-to-skin care, rest and heelstick procedure for capillary blood sampling in the incubator. The neonates were video recorded in these situations and recordings were coded using five observational pain assessment tools and numeric rating scales for pain and distress. We simultaneously collected heart rate, respiratory rate, arterial oxygen saturation, regional cerebral oxygenation and number of skin conductance peaks. All measures across the three conditions were compared using general linear modeling.

### ***Results***

The median gestational age was 27.1 weeks (range 24.1 to 28.7). Forty measurement periods across the three conditions were analyzed. Heart rate was significantly higher during heelstick procedures compared to during rest with a mean difference of 10.7 beats/minute (95% CI 2.7 to 18.6). Oxygen saturation was significantly higher during skin-to-skin care compared to during heelstick procedures with a mean difference of 5.5% (95% CI 0.2 to 10.8). The Premature Infant Pain Profile-revised (PIPP-R) score was significantly higher during heelstick procedures compared to skin-to-skin care with a mean difference of 3.2 points (95% CI 1.6 to 5.0).

### ***Discussion***

Pain measurement in clinical practice in prematurely born infants <29 weeks remains challenging. The included behavioral and physiological indicators did not adequately distinguish between a painful situation, rest and skin-to-skin care in premature neonates.

## INTRODUCTION

In a European Delphi study published in 2015, “pain and stress” were considered the most important research priority for all neonates in Neonatal Intensive Care Unit (NICU) nursing.<sup>1</sup> Previous research showed that the number of painful interventions (causing mucosal or skin injury) that NICU patients experience during their first 14 days of life is the highest for the most premature neonates (24-29 weeks) namely 14 per day compared to 10 for neonates of 30-32 weeks and 9 between 33-36 weeks.<sup>2</sup> Furthermore, neonates born extremely prematurely are at the highest risk of painful conditions, such as necrotizing enterocolitis<sup>3</sup> and potentially painful and stressful mechanical ventilation.<sup>2</sup> Nonetheless, pain responses of these vulnerable infants are still poorly understood.<sup>4</sup>

Because we started to treat neonates born extremely prematurely at many NICUs, it is our duty to protect them from pain and distress just as well as older patients. Experiencing pain is associated with poor growth,<sup>5</sup> impaired brain development,<sup>6</sup> altered corticospinal development,<sup>7</sup> and reduced school-age visual perceptual abilities in these infants.<sup>8</sup> To mitigate the effects of pain effectively, we must ensure that we can accurately assess pain in these patients.

Various validated pain assessment tools are available for use in the neonatal intensive care unit, for example the Premature Infant Pain Profile Revised (PIPP-R) and Neonatal Infant Pain Scale (NIPS) for acute pain, and the COMFORTneo scale and Neonatal Pain, Agitation and Sedation Scale (N-PASS) for more prolonged pain.<sup>9-12</sup> A review by Cong et al. shows that none of the published neonatal pain assessment tools was validated in neonates with a gestational age less than 29 weeks.<sup>13</sup> The tools partially (multi-dimensional scales) or fully (uni-dimensional scales) rely on behavioral cues, which may be difficult to assess in very premature neonates. Many pain scales rely heavily on facial indices, although very premature infants show less vigorous facial response than do neonates with higher gestational age at birth, as their neuro-muscular system is still developing.<sup>4</sup> Moreover, health care professionals find the responses short-lasting and unpredictable.<sup>4</sup>

Physiologically-based tools may be an alternative to behavioral pain assessment. For example, skin conductance measurement seems promising to assess acute pain in premature neonates with a gestational age between 22 and 27 weeks.<sup>14</sup> Studies measuring cerebral oxygen saturation using near infra-red spectroscopy (NIRS) in preterm infants

from 25 weeks gestational age showed that noxious stimuli caused by a heelstick or venipuncture were transmitted to the cortex.<sup>15, 16</sup> Vital signs such as heart rate increase in response to acute pain,<sup>17</sup> although the increases may also be the result of other physiologic factors, such as hypovolemia.

At this time there are no tools validated for assessing pain specifically in premature neonates < 29 weeks. As these infants may react differently to pain than do more mature neonates,<sup>4</sup> we hypothesized that existing pain measurement tools, both behaviorally and physiologically based, might be less valid to evaluate pain and comfort in a very premature patient. The aim of this observational study is to test the above hypothesis.

## **MATERIALS AND METHODS**

### ***Study design***

This was a prospective, observational, exploratory study.

### ***Patients and setting***

This study was conducted from September 2015 to June 2016 in the level 4 neonatal intensive care unit of the Erasmus MC – Sophia, Rotterdam, the Netherlands. Premature infants born with a gestational age less than 29 weeks were eligible for inclusion and subjects were selected by convenience sampling. Infants expected to die within 48 hours after birth, and those with severe intraventricular hemorrhage (grade 3 or greater) and/or other neurological damage based on screening cranial ultrasound were excluded. Data were collected until a postnatal age of 28 days or until discharge. The institutional ethics review board waived the need for approval (MEC-2014-324) because the study was judged to be an observational study. However, parents were asked to provide written consent for video-recording of their infants, for applying skin conductance electrodes and for using the NIRS and vital signs data collected as part of standard of care. We refrained from performing a power analysis as this was the first study on pain assessment parameters in extremely preterm infants and no data on variability of parameters were available.

### ***Assessment tools***

- Behavioral pain observation tools:
  - o PIPP-R: A seven-item scale including behavioral state, gestational age, change in heart rate, change in peripheral oxygen saturation, and three items for facial expression.

Items are scored 0 to 3 and the total score range is 0-21. Three points are added for neonates with a gestational age less than 28 weeks and 2 points if gestational age is between 28 and 32 weeks. A score less than 7 is taken to indicate no or minimal pain.<sup>9</sup>

- Neonatal Infant Pain Scale (NIPS): Includes six items; namely: facial expression, crying, breathing pattern, arms, legs, and state of arousal. Items are scored 0 to 1 or 2 and the total score range is 0-7. A score of 2 or less is taken to indicate adequate pain treatment.<sup>11</sup>
- Behavioral Indicators of Infant Pain (BIIP): Includes the assessment of behavioral state, five face expressions, and two hand movements. Items are scored 0 to 1 or 2 and the total score range is 0 to 9.<sup>18</sup> Scores between 3 and 6 and between 7 and 9 are taken to indicate respectively moderate and severe pain.
- COMFORTneo: Includes six items, namely alertness, calmness/agitation, crying (non-ventilated infants), respiratory response (ventilated infants), body movements, muscle tone, and facial tension. Each item has a score range of 1 to 5 and the total score range is 6-30. A score of 14 and higher is considered a sign of distress and pain.<sup>12</sup>
- Neonatal Pain, Agitation and Sedation Scale (N-PASS): A five-item scale including crying/ irritability, behavior state, facial expression, extremities tone, and vital signs. Each item is scored from 0 to 2; thus, the total score ranges from 0 (no pain) to 10 (pain/agitation). The same correction for gestational age is applied as for the PIPP-R. The goal of pain treatment is a score of 3 or less.<sup>10</sup>
- Numeric Rating Scale (NRS) pain and distress scores: NRS scores range from 0 to 10 with cut-off scores set at  $\geq 4$  for both NRS pain and NRS distress.
- Physiological parameters: Data on heart rate, respiratory rate and oxygen saturation (SpO<sub>2</sub>) were collected automatically from bedside monitors (Infinity M540, Drägerwerk AG & Co. KGaA, Lübeck, Germany).
- Regional cerebral oxygenation: regional cerebral oxygen saturation (crSO<sub>2</sub>) was measured with near infrared spectroscopy (NIRS via INVOS 5100C, Somanetics Corporation, USA). As per our NICU standard of care, one neonatal NIRS electrode was placed on the

frontolateral aspect of the head; either left or right depending on the infant's position. This placement site was chosen to minimize the number of interventions related to this study.

- Skin conductance: A skin conductance monitor (MED-storm Innovation AS, Oslo, Norway) was connected to three electrodes placed on the foot.

### ***Procedures***

As part of standard of care, preterm infants at the NICU often undergo a heelstick procedure, which is painful, and on the other hand receive skin-to-skin care, an intervention considered to bring comfort or even pain relief.<sup>19</sup> For a pain measurement indicator to be suitable for extremely premature infants, we would expect scores to be significantly different painful and comforting procedures

Therefore, we chose the following conditions to determine if indicators were able to discriminate between conditions of pain, rest and comfort:

Skin-to-skin care (comfortable); the infant was placed on the mother's or father's chest lying skin-to-skin, after which the NIRS and skin conductance electrodes were reconnected. The infant was not disturbed during skin-to-skin care.

Measurement period: Two minutes, from the start of video registration and the moment when clear signals for data collection from the NIRS and skin conductance measurements were received.

At rest (baseline); with the infant positioned in a nest and covered by a blanket, data collection started after no interventions had been applied for at least 30 minutes.

Measurement period: Two minutes starting at least 30 minutes after any handling of the neonate

Heelstick procedure (painful); by protocol, each infant received 0.5ml sucrose two minutes before a heelstick procedure. Facilitated tucking was applied from the administration of sucrose until the end of the procedure by a healthcare assistant, nurse or parent.

Measurement period: From the moment the heel was punctured until the band-aid had been applied to the heel.

We considered the two-minute measurement period for skin-to-skin care sufficient to observe a reaction to the stimulus. If clinically possible, the measurements under the different conditions took place on the same day. During data collection the full body was filmed using one camera (Sony HDR-PJ810E). Skin conductance electrodes were placed, if possible, on

the foot that was not to be punctured. Correct placement of the NIRS electrode on the frontolateral aspect of the head was checked before starting the measurement.

### **Data extraction**

Immediately before video recording, the exact time displayed on the monitors collecting data on vital parameters, crSO<sub>2</sub> and skin conductance was filmed for each condition. This was to synchronize these data with the corresponding video sequences.

Behavioral pain observation tools: For each condition, the research nurse (NM) applied the five validated pain assessment tools described above as well as the NRS for pain and the NRS for distress. Each video segment was viewed in real time and lasted two minutes; for condition 3 (heel stick), these two minutes followed the puncturing of the heel. Because the PIPP-R, for which a shorter, 30-second observation period is prescribed, the indicated amounts of time used for the classification of the items for facial expressions were multiplied by four (4x 30 secs). NM applied the following scoring strategy after having viewed a two-minute video fragment. For instance, first all items related to facial expression from all the scales were consecutively scored and so on for the other items. If necessary, the video segment was viewed multiple times until all items of the 5 pain assessment instruments were scored. Total pain assessment scores were calculated and a correction was applied if one or more of the items could not be assessed (for example a score was multiplied by 7/6 if one of seven items could not be observed). We adjusted for missing items because we considered it unjustified to completely ignore these scores. NM could not be blinded to the different conditions because these were clearly recognizable. Before start of the study, the interrater reliability of NM was determined for the PIPP-R and COMFORTneo scale. Linearly weighted kappa of NM compared to a trained neonatologist (for PIPP-R) and MvD (for COMFORTneo) was 0.85 and 0.92, respectively.

Physiological parameters and crSO<sub>2</sub>: These values were extracted once per second during the measurement period and mean and standard deviation of each patient's measurements were calculated for each parameter. These values had also been extracted during the two minutes immediately before the condition measurement period; the mean value was calculated. The change between the mean value of this baseline period and that of the measurement period was determined.

Skin conductance: The mean number of skin conductance peaks per second (sc peaks/sec) during the measurement period and the change in the number of peaks per second compared to that in the two minutes immediately before this period was calculated using the Med-Storm software with a pre-set threshold value of 0.005 micro Siemens. A higher number of skin conductance peaks suggests more pain [20].

### ***Data analysis***

Patient characteristics and other data are presented as median (interquartile range) for continuous variables and as percentages for categorical variables. General linear modeling, which is a generalization of linear regression analysis to account for repeated measurements, was applied to compare the previously described assessment tools between the three different conditions. The independent variables were condition (pain, rest or comfort) and postnatal age in days (coded as a continuous variable); the dependent variable was the pain indicator.

An unstructured error covariance matrix was assumed in the general linear models to account for the within-subject correlations. Dependent variables that were not normally distributed were transformed using the square root or the natural logarithm of the data for the general linear model. SPSS 21.0 was used for all analyses, and all statistical tests used a two-sided significance level of 0.05.

## **RESULTS**

### ***Patient characteristics***

Sixteen neonates were included, whose median gestational age was 27 weeks and 1 day (range 24.1 to 28.7 weeks; see Table 1 for background characteristics). The median postnatal age at the time of assessment was 17 days (interquartile range 14 to 23 days). Eleven neonates were assessed in all conditions on the same day; the other five at intervals from 2 to 17 days. If both skin-to-skin care and the heelstick procedure were assessed on the same day, the time interval between these two events was at least 3 hours. None of the patients received any analgesics or sedatives other than sucrose during the observation days.

**Table 1 - Patient and measurement characteristics**

Variables	N	Median	IQR
<b>Patient characteristics (N=16)</b>			
Boy/Girl	12/4		
Gestational age (weeks)		27.1	25.7 to 28.0
Birth weight (grams)		938	865 to 1261
<b>Measurement characteristics (N=40)</b>			
Postnatal age (days)		17	14 to 23
Time between observation days per patient (days) <sup>a</sup>		0	0 to 7
Ventilatory support			
Invasive ventilation			
Endotracheal tube	6		
Non-invasive ventilation			
Nasopharyngeal tube	19		
Silicone double nasal tube (Vygon®)	5		
Nasal cannula Optiflow	10		

<sup>a</sup>The number of days between the observations of the different conditions.

### ***Physiological and behavioral indicators***

Table 2 shows the main outcomes during the three different conditions. A total of 40 observations were included; six skin-to-skin care sessions had been missed for logistic reasons; one neonate did not require a heelstick procedure and one other had been disturbed at least every 30 minutes during the observation days. Physiological parameters for some observations were lacking because of technical difficulties (see Table 2).

The results of the general linear modeling are shown in Table 3. Significant differences between the different conditions were found for the heart rate, spO<sub>2</sub> and the PIPP-R. The mean heart rate was significantly higher during a heelstick procedure compared to rest (estimate 10.7, 95% CI 2.7 to 18.6,  $p=0.01$ ), but not compared to skin-to-skin care (5.5, 95% CI -1.7 to 12.8,  $p=0.12$ ). The heart rate varied greatly between patients and during the three conditions (Figure 1). The change in heart rate from baseline was significantly greater during the heelstick procedure than during both skin-to-skin care (estimate 8.8, 95% CI 5.9 to 11.8,  $p<0.001$ ) and rest (8.4, 95% CI 6.0 to 10.8,  $p<0.001$ ) (Figure 2). Also, both the mean oxygen saturation (estimate 5.5, 95% CI 0.2 to 10.8;  $p=0.04$ ) and the change in oxygen saturation from baseline (4.5, 95% CI 0.8 to 8.3;  $p=0.02$ ) were significantly higher during skin-to-skin care than during the heelstick procedure, while this difference was not significant when comparing rest with the heelstick procedure.

Table 2 - Physiological and behavioral parameters

	Skin-to-skin care (N=10)			Rest (N=15)			Heelstick (N=15)		
	N	Median	IQR	N	Median	IQR	N	Median	IQR
<b>Physiological parameters</b>									
SK peaks/sec	10	0.18	0.06 to 0.76	15	0.09	0.00 to 0.33	15	0.22	0.03 to 0.34
Heart rate <sup>a</sup>									
Mean	8	163	156 to 169	14	158	150 to 169	13	166	152 to 175
SD		2.2	2.0 to 5.5		1.8	1.6 to 2.9		3.1	2.6 to 3.7
Respiratory rate <sup>a</sup>									
Mean	8	39	31 to 50	14	50	38 to 62	13	48	34 to 59
SD		16.8	10.1 to 19.5		12.5	8.7 to 15.9		9.3	7.6 to 17.3
spO <sub>2</sub> <sup>a</sup>									
Mean	8	93	91 to 95	14	95	91 to 98	12	91	86 to 97
SD		1.2	0.8 to 1.3		0.8	0.6 to 2.2		1.8	1.0 to 4.6
crSO <sub>2</sub> <sup>a</sup>									
Mean	9	63	55 to 67	15	64	56 to 69	15	61	50 to 66
SD		1.4	0.9 to 2.7		1.4	1.0 to 2.9		1.4	1.1 to 2.9
<b>Pain assessment tools</b>									
COMFORTneo	10	12	9 to 15	15	11	8 to 16	14	12	11 to 13
NPASS	10	3	2 to 4	15	3	2 to 4	14	3	3 to 5
NIPS	10	1	0 to 3	15	0	0 to 4	14	1	0 to 3
PIPP-R	10	6	4 to 7	15	8	7 to 9	14	8	8 to 12
BIIP	10	1	0 to 2	15	0	0 to 2	14	2	0 to 4
NRS pain	10	0	0 to 0	15	0	0 to 0	14	1	0 to 2
NRS distress	10	0	0 to 2	15	0	0 to 3	14	0	0 to 2

<sup>a</sup>For the physiological parameters heart rate, respiratory rate, spO<sub>2</sub>, the mean and the standard deviation (SD) of the data per second during the measurement period were calculated for each patient separately.

**Table 3 - Estimated effects (general linear model)**

	Skin-to-skin care (N=10)#			Rest (N=15)#		
	Estimate	95% CI	P	Estimate	95% CI	P
<b>Physiological parameters</b>						
SC peaks/sec <sup>a</sup>	0.03	-0.26 to 0.31	0.84	-0.14	-0.32 to 0.04	0.13
Change	-0.04	-0.14 to 0.07	0.49	-0.03	-0.15 to 0.10	0.64
Heart rate						
Mean	-5.54	-12.8 to 1.7	0.12	-10.69	-18.6 to -2.7	0.01*
Mean change	-8.83	-11.8 to -5.9	<0.001*	-8.42	-10.8 to -6.0	<0.001*
SD <sup>b</sup>	-0.07	-0.05 to 0.38	0.75	-0.15	-0.57 to 0.27	0.46
Respiratory rate						
Mean	-4.42	-15.3 to 14.5	0.48	4.8	-7.9 to 17.5	0.43
Mean change	3.55	-5.6 to 12.7	0.42	-1.37	-13.0 to 10.3	0.80
SD	4.64	-1.56 to 10.84	0.13	1.22	-2.13 to 4.58	0.45
spO <sub>2</sub>						
Mean	5.48	0.2 to 10.8	0.04*	5.74	-0.6 to 12.1	0.07
Mean change	4.53	0.8 to 8.3	0.02*	3.43	-0.8 to 7.7	0.11
SD <sup>b</sup>	-0.36	-0.79 to 0.06	0.09	-0.40	-0.91 to 0.10	0.11
crSO <sub>2</sub>						
Mean	2.63	-3.8 to 9.0	0.39	3.53	-1.5 to 8.5	0.15
Mean change	3.26	0.1 to 6.5	0.05	1.70	-1.3 to 4.7	0.25
SD <sup>b</sup>	-0.12	-0.41 to 0.17	0.38	-0.02	-0.30 to 0.26	0.89
<b>Pain assessment tools</b>						
COMFORTneo	-1.5	-3.9 to 1.0	0.21	-1.9	-4.5 to 0.6	0.13
NPASS <sup>a</sup>	-0.2	-0.6 to 0.1	0.17	-0.2	-0.5 to 0.1	0.22
NIPS <sup>b</sup>	-0.3	-0.8 to 0.3	0.32	-0.2	-0.8 to 0.4	0.52
PIPP-R	-3.2	-5.0 to -1.6	0.002*	-1.0	-3.9 to 1.9	0.48
BIIP <sup>b</sup>	0.4	-1.0 to 0.1	0.13	-0.5	-1.1 to 0.1	0.10
NRS pain	-	-	-	-	-	-
NRS distress	-0.4	-1.3 to 0.5	0.37	-0.3	-1.4 to 0.8	0.61

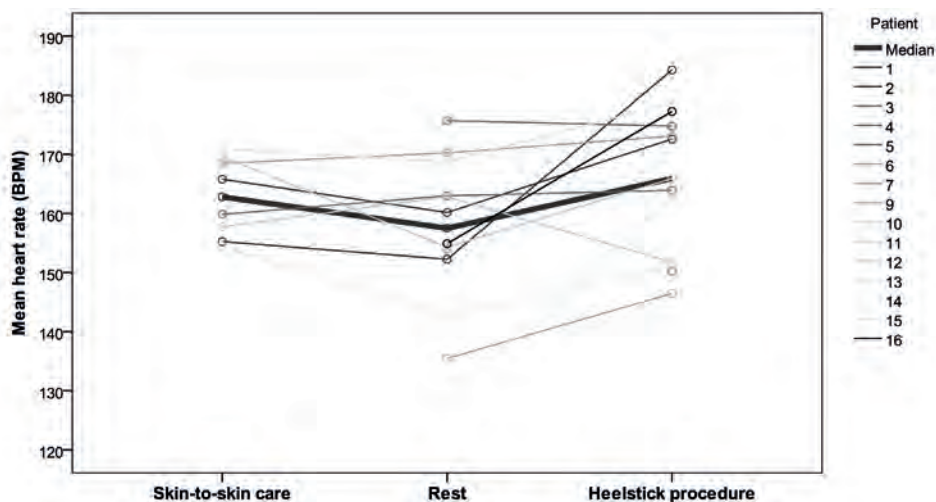
# Heelstick procedure (N=15) was the reference category for this model.

The model was adjusted for postnatal age for all outcomes.

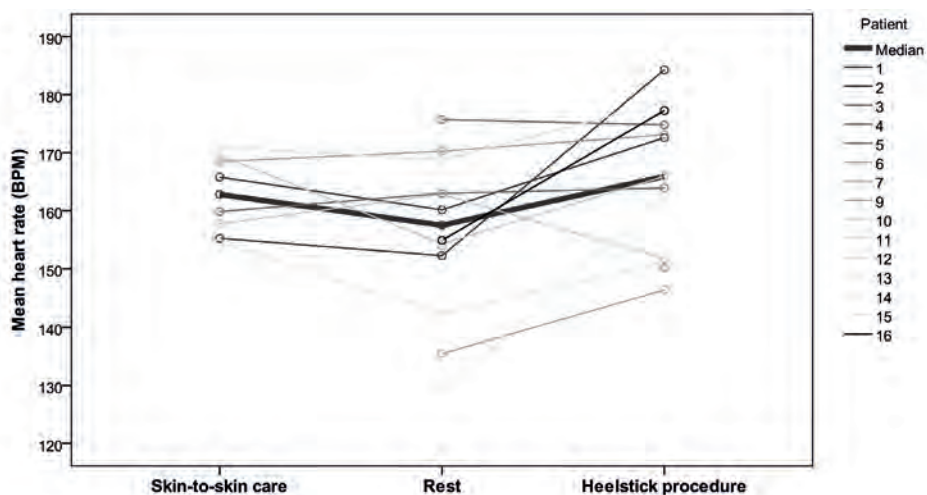
For the physiological parameters heart rate, respiratory rate, spO<sub>2</sub> and crSO<sub>2</sub>, the mean and the standard deviation (SD) of the second-to-second data during the measurement period were calculated for each patient separately. After this, the difference between the mean value during and before the measurement period was calculated and referred to as the "mean change".

For skin conductance, the average number of peaks per second during the measurement period was calculated for each patient. Next to this, the difference between this value and the average number of peaks per second during the baseline period was calculated and referred to as the "change".

\* <0.05 <sup>a</sup>Transformed using SQRT(variable) <sup>b</sup>Transformed using LN(variable+1)



**Figure 1 - Mean heart rate during different conditions**



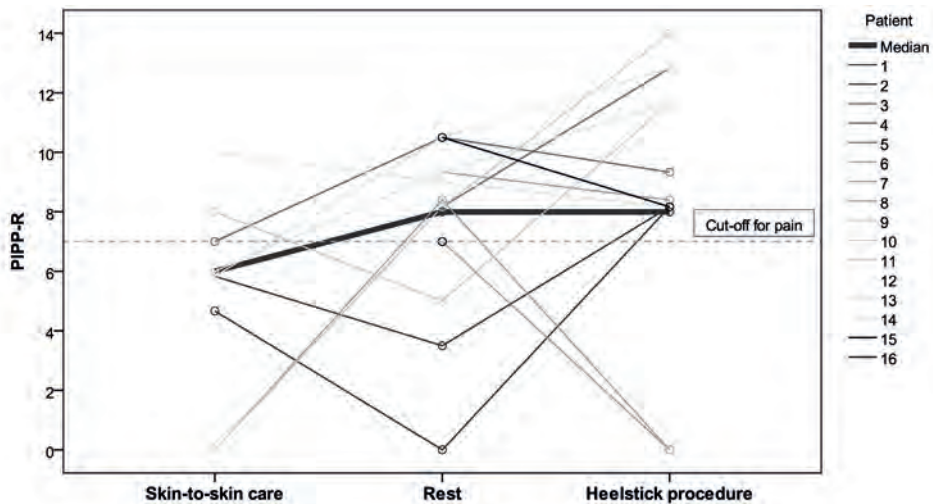
**Figure 2 - Mean heart rate compared with baseline during different conditions**

### ***Observational pain assessment***

General linear modeling was not possible for the NRS pain because 80% of the scores were 0. A significant difference between conditions was only found for the PIPP-R score. This score was on average 3.2 points lower during skin-to-skin care than during the heelstick procedure (95% CI -5.0 to -1.6,  $p=0.002$ ). The PIPP-R scores varied greatly between patients (Figure 3). For example, while the PIPP-R score during heelstick procedure

was higher than during rest for seven patients, the reverse was true for the six others patients. Because general linear modeling was already applied to compare the vital signs, the analysis of the PIPP-R and N-PASS scores was repeated after the exclusion of the item(s) related to vital signs. The PIPP-R during skin-to-skin care remained significantly lower than during the heelstick procedure (-2.0, 95% CI -3.1 to -0.9,  $p=0.03$ ), while the differences in PIPP-R score between rest and the heelstick procedure and the differences in N-PASS scores remained statistically insignificant.

Practical issues had prevented scoring a number of items of the five different scales. For 86 (43%) of the 200 pain scores all items could be assessed, all other scores had to be recalculated. Striking examples are muscle tension of the legs (NIPS) and nasolabial furrow (PIPP-R, BIIP), which could not be assessed in respectively 36 (90%) and 32 (80%) of the 40 observations. One infant appeared to be fully covered by the two hands of the caregiver and a blanket during the heelstick procedure, making it impossible to score any item.



