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Cerebral hemodynamic response to a therapeutic bed for procedural pain management in preterm infants in the NICU: a randomized controlled trial

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Abstract

Introduction: We developed a novel device, Calmer, that mimics key components of skin-to-skin holding to reduce stress in preterm infants. Our feasibility trial showed that Calmer worked 50% better than no treatment and no differently from our standard of care, facilitated tucking (FT), for reducing pain scores during a heel lance in preterm infants in the neonatal intensive care unit.

Objective: We compared the effects of Calmer on regional cerebral hemodynamic activity during a noxious stimulation to FT.

Methods: During a clinically required heel lance, we measured frontal cortex tissue oxygenation in a subsample of 29 preterm infants (27–33 weeks gestational age) from our larger randomized controlled trial. Infants were randomized to either FT (n = 16) or Calmer treatment (n = 12). The outcome measure, obtained using near-infrared spectroscopy, was a change in the tissue oxygenation index (TSI) across study phases (Baseline, Heel Lance, Recovery; median duration 517 seconds [421–906 seconds]).

Results: No statistically significant differences were found between groups in the median TSI during any of the study phases. In response to the heel lance, 7 infants (27.6%) had a TSI that dipped below the 60% threshold (3 in the Calmer group 25% and 4 in the FT group 25%); none below 50%.

Conclusions: Infants on Calmer maintained normal regional cerebral oxygen levels (55%–85%) no differently from infants receiving a human touch intervention during blood collection. Parental skin-to-skin holding is one of the most effective strategies to relieve procedural pain in preterm infants. When parents or FT are not available, Calmer shows potential for filling this gap in care.

Keywords: Prematurity, Cerebral hemodynamic, Painful procedure, Near-infrared spectroscopy, Skin-to-skin, Pain

1. Introduction

In the neonatal intensive care unit (NICU), preterm infants are unavoidably exposed to repeated pain from procedures, on average 10 to 12 times per day,[38] during a critical period of programming of stress systems[16] and of very rapid brain development.[3,48] The negative effects of early untreated pain have been demonstrated in both rodents[1,11] and in humans (reviewed in 36). Using effective pain management is crucial for brain protection in preterm children.

Parental skin-to-skin holding (SSH) is one of the most effective strategies for relieving acute procedural pain in infants.[27] Through SSH, infants experience the touch, warmth, heart beat sounds, and breathing motions which activate simultaneously putative multiple opioid and nonopioid pathways to improve weight gain, brain maturation, and reduce stress.[9,10,39,49] However, numerous barriers limit the implementation of SSH as the standard of care for procedural pain management in NICUs.[15] This is especially relevant in the current COVID-19 pandemic context, where many hospital settings must restrict visitors and contact.

We developed a medical device, Calmer, that safely delivers fundamental components of SSH (touch, motion, and sound) to reduce stress in preterm infants.[19,23,50] Results from our first feasibility randomized controlled trial (RCT) showed that Calmer worked 50% better than no treatment (using historical control sample), and no differently from a human touch treatment facilitated tucking (FT) for reducing pain behaviors and cardiac responses during a single blood collection.[23]

In introducing technology aiming to simulate aspects of parental contact, we considered in our design process[19] both the immediate health of the infant and longer-term, that of the family, including bonding and emotional health. We emphasize that Calmer does not fully embody the benefits of parental holding[45] nor does our study

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fully capture them. We based our approach on the premises that (1) expecting 24/7 parental availability may not be feasible for some families and can add stress and guilt, particularly for those who are socioeconomically challenged, (2) we are supporting rather than replacing parents, and (3) strong deployment guidelines must accompany NICU adoption.

Although mitigation of behavioral expression of pain remains important, measuring accurately and using effective treatments to prevent the biological effects of acute pain on the brain is essential.[37] Near-infrared spectroscopy (NIRS) has been used to measure brain activation in preterm and full-term infants, specifically for its potential to evaluate cerebral response to pain[4,7,12,41–43,46] and various therapeutic relieving modalities.[6,17,18,30] In a subset of preterm infants from our larger RCT, we report here the effects of the Calmer device on our secondary outcome measure, cerebral hemodynamic activity, compared with FT during a medically indicated blood collection.[23]

2. Materials and Methods

2.1. Study participants

The main feasibility trial study was conducted in a tertiary-level NICU between October 2014 and February 2018. The RCT study protocol was approved by the Clinical Research Ethics Board of the University of British Columbia and the BC Children's and Women's Health Centre Research Review Committee and was registered at www.ClinicalTrials.gov: NCT01433588. The full sample has been described in *PAIN Reports*.[23] In summary, the trial comprised preterm infants who were born between 27 and 36 completed weeks of gestational age (GA). Details regarding sample size estimate, inclusion/exclusion criteria, recruitment, and randomization procedures of the main feasibility RCT are reported in our main trial findings.[23] For this study, our subsample comprised preterm infants who underwent cerebral hemodynamic measurement with NIRS during a heel lance for blood procurement.

