PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/early/2012/01/04/peds.2011-1879

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Oral Sucrose and "Facilitated Tucking" for Repeated Pain Relief in Preterms: A Randomized Controlled Trial

AUTHORS: Eva L. Cignacco, PhD, RM,[a] Gila Sellam, MSN, RN,[a] Lillian Stoffel, BSN, RN,[b] Roland Gerull, MD,[b] Mathias Nelle, MD,[b] Kanwaljeet J. S. Anand, Prof, MBBS, DPhil,[c] and Sandra Engberg, Prof, PhD, CRNP, FAAN[a,d]

[a]Institute of Nursing Science, University of Basel, Basel, Switzerland; [b]Division of Neonatology, Children's Hospital, University Hospital Bern, Bern, Switzerland; [c]Pediatric Critical Care Medicine, Le Bonheur Children's Hospital, University of Tennessee Health Science Center, Memphis, Tennessee; and [d]School of Nursing, University of Pittsburgh, Pittsburgh, Pennsylvania

WHAT'S KNOWN ON THIS SUBJECT: Preterm infants are exposed to inadequately managed painful procedures during their NICU stay, which can lead to altered pain responses. Nonpharmacologic approaches are established for the treatment of single painful procedures, but evidence for their effectiveness across time is lacking.

WHAT THIS STUDY ADDS: Oral sucrose with or without the added technique of facilitated tucking has a pain-relieving effect even in extremely premature infants undergoing repeated pain exposures; facilitated tucking alone seems to be less effective for repeated pain exposures over time.

abstract

OBJECTIVES: To test the comparative effectiveness of 2 nonpharmacologic pain-relieving interventions administered alone or in combination across time for repeated heel sticks in preterm infants.

METHODS: A multicenter randomized controlled trial in 3 NICUs in Switzerland compared the effectiveness of oral sucrose, facilitated tucking (FT), and a combination of both interventions in preterm infants between 24 and 32 weeks of gestation. Data were collected during the first 14 days of their NICU stay. Three phases (baseline, heel stick, recovery) of 5 heel stick procedures were videotaped for each infant. Four independent experienced nurses blinded to the heel stick phase rated 1055 video sequences presented in random order by using the Bernese Pain Scale for Neonates, a validated pain tool.

RESULTS: Seventy-one infants were included in the study. Interrater reliability was high for the total Bernese Pain Scale for Neonates score (Cronbach's α: 0.90–0.95). FT alone was significantly less effective in relieving repeated procedural pain ($P < .002$) than sucrose (0.2 mL/kg). FT in combination with sucrose seemed to have added value in the recovery phase with lower pain scores ($P = .003$) compared with both the single-treatment groups. There were no significant differences in pain responses across gestational ages.

CONCLUSIONS: Sucrose with and without FT had pain-relieving effects even in preterm infants of <32 weeks of gestation having repeated pain exposures. These interventions remained effective during repeated heel sticks across time. FT was not as effective and cannot be recommended as a nonpharmacologic pain relief intervention for repeated pain exposure. *Pediatrics* 2012;129:1–10

The survival of preterm infants is dependent on highly sophisticated intensive care, associated with an exceedingly high number of painful procedures.[1] This is particularly true for infants with extremely low gestational ages (GAs) who also receive less analgesia.[2–5]

Repeated pain exposures during critical windows of central nervous system development[6,7] are associated with permanent changes in peripheral, spinal, and supraspinal pain processing; neuroendocrine function; and neurologic development. These changes can be manifested by alterations in pain thresholds, stress responses, cognitive function, behavioral disorders, and long-term disabilities.[7,8] Despite this knowledge, many painful procedures in NICUs are performed without pharmacologic or nonpharmacologic analgesia.[1–3,9] Disadvantages of pharmacologic analgesia include side effects, questionable efficacy, and possible negative impact on neonatal outcomes.[10–12] As an alternative approach, nonpharmacologic interventions (NPIs) are recommended for pain management.[13–15]

NPIs (eg, oral sucrose, breastfeeding, non-nutritive sucking, facilitated tucking [FT], kangaroo care, swaddling) effectively reduce pain for minor to moderately painful procedures.[15–17] They promote self-regulation of the infant and provide oro-tactile, oro-gustatory, and tactile stimulation, capable of reducing infants' pain responses during most painful procedures.[15,18–21] Sucrose is recommended extensively for pain relief in preterm infants[22–24] and has shown to be highly effective and safe for single procedures by Stevens et al.[17] Sweet taste solutions seem to trigger endogenous opioid and nonopioid pathways.[25,26] FT is described as holding the infant by placing a hand on his or her hands and feet and by positioning the infant in a flexed midline position while in either a side-lying, supine, or prone position.[27,28] This technique provides the infant with support and the chance to control his or her own body.[16] Several studies reported that FT stabilizes behavioral and physiologic states during single heel sticks and endotracheal suctioning, reducing the infant's stress in coping with pain.[16,27–31]

Although current evidence supports the effectiveness of NPIs for a single painful procedure, there is little research examining their effectiveness across repeated painful procedures. To date, few studies have evaluated the effectiveness of sucrose over time,[32–36] and none have evaluated FT across time. The combination of 2 NPIs (eg, oral sucrose and FT) may have additive effects by stimulating infants in a multisensorial way to cope with the painful experience.[18,37,38]

This study compared the impact of sucrose and FT alone and in combination on pain reactivity across multiple painful procedures. Randomized groups received oral sucrose, FT, and a combination of both strategies to evaluate possible additive effects. The primary outcome was pain response measured by the Bernese Pain Scale for Neonates (BPSN) total and component scores. The secondary outcome was the impact of gestational group (24 0/7 to 27 6/7 and 28 0/7 to 32 0/7 gestational weeks) on the effectiveness of these interventions.

METHODS

Setting and Sample

This randomized controlled trial was carried out in NICUs of 3 university hospitals in Switzerland from January 12 to December 31, 2009. Infants admitted to the NICU during this period were assessed for eligibility according to the following inclusion criteria: born between 24 0/7 and 32 0/7 weeks of gestation and anticipated clinical need for at least 5 routine capillary blood samples within 2 weeks after birth. Infants were excluded if they had severe intraventricular hemorrhage (grades III and IV), had life-threatening malformations or disorders affecting brain circulation or the cardiovascular system, had undergone a surgical procedure, had a pH <7.00, or had any problem that could impair pain expression.