**Figure 3 - PIPP-R (Premature Infant Pain Profile – Revised ) scores during different conditions**

## DISCUSSION

We found that pain measurement in extreme preterm infants is challenging. In the total population studied, the mean heart rate, spO<sub>2</sub> and PIPP-R each significantly differed between a painful procedure and either rest or skin-to-skin care. The change in heart rate from baseline was the only parameter that was significantly different between all three conditions. Although these studied indicators seem to be most promising to assess pain, their applicability in clinical practice is complicated by the large variability in pain expression of this specific population.

The heelstick procedure is a painful procedure, which is often used in validation studies. A valid tool is preferably also responsive, i.e. it should yield a higher score during the heelstick procedure compared to rest or skin-to-skin care. In our study population, the difference in scores between the three studied conditions was only statistically significant for the PIPP-R. It is unclear why the other pain scores could not discriminate between the different situations. A possible reason is the extreme prematurity of the study population. Pain processing in premature infants is still developing; in a previous study; infants with the youngest gestational age showed the least change in facial behavior during a heelstick procedure.<sup>20</sup> A recent study by Green et al. demonstrated that neonates were able to show discriminative facial expressions to tactile and noxious stimulation only from approximately 33 weeks' gestation.<sup>21</sup> The validation studies of the included instruments also included neonates older than 29 weeks.<sup>9-12, 22, 23</sup> Holsti et al. have found that more specifically defined extremity movements are increased in preterm infants at lower gestational ages.<sup>24</sup> The BIIP does include such movements, but other indicators may be required for this population. Regarding the N-PASS, Munsters et al. also did not find a significantly higher pain score during the heelstick procedure compared to baseline in a study among preterm infants with a gestational age less than 28 weeks.<sup>14</sup> In that study, the skin conductance during a heelstick procedure was significantly higher than that at baseline, suggesting more pain.<sup>14</sup> We could not duplicate these findings.

Heart rate and spO<sub>2</sub> are considered the most sensitive bedside-available physiological variables to measure pain in preterm and full-term infants.<sup>17</sup> The same seems to hold true in our study population. In our study, heart rate was significantly lower only during rest compared to during the heelstick procedure with a mean difference of 11 beats/minute. The change in heart rate compared to a baseline period shortly before the

measurement period was significantly smaller during skin-to-skin care and during rest than during the heelstick procedure. In a previous study in extreme prematures (<28 weeks), Gibbins et al. found similar heart rate responses during diaper change compared to the heelstick procedure.<sup>25</sup> The change in heart rate might not be specific for pain, but related to increased stress as a result of the diaper change and heelstick procedure. As in our study, in that study mean spO<sub>2</sub> did not statistically differ between a heelstick procedure and baseline. However, in our study, the mean spO<sub>2</sub> was significantly higher during skin-to-skin care compared to during the painful situation. In their meta-analysis, Boundy et al. found significantly higher oxygen saturations during skin-to-skin care compared to conventional care.<sup>19</sup>

We found no significant differences in cortical oxygenation measured with NIRS between the three studied conditions, in contrast to a study by Slater et al.<sup>16</sup> In that study, however, the difference in total cerebral hemoglobin measurement as an indicator for cerebral blood flow was measured before and after the heelstick procedure, whereas we were only able to measure regional oxygen saturation, as we used a different device (INVOS instead of NIRO-200). Also, we measured oxygen saturation in the prefrontal cortex instead of the somatosensory cortex in Slater's study. While both these brain areas are involved in pain processing, the cortical responses in somatosensory and prefrontal areas might vary in response to pain. Because measuring the hemoglobin concentration in the somatosensory cortex seems more promising, we would suggest further research to focus on this aspect of the cerebral circulation.

One or more items of a scale could often not be scored from the video footage. During rest, for example, fixation material for the ventilator tubes and a blanket sometimes blocked the view on the infant. The hands of the nurse providing facilitated tucking and the pacifier complicated the observation of facial expression during the heelstick procedure. These limitations are inseparably linked to filming these vulnerable and very small premature infants without disturbing the normal course of events. Munsters et al. found observing subtle changes in facial expression bedside in neonates less than 28 weeks gestational age difficult because of the presence of respiratory support, oral and nasal gastric tubes.<sup>14</sup> The difficulty of observing neonatal facial expression during current neonatology practices was the reason for Milesi et al. to develop the "faceless" acute neonatal pain scale (FANS), which does not rely on facial observation.<sup>26</sup>

On the basis of our findings, we conclude that the included pain indicators (except from the change in mean heart rate from baseline) fail to detect different levels of both pain and comfort in an individual very premature neonate. However, during the observations of these infants under the three different conditions we realized that this finding could also be influenced by other factors than the altered pain response of this specific population. We expected the premature infants to be more comfortable on the mother's or father's chest compared to lying in an incubator.<sup>19</sup> However, we were not able to detect this beneficial effect. In general, certain indicators may be able to detect changes in pain intensity, but be not sensitive to the level of comfort. Also, we think that environmental stressors such as noise and light might have exerted an influence and that our open-bay unit resulted in a greater exposure to stressors compared to a single-room NICU.<sup>27</sup> Another possible explanation for our finding could be that some neonates had not yet calmed down after the transfer from the incubator to the parent's chest.<sup>4</sup> It is also possible that the heelstick procedure was less painful than we anticipated. Our protocol prescribes the use of sucrose and facilitated tucking to minimize heelstick-related pain.<sup>28</sup> Because of the convincing evidence on the pain-related behavior effects of sucrose,<sup>29</sup> we considered it unethical to perform a heelstick procedure without the administration of sucrose. However, the lack of change in our measures is likely to be a result of the sucrose administration. Moreover, in view of the uncertainties with respect to the working mechanisms of sucrose,<sup>30</sup> and reported oxidative stress<sup>31</sup> and possible adverse effects on the brain,<sup>32, 33</sup> the American Academy of Pediatrics guidelines suggests that more research is needed to establish long-term safety.<sup>28</sup>

The study design originally also included electroencephalography (EEG), but none of the subjects received an EEG as part of their standard care. Recently, Hartley et al. validated an EEG-based measure of nociceptive brain activity in healthy neonates with a gestational age above 34 weeks.<sup>34</sup> Measuring brain activity using EEG in our study population is complicated by for example the very thin and vulnerable skin of the scalp. Another pain indicator which we were unable to include is heart rate variability, which can be analyzed using the Newborn Infant Parasympathic Evaluation (NIPE).<sup>35</sup> While results from previous studies using heart rate variability to assess prolonged pain in both term and preterm neonates are promising,<sup>36, 37</sup> Cremillieux et al. concluded that the NIPE index did not appear to reliably measure acute procedural pain in preterm infants.<sup>38</sup> More research is needed to confirm the validity and reliability to measure prolonged pain and comfort.

We were able to apply a combination of various physiological and behavioral indicators during different conditions in the same patient. It has been suggested that a multi-modal approach would help in the understanding and management of infant pain.<sup>39, 40</sup> The small sample size of the present study may have lowered the probability of finding significant differences between the three conditions. However, we aimed to find pain indicators that could be used in clinical practice, which requires showing a relatively large difference between painful and non-painful circumstances. A larger sample might have resulted in a higher number of significantly different outcomes between the conditions. Still, this would not necessarily mean that these indicators would be clinically relevant. We consider the large variation between the different patients as the most important complicating factor for using these indicators in clinical practice.

Our study is further limited by the fact that we wanted to intervene as little as possible. Our NIRS-device only measured oxygenation saturation in the prefrontal cortex and we were unable to include EEG registration.

We were also dependent on the interventions that were clinically necessary during the observation day and therefore patients' postnatal ages at the time of the measurements were not always the same. While we corrected for postnatal age in the model, factors other than pain may have influenced physiological indicators across the different circumstances. For example, body temperature influences skin conductance and NIRS values are positively correlated with postnatal age.<sup>15, 41</sup> Also, Grunau et al. showed that higher cumulative neonatal procedural pain exposure was related to lower facial responses to pain.<sup>42</sup> The influences of these factors would be minimized if measurements took place on the same day.

In conclusion, of the potential physiological pain indicators studied, only the change in heart rate was significantly different between skin-to-skin care, rest and heelstick procedure in these extremely premature infants; none of the potential behavioral pain indicators studied was. The heart rate, oxygen saturation and PIPP-R scores were most promising because they significantly discriminated between at least two of the three conditions. However, due to the large variation on these indicators between patients these are not readily applicable to discriminate pain from comfort in an individual patient. Dampened responses to the painful stimulus, vulnerability to environmental circumstances and practical issues seem to complicate pain measurement in these children. For the time being it seems that we still have a long way to go before pain in neonates born prematurely can be reliably measured.

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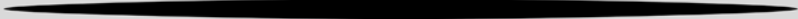
# PART II

Pain  
treatment



# Chapter 5

Waiting 2 minutes after sucrose administration unnecessary?



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## **ABSTRACT**

### ***Background***

Worldwide, oral sucrose is standard of care in many NICU's to relieve procedural pain in neonates. This study aims to determine if time-interval between sucrose administration and heelstick correlates with pain scores.

### ***Methods***

Neonates were prospectively studied with variable time-intervals and assessed with the Premature Infant Pain Profile revised (PIPP-R).

### ***Results***

150 neonates were included with a median gestational age of 30<sup>+6</sup> (IQR 27<sup>+6</sup>-33<sup>+2</sup>) weeks and a median time-interval of 72 (IQR 39 to 115) seconds between sucrose administration and heelstick. In multiple regression analysis this time-interval was not significantly related to the PIPP-R (B=0.004, 95%CI -0.005 to 0.013, p=0.37). Providing non-nutritive sucking combined with sucrose was significantly related to lower PIPP-R scores (B=-3.50, 95%CI -4.7 to -2.3, p<0.001).

### ***Conclusion***

Our study suggests that there is no need to wait 2 minutes after sucrose administration before a painful procedure. Sucrose-induced non-nutritive sucking shows a fast pain-relieving effect in neonates.

## INTRODUCTION

Oral administration of sucrose significantly reduces procedural pain in newborns.<sup>1</sup> It is most effective when combined with non-nutritive sucking (NNS).<sup>1</sup> This intervention is therefore recommended in international neonatal pain guidelines.<sup>2</sup>

In most studies sucrose is administered 2 minutes prior to the painful procedure.<sup>1</sup> To our knowledge, only one study evaluated the effect of this time-interval and found it optimal.<sup>3</sup> Because this study included healthy newborns only, we aimed to test whether this conclusion also holds true for premature or critically ill neonates.

We hypothesized that pain scores for premature or critically ill term neonates will be lowest when a time-interval of approximately two minutes is used. The aim of the study was to determine if the time-interval between sucrose administration and heelstick is correlated with pain scores.

## METHODS

This prospective study was conducted from September 2014 to February 2015 at a level 3 neonatal intensive care unit. Eligible for inclusion were all preterm and critically ill term neonates with an indication for blood sampling by heelstick. Patients were selected by convenience sampling and could be included only once. This study consisted of two consecutive parts, A and B. In part A 100 heelstick procedures were performed without any guidance on time-interval. In part B the medical team was instructed to adhere to a 2-minute time-interval<sup>3</sup> during 50 heelstick procedures. This way we expected a large variation of time-intervals and a sufficient population to perform a regression analysis. The institutional ethical review board waived the need for approval (MEC-2014-357).

### **Data collection**

The procedure, starting with the commencement of sucrose administration (T=0), was timed with a stopwatch. The pacifier was gently applied into the mouth and sucrose was administered inside the cheek. Without pressure the nurse held the pacifier in place until the infant started to suck.

Primary outcome was the pain score obtained with the validated Premature Infant Pain Profile-Revised (PIPP-R)<sup>4</sup>, applied during the first 30 seconds after the heelstick. A score <7 suggests no or little pain, 7-12 slight-to-moderate pain and scores >12 are thought to reflect moderate-to-severe

pain. All assessments were performed by a research nurse (NM) trained to score the PIPP-R (linearly weighted kappa compared to a trained neonatologist = 0.85). If one of the PIPP-R items could not be assessed, a proportional score was calculated by multiplying the total score by 7/6.

Other variables recorded were: gestational age, postnatal age, non-nutritive sucking at time of the prick, number of doses, total volume of sucrose administered, size of the lance (BD Microtainer® Quickheel™ Lancet Preemie or Infant), number of heel squeezes, and number of pricks needed. All heelsticks were performed by trained lab personnel while a nurse or healthcare assistant provided facilitated tucking.

Our clinical treatment protocol prescribed the use of sucrose 24% with a maximum volume of 0.5 cc or 2.0 cc in patients with bodyweight < 1000 or >1000g, respectively.

### ***Data analysis***

The association between PIPP-R and the time-interval was estimated with Spearman rank correlation coefficient. Multiple linear regression analysis with PIPP-R total score as outcome variable and the time-interval in seconds as predictor variable was applied. The relevant covariates postnatal age in days, NNS, total volume of sucrose in milliliters and gender were also entered into the regression model. Gestational age was not included because it is included in the PIPP-R score. A sensitivity analysis was performed by replacing time-interval in seconds with study phase (part A or part B) in the regression model.

## **RESULTS**

Hundred-and-fifty patients were included with a gestation age between 24<sup>+1</sup> and 42<sup>+1</sup> weeks. One patient in part B received a second dose of sucrose during the time-interval and was excluded from the analysis. Table 1 shows background characteristics and main study parameters.

The correlation between PIPP-R and time-interval was 0.11 (95% CI = -0.05 to 0.27, P = 0.17). Large variations in both time-interval and PIPP-R scores were found (Figure 1).

**Table 1 - Patients' background characteristics and main study parameters (N = 149)**

Variables	Part A (N = 100)	Part B (N = 49)	P value
Boy/Girl; N (%)	61 (61)/39 (39)	24 (49)/25 (51)	0.16
Gestational age in weeks <sup>+days</sup>	30 <sup>+6</sup> (28 <sup>+5</sup> to 33 <sup>+2</sup> )	30 <sup>+6</sup> (26 <sup>+6</sup> to 33 <sup>+2</sup> )	0.26
Birth weight in grams	1483 (1158 to 2015)	1280 (888 to 1950)	0.18
Postnatal age in days	4 (2 to 8)	5 (2 to 10)	0.11
Time-interval in seconds	48 (31 to 79)	127 (107 to 153)	<0.001
Non-nutritive sucking; N (%)	48 (48)	23 (47)	0.90
Patients with 1 dose; N (%)*	98 (98%)	44 (90%)	0.27
Total volume of sucrose in ml	0.5 (0.5 to 0.75)	0.5 (0.5 to 0.75)	0.78
Size of the lance:			
Preemie; N (%)	12 (12)	7 (14)	0.69
Infant; N (%)	88 (88)	42 (86)	
Unable to score nasolabial furrow; N (%)	44 (44)	30 (61)	0.05
Duration of procedure in seconds	112 (59 to 191)	154 (97 to 257)	0.014
Number of squeezes	17 (8 to 28)	22 (13 to 36)	0.04
Analgesics/sedatives; N (%)**	5 (5)	5 (10)	0.23
PIPP-R	6 (0 to 9)	7 (2 tot 9)	0.22

\*Patients who received one dose during the total procedure (from sucrose administration until the end of the blood collection)

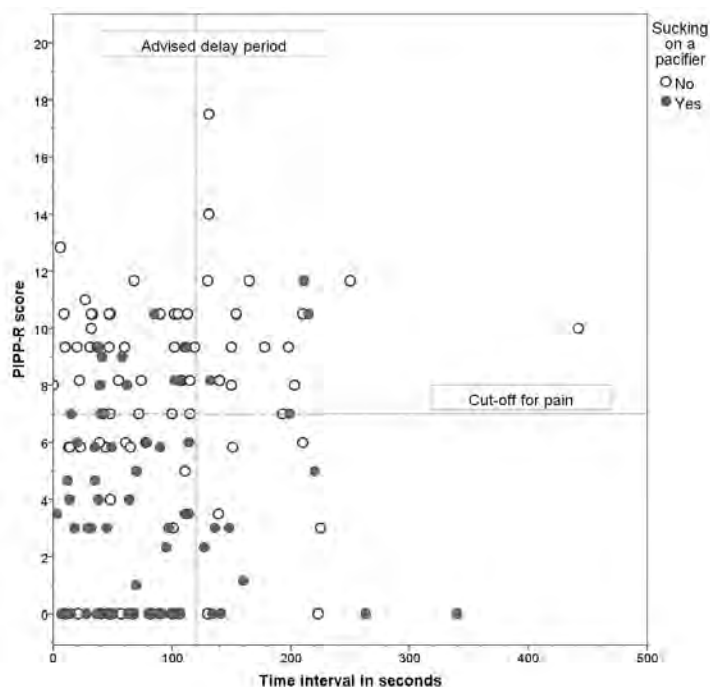
\*\* Patients who received continuous or intermittent morphine/fentanyl and/or midazolam during or <3 hours before the heelstick procedure.

Data are presented as median (IQR) for all continuous variables.

Part A and part B data were compared using the chi-square test for categorical variables and the Mann Whitney U test for continuous variables.

### **Multivariate analysis**

In multiple regression analysis, too, the time-interval was not significantly associated with PIPP-R scores, with an estimated association of 0.004 (95% CI -0.005 to 0.013,  $p=0.37$ ) points on the PIPP-R per second. Non-nutritive sucking was correlated with an average decrease in mean PIPP-R score of 3.5 points (95% CI -4.7 to -2.3,  $p < 0.001$ ). Replacing time-interval with study phase in the regression model, the PIPP-R score was on average 0.99 points higher in part B (95% CI -0.29 to 2.26,  $p=0.13$ ). Postnatal age, gender and volume of sucrose were not significantly correlated to PIPP-R scores.



**Figure 1 - Correlation between time-interval after sucrose administration and PIPP-R score (N = 149)**

Reference lines are at the time-interval of 120 seconds and the cut-off score for PIPP-R of 7 or higher. Markers differentiate between yes/no non-nutritive sucking.

## DISCUSSION

We found that in the studied hospitalized newborns, the heelstick-related pain intensity was not correlated with the length of the time-interval between the administration of sucrose and the heelstick. This is in contradiction with the only other comparable study, which led to the worldwide clinical implementation of a 2-minute time-interval<sup>3</sup>. In that study, however, the primary outcome was “crying” and only healthy newborn were included. We used the validated PIPP-R,<sup>4</sup> which was not yet available at the time of the previous study and included premature and critically ill term neonates.

Our finding does not correspond with the supposition that a certain length of time must elapse to mediate opioid responses and inhibit nociceptive impulses.<sup>5</sup> The absence of a time-interval versus effect relationship in our study suggests that sucrose induces a change in the patient’s behavioral state rather than a pharmacological effect. Our finding thus underlines the

uncertainties concerning the working mechanisms of sucrose.<sup>2</sup>

The PIPP-R was applied during the first 30 seconds following the heelstick, according to the instructions of the instrument, while blood sampling lasted for a median of two minutes. This way we focused on pain related to the insertion of the lance. According to previous research the effect of sucrose can persist 5 to 10 minutes after a painful stimulus.<sup>5</sup> Since time-interval after sucrose administration did not affect relief of the acute pain upon insertion of the lance, we expect that likewise it does not affect relief of the pain related to the preceding squeezing either. If faster onset of action is received, fewer sucrose doses may be needed, which would reduce the possible negative effect of sucrose on neurodevelopment.<sup>2</sup>

Strictly adhering to a 2-minute time-interval<sup>1</sup> was difficult, for example when an unstable infant needed time to recover before the heelstick procedure could start.

The study design led to several limitations with uncontrollable confounders that could possibly have influenced time-interval and pain intensity. Potential confounders were for example the intensity and number of times the heel was squeezed. Also, we did not take into account the administration of analgesics and sedatives. In addition, the research nurse observed the total procedure and thus was not blinded to the time-interval. Still, this is the first study that questioned if the worldwide implementation of the 2-minute time-interval based on one study was indeed justified. In future studies, blinded coders should score the PIPP-R from video recordings. A blinded randomized controlled trial comparing different time-intervals is underway.

## CONCLUSION

Our study does not justify the need to wait at least 2 minutes after sucrose administration but needs reevaluation in a randomized controlled trial. Shorter time-intervals importantly improve efficiency in busy intensive care units. It is best to give sucrose with a pacifier to stimulate sucrose-induced NNS to reduce pain responses.

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# Chapter 6

Infants operated on for necrotizing enterocolitis:  
towards evidence-based pain guidelines

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## **ABSTRACT**

### ***Background***

Necrotizing enterocolitis (NEC) is known as an extremely painful childhood condition.

### ***Objectives***

The objective of this study was to explore pain management around NEC-related surgery in our NICU from a chart review of prospectively collected data of sixty operated NEC patients admitted between 2008 and 2013 with a median (IQR) gestational age of 28.3 (25.5 – 31.6) weeks.

### ***Methods***

Pain medication data and pain scores (COMFORTneo, NRS pain and NRS distress) from 72 hours before surgery until 72 hours after surgery were collected.

### ***Results***

Ninety-five percent of patients received morphine pre-operatively versus 100% postoperatively with a median dosage of 10.0 (IQR 9.7 to 14.5) and 16.9 (IQR 10.1 to 20.0) mcg/kg/hour, respectively. Postoperatively 28 patients (46.7%) received additional fentanyl intermittently and 14 patients (23.3%) received midazolam, which was part of palliative treatment in 6 patients (42.9%). In patients receiving pain medication, median COMFORTneo scores were 10 (IQR 10 to 11) pre-operatively and 11 (10 to 12) post-operatively. Those pain scores were comparable with those of other patients admitted to the NICU in the same admission period.

### ***Conclusions***

Continuous morphine of 10 mcg/kg/h pre-operatively and an increase to 15 mcg/kg/h postoperatively seem a good starting dose for further individualized pain management guided by pain scores.

## INTRODUCTION

Necrotizing enterocolitis (NEC) is a dreadful and extremely painful complication that is related to very high morbidity and mortality.<sup>1, 2</sup> Research efforts so far have mainly focused on the aetiology, surgical and conservative treatment and prevention of the disease.<sup>3</sup> It is important, though, to protect hospitalized neonates from pain, not only for ethical reasons but also in view of possible negative short-term and long-term consequences of untreated pain.<sup>4, 5</sup> Yet, there is surprisingly little research about optimal pain management in NEC.<sup>6, 7</sup> In contrast to other intestinal diseases, such as an isolated perforation or congenital atresia, NEC is much more painful pre and postoperatively on account of the ongoing inflammatory and ischemic processes in the intestines as well as the related peritonitis.<sup>8, 9</sup> There is consensus among clinicians that NEC-related pain must be assessed and treated, but how this should be done is unclear and usually this is left to the discretion of the treatment team.<sup>10-12</sup> To our knowledge there are no guidelines for the assessment and management of NEC-related pain.

While the main focus of current research on neonatal pain assessment is on acute procedural pain, the assessment of NEC-related pain asks for an instrument validated for the assessment of prolonged pain.<sup>13</sup> In our hospital a modified version of the COMFORT-behaviour scale, the COMFORTneo scale, was designed and validated to assess prolonged pain in premature neonates.<sup>14</sup>

Opioids seem the most appropriate for the pain management in NEC.<sup>15</sup> For premature infants weighing less than 1000 grams morphine at 10 mcg/kg per hour or 0.5 to 2 mcg/kg per hour continuous fentanyl is considered a reasonable dosage to relieve NEC-related pain,<sup>16</sup> although there is no evidence for this assumption. Based on the latest population PK/PD model for morphine, lower post-operative dosages might be more appropriate in neonates undergoing major non-cardiac surgery, particularly when they are younger than 10 days of age,<sup>17, 18</sup> but the question remains whether this holds for NEC patients as well.

The current study describes pain management in neonates before and after NEC-related surgery on the guidance of validated pain scales. We also aimed to determine if pain assessment scores were comparable to those of patients admitted to the NICU with other diagnoses.

## **MATERIALS AND METHODS**

### ***Study design***

Retrospective chart review of prospectively collected data in the computerized Patient Data Management System (PDMS).

### ***Patients and setting***

All neonates admitted to the level III neonatal intensive care unit (NICU) of the Erasmus MC – Sophia Children's Hospital, Rotterdam, the Netherlands, who underwent a laparotomy for suspected or confirmed NEC (Bell stages 2 and 3) from January 2008 to December 2013 were included. Patients with a focal intestinal perforation (FIP) were excluded, as this was considered as a separate entity.<sup>19</sup> Because of the different histopathology and possible differences in painfulness, our study concentrated on operated infants with confirmed NEC.

The used pain management protocol is described in figure 1. Guided by pain scores analgesics could be titrated. In case of suspected pain during caregiving, intermittent fentanyl could be added. There is a probable synergistic sedative effect between morphine and midazolam.<sup>20</sup> Midazolam is therefore sometimes given to preterm neonates whose discomfort does not adequately respond to morphine therapy. This pain protocol is used for all NICU patients and not specifically for NEC patients.

### ***Data collection***

The following data were retrieved from the PDMS: sex, date of birth, gestational age at birth, date of surgery, medication data and pain and distress scores. The time of start of surgery and end of surgery and confirmation of NEC diagnosis were retrieved from surgery reports. The time of NEC diagnosis is often unclear. Therefore a time span of 72 hours was chosen for specific data collection. Medication data and COMFORTneo and Numeric Rating Scale (NRS) scores were collected, however, for the period spanning 72 hours before start of surgery through 72 hours after end of surgery, excluding intraoperative medication. For patients who died within 72 hours after surgery, the data collected until time of death were included in the analysis. The type of surgery was categorized by a surgeon (CKD). In addition, to enable comparison with other patients, pain scores (COMFORTneo and NRS pain and distress) for all other patients, surgical and non-surgical, admitted to the NICU in the research period were retrieved. The advised morphine dosages according to the PK/PD model of Krekels et al., based on the birthweight and postnatal age, were also

calculated.<sup>17</sup>

### Measurement instruments

Nurses in our NICU are trained to apply the COMFORTneo scale and a Numeric Rating Scale (NRS) for Pain and a NRS for distress. A nurse's inter-rater reliability for the COMFORTneo scale was assessed from the weighed Cohen's kappa.<sup>21</sup> calculated from the results of 10 paired assessments with a qualified nurse. The COMFORTneo score has been validated for the use in the NICU.<sup>14</sup> The cut-off score for pain is set at 14 and higher. The total score ranges from 6 to 30. NRS scores range from 0 to 10 and cut-off scores for NRS pain and NRS distress are both set at 4 and higher. The pain management protocol prescribes that each neonate is assessed during rest at least once during every 8-hour shift. Extra assessment is indicated after administration of sedatives or analgesics and if pain, over- or under sedation is suspected.

