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Breast Milk and Glucose for Pain Relief in Preterm Infants: A Noninferiority Randomized Controlled Trial

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KEY WORDS

newborn, pain, analgesia, human milk, glucose

ABBREVIATIONS

AE—adverse event
CCK—cholecystokinin
CG—control group
EBM—expressed breast milk
EG—experimental group
GA—gestational age
ITT—intention to treat
NFCS—Neonatal Facial Coding System
PIPP—Premature Infant Pain Profile
RCT—randomized controlled trial
RM-ANOVA—repeated-measures analysis of variance

Dr Bueno provided substantial contributions to conception and design, acquisition of data, analysis, and interpretation of data and elaborated and organized the manuscript; Dr Stevens provided substantial contributions to conception and design, and interpretation of data and reviewed earlier versions of the manuscript and provided important intellectual contribution; Dr Ponce de Camargo provided substantial contribution to acquisition of data and reviewed earlier versions of the manuscript and provided important intellectual contribution; Dr Toma provided substantial contribution to acquisition of data, reviewed earlier versions of the manuscript, and provided important intellectual contribution; Dr Krebs provided substantial contributions to conception and design and reviewed earlier versions of the manuscript and provided important intellectual contribution; Dr Kimura provided substantial contributions to conception and design, acquisition of data, analysis, and interpretation of data, reviewed earlier versions of the manuscript and provided important intellectual contribution, provided final approval of the version to be published, and obtained funding and supervised the research.

This trial has been registered at the Australian and New Zealand Clinical Trials Registry (ACTRN12609000712202), from the World Health Organization (WHO) Registry Network.

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WHAT'S KNOWN ON THIS SUBJECT: Numerous late preterm infants undergo repetitive heel lancing procedures during their first hours of life to evaluate glycemic control. Heel lances are painful and 25% glucose solution is effective on reducing procedural neonatal pain scores and crying behavior.

WHAT THIS STUDY ADDS: This noninferiority randomized controlled trial demonstrated that compared with breast milk, 25% glucose provided lower pain scores and reduced duration of cry. Further research is necessary to clarify breast milk's mechanisms and efficacy on neonatal pain relief.

abstract

OBJECTIVE: The study goal was to compare the efficacy of expressed breast milk (EBM) versus 25% glucose on pain responses of late preterm infants during heel lancing.

METHODS: In a noninferiority randomized controlled trial, a total of 113 newborns were randomized to receive EBM (experimental group [EG]) or 25% glucose (control group [CG]) before undergoing heel lancing. The primary outcome was pain intensity (Premature Infant Pain Profile [PIPP]) and a 10% noninferiority margin was established. Secondary outcomes were incidence of cry and percentage of time spent crying and adverse events. Intention-to-treat (ITT) analysis was used.

RESULTS: Groups were similar regarding demographics and clinical characteristics, except for birth weight and weight at data collection day. There were lower pain scores in the CG over 3 minutes after lancing ($P < .001$). A higher number of infants in the CG had PIPP scores indicative of minimal pain or absence of pain ($P = .002$ and $P = .003$ on ITT analysis) at 30 seconds after lancing, and the mean difference in PIPP scores was 3 (95% confidence interval: 1.507–4.483). Lower incidence of cry ($P = .001$) and shorter duration of crying ($P = .014$) were observed for CG. Adverse events were benign and self-limited, and there was no significant difference between groups ($P = .736$ and $P = .637$ on ITT analysis).

CONCLUSIONS: Results based on PIPP scores and crying time indicate poorer effects of EBM compared with 25% glucose during heel lancing. Additional studies exploring the vol and administration of EBM and its combination with other strategies such as skin-to-skin contact and sucking are necessary. *Pediatrics* 2012;129:1–7

Infants born between 34 and 36 completed weeks of gestational age (GA) are classified as late preterm neonates. This population is often of similar size and weight as term neonates and as a consequence is commonly treated as developmentally mature and of low risk.[1] However, studies demonstrate higher morbidity of late preterm compared with healthy term neonates[2,3] and indicate that late preterm infants are at risk for prematurity-related complications such as hypothermia, hypoglycemia, respiratory distress, jaundice, and feeding difficulties, among other problems.[4,5]

Monitoring of glycemic control through heel lancing during the first 24 to 48 hours of life is a common intervention for late preterm infants. Although minimally invasive, lancing is a painful procedure that activates cortical areas in term and preterm infants' brains.[6–8] Repetitive procedural pain can lead to changes in the pain sensitivity threshold[9,10]; therefore, adequate analgesic control is needed.

