Effect of music (Brahms lullaby) and non-nutritive sucking on heel lance in preterm infants: A randomized controlled crossover trial

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Abstract

Objectives: This study examined a more effective pain management method, without sucrose, on heel lance in preterm infants using the Premature Infant Pain Profile (PIPP).

Design: In a nonblinded, randomized controlled, two-period, two-sequence crossover trial, 25 infants were randomly allocated to intervention (a Brahms lullaby with non-nutritive sucking, facilitated tucking and holding) or standard care (facilitated tucking and holding).

Setting: Local Perinatal Medical Centre's NICU in Japan, July 2014 until June 2015.

Outcome measures: The primary outcome variable was PIPP, and secondary outcomes were heart rate (HR), oxygen saturation, and abnormal HR (> baseline mean plus 2 SDs, or <120 minus 2 SDs).

Results: The infants were 33.8 weeks gestational age at birth, 1,983.7 g birth weight, and 32 to 35 weeks postconceptual age. At all 10 measurement points, constructed of every 30 seconds postheel lance, mean PIPP of infants during the intervention (3.6 to 2.4) was significantly lower than during the standard care (8.0 to 4.6) (range, $P=0.0039$ to $P<0.0001$). All PIPP reduction rates from the 30 seconds point were similar between the two groups. The HR of preterm infants at the 120 seconds points were significantly lower ($P=0.0151$), and the HRs of 6 points were considerably lower during the intervention than during the standard care (range, $P\leq0.0879$ to $P\geq0.049$). The abnormal HR total number was significantly lower during the intervention (2) than the standard care (23) (frequency ratio=0.087, $P<0.0001$).

Conclusion: This method demonstrated stronger analgesia, early pain relief, and maintenance of homeostasis on heel lance in preterm infants.

Keywords: Facilitated tucking; Heel lance; Music (Lullaby: Brahms); Non-nutritive sucking; Pain; Preterm infant.

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Introduction

Preterm infants are at increased risk of impaired neurodevelopmental outcomes including cognitive abnormalities or motor deficits, and the risk of impairment increases with decreasing gestational age (1,2). Preterm infants are exposed to a large number of painful procedures (3), which have been linked to delayed postnatal growth, poor early neurodevelopment, and altered brain development (4).

Oral sucrose solutions are commonly administered to infants in the neonatal intensive care unit (NICU) as a non-pharmacologic intervention for managing acute procedural pain (5). However, the long-term effects of repeated oral sucrose usage have not been systematically studied (5,6). Non-nutritive sucking (NNS), facilitated tucking and swaddling are also effective for immediate pain control in preterm infants (7), but yield a Premature Infant Pain Profile (PIPP) score higher than 6 points (8-13). PIPP scores of 6 or less generally indicate minimal or no pain, and scores greater than 12 reflect moderate to severe pain (14). In previous studies of preterm infants during heel lance, mean PIPP scores were as follows; with NNS slight pain (6.3 to 8.4) (9,10), with swaddling slight pain (7 to 10.2) (12,13), with Kangaroo mother care slight pain (8.9) (13), with facilitated tucking slight – severe pain (7.2 to 14.4) (8,15), with sucrose no to slight pain (3.0 to 9.8) (16,17), and with both sucrose and NNS no to slight pain (4.6 to 8.2) (9,16). All studies confirmed that preterm infants experience significant pain from heel lance (18).

Music for preterm infants is a noninvasive, non-pharmaceutical intervention (15,19-21). Although the mean PIPP score of 21 preterm infants with music and facilitated tucking during heel lance indicated no pain (5.1), the standard deviation (SD) was 1.9, which indicates that some still had pain (15). Also, a reduction in the heart rate (HR), behavioral state and facial expression of pain during heel lance with a Brahms lullaby recording (7 heard the piano version and 7 an a capella version) appeared to only occur in infants at a minimum 32 weeks' post-conceptual age (PCA) (22). During heel lance in infants at minimum 32 weeks PCA, 20 infants with pacifier-activated female traditional lullabies had significantly lower behavior states and stress levels than 20 infants in the control group (23). Although music (22) and NNS and music (23) have a facilitating effect on returning to homeostasis, the sample size of the two studies was small. To develop a more effective pain management method than oral sucrose, this study evaluated the pain alleviation effect and the time to return to homeostasis facilitation effect of a recorded Brahms lullaby combined with NNS for heel lance in preterm infants using a more standardized pain scale (the PIPP) (5).