2.2. Treatment procedures

The main study was a 2-arm, single-blind, RCT. During a single, clinically required blood collection (heel lance), enrolled infants were allocated randomly to 1 of 2 intervention groups: Calmer or "control"-FT; infants in both groups also received a soother. The design of the Calmer prototype used for this trial is described elsewhere.[50] In brief, Calmer is a platform that fits inside standard NICU incubators and replaces the standard mattress. Key design features of Calmer include adjustable heart and breathing rates so that the parental physiological recordings can be individualized for each infant (ie, mother's mean heart and respiratory rates over a 2-min period). The heart beat sounds are volume controlled (max 55 dBA). To mimic breathing, the top plate of Calmer, which is covered with a skin-like surface made of silicone and biocompatible Gortex, moves up and down 10 mm in a smooth trajectory. Following are the 4 study phases.

2.2.1. Baseline 1 (B1)

The NIRS device's (Portalite Mini: Artinis Medical Systems, Elst) mini sensor (see Outcome measures section) was set-up before the start of the assessment to allow infants to settle. The sensor was positioned on the forehead approximately 2 cm above the left eyebrow, held in place on the infant's head with a disposable commercially available hat that is normally used to secure continuous positive airway pressure (Draeger, Inc.). For B1 measurements, all infants were in the prone position undisturbed in their incubator for a minimum of 15 minutes before the following phase—Baseline 2. Infants in the experimental group were placed on Calmer in the prone position (Calmer was not turned on). Infants in the control group were gently lifted up once (to match handling of infants in the Calmer group) then left prone in their incubators. Prone positioning was used to mimic the position the infants would be in had they been held skin-to-skin with their mother.

2.2.2. Baseline 2 (B2)

After the 15-minute B1, the Calmer breathing and HR sounds were started for the infants in the experimental group; 15 minutes of exposure is the minimum time parents would provide SSH for pain management.[28] Infants in the control group were left undisturbed in the prone position. After the 15 minutes of undisturbed B2, 2 minutes before the first contact by the laboratory technician for the blood collection, all infants were given a soother.

2.2.3. Painful procedure—heel lance/squeeze

Infants in the Calmer group received treatment continuously from B2, throughout the heel lance/squeeze procedure and recovery phases. For the control group infants, FT and nonnutritive sucking were started 2 minutes before the heel lance and continued until the blood collection was complete (standard practice in our unit.) All heel lances were performed by a trained laboratory technician using a BD Quikheel infant safety lancet for preemies (lancet 1.75 × 0.85 mm) during the early morning (~7 AM) blood collection rounds. The right or left heel was first warmed up with a heel warmer (DeNovo Gel Infant Heel Warmer) for ~2 minutes.

2.2.4. Recovery

The recovery phase was the 5 minutes after the last touch from the laboratory technician.[22] Calmer treatment continued throughout the recovery phase. FT continued until the infant had settled, which, for the majority, was within 5 minutes after the last touch from the technician (3–5 minutes). Within each group (Calmer or FT), infants had additional handling only if it was needed to maintain infant physiological stability (ie, HR >100 beats/minute or oxygen saturation >86%). The NIRS minisensor and related equipment was removed, and recording was discontinued after the 5 minutes recovery.

2.3. Outcome measures

2.3.1. Bedside and clinical data collection

Study phases related to the blood collection procedure were digitally recorded to provide a close-up image of each infant's face and upper body. All recordings were synchronized, and events were marked.

Clinical information about the infants from birth to day of testing were collected prospectively. Infant data included but were not limited to birth weight, GA at birth, daily opioid and other analgesic/sedative exposure, numbers/types of invasive skin-breaking procedures, respiratory support, and type/time of last handling before blood collection. Maternal demographic information was also collected.

2.3.2. Cerebral hemodynamic—near-infrared spectroscopy

The cerebral oxygenation signal obtained with the NIRS technique is based on the absorption of near-infrared light by hemoglobin, which

in turn depends on the oxygenation state of hemoglobin circulating through the tissue (mix of venous, arterial, and capillary sources). The NIRS technology used in this study measures changes (from an unknown baseline set by the NIRS device) in the tissue concentration of intravascular oxygenated and deoxygenated hemoglobin.[44,51] The Portalite is a portable wireless NIRS device, which provides continuous NIRS wave using modified Lambert–Beer Law and spatially resolved spectroscopy. It measures oxyhemoglobin and deoxyhemoglobin concentrations ([O_2Hb], [HHb]), and provides 2 calculated values, total hemoglobin concentrations ([tHb] = [O_2Hb + HHb]), and local tissue saturation—ie, tissue saturation index (TSI). The Portalite uses the standard nominal 760 and 850 nm wavelengths.

