



Calmer: a robot for managing acute pain effectively in preterm infants in the neonatal intensive care unit

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Abstract

Introduction: For preterm infants in the neonatal intensive care unit, early exposure to repeated procedural pain is associated with negative effects on the brain. Skin-to-skin contact with parents has pain-mitigating properties, but parents may not always be available during procedures. Calmer, a robotic device that simulates key pain-reducing components of skin-to-skin contact, including heart beat sounds, breathing motion, and touch, was developed to augment clinical pain management.

Objective: Our objective was to evaluate the initial efficacy of Calmer for mitigating pain in preterm infants. We hypothesized that, compared to babies who received a human touch-based treatment, facilitated tucking, infants on Calmer would have lower behavioural and physiological pain indices during a single blood test required for clinical care.

Methods: Forty-nine preterm infants, born between 27 and 36 weeks of gestational age, were randomized either to facilitated tucking or Calmer treatment. Differences between groups in changes across 4 procedure phases (baseline 1, baseline 2, poke, and recovery) were evaluated using (1) the Behavioral Indicators of Infant Pain scored by blind coders from bedside videotape and (2) heart rate and heart rate variability continuously recorded from a single-lead surface ECG (lead II) (Biopac, Canada) sampled at 1000 Hz using a specially adapted portable computer system and processed using Mindware.

Results: No significant differences were found between groups on any outcome measures.

Conclusion: Calmer provided similar treatment efficacy to a human touch-based treatment. More research is needed to determine effects of Calmer for stress reduction in preterm infants in the neonatal intensive care unit over longer periods.

Keywords: Preterm infant, Pain, NICU

1. Introduction

Providing effective pain management for routine procedures for preterm infants in the neonatal intensive care unit (NICU) is a high priority in neonatal care.³ Early pain exposure in preterm infants has negative effects on neurodevelopmental outcomes.^{4,19,20,23} Sensory-based interventions have been tested for pain mitigation

during routine procedures in preterm infants; oral sweeteners (eg, sucrose) are recommended as the clinical standard.^{1,16} However, concern regarding the potential negative consequences of repeated oral sweetener use in preterm infants means that other interventions capitalizing on the significant benefits of human contact, such as skin-to-skin holding, may be preferable.^{6,10,23,26} Yet, parents may not be able to hold their infants during all painful procedures.

To address this gap in pain treatment, our group invented a therapeutic robot, Calmer, that simulates key components of skin-to-skin holding, which are purported to mitigate pain.^{14,15,21,22,27} The purpose of this randomized controlled trial was to evaluate the efficacy of Calmer to reduce biobehavioral acute pain indices in stable preterm infants in the NICU compared with a human touch-based treatment, facilitated tucking (FT).⁵ Facilitated tucking is a strategy whereby a caregiver places his/her hands gently but firmly to contain the infant's head and extremities in a flexed position. We used FT as the comparison group because this strategy is the standard of care in our NICU when skin-to-skin holding by parents is not possible; FT has been shown to reduce pain indices in preterm infants undergoing blood collection.⁵ Our hypotheses were that compared to control infants (who received FT), infants on Calmer would have (1) lower behavioral pain scores (primary outcome measure), (2) lower mean heart rate (HR), (3) greater activation of parasympathetic modulation, and (4) better sympathovagal balance. The hypotheses were informed by indications of benefit obtained in an initial randomized trial pilot study evaluating the first Calmer prototype.²⁸

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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2. Patients and methods

2.1. Patients

The study was conducted in a tertiary-level NICU between October 2014 and February 2018. The randomized clinical trial study protocol was approved by the clinical research ethics board of the University of British Columbia and the Children's and Women's Health Centre of British Columbia Research Review Committee and is registered at www.ClinicalTrials.gov: NCT01433588. Preterm infants were included if they were born between 27 and 36 completed weeks of gestational age (GA). Gestational age was based on early gestation ultrasonogram (the standard of care in our region) or calculated using the last menstrual period. Infants on continuous positive airway pressure or who were ventilated were included. Exclusion criteria were congenital anomalies, a history of maternal abuse of controlled drugs and substances, current treatment for infection, history of any type of surgery, receipt of pharmacological analgesics or sedatives within 72 hours of the assessment, blood collection beyond the 36th completed week of GA (36 weeks + 6 days), and higher-order multiple births (eg, triplets).

