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ARTICLE

Breastfeeding or Oral Sucrose Solution in Term Neonates Receiving Heel Lance: A Randomized, Controlled Trial

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What's Known on This Subject

Breastfeeding and oral sucrose have shown an analgesic effect in newborn infants for minor painful procedures.

What This Study Adds

Breastfeeding provides superior analgesia to oral sucrose in term neonates during heel lance. The analgesic properties of breastfeeding also prevent tachycardia and the decrease in oxygen saturation that usually accompany blood sampling.

ABSTRACT

OBJECTIVE. The purpose of this work was to compare the efficacy of breastfeeding versus orally administered sucrose solution in reducing pain response during blood sampling through heel lance.

METHODS. We conducted an open-label, randomized, controlled trial at a neonatal unit of a public hospital in northern Italy on 101 term neonates undergoing heel lance with an automated piercing device for routine neonatal screening for congenital disorders. Newborn infants were randomly assigned to breastfeeding during blood sampling or to the oral administration of 1 mL of 25% sucrose solution. We validated the multidimensional acute pain rating scale of the Premature Infant Pain Profile, heart rate increase, oxygen saturation decrease, crying behavior (duration of first cry, cry percentage in 2 minutes, and during blood sampling), duration of sampling, and the number of performed heel lances.

RESULTS. Median Premature Infant Pain Profile scores were lower in the breastfeeding group (3.0) than in the sucrose-solution group (8.5), and the median group difference was −5.0. The median heart rate increase, oxygen saturation decrease, and duration of first cry for the breastfeeding group were, respectively, 13.0, −1, and 3 and for sucrose group were 22, −3, and 21. Medians were significantly different between the groups. There were no significant differences in the sampling duration and numbers of heel lances.

CONCLUSIONS. This study suggests that breastfeeding provides superior analgesia for heel lance compared with oral sucrose in term neonates. *Pediatrics* 2008;122:e716–e721

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This trial has been registered at www.clinicaltrials.gov (identifier NCT00482560).

Key Words
pain, neonates, sucrose, breastfeeding, heel lance

Abbreviation
PIPP—Premature Infant Pain Profile

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HEEL LANCE FOR neonatal screening is the most frequent painful maneuver in healthy neonates in neonatal units. It is used worldwide to identify recognizable biochemical markers of specific congenital disorders that can be precociously treated. Until recently, it was believed that infants and young children could not feel pain because of the immaturity of the central nervous system. However, now we know that anatomic, physiologic, and neurochemical structures that convey pain are well developed weeks before birth.[1] There is some evidence that suggests an increased sensitivity to pain in neonates compared with older age groups probably attributable to not fully functional pain modulation systems.[2]

Pain stimuli in neonates generate short- and long-term effects. Short-term effects consist of physiologic responses (increase in heart and breath rate, decrease in oxygen saturation, and increase in intracranial pressure) and behavioral responses (brow bulge, eye squeeze, nasolabial furrow, and cry). Although long-term effects are less easy to prove, some studies on circumcised boys showed that newborn early pain experience can alter pain response in later infancy.[3] Some studies have reported a reduction in pain response from minor procedures for pacifier,[4,5] multisensory stimulation,[6] skin-to-skin contact,[7] venapuncture versus heel lances,[8–10] breast milk,[11,12] and leg massage.[13]

In a recent systematic review, orally administered sucrose was effective in reducing behavioral pain indicators (total cry duration, mean percentage of crying time, duration of first cry, and facial action) and composite multidimensional scale scores in term and preterm neonates.[14] Premature Infant Pain Profile (PIPP) scores were

significantly reduced in infants who were given sucrose compared with the control group (weighted mean difference at 30 seconds after heel lance: −1.64 [range: −2.47 to −0.81]). There were no significant differences between changes in heart rate for infants given sucrose compared with the control group (weighted mean difference: 0.90 [range: −5.81 to 7.61]). Although sucrose solutions have been recommended in evidence-based guidelines, there is inconsistency in the dose of sucrose that is effective.[15,16]