To improve the accuracy of the NIRS assessment in preterm neonates, we used a custom made NIRS optode—minisensor (Artinis Medical Systems, Elst) which is a 1-channel system with 2 light sources (or transmitters) and 1 receiver (interspaced 22.5 mm) housed in a very small flexible casing. A sampling rate of 10 Hz and a differential pathlength factor of 4.4 (based on Benaron et al[8]) were used.

For each infant, relative concentrations in O_2Hb, HHb, tHb, and the TSI were measured continuously throughout the experiment and stopped/interrupted only if issues with the measurement or medically required. Here, we report the continuous TSI signal captured during the 4 study phases (B1-2, heel lance/squeeze procedure, recovery) because this measure is the most clinically relevant indicator. The TSI is the estimation of the regional oxygen saturation ($rStO_2$) expressed in percentage, which is the concentration of O_2Hb in relation to the total amount of hemoglobin (O_2Hb/tHb). The parameters used to calculate the TSI include the absorption and scatter coefficients, distances of the optode template, wavelengths, and concentrations of O_2Hb and HHb. Tissue oxygenation index percentage varies between 0% and 100% and depends on GA, days of life, and comorbidities, among other factors.[25] At rest, the typical TSI range is 55% to 85% (assuming SpO_2 is >90%). Although a precise safe range for $rStO_2$ is still not established,[25] a common intervention trigger is when TSI <50% (or 20% change from TSI baseline); the critical threshold for intervention corresponds to TSI <45% (or 25% change from TSI baseline).[14] The association between lower regional cerebral tissue oxygenation (~50%; hypoxia) and cerebral injury, as well as poorer neurodevelopmental outcomes has been reported.[25,35] We have chosen to use these specific thresholds to guide our analysis (see data processing/analysis).

2.3.3. Pain scores—the behavioral indicators of infant pain

A single coder, blinded to all aspects of the study determined the presence or absence (0/1) of each of the behavioral indicators on the behavioral indicators of infant pain (BIIP), a reliable, valid scale for assessing acute procedural pain in infants.[21] Video recordings of study phases were randomized for viewing by the coder; total scores were summed for the 4, 1-minute study phases and described in more detail elsewhere.[23] The video coder was trained to achieve interrater reliability on the BIIP above 0.85 (kappa).

2.4. Data processing

Predata processing involved NIRS data filtering to reduce undesired parts of measured data, such as noise or trends. A moving Gaussian filter (average) was applied, which is a generic smoothing filter that reduces high frequency noise and has the advantage of corresponding to the weighted mean rather than the unweighted mean, giving a smoother result. The continuously measured regional cerebral oxygenation parameters were then truncated to 30 seconds before the end of B1 period and 300 seconds past the end of the procedure (last touch by a laboratory technician). Some epochs were of constant time length for each infant (eg, recovery phase—300 seconds), the heel lance/squeezing phase varied between infants (eg, 70 seconds ID-17 vs 160 seconds ID-30). To remove remaining artifactual spikes, traces were passed through a Hampel filter with a moving window of ±3 seconds and a threshold of K = 2. This replaces any outliers that are more than 2 median absolute deviation units away from the median of the points in the 3 seconds preceding and 3 seconds postwindow, and replaces these outliers with the median value in the window.[32] Traces were then band pass filtered using a third degree Savitzky–Golay filter by removing low-frequency noise with a window of 80 seconds and higher frequency noise with a window of 10 seconds.[34] These windows were chosen to remove very short artifactual spikes across the entire TSI collection period. Different filtering parameters did not change which infants were considered to have had significant dips in the TSI during either the heel lance/squeeze procedure or recovery phases. Data processing and statistical analyses were conducted blindly (A.A.).

2.5. Statistical analyses

Traces were divided into 4 epochs: B1 (30 seconds), B2 (after Calmer started for infants in the experimental group, 30 seconds before first touch by the laboratory technician), heel lance/squeeze procedure (from heel lance to last touch by the laboratory technician, varying in length), and recovery (300 seconds after the last touch by the laboratory technician). The median TSI for each infant was calculated during all 4 epochs. Two infants (ID-1 and ID-11) were missing data for B2 and were excluded from comparisons using the B2 period. These medians were compared between groups using 2-sample *t*-tests. To compare potential differences in the 2 baseline periods, we compared the medians in B2 to B1 in the Calmer group using a paired samples *t* test.

To examine if infants in both groups stayed in a typical range for TSI (≥60%), and above the threshold for intervention (>50%), we examined each TSI trace and determined whether it dipped (and duration) below 60% or 50% during the heel lance/squeeze procedure and recovery epochs. The proportion of infants with traces below these thresholds was compared between groups using Fisher's exact tests. All analyses were performed in R v3.5.3 and filtering using functions in the "pracma" package.