Sweet-tasting solutions are well described as effective strategies for pain relief in infants undergoing minor invasive procedures.[11,12] Sucrose and glucose are the most widely investigated solutions,[13] and the analgesic effect is achieved by administering small amounts of the solution onto the anterior portion of the tongue of infants 2 minutes before the procedure. Because it is readily available in clinical settings, glucose is an alternative to the sucrose solution. Meta-analyses indicated that glucose reduced pain scores and crying time during heel lances and venipunctures in neonates.[14] Expressed breast milk (EBM) is considered an alternative intervention to sweet solutions, although less consistent evidence is available regarding its analgesic efficacy.[15,16]

The hypothesis of this study is that the efficacy of EBM is not inferior to the efficacy of 25% glucose on pain intensity in late preterm infants undergoing heel lancing. The aim of this study was to compare the effects of EBM versus 25% glucose on pain scores, crying, and adverse events (AEs) after heel lancing in late preterm neonates.

METHODS

A noninferiority randomized controlled trial (RCT) was conducted in the neonatal unit of a university-affiliated Level III hospital from August 2009 to May 2010. The study protocol was approved by the local research ethics committee and was registered at the Australian and New Zealand Clinical Trials Registry (ACTRN12609000712202) of the World Health Organization Registry Network. Parental consent was obtained for all neonates.

Sample size calculation was based on the hypothesis and on data from a previous trial.[17] A noninferiority margin of 10% was established considering the primary outcome (Premature Infant Pain Profile [PIPP][18] scores at 30 seconds after lancing). Based on the noninferiority margin, α = 5%, and β = 90%, a total of 78 neonates (39 per group) were needed. The sample was increased by 12% to account for the possible loss of data; therefore, 88 infants for whom data collection was completed were included. Data for the infants for whom data collection was not completed were analyzed on an intention-to-treat (ITT) basis.

Eligible infants were between 34 and 36 complete weeks of GA at birth; were between 24 and 72 hours old; had 5-minute Apgar scores of $\geq$7; were fed at least 1 hour before data collection; had no syndromes, congenital anomalies, or previous surgery; were not born to mothers with hepatitis C or HIV infection; were born to mothers not known to be a user of illicit drugs; and had clinical indication for blood sampling. Infants were excluded if they were diagnosed with neurologic problems of any type, if they had received analgesic or sedative drugs within 24 hours of enrollment, or if their mother had any breast problem that hindered breastfeeding.

A statistician used the Statistical Analysis System (SAS), version 8.2 (SAS Institute, Inc, Cary, NC), to generate blocked randomization lists. Randomization was stratified according to the infant's type of feeding (eg, breastfeeding versus artificial milk). Rationale for stratification was based on the published effects of breastfeeding as an analgesia for neonatal procedural pain.[15] Allocation concealment was achieved by using numbered, opaque, sealed envelopes containing intervention codes. Envelopes were exclusively accessed by research assistants.

Interventions investigated were 2 mL of EBM (experimental group [EG]) and 2 mL of 25% glucose (control group [CG]), applied via a needleless syringe to the anterior portion of the tongue 2 minutes before the lancing procedure. Research assistants prepared syringes containing both solutions for all infants. Syringes were covered to mask the intervention and were labeled according to the envelope's codes.