Another systematic review evaluated the effectiveness of breastfeeding or supplemental breast milk in reducing procedural pain in neonates. PIPP scores were significantly different between the breastfeeding group and the placebo group (weighted mean difference: −6 [range: −7 to −4]), but these scores were not so different when compared with the glucose plus pacifier group (weighted mean difference: 1.30 [range: 0.05 to 2.56]).[12]

Our purpose was to investigate the analgesic effect of breastfeeding versus oral sucrose solution during blood sampling through heel lance in healthy term neonates.

METHODS

Protocol

The study was performed in the neonatal unit of Agnelli Hospital. The inclusion criteria were as follows: term neonates (37–42 weeks of gestation) who underwent heel lance for routine neonatal screening, age ≥60 hours, no feeding occurred in the previous 30 minutes, and Apgar score of ≥7 at 5 minutes. Exclusion criteria were as follows: at-risk pregnancy, medical instability, birth in general anesthesia, maternal use of opioids, administration of naloxone or phenobarbital in the previous 48 hours, and artificial feeding.

Written, informed consent was asked of parents during consultation by the 9 pediatricians of the staff within 12 hours after birth. Study protocol and informed-consent forms were approved by the local ethics committee.

Intervention

Participating neonates were randomly assigned to the breastfeeding group or oral sucrose-solution group and were taken to a quiet nursery room for heel lance without a pacifier. The heel was warmed up by a pad at 40°C 2 minutes before heel lance. Oxygen saturation and heart rate were monitored by a pulse oximeter (Radical MasimoSet Datascope, Masimo Corporation, Irvine, CA) set on the infant's hand. In 1 group, neonates were held in the mother's arms and breastfed until the operator observed a continuous active suction (large amount of areola in the mouth, flanged lips, and active jaw movements). In the other group, 2 minutes before heel lance, a bolus of 1 mL of 25% sucrose solution was administered through a sterile syringe in the mouth to neonates laid on a changing table. Blood sampling was performed in a standardized manner by experienced pediatric nurses through an automated piercing device set at level 3 (Accu-Chek Softclix Pro, Roche Diagnostics, Burgess Hill, West Sussex, UK) obtaining 4 dried spots of blood collected on a filter paper card. If the collected sample was not enough to complete all of the dried spots on the filter card, a new heel lance was practiced in few seconds. In this case, neonates were assessed for PIPP scale measure only after the first heel lance; secondary outcomes were evaluated during the whole sampling. A second pediatric nurse administered a pain scale and recorded the duration of blood sampling, collateral effects, and infant's voice for 2 minutes after the heel lance. Infants' voices were collected by a digital voice recorder (Olympus VN-240PC Digital Voice Recorder, Olympus Imaging Europe GMBH, Hamburg, Germany), and voice analysis was performed through the Olympus Original Wave Player 2.0.2 software (Olympus Imaging Europe GMBH, Hamburg, Germany). The procedure lasted between 5 and 7 minutes. Operators were among the pediatric staff of the neonatal unit, and 1 year before the beginning of the study, an expert in pediatric pain therapy trained them with respect to the use of the PIPP scale. This scale entered the daily routine of the neonatal unit for minor procedures throughout the period before the study. Two assistants, blind to allocation, independently assessed the recorded voices for the outcomes regarding cry behavior.

The primary outcome of the study was to evaluate pain induced by heel lance in newborns through the PIPP scale. Secondary outcome measures were as follows: heart rate increase, oxygen saturation decrease, duration of first cry, percentage of crying time in 2 minutes after heel lance and during blood sampling, and the numbers of heel lances performed for each blood sampling. Duration of first cry was defined as audible vocalization that lasted ≥5 seconds without a 5-second quiet interval.