3. Results

3.1. Infant and maternal characteristics

The patient flow diagram for the full RCT and for this subsample is shown in **Figure 1**. Maternal demographic and neonatal clinical data are presented in **Table 1**. In short, infants included in this subsample were, on average, born at 29 weeks GA for both control and Calmer groups (range [27–33] and [27–32], respectively), and at the time of the study, on average, infants in both groups were 25 days after delivery (range [8–52] and [9–39], respectively). Over 50% of the infants included in this subsample were receiving noninvasive respiratory support from continuous positive airway pressure or nasal prongs high flow (64% control and 58% Calmer), and none were intubated at the time of study or were receiving supplemental oxygen (FiO_2 >21%). Infant clinical and maternal demographic measures did not differ between the 2 groups for the subsample (**Table 1**). However, when comparing

infants who had NIRS monitoring (n = 28) with those who did not (n = 16; sample from the full RCT[23]), the NIRS infants had significantly lower BIIP scores during recovery (0.3 ± 0.6 [NIRS] and 1.2 ± 1.7 [Non-NIRS] *t* test −2.132, *P* = 0.039).

3.2. Cerebral hemodynamic responses

Reliable NIRS measures were obtained in 28 infants, control n = 16 and Calmer n = 12. There were no differences between the groups in median TSI during any of the epochs (**Table 2**). Similarly, there was no differences between B1 and B2 within the Calmer group (mean B1 = 69.2% ± 8.7, mean for B2 = 72.6% ± 7.8; *P* = 0.18).

3.2.1. Heel lance/squeeze procedure phase

Seven infants (27.6%) had TSI traces which dipped below the 60% threshold during the heel lance/squeeze phase. Three were in the Calmer group (25.0%) and 4 in the control (FT) group (25.0%) (Fisher's exact test *P* = 1.0). Among these 7 infants, none dipped below 50% (**Fig. 2**). Importantly, no infant dipped below 45%, which is considered a critical threshold. The 3 infants in the Calmer group spent 16 seconds (ID-10), 46 seconds (ID-20), and 476 seconds (ID-21) below 60% TSI (**Fig. 2A–C**), whereas the 4 control infants spent 152 seconds (ID-54), 213 seconds (ID-5), 304 seconds (ID-27), and 551 seconds (ID-33) below 60% (**Fig. 2D–G**).

Of note, infant ID-54 in the control (FT) group had a significant drop in the TSI after an important overshoot in TSI (**Fig. 2G**). In addition, 3 preterm infants in the control (FT) group had a bradycardia (without any peripheral oxygen desaturation) during the heel lance/squeeze procedure and/or recovery phases (IDs 5, 27, and 33). Either infants recovered on their own (IDs 5 and 27) or needed a brief stimulation by the research nurse (ID-33). These events coincide with the observed TSI dips below 60% (**Fig. 2D–F**). Finally, the infant ID-21 in the Calmer group experienced a difficult and longer blood draw with a less experienced lab technician (replaced during the squeezing phase by a more experienced laboratory technician), which could explain why this particular infant's TSI remained between 50% and 60% for 555 seconds throughout the heel lance/squeeze procedure and recovery phases.