Neonates were placed on a bench or remained in their incubator during data collection. An oxygen saturation monitor (NewMed/Oxilyne, Make Line Comercial Ltda; São Paulo, Brazil) was applied to the infant's hand or foot to monitor heart rate and oxygen saturation. After 2 minutes with no handling of baseline, the research assistant offered the assigned solution to the infant. Neonates were placed in a semiseated position and the duration of administration varied between 30 and 90 seconds according to the neonate's ability to swallow and breathe. By the end of solution administration, research assistants confirmed whether neonates had swallowed the entire vol offered and removed any solution residue from

the infants' face. After an additional 2 minutes, lancing was performed by the research assistant with an automated lance device (Accu-Chek Softclix Pro; Roche, Brazil). Infants' faces and the monitor screen were filmed in real time by using independent video cameras during the entire data collection procedure (Handycam DCR-SR87; Sony, Brazil). The focus of the video camera was deviated from the infants' faces during solution administration to guarantee masking of the interventions during facial coding. Voice commands during filming were used to synchronize both videos.

The primary outcome was pain intensity as assessed with the PIPP.[18] The PIPP is a composite pain measure that includes contextual (behavioral state and GA), behavioral (brow bulging, eye squeezing, and nasolabial furrowing), and physiologic (heart rate and oxygen saturation) indicators of pain. Each indicator is scored in a 4-point scale (0–3), and pain intensity scores range from 0 to 21 for preterm infants. Scores of 6 or less represent absence of pain or minimal pain. PIPP scores were measured every 30 seconds during the 3 minutes after the lancing procedure (T30–T180). Secondary outcomes included crying incidence, percentage of time spent crying during the 3 minutes after lancing, and the incidence of AEs (eg, nausea, regurgitation, vomiting, choking, desaturation, tachycardia, and bradycardia).

Brow bulging, eye squeezing, and nasolabial furrowing were coded by a trained coder who was masked to the intervention received. Interrater reliability was assessed on 7% of the coded videos, and a high intraclass correlation coefficient was observed (≥0.93). Incidence of cry, percentage of time spent crying, and physiologic indices were also obtained from videos. Data were double entered into a data management spreadsheet, and a very low data entry error rate was noted after logic checks (<1%). PIPP scores were calculated by preset formulas. When ≥2 indicators of the PIPP were missing (due to poor quality of monitor signal or impossibility of coding facial action), the score was not calculated for that specific interval of time.

Statistical analysis was performed by using Minitab 15.1 (Minitab, State College, PA). Demographic variables, incidence of cry, time spent crying, and AEs were compared between treatment groups by using descriptive analyses. Repeated-measures analysis of variance (RM-ANOVA) was performed by using the total PIPP scores to determine the efficacy of the interventions over the time. Per-protocol and ITT analyses were performed.

RESULTS

A total of 113 neonates were randomized and 88 neonates had data collection completed (Fig 1). Groups were similar with regard to type of feeding ($P = .938$) and to the number of infants for whom data collection was not complete ($P = .824$).

No differences between the groups were observed with regard to demographic variables, except for birth weight ($P = .013$) and weight on data collection day ($P = .017$) (Table 1).

Significantly lower PIPP scores were observed for infants who received glucose at all time points. Mean pain intensity scores during the 3 minutes after lancing are described in Table 2. At the first 30 seconds after the procedure, a lower number of infants who received glucose had PIPP scores of ≥7 compared with the EBM group (CG: 11/43 [25.6%], EG: 24/40 [60.0%]; $P = .002$). On the ITT analyses, results favor glucose (25/57 [43.9%]) in comparison with EBM (40/56 [71.4%]; $P = .003$). The mean difference in PIPP scores at 30 seconds after lancing was 2.995 points with a 95% confidence interval of 1.507 to 4.483.

Based on the RM-ANOVAs, there was no interaction between intervention and time ($F = 1.02$, $P = .310$). A significant between-group main effect of the intervention was observed favoring glucose ($F = 18.08$, $P < .001$), and a significant within-group effect of the time occurred for both groups ($F = 15.62$, $P < .001$).