2.2. Sample size estimate

In infant studies where pain self-reporting is not possible, a 2-point difference in the Behavioral Indicators of Infant Pain (BIIP) or on other valid neonatal pain scale scores is cited widely as being the minimum clinically significant difference.^{7,24} Pilot data were also used to support an estimated SD of 2.5, yielding a target sample size of 25 per group.²⁸

2.3. Randomization procedures

Subject allocation was based on a sequence of computer-generated random numbers with block sizes of 4 or 6 allocated randomly. Because we had only one Calmer prototype, we could test only one infant/day, thus twins were randomized individually. Access to the randomization list was through Research Electronic Data Capture (REDCap) that ensured online interactive checking of the inclusion/exclusion criteria before authorizing random allocation. We allocated infants to the treatment groups the night before the 6 AM blood work due the following day. This ensured that the research nurse had adequate time to obtain the heart and breathing rates of the mothers whose infants were randomized to Calmer.

2.4. Recruitment procedures

A NICU research nurse dedicated to the study screened all infants admitted to the NICU to assess eligibility. After this screening, the nurse approached eligible families to discuss the study. Translators were used when English was not the first language. Families were given 24 hours or longer to decide to participate. Once informed consent was obtained, for infants randomized to the Calmer group, the nurse obtained the physiological parameters needed to program Calmer for treatment as outlined below.

2.5. Treatment procedures

This was a 2-arm, single-blind, randomized controlled trial. Infants were allocated to 1 of 2 intervention groups: Calmer or "Control"-FT; infants in both groups also received a soother. The method of blood collection for the study was heel lance. The complete details of the design of Calmer prototypes are reported

elsewhere.²⁶ In brief, Calmer is a robotic platform that fits inside standard NICU incubators (eg, GE Giraffe) and replaces the standard mattress (**Fig. 1**). The key features of Calmer are an adjustable heart and breathing rate so that the parental physiological recordings are individualized for each infant. The heart beat sounds are volume controlled so as not to exceed 55 dBA. The top plate of Calmer is covered with a skin-like surface and moves up and down 10 mm in a smooth trajectory to simulate a breathing motion. Calmer was certified for use for research purposes to Canadian Safety Association standards.

2.5.1. Baseline 1 phase (both groups)

ECG leads were placed before the start of the assessment to allow infants to settle. Then, for baseline 1, infants were left in the prone position undisturbed in their incubator for 15 minutes before testing. Prone positioning was used to mimic the position infants would be in had they been held skin-to-skin with their mothers.

2.5.2. Baseline 2 and intervention phases (Calmer and facilitated tucking group)

On the day before the study, after the infant's mother had rested for 10 minutes to stabilize her heart and breathing rates, the NICU research nurse recorded the mother's heart and respiratory rates for a 2-minute period. The 1-minute average was used to program Calmer for each infant. After the 15-minute baseline 1 on the regular mattress, the infant was placed in the prone position on Calmer. Then, 15 minutes before the first contact by the lab technician, the Calmer breathing and HR sounds were started (baseline 2); 15 minutes of exposure is the minimum time parents would provide skin-to-skin holding for pain management.¹¹ Then, 2 minutes before the heel lance, the research nurse gave the baby the soother. She ensured that the soother was held in the infant's mouth throughout the blood collection procedure.

2.5.3. Baseline 2 and intervention phases (control group: facilitated tucking only)

To match the handling and positioning of the infants in the Calmer group, after baseline 1, the FT group infants were lifted gently and replaced in the prone position before baseline 2. Facilitated tucking and non-nutritive sucking on a soother were started 2 minutes before the heel lance and continued until the blood collection was complete as per standard NICU practice.