Methods

Design

This non-blinded, randomized controlled, two-period, two-sequence crossover trial was approved by the institutional review board at the Takamatsu Red Cross Hospital in Japan (approval number 14-008). A crossover design was used to reduce the impact of confounding variables outside the control of the study itself (24,25). This trial was registered at UMIN Clinical Trials Registry (UMIN-CTR) (UMIN 000024876). The study followed the CONSORT guidelines for reporting randomized controlled trials.

Sample and setting

Inclusion criteria of infants were as follows: (a) 28 to 35 weeks PCA at birth (infants born at < 36 weeks PCA receive heel lance), (b) 32 to 35 weeks PCA at the time of the intervention, based on the evidence that infants at 32 weeks PCA have fully coordinated sucking (8,26), and are able to listen to the voice version of lullabies (19), (c) Apgar score of 6 or more at 5 minutes after birth, (d) intraventricular hemorrhage grade of 2 or less, (e) 48 hours or older in the case of birth by cesarean operation, and f) permission of the attending physician. Exclusion criteria included: (a) a congenital anomaly or a serious condition, and (b) sedative or analgesic drug usage within 48 hours prior to the heel lance.

To calculate study power, we first determined that the effect size was 0.63 (8). Thus, using the Wilcoxon signed-rank test in G*power 3.1.9.2, we estimated that 25 preterm infants would be needed to detect the effect size of 0.6 with an alpha level of 0.05 and a power of 80%.

Standard care or pain-relief intervention was performed when preterm infants met the following conditions established by the NICU for performing heel lance: one hour or more after suckling milk, quiet rest condition in a face up position, and not crying.

Measures

Outcome variables of PIPP selected as primary outcome included preterm infants' behavioral responses and physiological responses {HR and oxygen saturation (O_2 Sat)} (8,22,23). The PIPP is a reliable, valid, feasible measure of acute pain as an effective outcome measure in pain intervention studies in infants (18,27), and a previous study demonstrated the reliability and validity of the Japanese versions (28).

HR and O_2 Sat were used to determine return to homeostasis as a secondary outcome (13,22,23). Abnormal HR was defined as 2 SDs above the baseline, or <120 beats/minute minus 2 SDs (8). The frequency of abnormal HR was calculated (total number of abnormal HRs for each observation). Potential stress O_2 Sat was considered more than 2 SDs below the baseline mean; abnormal O_2 Sat

was defined as <87% (29). The sampling points of PIPP indicators, HR and O_2 Sat were constituted from the baseline and 10 points that were constructed at every 30 seconds after heel lance.

Adverse events recorded included choking, vomiting, oxygen desaturation, apnea and self-limiting bradycardia (5).

Procedures

The study was from July 2014 through June 2015. Following parental consent, each infant was assigned using a random table format to two sequences: sequence one with pain-relief intervention first (period 1), followed by standard care (period 2), sequence two with standard care first (period 1), followed by pain-relief intervention (period 2). Based on the random table, a research assistant sealed an envelope containing the written randomized method (the order of the 2 interventions). The practitioner of the heel lance and the researcher did not know the order until opening the envelope. The washout period was set for at least eight hours between the two periods.

To analyze the recovery response from pain of heel lance, and to ascertain whether adjustment of database scores between the 2 groups was requisite or not, the researcher measured the baseline scores of preterm infants in 2 groups. HR and O_2 Sat were measured using pulse oximeters (MAsimoSET® radical, IMI). The preterm infant's facial expressions and the monitor screen displayed HR and O_2 Sat were recorded by two video cameras (Panasonic, HC-V550M) from before baseline (before intervention) until five minutes post heel lance, and stored on DVD. The PIPP was derived from videos by a blinded research assistant or by an investigator who was not blinded. Prior to the study, to quantify the reliability of the PIPP provided by the two coders, an assessment of inter-rater reliability was completed. The inter-rater reliability of the PIPP of six preterm infants ranged from 0.851 to 1.0, which was considered satisfactory (30, 31).