Sample Size Calculation

By using sucrose only, we performed a feasibility study to calculate a preliminary power analysis.[39] We formulated our calculations based on the assumptions that sucrose and FT would have equivalent effects that would sustain over time. According to this analysis, a group size of $n = 24$ for each intervention group ($n = 72$ total sample size) provided adequate power to detect a pain reduction of 33% for the combination group relative to the 2 single intervention groups with a power of 80%.

Data Collection and Management

Data were collected during 5 nonconsecutive routine heel sticks (T1–T5) between postnatal days 2 and 16, with the first heel stick performed no later than day 4. For other painful procedures including heel sticks where data were not being collected, the infants were provided with sucrose 20%, which was the standard of care in all participating NICUs. Because the timing of blood sampling was determined by clinical considerations, there were no fixed time points for data collection. Demographic data were collected from medical records.

Data collection occurred during (1) baseline (before any manipulation), (2) heel stick (skin preparation, heel stick, and hemostasis after blood was drawn), and (3) recovery (3 minutes after the heel stick). Most heel sticks took place in the morning and each infant was undisturbed for at least 30 minutes before data collection. Phases were videotaped (Panasonic high-definition camcorder, model HDC-HS9, Osaka, Japan) for at

least 3 minutes by a trained study nurse by using a standardized procedure. No recording occurred during heel warming (2–3 minutes) between the first and second phases. The infant's nurse performed the heel stick. Sucrose was administered by the nurse, whereas the FT was performed by a second nurse or trained study nurse. The exact time of the videotaping of each phase was documented, as well as the duration of heel sticks. Fifteen videotape segments were produced per infant (3 sequences per procedure × 5 heel sticks = a total of 1065 video sequences for the study).

Each video segment was checked for quality and digitally edited by trained study nurses by using the Final Cut Express software (version 4.0.1. 2002–2008 Apple Inc, Cupertino, CA) to eliminate any information that would have indicated the heel stick phase. Video recordings of poor quality were discarded ($n = 10$). The final sample of 1055 sequences was assigned in random order in relation to the number (T1–T5) and the phase (baseline, heel stick, recovery) of the heel stick being recorded. All digital records were provided to 4 nurses for assessment of pain responses during each sequence. The videotaping procedure was designed to ensure that the raters could not see if the heel stick procedure was being performed.

The NPI groups were (1) oral sucrose 20% (0.2 mL/kg), (2) FT, and (3) a combination of both interventions. Sucrose was administrated orally ∼2 minutes before the heel stick. If the infant seemed to be in pain during the heel stick phase, up to 2 additional doses of sucrose were administered and noted in the study chart. FT was started at the beginning of the baseline phase, and the infant was "tucked" through all 3 phases. In the combination group, the FT was started at the beginning of the baseline phase and sucrose was given 2 minutes before the heel stick.

Variables and Measures

Information about GA, method of delivery, gender, parity, birth weight, Apgar scores, mechanical ventilation or continuous positive airway pressure during the heel stick, and number of painful procedures each day was collected.

Pain response, the dependent variable, was measured by using the BPSN total and component scores. The BPSN contains 9 items: 3 physiologic (heart rate, respiratory rate, and oxygen saturation) and 6 behavioral (grimacing, body movements, crying, skin color, sleeping patterns, consolation) items. Physiologic data (heart rate and oxygen saturation) synchronized with the 3 phases of data collection were downloaded from the clinical monitoring database for the BPSN. Raters counted the breathing rate while viewing the video sequences. Raters scored behavioral items and breathing only; heart rate and oxygen saturation were scored by using physiologic data collected during each phase. Each item was scored on a 3-point scale (0–3 points). Higher scores for the behavioral items and greater changes in the physiologic items indicated increased pain, whereas a total score of ≤11 was considered nonpainful.[40] The neonatal nursing experts who rated the video sequences attended a standardized instruction session about how to perform the rating and they rated the sequences independently.

Initial psychometric testing of the BPSN demonstrated good construct validity with differentiation between painful and nonpainful procedures ($F = 41.27$, $P \leq .0001$) and intrarater and interrater reliability correlation coefficients of $r = 0.98$ to 0.99 and $r = 0.86$ to 0.97, respectively. In a recent revalidation of the BPSN, a cutoff score of ≤11 was considered nonpainful (sensitivity of 100.0% and specificity of 89.4%).[41] For this study, 3 BPSN scores were calculated: the total (T-BPSN), behavioral (B-BPSN), and physiologic (P-BPSN) BPSN scores.

Interrater Agreement

Interrater reliability for the T-BPSN scores in this study averaged 99.2% for the 5 heel sticks (range: 98.8% for heel stick 1 and 99.8% for heel stick 5). Because the interrater reliability was very high, we used the average raters' BPSN scores within infants over time (5 heel sticks). Within-infant variability in T-BPSN scores across time was high (86.3%, $P < .0001$). Interrater reliability for B-BPSN scores was 98.8%. Interrater reliability, measured by Cronbach's α coefficient, ranged between 0.90 and 0.95 for the different phases.

Randomization

To ensure equal balance of the intervention group per site, block randomization by using SPSS, version 16 (SPSS Inc, Chicago, IL) was performed. For each site, 8 infants were randomly allocated to each of the 3 interventions (24 infants per site, and 24 infants per intervention group for the entire study sample). For each site, group assignments were sealed in opaque envelopes and consecutively numbered. When parents consented to participation, the envelope was opened by a study nurse and the intervention group was revealed. Envelopes were prepared by a study nurse not involved in the data collection process.

During the study period, 201 infants of <32 weeks of gestation were assessed for eligibility to participate in the study. In each site, a study nurse called the referring NICU daily and asked if any new infants were eligible to participate in the study.

Ethical Consideration

The study was approved by the ethical boards of the Cantons of Basel, Bern, and Zürich. Written informed consent was obtained from a parent. The study design did not include a no-intervention control group based on the evidence that exposure of preterm infants to

pain procedures without treatment is harmful.[14]

Data Analysis Procedures

All data were analyzed by using IBM SPSS statistics software (version 19) and SAS (version 9.1) (SAS Institute, Inc, Cary, NC). Data entry quality was controlled by double-entry procedures and an error rate of <1% was detected. Descriptive statistics were used to describe the demographic and medical characteristics of the infants, whereas the χ^2 test and Kruskal–Wallis or Mann–Whitney U tests were used for comparisons among the 3 intervention groups and between the 2 GA groups. The mean number of painful procedures was compared per site per infant per day, by using 1-way analysis of variance and post hoc Tukey test. Correlations between physiologic and behavioral items of the BPSN were calculated with the Pearson coefficient. Clinical site, GA group, number of painful procedures, and heel stick duration were examined as possible confounders on the impact of the NPIs on BPSN scores; none had a confound effect. The primary hypothesis was tested by using a repeated measures analysis. We used a random slopes regression model, which allowed each subject to have his or her own regression over the 5 heel sticks. Because of high interrater reliability, scores of the 4 raters were averaged and transformed logarithmically to satisfy the assumption of normally distributed residuals. For comparisons among the 3 phases, scores across the 5 heel sticks were also averaged. An α of 0.05 was considered significant.