2.5.4. Recovery (both groups)

The recovery phase was defined as the 5 minutes after the last contact of the lab technician.⁹ During each intervention (Calmer or FT control), infants had additional handling only if it was required to maintain physiological stability (defined as a HR above 100 beats/minute or oxygen saturation above 86%).

2.5.5. Bedside data collection

Each blood collection procedure was videotaped before, throughout, and up to 5 minutes after the procedure using a color, digital video camera to provide a close-up image of each infant's face and upper body. Each video was matched with simultaneous recordings of HR. The research assistant used a foot pedal to synchronize recordings and mark events.



Figure 1. Premature infant lying on Calmer.

2.6. Outcome measures

2.6.1. Primary outcome measure: Behavioral Indicators of Infant Pain

Video recordings of study phases were randomized for viewing by a coder who determined the presence or absence (0/1) of each of 8 indicators on the BIIP, a valid and reliable infant pain scale.⁸ Total scores were summed for 4, 1-minute phases:

- (1) Baseline 1: 1 minute before pick up when infants in both groups were in their regular beds;
- (2) Baseline 2: 1 minute before the first contact by the lab technician;
- (3) Lance/squeeze: 1 minute beginning at the start of skin breaking followed by squeezing;
- (4) Recovery: 1 minute after the last contact by the lab technician.

The video coder was blind to the purpose of the study, the study hypotheses, study intervention, and any information regarding the infants' medical history. The coder was trained to achieve interrater reliability on the BIIP to above 0.85 (kappa). An additional 20% of the video segments selected randomly were scored by the research coordinator and the video coder. Interrater reliability was assessed using the intraclass correlation coefficient and was maintained above 0.85 throughout the study.

2.7. Secondary outcome measures

2.7.1. Heart rate and heart rate variability

Heart rate was recorded continuously from a single-lead surface ECG (lead II) (Biopac, Goleta, CA) sampled at 1000 Hz using a specially adapted portable computer system. Custom physiologic signal processing software (MindWare) was used to acquire, process, and analyze the data. From the 4 acute pain phases, 2-minute periods of stable data for each phase were chosen for further analysis. For the HR analysis, a stable period was defined as one having minimal variation in mean and variance of the data.¹⁸ Means (SD) of the HR and power spectra were calculated for each study phase. Power spectral estimates of HR were quantified using the area (power) of the spectrum in low frequency (LF) (parasympathetic and sympathetic activity) (LF: 0.04–0.15 Hz), in high frequency (HF) ([respiratory sinus arrhythmia power]; parasympathetic activity) (HF: 0.15–0.80 Hz) regions, and in the LF/HF ratio (sympathovagal balance).^{17,18}

2.7.2. Maternal and perinatal/demographic data collection

Clinical information about the infant from birth to the day of testing was collected and included for descriptive purposes including: birth weight, GA at birth, respiratory support, maternal demographic information, type, and time of last handling just before blood collection.

2.7.3. Data analyses

Using an intention-to-treat approach, all analyses were completed by a statistician blind to the treatment groups. In the primary analysis, treatment group means for change in the BIIP from baseline 1 to lance/squeeze in the BIIP were compared using a two-sample *t* test and associated confidence interval (CI). In secondary analyses, repeated-measures analysis based on generalized least squares (with unconstrained variance structure) was applied to examine the trajectory of means over the 4 observation periods for BIIP, HR, and other variables. Log transformations were applied to correct for skewness in RSA-power and LF/HF ratio. To allow for comparisons with other trials, means and SDs are reported in the text for continuous variables as mean \pm SD. Ninety-five percent CIs are provided for differences in means.