A lower incidence of cry was observed for infants in the CG (19/45 [42.2%]) compared with the EG (33/42 [78.6%], $P = .001$). On the ITT analysis, a lower number of infants who received glucose cried after the procedure (31/57 [54.4%]) compared with those who received EBM (47/56 [83.9%], $P = .001$). Neonates who received glucose cried less (mean, 14.53%, ± 19.98%) than did those who received EBM (mean 32.02%, ±29.02; $P = .014$).

There was no difference in the incidence of AEs between the EG (5 [11.6%]) and the CG (4 [8.9%], $P = .736$). The ITT analysis indicated no difference between the groups ($P = .637$) (Table 3).

DISCUSSION

This is a noninferiority RCT that compared the effects of EBM versus 25% glucose on pain scores, incidence of cry, percentage of time spent crying after the procedure, and AEs on late preterm infants during heel lancing for glycemic control. The intent of a noninferiority RCT is to demonstrate that a new treatment has at least as much efficacy as the reference treatment or is worse by an amount that is less than the noninferiority margin established.[19] Based on the literature,[20,21] we stated a noniferiority margin of 10% (eg, 2 points on the PIPP scale).

Ethical issues regarding the conduct of trials with vulnerable populations are of particular importance and must be considered during the conception and implementation of research. Sweet-tasting solutions have been extensively studied during the past 2 decades.

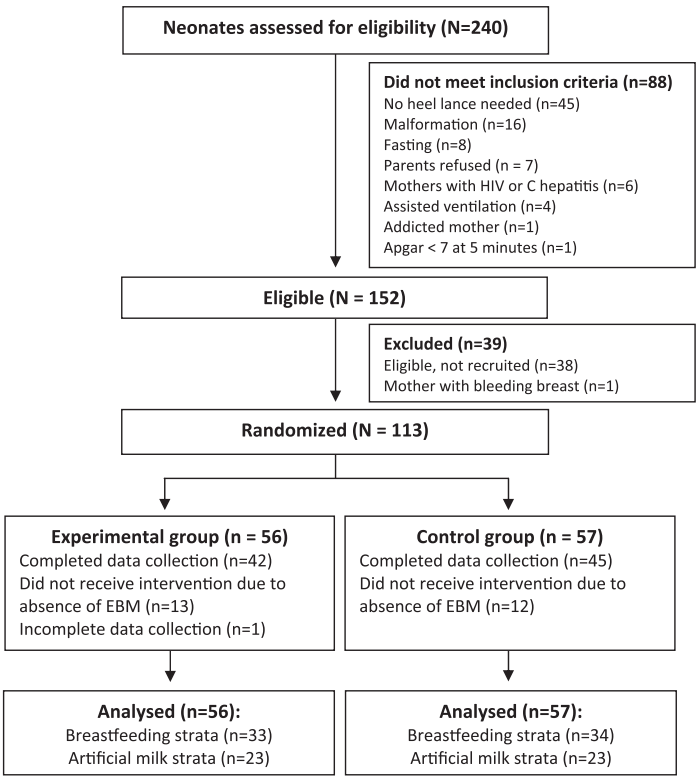

FIGURE 1
Study flow of participants.

Research findings indicate that equipoise no longer exists regarding the analgesic effects of sweet solutions during minor painful procedures in healthy neonates and infants.[13] Therefore, we chose 25% glucose as the control intervention for this trial due to its clinical availability for intravenous use. As a result of limited data on the effects of EBM on neonatal pain relief,[16] a noninferiority hypothesis was considered as appropriated.

Of the 113 randomized infants, 26 (23%) did not have complete data collection, with the absence of or an insufficient vol of EBM accounting for the main reasons for withdrawal (25 infants [22%]). There was no significant difference between groups in the number of infants for whom data collection was not complete. This finding is consistent with a study involving 6 intervention groups (sucrose, breast milk, and water, delivered via syringe or pacifier), in which Blass and Miller[22] described difficulties in obtaining a sufficient amount of colostrum from mothers. As a result, the authors decided to stratify the randomization. We could not implement this strategy since our study was composed of only 2 intervention groups and we decided to prepare both solutions for all included neonates to minimize the risk of bias related to allocation concealment and blinding. Thus, we decided to include all infants and to use ITT analyses for the infants for whom data collection was not complete.