RESULTS

Sample Characteristics and Number of Daily Procedures

Seventy-one infants were enrolled in the study and all but 1 had complete data.
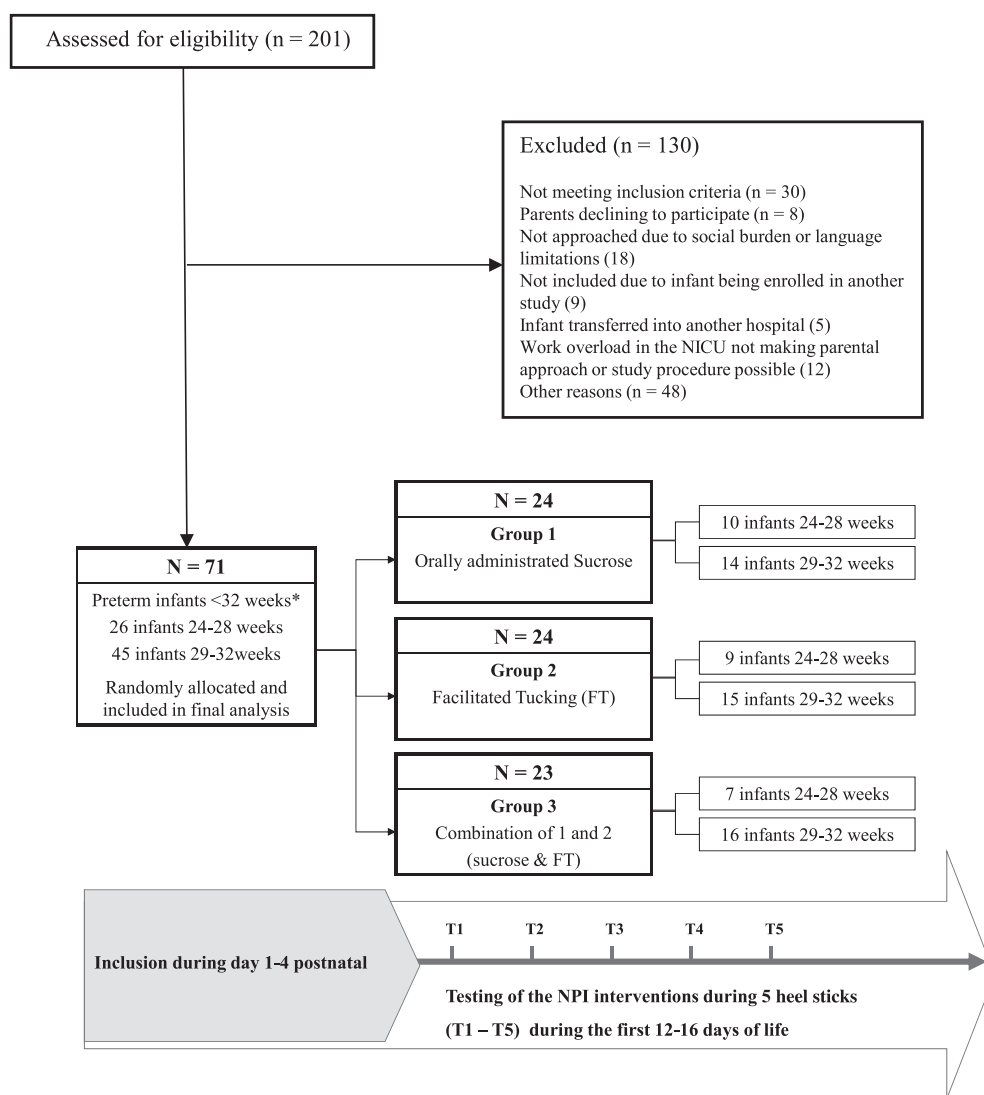
FIGURE 1
Flow diagram of the recruitment and randomization process.

TABLE 1 Demographic and Medical Characteristics of the Sample

| | | Total Sample | NPI Group | | | |
| | | | Sucrose | FT | Combination | |
		n (%)	n (%)	n (%)	n (%)	P, χ^2
Sample		71 (100)	24 (33.8)	24 (33.8)	23 (32.4)	.986
Gender						.983
	Female	32 (45.0)	11 (45.8)	11 (45.8)	10 (43.5)	
	Male	39 (55.0)	13 (54.2)	13 (54.2)	13 (56.5)	
Way of delivery						.805
	Normal birth	6 (8.5)	3 (12.5)	1 (4.2)	2.(8.7)	
	Planned cesarean delivery	16 (22.5)	4 (16.7)	6 (25.0)	6 (26.1)	
	Emergency cesarean delivery	49 (69.0)	17 (70.8)	17 (70.8)	15 (65.2)	
Number of birth						.462
	Single	50 (70.4)	19 (79.2)	14 (58.3)	17 (73.9)	
	One of twins	14 (19.7)	3 (12.5)	8 (33.3)	3 (13.0)	
	One of triplet	5 (7.0)	2 (8.3)	1 (4.2)	2 (8.7)	
	One of quadruplet	2 (2.8)	0 (0)	1 (4.2)	1 (4.3)	
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	P, Kruskal-Wallis
GA at birth, wk and d		29.24 (1.8)	28.95 (1.7)	29.20 (1.7)	29.5 (2)	.389
Duration of HS, min	HS 1	5.04 (5.2)	4.38 (3.8)	4.12 (3.6)	6.7 (7.4)	.687
	HS 2	4.75 (4.3)	4.54 (4.5)	4.67 (3.5)	5.04 (5.0)	.851
	HS 3	5.01 (4.8)	4.46 (3.1)	4.95 (4.7)	5.65 (6.2)	.878
	HS 4	4.73 (3.7)	5 (3.9)	5.33 (4.0)	3.83 (3)	.305
	HS 5	4.77 (3.6)	4.65 (3.7)	5.38 (4.1)	4.26 (2.9)	.751
Birth weight, g		1174.44 (337)	1080 (286)	1228 (397)	1217 (309)	.308
Apgar scores	1 min	5.97 (2.1)	5.65 (2.3)	5.46 (2.3)	6.83 (1.6)	.070
	5 min	7.58 (1.6)	7.21 (1.4)	7.29 (1.8)	8.26 (1.2)	.030[a]
No. of painful procedures per day		14.38 (7.4)	15 (10)	15 (9)	13 (9)	.012[a]
No. of HSs per infants per day		1.07 (1.2)	1 (1)	1 (1)	1 (1)	.539

HS, heel stick.