Pain Scale

The PIPP scale is a validated 7-indicator scale for the assessment of acute pain in preterm and term infants.[17] It measures gestational age, behavioral state, heart rate, oxygen saturation, and 3 facial actions (brow bulge, eye squeeze, and nasolabial furrow). Score ranges from 0 (no pain) to 21 (maximum pain). Because the first item is gestational age, in our study the eligibility criteria included only term neonates, so the maximum rate on the PIPP scale was 18. Validation of the PIPP score showed an ability to differentiate painful from not painful or baseline events ($F = 48$; $P = .0001$), with interrater reliability coefficients of .93 to .96, whereas the intrarater reliability coefficients for individual events were .94 to .98. More recent studies showed similar results.[18]

Sample Size

A sample size of 50 infants in each group was calculated to achieve 80% power to detect a 2-point difference in the PIPP scale (assuming SD = 3.5, corresponding with a reduction of 0.6 SD) between breastfeeding and sucrose, with a significance level of .05 (2-tailed).

Randomization

Newborns were allocated to each group according to a computer-generated randomization list created by an independent statistician and masked to investigators.

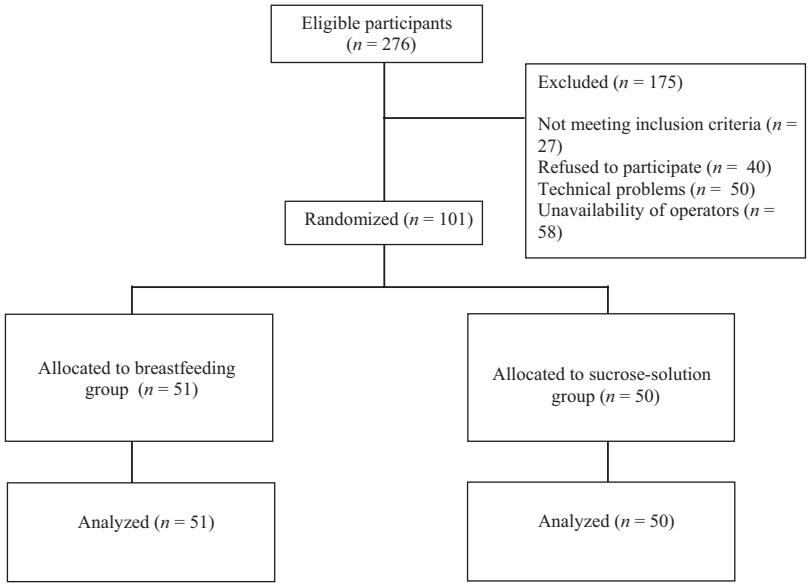

FIGURE 1
Trial profile and participant flow.

Random allocation was made in variable blocks. Treatment allocations were inserted in opaque sealed envelopes numbered 1 to 101. Envelopes were opened sequentially by the pediatric nurse who performed blood sampling, under the control of a supervisor, who ensured that there was no bias of contamination in the randomization process. All of the pediatric nurses and mothers were not blinded to the treatment assignment.

Statistical Analysis

The Wilcoxon-Mann-Whitney test was used to compare nonparametric data between groups. The independent-samples *t* test and χ^2 test were used for the normally distributed variable and for categorical variables, respectively. Subgroup analyses were performed according to protocol by birth weight, gender, maternal age, number of previous children, and maternal education.

The difference in the heart rate and oxygen saturation between baseline and 30 seconds after blood sampling was calculated for each subject. Mean intragroup differences were compared with Wilcoxon signed rank-sum test. All of the analyses were conducted on an intention-to-treat basis with SAS 8.02 (SAS Institute, Inc, Cary, NC). Confidence intervals of the median difference between groups were estimated with Confidence Intervals Analyses Software (*Statistics with Confidence*, 2nd Edition, 2000, BMJ Books, London, United Kingdom).