3. Results

Data for 2 infants in the Calmer treatment group (one infant was determined to be on low-level sedation after the assessment and one study had technical difficulties interrupting data collection) and one infant in the FT group (infant discharged right before the assessment) were not included in the analyses (**Fig. 2**). Thus, 22 (Calmer) and 27 (FT) infants were included in the analyses. Infants enrolled in the study were, on average, born at 29 weeks of GA and were tested within the first month of life (**Table 1**). During the assessments, no infants required additional handling to help recover their physiological stability. There were no statistically significant between-group differences for baseline 1 or 2 BIIP scores (**Fig. 3**). For the primary and secondary outcomes, no statistically significant differences were found between the human touch-based treatment, FT, and the robot Calmer for reducing pain behaviors (BIIP scores), HR, or modulating HR variability parameters (**Fig. 3**). During the peak pain phases (lance), mean BIIP scores were 3.2 ± 2.7 (FT group) and 4.0 ± 2.7 (Calmer group) (95% CI: -0.45 to 2.72), both falling within the low-moderate pain range for the BIIP scale.⁷ Mean HR during the lance phase was 180 ± 13 bpm for the FT group and 180 ± 12 bpm for the Calmer group (95% CI: -9.46 to 5.7).

4. Discussion

Ours is the first study to evaluate the efficacy of a robotic device, which mimics aspects of skin-to-skin holding for managing acute procedural pain in preterm infants in the NICU. Our outcomes are important because a nonhuman touch-based intervention appears to be performed no differently from a human touch intervention. Importantly, we had no safety issues during the trial related to Calmer for short-term use. To put the Calmer treatment effect into context, in a historical sample of infants with a similar GA and chronological age at testing, average pain scores with no treatment during blood collection were 6 points (of 9) on the BIIP, indicating high-moderate pain.⁷ Based on the data from this trial, both FT and Calmer meet the clinically significant standard of reducing pain indices 2 points or more.²⁴

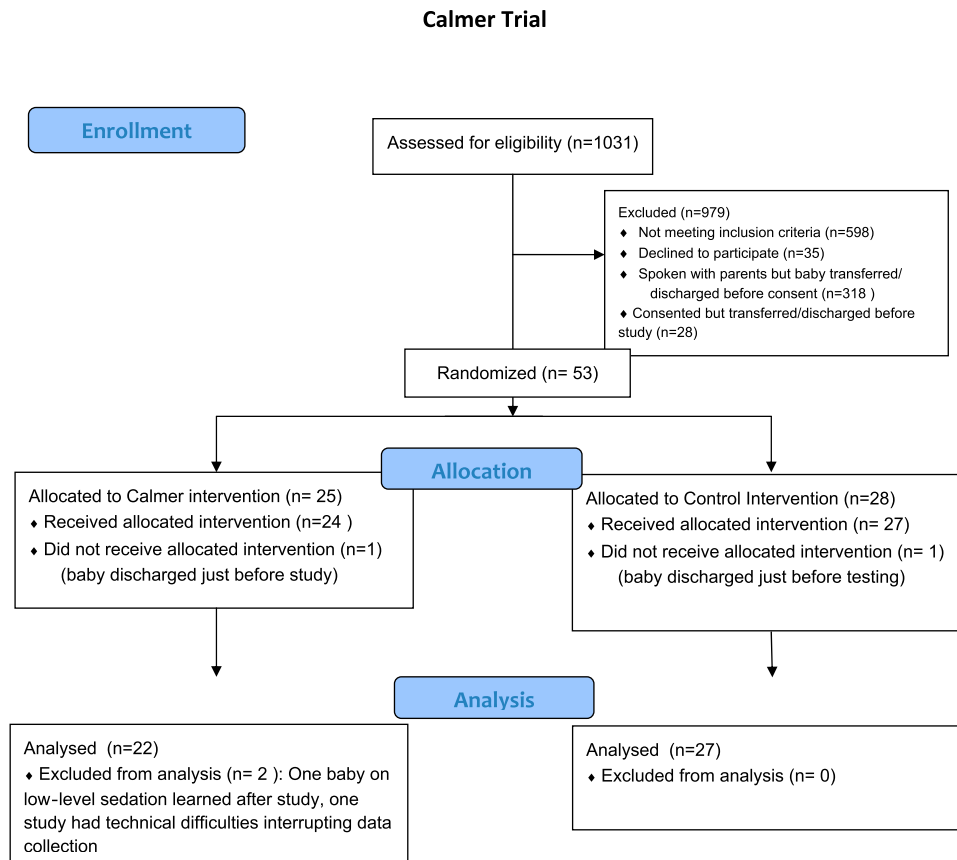


Figure 2. Patient flow diagram.