The time of blood collection was defined as the time from pricking the heel to putting an adhesive plaster on the wound.

The pain relief intervention included the addition of the Brahms lullaby and a pacifier. After the baseline score was measured for one minute, a pacifier (Soothie®21307, ATOM) was placed in the mouth, the infant was held and facilitated tucking was used. Then a Brahms lullaby by a Japanese female vocalist with instrumental music (World lullaby, A collection of famous children's songs, Nippon Crown) was played (this version was selected because preterm infants are sensitive to native language speech based on exposure to the native language in utero (32,33). The lullaby volume was below 65 to 75 dB, scale C (34) played from a CD player (CD ZABADY Orange AV-J165OR, TWINBIRD) set 20 to 25 cm away from the head of the infant. NNS use was coded as an infant sucking on or holding a pacifier in his/her mouth without being fed breast milk or formula.

One minute after the lullaby was started, the practitioner (pediatrician or nurse) disinfected the heel of the preterm infant with alcohol raw cotton. Fifteen seconds after disinfecting, the practitioner

performed the heel lance to the preterm infants using the BD Quikheel lancet (Japan Becton, Dickinson, BD Microtainer® Quikheel TM Lancet ®368102). The pain-relief intervention was continued until five minutes post heel lance.

When infants were in the standard care group, they received only facilitated tucking and holding. After a 1-minute baseline check by the researcher, the practitioner performed the heel lance. The practitioner continued the standard care until infants' calmness resumed, such as the disappearance of crying and agitation after blood collection. All the infants in the standard care group became calm within 5 minutes of blood collection.

Statistical Analysis

Differences in PIPPs, HRs and O_2 Sats were tested using a 2-sided type 3 F test of the intervention effect in a general linear mixed model, where the final model included fixed-effects for intervention, sequence, period, and with random effects for participants (35-37). The model was fit using the MIXED procedure in SAS. The protocol-defined model included evaluation of carry-over effect, period effects, and intervention effect. The difference-in-differences model was selected as the appropriate strategy comparing change from baseline or 30 seconds post heel lance between the 2 groups (38,39). The Mantel-Haenszel Test was used to compare the frequencies of abnormal HR, potential stress O_2 Sat and abnormal O_2 Sat between the 2 groups. The PIPP reduction rate was calculated by dividing the value of subtracting the PIPP at each point from the PIPP at 30 seconds by the PIPP at 30 seconds. SAS version 9.4 for Windows was used for statistical analysis.

Results

The parents of 34 infants were approached and 32 parents consented (Figure 1). Four infants were eventually excluded because blood collection was not performed.

Comparison of infants between the 2 groups showed no differences in baseline characteristics (Table 1). No carry-over effect or period effects were found in PIPP, HRs and O_2 Sats for all points in a general linear mixed model.

At all measurement points post heel lance, the PIPP of the preterm infants in the intervention group was significantly lower than the PIPP in the standard care group (range, $P<0.0001$ ~ $P=0.0039$) (Figure 2, Table 2). The odds ratios of pain (PIPP>6) for preterm infants in the intervention group versus standard care group ranged from 0.1497 to 0.0212, where all differences were statistically significant with the corresponding p-values ranging from $P=0.0072$ to $P<0.0001$. At the 120 seconds point, the HR of preterm infants was significantly lower in the intervention group than in the standard care group ($P=0.0151$). The HRs of 6 points were considerably lower in the intervention group than in the standard care group (range, $P\leq0.0879$ ~ $P\geq0.049$). The abnormal HR total number was significantly lower in the intervention group (2) than in the standard care group (23)

(frequency ratio=0.087, P<0.0001). O_2 Sats of point post heel lance were similar between the 2 groups except the 90 seconds point.

Difference-in-differences estimated that all changes of PIPP between baseline and each point post heel lance were significantly higher in the intervention group than in the standard care group. However, all PIPP reduction rates were similar between the 2 groups. All changes in HR between baseline and each point post heel lance were similar between the 2 groups. The O_2 Sat could not be subjected to difference-in-differences analysis because there were no parallel trends between the 2 groups.

