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Acute Pain Assessment in Prematurely Born Infants Below 29 Weeks

A Long Way to Go

Naomi J. Meesters, RN, MSc, Sinno H.P. Simons, PhD, MD,* Joost van Rosmalen, PhD,† Liisa Holsti, PhD,‡ Irwin K.M. Reiss, PhD, MD,* and Monique van Dijk, PhD*§*

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 explored whether existing pain assessment tools and physiological indicators measure pain and comfort accurately in this population.

Materials and Methods: We prospectively collected data in 16 neonates born at less than 29 weeks' gestational age during 3 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 5 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 the number of skin conductance peaks. All measures across the 3 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 3 conditions were analyzed. Heart rate was significantly higher during heelstick procedures compared with during rest, with a mean difference of 10.7 beats/min (95% confidence interval [CI]: 2.7-18.6). Oxygen saturation was significantly higher during skin-to-skin care compared with during heelstick procedures with a mean difference of 5.5% (95% CI: 0.2-10.8). The Premature Infant Pain Profile-revised (PIPP-R) score was significantly higher during heelstick procedures compared with skin-to-skin care with a mean difference of 3.2 points (95% CI: 1.6-5.0).

Discussion: Pain measurement in clinical practice in prematurely born infants below 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.

Key Words: pain assessment, premature, ELGA

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From the *Department of Pediatrics, Division of Neonatology; §Intensive Care and Department of Pediatric Surgery, Erasmus MC—Sophia Children's Hospital; †Department of Biostatistics, Erasmus MC, Rotterdam, The Netherlands; and ‡Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada.

The authors declare no conflict of interest.

Reprints: Naomi J Meesters, RN, MSc, Department of Pediatrics, Division of Neonatology, Erasmus MC-Sophia Children's Hospital, Wytemaweg 80, Rotterdam 3015 CN, The Netherlands (e-mail: n.meesters@erasmusmc.nl).

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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.[1] 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 to 29 wk), namely 14 per day compared with 10 for neonates of 30 to 32 weeks and 9 for those between 33 and 36 weeks.[2] Furthermore, neonates born extremely prematurely are at the highest risk of painful conditions, such as necrotizing enterocolitis[3] and potentially painful and stressful mechanical ventilation.[2] Nonetheless, pain responses of these vulnerable infants are still poorly understood.[4]

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,[5] impaired brain development,[6] altered corticospinal development,[7] and reduced school-age visual perceptual abilities in these infants.[8] 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.[9–12] A review by Cong et al[13] shows that none of the published neonatal pain assessment tools was validated in neonates with a gestational age younger than 29 weeks. The tools partially (multidimensional scales) or fully (unidimensional 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 neuromuscular system is still developing.[4] Moreover, health care professionals find the responses short-lasting and unpredictable.[4]

Physiologically based tools may be an alternative to behavioral pain assessment. For example, skin conductance (SC) measurement seems promising to assess acute pain in premature neonates with a gestational age between 22 and 27 weeks.[14] Studies measuring cerebral oxygen saturation using near infrared 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.[15,16] Vital signs such as heart rate (HR) increase in response to acute pain,[17] 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,[4] 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 was 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 below 29 weeks were eligible for inclusion, and neonates 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 SC electrodes, and for using the NIRS and vital signs data collected as part of the 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:
  - PIPP-R: This is a 7-item scale including behavioral state, gestational age, change in HR, change in peripheral oxygen saturation, and 3 items for facial expression. Items are scored 0 to 3, and the total score range is 0 to 21. Three points are added for neonates with a gestational age below 28 weeks and 2 points if gestational age is between 28 and 32 weeks. A score <7 is taken to indicate no or minimal pain.[9]
  - NIPS: This includes 6 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 to 7. A score of 2 or less is taken to indicate adequate pain treatment.[11]
  - Behavioral Indicators of Infant Pain (BIIP): This includes the assessment of behavioral state, 5 facial expressions, and 2 hand movements. Items are scored 0 to 1 or 2, and the total score range is 0 to 9.[18] Scores between 3 and 6 and between 7 and 9 are taken to indicate, respectively, moderate and severe pain.
  - COMFORTneo: This includes 6 items, namely alertness, calmness/agitation, crying (nonventilated 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 to 30. A score of 14 and higher is considered a sign of distress and pain.[12]
  - Neonatal Pain, Agitation and Sedation Scale (N-PASS): This is a 5-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.[10]
  - Numeric Rating Scale (NRS) pain and distress scores: NRS scores range from 0 to 10 with cut-off scores set at ≥ 4 for both NRS pain and NRS distress.
- Physiological parameters: Data on HR, respiratory rate, and oxygen saturation (SpO_2) were collected automatically from bedside monitors (Infinity M540, Drägerwerk AG & Co. KGaA, Lübeck, Germany).
- Regional cerebral oxygenation: regional cerebral oxygen saturation ($crSO_2$) was measured with NIRS (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 SC monitor (MED-storm Innovation AS, Oslo, Norway) was connected to 3 electrodes placed on the foot.