[a] The significance level is .05.

The fifth heel stick was missed for 1 infant. Figure 1 presents the flow diagram of the recruitment and randomization process based the Consolidated Standards of Reporting Trials guidelines.[42] The mean GA of the participating infants at birth was 29.2 (SD ±1.8) weeks, mean birth weight was 1174 g (SD ±337), and mean number of painful procedures during 0 to 14 days was 201 (SD ±104). Sample characteristics are summarized in Table 1.

Testing the Effectiveness of the NPIs

We compared the effectiveness of sucrose, FT, and their combination in reducing pain responses during heel stick procedures. Table 2 presents the mean scores of the T-BPSN, B-BPSN, and P-BPSN scores for the 3 intervention groups. The correlation between the infants' mean behavioral and physiologic pain sco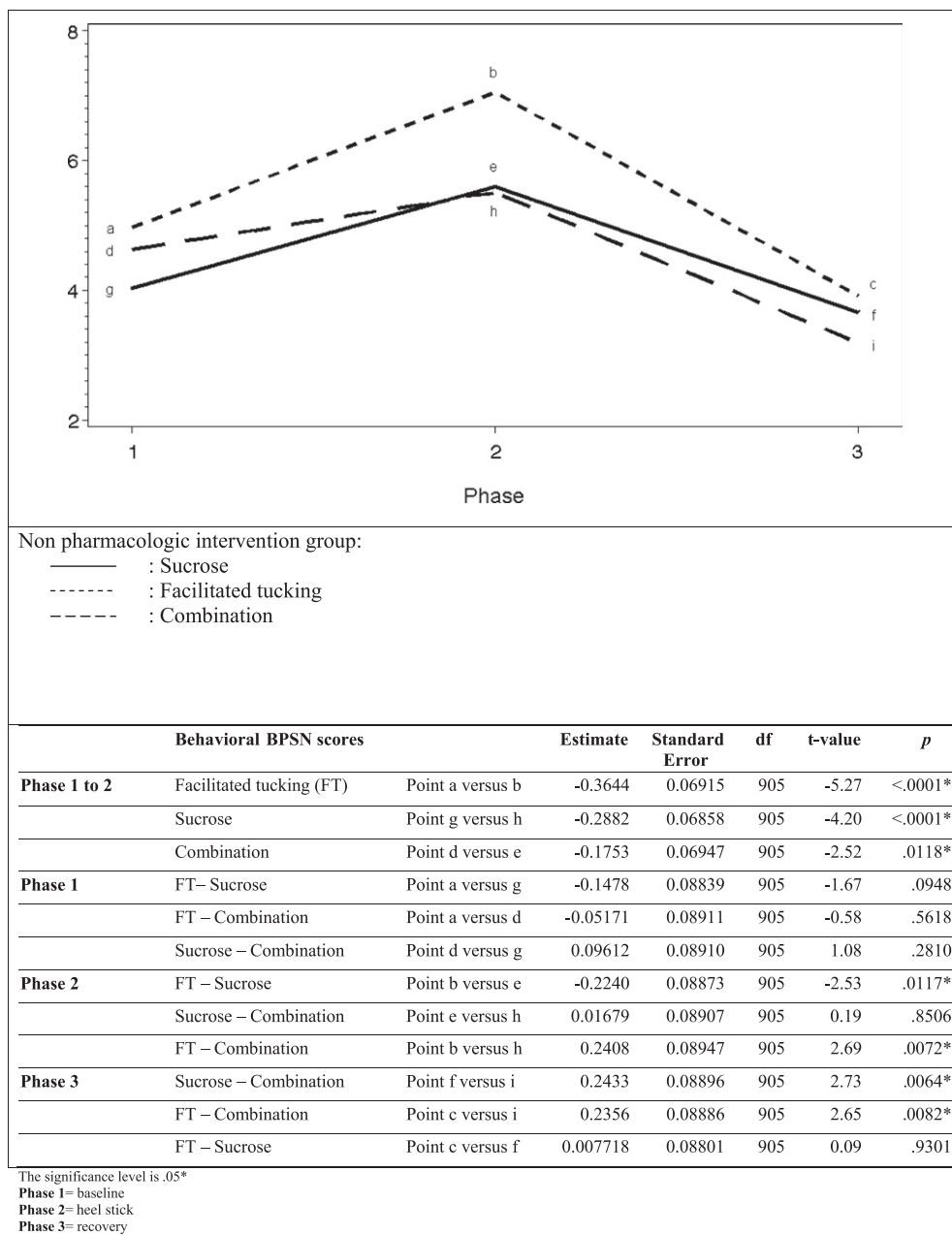res across the raters and phases of the heel stick was low ($r = 0.19$). Effectiveness of the interventions was examined by comparing mean pain responses over all heel sticks. Figure 2 presents the mean behavioral and physiologic pain scores over all 5 heel sticks as predicted by the regression analysis. During heel stick phase, the FT group had significantly higher B-BPSN ($P = .01$; .007) and P-BPSN ($P = .0002$; .003) scores than the sucrose and combination groups. During the recovery phase, there were no significant differences in P-BPSN scores, but the combination group had significantly lower B-BPSN scores than both the other groups ($P = .006$; .008).