As the washout periods were not done at regular intervals due to participants' treatment, the washout periods included outliers in both groups. Data were analyzed according to intention to treat, and all results including washout were the same as all results that did not include washout. No adverse events from the intervention were detected.

Discussion

The addition of the recorded Brahms lullaby to NNS with facilitated tucking and holding, resulted in decreased pain levels during heel lance in preterm infants. In the intervention group, all mean PIPP scores post heel lance were less than 6 points, which suggests minimal or no pain. The number of preterm infants who felt slight pain in the intervention group was about 15% lower than that of the preterm infants in the standard care group.

The mean PIPP score during intervention at 30 seconds post heel lance in the current study (3.6, SD 2.0) was lower than the mean PIPP score over 1 minute after the end of the heel lance in the previous music study (5.1, SD 1.9) (15), and also indicates that about 80% of preterm infants had no pain. The mean PIPP scores in the current study were lower than those of previous interventions, such as NNS, swaddling, Kangaroo mother care, and facilitated tucking (8-13,15). Although the PIPP scores of the preterm infants receiving sucrose with or without NNS were lower than 6 (9,17), sucrose usage has some problems such as a risk of poorer neurobehavioral development due to repeated oral sucrose usage (40) and oxidative stress (9,41). The alleviation effect of the current study shows a possible combination effect from using many methods (Brahms lullaby, pacifier, facilitated tucking and holding). Also, the similarity in the PIPP reduction rate between the 2 groups indicated that a lower value of PIPP post heel lance may induce shorter pain duration (PIPP<6).

The HRs were considerably lower in the intervention group than in the standard care group. The incidence of abnormal HR was less than 10% of that with standard care. The current study demonstrated stronger pain relief and the maintenance of homeostasis for heel lance in preterm infants.

These results are supported by the findings of many non-pharmacological interventions on heel lance in preterm infants: kangaroo care (13), facilitated tucking (8,42), swaddling (12), music (22) and NNS and lullaby (23).

The results showing no adverse events detected from the intervention in the current study indicate the safety of this intervention.

One limitation is that the sample size of this study was small. The sample size in previous studies using music was also small: 28 preterm infants (22), 42 preterm infants (15), and 60 preterm infants (23). Secondly, the washout periods were non-uniform, ranging from 8 hours to 15 days. It is necessary to consider setting the washout period in post-menstrual ages as uniformly as possible because post-menstrual age is the dominant predictor regarding maturation of NNS patterns (43). Finally, this intervention was carried out for a limited set of participants (32 to 35 weeks PCA) and procedures (heel lance). However, preterm infants and term infants with disease in the NICU frequently suffer a variety of procedural pains from the pain of routine care to severe pain associated with an examination for retinopathy at prematurity (3). Therefore, further research is necessary to determine whether implementing this intervention during a variety of procedures significantly reduces the pain of preterm infants.

Conclusion

A new pain management method, the addition of a recorded Brahms lullaby to non-nutritive sucking, facilitated tucking and holding, demonstrated stronger analgesia and maintenance of homeostasis on heel lance in preterm infants.

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Conflict of interest: None declared.

Ethical approval: This study received approval from the ethical boards of Takamatsu Red Cross Hospital (No. 14-08).

This trial has been registered at http://www.umin.ac.jp/ (UMIN 000024876).