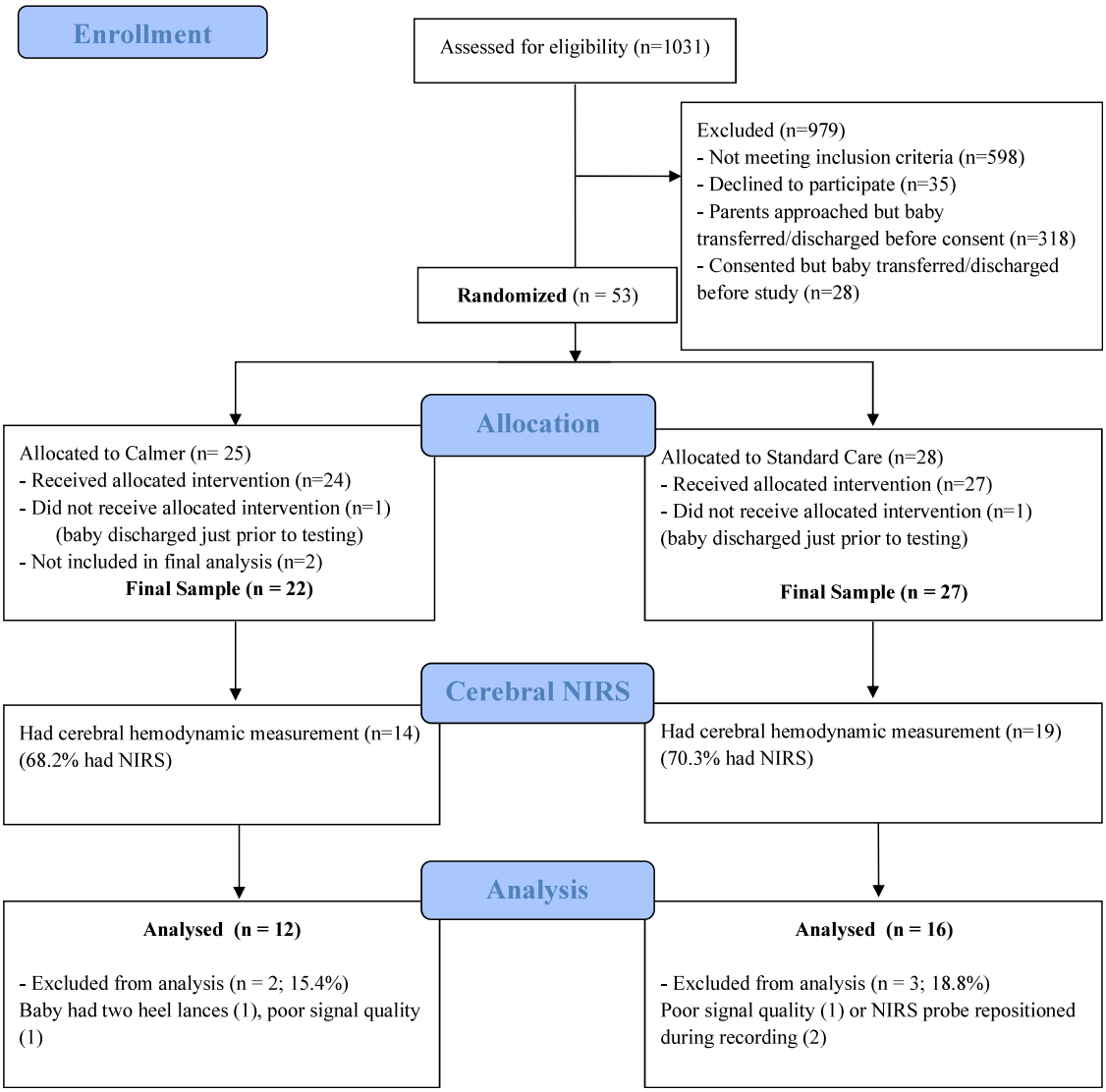

Figure 1. Calmer study flow diagram. Patient flow diagram for the general randomized controlled trial, as well as the subsample included in this study. NIRS, near-infrared spectroscopy.

Table 1

Infant clinical and maternal demographic characteristics in NIRS subsample.

	Calmer (n = 12)	Control—facilitated tucking (n = 16)
Birth weight (g)	1350 ± 276 (1015–1815)	1336 ± 276 (893–2029)
Gestational age (wk)	29 ± 1.7 (27–32)	29 ± 1.8 (27–33)
Sex (n/% male)	4 (33)	11 (69)
Age on the study day (days)	25 ± 10 (9–39)	25 ± 14 (8–52)
Respiratory support (n/%)	7 (58%)	10 (64%)
Most recent hematocrit level	0.37 ± 0.09 (0.27–0.58)	0.41 ± 0.09 (0.27–0.55)
APGAR 1 min/5 min	5 ± 2 (2–8)/7 ± 2 (4–9)	5 ± 3 (0–8)/7 ± 1 (4–9)
Severity of illness scores on day 1 (SNAP-II score)	17 ± 13 (0–34)	18 ± 11 (0–40)
Time since last handling before the assessment (min)	137 ± 60 (42–240)	153 ± 94 (3–290)
Time since last painful procedure (hours)	86 ± 75 (9–263)	60 ± 49 (5–167)
BIIP baseline 1/2	0.6 ± 1.2 (0–4)/0.7 ± 1.3 (0–5)	0.6 ± 1.2 (0–4)/0.7 ± 1.3 (0–5)
BIIP painful procedure	4.0 ± 3.2 (0–9)	3.9 ± 3.0 (0–8)
BIIP recovery	1.3 ± 2.2 (0–8)	1.1 ± 1.2 (0–4)
Maternal age (years)	35 ± 6 (28–48)	34 ± 5 (26–48)
Maternal postsecondary education (n/%)	11 (92%)	14 (88%)

Respiratory support is defined as continuous positive airway pressure (CPAP) or nasal prong high flow with FiO_2 21%. Means and (±) SDs are provided unless indicated otherwise; none of the characteristics were statistically different between the groups.