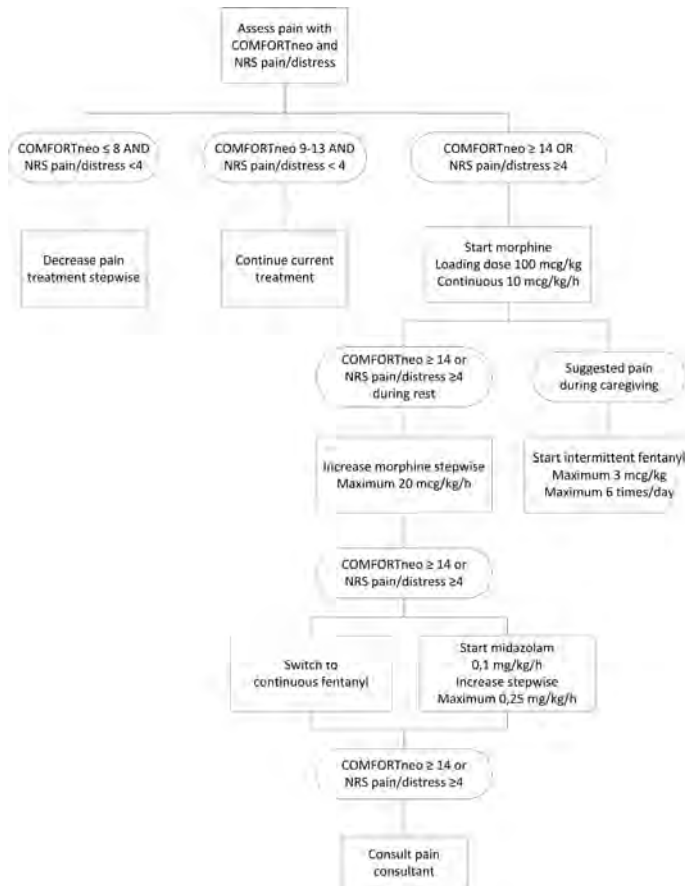


Figure 1 - Pain treatment flow diagram

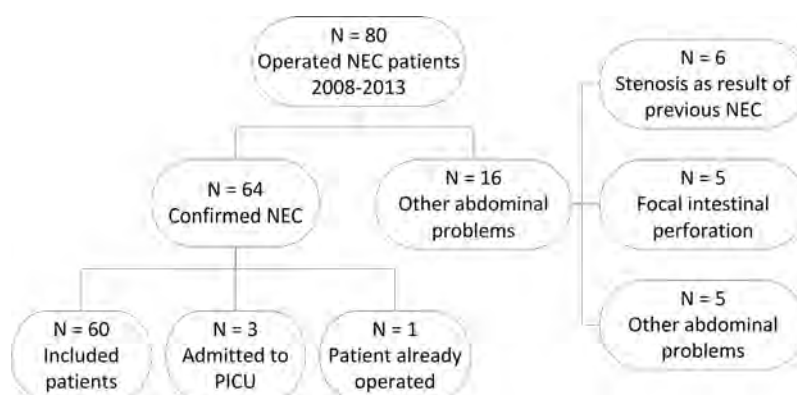
## Data analysis

Data were exported from the PDMS automatically to SPSS 21.0 (SPSS Inc., Chicago, USA). Postoperative morphine dosages were compared with the recently advised morphine dosing for postoperative neonates after major non-cardiac surgery by Krekels et al.<sup>17</sup> Median COMFORTneo scores, NRS pain and NRS distress before and after surgery were compared with the Wilcoxon signed-rank test. The institutional ethical review board waived the need for approval because the participants did not have to undergo medical procedures or follow special rules of behaviour (MEC-2014-547).

## RESULTS

### Patients

Figure 2 shows the patient flow diagram for this study. Of the 80 neonates operated on because of suspected or proven NEC between 2008 and 2013, 60 patients were included in this study. Three patients were admitted to the PICU and one patient had already undergone a laparotomy in another NICU; these four patients were excluded because of possible differences in pain management.



**Figure 2 - Patient flow diagram**

Table 1 shows patients' background characteristics. The median gestational age was 28 weeks and 3 days; median postnatal age at the time of surgery was 10 days (range 5-57 days). Fourteen patients (23.3%) died within 72 hours after surgery. All of these deaths were related to NEC and were preceded by the decision to withdraw IC treatment. Ten patients had (almost) complete necrotic intestines; the four other patients had undergone a 'second look' operation to evaluate viability of the intestines within 72 hours.

**Table 1 - Patients' background characteristics (N=60)**

Variables	
Boy/Girl; N (%)	24 (40) / 36 (60)
Gestational age in weeks <sup>+days</sup> ; median (IQR)	28 <sup>+3</sup> (25 <sup>+5</sup> to 31 <sup>+6</sup> )
Birth weight in grams; median (IQR)	1053 (836 to 1525)
Postnatal age at surgery in days; median (IQR)	10 (8 to 22)
Death within 72h after surgery; N (%)	14 (23.3)
Re-laparotomy within 72h; N (%)	4 (6.7)
Bell staging *; N (%)	
2B	5 (8.3)
3A	17 (28.3)
3B	38 (63.3)
Pre-operative drain	3 (5.0%)
Surgery; N (%)	
(Almost) complete necrotic intestines	10 (16.7)
Partial jejunal/ileal resection	18 (30.0)
Ileocecal resection/hemicolectomy/partial colon resection	15 (11.7)
Subtotal colectomy	7 (11.7)
Partial jejunal/ileal and partial colon resection	6 (10.0)
Isolated creation of stoma/clip and drop	4 (6.7)

\* Adapted Bell's criteria <sup>22</sup>

### ***Pain assessment***

COMFORTneo and NRS pain and distress scores were available for 56 patients (93.3%) pre-operatively and 52 patients (86.7%) post-operatively. The patients without preoperative pain scores had been admitted from 5 to 15 hours before surgery. The patients without pain scores postoperatively had died within 2 to 9 hours after surgery. COMFORTneo scores 72 hours after surgery were significantly higher than those 72 hours before surgery (Wilcoxon signed-rank test,  $P = 0.012$ ). Median NRS pain was higher pre-operatively than post-operatively, but the difference was not statistically significant (Wilcoxon signed-rank test,  $P = 0.117$ ). Median NRS distress tended to be higher after surgery than before but this was not statistically significant (Wilcoxon signed rank,  $P = 0.099$ ).

Table 2 shows pain scores of included NEC patients in the 72 hours pre-operative period and in the 72 hours post-operative period, and of all other patients admitted in the study period. These results are presented in figure 3 as median COMFORTneo and NRS pain scores per patient. Thirteen patients received only morphine (21.7%). One, two or three additional analgesic or sedative drugs were administered to 36 (60.0%), 10 (16.7%), 1 (1.7%) patients, respectively.

**Table 2 - Pain assessment results and administered analgesics and sedatives before and after surgery in NEC patients. Additionally, pain assessment results for all other admitted patients.**

	72 hours before surgery	72 hours after surgery	All NICU patients (2008- 2013)
Patients assessed; N (%)	56 (93.3)	52 (86.7)	3685
Total number of COMFORTneo scores per patient; median (IQR)	9 (5-12)	13 (11-16)	8 (3 to 22)
<b>COMFORTneo</b>			
Median (IQR)	10 (10-11)	11 (10-12)	10 (10 to 11)
Patients with at least one score $\geq$ 14; N (%)	27 (45.0)	37 (61.7)	1760 (47.7)
Patients with at least one score $\leq$ 8; N (%)	33 (55.0)	33 (55.0)	1659 (45.0)
<b>NRS pain</b>			
Median (IQR)	0 (0 to 2)	0 (0 to 1)	0 (0 to 0)
Patients with at least one score $\geq$ 4; N (%)	31 (51.7)	23 (38.3)	516 (14.0)
<b>NRS distress</b>			
Median (IQR)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Patients with at least one score $\geq$ 4; N (%)	11 (18.3)	17 (28.3)	1193 (32.4)
<b>Morphine</b>			
Patients; N (%)	57 (95.0)	60 (100)	-
Cumulative dose in mcg/kg/72h; median (IQR)	307 (133 to 626)	895 (459-1177)	
Maximum dose per hour in mcg/kg/h; median (IQR)	14.6 (10.0-19.8)	19.8 (15.0-20.5)	
Median dose per hour in mcg/kg/h; median (IQR)	10.0 (9.7-14.5)	16.9 (10.1-20.0)	
<b>Fentanyl</b>			
Patients intermittent; N (%)	21 (35.0)	28 (46.7)	-
Patients continuous; N (%)	-	2 (3.3)	
Median dose in mcg/kg; median (IQR)	2.0 (1.7-2.3)	2.0 (1.3-2.2)	
Number of doses; median (IQR)	1.0 (1.0-2.5)	4.0 (2.0-8.0)	
<b>Acetaminophen</b>			
Patients; N (%)	1 (1.7)	5 (8.3)	-
<b>Midazolam</b>			
Patients; N (%)	3 (5.0)	14 (23.3)	-
Cumulative dose in mg/kg/72h; median (IQR)	3.5 (0.5-3.6)	(0.4-1.8)	
Used for palliative treatment; N(%)	-	6 (42.9)	
<b>Clonidine</b>			
Patients; N (%)	-	1 (1.7)	-

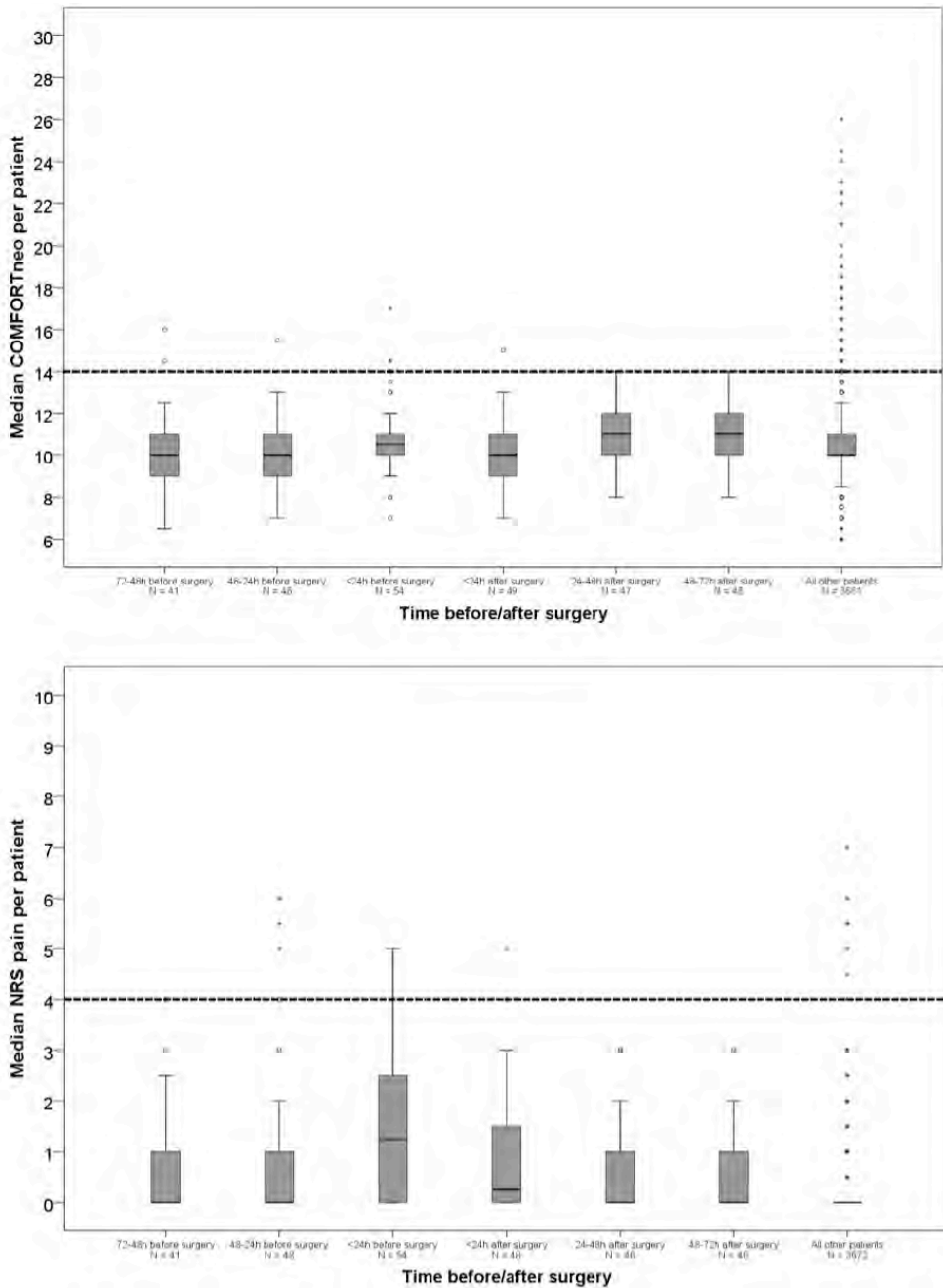
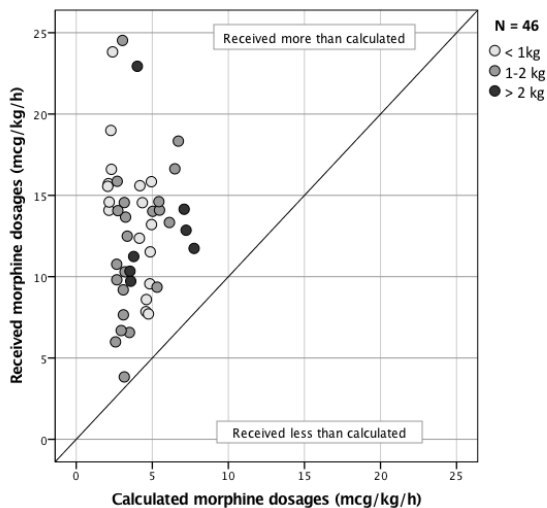


Figure 3 - Boxplots showing COMFORTneo scores (upper panel) and NRS pain scores (lower panel) for the patients with NEC

## Pain management

All patients received morphine after surgery. Fifty-seven of them (95.0%) also received morphine before surgery (table 2). Both the maximum dose and the median dose per patient in mcg/kg/hour were significantly higher after surgery (both Wilcoxon Signed Rank,  $P < 0.001$ ). After surgery, almost half of the patients (46.7%) additionally were given intermittent fentanyl before procedures that are painful in these patients, such as diaper change. Fourteen patients (23.3%) additionally received midazolam after surgery; for six patients as part of the palliative treatment. Median doses are presented as median per patient.

Figure 4 shows the relation between postoperative morphine dosages in our research population, with exclusion of those who died within 72 hours after surgery, and the calculated morphine dosages according to the PK/PD model of Krekels et al. This validated model is based on term newborns undergoing major non-cardiac surgery who received a loading dose of 100 ug/kg at the OR. Dosage recommendations are based on their postnatal age ( $\leq 10$  days or  $> 10$  days) and weight.<sup>17</sup> It shows that all neonates in our research population required more morphine than the calculated dosages.



**Figure 4.** Calculated PK/PD model-based morphine maintenance doses for neonates after major non-cardiac surgery as a follow up to 100 mcg/kg loading dose<sup>17</sup> (X-axis) compared to the average received morphine dosages in neonates after NEC surgery over 72 hours (Y-axis)

Doses are provided for different groups of patients based on birthweight.

## DISCUSSION

We found that pain scores for neonates who underwent surgery for NEC were acceptable and comparable to pain scores of all other patients admitted to the NICU in the same period. Median continuous morphine dosages of 10 and 17 mcg/kg/hour before and after surgery were needed, respectively, to reach adequate analgesia. One or more additional analgesics, particularly fentanyl, were needed in 78.3% of the patients.

To our knowledge, only one other paper has been published on pain assessment and pharmacological management in infants with NEC.<sup>23</sup> This retrospective study included 25 infants with stage II NEC and pain was assessed with the Premature Infant Pain Profile (PIPP), validated for acute painful procedures only. Nurses' compliance with pain assessment was poor and PIPP scores were not presented. Mean morphine infusion during 5 days after initial diagnoses was 15 mcg/kg/hour combined with a mean dose of fentanyl of 3 mcg/kg/hour. The morphine doses in that study are comparable to ours and slightly higher than suggested by Thiagarajah et al, i.e. 10 mcg/kg per hour for premature infants weighing less than 1000 grams in the post-operative period after a laparotomy for NEC.<sup>16</sup>

The recently advised morphine dosing for postoperative neonates after major non-cardiac surgery by Krekels et al is much lower than what patients in the present study needed,<sup>17</sup> as shown in Figure 4. Although Krekels et al did not study preterm neonates weighing less than 2 kg, it seems that for NEC and NEC related surgery separate dosing guidelines for morphine and additional analgesics administration are necessary. Neonates received significantly more morphine postoperatively and also received more additional analgesic or sedative drugs compared to preoperatively. Based on the present study, we would advise to start morphine at 10 mcg/kg/h after a loading dose when NEC is diagnosed. Postoperatively this dose should be increased to 15 mcg/kg/h. Intermittent fentanyl can be added if pain assessments during caregiving indicate pain. If subsequently pain scores during rest remain too high, morphine dosages should be increased up to 20 mcg/kg/h. Continuous fentanyl and the addition of midazolam are alternatives if this maximum dose is still insufficient to achieve sufficient comfort. Although not frequently used in our study, intermittent intravenous paracetamol administration might be beneficial<sup>18</sup> but needs further study in this specific population.

Dosing of analgesics and sedatives needs to be adjusted on the guidance of pain scores to prevent over sedation and under sedation. Pain

assessment should always be performed before and after changes in analgesic treatment with for instance the COMFORTneo scale or the EDIN<sup>13, 14</sup> validated for prolonged pain. We showed that median COMFORTneo scores for patients with NEC were comparable to those of other NICU patients admitted in the same period. Both pre-surgery and post-surgery 55% of patients in our study population were assigned a COMFORTneo score of 8 or more versus 45% of the other patients. If over sedation was a problem in our study population, the difference between the groups would expectedly have been larger. We do realize, however, that COMFORTneo scores of 8 or lower are acceptable in patients who do not receive opioids or sedatives but are simply deep asleep. Because of the possibility of unjustifiably low pain scores due to the lack of body movements and blank facial expression which are common in NEC patients, it is important that not only COMFORTneo scores but also NRS scores are acceptable.<sup>13</sup>

The findings of this study offer a first step towards evidence based guidelines. Because the management of pain in NEC patients is still neglected in the scientific literature, prospective studies are needed to validate pain management guidelines and an adequate pain assessment instrument. Further research is also needed on specific behavioural, physiological item changes related to pain in NEC patients and to search for biomarkers and specific stress responses in these patients.

A strength of this study is the relatively large cohort studied, which allowed for reliable insight in the pain management in these very ill patients. This study, however, had a retrospective design and could only describe pain management in our NICU during the research period. Furthermore, non-operated NEC patients were not included which limits the generalizability of our results.

In conclusion, pain management, based on pain scores, for patients with severe NEC in our NICU was acceptable. This assumption is strengthened by the finding that both preoperative and postoperative COMFORTneo scores are comparable to those of all other patients admitted to the NICU in the same period. The morphine dosages needed were much higher than the morphine dosages suggested for paediatric non-cardiac surgery in a recent PK/PD model. In patients with severe NEC, continuous morphine of 10 mcg/kg/h pre-operatively and an increase to 15 mcg/kg/h postoperatively seem a good starting dose for further individualized pain management guided by pain scores.

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# PART III

Stress  
exposure



# Chapter 7

Quantification of stress exposure in very preterm infants: development of the NeO-stress score

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## **ABSTRACT**

### ***Background***

Stress during treatment at the Neonatal Intensive Care Unit (NICU) has long-term negative consequences on preterm infants' development.

### ***Aims***

We developed an instrument suited to validly determine the cumulative stress exposure for preterm infants in a NICU.

### ***Study design***

This survey study made use of two consecutive questionnaires.

### ***Subjects***

NICU nurses and physicians from the nine NICUs in the Netherlands.

### ***Outcome measures***

First, respondents rated the relevance of 77 items encompassing potentially stressful procedures, commented on their comprehensibility and the comprehensiveness of the list. We calculated the content validity per item (CVI-I) and included only the relevant items in a second questionnaire in which the participants rated the stressfulness from 0 (not stressful) to 10 (extremely stressful). A stressfulness index – representing the median score – was calculated for each included item.

### ***Results***

Based on the CVI-I of the 77 items, step 1 resulted in 38 items considered relevant to quantify stress in preterm infants during the first 28 days of life. This list of 38 items exists of 34 items with a CVI-I if 0.78 or higher, one of these items was split into two items, and three items were added to improve comprehensiveness. The stressfulness index ranged from five to nine.

### ***Conclusions***

The NeO-stress score consists of stressful items including their severity index and was developed to determine cumulative stress exposure of preterm infants. Evaluating the cross-cultural validity, correlating it to behavioural and biological stress responses, and evaluating its ability to predict preterm infants at risk for the negative effects following stress might expand the possibilities for this instrument.

## INTRODUCTION

The World Health Organization (WHO) has defined stress as any type of change that causes physical, emotional or psychological strain. Vulnerable preterm neonates admitted to the NICU will inevitably experience stress due to various stressors with negative impact on their health and development.<sup>1-3</sup> To start with, the maternal-placental-fetal unit is disrupted prematurely, which is a stressful event with direct consequences for the metabolic-endocrine balance and brain maturation.<sup>4, 5</sup> Moreover, the NICU admission is stressful due to medical treatment such as invasive ventilation and to being partly separated from the parents.<sup>6</sup> Even routine care such as diaper changes may increase infants' stress levels.<sup>7, 8</sup> Next to this, they have to endure acute pain from more than 10 painful procedures per day,<sup>9, 10</sup> and painful conditions such as necrotizing enterocolitis<sup>11, 12</sup> or postoperative pain may lead to more prolonged pain – and stress – exposure.<sup>12</sup>

Acute stress immediately decreases an infant's cardiorespiratory stability.<sup>13</sup> Moreover, stress exposure negatively affects a premature infant's cognitive, motor, behavioral and neurological development and results in an altered pain sensitivity at a later age.<sup>1, 14-18</sup> Long-term consequences like these might primarily result from altered brain development and epigenetic changes.<sup>15, 19</sup>

Quantifying the cumulative amount of stress exposure helps to gain insight in the negative short- and long-term consequences of stress and to evaluate interventions aimed at mitigating stress. Different instruments have been developed to quantify stress exposure. The Neonatal Infant Stressor Scale" (NISS), developed in Australia, measures stress in preterm infants (gestational age below 37 weeks), while the "Procedural Load Index" (PLI) and "Accumulated Pain/Stressor Scale" (APSS), developed in the United States, focus on all NICU patients.<sup>20-22</sup> None of these instruments have been validated for NICU populations outside the US or Australia. A first step towards using these instruments in our country would be to validate them in the Netherlands. However, regarding face validity, Dutch NICU nurses and physicians were of the opinion that these instruments did not just include relevant procedures and the estimated stressfulness of the included procedures did not match current clinical practice (unpublished). We therefore performed a study aiming to develop a bedside instrument with which NICU staff can determine a very preterm infants' daily cumulative stress level during the first 28 days of life.

## **MATERIALS AND METHODS**

### ***Construct to be measured***

This study focuses on the stress exposure from stimuli primarily related to NICU treatment, caregiving, and stressful conditions. The physical and biological responses to stress, such as oxidative and inflammatory stress, were not the focus of this study.

### ***Design***

This survey study made use of two consecutively administered questionnaires. First, participants scored the relevance and comprehensibility of potentially stressful items as well as the comprehensiveness of this list (first questionnaire). Secondly, the stressfulness of each finally included item was determined (second questionnaire). Both questionnaires started with a short explanation of the topic and inventory of the participants' basic characteristics. The institutional ethics review board waived the need for approval (MEC-2019-0574) because the study was judged to be an observational study without exposing infants to procedures or additional rules of behavior.

### ***Study population***

The first questionnaire was sent by email in February 2019 to 83 healthcare professionals (31 physicians and 52 nurses) representing three national expert groups of NICU nurses, nurse specialists/scientists and physicians from each Dutch NICU with a special interest in stress and/or research. A reminder was sent after two weeks and participation was closed three weeks after the questionnaire distribution. The second questionnaire was sent by email in January 2021 to representatives from all nine Dutch NICUs. They distributed the questionnaire amongst all physicians and nurses working in their NICU. We aimed for a minimum of 50 included healthcare professionals, which number is considered a very good sample size for quantitative studies on content validity based on the COSMIN guidelines ([https://www.cosmin.nl/wp-content/uploads/COSMIN-study-designing-checklist\\_final.pdf](https://www.cosmin.nl/wp-content/uploads/COSMIN-study-designing-checklist_final.pdf)). Moreover, to ensure a national representative overview, we wished to receive responses from at least five physicians and ten nurses from each hospital, and sent a reminder after two weeks when this criterion was not yet met. The questionnaire has been closed on 1st February 2021.

## **The questionnaires**

### *Step 1 - Content*

Taking all items of the NISS, APSS and PLI instruments and adding the items from an unpublished, unvalidated item list called "Dutch Point Prevalence List" (DPPL), composed by ten Dutch NICU nurses in 2016, resulted in a list of 231 potentially stressful items. Two researchers (NM, nurse scientist, and GvdB, neonatologist) screened this list until they reached consensus regarding the following changes (shown in Fig. 1):

- |        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Step 1 | 116 duplicate items were removed                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Step 2 | 16 items were combined with another item because of presumable overlap (e.g. dressing change was combined with wound care)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Step 3 | 26 items were removed for various reasons: <ul style="list-style-type: none"> <li>- Not applicable in any premature with a gestational age less than 29 weeks during the first 28 days (N = 12, e.g. extra corporal membrane oxygenation)</li> <li>- Applicable for all premature neonates with a gestational age less than 29 weeks during the first 28 days (N = 3, e.g. nasogastric tube in situ)</li> <li>- Included in another item that was listed (N = 7, e.g. removal of adhesives included in extubation)</li> <li>- Considered unclear (N = 4, e.g. recovering from lumbal puncture)</li> </ul> |
| Step 4 | 3 items were separated into 7 items because of the possible difference regarding the stress level (e.g. surfactant administration via MIST vs. via INSURE).                                                                                                                                                                                                                                                                                                                                                                                                                                               |

**Relevance and comprehensibility of the items:** The final list of 77 items was included in the first questionnaire. Participants scored the relevance of each item on a 4-point Likert scale: 1: not relevant, 2: somewhat relevant, 3: quite relevant or 4: highly relevant. Participants also indicated if each item was clear and, if not, to suggest changes to improve the comprehensibility.