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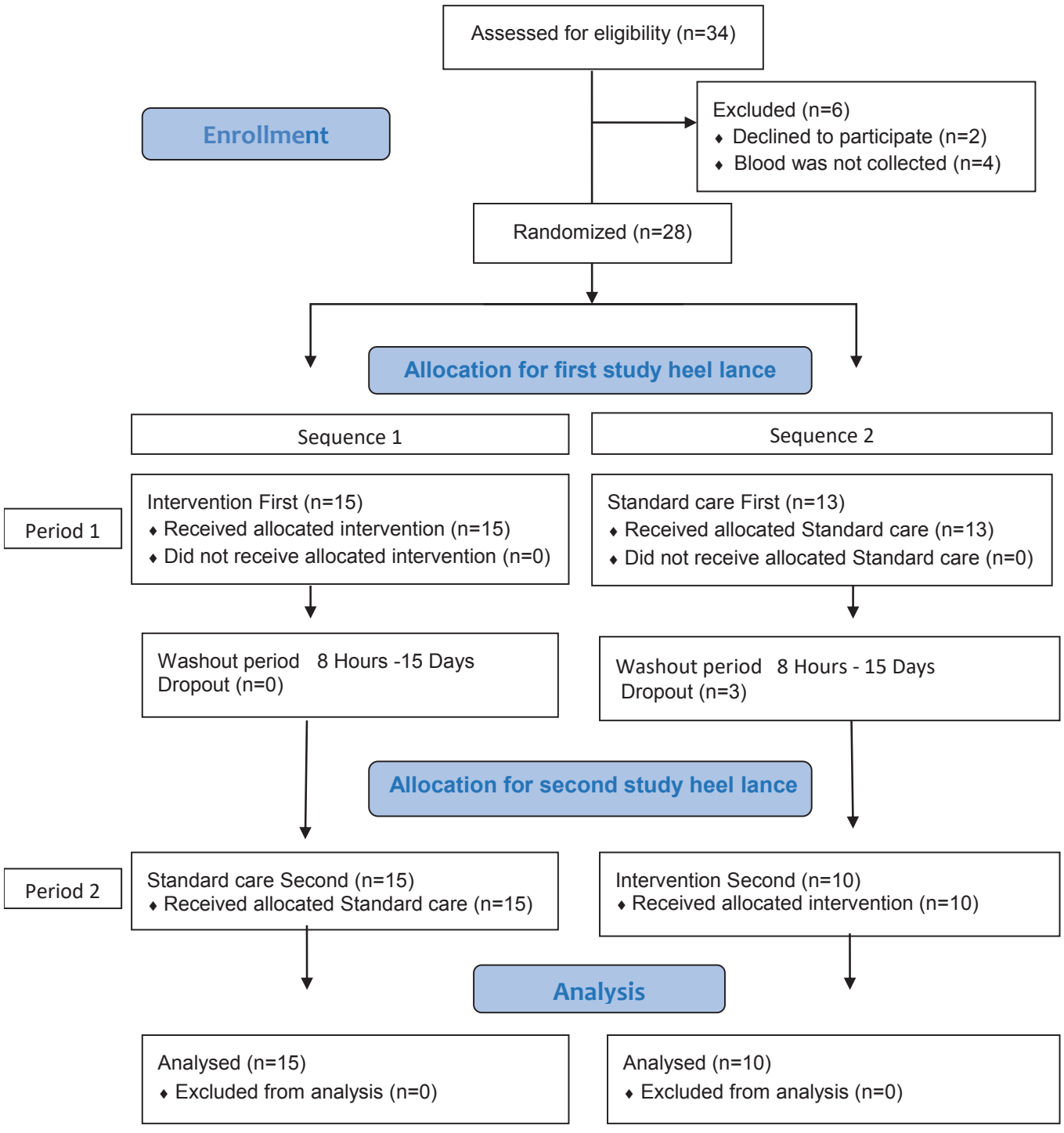

Figure 1. Flowchart of participant recruitment according to CONSORT 2010 guidelines

Table 1. Demographic variables and confounding variables N=25

Variable			During intervention		During standard care		P-value
	Mean	SD	Mean	SD	Mean	SD	
Gestational age at birth (weeks)	33.8	1.5					
Birth weight (gram)	1983.7	383.9					
Apgar score (1 min)	6.9	2.3					
Apgar score (5 min)	8.5	1.1					
Male (n)	15						
Female (n)	10						
Post conceptual age (weeks)			34.6	0.8	34.5	1.0	0.11
Post natal age (days)			5.2	6.5	5.0	5.3	0.36
Weight on day of study (gram)			1818.5	339.6	1810.3	352.8	0.38
Duration from last feeding (minutes)			154.6	31.5	149.1	26.6	0.78
Blood glucose level (mg/dl)			75.8	13.6	84.9	20.7	0.13
Blood collection time (seconds)			74.9	64.6	55.5	32.3	0.69
Baseline: the Premature Infant Pain Profile			2.1	1.7	2.3	1.4	0.46
Baseline: Heart rate (/minutes)			150.9	18.3	152.8	19.0	0.67
Baseline: Oxygen saturation (%)			96.6	2.6	96.8	2.3	0.66