Figure 3 shows how the B-BPSN and P-BPSN of heel stick phase scores for each group changes across the 5 heel sticks. P-BPSN scores for the FT group

TABLE 2 Mean Pain Scores for All Raters Across All Heel Sticks Measured by the BPSN

| | | NPI Group | | | | | |
| | | Sucrose | | FT | | Combination | |
Score	Phase	Mean	SD	Mean	SD	Mean	SD
T-BPSN	Baseline	4.03	2.08	4.99	3.24	4.62	2.88
	Heel stick	7.48	3.64	9.75	4.73	7.53	3.75
	Recovery	4.87	2.04	5.18	2.87	4.23	2.68
B-BPSN	Baseline	4.02	2.08	4.97	3.25	4.62	2.88
	Heel stick	5.58	2.95	7.01	3.59	5.49	2.95
	Recovery	3.66	1.71	3.90	2.47	3.18	2.24
P-BPSN	Baseline	0	0	0.04	0.22	0	0.03
	Heel stick	1.89	1.79	2.72	1.98	2.03	1.73
	Recovery	1.23	1.35	1.28	1.31	1.05	1.23

Non pharmacologic intervention group:
——— : Sucrose
------- : Facilitated tucking
– – – – : Combination

	Behavioral BPSN scores		Estimate	Standard Error	df	t-value	p
Phase 1 to 2	Facilitated tucking (FT)	Point a versus b	-0.3644	0.06915	905	-5.27	<.0001*
	Sucrose	Point g versus h	-0.2882	0.06858	905	-4.20	<.0001*
	Combination	Point d versus e	-0.1753	0.06947	905	-2.52	.0118*
Phase 1	FT– Sucrose	Point a versus g	-0.1478	0.08839	905	-1.67	.0948
	FT – Combination	Point a versus d	-0.05171	0.08911	905	-0.58	.5618
	Sucrose – Combination	Point d versus g	0.09612	0.08910	905	1.08	.2810
Phase 2	FT – Sucrose	Point b versus e	-0.2240	0.08873	905	-2.53	.0117*
	Sucrose – Combination	Point e versus h	0.01679	0.08907	905	0.19	.8506
	FT – Combination	Point b versus h	0.2408	0.08947	905	2.69	.0072*
Phase 3	Sucrose – Combination	Point f versus i	0.2433	0.08896	905	2.73	.0064*
	FT – Combination	Point c versus i	0.2356	0.08886	905	2.65	.0082*
	FT – Sucrose	Point c versus f	0.007718	0.08801	905	0.09	.9301

The significance level is .05*
Phase 1= baseline
Phase 2= heel stick
Phase 3= recovery

FIGURE 2
Slope testing NPI groups and phases.

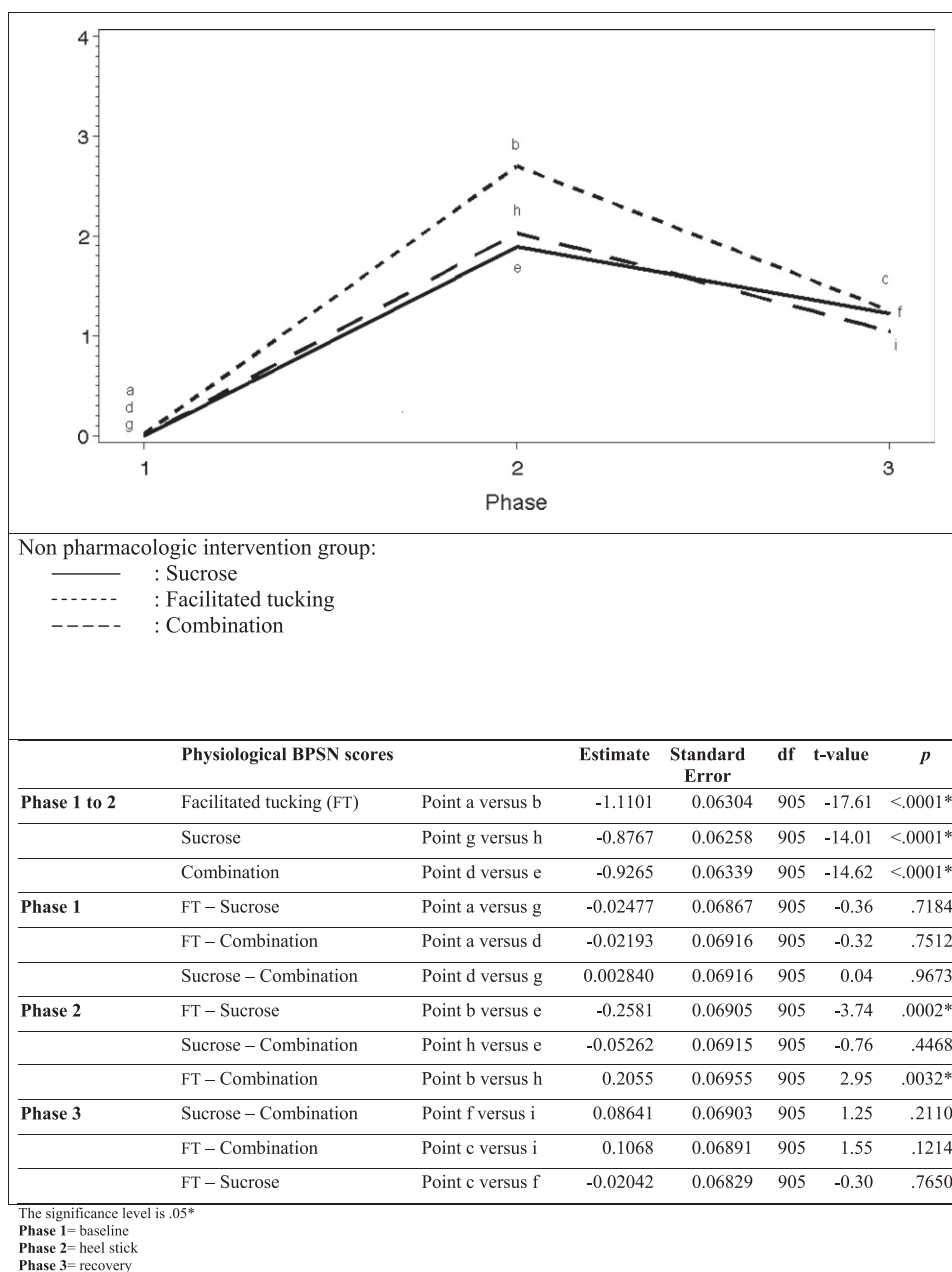increased significantly from heel stick 1 to 5 (P = .01), whereas there were no significant changes for the sucrose (P = .08) and combination (P = .43) groups. Overall, B-BPSN scores showed no significant changes over time, but the slope between heel stick 1 and 2 decreased significantly (P = .01) for the FT group and the slope between heel stick 4 and 5 increased significantly (P = .03) for the sucrose group.