NIRS, near-infrared spectroscopy; BIIP, Behavioral Indicators of Infant Pain.[21]

3.2.2. Recovery study phase

Four infants in the recovery period had TSIs below 60%, one in the Calmer group (8.3%) and 3 in the control group (18.8%) (Fisher's exact test $P = 0.6$); none had a TSI below 50%. The infant in the Calmer group spent 79 seconds (ID-21) below 60%, whereas the 3 infants in the control group spent much longer time below 60%: 139 seconds (ID-54), 216 seconds (ID-27), and 247 seconds (ID-33) (**Fig. 2**).

3.3. Behavioral pain measures—behavioral indicators of infant pain

Analogous to our findings from our main feasibility RCT sample,[23] we did not find any significant differences in BIIP scores between the 2 groups during the study phases. The mean BIIP score in response to the heel lance (1-minute observation after heel lance including foot squeeze) were 3.9 ± 3.0 (range 0–8) for the preterm infants receiving FT compared with 4.0 ± 3.2 (range 0–9) for those receiving Calmer (**Table 1**). Both these scores fall within the low–moderate pain range for the BIIP scale[20] (**Table 3**).

Table 2

Medians and means of the median within infant TSI values for each group during each study phase.

	Calmer (n = 12)	Control (n = 16)	*P*
	Mean (SD)	Mean (SD)	
Baseline 1	69.5 (±8.3)	70.5 (±6.9)	0.75
Baseline 2*	72.6 (±7.8)	71.5 (±6.6)	0.71
Heel lance	70.2 (±7.9)	68.2 (±6.8)	0.49
Recovery	71.3 (±9.4)	70.0 (±6.9)	0.70

All means provided represent percentages (%); *P*-values are for 2-sample *t*-tests.

* Comparisons with baseline 2 exclude the 2 infants where NIRS was not properly recorded.

TSI, tissue saturation index.

4. Discussion

We are the first to report the effects of a novel medical device, Calmer, on frontal brain tissue oxygenation using NIRS in preterm infants in the NICU,[23] during a clinically required noxious procedure. We found no differences between infants receiving the human touch–based treatment (control), FT, and the Calmer in regional cerebral tissue oxygenation (TSI) response patterns during the heel lance. Important for the potential brain protection, the infants' measures in both groups remained on average within the typical range. Adding this crucial outcome enriched our multimodal reported behavioral pain and cardiac responses.[23] Our aim with Calmer is not to replace human touch–based treatments, such as FT or SSH; however, when these treatments are not available, Calmer shows potential for filling this gap in care.

Despite certain limitations, cerebral NIRS monitoring is becoming part of the standard of care for extremely preterm infants and infants with hypoxic–ischemic encephalopathy in many NICUs.[25,35] Recent research efforts have focused on determining proper cerebral oxygenation targets to establish clinical treatment guidelines on when to intervene when $rStO_2$ is out of range to protect the brain of this vulnerable population, especially in those born extremely preterm (<26 weeks gestation).[25,26,33] We found that in response to the painful procedure, less than 30% of the preterm infants (in both treatment groups) had a drop in frontal cortex tissue oxygenation below 60% (duration range 16–551 seconds); none went below 50%. Most had restored their frontal tissue oxygenation levels during the recovery phase (TSI between 60% and 85%), (1 Calmer infant and 3 in FT group had a TSI between 50% and 60%).

In addition to our contribution related to Calmer's potential for improving preterm infant pain management, we also analyzed our data in a unique way. Typically, the cerebral activity in response to pain has been reported as group averages and for only a very brief time window immediately after the stimuli (ie, 1000 ms–30 seconds),[4,6,7,13,30,31,41,43,46,47] rather than by examining