Unpaired *t*-test or Wilcoxon rank sum test P<0.05

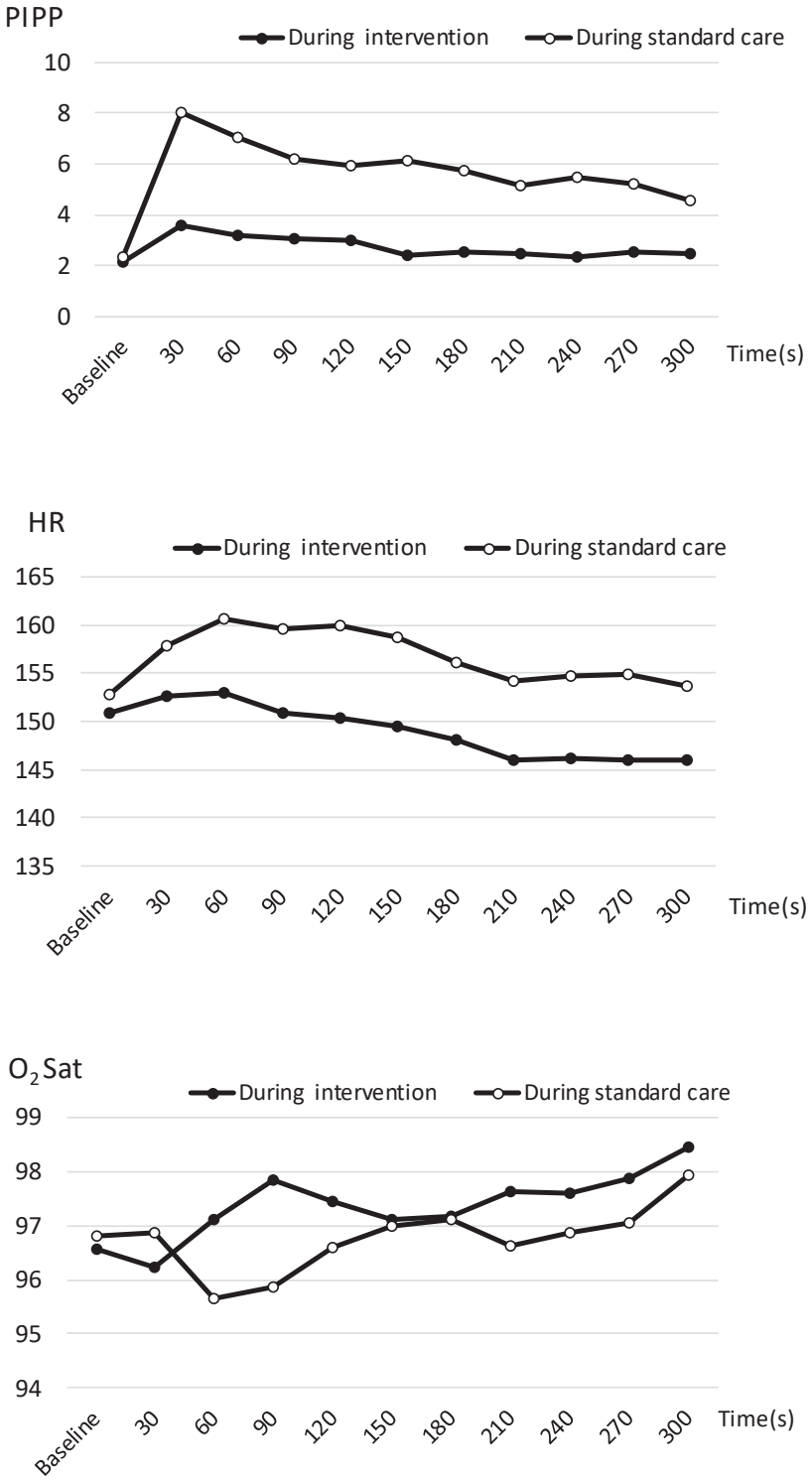

Figure 2. Comparison of PIPP, HR, and O_2 Sat between the intervention group and the standard care group. HR Heart rate; PIPP Premature Infant Pain Profile; O_2 Sat Oxygen saturation.