**Comprehensiveness of the list:** After rating the relevance and the comprehensibility of each item separately, participants were asked to suggest missing relevant items. We had provided the 26 items that had been removed during step 3 of the item selection to determine if these should have been included after all.

### *Step 2 – Stressfulness*

Participants were asked to rate the remaining 38 items from step 1 on a numeric rating scale from 0 (not stressful) to 10 (extremely stressful) and take into account the full procedure (including all handling of the infant) and the standard-of-care stress-reducing treatments. Any comments could be provided at the end of this questionnaire.

### **Data analysis**

Participant characteristics are presented as mean (standard deviation, SD) for continuous variables and as the number of participants for categorical variables. Data were analyzed using IBM SPSS Statistics, version 27.

### *Step 1 - Content*

The Content Validity Index for each item (CVI-I) was calculated for each of the 77 items, defined as the percentage of experts giving a rating of either 3 or 4 divided by the total number of experts. As suggested by Lynn et al., items with an CVI-I of at least 0.78 were considered relevant.<sup>23</sup> In addition, we analyzed the nurses' and physicians' ratings separately and included all items with a CVI-I of 0.78 or higher for one of these groups (nurses or physicians) to ensure that we would not unjustifiably remove an item from the list.

All items that were considered unclear were adjusted based on the remarks of the participants. Any item considered missing was added if mentioned more than once. The study team (NM, GvdB, SS, MvD) discussed the need to adjust or add an item until they reached consensus.

### *Step 2 – Stressfulness of each item*

The median stress ratings are presented for all relevant items as the stressfulness index (SI) together with the inter-quartile range. Items added in Step 1 to improve the comprehensiveness were excluded from the final list (step 2) if the SI was less than the lowest SI for the original items. This NeO-stress score can be calculated daily by multiplying the number of times each stressful item occurs by the SI (NeO-stress =  $N_{\text{item1}} \times SI_{\text{item1}} + N_{\text{item2}} \times SI_{\text{item2}} + \text{etc.}$ ).

## **RESULTS**

Sixty-two of the 83 distributed questionnaires during Step 1 were returned; i.e., by 40 nurses and 22 physicians (response rate 75%, three to nine per NICU). The second questionnaire was sent to 1127 NICU staff, and

64 physicians and 196 nurses completed the questionnaire (response rate 23%, 22 to 41 per NICU). Table 1 shows demographic characteristics of the healthcare professionals who completed the questionnaire.

**Table 1 - Respondent characteristics**

Variable	Step 1 - Content		Step 2 - Stressfulness	
	N	%	N	%
<b>Sex</b>	N=62		N=260	
Male	17	27%	26	10%
Female	45	73%	234	90%
<b>Function</b>				
Nurses	40	65%	196	75%
NICU nurse	38		181	
Nurse specialist/ physician assistant	2		15	
Physicians	22	35%	64	25%
Neonatologist	20		48	
Fellow neonatology	2		16	
<b>NICU experience in years</b>				
Mean (SD)	19 (10)		14 (10)	

*Step 1 - Relevance of the items:*

The CVI-I was 0.78 or higher for 27 of the 77 items. Analyzing the nurses' and physicians' scores separately resulted in eight additional items with a CVI-I of 0.78 or higher for the nurses and none for the physicians. This resulted in 35 items considered to be relevant (see figure 1).

*Step 1 - Comprehensibility of the items:*

The respondents suggested clarification for three items. The application of EEG electrodes was broken down depending on the method for EEG registration (e.g. self-adhesive electrodes or needles, see figure 1). Also, to clarify 'insertion of arterial catheter', the wording was replaced by 'insertion of a peripheral arterial catheter'. The possibility of a nasoduodenal feeding tube was mentioned to be lacking and therefore combined with the nasogastric tube.

*Step 1 - Comprehensiveness of the list:*

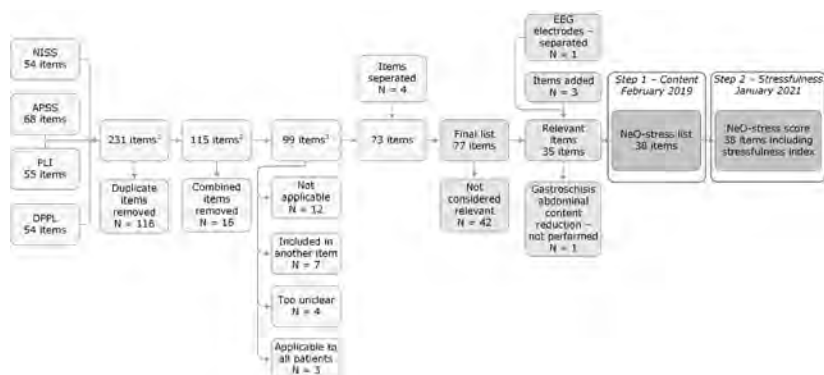
Two nurses found administering an enema or rectal cannula lacking, and this item was added to the final list. The retinopathy of prematurity screening, mentioned by two others, was not added because none of the NICUs performed this examination within the first 28 days of life. While five respondents stated that the exposure to light or noise was missing, this aspect was considered beyond the scope of the current instrument since it cannot be quantified without additional measurement instruments.

The study team screened a list containing all relevant items identified for comprehensiveness. Two items – closely related to already included items were then added: insertion of a CPAP system with prongs and mask (CVI-I 0.66), and umbilical venous/arterial line placement (CVI-I 0.63).

The other items that were not considered relevant to measure cumulative stress included items primarily related to daily caregiving (N=18, e.g. diaper changes, mouth/eye care), certain material being removed or being in place (N=11, e.g. removal of an intravenous catheter or nasogastric tube) and procedures related to diagnostics (N=7, e.g. near-infrared spectroscopy, noninvasive blood pressure measurement).

### Step 2 - Stressfulness index:

Figure 2 presents the SI (median) per item with interquartile range for all NICU staff and broken down by profession for the 38 included items. The SI ranges from nine for the insertion of a pneumothorax chest drain and for surgery to five for a ventricular puncture, removing an infant from a bed/incubator and the administration of an enema or rectal cannula. For ‘CPAP ventilation’ the SI could not be calculated since it was accidentally not included in the second questionnaire.



**Figure 1 - Development of the NeO-stress score**

116 items were combined with another item because of presumable overlap (e.g. dressing change was combined with wound care).

226 items were removed for various reasons such as not applicable in any premature with a gestational age less than 29 weeks during the first 28 days (N = 12, e.g. extra corporal membrane oxygenation) and included in another item that was listed (N = 7, e.g. removal of adhesives included in extubation).

33 items were separated into 7 items because of the suspected difference regarding the stress level (e.g. surfactant administration via MIST vs. via INSURE).

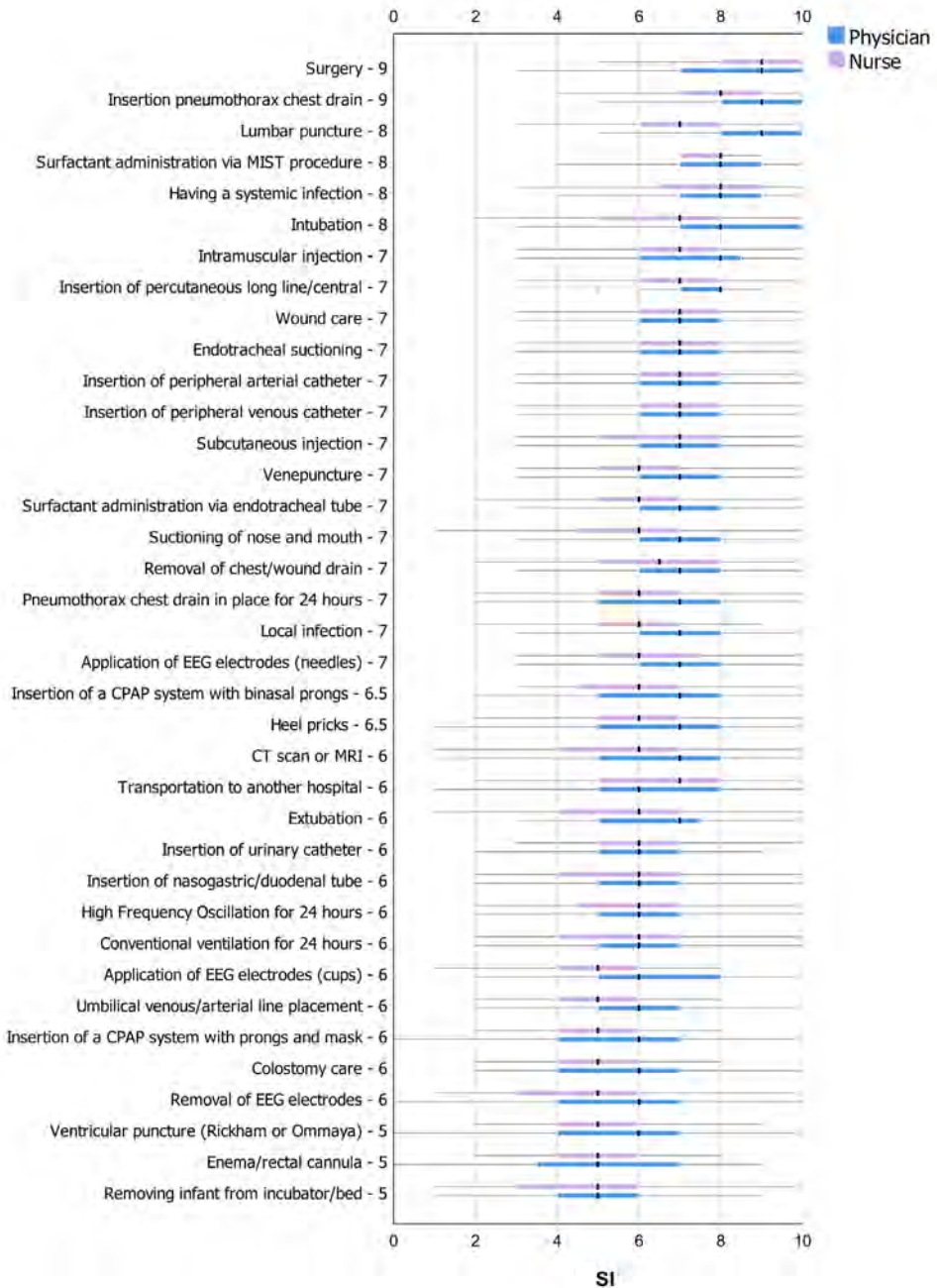


Figure 2 - NeO-Stress score including SI per item and interquartile range

### ***Comments***

In the comment section at the end of the second questionnaire, 24 NICU professionals remarked that stress levels during procedures are related to whether or not the infant has received analgosedatives. Twenty-one NICU professionals mentioned other factors that impact on stress severity such as gestational age, the way an intervention is performed and the number of attempts needed for a procedure. Based on the latter comment, we scored each attempt separately.

Table 2 shows a comparison between the existing instruments and the newly developed NeO-stress score. Per instrument, the degree of overlap varied from 17 (45%) to 24 (63%) of the 38 items included in the NeO-stress score.

Table 2 - Comparison between NeO-Stress score and existing instruments

	NISS	APSS	PLI	DPPL	NeO-stress score
First author	Newnham	Xu	Schiavenato	NA	Meesters
Publication year	2009	2016	2013	2016	2021
Country	Australia	United States	United states	Netherlands	Netherlands
Population	NICU patients with GA <28 weeks, 28-32 weeks or 32-37 weeks	NICU patients	NICU patients	NICU patients	NICU patients with GA <29 weeks
Number of items	54 items	68 items	55 items	54 items	38 items
Item selection	Authors	Focus group with 5 nurses and 9 physicians	Panel of 1 nurse practitioner, 3 nurses and 2 physicians	Panel of 10 nurses	Questionnaire with 40 nurses and 22 physicians
Item rating	Questionnaire study with 130 nurses and 17 physicians in two level 3 NICUs	Questionnaire with 84 nurses	Questionnaire with 78 nurses and 8 physicians	NA	Questionnaire with 196 nurses and 64 physicians
Scoring per item	Median score on a 1-5 scale	Mode score on a 1-5 scale	Magnitude estimation (compared to heelstick) and general labeled magnitude scale (scale from 0 to 999)	NA	Median score on a 1-10 scale
Overlapping items with NeO-stress score	19 items (50%)	17 items (45%)	24 items (63%)	21 items (55%)	NA

## DISCUSSION/CONCLUSION

Our study resulted in an instrument with established content validity that enables NICU staff to determine very preterm infants' daily cumulative level of stress exposure at the NICU.

This is the first instrument to quantify cumulative stress exposure related to NICU care developed for Dutch preterm NICU patients with a gestational age below 29 weeks. In general, the assessors considered skin breaking procedures and painful procedures such as intubation more relevant for this instrument than procedures related to daily caregiving such as diaper changes. This realization corresponds with what the developers of the existing instruments experienced.<sup>20-22</sup> The first part of our study resulted in 38 items, which number is lower than that of the existing instruments, and has the potential of enhancing feasibility in daily practice. Half of the items included in the initial list that were removed related to daily caregiving – e.g. diaper changes – that all NICU infants will be exposed to. Therefore, these items will have limited added value when trying to differentiate between patients with more or less cumulative stress exposure. We hypothesize that the item selection would be relatively similar in other countries. In other countries, however, the stressfulness of certain procedures might differ depending on policies on, for example, the administration of analgesedative drugs.

The reason to develop this bedside instrument was the start of a Dutch nation-wide study in 2020, the "Happiness for improvement of Premature and Parental Outcome (HIPPO) study". This study focuses on the impact of stress exposure during the first 28 days of life in preterm infants born with a gestational age less than 29 weeks. Since NICU staff had raised concerns about the validity of the existing instruments for our study population, we decided to develop this new instrument – though based on the existing instruments. Table 2 confirms that the maximum overlap in items between the existing instruments and the NeO-stress score is 63%. Another consideration was both nurses and physicians in the Dutch NICUs had agreed that important items were missing from the existing instruments. Newnham et al. suggest that items could be added to their NISS based on the clinicians' judgement.<sup>20</sup> While adding and adjusting items might improve the comprehensiveness and comprehensibility of an instrument, this practice also asks for additional validation studies. The APSS developed by Xu et al. in 2016 is an extensively modified and more recent version of the NISS,<sup>22</sup> but this did not result in a larger overlap in

items with the currently developed NeO-stress score.

Non-pharmacological interventions such as facilitated tucking, sucrose and skin-to-skin care have been found effective to alleviate stress levels.<sup>24</sup> For example, Cong et al. found that skin-to-skin can reduce stress and is associated with improved neurodevelopment.<sup>1</sup> Still, depending on stress intensity and duration, additional treatment with analgesedatives might be necessary.<sup>25</sup> Prescribing these drugs should always be carefully considered and tailored to individual needs because of possible side effects and long-term effects.<sup>26</sup> Stress will only result in important physical impairments when it exceeds a certain level and duration.<sup>27</sup> Here lies an important role for both health caregivers and parents as the infants' primary buffer to stress.<sup>28</sup>

Allegaert et al. showed that the systematic evaluation of pain increased NICU staff's awareness of the treatment and prevention of pain in neonates, which is a major cause of stress.<sup>29</sup> Regularly applying the NeO-stress score enables NICU staff to monitor stress exposure systematically and, by increasing awareness, could help preventing stress. A next step would be to determine the predictive value of the NeO-stress score on the child's neurodevelopment.

We calculated the SI based on the scores of 260 NICU staff. These respondents found it difficult to assign one static stressfulness score to the procedures because of interindividual differences. A dynamic stressfulness index assigned by the caregiving nurses or the parents based on the actual stress experience for the specific patient might be worth considering. In addition, it is not yet proven that the SI has indeed added value compared to a simple summing-up of the number of stressful events. Applying the NeO-stress in clinical practice will enable us to study if weighing the stressfulness of items as calculated with the SI results in a better prediction of neurodevelopmental outcome following preterm birth.

A major strength of this study was that a large multidisciplinary group of NICU staff was involved from the start. Our study specifically focused on the content validity for preterm infants admitted to a Dutch NICU, which resulted in an instrument that fits our nationwide preterm patient population. In order to enable international benchmarking and optimize stress management for NICU populations, we consider it important that a valid instrument with international applicability becomes available. The current NeO-stress score, for which the previously developed instruments formed the basis, provides a starting point. Other measurement properties

such as reliability, construct validity and the responsiveness should be evaluated in a patient cohort, and parents should be involved in future studies. To further establish construct validity, it is important to correlate the NeO-stress score – based on the opinion of NICU professionals – to the infants' behavioural (e.g. COMFORTneo scores) and biological responses to stress (e.g. biomarkers including cortisol levels). For future studies in this field, researchers should realize that a spot salivary cortisol measurement reflects an acute stress response, and therefore might not be associated with the total cumulative stress score of multiple days. Moreover, it is important to realize that salivary cortisol levels are influenced by caffeine treatment and postmenstrual age.<sup>30</sup> Also, it is necessary to further validate the NeO-stress score for patients born at later gestational age. Moreover, future studies could extend the NeO-stress score with environmental stressors including light, noise, single room versus open bay units.

This study has several limitations. First, prescribed use of analgesedatives probably reduces the stressfulness of certain procedures. Since practices might differ between NICUs, the type of pharmacological practice could influence the cumulative stress score. Second, the opinion of parents regarding stressfulness of the included procedures is not taken into account. Last, the NeO-stress score is based on a (content) valid, but partly subjective score in the absence of objective measures. It would be interesting to compare the NeO-stress score with physiological and hormonal biomarkers in future studies.

In conclusion, we developed an instrument to measure daily cumulative stress exposure in very prematurely born neonates, including 38 stressful procedures. Content validity was established with the help of a large multidisciplinary group of NICU staff. This NeO-stress score enables evaluating the impact of stress exposure and interventions to reduce stress or its consequences. A future prospective multicenter cohort study will further validate this instrument by correlating it to infants' behavioural and biological responses to stress. The ultimate aim is to predict which preterm infants are at risk for stress related to preterm birth.

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# Chapter 8

Exposure to clinical stressors during NICU admission in preterm infants

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## **ABSTRACT**

### ***Objective***

This study aims to quantify stress exposure related to clinical stressors in preterm infants during NICU admission and identify risk factors for high stress exposure.

### ***Methods***

In this national cohort study, preterm infants (gestational age <29 weeks) were prospectively followed during the first 28 days of their admission to one of the 10 NICUs in the Netherlands. The NeO-stress score, consisting of 38 clinical stressors graded with a severity index, was applied to describe stress exposure. We assessed the impact of infant characteristics at birth and postnatal age on NeO-stress scores using linear mixed modelling.

### ***Results***

In total 447 infants were included with a median gestational age of 27<sup>+2</sup> weeks (IQR 26<sup>+2</sup>-28<sup>+2</sup>). The median NeO-stress score per day was 61 (IQR 39-87) and highest (74, IQR 52-101) on the day of admission. Nasal/oral (37%) and endotracheal (14%) suctioning were key contributors to the cumulative NeO-stress scores. Linear mixed modelling showed that lower gestational age (B=-0.70, 95%CI -0.95--0.45, p<0.001), no antenatal administration of corticosteroids (B=12.9, 95%CI 3.2-22.5, p=0.009), and lower 5-minute Apgar score (B=-1.6, 95%CI -3.0--0.27, p=0.02) were significantly related with higher daily NeO-stress scores. Our model predicts that the NeO-stress score increases over time for the youngest infants.

### ***Conclusions***

Stress exposure in preterm infants during NICU admission varies over time with infants with the lowest gestational age at risk for experiencing the highest levels of stress throughout NICU admission. This highlights the importance stress reduction and provides opportunities for future interventions aimed at reducing stress exposure.

## INTRODUCTION

Extremely preterm born infants receive long lasting treatment in a Neonatal Intensive Care Unit (NICU). Many of the available treatment options are inevitably stressful for the infants and induce acute and prolonged pain and stress, e.g., skin-breaking procedures and mechanical ventilation.<sup>1, 2</sup> While NICU treatment aims to increase survival after preterm birth, the exposure to pain and stress itself can negatively impact long-term developmental outcome.<sup>3-9</sup>

Defining “stress” in preterm born infants admitted to a NICU is difficult. Lu et al. recently proposed a framework that identifies five consecutive basic elements: stimulus, stressor, stress, stress response and stress effect.<sup>10</sup> Stressful stimuli may become stressors if they directly challenge the homeostasis, referred to as stress. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis, which results in a stress response. This response can ultimately lead to physical and psychological disorders, the stress effect.<sup>10</sup> Potential stressors related to NICU environment can be categorized by their origin: clinical stressors (e.g., NICU treatment), physical stressors (e.g., noise), and psychological stressors (e.g., lack of parental presence).<sup>9</sup> In this study, we will focus on stress induced by clinical NICU stressors, which we refer to as ‘stress exposure’.

Previous studies showed that a higher stress exposure in preterm infants is associated with adverse neurobehavioral outcome at term equivalent age and beyond.<sup>7, 8</sup> A first step to protect infants from these negative consequences would be to reduce the number of clinical stressors as much as possible. Secondary, we should reduce the level of stress associated with each stressor, for example by applying skin-to-skin care.<sup>11, 12</sup>

We report a prospective national cohort study with the primary aim to quantify stress exposure in preterm infants (born at a gestational age less than 29 weeks) during the first 28 days of their NICU admission and identify the most important clinical stressors. As secondary aims we identified infant characteristics at birth that may predict the infant’s daily stress exposure and determined differences in stress exposure across all Dutch level III/IV NICUs.

## **METHODS**

### ***Design***

This national multicenter observational cohort study (Happiness for the Improvement of Premature and Parental outcome - HIPPO study, Dutch trial register NL8939) followed preterm infants prospectively during their NICU admission. Data collection started immediately after birth (day 1) and continued until the 28<sup>th</sup> day of life. Parents were informed about this study as soon as possible. Data collection stopped before day 28 in case no parental consent was granted, or after death or NICU discharge.

### ***Patients and setting***

All preterm infants born at a gestational age below 29 weeks admitted to one of all 10 level III/IV NICUs across the Netherlands were eligible for inclusion. This cut-off for gestational age was chosen since infants may leave the NICU from a postmenstrual age of 30 weeks onwards. With on average 600 to 700 preterm infants with a gestational age below 29 weeks admitted to Dutch NICUs annually, we aimed to include at least 400 infants.

As not all NICUs started patient enrolment at the same time, the total inclusion period ranged from 1<sup>st</sup> of July 2020 until 1<sup>st</sup> of March 2022, with a one year inclusion period for each NICU. Infants were recruited by the local research team and only excluded if parents were not able to read the written information (Dutch, English, Turkish, Arabic or Polish). The medical ethical committee of the Erasmus MC waived the need for approval within the Dutch Law on research with humans (MEC-2019-0574) because the study was judged to be a non-interventional study without exposing infants to procedures or additional rules of behavior. The medical ethical committees of the other participating NICUs subsequently adhered to this decision.

### ***Data collection***

All data were entered in Castor® Electronic Data Capturing system (Amsterdam, the Netherlands) after discharge by the local research teams, an online database that complies with Good Clinical Practice (GCP) guidelines.

### ***Infant characteristics***

Collected infant characteristics included gestational age, birthweight, sex, small for gestational age (<10<sup>th</sup> percentile according to Fenton 2013

growth charts<sup>13</sup>), inborn (born in a hospital with a NICU) or outborn, singleton/twin/triplet, and 5-minute Apgar score. Maternal characteristics (antenatal administration of corticosteroids or magnesium sulfate ( $\text{MgSO}_4$ ) and smoking during pregnancy) were retrieved from the electronic patient records. We registered if the infant was admitted to a NICU with single beds (2 NICUs) or an open bay (8 NICUs).

### **NeO-stress score**

We developed the NeO-stress score in preparation of the current study to gain insight in a preterm infant's stress exposure and estimate the cumulative amount of stress.<sup>14</sup> The NeO-stress score consists of 38 clinical stressors, including a weighting factor to take into account the level of stress each item induces, the stressfulness index (SI, see supplement 1). The NeO-stress score per day is calculated by multiplying the number of times each stressor occurred by the SI ( $\text{NeO-stress} = N_{\text{item1}} \times \text{SI}_{\text{item1}} + N_{\text{item2}} \times \text{SI}_{\text{item2}} + \text{etc.}$ )<sup>14</sup>. The stressors were registered prospectively in a study diary by the health caregivers or retrieved from the electronic health record system.

Since "Continuous Positive Airway Pressure (CPAP) respiratory support" accidentally did not receive a SI in our initial instrument development study, we calculated the median SI for non-invasive respiratory support based on the rating of 12 nurses and 13 physicians from all Dutch NICUs and added this item to the NeO-stress score (Non-invasive respiratory support for 24 hours = SI 6).

### **Statistical analysis**

Infants' characteristics are presented as median and interquartile range (IQR) for continuous non-normally distributed variables and as the number of participants (percentage) for categorical variables.

#### *Part A – Quantification of stress exposure during NICU admission*

We calculated the cumulative NeO-stress scores per day per infant. In order to determine the contribution of each individual stressor, for each item we multiplied the number of times the item occurred during the first 28 days by the SI ( $N_{\text{item}} \times \text{SI}_{\text{item}}$ ), and divided this score by the total cumulative NeO-stress score during the admission days (maximum 28 days).

*Part B – Factors associated with the level of stress exposure*

B.1 Infant characteristics associated with the level of stress exposure

a. Linear mixed-effects modelling was applied with the NeO-stress scores per day as outcome variable and infant and maternal characteristics as predictor variables based on their judged clinical relevance (Model 1). A random intercept and slope per infant were included in the model together with an AR(1) covariance matrix to account for within-infant correlations. Infants with missing data were excluded since this data might be missing not at random.

b. The interaction term of postnatal age and gestational age was added in Model 2 in order to examine whether the change in stress exposure over time varied between infants of different gestational ages. Possible nonlinear effects of postnatal age and gestational age were assessed by including natural cubic splines of these variables. Because the spline variables did not improve the model fit, only linear terms of postnatal age and gestational age were retained in the final model.