A study evaluating a device with some similar features compared the robotic device with maternal skin-to-skin holding for modulating HR variability. In this study, the robotic device did not appear effective.¹² However, their study did not test the device in a pain context when greater physiological reactivity occurs. Most importantly, it is our position that we are not trying to replace maternal care; therefore, we will not test Calmer against the infants' own family for providing stress relief. Instead, our goal is to provide alternative treatment options when parents are not available.

Further benefits of Calmer may relate to economic savings. When parents are not available, extra staff are needed to provide FT treatment; indeed, some have argued that implementing FT is too costly.² Our long-term vision is that Calmer-like functions would be built directly into incubators. This strategy would then negate the necessity for the devices to be moved in and out of the bedspace. Even if we take into consideration 2 to 3 minutes of time nurses would be needed to record the parents' physiological parameters to program Calmer functions the first time, parents can be easily taught how to do this themselves in 5 to 10 minutes, thereby providing their own data so that Calmer can be adjusted over time. In our 60 bed NICU alone, the annual savings in nursing time would be approximately \$380,000/y (US).

Consistent implementation of nonpharmacological pain treatments remains a problem in NICUs despite years of advocating for their use.²⁵ As part of our trial, qualitative interviews with mothers and NICU staff to evaluate the acceptability and ease of implementation of Calmer into routine workflow showed a high acceptance and low disruption to NICU workflow (unpublished data). Moreover, new treatment options are important to complement the low effect sizes and/or concerns of potential negative long-term effects of currently used treatments.^{23,26}

Some limitations of our research remain. We chose the shortest exposure time of 15 minutes for Calmer before the blood collection; a longer, preblood test exposure may have altered our findings.¹³ At this young age, the risk of bias is low, as is true for all research with behavioral interventions in preterm infants, and blinding of the infants to the treatment group is not possible. In addition, the coder may have been able to see that infants on Calmer were moving gently

Table 1
Characteristics of infants, n = 49.

	Control-facilitated tucking (n = 27)	Calmer (n = 22)
Mean birth weight (g)	1387 ± 331	1344 ± 286
Mean gestational age at birth (wk)	29 ± 1.7	29 ± 1.7
Sex (% male)	70	50
Mean age on the study day (d)	23 ± 14	28 ± 11
Intubated and ventilated study day	0	0
CPAP on the study day (n/%)	12 (44)	8 (36)
Time of blood collection (median, range) (min)	6.0 (3–17)	6.5 (2–13)
Time since last handling before the assessment (median, range) (min)	161 (3–290)	123 (19–294)
Time since last painful procedure (median, range) (min)	2806 (190–10333)	2932 (647–15780)
Mean maternal age (y)	33.5 ± 4.0	34 ± 6.0
Maternal education postsecondary education (n/%)	25 (92)	19 (87)

CPAP, continuous positive airway pressure.