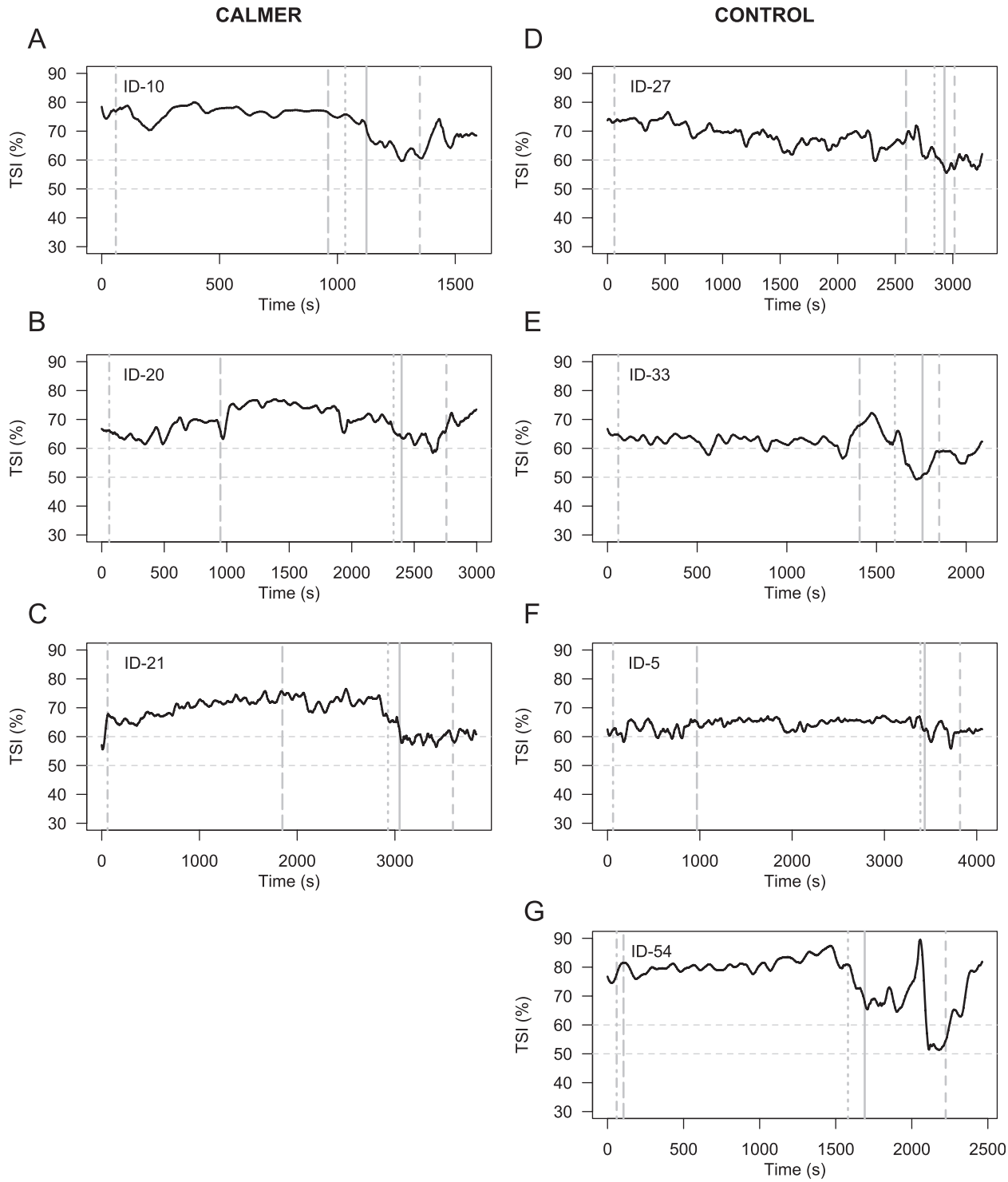

Figure 2. Individual NIRS TSI tracings during the 4 study phases for the preterm infants with the TSI below 60%. Continuous tracing of collated measures of the tissue saturation index (TSI in %) through the 4 study phases: baseline 1, baseline 2, heel lance/squeeze procedure, and recovery. 2A-G: individual TSI tracing for the 7 preterm infants (separated by groups) whose TSI dropped <60% during the heel lance/squeeze procedure and/or recovery phases. NIRS: near-infrared spectroscopy; end of baseline 1: ; end of baseline 2: ; first touch laboratory technician: ; heel lance: ; last touch laboratory technician: . TSI, tissue oxygenation index.

individual variations during a longer period after stimulation. Instead, we looked in more detail individual infant cerebral hemodynamic responses with longer time series, while also comparing their responses between the 2 treatments. As have others,[46] we found highly variable interinfant frontal cortex tissue oxygenation response patterns during the noxious stimulation and recovery, even in the absence of overt behavioral responses (high BIIP scores). Irrespective of treatment (FT or Calmer), individual TSI tracings indicate that some infants respond with a decrease in frontal tissue oxygenation whereas others respond with an increase.

Moreover, the extent of the frontal cortex hemodynamic response is not always linked to overt behavioral pain expression; some preterm infants displayed high BIIP scores

Table 3

Comparison of individual BIIP scores for each study phase.

Calmer (n = 12)					Control (n = 16)				
	B1	B2	HL	Rec		B1	B2	HL	Rec
ID-10*	0	0	9	1	ID-1	0	2	6	2
ID-11	0	0	8	8	ID-2	0	1	0	0
ID-13	1	0	1	0	ID-5*	0	1	1	2
ID-18	0	0	0	1	ID-9	1	1	8	0
ID-19	2	5	7	0	ID-12	3	0	3	1
ID-20*	2	4	2	0	ID-16	0	1	3	1
ID-21*	1	1	5	0	ID-17	0	0	0	0
ID-22	0	0	7	1	ID-24	0	0	8	1
ID-26	1	0	2	2	ID-25	0	0	2	1
ID-30	0	0	0	0	ID-27*	0	0	3	0
ID-38	0	1	2	1	ID-33*	0	0	4	1
ID-46	0	0	7	0	ID-34	0	0	2	0
					ID-37	0	0	1	0
					ID-45	1	0	7	3
					ID-48	4	5	8	4
					ID-54*	0	0	7	2

BIIP, Behavioral Index of Infant Pain—possible score range 0 to 9. In control 37.5% (6/16) have moderate–high pain; in Calmer 50% (6/12) have moderate–high pain. 43% sample had moderate–high BIIP scores (>5).