B.2 Differences in stress exposure between NICUs

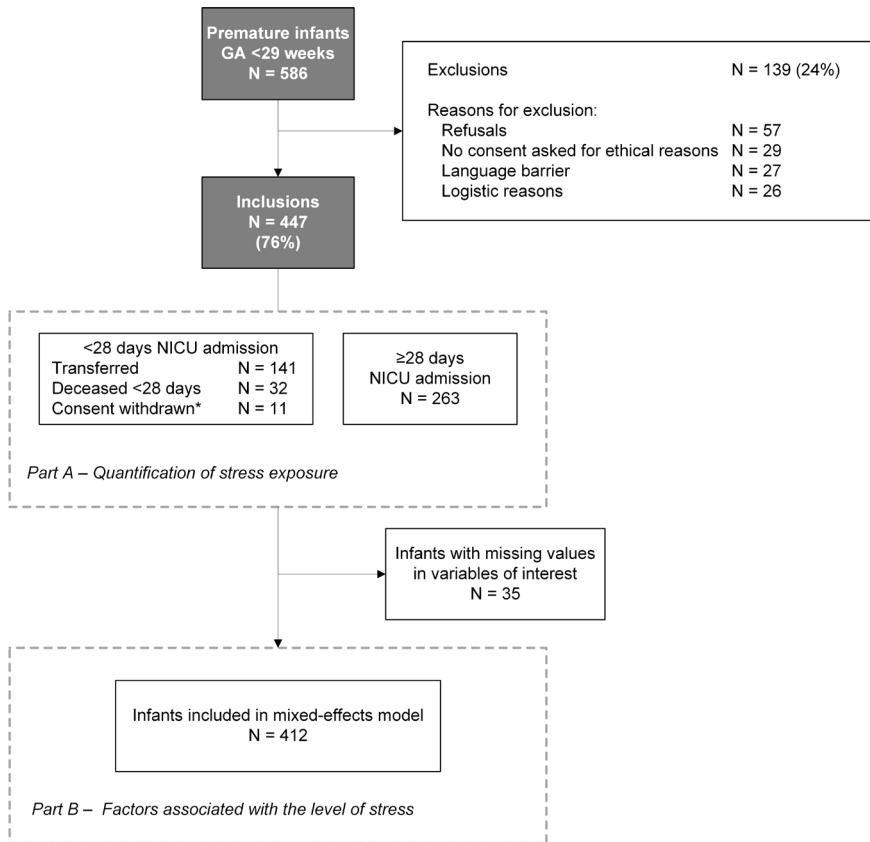
The unit of admission and the unit type (open bay or single bed unit) were separately added as predictor variables to the final model in Model 3 and Model 4, respectively. This enabled us to compare the differences in NeO-stress scores, taking into account the possible differences between units with respect to the infant characteristics included in the model.

A p-value < 0.05 was considered statistically significant in all analyses. Data were analyzed using IBM SPSS Statistics for Windows, version 27.0. Armonk, NY and R version 4.2.1 with the nlme package (version 3.1-157) to estimate linear mixed models.

## **RESULTS**

### ***Infant characteristics***

During the inclusion period, 586 infants with a gestational age less than 29 weeks were born in the 10 NICUs, of whom 447 (76%) were included in this study (Figure 1). A median of 40 infants (range 29 to 101) were included per NICU. Table 1 presents an overview of the baseline infant characteristics for the 447 preterm infants included in this study.



**Figure 1 - Inclusion flowchart**

\* Permission to analyze the collected data until consent withdrawal

**Table 1 - Infant characteristics (N=447)**

Variable	N	n (%)	Median (IQR)
Gestational age (weeks <sup>+</sup> days)	447		27 <sup>+2</sup> (26 <sup>+2</sup> to 28 <sup>+2</sup> )
23 <sup>+6</sup> weeks		3 (1%)	
24 <sup>+0-6</sup> weeks		31 (7%)	
25 <sup>+0-6</sup> weeks		58 (13%)	
26 <sup>+0-6</sup> weeks		90 (20%)	
27 <sup>+0-6</sup> weeks		120 (27%)	
28 <sup>+0-6</sup> weeks		145 (32%)	
Birthweight	447		950 (780 to 1135)
Twin / triplet	447	115 (26%) / 9 (2%)	
Boys	447	262 (59%)	
Outborn, yes	447	22 (5%)	
Antenatal corticosteroids <sup>a</sup>	441		
None		31 (7%)	
Incomplete		143 (32%)	
Complete		267 (60%)	
Antenatal magnesium sulfate, yes	441	321 (72%)	
Maternal smoking, yes	423	33 (7%)	
Apgar score 5 minutes	447		8 (7 to 9)
SGA <sup>b</sup> , yes	447	41 (9%)	

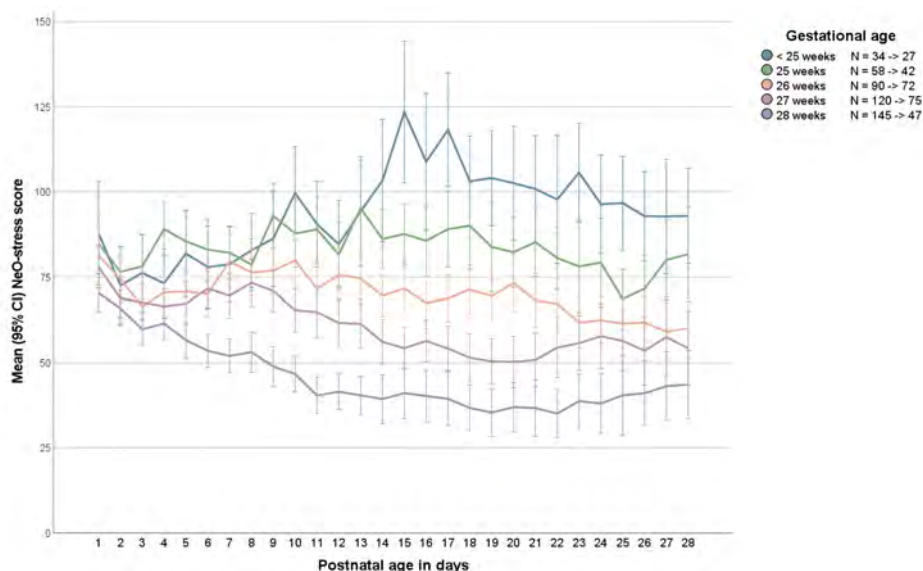
<sup>a</sup> Incomplete = birth <24 hours after first dose of Betamethasone or last dose of Betamethasone administered  $\geq 7$  days before birth, complete = birth after second dose of Betamethasone and last dose of Betamethasone administered <7 days before birth

<sup>b</sup> <10<sup>th</sup> percentile and LGA >90<sup>th</sup> percentile according to Fenton 2013 charts <sup>13</sup>

### **Part A - Quantification of stress exposure during NICU admission**

NeO-stress scores per day ranged from 0 to 317 with a median of 61 (IQR 39 to 87). Stress exposure was highest on the day of admission with a median score of 74 (IQR 52 to 101). Figure 2 presents the mean NeO-stress scores including 95%CI during the first 28 days of life for different gestational age groups.

Supplement 1 shows a complete overview of the contribution of each stressor ( $N_{item} \times SI_{item}$ ) to the total cumulative NeO-stress score. The stressors which contributed most to the total NeO-stress score were suctioning of nose and mouth (37%) together with endotracheal suctioning (14%). Preterm infants were suctioned (either endotracheal or via nose/mouth) a median of 3.8 times per day (IQR 1.7 to 6.7).



**Figure 2 - Mean NeO-stress scores (and 95%CI) per gestational age group for the first 28 days of life**

## **Part B – Factors associated with the level of stress exposure**

### *B.1 Infant characteristics associated with the level of stress exposure*

a. Linear mixed modelling (see Table 2) including the 412 infants (92%) with complete cases revealed that gestational age and postnatal age are strongly inversely correlated with daily NeO-stress scores with a p-value of <0.001 (Model 1). Among the 35 infants with missing data, more infants were outborn, namely 8 (23%) excluded infants compared to 14 out of 412 (3%) included infants.

b. Model 2 shows, however, that the interaction between gestational age and postnatal age significantly affects the NeO-stress score ( $B = -0.09$ , 95%CI  $-0.10$ - $0.06$ ,  $p < 0.001$ ): infants with higher gestational age experience a stronger decline of NeO-stress scores during NICU admission than those with lower gestational age. This model predicts that the NeO-stress score decreases over time for infants with a gestational age above 25<sup>+3</sup> weeks, but actually increases during NICU admission for the younger infants up to 0.9 points per day.

Moreover, infants in which the mothers did not receive antenatal corticosteroid therapy had significantly higher stress exposure with a mean of 12.9 points per day compared to infants from mothers with a complete course of corticosteroids ( $B = 12.9$ , 95%CI  $3.2$ - $22.5$ ,  $p = 0.009$ ).

A lower 5-minute Apgar score was significantly related to higher NeO-stress scores, with each additional point associated with a 1.6 points lower NeO-stress score per day ( $B=-1.6$ , 95%CI  $-3.0--0.27$ ,  $p=0.02$ ).

### *B.2 Differences in stress exposure between NICUs*

The differences between NICUs in model 3 and 4 are corrected for the infant and maternal characteristics included in model 1 and 2. The infant characteristics of the 412 analyzed infants are presented per NICU in supplement 2.

Model 3 shows significant differences depending on the unit of admission ( $p<0.001$ , table 2). Compared to NICU 1 (reference unit), NeO-stress scores per day were on average between 8 points lower (NICU 3) and 30 points higher (NICU 7). The NeO-stress scores for infants born small for gestational age were also significantly higher compared with infants that were appropriate or large for gestational age ( $B=6.7$ , 95%CI  $0.75-12.6$ ,  $p=0.006$ ).

Model 4 showed that there was no significant difference in NeO-stress scores between a single bed unit (NICU 4&5,  $N=74$ , 18%) compared to an open bay unit ( $B=-4.5$ , 95%CI  $-9.6-0.6$ ,  $p=0.08$ ), see table 2.

Table 2 - Linear mixed modelling with daily NeO-stress score as outcome variable

Outcome NeO-stress score	Model 1 Main effects			Model 2 Main effects & interaction effect			Model 3 Unit differences			Model 4 Open bay vs single bed		
	B	95%CI	p-Value	B	95%CI	p-Value	B	95%CI	p-Value	B	95%CI	p-Value
Intercept	112.4	100.8-124.0	<0.001**	99.4	87.6-111.2	<0.001**	93.1	81.4-104.7	<0.001**	100.6	88.8-112.5	<0.001**
Postnatal age (PNA; days)	-1.0	-1.1-0.8	<0.001**	0.94	0.52-1.4	<0.001**	0.95	0.53-1.37	<0.001**	0.94	0.52-1.4	<0.001**
Gestational age (GA; days)	-1.3	-1.5-1.1	<0.001**	-0.70	-0.95-0.45	<0.001**	-0.57	-0.79-0.35	<0.001**	-0.70	-1.0-0.45	<0.001**
Boys	0.4	-3.6-4.4	0.85	0.41	-3.6-4.4	0.84	1.8	-1.7-5.3	0.32	0.49	-3.5-4.5	0.81
Antenatal steroids												
No	13.2	3.5-22.8	0.008*	12.9	3.2-22.5	0.009*	7.7	-0.82-16.2	0.08	12.2	2.5-21.8	0.01*
Incomplete	-0.4	-4.7-3.9	0.85	-0.30	-4.6-4.0	0.89	-1.3	-5.1-2.6	0.52	-0.70	-5.0-3.6	0.75
Complete	REF			REF			REF					
Antenatal MgSO4; yes	1.1	-3.6-5.7	0.65	1.1	-3.6-5.7	0.65	0.46	-3.7-4.7	0.83	1.1	-3.5-5.8	0.62
Maternal smoking; yes	-0.8	-8.3-6.6	0.82	-0.78	-8.2-6.7	0.84	-1.8	-8.3-4.7	0.58	-1.0	-8.4-6.4	0.79
Outborn; yes	9.3	-1.9-20.6	0.10	9.4	-1.8-20.7	0.10	6.3	-3.4-16.1	0.20	9.4	-1.8-20.6	0.10
SGA; yes	5.8	-1.0-12.5	0.10	6.0	-0.73-12.8	0.08	6.7	0.75-12.6	0.03*	6.4	-0.41-13.1	0.07
5-minute Apgar score	-1.6	-2.9-0.2	0.03*	-1.6	-3.0-0.27	0.02*	-1.8	-3.0-0.56	0.004*	-1.7	-3.0-0.31	0.02*

Site of admission	
NICU 1	REF
NICU 2	6.5 0.11-12.8 0.05
NICU 3	-8.2 -15.7-0.66 0.03*
NICU 4	-5.6 -12.9-1.7 0.13
NICU 5	9.5 1.6-17.4 0.02*
NICU 6	12.0 3.9-20.2 0.004*
NICU 7	30.2 21.4-39.1 <0.001**
NICU 8	23.7 15.7-31.6 <0.001**
NICU 9	-7.0 -15.0-1.0 0.09
NICU 10	0.25 -7.2-7.7 0.95
Unit type	
Singe Room Unit	-4.5 -9.6-0.58 0.08
Open Bay Unit	REF
Interaction effect	
PNA x GA	-0.09 -0.10-0.07 -0.09 -0.10-0.07 <0.001** <0.001** -0.09 -0.10-0.07 <0.001** <0.001**

This table describes the 4 models used to analyze the effect of the infant and maternal characteristics that were determined in advance together with the interaction between gestational age and postnatal age (model 2, 3 and 4), the NICU of admission (model 3) and the layout of the unit (model 4) on the Neo-stress score per patient per day. REF = reference, \*\* p<0.001, \*p<0.05

## DISCUSSION

This multicenter study among all NICUs in the Netherlands shows that in preterm infants (gestational age 23<sup>+6</sup> to 29 weeks) the stress exposure, measured with the NeO-stress score, varied significantly over time with an overall decrease, but remained high or even increased for the infants with the lowest gestational ages.

The significant role of gestational age in relation to the daily amount of stress in our statistical model aligns with previous findings.<sup>15, 16</sup> This makes our most vulnerable extreme preterm infants prone for highest negative impact of stress. The highest stress exposure on the day of birth might be an underestimation because the day of birth may be less than 24 hours. This finding emphasizes that protection against stress should start immediately after birth. The unexpected finding that stress exposure increases during the first 28 days of life in the most premature infants is in contrast with previous studies.<sup>7, 15</sup> This finding might reflect the difficult journey before extremely premature infants reach and maintain clinical stability.

We found that endotracheal and oral/nasal suctioning contributed considerably to the daily stress exposure. The evaluation of the currently applied suctioning practices is therefore important to minimize stress exposure. The American Association for Respiratory Care recently developed a clinical practice guideline on endotracheal suctioning of neonatal, pediatric and adult patients.<sup>17</sup> Though suctioning is already only performed as-needed in the participating NICUs, the need for suctioning is based on the expert opinion of the health caregivers and therefore subjective. One way to objectify this need for suctioning could be by checking the airway resistance during mechanical ventilation.<sup>17</sup> The guideline prescribes to keep suction pressure in neonates below -120mmHg and avoid the routine use of saline irrigation solution. Together with providing facilitated tucking this might lower the stress response.<sup>18</sup>

Our model showed that a higher 5-minute Apgar score and the antenatal administration of corticosteroids were related to lower stress exposure. This is in line with the results of Van Dokkum et al. in their cohort of 45 preterm infants.<sup>15</sup> We hypothesize that corticosteroid therapy primarily decreases the need for clinical stressors related to respiratory problems such as mechanical ventilation. Both a lower Apgar score and lack of antenatal corticosteroid administration are significantly related to an increased risk of mortality in preterm infants.<sup>19-21</sup> The exposure to stress

might play a role as a mediating factor in the association between the Apgar score or corticosteroid administration and neonatal outcome.

We showed that stress exposure varied significantly across the Dutch NICUs, which highlights the importance of benchmarking to explore opportunities to decrease the amount of stress. Important infant characteristics at birth are included in our model. We realize, however, that these NICUs might not be comparable with respect to other factors, such as access to surgery and parents' socioeconomic status.<sup>22</sup> The differences between NICUs regarding pain assessment and analgosedation have been previously showed.<sup>23-25</sup> To our knowledge this is the first study that analyzed differences in stress exposure. We did not find a significant difference in stress exposure between the eight open bay NICUs and the two single bed NICUs. Single family rooms are important when it comes to parental presence, involvement and skin-to-skin care,<sup>26</sup> which is expected to decrease the stress response in infants. Although the unit type was not significantly associated with the stress exposure in our study, the stress response might have been affected but was beyond the scope of this study. Our current findings will form the basis to compare differences in clinical practice and benchmark across centers.

Our insights in clinical stressors provide NICU professionals with opportunities to decrease stress exposure. We should first aim to decrease the frequency of the clinical stressors. Evidence on how to achieve this decrease is currently lacking and it is assumed that this ability might be limited.<sup>2, 27</sup> Focusing on the procedure itself (e.g. providing containment) is therefore also important to minimize the stress effect.<sup>28</sup> Reducing both the frequency and the stressfulness of each clinical stressor, resulting in a lower Severity Index, will optimally decrease stress exposure. We realize that parents may also play an essential role in reducing the stressfulness of the clinical stressors, for example by providing skin-to-skin care.<sup>11, 29</sup> Their participation is likely to benefit the infant but also themselves.<sup>30</sup> The European Standards of Care for Newborn Health therefore state that skin-to-skin care between the infants and their mother or father should be initiated as early as possible and maintained continuously.<sup>31</sup>

A major strength of this study is the quantification of the stress exposure in a large, national cohort of 447 preterm infants. Our study is limited by the fact that we specifically focused on the exposure to clinical stressors during NICU admission and used a fixed severity index for all stressors. In clinical practice the associated stress levels vary, depending on for instance the application of stress-reducing interventions and the individual infant's

condition. Moreover, the occurrence of clinical stressors was registered prospectively by the nurses, with the risk of under-registration.

Our focus on the exposure to clinical stressors is an important step in minimizing stress, since the stress stimulus itself is the starting point leading to the infant's response.<sup>10</sup> The next steps are to put further focus on the other elements of the stress framework as proposed by Lu et al., such as the stress response and stress effect, in order to better understand the way stress thereafter impacts the infant's development. Focusing on other stressors related to the NICU environment, such as light or noise and the lack of parental presence, will also improve our insights into opportunities to decrease stress exposure. We need to take into account the interventions that may impact the stress response, both non-pharmacological interventions and the administration of analgesedation, in order to better understand the consequences of stress on the infant's development.

The ultimate goal would be to minimize the negative consequences of stress and improve quality of life for all preterm born children and their families.<sup>32</sup> Protective quality improvement programs should include evidence-based interventions that help to decrease either the frequency or the stressfulness of clinical stressors. Most interventions with a proven stress reduction, such as skin-to-skin care, should be provided to all (preterm) infants.<sup>33, 34</sup> Other interventions might be either considered not feasible to provide continuously to all preterm NICU infants, e.g., music therapy,<sup>35</sup> or even harmful, e.g. the routine use of analgesedatives.<sup>36, 37</sup> Risk profiles based on our insights can guide in determining the most effective basic (non)pharmacological strategies for each infant directly after birth that should be individualized based on the infants' or parents' needs.

## CONCLUSION

The youngest, most vulnerable infants are being exposed to the highest levels of cumulative stress throughout NICU admission. Prevention of stress should start immediately after birth and continue during NICU admission. Lower 5-minute Apgar score and the absence of antenatal corticosteroid administration might help in identifying at birth the infants with the highest risk of high stress exposure. Insights into the enormous daily stress exposure and variation between individuals and hospitals provide valuable opportunities to determine factors to decrease

stress exposure and identify high-risk patients. Stress reduction quality improvement programs need to be prioritized to protect preterm infants against the potential negative impact of early life stress.

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**Supplement 1 - NeO-stress score including contribution per item**

Stressor	SI	%*
1 Suctioning of nose and mouth	7	37.4%
2 Endotracheal suctioning	7	13.8%
3 Insertion of a CPAP system with prongs and mask	6	13.8%
4 Insertion of a CPAP system with binasal prongs	6.5	6.5%
5 Non-invasive respiratory support for 24 hours	6	5.9%
6 Heel pricks	6.5	5.6%
7 Removing infant from incubator/bed (unwrapped)	5	3.2%
8 Insertion of peripheral venous catheter	7	2.7%
9 Insertion of nasogastric/duodenal tube	6	1.4%
10 Conventional ventilation for 24 hours	6	1.2%
11 High Frequency Oscillation for 24 hours	6	0.80%
12 Enema/rectal cannula	5	0.77%
13 Intubation	8	0.67%
14 Insertion of percutaneous long line/central venous line	7	0.50%
15 Venepuncture	7	0.49%
16 Having a systemic infection	8	0.47%
17 Wound care	7	0.40%
18 Insertion of peripheral arterial catheter	7	0.39%
19 Surfactant administration via MIST procedure	8	0.35%
20 Umbilical venous/arterial line placement	6	0.33%
21 Extubation	6	0.29%
22 Local infection	7	0.27%
23 Intramuscular injection	7	0.25%
24 Colostomy care	6	0.25%
25 Surfactant administration via endotracheal tube	7	0.20%
26 Insertion of urinary catheter	6	0.16%
27 Lumbar puncture	8	0.15%
28 Transportation to another hospital	6	0.10%
29 Application of EEG electrodes (needles)	7	0.08%
30 Pneumothorax chest drain in place for 24 hours	7	0.08%
31 Ventricular puncture (Rickham or Ommaya)	5	0.07%
32 Surgery	9	0.06%
33 Removal of EEG electrodes	6	0.04%
34 CT scan or MRI	6	0.03%
35 Subcutaneous injection	7	0.02%
36 Insertion pneumothorax chest drain	9	0.02%
37 Removal of chest/wound drain	7	0.01%
38 Application of EEG electrodes (cups)	6	0.01%

This percentage represents the contribution to the total stress exposure, calculated as follows:  $(N_{item} \times SI_{item}) / \text{total cumulative NeO-stress score}$

Supplement 2 - Infant characteristics per NICU (N=412)

NICU	1	2	3	4	5	6	7	8	9	10	
	N = 47	N = 93	N = 40	N = 42	N = 32	N = 28	N = 23	N = 33	N = 31	N = 43	
Variable	n (%) / Median (IQR)										
Gestational age (weeks+days)	27 <sup>+3</sup> (26 <sup>+4</sup> -, 28 <sup>+2</sup> )	27 <sup>+3</sup> (25 <sup>+4</sup> -, 28 <sup>+2</sup> )	27 <sup>+6</sup> (26 <sup>+5</sup> -, 28 <sup>+3</sup> )	27 <sup>+3</sup> (26 <sup>+2</sup> -, 28 <sup>+2</sup> )	27 <sup>+1</sup> (26 <sup>+2</sup> -, 28 <sup>+2</sup> )	27 <sup>+3</sup> (25 <sup>+6</sup> -, 28 <sup>+5</sup> )	26 <sup>+6</sup> (25 <sup>+5</sup> -, 27 <sup>+5</sup> )	27 <sup>+0</sup> (26 <sup>+4</sup> -, 27 <sup>+6</sup> )	27 <sup>+6</sup> (26 <sup>+4</sup> -, 28 <sup>+3</sup> )	27 <sup>+6</sup> (26 <sup>+4</sup> -, 28 <sup>+3</sup> )	27 <sup>+3</sup> (26 <sup>+4</sup> -, 28 <sup>+1</sup> )
Birthweight	1025 (843- 1190)	935 (760- 1105)	998 (888- 1123)	950 (800- 1130)	875 (735- 1025)	928 (815- 1040)	844 (760- 1180)	1000 (830- 1090)	980 (780- 1200)	980 (780- 1200)	945 (735- 1215)
Twin / triplet	13 (28%)	27 (29%)	6 (15%)	18 (43%)	6 (19%)	9 (32%)	8 (35%)	7 (21%)	7 (23%)	7 (23%)	12 (28%)
Boys	29 (62%)	46 (50%)	27 (68%)	25 (60%)	19 (59%)	17 (61%)	14 (61%)	18 (55%)	20 (65%)	20 (65%)	29 (67%)
Antenatal corticosteroids <sup>a</sup>											
None	6 (13%)	1 (1%)	1 (3%)	0 (0%)	1 (3%)	1 (4%)	5 (22%)	2 (6%)	2 (7%)	2 (7%)	2 (5%)
Incomplete	8 (17%)	46 (50%)	13 (33%)	7 (17%)	10 (31%)	7 (25%)	6 (26%)	10 (30%)	12 (39%)	12 (39%)	16 (37%)
Complete	33 (70%)	46 (50%)	27 (65%)	35 (83%)	21 (66%)	20 (71%)	12 (52%)	21 (64%)	17 (54%)	17 (54%)	25 (58%)
Antenatal MgSO <sub>4</sub> ; yes	32 (68%)	79 (85%)	35 (88%)	32 (76%)	26 (81%)	19 (68%)	14 (61%)	28 (85%)	23 (74%)	23 (74%)	17 (40%)
Maternal smoking; yes	1 (2%)	8 (9%)	6 (15%)	1 (2%)	3 (9%)	0 (0%)	4 (17%)	3 (9%)	3 (10%)	3 (10%)	2 (5%)
Outborn; yes	1 (2%)	2 (2%)	1 (3%)	0 (0%)	1 (3%)	1 (4%)	2 (9%)	2 (6%)	2 (7%)	2 (7%)	2 (5%)
SGA <sup>b</sup> ; yes	3 (6%)	9 (10%)	2 (5%)	6 (14%)	3 (9%)	0 (0%)	1 (4%)	4 (12%)	3 (10%)	3 (10%)	7 (16%)
Apgar score 5 minutes	8 (7-9)	8 (7-9)	7 (6-8)	8 (7-9)	8 (6-8)	8 (7-9)	7 (6-8)	8 (7-10)	8 (8-9)	8 (8-9)	8 (6-8)

<sup>a</sup>Incomplete = birth <24 hours after first dose of Betamethasone or last dose of Betamethasone administered ≥7 days before birth, complete = birth after second dose of Betamethasone and last dose of Betamethasone administered <7 days before birth

<sup>b</sup><10<sup>th</sup> percentile and LGA >90<sup>th</sup> percentile according to Fenton 2013 charts<sup>13</sup>



# Chapter 9

COVID-19 lockdown impacts the wellbeing of parents with infants on a Dutch neonatal intensive care unit

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## **ABSTRACT**

### ***Purpose***

Parents of infants admitted to a neonatal intensive care unit (NICU) experience additional stress due to restrictions on their presence and visits by other family members during the COVID-19 pandemic. Our study aims to describe how this impacted parents and how NICU staff could support them.

### ***Design and methods***

This was a cross-sectional study in which 25 parents (16 mothers, 9 fathers) of infants admitted to our NICU during the first COVID-19 lockdown completed online questionnaires with socio-demographic questions, the Parental Stressor Scale: NICU (PSS: NICU) and questions related to COVID-19.