Procedures

As part of the 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.[19] 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 whether 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 SC electrodes were reconnected. The infant was not disturbed during skin-to-skin care.
  Measurement period: This lasted 2 minutes, from the start of video registration and the moment when clear signals for data collection from the NIRS and SC 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: This lasted 2 minutes starting at least 30 minutes after any handling of the neonate.
- Heelstick procedure (painful): By protocol, each infant received 0.5 ml sucrose 2 minutes before a heelstick procedure. Facilitated tucking was applied from the administration of sucrose until the end of the procedure by a health care 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 2-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). SC 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, $crSO_2$, and SC 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 (N.J.M.) applied the 5 validated pain assessment tools described above and the NRS for pain and the NRS for distress. Each video segment was viewed in real-time and lasted 2 minutes; for condition 3 (heelstick), these 2 minutes followed the puncturing of the heel. With regard to 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 4 (4×30 s). N.J.M. applied the following scoring strategy after having viewed a 2-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 (eg, a score was multiplied by 7/6 if one of 7 items could not be observed). We adjusted for missing items because we considered it unjustified to completely ignore these scores. N.J.M. could not be blinded to the different conditions because these were clearly recognizable. Before start of the study, the interrater reliability of N.J.M. was determined for the PIPP-R and COMFORTneo scale. Linearly weighted κ of N.J.M. compared with a trained neonatologist (for PIPP-R) and MvD (for COMFORTneo) was 0.85 and 0.92, respectively.
- Physiological parameters and $crSO_2$: These values were extracted once per second during the measurement period, and mean and SD of each patient's measurements were calculated for each parameter. These values had also been extracted during the 2 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 SC peaks per second (sc peaks/s) during the measurement period and the change in the number of peaks per second compared with that in the 2 minutes immediately before this period was calculated using the Med-Storm software with a preset threshold value of 0.005 micro Siemens. A higher number of SC peaks suggests more pain.[20]

Data Analysis

Infant 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 3 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 2-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 wk; see Table 1 for background characteristics). The median postnatal age at the time of assessment was 17 days (interquartile range: 14 to 23 d). Eleven neonates were assessed in all conditions on the same day, the other 5 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 2 events was at least 3 hours. None of the patients received any analgesics or sedatives other than sucrose during the observation days.

Physiological and Behavioral Indicators

Table 2 shows the main outcomes during the 3 different conditions. A total of 40 observations were included; 6 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 (Table 2).

The results of the general linear modeling are shown in Table 3. Significant differences between the different conditions were found for the HR, SpO_2, and the PIPP-R. The mean HR was significantly higher during a heelstick procedure compared with rest (estimate 10.7, 95% confidence interval [CI]: 2.7-18.6, $P = 0.01$), but not compared with skin-to-skin care (5.5, 95% CI: −1.7 to 12.8, $P = 0.12$). The HR varied greatly between patients and during the 3 conditions (Fig. 1). The change in HR from baseline was

TABLE 1. Patient and Measurement Characteristics

Variables	N	Median	IQR
Patient characteristics (N = 16)			
Boy/Girl	12/4		
Gestational age (wk)		27.1	25.7-28.0
Birth weight (g)		938	865-1261
Measurement characteristics (N = 40)			
Postnatal age (d)		17	14-23
Time between observation days per patient (d)*		0	0-7
Ventilatory support			
Invasive ventilation			
Endotracheal tube	6		
Noninvasive ventilation			
Nasopharyngeal tube	19		
Silicone double nasal tube (Vygon)	5		
Nasal cannula Optiflow	10		

*The number of days between the observations of the different conditions.

IQR indicates interquartile range.