In the sucrose and combination groups (n = 47), 21 infants (44.7%) received additional doses of sucrose. During heel stick phase, infants who received additional doses of sucrose had significantly higher B-BPSN scores than those who did not receive additional doses (P = .02), whereas their P-BPSN scores were not significantly different (P = .50). There were no significant differences in the recovery phase

behavioral (P = .85) or physiologic (P = .26) pain scores of infants who did or did not receive additional doses of sucrose.

DISCUSSION

The findings of this study show that either sucrose alone or sucrose in combination with FT remains effective across 5 heel sticks in preterm infants

Non pharmacologic intervention group:
———— : Sucrose
- - - - - - - : Facilitated tucking
— — — — : Combination

	Physiological BPSN scores		Estimate	Standard Error	df	t-value	p
Phase 1 to 2	Facilitated tucking (FT)	Point a versus b	-1.1101	0.06304	905	-17.61	<.0001*
	Sucrose	Point g versus h	-0.8767	0.06258	905	-14.01	<.0001*
	Combination	Point d versus e	-0.9265	0.06339	905	-14.62	<.0001*
Phase 1	FT – Sucrose	Point a versus g	-0.02477	0.06867	905	-0.36	.7184
	FT – Combination	Point a versus d	-0.02193	0.06916	905	-0.32	.7512
	Sucrose – Combination	Point d versus g	0.002840	0.06916	905	0.04	.9673
Phase 2	FT – Sucrose	Point b versus e	-0.2581	0.06905	905	-3.74	.0002*
	Sucrose – Combination	Point h versus e	-0.05262	0.06915	905	-0.76	.4468
	FT – Combination	Point b versus h	0.2055	0.06955	905	2.95	.0032*
Phase 3	Sucrose – Combination	Point f versus i	0.08641	0.06903	905	1.25	.2110
	FT – Combination	Point c versus i	0.1068	0.06891	905	1.55	.1214
	FT – Sucrose	Point c versus f	-0.02042	0.06829	905	-0.30	.7650

The significance level is .05*
Phase 1= baseline
Phase 2= heel stick
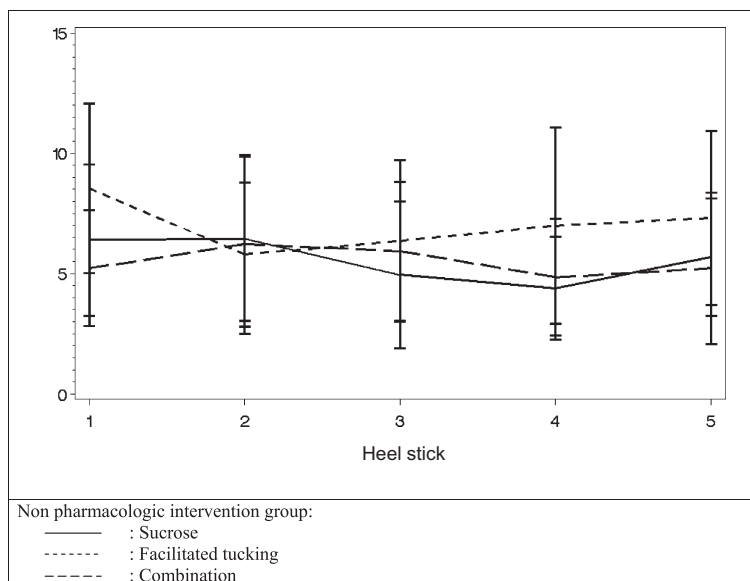**Phase 3**= recovery

FIGURE 2
(Continued)

of <32 weeks of gestation, whereas FT alone appears to be less effective. Furthermore, the results indicate that the combination of sucrose and FT may have additive pain-relieving effects during the recovery phase.

Our findings are consistent with previous studies regarding the efficacy of sucrose over time.[32–35] No sign of tolerance to the analgesic effects of sucrose was observed. It is important to note that FT was not lacking efficacy but rather was less effective than the 2 other interventions. The mean T-BPSN and B-BPSN scores during all phases were <10 points, even for infants in the FT group. Previous data suggest that a T-BPSN score ≤11 points or a B-BPSN score <8 points is considered as "no pain." The efficacy of FT has been described in several studies,[16,27–29,43] although these studies did not compare FT with other NPIs. Our study is the first to compare the efficacy of FT or sucrose across time with its efficacy when used in combination with sucrose.

Infants in the sucrose and combination groups who received additional doses of sucrose had significantly higher behavioral pain scores across all 5 heel

FIGURE 3
Pain scores over the heel sticks for phase 2 (heel stick) measured by the BPSN.
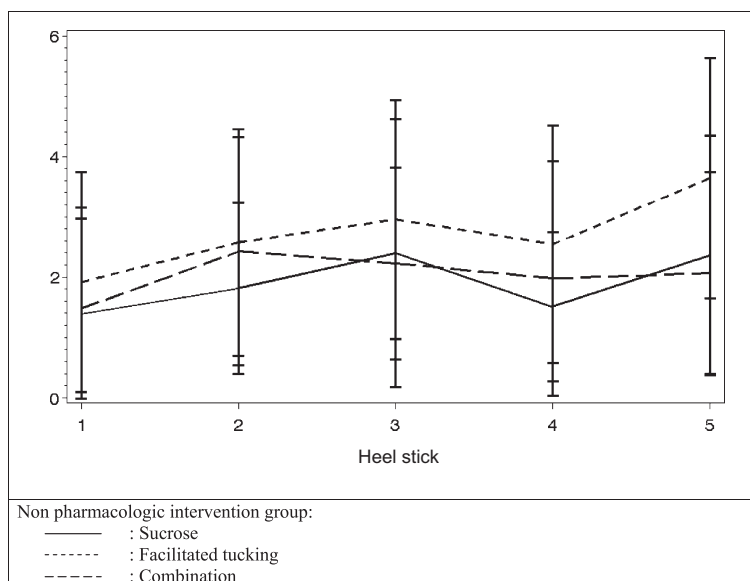
FIGURE 3
(Continued)

sticks. Regardless of these findings, there were no differences in recovery phase between infants who did or did not receive additional doses of sucrose. Our findings correspond to those of Johnston et al,[44] who examined the effects of repeated doses of sucrose in preterm infants receiving sucrose solution or sterile water either 2 minutes before, just before, or 2 minutes after the heel stick. Their results showed that repeated doses of sucrose, at 2-minute intervals, increases the analgesic effect in preterm infants.