### ***Results***

Being separated from, and not being able to hold their infant at all times were amongst the most important PSS: NICU stressors. Parents experienced additional stress because other family members were not allowed to visit. They indicated that NICU staff could support them by clearly explaining the reasons for visitor restrictions and by ensuring that they felt heard. Most parents supported the restrictions, but also mentioned that less strict measures would really help them.

### ***Conclusions***

Parents who participated in this study found it very stressful that they could not be with their infant together with their partner and other family members. Furthermore, parents recommended the hospital management to continuously reconsider whether particular restrictions could be lifted in case of a new lockdown. Together with clear communication, this would result in less parenteral stress.

### ***Practice implications***

Hospital management should be cautious on restricting the presence of parents and other family members and scale restrictions back whenever possible.

## INTRODUCTION

Newborn infants admitted to a neonatal intensive care unit (NICU) are exposed to both external (e.g. painful procedures) and internal stressors (e.g. sepsis).<sup>1</sup> Parents can help minimize their infant's stress by providing, among other things, skin-to-skin care.<sup>2-5</sup> However, these parents also experience high levels of stress themselves because of the premature birth and NICU admission, possibly resulting in anxiety, depression symptoms, posttraumatic stress symptoms and feelings of guilt and shame.<sup>6, 7</sup> Previous studies showed that parental stress related to the NICU admission might have negative long-term consequences regarding the parent-child interaction and the child's development.<sup>8-11</sup>

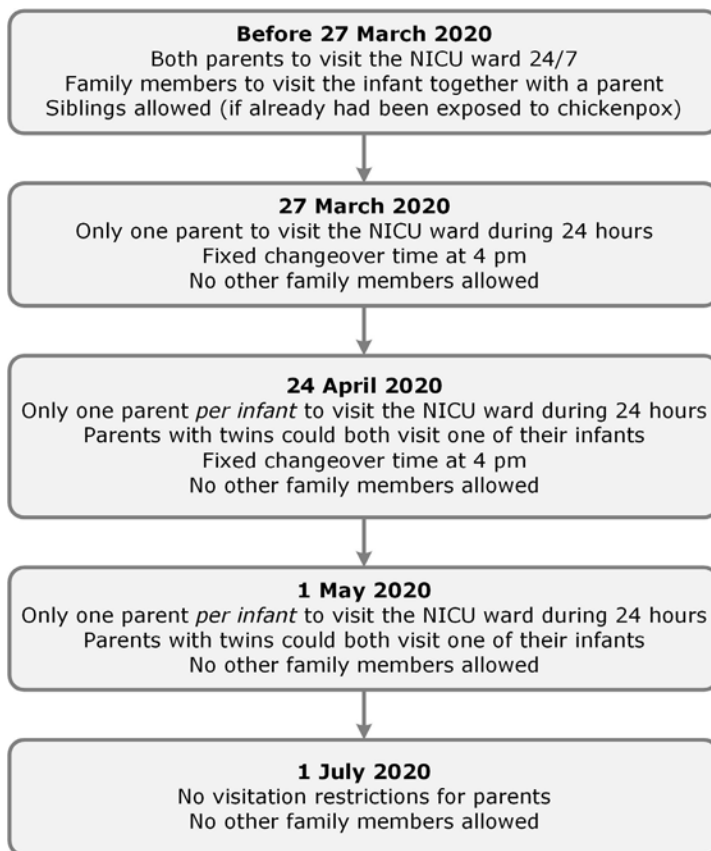
Parents feel the need to be close to their newborn, and thus should be able to visit their admitted infant anytime.<sup>12, 13</sup> As parent-infant closeness during the NICU stay is considered beneficial for both infants and parents, many European NICUs, including those in the Netherlands, do not restrict parental presence in normal circumstances.<sup>14</sup> During the COVID-19 pandemic, however, many NICUs decided to impose a stricter visitation policy.<sup>15, 16</sup> This decision was made based on the knowledge regarding COVID-19 obtained during springtime 2020.

Added to the stress of a NICU admission, in spring 2020 parents were facing restricted visitation policies. Verweij and colleagues underlined that it is important to register the consequences of the COVID-19 pandemic on perinatal care because of the implied long-term bonding problems and psychosocial implications for parents.<sup>17</sup> This information can help to determine visitation policies in case of a new pandemic and help to optimally support parents during the NICU admission. We report a study aiming to describe the impact of COVID-19 –related visitation restrictions at the NICU on parents' wellbeing.

## PATIENTS AND METHODS

### *Setting*

This cross-sectional study was conducted from 21 April 2020 until 31 June 2020 in the open bay level 4 NICU of the Erasmus MC–Sophia Children's Hospital, Rotterdam, the Netherlands. Figure 1 summarizes restrictions on the presence of parents and other family members prior to and during this inclusion period.



**Figure 1 - Restrictions on the presence of parents and other family members during COVID lockdown**

### ***Participants***

Eligible were parents of neonates already admitted when the restrictions were imposed and parents of neonates admitted during the study period. Another criterion was being admitted for more than seven days, since we wanted to include parents who had ample experience with the restrictions. Those who were unable to read Dutch were excluded because only questionnaires in Dutch were available. After signed agreement of participation and use of the data, parents were asked to register on the *KLIK* website ([www.hetklikt.nu](http://www.hetklikt.nu)). Parents completed the online questionnaires once on postnatal day 8 or later (before discharge). The institutional ethics review board waived the need for approval because the study was judged to be an observational study without the exposure to procedures or additional rules of behavior.

## **Measures**

### *Parent and infant characteristics*

Parents provided information about their birth country, older siblings at home, education level and working situation. The infant characteristics (gestational age and postnatal age) were retrieved from the medical records.

### *General stress levels*

Parents indicated on a visual analogue scale (VAS) from 0 (no stress) to 10 (much stress) their current level of stress related to NICU admission and COVID-19.

### *NICU-related stress symptoms*

The Parental Stressor Scale: Neonatal Intensive Care Unit (PSS:NICU) was developed as a means to give insight in the parental perception of stressors arising from the NICU environment.<sup>18</sup> This validated questionnaire consists of 26 items, with 3 subscales (see Table 2). All items are scored on a Likert scale from 1 (not at all stressful) to 5 (extremely stressful). If parents reported 'not applicable' on an item, the stress level on that item was scored as 1 (no stress) as advised by the authors (metric 2).<sup>18, 19</sup> The total score therefore ranges from 26 to 130; the reliability for this metric ranges from 0.73 to 0.83 for the subscales.<sup>18</sup>

### *Questions specifically related to experiences during COVID-19*

Eight closed questions were related to COVID-19 (table 3). One open question regarded any other concerns related to COVID-19 not included in the closed questions. Another open question focused on what helped them to deal with possible stress. Lastly, two open questions dealt with parents' perspective on how the COVID-19 restrictions were communicated, and how the NICU staff could help them deal with stress.

## **Data analysis**

All data were extracted from the *KLIK* database, and analyzed with IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM. Infant and parent characteristics and all ratings are presented as median (interquartile range) for continuous variables. All data are presented for the total population and for mothers and fathers separately.

It appeared that one of the seven items of the PSS:NICU subscale "Parental Role Alteration" ('not able to be alone with the infant') was missing on the *KLIK* website. Therefore, we recalculated this total subscale score by

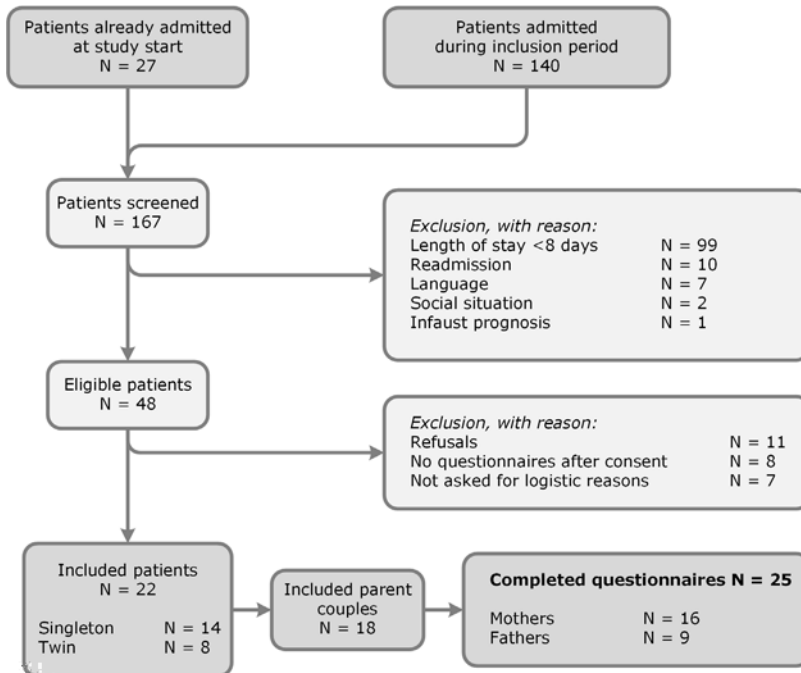
multiplying the score by 7/6.

With respect to the open questions, all individual responses were coded into topics by the first author (NM). Topics were then classified into themes. For example, both 'talking 'with the partner' and 'talking with a psychologist' were assigned to the theme "talking about their situation".

## RESULTS

### *Parent and infant characteristics*

Parents of 48 infants were eligible for inclusion; see Figure 2. Eventually, parents of 22 infants agreed to participate (response rate 46%). Gestational ages ranged from 25 weeks and 4 days to 41 weeks and 1 day (median 28<sup>+2</sup> weeks). Since the infant population included four twins, 18 parental couples were invited to fill in the questionnaires, of whom 16 mothers and 9 fathers actually filled them in. The parental characteristics are presented in Table 1. The infant's postnatal age on the day the questionnaire was filled in ranged from 8 to 88 days.



**Figure 2 - Inclusion flowchart**

**Table 1 - Parental characteristics**

Variables	All	Mother	Father
Parent couples	18		
Questionnaires filled in by			
Mother and father (separately)	7	7	7
Mother only	9	9	
Father only	2		2
Postnatal age in days <sup>a</sup> , median (IQR)	28 (14 to 56)		
Individual parents	25	16	9
Birth country			
The Netherlands	20	11	9
Other	5	5	0
Older siblings at home	9	6	3
Educational level			
Low	7	6	1
Middle	15	8	7
High	3	2	1
Work			
Maternity leave		15	
Student		1	
Paid employment			8
Sick leave			1

<sup>a</sup>Postnatal age on the day the questionnaire was filled in

### **General stress levels**

The median stress level related to the NICU hospitalization was higher than the stress level related to COVID-19; i.e. 8 (IQR 4 to 10) compared to 6 (IQR 4 to 9.5), respectively. Figure 3 presents the VAS stress related to both the NICU hospitalization and the COVID-19 restrictions for mothers and fathers separately.

### **NICU-related stress symptoms**

Total PSS:NICU scores varied from 35 to 115 (Table 2). Parental role alteration was the subscale with the highest rating (median 2.8 (IQR 1.9 to 3.7)). Five of the 26 items had a median score of 4 (very stressful, the highest median score), namely: 'being separated from my baby' (IQR 3 to 5), 'not being able to hold my baby when I want' (IQR 2 to 4.5), 'when my baby seemed to be in pain' (IQR 3 to 5), 'the limp and weak appearance of my baby' (IQR 3.5 to 5), and 'when my baby looked sad' (IQR 2 to 5).

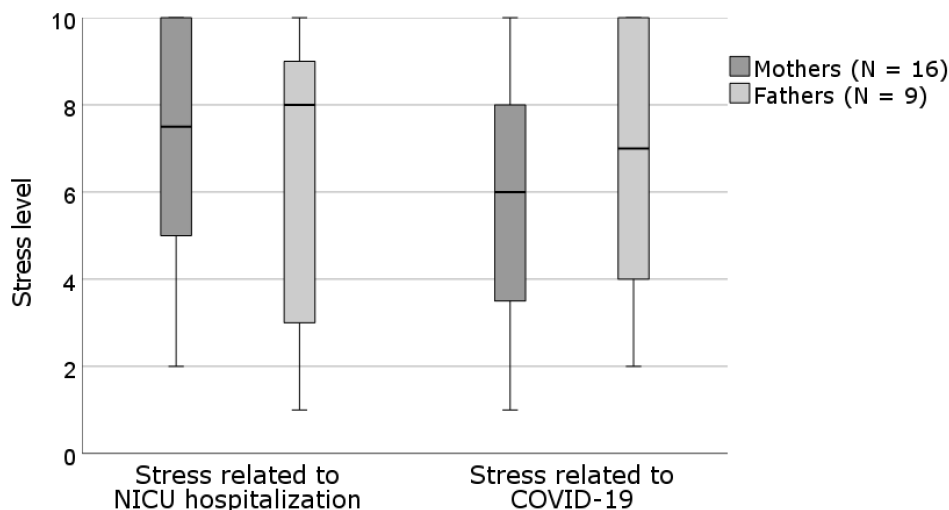


Figure 3 - General stress level on a scale from 0 (no stress) to 10 (a lot of stress)

Table 2 - Stress related to NICU admission as a parent during COVID-19

	All (N=21)	Mother (N=14)	Father (N=7)
	Median (IQR)	Median (IQR)	Median (IQR)
PSS: NICU total score	67 (50 to 89)	66 (50 to 91)	67 (45 to 87)
Subscale scores <sup>a</sup>			
Sights and Sounds	2.3 (1.8 to 3.0)	2.4 (1.7 to 3.0)	2.3 (1.8 to 3.2)
Infant Behavior and Appearance	2.8 (1.9 to 3.4)	2.6 (2.0 to 3.5)	2.9 (1.9 to 3.3)
Parental Role Alteration	2.8 (1.9 to 3.7)	2.8 (2.3 to 4.3)	1.2 (1.7 to 3.5)

<sup>a</sup> Mean subscale scores were calculated per subscale and per parent  
 1 = not at all stressful; 2 = a little stressful; 3 = moderately stressful; 4 = very stressful,  
 5 = extremely stressful

### ***Stress related to COVID-19***

Table 3 shows the level of stress that parents experienced related to specific consequences of the COVID-19 restrictions. They experienced most stress from not being allowed to be with their infant limitlessly and be with their infant together with their partner, with 15 (68%) and 14 (64%) of the parents rating this as being 'very' to 'extremely stressful', respectively. Almost all parents stated that they were sufficiently to excellently able to share their concerns with both friends and family (N=24, 96%) and healthcare providers (N=23, 88%). Twelve of the 25 participants (48%) rated their abilities to experience closeness to their infant as good or excellent.

The most frequently mentioned concern (N = 7, 28% of parents) not included in the closed questions was that other visitors were not allowed. One mother wrote: "if I would have been able to introduce my infant to my family this would have helped to take away some of the worries during this traumatic period". A father highlighted that it worried him "not being able to receive any visitors while you really have a need for this in the current situation". In contrast, another mother considered the current COVID-19 restrictions as positive because these protected them from all stimuli outside of the hospital.

Four parents with other children notably regretted that siblings could not visit the newborn sibling. One mother explained "the fact that my other children cannot meet their twin brothers is very difficult and emotionally extremely tough".

### ***Ways to deal with the COVID-19 restrictions as a NICU parent***

Talking about the situation, primarily with the partner but also with other family members or as psychologist, was mentioned as most effective (9 mothers and 3 fathers) in dealing with stress. Five fathers mentioned playing sports or a game as a distraction from stress. Two mothers mentioned that the moments they were able to be with their infant helped. One of these mothers explained that it helped "to talk about our situation with a psychologist, friends and family and be with our girl as much as possible". Other factors that were considered helpful were positive thinking, putting things into perspective and using the webcam to see their infant. One mother mentioned that taking medication helped deal with her stress. Another mother explained that she found it important to deal with the stress, since she realized that her admitted twin boys would also notice her stress.

### ***Parental perspective on COVID-19 restrictions on the NICU ward***

While 15 parents (60%) were satisfied with how the restrictions on the presence of parents and other family members had been communicated, the other ten found the restrictions unclear and/or the way staff members adhered to these restrictions not consistent. Four of these parents specifically were frustrated because they failed to grasp why certain decisions had been made. One father illustrated that "without a clear explanation, the logic behind the measures was lacking, while this was much clearer after talking about this to the neonatologist during our weekly appointment".

One mother stated that the situation of the individual parent should be taken into account since she experienced her physical recovery after a cesarean section as a complicating factor in visiting her infant without her partner.

Parents mentioned that the following measures could help them cope: clear, transparent communication (7 parents), health professionals initiating a conversation with parents and listening to their needs and experiences (6 parents), and making an exception to the rule depending on the situation of the parents and the infant (3 parents). In general, most parents could appreciate the restrictions on the presence of parents and other family members, but also mentioned that less strict measures would really help them.

Table 3 - Parental stress related to COVID-19

	All (N=25)			Mother (N=16)		Father (N=9)	
	Rating 4 or 5; N (%)	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)
<b>How much stress do you experience related to...<sup>a</sup></b>	Very/ extremely stressful						
Become sick by COVID yourself	4 (17%)	24	2 (1-3)	15	2 (1-3)	9	2 (1-2.5)
Your infant becoming sick by COVID	8 (32%)	25	3 (1.5-4)	16	3 (2-4)	9	2 (1-3)
Infect your infant with COVID	6 (24%)	25	3 (1-3.5)	16	3 (1-4)	9	2 (1-3)
Healthcare professionals infecting your child	5 (20%)	25	3 (1-3)	16	2.5 (1-4)	9	3 (1-3)
Not being able-be with your child	15 (68%)	22	4 (3-5)	13	4 (3.5-5)	9	4 (3-4.5)
limitless <i>singletons only</i>	14 (74%)	19	4 (3-5)	12	4.5 (4-5)	7	4 (3-4)
Not being able-be with your child together with your partner	14 (64%)	22	4 (3-5)	13	4 (3-5)	9	4 (3-5)
<i>singletons only</i>	13 (68%)	19	4 (3-5)	12	4 (3-5)	7	4 (3-5)
<b>To what extent are you able to...<sup>b</sup></b>	Good/ excellent						
Share your concerns with friends and family	18 (72%)	25	4 (3-5)	16	4 (4-5)	9	4 (3-5)
Share your concerns with healthcare givers	17 (68%)	25	4 (3-4)	16	4 (3-4)	9	4 (3-5)
Experience closeness-your infant	12 (48%)	25	3 (3-4)	16	3 (3-4)	9	4 (3-4)

<sup>a</sup> 1 = not at all stressful; 2 = a little stressful; 3 = moderately stressful; 4 = very stressful; 5 = extremely stressful

<sup>b</sup> 1 = inadequately; 2 = mediocre; 3 = sufficient; 4 = good; 5 = excellent

## DISCUSSION

Our study results confirm that most parents of infants admitted to the NICU during COVID-19 lockdown found this period very stressful, among other things because of the restricted visiting rules. Not being able to hold their infant whenever they liked, and not being able to visit the infant together with their partner were often mentioned.

As Veenendaal and colleagues described in their systematic review on family integrated care practices during COVID-19 pandemic, the psychological impact of the visitation restrictions on parents is often not assessed).<sup>16</sup> A survey study among parents focused on the practical consequences of the restrictions on parents' ability to visit and care for their child.<sup>20</sup> Only one preliminary report from Italy, based on interviews with nine mothers and one father, specifically described parents' experiences during a period of COVID-19 visitation restrictions (one parent per baby, one hour per day).<sup>21</sup> Most of these parents had suffered from being separated from the partner and the newborn. To our knowledge, we are the first to both quantitatively and qualitatively report the impact of these restrictions on parents' wellbeing during the NICU stay.

One of the most important consequences of the COVID-19 restrictions seems to be that parents were unable to support each other in the NICU ward. This is in line with a study which reported that mothers seem to experience more stress when being with the baby in the NICU without the father.<sup>22</sup> Our results highlight the importance of allowing siblings and other family members to the NICU, in line with a previous study by Hagen and colleagues.<sup>23</sup> The roles of other family members, such as grandparents, is not well investigated, apart from a Scottish study that showed that grandparents played an important supportive role.<sup>24</sup>

Only half of the parents in our study stated that they experienced "good" to "excellent" closeness to their infant. For parents in general, closeness is not simply about being with their infant physically (being able to hold and take care of their infant), but also having an autonomous role in taking care of the infant.<sup>13</sup> Closeness is considered important for its positive impact on the child's brain development on the long term, as well as on well-being of the parent and the parent-infant dyad.<sup>25</sup> Murray and Swanson (2020) suggest that alternative methods of communication such as videoconferencing may help families at home to feel close to their infant.<sup>15</sup>

Parents in our study mentioned that talking about their situation with family or friends or a psychologist helped them cope with the stress experienced during the COVID-19 visitation restrictions. It is therefore imperative that mental health professionals such as psychologists support families during COVID-19.<sup>15, 26</sup> Mothers and fathers in our study seemed to cope with stress a little differently. While some fathers sought for distraction, mothers specifically mentioned that being with their infant helped them to cope. Hagen and colleagues described that fathers often tried to hide emotions in order to protect themselves against further pain.<sup>22</sup>

The parents in our study highlighted that being told why certain COVID restrictions are imposed is helpful. They also seemed to appreciate that exceptions were made based on the clinical condition of the mother and the infant, though this should always be weighed against the need for restrictions.

In a meta-analysis by Caporali et al (2020), the 'sights and sounds' subscale of the PSS:NICU was found the least relevant source of stress for NICU parents.<sup>27</sup> corresponding with our study results. We would expect the COVID-19 restrictions to have the greatest impact on the 'parental role alteration' subscale, which Caporali and colleagues already found to be the most relevant source of stress for NICU parents in general by. Since studies from countries worldwide and up to 1991 were included in this meta-analysis, it is difficult to compare findings because of the possible impact of different parental visitation restrictions and cultural differences.

We do not know how the restrictions on the presence of parents and other family members affected the spread of the COVID-19 virus. Neither do we the long-term consequences of these restrictions on a family after NICU discharge. During a second, partial COVID-19 lockdown, parental presence was not restricted, but siblings, grandparents and others were still not allowed. We believe NICU wards should be very reluctant in restricting the presence of parents and other family members, in view of minimizing the consequences on psychosocial wellbeing and bonding.<sup>17</sup> Testing NICU parents for COVID-19 could be considered, which should enable scaling back restrictions as much as possible and determine the effect of any restrictions on the spread of the COVID-19 virus. Because of this additional stress factor for a parent population already at risk for psychological disorders such as PTSS, follow-up studies are necessary.

### ***Practice implications***

In summary, the following recommendations for the hospital management during a period of restricted parental visitation in the NICU. To start with, families (parents, siblings and other family members) should be kept together where possible. It is important to communicate clearly why restrictions on the presence of parents and other family members have been imposed. Make sure that mental health professionals can be consulted and consider videoconferencing, so that parents can feel closer to the infant and participate in decision-making.

### ***Limitations***

This study has some limitations. First, we could not compare our results with a historical control group, and thus could not distinguish between stress related to the NICU hospitalization and stress related to COVID-19-related restrictions. Figure 3 does show, however, that both mothers and fathers indicate the NICU hospitalization and COVID-19 to cause high stress levels with a median VAS stress between six and eight. This VAS stress scale was not validated, though in general a VAS is recommended to determine the level of perceived stress.<sup>28</sup> Second, the sample size was relatively small and there was a large range in postnatal age at the time of the data collection. The first lockdown in the beginning of 2020 is too recent, however, to study the long-term consequences of this stressful experience.

## **CONCLUSION**

In conclusion, parents of infants admitted to the NICU during COVID-19 lockdown primarily experienced stress because they could not be with their infant together with their partner, and because siblings and others were not allowed to visit. This study emphasizes that it is key to be very cautious concerning these restrictions and scale these down whenever considered possible. Future studies should focus on the long-term psychological consequences and follow-up of these parents.

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## Discussion & Summary



# Chapter 10



General discussion

## **GENERAL DISCUSSION**

Infants admitted to the Neonatal Intensive Care Unit (NICU) depend on healthcare professionals for the prevention, assessment and treatment of pain and stress. Moreover, the NICU admission is a highly stressful period for parents. This thesis offers helpful insights essential for enhancing pain and stress management in the NICU. This chapter discusses the main findings, offers clinical guidance for optimal pain and stress management, and explores future perspectives.

### **PART I – PAIN ASSESSMENT**

While many observational pain measurement instruments have been developed over the past 40 years, accurately assessing pain intensity among infants admitted to the NICU remains challenging. The absence of a gold standard for pain assessment in this specific patient population has important consequences both for clinical practice and research.<sup>1</sup>

The observational pain measurement instruments can be roughly categorized into those developed to measure acute pain (related to a procedure or events with an immediate onset) and those developed to measure prolonged pain (also referred to as persisting or chronic pain, often associated with disease or therapy) in infants.<sup>2,3</sup> Some of these instruments are unidimensional, focusing on a single pain dimension, usually behavior.<sup>4</sup> Others are multidimensional instruments incorporating behavioral, physiologic, and contextual indicators. Most instruments are validated for acute procedural pain in infants admitted to the NICU.<sup>5</sup> In any case, NICU nurses and physicians should acknowledge that certain procedures cause unavoidable acute pain in these infants, necessitating consistent use of non-pharmacological pain-reducing interventions without exemption.<sup>6</sup> Pain assessment during a painful procedure helps to determine if non-pharmacological treatment is sufficient or if additional pharmacological interventions are indicated.

Prolonged pain generally has a less clear cause and starting point compared to acute pain, making it challenging yet crucial to accurately identify. A European study, however, demonstrated that daily pain assessment – crucial to recognize prolonged pain – was done in only 10% of the infants admitted to the NICU.<sup>7</sup> The COMFORTneo scale stands out as one of the few instruments developed to measure prolonged neonatal pain.<sup>8,9</sup> We showed that this instrument can be used to reliably and

validly assess pain in NICU patients (CHAPTER 3). To ensure accurate assessment of prolonged pain in clinical practice, strict adherence to clinical guidelines in applying the COMFORTneo scale is imperative,<sup>10,11</sup> including the recommended two-minute observation period and optimal timing of the assessments. Nevertheless, the pain scores in specific patient groups might be deceptively low. For example, critically ill infants with necrotizing enterocolitis (NEC) may show a blank facial expression and few body movements despite experiencing great pain.<sup>12</sup> This poses challenges to the valid assessment of pain, not only for the COMFORTneo scale but also for all other behavioral pain measurement instruments with comparable items.<sup>4</sup> Assessing pain in extremely premature infants is also complex due to their dampened behavioral responses to pain compared to older infants.<sup>13</sup> Our research showed that the existing pain measurement tools, both behavioral pain measurement instruments and physiological indicators, failed to distinguish between a painful situation, in rest and during skin-to-skin care in this group (CHAPTER 4). Given these limitations, NICU clinicians' clinical expertise becomes paramount in critically observing infants and identifying pain scores that might be unjustifiably low. Applying a Numeric Rating Scale (NRS) for pain could help quantify their expert opinions.