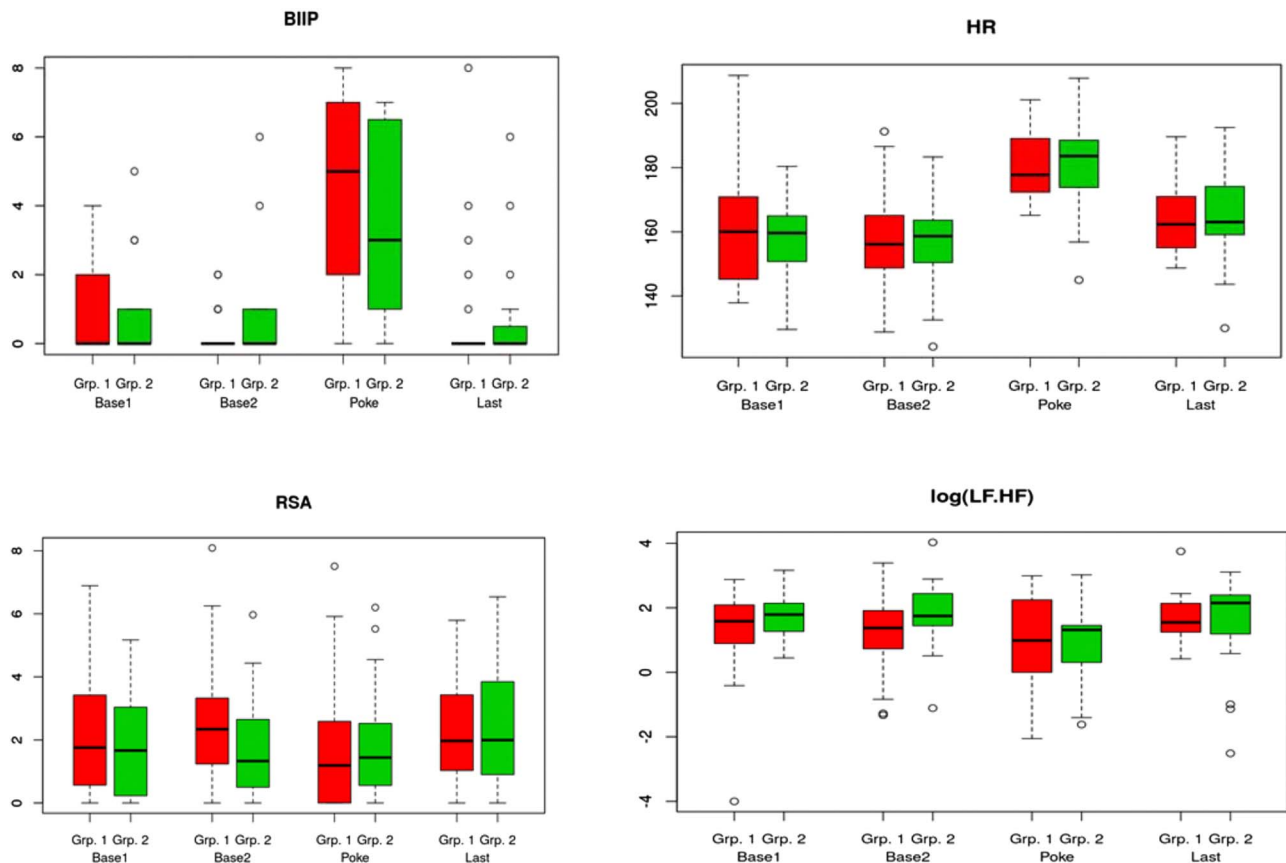


Figure 3. Main outcomes (medians, ranges). BIIP, Behavioral Indicators of Infant Pain; HF, high frequency; HR, heart rate; LF, low frequency.

during the coding; however, the trajectory of movement was only 1 cm; in addition, multiple randomization strategies were used for the segmented coding blocks so that it is unlikely the coder could make a connection between the infant motion and the pain response. Finally, because the difference in BIIP mean scores extends beyond a numerical value of 2, we may not be able to rule out a clinically significant difference between treatments. Thus, further research using equivalence or noninferiority designs is warranted.

Future work will examine the effects of longer exposure to a new Calmer prototype. Moreover, the treatments in this study differed between groups in their sensory stimuli. These differences are important avenues for further research related to determining which combination of treatments could potentially improve management for acute procedural pain in preterm infants.

5. Conclusion

Calmer reduced biobehavioral pain indices in preterm infants no differently from a human touch-based intervention. Calmer shows promise as an adjunctive management strategy when human touch-based treatments are not possible. Parents should always be the first choice.

Disclosures

K. MacLean and L. Holsti are coinventors of the Calmer medical device for pain management for preterm infants. In partnership with the Provincial Health Services Association of British Columbia, Canada, we could, in the future, receive royalties as

a result of licensing agreements made with private industry for commercialization of the device. We have not received any remuneration to date. L. Holsti supervised data collection at arms-length; she had no access to the data during the study, nor did she; or K. MacLean conducted the data analysis of the outcome measures reported in this article. The remaining authors have no conflicts to declare.

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