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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
Physiological parameters									
SK peaks/s	10	0.18	0.06-0.76	15	0.09	0.00-0.33	15	0.22	0.03-0.34
Heart rate*									
Mean	8	163	156-169	14	158	150-169	13	166	152-175
SD		2.2	2.0-5.5		1.8	1.6-2.9		3.1	2.6-3.7
Respiratory rate*									
Mean	8	39	31-50	14	50	38-62	13	48	34-59
SD		16.8	10.1-19.5		12.5	8.7-15.9		9.3	7.6-17.3
SpO_2*									
Mean	8	93	91-95	14	95	91-98	12	91	86-97
SD		1.2	0.8-1.3		0.8	0.6-2.2		1.8	1.0-4.6
$crSO_2$*									
Mean	9	63	55-67	15	64	56-69	15	61	50-66
SD		1.4	0.9-2.7		1.4	1.0-2.9		1.4	1.1-2.9
Pain assessment tools									
COMFORTneo	10	12	9-15	15	11	8-16	14	12	11-13
N-PASS	10	3	2-4	15	3	2-4	14	3	3-5
NIPS	10	1	0-3	15	0	0-4	14	1	0-3
PIPP-R	10	6	4-7	15	8	7-9	14	8	8-12
BIIP	10	1	0-2	15	0	0-2	14	2	0-4
NRS pain	10	0	0-0	15	0	0-0	14	1	0-2
NRS distress	10	0	0-2	15	0	0-3	14	0	0-2

*For the physiological parameters heart rate, respiratory rate, SpO_2, and $crSO_2$, the mean and the SD of the data per second during the measurement period were calculated for each patient separately.

BIIP indicates Behavioral Indicators of Infant Pain; IQR, interquartile range; NIPS, Neonatal Infant Pain Scale; N-PASS, Neonatal Pain, Agitation and Sedation Scale; NRS, Numeric Rating Scale; PIPP-R, Premature Infant Pain Profile-revised.

significantly greater during the heelstick procedure than during both skin-to-skin care (estimate 8.8, 95% CI: 5.9-11.8, $P < 0.001$) and rest (8.4, 95% CI: 6.0-10.8, $P < 0.001$) (Fig. 2). Moreover, both the mean oxygen saturation (estimate 5.5, 95% CI: 0.2-10.8; $P = 0.04$) and the change in oxygen saturation from baseline (4.5, 95% CI: 0.8-8.3; $P = 0.02$) 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.

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 (Fig. 3). For example, while the PIPP-R score during heelstick procedure was higher than during rest for 7 patients, the reverse was true for the 6 other 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 5 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 2 hands of the caregiver and a blanket during the heelstick procedure, making it impossible to score any item.

DISCUSSION

We found that pain measurement in extremely preterm infants is challenging. In the total population studied, the mean HR, SpO_2, and PIPP-R each significantly differed between a painful procedure and either rest or skin-to-skin care. The change in HR 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, that is, it should yield a higher score during the heelstick procedure compared with rest or skin-to-skin care. In our study population, the difference in scores between the 3 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.[21] A recent study by Green et al[22] demonstrated that neonates were able to show discriminative facial expressions to tactile and noxious stimulation only from ~33 weeks' gestation. The validation studies of the included instruments also included neonates

TABLE 3. Estimated Effects (General Linear Model)

	Skin-to-Skin Care (N = 10)			Rest (N = 15)			
	Estimate	95% CI	*P*	Estimate	95% CI	*P*	Heelstick (N = 15)
Physiological parameters							
SC peaks/s†	0.03	−0.26 to 0.31	0.84	−0.14	−0.32 to 0.04	0.13	Reference
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‡	−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_2							
Mean	5.48	0.2-10.8	0.04*	5.74	−0.6 to 12.1	0.07	
Mean change	4.53	0.8-8.3	0.02*	3.43	−0.8 to 7.7	0.11	
SD‡	−0.36	−0.79 to 0.06	0.09	−0.40	−0.91 to 0.10	0.11	
$crSO_2$							
Mean	2.63	−3.8 to 9.0	0.39	3.53	−1.5 to 8.5	0.15	
Mean change	3.26	0.1-6.5	0.05	1.70	−1.3 to 4.7	0.25	
SD‡	−0.12	−0.41 to 0.17	0.38	−0.02	−0.30 to 0.26	0.89	
Pain assessment tools							
COMFORTneo	−1.5	−3.9 to 1.0	0.21	−1.9	−4.5 to 0.6	0.13	Reference
N-PASS†	−0.2	−0.6 to 0.1	0.17	−0.2	−0.5 to 0.1	0.22	
NIPS‡	−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‡	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	

The model was adjusted for postnatal age for all outcomes.

For the physiological parameters heart rate, respiratory rate, SpO_2, and $crSO_2$, the mean and the SD of the second-to-second data during the measurement period were calculated for each patient separately. Next to 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. After 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.

†Transformed using SQRT (variable).

‡Transformed using LN (variable+1).

BIIP indicates Behavioral Indicators of Infant Pain; CI, confidence interval; NIPS, Neonatal Infant Pain Scale; N-PASS, Neonatal Pain, Agitation and Sedation Scale; NRS, Numeric Rating Scale; PIPP-R, Premature Infant Pain Profile-revised.