RESULTS

From January to April 2007, a total of 276 infants were eligible for inclusion. Subjects whose parents did not give informed consent ($n = 40$) and those who did not met inclusion criteria ($n = 27$) were excluded. Because of technical problems or unavailability of the observer, 108 infants were also not evaluated. The remaining 101 subjects were equally distributed between the 2 groups (Fig 1).

Table 1 summarizes the perinatal characteristics at the baseline for the intention-to-treat population. The 2 groups were balanced with regard to some maternal and newborn characteristics.

TABLE 1 **Maternal and Neonatal Infant Baseline Characteristics**

Baseline Characteristics	Breastfeeding Group ($n = 51$)	Sucrose-Solution Group ($n = 50$)
Maternal characteristics		
Maternal age, mean (SD), y	30.9 (4.5)	30.9 (4.6)
No. of previous children, median (range)	1 (0–3)	0 (0–2)
Education, *n* (%)		
Secondary school	43 (84.3)	40 (80.0)
Higher education	6 (11.7)	6 (12.0)
Not evaluable	2 (4.0)	4 (8.0)
Newborn characteristics		
Gestational age, mean (SD), wk	39.3 (1.2)	39.4 (1.1)
Postnatal age, mean (SD), d	3.5 (0.8)	3.4 (0.7)
Birth weight, mean (SD), g	3318.3 (402.2)	3307.35 (429.6)
Weight, mean (SD), g	3121.0 (413.2)	3099.3 (423.9)
Apgar score at 5 min, median (range)	10 (9–10)	10 (9–10)
Male, *n* (%)	24 (47.0)	29 (58.0)
Cesarean deliveries, *n* (%)	14 (27.4)	17 (34.0)
Heart rate, mean (SD)	129.8 (15.7)	123.6 (15.9)
Oxygen saturation, mean (SD)	98.2 (1.7)	98.7 (1.6)

The median pain score for each group, as well as the heart rate increase, oxygen saturation decrease, crying time, sampling duration, and between-group median differences are shown in Table 2. For the primary and secondary end points, the breastfed group of infants achieved a significant improvement compared with the oral sucrose-solution group subjects. The median reduction for the primary end points was ~5 points of the PIPP score.

There were no differences in the sampling duration and numbers of heel lances. There were no significantly different effects of treatments for all of the outcomes by analyzed subgroups: birth weight, gender, maternal age, number of previous children, and maternal education (data not shown). No adverse effects were noted in any

TABLE 2 **Measures of PIPP Scale and Other Outcomes**

Variable	Breastfeeding Group ($n = 51$)	Sucrose-Solution Group ($n = 50$)	Median Group Difference (Breastfeeding − Sucrose Scores)	95% Confidence Intervals	*P*
PIPP scale, median (range)	3.0 (0.0 to 14.0)	8.5 (0.0–16.0)	−5.0	7.0 to −3.0	<.0001
Increase in heart rate from baseline to 30 s after the start of the procedure, median (range)	13.0 (−12.0 to 54.0)	22.0 (−32.0 to 65.0)	−9.0	−15.0 to −3.0	.005
Decrease in oxygen saturation from baseline to 30 s after the start of the procedure, median (range)	−1 (−14.0 to 2.0)	−3.0 (−30.0 to 1.0)	2.0	1.0 to 3.0	.001
Crying time, median (range), s					
First cry	3.0 (0.0 to 120.0)	21.0 (0.0 to 120.0)	−10.0	−32.0 to −3.0	.0004
Percentage in 2 min	4.0 (0.0 to 100.0)	45.5 (0.0 to 100.0)	−29.0	−46.0 to −11.0	<.0001
Percentage in blood sampling	8.0 (0.0 to 100.0)	56.5 (0.0 to 100.0)	−25.0	−51.0 to −7.0	.0003
Sampling duration, mean (SD), s	62.9 (27.1)	61.2 (26.9)	1.6	−9.0 to 12.3	.75
No. of heel lances, *n* (%)					.77
1	45 (88.2)	43 (86.0)			
2	6 (11.8)	7 (14.0)			

infant, and only in 1 case of breastfeeding was a detachment of infant from the mother's breast recorded.