Groups were similar with regard to the majority of demographic and clinical characteristics assessed except for birth weight and weight on the data collection day. In both situations, mean weight of included infants was >2000 g and mean differences were <250 g, which can be considered a non–clinically relevant difference. There is no evidence relating to the ideal dose of sweet solutions based on infants' weight.[11,12,14] In 3 trials, weight-related doses of 24% to 25% sucrose were offered and neonates of >2000 g received 2 mL of solution.[23–25] Therefore, it is likely that infants who were included in the CG received a sufficient dose of sweet solution although no data on weight-related doses of breast milk were retrieved.

In our study, lower PIPP scores were found in the CG throughout the 3 minutes after lancing, although there was a significant decrease in PIPP scores for both intervention groups across the time period. For the hypothesis testing, the

TABLE 1 Neonatal Demographics and Clinical Characteristics

	EG	CG	*P* Value
Delivery[a]			
Cesarean delivery	39 (69.6)	44 (77.2)	0.364
Vaginal/forceps	17 (30.4)	13 (22.8)	
Gender[a]			
Female	26 (46.4)	22 (38.6)	0.400
Male	30 (53.6)	35 (61.4)	
Apgar at 5 min[b]	9.3 (0.6)	9.3 (0.7)	0.834
Gestational age at birth, wk[b]	35.5 (0.7)	35.8 (0.7)	0.228
Corrected GA, wk[b]	35.8 (0.7)	36.0 (0.7)	0.272
Birth wt, g[b]	2460.5 (482.2)	2235.7 (456.8)	0.013
Wt on data collection day, g[b]	2395.5 (482.2)	2184.7 (444.3)	0.017
Age, h[b]			
<24	15 (26.8)	19 (33.3)	0.478
24–28	31 (55.4)	32 (56.2)	
>48	10 (17.8)	6 (10.5)	
Interval between data collection and last feeding, h[b]	2.2 (0.6)	2.2 (0.6)	0.977
Glycemia, mg/dL[b]	72.5 (15.0)	71.4(21.5)	0.782

[a] Values given as *n* (%).
[b] Values given as mean (SD).

TABLE 2 Mean (SD) PIPP Scores After Lancing Procedure According to Intervention Group

Postlancing Time Interval, s	EG	CG
30	7.54 (3.61)	4.55 (3.17)
60	6.29 (4.09)	3.60 (3.02)
90	4.79 (2.77)	2.76 (2.58)
120	4.74 (3.10)	3.09 (2,80)
150	5.50 (3.55)	3.30 (2.78)
180	4.72 (3.48)	2.87 (2.54)

mean difference between PIPP scores at 30 seconds after lancing was considered as this is the most painful phase due to puncture and squeezing of the heel. As the noninferiority margin established (2 points on the PIPP score) is included on the 95% confidence interval for the mean PIPP score differences, the hypothesis testing is inconclusive regarding the noninferiority effects of EBM compared with 25% glucose on pain scores of late preterm infants undergoing lancing.

With regard to crying, lower incidence and less time spent crying after lancing were observed for infants who received 25% glucose in comparison with those who received EBM.

Researchers have compared the effects of EBM and sweet solutions on neonatal pain scores and crying. Cry behavior is a widely used pain indicator, although it is not specific enough for pain occurrence. In a trial that included 125 term infants during their first week of life, Jatana et al[26] compared the effects of 1 mL of water, breast milk, or 10%, 25%, and 50% glucose on facial expression and duration of first cry during heel lancing. EBM was comparable to 10% glucose for facial action and cry, whereas the effects of 25% and 50% glucose were superior to those for both 10% glucose and milk.