Table 2. Comparison of outcomes between the intervention group and the standard care group N=25

Outcome	Measurement time	During intervention		During standard care		Intervention effect	Difference in differences	Difference in differences
		Mean	SD	Mean	SD	P-value *	P-value †	P-value ‡
PIPP	Baseline	2.1	1.7	2.3	1.4	0.595	-	-
	30S	3.6	2.0	8.0	3.2	<.0001	<.0001	-
	60S	3.2	2.1	7.0	3.7	0.0001	<.0001	0.7144
	90S	3.0	2.2	6.2	3.3	0.0006	0.0008	0.3478
	120S	3.0	1.7	5.9	3.4	0.0009	0.001	0.4151
	150S	2.4	1.2	6.2	3.4	<.0001	<.0001	0.6636
	180S	2.5	1.5	5.7	3.5	0.0005	0.0004	0.9376
	210S	2.4	1.3	5.1	3.2	0.0007	0.0008	0.9376
	240S	2.4	1.3	5.5	3.3	<.0001	0.0003	0.6017
	270S	2.5	1.5	5.2	3.1	0.001	0.0013	0.5819
	300S	2.5	1.2	4.6	3.0	0.0039	0.0118	0.7579
HR	Baseline	150.9	18.3	152.8	19.0	0.6429	-	
	30S	152.6	15.8	157.9	18.7	0.188	0.5259	
	60S	152.9	16.0	160.6	22.3	0.0879	0.3162	
	90S	150.9	15.3	159.7	20.1	0.049	0.2121	
	120S	150.3	15.6	159.9	21.6	0.0151	0.1521	
	150S	149.5	13.6	158.8	23.0	0.0567	0.1888	
	180S	148.2	13.8	156.1	23.1	0.0804	0.2752	
	210S	146.0	12.8	154.2	22.7	0.112	0.2726	
	240S	146.2	12.1	154.8	21.4	0.0652	0.2226	
	270S	146.1	12.4	154.9	21.3	0.0641	0.2113	
	300S	146.0	13.0	153.6	19.6	0.1019	0.3116	
O_2 Sat	Baseline	96.6	2.6	96.8	2.3	0.5578		
	30S	96.2	5.0	96.9	2.5	0.625		
	60S	97.1	4.8	95.7	4.1	0.1145		
	90S	97.8	2.5	95.9	4.5	0.0293		
	120S	97.4	3.3	96.6	3.6	0.1642		
	150S	97.1	3.6	97.0	2.9	0.938		
	180S	97.2	3.5	97.1	2.9	0.9832		
	210S	97.6	3.4	96.6	2.7	0.3041		
	240S	97.6	3.8	96.9	2.6	0.5218		
	270S	97.9	3.8	97.0	2.8	0.3993		
	300S	98.4	2.1	97.9	1.8	0.3246		

HR Heart rate; PIPP Premature Infant Pain Profile; SD Standerd deviation.

* A general linear mixed model included fixed-effects for intervention, sequence, period, and with random effects for participants, using the MIXED procedure in SAS. † Difference-in-differences analysis estimated the difference in baseline-post heel lance changes in an outcome between an intervention and a standard care group, where the analysis included fixed-effects for intervention, sequence, period, and with random effects for participants, using the MIXED procedure in SAS. Difference-in-differences analysis of O_2 Sat could not be performed because there were no parallel trends between the 2 groups. ‡ The PIPP reduction rate was calculated by dividing the value of subtracting the PIPP at each point from the PIPP at 30 seconds by the PIPP at 30 seconds. A general linear mixed model for the reduction rate of PIPP included fixed-effects for intervention, sequence, period, and with random effects for participants, using the MIXED procedure in SAS. $P<0.05$.

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