Another previous randomized trial questions the analgesic efficacy of sucrose, based on EEG and electromyogram recordings in healthy term newborns (37–43 weeks), receiving sucrose or sterile water 2 minutes before a heel stick. Slater et al[45] found no differences in nociceptive brain activity or in the magnitude or latency of the spinal nociceptive reflexes after the heel stick, between infants who received sucrose and those who received water, although Premature Infant Pain Profile scores and pain-related facial expressions were significantly reduced in the sucrose-treated infants. These findings contradict data from a large body of literature supporting the analgesic efficacy of sucrose or other sweet solutions. Moreover, there are several methodological concerns related to the Slater et al study[45] that make it seem premature to conclude that sucrose is ineffective based only on its findings.[46]

Although the differences between the sucrose and combination groups in behavioral and physiologic scores during the recovery phase were statistically significant, the magnitude of these differences is probably not clinically meaningful. This poses a critical question related to the cost-effectiveness of this intervention. FT is a time-consuming intervention, which could be used as a procedure to enhance parenting or bonding, but needs to be questioned as a nursing intervention. Although there are promising findings regarding FT as an effective NPI,[30] the challenges of this specific intervention in nursing practice need to be reconsidered in an environment characterized by economic constraints.[47]

The methodological strengths of this study are the strategies undertaken to enhance the internal validity of these results. The use of 4 trained and experienced nurses to perform pain assessment, the randomization of the sequences to blind the raters to the phase of the procedure, and the thorough elaboration of each single video sequence reduced potential biases.

There are some methodological limitations in this study, however. The raters could be only partially blinded to the NPI group because the clear visibility of the FT procedure could cause possible bias. Nevertheless, raters did not know if the infant was in the FT-only group or in the combination group. A further limitation was the exclusion of a no-intervention control group owing to ethical considerations. Long-term consequences of repeated doses of sucrose were investigated in a small number of studies, but there are no conclusive findings regarding the risk for poor neurologic outcomes. In the current study, we did not follow infants for neurologic outcomes. Further research regarding consequences of prolonged use of sucrose is needed. Another limitation of this study was that although the original protocol was for infants in the FT-only group to receive FT for all painful procedures during the time they were enrolled in the study, staff shortages made it impossible for nurses to implement this procedure consistently for nonstudy painful procedures.[47] Consequently, these infants were treated with oral sucrose 20% (the standard of care in the units) for nonstudy procedures. The impact that this had on the efficacy of FT alone is unknown but it is possible that consistent use of this procedure may have altered its efficacy.

CONCLUSIONS

The results of this randomized controlled trial provide evidence that oral sucrose alone or combined with FT remains effective in reducing heel stick-related pain over time in preterm infants (24–32 weeks), during the critical phase of the first 14 days of NICU stay. These findings have important clinical implications for the management of pain in preterm infants of low GA, who are at risk for a high frequency of painful procedures during their NICU stay. During the recovery phase of the heel stick, the combination of FT and oral sucrose was slightly more effective in reducing pain than sucrose alone. This difference was not, however, clinically meaningful, particularly given the additional resources needed to implement the combined intervention.

REFERENCES

1. Cignacco E, Hamers J, van Lingen RA, et al. Neonatal procedural pain exposure and pain management in ventilated preterm infants during the first 14 days of life. *Swiss Med Wkly*. 2009;139(15–16):226–232

2. Simons SH, van Dijk M, Anand KS, Roofthooft D, van Lingen RA, Tibboel D. Do we still hurt newborn babies? A prospective study of procedural pain and analgesia in neonates. *Arch Pediatr Adolesc Med*. 2003;157(11):1058–1064

3. Carbajal R, Rousset A, Danan C, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. *JAMA*. 2008;300(1):60–70

4. Johnston C, Barrington KJ, Taddio A, Carbajal R, Filion F. Pain in Canadian NICUs: have we improved over the past 12 years? *Clin J Pain*. 2011;27(3):225–232

5. Stevens B, McGrath P, Ballantyne M, et al. Influence of risk of neurological impairment and procedure invasiveness on health professionals' management of procedural pain in neonates. *Eur J Pain*. 2010;14(7):735–741

6. Anand KJS. Pain, plasticity, and premature birth: a prescription for permanent suffering? *Nat Med*. 2000;6(9):971–973

7. Anand KJS, Scalzo FM. Can adverse neonatal experiences alter brain development and subsequent behavior? *Biol Neonate*. 2000;77(2):69–82

8. Grunau RE, Tu MT. Long-term consequences of pain in human neonates. In: Anand KJS, Stevens B, McGrath P, eds. *Pain in Neonates and Infants*. 3rd ed. Edinburgh, UK: Elsevir; 2007:44–45

9. Badr LK, Abdallah B, Hawari M, et al. Determinants of premature infant pain responses to heel sticks. *Pediatr Nurs*. 2010;36(3):129–136

10. Anand KJS, Barton BA, McIntosh N, et al. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates. *Arch Pediatr Adolesc Med*. 1999;153(4):331–338

11. Simons SH, van Dijk M, van Lingen RA, et al. Routine morphine infusion in preterm newborns who received ventilatory support: a randomized controlled trial. *JAMA*. 2003;290(18):2419–2427

12. Anand KJS, Hall RW, Desai N, et al; NEOPAIN Trial Investigators Group. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. *Lancet*. 2004;363(9422):1673–1682

13. Batton DG, Barrington KJ, Wallman C; American Academy of Pediatrics Committee on Fetus and Newborn; ; American Academy

of Pediatrics Section on Surgery; ; Canadian Paediatric Society Fetus and Newborn Committee. Prevention and management of pain in the neonate: an update. *Pediatrics.* 2006;118(5):2231–2241

14. Anand KJS; International Evidence-Based Group for Neonatal Pain. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med.* 2001;155(2):173–180

15. Cignacco E, Hamers JP, Stoffel L, et al. The efficacy of non-pharmacological interventions in the management of procedural pain in preterm and term neonates. A systematic literature review. *Eur J Pain.* 2007;11(2): 139–152

16. Axelin A, Salanterä S, Lehtonen L. 'Facilitated tucking by parents' in pain management of preterm infants—a randomized crossover trial. *Early Hum Dev.* 2006;82(4): 241–247

17. Stevens B, Yamada J, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev.* 2010;(1):CD001069

18. Bellieni CV, Buonocore G, Nenci A, Franci N, Cordelli DM, Bagnoli F. Sensorial saturation: an effective analgesic tool for heel-prick in preterm infants: a prospective randomized trial. *Biol Neonate.* 2001;80(1):15–18