* Indicate preterm infants that had a TSI below 60% during the heel lance/squeeze procedure and/or recovery study phases.

B1, baseline 1; B2, baseline 2; HL, heel lance/squeeze procedure; Rec, recovery.

while exhibiting very minimal frontal tissue oxygenation variability. The opposite was also true in some infants (ie, low BIPP scores and large TSI response). Others have reported lack of concordant findings.[5,6,40] Slater et al.[40] reported that in 30% of their test occasions, preterm infants mounted a cortical hemodynamic response (change in tHb in the contralateral somatosensory cortical area) during a heel lance while showing no facial expression of pain. By contrast, in healthy full-term newborns, Bembich et al.[6] reported varying cortical hemodynamic activity (eg, increase in O_2Hb) in parietal, temporal, posterior, and frontal areas during a heel lance depending on which 1 of 4 nonpharmacological pain treatments (glucose, breastfeeding, maternal holding, and glucose combined) they received. In a previous study, maternal holding alone during a heel lance procedure was associated with significant increase in cerebral O_2Hb in the somatosensory and frontal areas in healthy newborns, whereas no cortical response was found in those who received glucose.[5] The authors in both these studies suggest that the *analgesia* through maternal holding or breastfeeding, mediated by multisensory stimulation (tactile, proprioceptive, and thermal), may explain the significant activation in both the somatosensory cortex and frontal area matched with minimal pain scores.[5,6] Finally, in a cross-over study, maternal SSH plus glucose treatment significantly dampened the cortical hemodynamic response (lower increase from baseline in O_2Hb) to a venipuncture in preterm infants compared with when the infants were laying in their bed (with glucose alone).[30] In that study, infants had minimal pain scores in both conditions.

Regional cerebral activation typically results in regional increases in both oxygenated (O_2Hb) and total (tHb) hemoglobin with a decrease in deoxygenated hemoglobin (HHb).[24] However, contrasting results have been reported, such as no change or increases in O_2Hb with increases in both HHb and tHb.[29] Many factors influence preterm infants' hemodynamic responses to neural activation, such as GA, day of life, the investigated cerebral area, sleep state, and arterial oxygen saturation, among others.[2,41,43] In our sample, infants were on average 25 days. Thus, days of life likely did not influence our findings, since the first week of life is when the neonates go through significant cerebral hemodynamic adjustments to exutero life.[25]

Several limitations of our study require mention. Because this subsample of preterm infants was part of the larger sample,[23] we were not powered to fully evaluate cerebral oxygenation responses to Calmer (secondary outcome). Further research with a larger sample size is needed to assess and account statistically for important clinical factors, such as GA and physiological measures (eg, SpO_2, blood pressure, and CO_2). Sensor placement, capturing hemodynamic changes in the region of interest (eg, somatosensory vs frontal area), and consistent recording of the same brain region are concerns with NIRS. Multichannel devices can be quite cumbersome for use in tiny infants and have limited clinical utility. Alternatively, we used a single probe placed on the forehead to mirror how NIRS is typically used in NICUs worldwide and report a clinically relevant and similar measure to cerebral regional tissue oxygenation ($rStO_2$).

Very preterm infants (<32 weeks gestation) are cared for in the NICU during a time of critical and rapid brain development.[3,48] Using Calmer was not different from a human touch intervention, FT, at preventing overt changes in regional brain oxygen perfusion in response to a common skin-breaking procedure. Future research is needed to evaluate the clinical efficacy of Calmer over longer exposure. If a longer exposure to Calmer (eg, throughout preterm infants' NICU admission) is shown to improve growth and reduce life-long disabilities by protecting the brain, this could ultimately impact preterm infant outcomes worldwide and health care and societal costs. Finally, clear guidelines for deployment must be developed to ensure parent/families remain the first line of treatment whenever possible.

Disclosures

K. MacLean and L. Holsti are inventors of the Calmer medical device for pain management for preterm infants. In partnership with the Provincial Health Services Association of British Columbia, Canada, they could, in the future, receive royalties as a result of licensing agreements made with private industry for commercialization of the device. They have not received any remuneration to date. L. Holsti supervised data collection at arms length; neither authors had access to the data during the study. They had no access during data transfer to the statistician (A. Albert) nor did they conduct the data analysis of the outcome measures reported in this article. The remaining authors have no conflicts of interest to declare.

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