Median quartile distribution of the baseline and maximum heart rate (Fig 2), as well as baseline and minimum oxygen saturation (Fig 3), are represented for the breastfeeding and sucrose groups. Mean intragroup differences between baseline and after heel lancing evaluation were significantly different in both groups ($P <$ .0001 in each comparison). Two neonates in the breastfeeding group had desaturations slightly <85%, and 1 neonate in the sucrose group had down to 95%, but these episodes were transient and receded spontaneously without any interventions of operators.

DISCUSSION

This study suggests that breastfeeding provides superior analgesia to oral sucrose in term neonates during heel lance. We detected a 5-point difference in terms of PIPP median score (scale range: 0–18). The median PIPP score of ~3 points in the breastfeeding group should be considered a minimal pain response. Moreover, the heart rate increase and oxygen saturation decrease that normally accompany this procedure were significantly lower (P = .005 and .001, respectively) in the breastfeeding group as compared with the sucrose group, and the outcomes regarding crying behavior were better in the first group.

Actually we cannot discriminate the role of the different components of breastfeeding or the mechanisms behind the analgesic effect of sucrose solutions: skin-to-skin contact, holding, orotactile stimulation because of oral liquid, or orogustatory stimulation.[19–21] Pain relief by sweet solutions is usually attributed to an endogenous opioid mechanism. In newborn rats, pain threshold is doubled by oral sucrose infusion, and this effect is fully reversed by naltrexone, suggesting a relationship between sucrose and endogenous opioids.[22] However, this hypothesis is not confirmed in human newborns. In a recent study by Gradin et al,[23] the administration of an opioid antagonist such as naloxone does not decrease the analgesic effect of orally administered glucose given before blood sampling: these results disagree with the role of an endogenous opioid mechanism in neonates. Therefore, at the present time, we are far from identifying the analgesic mechanisms behind the analgesic effect

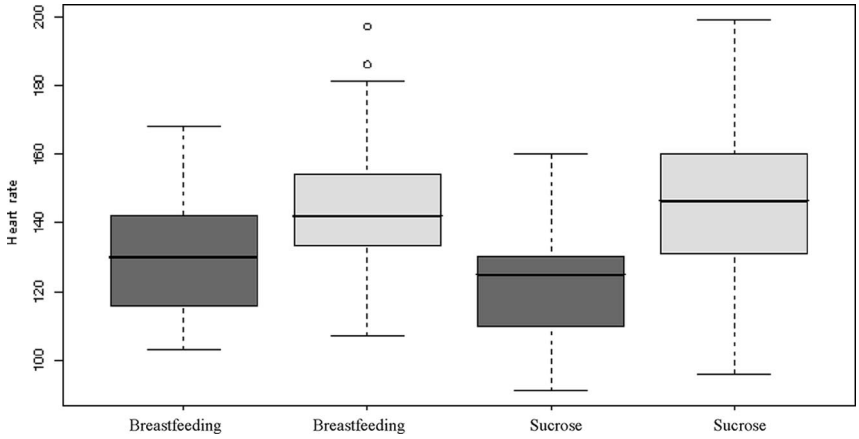

FIGURE 2
Comparing baseline heart rate and maximum heart rate saturation between groups.