19. Stevens B, Gibbins S, Franck LS. Treatment of pain in the neonatal intensive care unit. *Pediatr Clin North Am.* 2000;47(3):633–650

20. Als H, Gilkerson L, Duffy FH, et al. A three-center, randomized, controlled trial of individualized developmental care for very low birth weight preterm infants: medical, neurodevelopmental, parenting, and caregiving effects. *J Dev Behav Pediatr.* 2003;24 (6):399–408

21. Carbajal R, Chauvet X, Couderc S, Olivier-Martin M. Randomised trial of analgesic effects of sucrose, glucose, and pacifiers in term neonates. *BMJ.* 1999;319(7222):1393–1397

22. Lefrak L, Burch K, Caravantes R, et al. Sucrose analgesia: identifying potentially better practices. *Pediatrics.* 2006;118(suppl 2):S197–S202

23. Blass EM, Watt LB. Suckling- and sucrose-induced analgesia in human newborns. *Pain.* 1999;83(3):611–623

24. Gibbins S, Stevens B, Hodnett E, Pinelli J, Ohlsson A, Darlington G. Efficacy and safety of sucrose for procedural pain relief in preterm and term neonates. *Nurs Res.* 2002;51(6):375–382

25. Bach FW. Beta-endorphin in the brain. A role in nociception. *Acta Anaesthesiol Scand.* 1997;41(1 pt 2):133–140

26. Blass EM, Ciaramitaro V. A new look at some old mechanisms in human newborns: taste and tactile determinants of state, affect, and action. *Monogr Soc Res Child Dev.* 1994;59(1):I–V, 1–81

27. Corff KE, Seideman R, Venkataraman PS, Lutes L, Yates B. Facilitated tucking: a non-pharmacologic comfort measure for pain in preterm neonates. *J Obstet Gynecol Neonatal Nurs.* 1995;24(2):143–147

28. Ward-Larson C, Horn RA, Gosnell F. The efficacy of facilitated tucking for relieving procedural pain of endotracheal suctioning in very low birthweight infants. *MCN Am J Matern Child Nurs.* 2004;29(3):151–156, quiz 157–158

29. Huang CM, Tung WS, Kuo LL, Ying-Ju C. Comparison of pain responses of premature infants to the heelstick between containment and swaddling. *J Nurs Res.* 2004;12(1): 31–40

30. Obeidat H, Kahalaf I, Callister LC, Froelicher ES. Use of facilitated tucking for non-pharmacological pain management in preterm infants: a systematic review. *J Perinat Neonatal Nurs.* 2009;23(4):372–377

31. Axelin A, Salanterä S, Kirjavainen J, Lehtonen L. Oral glucose and parental holding preferable to opioid in pain management in preterm infants. *Clin J Pain.* 2009;25(2):138–145

32. Johnston CC, Filion F, Snider L, et al. Routine sucrose analgesia during the first week of life in neonates younger than 31 weeks' postconceptional age. *Pediatrics.* 2002;110(3):523–528

33. Stevens B, Yamada J, Beyene J, et al. Consistent management of repeated procedural pain with sucrose in preterm neonates: is it effective and safe for repeated use over time? *Clin J Pain.* 2005;21(6):543–548

34. Harrison D, Loughnan P, Manias E, Gordon I, Johnston L. Repeated doses of sucrose in infants continue to reduce procedural pain during prolonged hospitalizations. *Nurs Res.* 2009;58(6):427–434

35. Gaspardo CM, Miyase CI, Chimello JT, Martinez FE, Martins Linhares MB. Is pain relief equally efficacious and free of side effects with repeated doses of oral sucrose in preterm neonates? *Pain.* 2008;137(1):16–25

36. Taddio A, Katz J. The effects of early pain experience in neonates on pain responses in infancy and childhood. *Paediatr Drugs.* 2005;7(4):245–257

37. Bellieni CV, Cordelli DM, Marchi S, et al. Sensorial saturation for neonatal analgesia. *Clin J Pain.* 2007;23(3):219–221

38. Chermont AG, Falcão LF, de Souza Silva EH, de Cássia Xavier Balda R, Guinsburg R. Skin-to-skin contact and/or oral 25% dextrose for procedural pain relief for term newborn infants. *Pediatrics.* 2009;124(6). Available at: www.pediatrics.org/cgi/content/full/124/6/e1101

39. Cignacco E, Denhaerynck K, Nelle M, et al. Variability in pain response to a non-pharmacological intervention across repeated routine pain exposure in preterm infants: a feasibility study. *Acta Paediatr.* 2009;98(5):842–846

40. Cignacco E, Mueller R, Hamers JP, Gessler P. Pain assessment in the neonate using the Bernese Pain Scale for Neonates. *Early Hum Dev.* 2004;78(2):125–131

41. Brunner C, Nelle M, Stoffel L, et al. *Revalidation of the Bernese Pain Scale for Neonates.* Basel, Switzerland: University of Basel; 2010

42. Moher D, Hopewell S, Schulz KF, et al; Consolidated Standards of Reporting Trials Group. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol.* 2010;63(8):e1–e37

43. Hill S, Engle S, Jorgensen J, Kralik A, Whitman K. Effects of facilitated tucking during routine care of infants born preterm. *Pediatr Phys Ther.* 2005;17(2):158–163

44. Johnston CC, Stremler R, Horton L, Friedman A. Effect of repeated doses of sucrose during heel stick procedure in preterm neonates. *Biol Neonate.* 1999;75(3):160–166

45. Slater R, Cornelissen L, Fabrizi L, et al. Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial. *Lancet.* 2010;376 (9748):1225–1232

46. Lasky RE, van Drongelen W. Is sucrose an effective analgesic for newborn babies? *Lancet.* 2010;376(9748):1201–1203

47. Cignacco E, Axelin A, Stoffel L, et al. Facilitated tucking as a non-pharmacological intervention for neonatal pain relief: is it clinically feasible? *Acta Paediatr.* 2010, Epub ahead of print. DOI: 10.1111/j.1651-2227.2010.01941.x.

Oral Sucrose and "Facilitated Tucking" for Repeated Pain Relief in Preterms: A Randomized Controlled Trial

Eva L. Cignacco, Gila Sellam, Lillian Stoffel, Roland Gerull, Mathias Nelle, Kanwaljeet J. S. Anand and Sandra Engberg

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/early/2012/01/04/peds.2011-1879
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Therapeutics & Toxicology** http://pediatrics.aappublications.org/cgi/collection/therapeutics_and_toxicology
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://pediatrics.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://pediatrics.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™