The availability of an instrument with established responsiveness – i.e., the ability to detect changes in pain intensity over time – is essential to evaluate the need and the effects of non-pharmacologic and pharmacologic pain reducing interventions. The instrument should be responsive to the type of pain and the patient population for which it is intended. We systematically reviewed the level to which this measurement property is determined in 43 existing neonatal pain measurement instruments (CHAPTER 2). The nine included studies that evaluated the responsiveness of 10 instruments were of poor to moderate quality, highlighting a lack of attention for responsiveness. Future validation studies should take the evaluation of the responsiveness into account. Studies exploring the pain-reducing effect of existing and new pain reducing interventions also depend on a responsive measurement instrument. To ensure quality, both validation and intervention studies should formulate their specific hypotheses before the start of data collection, and pay attention to blinding.

The development of new observational pain measurement instruments is not the answer for improved pain assessment, since there already is a large overlap in the content of the numerous existing instruments.<sup>2</sup> Instead, adjusting existing instruments based on new knowledge and research

findings is a viable option, to be followed by further validation following the COnsenses-based Standards for the selection of health Measurement INstruments (COSMIN) guidelines to give insight into the strengths and limitations of these instruments.<sup>14,15</sup> Only a few of the many observational measurement instruments are commonly used in both clinical practice and research.<sup>9,16</sup> Of these, the Premature Infant Pain Profile (PIPP(-R)), focusing on acute pain, is by far the most frequently applied.<sup>9</sup> The COMFORTneo scale and the EDIN scale are the most used instruments for the assessment of prolonged pain. These three instruments have been proven to be valid in the general NICU population.<sup>8,12,17-19</sup> Prioritizing their further validation and optimization could prove advantageous, specifically for patient populations characterized by complex pain behaviors, such as extremely preterm infants and infants with NEC.

To ensure accurate pain assessment in clinical practice, it is important to apply a pain measurement instrument that has been validated for the relevant patient population and type of pain (i.e., acute or prolonged), along with an optimal timing.<sup>5</sup> Nevertheless, it could well be that not any instrument would be capable of accurately measuring pain in highly complex patient populations. It is therefore important to also focus on potential other methods to measure pain in infants. The utilization of vital signs such as heart rate and oxygen saturation for the assessment of pain in infants has been documented since 1993.<sup>20</sup> Analysis of the heart rate variability, more specifically using the Newborn Infant Parasympathetic Evaluation (NIPE) index, offers potential for assessing both acute and prolonged pain in infants.<sup>21,22</sup>

Our recent review (2024) thoroughly explored the potential integration of biomarkers in pain assessment in the NICU.<sup>23</sup> This review assessed the validity for evaluating both procedural and prolonged pain, considering factors such as invasiveness, timeliness and evidence from clinical studies. Biomarkers encompassed autonomic (e.g., heart rate), hormonal (e.g., cortisol), proteomic (i.e., the entire set of proteins), metabolomic (i.e., metabolite profiles), and oxidative stress (e.g., advanced oxidation protein products) indicators. Particularly in sick and preterm infants, physiological biomarkers are generally not specific to pain (e.g., heart rate and blood pressure, highly influenced by respiratory and circulatory stability) and may be too invasive (e.g., biomarkers requiring blood collection or electroencephalography). Additionally, many biomarkers cannot be assessed at the bedside, causing delays in pain assessment. In theory, integrating biomarkers into pain management offers benefits due

to objectivity and continuous pain assessment support.

The more readily available autonomic biomarkers are less invasive but less specific to pain, whereas laboratory biomarkers are typically more specific but more invasive. Further research is required to determine optimal biomarker implementation strategies to make the most of their benefits.<sup>23</sup> Studies should focus on either combining existing methods or developing a single innovative method that does not induce additional pain or stress. In the absence of a gold standard, validation studies must hypothesize the expected relationship between the studied outcome measure and other instruments.<sup>15</sup> Future studies must also consider the feasibility of implementing the measurement method in clinical practice, including developing techniques for analyzing and interpreting continuous data for direct use in clinical care.

### ***Next steps in neonatal pain assessment***

Up till now we still do not have a gold standard for pain assessment, while existing behavioral pain instruments are merely proxies. Identifying a single perfect pain assessment tool that enables the valid assessment of all types of pain in all types of patients is likely unachievable.<sup>1</sup> Instead, we should consider combining different pain assessment methods, thereby making optimal use of the benefits and mitigating the disadvantages of each method. This multi-modal pain measurement approach has been initially described in healthy infants.<sup>24</sup> Additionally, van der Vaart et al. showed that their multimodal model of behavioral, autonomic, and neural modalities discriminated between noxious and non-noxious stimuli in infants from 28 weeks postmenstrual age.<sup>25</sup> Applying a machine learning approach could significantly enhance the effectiveness of these models, making them viable for clinical use.<sup>26</sup> These models can include multiple combinations of objective variables, such as behavioral items like facial expression and body movements, but also autonomic biomarkers. Artificial intelligence might also enable the automation of continuous pain assessment, for example by continuously analyzing facial expression.<sup>27</sup> Bridging the gap between computational methods developed for automated face-based pain assessment in the NICU and the practical application at the bedside is crucial.<sup>27</sup> This includes addressing challenges such as how to deal with facial expressions in neonates with partially covered faces (e.g., due to fixation material for feeding tube or respiratory support), natural infant movements, and varying light intensities.

Currently, the timing of assessments largely depends on healthcare professionals' availability, posing a risk of delays in recognizing and

treating pain.<sup>28</sup> It is neither feasible nor desirable to expect frequent pain assessments from healthcare professionals to very frequently assess pain, since workload is already high and this might lead to missed care in other caregiving areas.<sup>29</sup> Therefore, pain assessment presently relies on optimal timing for patients at high risk of pain, such as those requiring pharmacological pain treatment. However, the aforementioned technological advancements could also facilitate the continuous assessment of neonatal pain instead of relying on periodic observations. This approach would greatly benefit the timely recognition of pain and enable the continuous evaluation of pain management for all infants admitted to the NICU.

## **PART II – PAIN TREATMENT**

Following pain assessment, the next step is the adequate treatment of pain. In general, non-pharmacological pain-reducing methods, which are considered safe for all infants admitted at the NICU, are the first step. Pharmacological interventions, such as the administration of paracetamol or opioids, should be considered on indication since many of these are associated with side-effects and unknown risks for long-term safety.<sup>30</sup>

By general expert consensus, the administration of sucrose is a non-pharmacological pain-reducing intervention.<sup>31</sup> The exact underlying mechanism of action for sucrose is still unclear, although it has been hypothesized that sucrose stimulates the endogenous opioid system.<sup>32</sup> The extensive exposure to painful procedures explains the widespread use of sucrose in every infant admitted to the NICU.<sup>33</sup> We showed that the duration of the waiting period after sucrose administration did not influence the pain intensity associated with a heelstick procedure (CHAPTER 5). This questions the necessity of the two-minute waiting period suggested in clinical guidelines and research protocols.<sup>6</sup> Little knowledge is available regarding many practical aspects of sucrose administration, such as the optimal dose and its effect when combined with other non-pharmacological interventions.<sup>34</sup> Additionally, both preclinical and clinical studies raise concerns about potential long-term adverse effects on brain development after repeated exposure to sucrose.<sup>32</sup>

The repeated administration of a sucrose dose whose safety is unclear in vulnerable infants admitted to the NICU,<sup>35</sup> raises questions about its qualification as a non-pharmacological intervention. In clinical practice, sucrose is inconsistently administered and recorded, and sometimes serves

merely as a comforting intervention unrelated to a painful procedure. Given the lack of evidence regarding its efficacy in reducing discomfort unrelated to acute pain, alternative non-pharmacological evidence-based comforting interventions should be considered like skin-to-skin care or offering a pacifier, possibly together with the administration of breast milk.<sup>36-38</sup> In case of procedural pain, the evidence to replace sucrose with supplemental breast milk is scarce, especially in preterm infants.<sup>39</sup> Given the uncertainties regarding sucrose, breast milk might be a promising alternative for repeated use during NICU stay. Additional research is needed to determine the effectiveness of breast milk to reduce procedural pain as an alternative to sucrose when administered together with a pacifier.

While all infants admitted to the NICU will be exposed to procedural pain, a subset of infants will additionally be exposed to more prolonged pain. A striking example is the pain related to the earlier mentioned NEC, which is an inflammatory bowel condition associated with prolonged pain during a median disease period of seven days, necessitating continuous analgesic therapy.<sup>28</sup> In 2016, we demonstrated that infants undergoing surgery for NEC in our ward received a median continuous morphine dosage of 17 µg/kg/h postoperatively, with over three-quarters of them requiring additional analgesics (CHAPTER 6). Eight years later, ten Barge et al. re-evaluated the pain management in infants with NEC.<sup>28</sup> One of the most noticeable differences regarding analgesic therapy since 2016 is the administration of acetaminophen as an opioid-sparing method.<sup>40</sup> Despite this change in analgesic therapy, ten Barge et al. found that most NEC patients still experienced pain.<sup>28</sup> This indicates the necessity for further improvement in pain treatment in these patients, for instance by standardized use of strong opioids such as fentanyl. However, presently there is no consensus across European NICUs regarding the optimal assessment and treatment of pain in NEC patients.<sup>41</sup> Since NEC is rare, with typically fewer than 20 infants with NEC treated in European NICUs yearly,<sup>41</sup> optimal pain management for this extremely painful condition must be evaluated in multicenter clinical trials.

### ***Next steps in neonatal pain treatment***

Chapter 5 and 6 underscore the absence of consensus on both pharmacological and non-pharmacological pain treatment within the NICU, although these have already been applied for years. This lack of consensus impedes the optimal application and implementation of pain reducing strategies.

The stepwise approach to neonatal analgesia, as proposed by Durrmeyer et al. (see Figure 2), closely reflects clinical practice and could provide clarity on ways to enhance neonatal pain treatment.<sup>42</sup> This approach clearly illustrates the importance of the initial two steps in neonatal analgesia, i.e., avoiding painful procedures and physical handling as much as possible, followed by non-pharmacological intervention, including sucrose. Only after the application of these two steps, pharmacological interventions should be considered while keeping in mind those two initial steps to minimize the required dosing of analgesedatives and consequently their potential side effects.

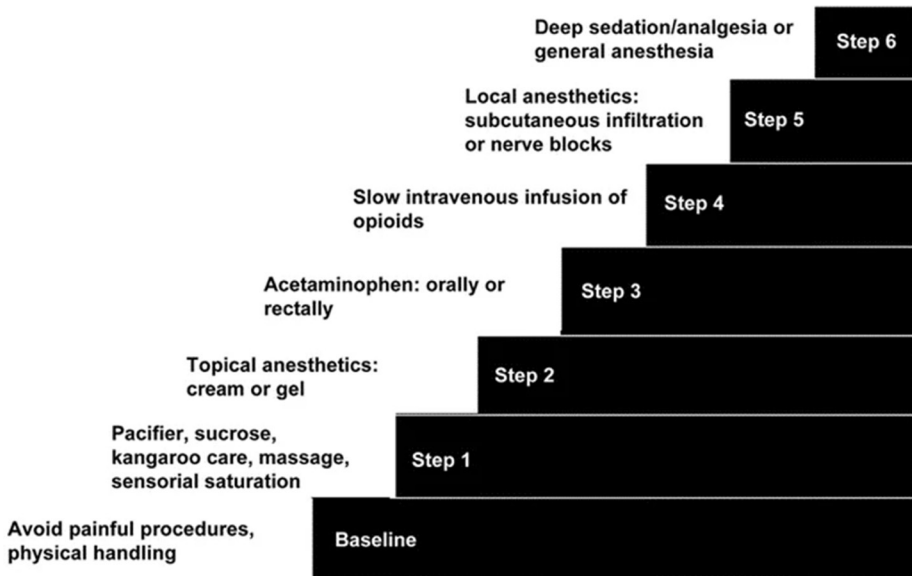


Figure 2 - Stepwise approach to neonatal analgesia<sup>42</sup>

We have been able to reduce infants' exposure to painful procedures in our ward from approximately 14 procedures per day in 2001 to 11 in 2009<sup>33</sup> Although at the time it was concluded that achieving further reduction was unlikely, we should keep searching for ways to further lower this frequency. Benchmarking offers the chance to explore potential variances among NICUs, both nationally and internationally.<sup>43</sup> Improved technologies over the past 15 years might provide new opportunities to prevent a painful procedure. An example is the transcutaneous measurement of bilirubin, which might be an alternative for measuring serum bilirubin levels even in preterm infants.<sup>44</sup> Clinicians may find it challenging to stay up-to-date with technological advancements, while technologists may struggle to recognize how technologies can support NICU care. Therefore, close

multidisciplinary collaboration is crucial for staying informed about all available opportunities. Additionally, using an implementation framework, such as the Non-adoption, Abandonment, and Challenge to the Scale-up, Spread and Sustainability (NASS) framework specifically designed for the implementation of technology in health care, can help ensure successful utilization of these technologies in clinical practice.<sup>45</sup>

Although there is evidence for the effectiveness of multiple pain-reducing non-pharmacological interventions, implementation of these interventions seems suboptimal. For example, the inconsistent administration of sucrose in our ward consequently leads to suboptimal pain treatment during painful procedures. Additionally, there are seldom occasions when painful procedures are performed during skin-to-skin care, despite its proven effectiveness in reducing pain.<sup>46</sup> Clinicians have raised the fear of negative conditioning when painful procedures are combined with skin-to-skin care. We know that experiencing pain can have negative consequences on the development of the infant and that skin-to-skin care is known to help reduce acute procedural pain.<sup>46,47</sup> Studying the potential negative effects of conditioning on developmental outcomes is challenging and therefore, applying this intervention should be discussed with the parents. It is crucial to clearly communicate the current understanding of the effect of skin-to-skin care on acute pain together with other available strategies to minimize pain, such as facilitated tucking and talking to their infant.<sup>48,49</sup> By integrating scientific knowledge, best practice information, and parental preferences together with the infant's needs, we can provide excellent, evidence-based nursing care.<sup>50</sup>

Optimizing non-pharmacological treatment will establish a stronger foundation for initiating pharmacological treatment if deemed necessary. In the stepwise approach to analgesia, steps 2 through 6 involve pharmacological interventions ranging from topical anesthetics to general anesthesia.<sup>42</sup> Understanding the pharmacokinetics (PK) and pharmacodynamics (PD) of analgesedatives is crucial in optimizing these steps in NICU care.<sup>51</sup> Knowledge regarding the PK/PD of these drugs will enable physicians to define an optimal choice of drugs and dosing regimen for each individual patient. Additionally, understanding PK/PD will help NICU nurses choose the optimal timing to evaluate the effectiveness of the treatment. PD studies in infants admitted to the NICU are scarce, yet they are highly necessary to ensure optimally designed pharmacological pain treatment.<sup>52</sup>

## **PART III – STRESS EXPOSURE**

While parts I and II of this thesis focused on the assessment and treatment of neonatal pain, part III expands its focus to the broader concept of exposure to stress. While pain is considered a subjective experience,<sup>53</sup> stress is acknowledged as a biological concept.<sup>54</sup> Experiencing stress is related to the activation of the hypothalamic-pituitary-adrenal (HPA) axis in response to the exposure to a type of stressor. Experiencing some stress may not be harmful as long as homeostasis is only mildly challenged, also referred to as “eustress” or good stress.<sup>54</sup> Traditionally, stress is associated with the fight-or-flight response needed to improve survival.<sup>55</sup>

Distinguishing between pain and stress in infants poses several challenges. Firstly, in infants the distinction is hard to make because we cannot ask them about their pain, and therefore the assessment of pain might primarily be based on the pain-related stress response. Secondly, behavioral, physiological and metabolic changes due to pain are very similar to those due to stress, either related or unrelated to pain.<sup>56</sup> And thirdly, particularly in preterm infants, their developing brain is not yet able to discriminate between touch and a potentially painful stimulus.<sup>57</sup> To select the optimal interventions, it might be important to distinguish pain-related stress from non-pain-related stress. However, both the exposure to pain and stress should be prevented and treated in order to protect the infants from experiencing distress, and consequently its negative short- and long-term effects. As a first step in protecting these infants against these effects, we need a detailed insight into stress exposure in preterm infants.

In this thesis we assumed that pain is always stressful. However, even routine non-painful care can be stressful in preterm infants.<sup>58,59</sup> Consequently, our studies that focused on stress in preterm infants included pain as a stressor among other sources of stress such as the need for continuous respiratory support. With the input of NICU nurses and physicians, we developed the NeO-stress score to validly quantify preterm infants’ daily stress exposure on a daily basis (CHAPTER 7). Our study shows very high stress exposure among preterm infants admitted at the Dutch NICUs, of which both the amount and the course depend on gestational age (CHAPTER 8). This exposure to stressors will strongly challenge homeostasis, exceeding the limits of eustress and leading to distress, characterized as “bad stress”.<sup>54</sup> Research in adults has clearly shown that distress can be detrimental to the neurological, cardiovascular, gastrointestinal and endocrine systems.<sup>60</sup>

This corresponds with the negative impact of stress during NICU stay on infants' health and development.<sup>61</sup>

The NeO-stress score focuses on the level to which infants are exposed to clinical stressors that are deemed relevant by NICU clinicians, without considering the way the infant responds to this exposure. In clinical practice, it is crucial to take into account this individual response when selecting and applying interventions to minimize distress as much as possible. In the context of this individualization, The Newborn Individualized Developmental Care and Assessment Program (NIDCAP) holds an essential place in NICU care in the Netherlands. This individualized caregiving approach aims at diminishing the stressfulness of the NICU stay and enhancing the infant's strengths with a potential positive effect on neurobehavioral outcome.<sup>62,63</sup>

Skin-to-skin care is a frequently applied non-pharmacological intervention proven effective in reducing stress, irrespective of its cause.<sup>36,46,64</sup> Distinguishing between stress related to pain or other factors might be particularly important for pharmacological interventions, as different drugs may have a different mechanism of action.<sup>65</sup> In short, while pharmacological pain treatment requires analgesics, non-pain-related stress might need treatment with sedatives. The binding of opioids such as morphine and fentanyl to opioid receptors will result primarily in analgesia, while midazolam, for instance, exerts its sedative effect by binding to gamma-aminobutyric acid (GABA) receptors.<sup>66,67</sup> To optimally treat discomfort while minimizing unnecessary side effects, it is important to select the drug in accordance to the cause of stress, either related to pain or not.<sup>42</sup> As pain and stress in preterm infants are hard to detangle in clinical practice and safety of sedatives is still under discussion, the current approach mostly involves initiating treatment with opioids, which also have sedative effects.<sup>68</sup> If considered necessary afterward, sedatives may be introduced.

While it is generally acknowledged that NICUs are extremely stressful environments, the concept of stress during NICU admission may not always be interpreted in the same way. For instance, we cannot rule out that admitted infants experience psychological stress, for example due to being separated from the parents.<sup>69</sup> A child's NICU admission is very stressful for parents, too, often leading to mental health problems after discharge.<sup>70</sup> Alleviating parental psychological stress is not only important for their own wellbeing but also for an adequate parent-child interaction and development of the child.<sup>71-73</sup> We focused on psychological stress when studying the impact on parents' wellbeing of the COVID-19 restrictions on

parental presence (CHAPTER 9). The study findings underscored these restrictions were extremely stressful for parents, suggesting that in the event of a next epidemic such restrictions should be limited as much as possible.

### ***Next steps in managing neonatal stress exposure***

While improved pain management in the NICU as discussed in Part I and Part II can significantly reduce stress, minimizing the exposure to stressors unrelated to pain offers additional opportunities for stress reduction. Environmental factors such as noise and light, for example, are considered negative stimuli for infants in the NICU. Though exposure to light is generally prevented in our NICUs nowadays, cycling light conditions prove to have beneficial effects.<sup>74</sup> While noise in general can have negative short-term effects on both cardiovascular and respiratory systems,<sup>75,76</sup> exposure to white noise or recorded mother's voice has demonstrated effectiveness in alleviating pain related to the heelstick procedure.<sup>77</sup> A study in which both light and noise exposure were minimized reported that infants wearing eye goggles and earmuffs showed a higher maximum heart rate and lower heart rate variability, suggesting increased stress responses.<sup>78</sup> The layout of the NICU might also impact exposure to environmental stressors. Although there is a trend towards single family rooms, which are favorable due to their positive impact on weight gain, breastfeeding, neurobehavioural development, and parental satisfaction on the short term, conflicting results regarding long-term neurodevelopmental consequences have been reported.<sup>79,80</sup> Factors such as isolation and the subsequent sensory deprivation might have a negative effect on neurodevelopmental outcome.<sup>81,82</sup> One of the underlying mechanisms for achieving an optimal balance between protecting infants and exposing them to the environment is aligning exposure to light and noise with the circadian rhythm.<sup>74</sup> Since a disruption of the circadian rhythm could lead to disease later in life, this approach had the potential to improve infant outcomes.

Pursuing an infant's comfort extends beyond stress prevention and is facilitated by positive stimuli such as skin-to-skin care and the presence and voice of parents.<sup>36,83,84</sup> Comforting touch by clinicians can also be provided as part of a comprehensive stress management plan.<sup>85</sup> Another possibly beneficial intervention is music therapy,<sup>86</sup> preferably offered as live music early during the NICU admission.<sup>87</sup> Live music enables individually adapted strategies, ensuring that the timing, volume and type of music corresponds with the preferences of the family and can be

adjusted during the therapy if needed. Still, even though it is assumed that non-pharmacological comforting strategies can be applied without side effects, caution is warranted since too much of a specific stimulus, e.g., touch or music, might transition into a negative stimulus.

Chapter 8, which provided insight in the exposure to clinical stressors in very preterm infants, was the first step in analyzing the data collected during the HIPPO study. Further analysis of these data will help us to answer many more research questions. In addition to stress exposure, we also have insight into the amount of positive stimuli such as the frequency of skin-to-skin care, the duration of parental presence, and the causes and level of parental stress. Several previous studies demonstrated that cortisol levels are positively correlated with stress exposure in preterm infants,<sup>88,89</sup> while another highlighted cortisol levels decreased in response to skin-to-skin care.<sup>36</sup>{Pavlyshyn, 2022 #297} These studies focus on either the exposure to stress or to comforting interventions. The HIPPO study will examine the effects of stress exposure and comforting interventions such as skin-to-skin care on the biological stress effect, determined by the levels of cortisol and its metabolites. Additionally, the design of the HIPPO study enables determining the correlation between stress exposure and infants' adverse short- and long-term outcomes. Considering the comforting interventions that may impact this stress response will clarify potential benefits of decreasing stress and pursuing comfort.

We should primarily use this data to gain insight into ways to prevent stress or its negative consequences. Chapter 8 already highlighted that it is important to focus on ways to decrease the frequency and stressfulness of endotracheal and nasal/oral suctioning. By analyzing potential differences in practice routines between the participating NICUs in more detail, we expect to learn from those with the lowest stress exposure and find ways to further decrease stress in admitted infants. Together with the previously mentioned promising strategies, such as music therapy, these findings should be carefully implemented and evaluated on their feasibility and effectiveness.

In clinical practice, the parents' and the infant's stress are closely linked. Maternal high levels of stress related to NICU admission are significantly correlated with the prevalence of maternal post-traumatic stress disorder (PTSD)<sup>90</sup> Fathers are often largely underrepresented in studies focusing on the prevention of PTSD.<sup>91</sup> We will be able to determine the impact of the neonatal stress exposure, together with other potential determinants

such as their psychological history, on the wellbeing of both parents. Determining factors that contribute to the psychological impact of preterm birth in parents can help define ways to diminish this impact. Within the HIPPO study, we therefore asked parents to complete the Parental Stressor Scale: NICU, in order to bring to light factors potentially related to the infant's behavior and appearance, the sights and sounds, and alterations in the parental role considered most stressful.<sup>92</sup> Improving their long-term wellbeing and assuring the quality of parent-infant interaction{Hartzell, 2023 #407} requires a multidisciplinary approach with essential roles not only for the psychosocial team, but also for nurses and physicians. They have the ideal position to prevent stress in the NICU for all infants and their parents but also to identify when parents require additional support. It would be helpful if we could identify parents at risk of high stress mental problems before admission to the NICU. For example, a history of mental health problems might be a strong predictor for the development of PTSD after NICU admission, in which case early additional support is indicated.<sup>93,94</sup>

The psychological support for parents with an increased risk for developing mental problems should continue after discharge. The discharge procedure itself and the consequent task of caring themselves for a fragile infant may increase their risk for mental health issues for years afterwards.<sup>94</sup> Since, the impact of experiencing stress during NICU admission for the infants also continues after NICU discharge, an adequate follow-up program is crucial for these families with respect to both the development of the infants and the mental health of the entire families.

Although the HIPPO study only involves two chapters in this thesis, it represents the most extensive and time-consuming project. One of the strengths of this HIPPO study is the inclusion of infants from all Dutch NICUs, offering a nationally representative overview. Given the need to inform parents about the study shortly after the infant's birth, retrieve their consent, and accurately collect both infant and parental data nationwide, the collaboration with local research teams was crucial. These teams typically consisted of a principal investigator (a neonatologist or nurse specialist), one or more nurses and a psychologist. Next to the role of principal investigator, it is important to also recognize the crucial contribution of the entire supporting team and the added value of this multidisciplinary approach.

The expertise of the psychologists in in aspects related to parental stress were indispensable in designing, conducting and analyzing the data of the

HIPPO study. Parent representatives were actively involved throughout all phases of the HIPPO study, greatly enhancing the feasibility of parent participation, the selection of relevant infant and parental outcomes and the study's potential to improve care for these families. The nurses actively contributed with their experience and expertise in daily caregiving for the infants and fulfilled the roles of clinical research nurses, focusing on the coordination and management of the whole research pathway of clinical trials.<sup>95</sup> Pye et al. described the involvement of a clinical research nurse as a member of a multidisciplinary research team to, among other things, facilitate maximum involvement of participating sites, support quality of the data captured, facilitate recruitment, and promote trial integrity.<sup>96</sup> Monthly meetings with the local research teams and the participating nurses served as a platform to discuss study progress and often brought to light issues requiring clarification or providing opportunities to enhance study success.