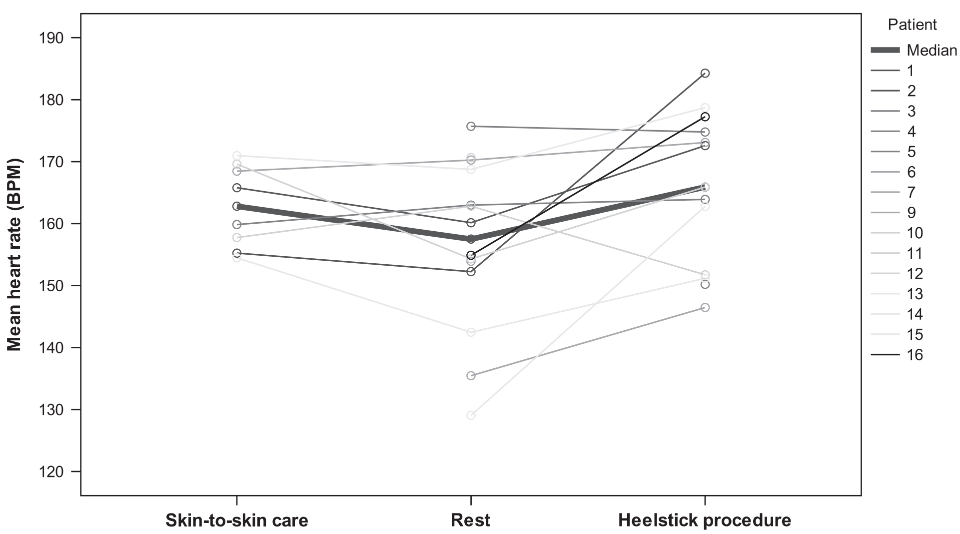

FIGURE 1. Mean heart rate during different conditions.

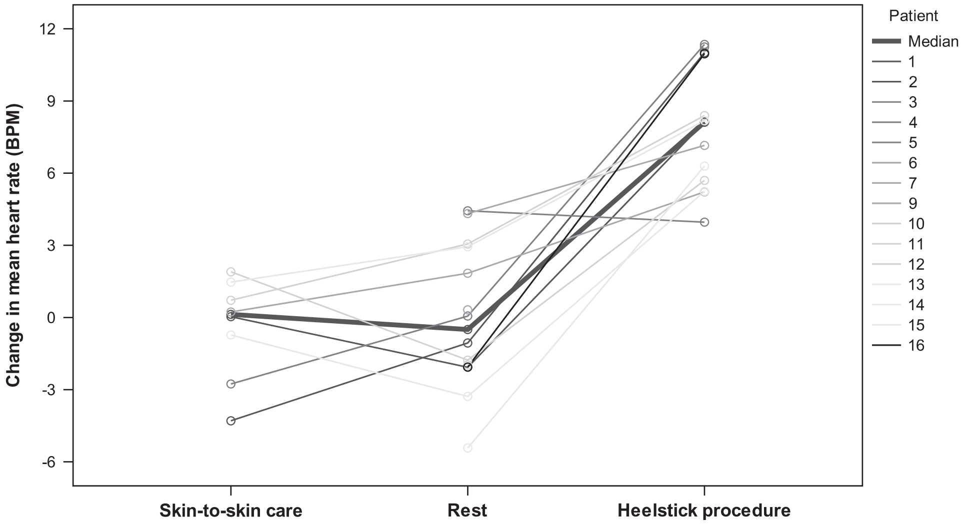

FIGURE 2. Mean heart rate compared with baseline during different conditions.

older than 29 weeks.[9–12,23,24] Holsti et al[25] have found that more specifically defined extremity movements are increased in preterm infants at lower gestational ages. The BIIP does include such movements, but other indicators may be required for this population. As regards the N-PASS, Munsters et al[14] also did not find a significantly higher pain score during the heelstick procedure compared with baseline in a study among preterm infants with a gestational age younger than 28 weeks. In that study, the SC during a heelstick procedure was significantly higher than that at baseline, suggesting more pain.[14] We could not duplicate these findings.

HR and SpO_2 are considered the most sensitive bedside-available physiological variables to measure pain in preterm and full-term infants.[17] The same seems to hold true in our study population. In our study, HR was significantly lower only during rest compared with during the heelstick procedure, with a mean difference of 11 beats/min. The change in HR compared with 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 extremely premature babies (below 28 wk), Gibbins et al[26] found similar HR responses during diaper change compared with the heelstick procedure. The change in HR 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_2 did not statistically differ between a heelstick procedure and baseline. However, in our study, the mean SpO_2 was significantly higher during skin-to-skin care compared with during the painful situation. In their meta-analysis, Boundy et al[19] found significantly higher oxygen saturations during skin-to-skin care compared with conventional care.