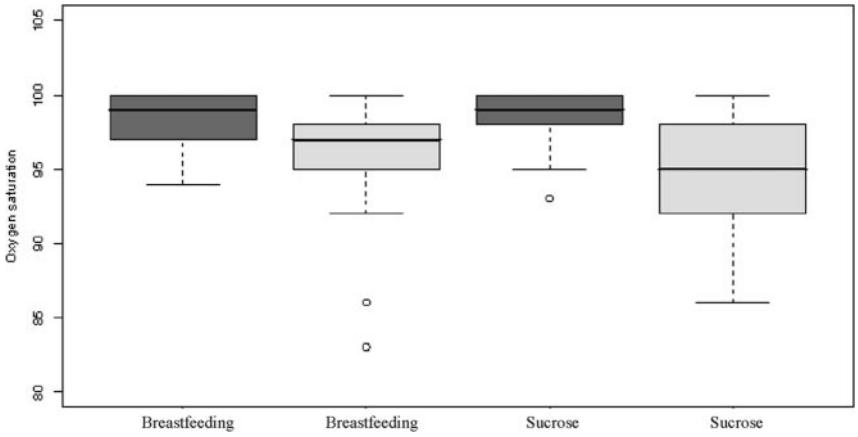

FIGURE 3
Comparing baseline oxygen saturation and minimum oxygen saturation between groups.

of sweet solutions, and we can only detect its protective effect on pain response.

Several studies have assessed the efficacy of noninvasive techniques in reducing pain from minor procedures in newborns. A Cochrane systematic review of trials comparing sucrose solution with a control (water, pacifier, or positioning or containing) found 21 trials with different methodologic quality.[14] Pain scores, pooled across 3 studies, were significantly reduced in infants who were given sucrose (weighted PIPP mean difference: −1.64 [range: −2.47 to −0.81] at a dose range 0.012 to 0.120 g) compared with a placebo control group. Breastfeeding also showed a significant analgesic effect.[24] A recent systematic review analyzed 11 controlled trials showing a superior efficacy of both breastfeeding and breast milk compared with placebo, positioning, or no intervention.[12] The randomized trial by Carbajal et al,[20] selected in this review, found similar effectiveness of breastfeeding (median PIPP score: 4.5 [range: 2.25–8.00]) and the administration of 30% glucose solution plus pacifier (median PIPP score: 4 [range: 1–6]). In this study, blood sampling was performed through venapuncture, and a pacifier was used together with a sucrose solution. Recently, Gray et al[7] reported a crying and grimacy reduction by 91% and 84%, respectively, in held and breastfed neonates as compared with a swaddled control group undergoing heel lance. Breastfeeding also prevented tachycardia induced by blood collection. Phillips et al[21] studied 3 groups of newborns undergoing blood collection with regard to crying behavior: breastfeeding, pacifier while held by mothers, and pacifier while held by an assistant. They found that breastfeeding and maternal holding reduce crying behavior during heel stick procedures.

PIPP scale indicators include changes in heart rate and oxygen saturation, rated on a 4-point scale (0–3) for a possible total score of 0 to 18 in term neonates. Among secondary outcomes we also added heart rate increase and oxygen saturation decrease as absolute values to evaluate, as shown in previous studies,[24] whether breastfeeding was the only analgesic technique able to prevent tachycardia and desaturation as compared with sucrose solutions.

STUDY LIMITATIONS

The main weakness of our trial design is the lack of blindness. In breastfeeding studies, it is not possible to "blind" subjects by including a placebo treatment. In this case, a potential bias in the pain score evaluation could be introduced, but the main results in our study were confirmed by the objective outcomes that did not depend on the observers: heart rate increase, oxygen saturation decrease, and cry behavior. Another weakness of all of the studies on newborn pain is attributable to scale use. In the PIPP scale, we only assume that a modification in physiologic and behavioral pain indicators reflects the real pain felt by neonates, because verbal and self-reporting measurements are impossible. Although the PIPP scale has been validated, has shown an ability to discriminate painful from nonpainful stimuli, and was used by many other authors in past years, pain is a subjective experience, and its evaluation is only a first step to assess the effectiveness of analgesic interventions.

CONCLUSIONS

If our results are confirmed, breastfeeding during a minor pain procedure could be regarded as a noninvasive, natural, and feasible way of reducing pain in neonatal units.

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