The HIPPO study itself was the very first step in raising awareness about the importance of a continuous focus on stress from the infant's day of admission until discharge and beyond. I strongly believe that to change clinical practice, it is crucial for the entire multidisciplinary team to collaborate and feel responsible for the optimal prevention of stress. If it takes a village to raise a child, building a village for preterm born children should not be delayed due to the NICU admission.

## **CONCLUDING REMARKS**

Over 35 years ago, Anand and colleagues first demonstrated the significance of pain management in infants. Today, it is widely accepted knowledge that infants can experience pain, and treating it is crucial both ethically and to mitigate short- and long-term negative consequences. Despite important advancements since then, this thesis highlights that there is still much room for improvement to ensure patient comfort and consequently optimal outcomes in our NICUs.

The thesis also emphasizes the importance of addressing stress unrelated to pain. While generating new insights and knowledge regarding pain management is essential, it is equally crucial to continuously evaluate the balance between providing positive stimuli and administering non-pharmacological or pharmacological pain and stress treatment in clinical NICU practice. Lastly, preventing parental stress and offering adequate psychological support are beneficial for the entire family.

Adequate pain treatment and its evaluation are impossible without valid pain assessment. Even when pain is recognized and treated, ensuring infant comfort in the NICU also requires eliminating other potential causes of stress and offering non-pharmacological and, if necessary, pharmacological treatment for unavoidable stress. Pain assessment, pain treatment, and stress exposure are largely intertwined in clinical NICU practice. A multidisciplinary approach to these issues will aid researchers and healthcare professionals in pursuing comfort for all infants admitted to the NICU.

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# Chapter II



Summary

## SUMMARY

This thesis is structured into three main parts, each addressing an essential aspect to pursue comfort in infants admitted to the NICU.

The **first part** of this thesis focuses on the assessment of pain in (premature) infants admitted to the NICU.

The level of comfort and effectiveness of pain-reducing interventions in infants can only be determined if pain measurement instruments are responsive; i.e. able to detect a decrease in pain intensity after the pain-reducing intervention. In **chapter 2** we reviewed the extent to which the responsiveness of neonatal pain measurement instruments is evaluated, alongside with the methodological quality of the included studies. We showed that the responsiveness was studied for only ten of the 43 existing neonatal pain measurement instruments, with none of these studies meeting the criteria for good methodological quality according to the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist. More research on this topic is needed with particular emphasis on factors like blinding and formulating a specific hypothesis before start of data collection to ensure accurate methodological quality.

One of the few instruments that has been developed to assess prolonged pain in infants is the COMFORTneo scale. In **chapter 3** we studied the reliability and construct validity of this scale from NICU nurses' assessments of pain in infants with varying gestational ages admitted to the NICU. We showed that the COMFORTneo scale is an instrument with good inter-rater reliability and acceptable intra-rater reliability and construct validity to measure prolonged pain in these infants.

In **chapter 4** we determined existing pain assessment tools and physiological indicators in infants born less than 29 weeks gestational age across three conditions: skin-to-skin care, rest and a heelstick procedure for capillary blood sampling in the incubator. We found that none of the studied behavioral and physiological potential pain indicators adequately distinguished between pain and comfort.

The **second part** focuses on the treatment of two different types of pain, namely acute procedural pain related to a heelstick procedure and prolonged pain related to the highly painful inflammatory bowel disease necrotizing enterocolitis (NEC).

Sucrose administration is standard of care to reduce acute procedural pain in all infants admitted to the NICU. In **chapter 5** we applied the PIPP-R, validated to measure acute pain in infants, in order to determine the correlation between the time-interval after sucrose administration and pain related to a heelstick procedure. Our results suggest that adhering to a two-minute waiting period after sucrose administration has no beneficial effect. However, it is noteworthy that sucrose-induced non-nutritive sucking significantly reduced the PIPP-R score.

In **chapter 6** we explored pain management 72 hours before surgery until 72 hours after surgery in infants undergoing NEC surgery in our NICU. These patients received morphine with a median dosage of 10 mcg/kg/hour pre-operatively and 17 mcg/kg/hour post-operatively, with additional fentanyl intermittently and/or midazolam as needed. During this pain treatment regimen, COMFORTneo scores were 10 (IQR 10 to 11) pre-operatively and 11 (10 to 12) post-operatively, which is comparable with those of other infants in the NICU during the same admission period. Our results suggest that continuous morphine of 10 mcg/kg/h pre-operatively and an increase to 15 mcg/kg/h postoperatively seemed a good starting dose for further individualized pain management guided by pain scores.

The **third part** focuses on the exposure to stress in preterm infants admitted to the NICU and their parents.

In **chapter 7** we described the development of the NeO-stress score, a cumulative score to quantify the daily exposure to stress in very preterm infants. First, NICU clinicians assessed the relevance of potentially stressful procedures and situations together with the comprehensibility of each item and the comprehensiveness of the list. Next, the stressfulness of all 38 relevant items was rated by 260 NICU clinicians, resulting in a severity index for each item. The NeO-stress score consists of the relevant stressful items including their severity index. The cumulative NeO-stress score can be calculated daily by multiplying the number of times each stressful item occurs by the SI. This score serves as a crucial basis for the national multicenter Happiness for the Improvement of Premature and Parental Outcome (HIPPO) study.

**Chapter 8** presented the first results of this HIPPO study. It outlined the daily NeO-stress scores for premature infants with a gestational age less than 29 weeks during NICU admission in the Netherlands. Our analysis revealed that, in general, the highest stress exposure occurred on the day of admission. Stress exposure varied over time with infants of the

lowest gestational age at risk for experiencing the highest levels of stress throughout their NICU admission. Notably, endotracheal and nasal/oral suctioning were the most important contributors to the cumulative NeO-stress scores. Our model suggested that gestational age, the antenatal administration of corticosteroids, and 5-minute Apgar score might be important risk factors for high stress exposure. These results emphasize the importance of alleviating stress from the day of admission throughout NICU stay and provide possibilities to identify infants at a high risk of experiencing stress and to mitigate stress exposure.

Admission to the NICU is not only stressful to the infants, but also to their parents. Additionally, visitation restrictions further challenged parents' wellbeing during COVID-19 pandemic.

**Chapter 9** described the impact of COVID-19 –related restrictions at the NICU, regulating the presence of parents and other family members, on parents' wellbeing. The parents in our study highlighted that they found it very stressful that they could not be with their child together with their partner as well as other family members. NICU professionals could support them by clearly explaining the reasons for the instructions and making sure that the parents felt heard. Our results show that hospital management should be very cautious on restricting the presence of parents and other family members.

In **chapter 10** the results of our studies are discussed and the next steps in neonatal pain and stress management are outlined. The ongoing challenges and complexities in ensuring their comfort are highlighted. The lack of a gold standard in neonatal pain assessment necessitates the continued validation and optimization of existing behavioral pain measurement instruments together with the further development and evaluation of other biomarkers and the application of new technologies. Preventive and treatment strategies to pursue comfort should target both pain-related and non-pain-related stress, both for the infants and their parents. Balance is key regarding the implementation of these strategies for stress reduction in the NICU. Ultimately, prioritizing neonatal comfort, reducing unnecessary stressors, effective treatment including promoting positive stimuli, and providing adequate follow-up and support aligned with the specific needs of the infants and their parents are essential for optimal outcomes in pursuing comfort during NICU admission.

## SAMENVATTING

Dit proefschrift is opgedeeld in drie delen, waarbij telkens een essentieel onderdeel wordt uitgelicht van het streven naar optimaal comfort bij pasgeborenen die zijn opgenomen op de Intensive Care Neonatologie (ICN).

Het **eerste deel** van dit proefschrift richt zich op de beoordeling van pijn bij (te vroeg geboren) pasgeborenen tijdens hun opname op de ICN.

De mate van comfort en effectiviteit van pijn reducerende interventies bij pasgeborenen kan alleen worden vastgesteld als pijnmeetinstrument responsief zijn, wat wil zeggen dat zij in staat zijn om een afname in de pijnintensiteit na de interventie te detecteren. In **Hoofdstuk 2** gaven we een overzicht van de mate waarin deze responsiviteit is onderzocht voor neonatale pijnmeetinstrumenten, samen met de methodologische kwaliteit van deze studies. We lieten zien dat de responsiviteit voor slechts 10 van de 43 bestaande neonatale pijnmeetinstrumenten, waarbij geen van deze studies voldeed aan de criteria voor een goede methodologische kwaliteit volgens de COSMIN (CONsensus-based Standards for the selection of health Measurement INSTRUMENTS) checklist. Er is meer onderzoek naar dit onderwerp nodig, met specifieke nadruk op het formuleren van hypothesen vóór de start van de dataverzameling en blinding van de onderzoekers om de kwaliteit hiervan te kunnen waarborgen.

Een van de weinige pijnmeetinstrumenten die is ontwikkeld om langdurige pijn bij pasgeborenen te kunnen beoordelen is de COMFORTneo schaal. In **Hoofdstuk 3** onderzochten we de betrouwbaarheid en constructieve validiteit van dit instrument. Hierbij maakten we gebruik van de scores die werden afgenomen door ICN verpleegkundigen bij pasgeborenen geboren na een verschillende zwangerschapsduur. We lieten zien dat de COMFORTneo schaal een goede inter-beoordelaarsbetrouwbaarheid heeft en een acceptabele intra-beoordelaarsbetrouwbaarheid en constructieve validiteit om langdurige pijn bij pasgeborenen te beoordelen.

In **Hoofdstuk 4** hebben we bestaande pijnmeetinstrumenten en fysiologische indicators gemeten bij pasgeborenen geboren na een zwangerschapsduur minder dan 9 weken tijdens drie verschillende omstandigheden: huid-op-huidcontact, rust en een hielprik in de couveuse. We concludeerden dat geen van de onderzochte pijnindicators adequaat onderscheid kon maken tussen zowel pijn als comfort.

**Deel twee** richt zich op de behandeling van twee verschillende soorten pijn, namelijk acute pijn gerelateerd aan procedures en langdurige pijn gerelateerd aan de zeer pijnlijke inflammatoire darmaandoening necrotiserende enterocolitis (NEC).

Het toedienen van sucrose is standaardzorg voor alle pasgeborenen opgenomen op de ICN om pijn gerelateerd aan acute procedures te reduceren. In **Hoofdstuk 5** bepaalden we de relatie tussen de PIPP-R, gevalideerd voor het meten van acute pijn bij pasgeborenen, tijdens een hielprik procedure en het tijdsinterval tussen de toediening van sucrose en deze procedure. Onze resultaten laten zien dat een wachtperiode van twee minuten na de toediening van sucrose geen meerwaarde lijkt te hebben wat betreft de pijnstillende werking. Het is echter van belang om op te merken dat het zuigen op een speen wel significant gerelateerd was aan een reductie van de PIPP-R score.

In **Hoofdstuk 6** onderzochten we de pijnbeoordeling en pijnbehandeling bij pasgeborenen op onze ICN gedurende de 72 uur voor tot en met 72 uur na een operatie voor NEC. Deze pasgeborenen kregen morfine met een mediane dosering van 10 mcg/kg/uur voor de operatie en 17 mcg/kg/uur na de operatie, met daarnaast extra bolussen fentanyl en/of midazolam indien nodig. Tijdens deze periode was de mediane COMFORTneo score voor en na de operatie 10 en 11, respectievelijk. Dit is vergelijkbaar met andere pasgeborenen opgenomen op de ICN in dezelfde opnameperiode. Onze resultaten suggereren dat continue morfine met een dosering van 10 mcg/kg/uur en een verhoging van de dosering tot 15 mcg/kg/uur postoperatief een goed startpunt lijken voor een verdere geïndividualiseerde behandeling op basis van pijnscores.

Het **derde deel** richt zich op de blootstelling aan stress voor te vroeg geboren kinderen opgenomen op de ICN en hun ouders.

In **Hoofdstuk 7** beschreven we de ontwikkeling van de NeO-stress score, een cumulatieve score met als doel het kwantificeren van de dagelijkse blootstelling aan stress voor zeer vroeg geboren pasgeborenen. Eerst beoordeelden artsen en verpleegkundigen werkzaam op een van de ICN afdelingen in Nederland de relevantie en begrijpelijkheid van potentieel stressvolle procedures en situaties samen met de volledigheid van de volledige lijst. Vervolgens beoordeelden 260 artsen en verpleegkundigen de mate van stress voor alle 38 relevante items. De NeO-stress score bestaat uit deze lijst met stressvolle items samen met een score voor de mate van stress voor ieder item. De cumulatieve NeO-stress score

kan berekend worden door het maken van een optelsom waarbij telkens de SI wordt vermenigvuldigd met het aantal keren dat dit item plaats vond gedurende de dag. Deze score dient als een belangrijke basis voor de nationale multicenter HIPPO (Happiness for the Improvement of Premature and Parental Outcome) studie.

In **Hoofdstuk 8** lieten we de eerste resultaten van deze HIPPO studie zien. We beschreven hierin de dagelijkse NeO-stress scores voor kinderen die na een zwangerschapsduur minder dan 29 weken werden opgenomen op een van de ICN afdelingen in Nederland. Onze analyse liet zien dat, over het algemeen, de hoogste blootstelling aan stress plaats vond op de dag van de geboorte. De blootstelling aan stress varieerde over de tijd, waarbij kinderen met de laagste zwangerschapsleeftijd gedurende de volledige opname werden blootgesteld aan de meeste stressvolle procedures en situaties. Endotracheaal, nasaal en oraal uitzuigen hadden de belangrijkste bijdrage wat betreft de blootstelling aan stress voor deze pasgeborenen. Ons model liet zien dat zwangerschapsduur, antenatale blootstelling aan corticosteroïden en de Apgar score na 5 minuten belangrijke risicofactoren kunnen zijn voor een hoge stress blootstelling. Deze resultaten benadrukken het belang van het minderen van stress gedurende de volledige opname, startend direct vanaf de dag van geboorte. Het is van belang om patiënten met een hoog risico op stress te kunnen identificeren om zo bij deze patiënten optimaal strategieën toe te kunnen passen om de blootstelling aan stress te verminderen.

Een opname op de IC Neonatologie is niet alleen stressvol voor de pasgeborenen, maar ook voor hun ouders. Daarnaast kregen ouders tijdens de COVID-19 pandemie te maken met bezoeksregels.

**Hoofdstuk 9** beschreef de impact van deze COVID-19 gerelateerde bezoeksregels wat betreft de aanwezigheid van ouders en andere familieleden tijdens de opname op de ICN op het welzijn van de ouders. De ouders in onze studie benadrukten dat ze het zeer stressvol vonden dat zij niet samen met hun partner of andere familieleden bij hun kind konden zijn. Zorgprofessionals op de ICN zouden het kunnen ondersteunen door een duidelijke toelichting van de redenen waarom deze bezoeksregels nodig waren en ervoor te zorgen dat zij zich gehoord voelen. Onze resultaten tonen aan dat ziekenhuismanagement zeer terughoudend moet zijn wat betreft het beperken van de aanwezigheid van ouders en andere familieleden.

In **Hoofdstuk 10** werden de resultaten van deze studies besproken en de

vervolgstappen wat betreft het meten en behandelen van pijn en stress op de ICN geschetst. Hier werden ook de voortdurende uitdagingen en complexiteit bij het waarborgen van comfort voor deze pasgeborenen benadrukt. Het gebrek aan een gouden standaard in de beoordeling van neonatale pijn vraagt om de continue optimalisering en validatie van bestaande pijnmeetinstrumenten gebaseerd op gedrag, samen met de ontwikkeling en evaluatie van andere biomarkers en de toepassing van nieuwe technologieën. Strategieën om comfort na te streven zouden zich moeten richten op de preventie en behandeling van stress, zowel gerelateerd als ongerelateerd aan pijn, en zowel voor de pasgeborene als zijn of haar ouders. Een optimale balans is essentieel wat betreft de implementatie van deze strategieën om pijn en stress op de ICN te verminderen. Uiteindelijk zijn het vooropstellen van het comfort, het verminderen van onnodige blootstelling aan stressoren, een adequate behandeling inclusief het bevorderen van positieve stimuli en het bieden van een adequate ondersteuning en opvolging van de pasgeborenen en ouders na ontslag essentieel voor optimale resultaten bij het nastreven van comfort tijdens de opname op de ICN.







# Appendices

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## ABBREVIATIONS

AED	Accident and emergency department
APSS	Accumulated Pain/Stressor Scale"
BIIP	Behavioral Indicators of Infant Pain
BPSN	Bernese Pain Scale for Neonates
COSMIN	COnsensus-based Standards for the selection of health Measurement INstruments
CVI-I	Content validity per item
DPPL	Dutch Point Prevalence List
EDIN	Échelle Douleur Inconfort Nouveau-Né
EEG	Electroencephalography
FANS	Faceless acute neonatal pain scale
FIP	Focal intestinal perforation
GABA	Gamma-aminobutyric acid
HIPPO	Happiness for improvement of Premature and Parental Outcome
HPA	Hypothalamic-pituitary-adrenal axis
ICC	Intraclass correlation coefficient
IQR	Interquartile range
NASS	Non-adoption, Abandonment, and Challenge to the Scale-up, Spread and Sustainability framework
NDI	Neurdevelopmental impairment
NEC	Necrotizing enterocolitis
NIAPAS	Neonatal Infant Acute Pain Assessment Scale
NICU	Neonatal IntensiveE Care Unit
NIDCAP	Newborn Individualized Developmental Care and Assessment Program
NIPE	Newborn Infant Parasympathic Evaluation
NIPS	Neonatal Infant Pain Scale
NIRS	Infrared spectroscopy
NISS	Neonatal Infant Stressor Scale
NNS	Non-nutritive sucking
N-PASS	Neonatal Pain, Agitation and Sedation Scale
NRS	Numeric rating scales
PK	Pharmacokinetics

PD	Pharmacodynamics
PDMS	Patient Data Management System
PI	Principal investigator
PIPP(-R)	Premature Infant Pain Profile(-R)
PLI	Procedural Load Index
PSS: NICU	Parental Stressor Scale: NICU
PTSD	Post-traumatic stress disorder
RDS	Respiratory distress syndrome
Sc peaks/sec	Skin conductance peaks per second
SpO <sub>2</sub>	Oxygen saturation
VAS	Visual analogue scale
WHO	World Health Organization

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## LIST OF PUBLICATIONS

### THIS THESIS

**Meesters, N. J.**, van Dijk, M., Knibbe, C. A., Keyzer-Dekker, C. M., Tibboel, D., & Simons, S. H. P. (2016). Infants Operated on for Necrotizing Enterocolitis: Towards Evidence-Based Pain Guidelines. *Neonatology*, *110*(3), 190-197.

**Meesters, N.**, Simons, S., van Rosmalen, J., Reiss, I., van den Anker, J., & van Dijk, M. (2017). Waiting 2 minutes after sucrose administration-unnecessary? *Arch Dis Child Fetal Neonatal Ed*, *102*(2), F167-F169.

**Meesters, N.**, Dilles, T., Simons, S., & van Dijk, M. (2019). Do Pain Measurement Instruments Detect the Effect of Pain-Reducing Interventions in Neonates? A Systematic Review on Responsiveness. *J Pain*, *20*(7), 760-770.

**Meesters, N. J.**, Simons, S. H. P., van Rosmalen, J., Holsti, L., Reiss, I. K. M., & van Dijk, M. (2019). Acute Pain Assessment in Prematurely Born Infants Below 29 Weeks: A Long Way to Go. *Clin J Pain*, *35*(12), 975-982.

**Meesters, N.**, van Dijk, M., Sampaio de Carvalho, F., Haverman, L., Reiss, I. K. M., Simons, S. H. P., & van den Bosch, G. E. (2022). COVID-19 lockdown impacts the wellbeing of parents with infants on a Dutch neonatal intensive care unit. *J Pediatr Nurs*, *62*, 106-112.

**Meesters, N. J.**, Dilles, T., van Rosmalen, J., van den Bosch, G. E., Simons, S. H. P., & van Dijk, M. (2023). COMFORTneo scale: a reliable and valid instrument to measure prolonged pain in neonates? *J Perinatol*, *43*(5), 595-600.

**Meesters, N. J.**, van den Bosch, G. E., van Het Hof, L. J., Benders, M., Tataranno, M. L., Reiss, I. K. M., van Kaam, A., Haverman, L., Simons, S. H. P., & van Dijk, M. (2023). Quantification of stress exposure in very preterm infants: Development of the NeO-stress score. *Early Hum Dev*, *176*, 105696.

**Meesters, N.J.**, van den Bosch, G.E., Tataranno M.L., van den Akker, C.H.P., van Ganzewinkel, C.J., Schuerman, F.A.B.A., Lopriore, E., de Boode, W.P., Raets, M.M.A., Dijk, P.H., van Rosmalen, J., Vermeulen, M.J., Onland, W., Haverman, L., Reiss, I.K.M., van Kaam, A.H., Benders,

M., van Dijk, M., Simons, S.H.P., HIPPO study group. Exposure to clinical stressors during NICU admission in preterm infants. *Submitted*.

## OTHER PUBLICATIONS

Flint, R., Halbmeijer, N., **Meesters, N.**, van Rosmalen, J., Reiss, I., van Dijk, M., & Simons, S. (2017). Retrospective study shows that doxapram therapy avoided the need for endotracheal intubation in most premature neonates. *Acta Paediatr*, 106(5), 733-739.

Ten Barge, J. A., Baudat, M., **Meesters, N. J.**, Kindt, A., Joosten, E. A., Reiss, I. K. M., Simons, S. H. P., & van den Bosch, G. E. (2024). Biomarkers for assessing pain and pain relief in the neonatal intensive care unit. *Front Pain Res (Lausanne)*, 5, 1343551.

Ten Barge, J. A., van den Bosch, G. E., **Meesters, N. J.**, Allegaert, K., Arribas, C., Cavallaro, G., Garrido, F., Raffaelli, G., Vermeulen, M. J., Simons, S. H. P., Pain, ESPR Special Interest Group for Neonatal Pain and the NEC Pain Study Group (2023). Current pain management practices for preterm infants with necrotizing enterocolitis: a European survey. *Pediatr Res*, 94(2), 555-563.

## PHD PORTFOLIO

Erasmus MC Department: Neonatal and Paediatric Intensive Care,  
division of Neonatology

PhD period: 2017 - 2024

Promotor: Prof. dr. M. van Dijk

Copromotor: Dr. S.H.P. Simons and Dr. G.E. van den Bosch

Activity	Year	ECTS
<b>General courses</b>		
Erasmus MC - CPO-course: Patient Oriented Research	2017	0.3
Erasmus MC - Scientific Integrity	2018	0.3
Clinimetrics	2018	3.0
BROK recertification (2020)	2020	1.0
BROK recertification (2023)	2023	0.5
<b>Conferences</b>		
2nd Congress of joint European Neonatal Societies, Venice, Italy (oral presentation)	2017	1.0
7th Congress of the European Academy of Paediatric Societies, Paris, France (oral presentation)	2018	1.0
Perinatal & neonatal pharmacology 1st Erasmus Symposium, Rotterdam, the Netherlands (oral presentation)	2018	0.3
3rd Congress of joint European Neonatal Societies, Maastricht, the Netherlands (attendance)	2019	0.5
HIPPO symposium, virtual (oral presentation & organization)	2020	1.0
8th Congress of the European Academy of Paediatric Societies, virtual (oral presentation)	2020	0.5
Symposium "zorg rond de pasgeborene" SCEM, Ede, the Netherlands (oral presentation)	2022	0.3
5th Congress of joint European Neonatal Societies - Faculty member, Rome, Italy (poster presentation, 2 oral presentations)	2023	1.5

**Teaching**

Lessons pain & Nursing research	2017 - 2023	3.0
Supervising medical students minor "mystery of creation"	2019	0.5
Supervising master thesis medical students	2019 - 2021	7.0
Supervising Critically appraised Topic NICU nurses in training	2020 - 2022	2.0
Supervising master thesis advanced nursing practice student	2021	2.5
Supervising thesis bachelor in nursing	2022	1.5

**Other**

Weekly Neonatology Research Meetings	2017-2023	1.0
Annual Sophia Research days	2017-2023	0.6
Member of the national Neonatal Innovation & Research Nursing group	2017-2024	2.0
Reviewing nine articles	2018-2023	1.8
VIP2 symposium "Wat geeft jou energie?"	2019	0.2
Journal club Nursing science	2019-2024	0.5
TULIPS PhD curriculum 20-22	2020-2022	3.0
Co-applicant "the impact of preterm birth" NWA-ORC 2020-2021	2021	2.0
Presentations HIPPO(VID) - Local research meetings	2021-2024	0.4
Revising and implementing the NICU pain protocol	2022-2024	2.0
Co-applicant PREVENT EARLY: Prevention of causes and consequences of preterm birth	2023	2.0



## ABOUT THE AUTHOR

Naomi Meesters was born on July the 14th 1989 in Roosendaal, the Netherlands. She completed her Gymnasium degree at Gertrudis college in Roosendaal in 2007. Following her graduation, Naomi started her studies in Nursing and Midwifery, and in 2012 she completed both bachelors successfully.



After this, she started her training as a Neonatal Intensive Care nurse at the Erasmus MC Sophia Children's Hospital in Rotterdam, the Netherlands. In the neonatal intensive care unit (NICU), she became increasingly interested in research and was appointed a research nurse in April 2014. Motivated to enhance her research skills, in September 2014 she began with a master's program in Nursing and Midwifery, receiving the Leo Bossaert Prize in 2016 as the most commendable student.

During her master's program, Naomi started initiating her own research projects under the guidance of Prof. Dr. Monique van Dijk and Dr. Sinno Simons, soon joined by Dr. Gerbrich van den Bosch. This experience made her very enthusiastic to continue her research, which evolved into a PhD program. Her PhD program allowed her to collaborate with physicians, nurses, psychologists, and parent representatives, a multidisciplinary approach she believes significantly contributed to the quality and impact of her research.

Naomi's research initially focused on pain assessment and non-pharmacological pain treatment in (preterm) infants. Over time, the scope of her research expanded towards neonatal and parental stress in the NICU. She is committed to continue her work aimed at minimizing stress related to NICU admission and its impact on families.

Simultaneously to her PhD program, Naomi and her husband Pelle transformed an old farm into their dream home. They live there with their three children Jorah (2016), Lea (2019) and Edith (2022).

## DANKWOORD

Mijn dankwoord. Datgene wat gevoelsmatig een belangrijke periode afsluit. Maar waar begin je als je zoveel kansen hebt gekregen die geresulteerd hebben in deze afsluiting?

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