We found no significant differences in cortical oxygenation measured with NIRS between the 3 studied conditions, in contrast to a study by Slater et al.[16] 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

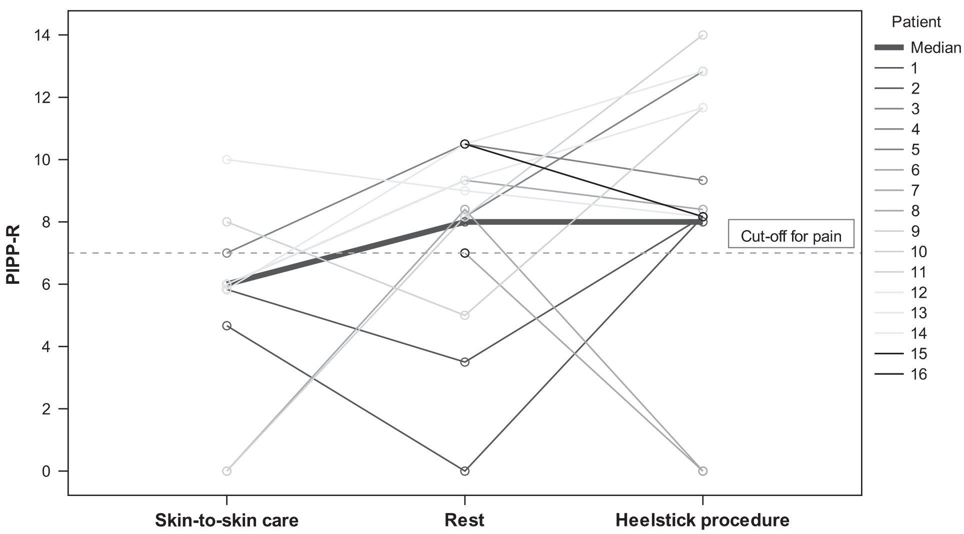

FIGURE 3. PIPP-R (Premature Infant Pain Profile—Revised) scores during different conditions.

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were only able to measure regional oxygen saturation, as we used a different device (INVOS instead of NIRO-200). Moreover, 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[14] found observing subtle changes in facial expression at the bedside in neonates below 28 weeks' gestational age difficult because of the presence of respiratory support, and oral and nasal gastric tubes. The difficulty of observing neonatal facial expression during current neonatology practices was the reason for Milesi et al[27] to develop the "faceless" acute neonatal pain scale (FANS), which does not rely on facial observation.

On the basis of our findings, we conclude that the included pain indicators (except from the change in mean HR 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 3 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 with lying in an incubator.[19] 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. Furthermore, 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 with a single-room NICU.[28] 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.[4]

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 minimalize heelstick-related pain.[29] Because of the convincing evidence on the pain-related behavior effects of sucrose,[30] 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,[31] and reported oxidative stress[32] and possible adverse effects on the brain,[33,34] the American Academy of Pediatrics guidelines suggest that more research is needed to establish long-term safety.[29]

The study design originally also included electroencephalography (EEG), but none of the neonates received an EEG as part of their standard care. Recently, Hartley et al[35] validated an EEG-based measure of nociceptive brain activity in healthy neonates with a gestational age above 34 weeks. 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 was HR variability, which can be analyzed using the Newborn Infant Parasympathetic Evaluation (NIPE).[36] While results from previous studies using HR variability to assess prolonged pain in both term and preterm neonates are promising,[37,38] Cremillieux et al[39] concluded that the NIPE index did not appear to reliably measure acute procedural pain in preterm infants. 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 multimodal approach would help in the understanding and management of infant pain.[40,41]

The small sample size of the present study may have lowered the probability of finding significant differences between the 3 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 nonpainful circumstances. A larger sample might have resulted in a higher number of significantly different outcomes between the conditions. Yet, 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 neonates 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 SC, and NIRS values are positively correlated with postnatal age.[15,42] In addition, Grunau et al[43] showed that higher cumulative neonatal procedural pain exposure was related to lower facial responses to pain. The influences of these factors would be minimalized if measurements took place on the same day.

In conclusion, of the potential physiological pain indicators studied, only the change in HR 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 HR, oxygen saturation, and PIPP-R scores were most promising because they significantly discriminated between at least 2 of the 3 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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