Three trials indicated better efficacy of sucrose compared with breast milk. The effects of 2 mL of 12.5% sucrose, human milk, and water on crying time of 102 healthy term infants (between 1 and 15 days of life) were investigated in an RCT by Örs et al.[27] Sucrose was superior to milk and water. Blass and Miller[22] studied 60 two-day-old term infants who received 2 mL of water, EBM, or 12% sucrose administered via syringe or combined with nonnutritive sucking. The effect of EBM was comparable to that of water, while sucrose was superior to both in reducing facial action and cry. Similarly, Ozdogan et al[28] described lower Neonatal Facial Coding System (NFCS) scores for 142 term infants who received 2 mL of 1 or 2 doses of 12.5% sucrose compared with 1 or 2 doses of EBM during their first 48 hours of life. However, no significant differences in cry duration were observed across the intervention groups.[28]

In conjunction with results of earlier trials, it is possible to conclude that small amounts of human milk given 2 minutes before a painful procedure is not an effective analgesic strategy for neonates. Nevertheless, it is fundamental not to assume these results as definitive regarding the role of EBM in neonatal analgesia.

Mechanisms underlying the analgesic effects of EBM are unclear. Milk and its components are thought to influence neonatal reactivity to pain, although trials investigating the effects of each component in animal and human neonates present conflicting findings. Blass and Fitzgerald[29] observed reduction in rat pups' vocalization and an increase in pain threshold after milk administration. These effects were blocked by naltrexone. Lactose did not reduce ultrasonic vocalization in rat pups[30] or reduce crying in infants.[31,32] Fat and polysaccharide increased pain threshold and reduced vocalization in rat pups,[33] but fat and protein solutions did not reduce crying time in infants undergoing heel lancing.[34] In addition, Uyan et al[35] reported no statistically significant differences in the effects of foremilk (lower fat concentration), hindmilk (higher fat concentration), and water on NFCS scores[36] and crying behavior of term infants. β-Casomorphin, which is obtained from casein, was demonstrated to increase pain threshold in animal models,[37] and melatonin, which is obtained from tryptophan, influenced pain threshold in rats.[38]

Larger volumes of EBM have been associated with positive effects on neonatal pain. Upadhyay et al[39] included 87 term infants up to 4 weeks of life who were undergoing venipuncture. Pain was assessed with the use of modified NFCS scores (composed of 5 facial actions plus limb movements), and interventions were 5 mL of EBM or water. Lower pain scores and shorter crying time were observed for the infants who received EBM. Storm and Freeming[40] described reduced cry duration for infants who were fed via gastric tube during the hour before heel lancing compared with infants who were fasted. The results of both trials suggest that mechanisms related to colecystokinin (CCK) release and food intake might play an important role in EBM analgesia.

CCK is a neuropeptide and gut hormone released as a result of feeding, sucking, and skin-to-skin contact.[41] Calming effects on animal models were described by Blass and Shide[42] as a result

TABLE 3 Type of AEs Observed According to Intervention Group

AE	EG		CG		Total	
	n	%	*n*	%	*n*	%
Oxygen saturation <80%	2	40.0	2	50.0	4	44.44
Nausea, regurgitation, and/or vomiting	2	40.0	1	25.0	3	33.34
Oxygen saturation <80% and choking	1	20.0	0	—	1	11.11
Heart rate <100 bpm, oxygen saturation <80%, and choking	0	—	1	25.0	1	11.11
Total	5	100	4	100	9	100

of CCK release. In human infants, a trial involving 58 healthy term neonates demonstrated that high plasma concentrations of CCK were observed immediately after breastfeeding, as a result of sucking and skin contact, and at 30 and 60 minutes after breastfeeding, due to the presence of milk in the intestines.[43] Breastfeeding is an acknowledged intervention for neonatal procedural pain relief.[15] However, some neonates may not be mature enough or clinically stable to benefit from this intervention and alternative analgesic strategies need to be investigated.

The odor of mother's milk has also been associated with reducing crying time, grimacing, and motor activity in term neonates during lancing.[44,45] Nishitani et al[45] compared infants' mother's milk, human milk, and artificial milk odors.

The results of this study combined with previous evidence indicate that further research is required on EBM. Single doses and small volumes of milk are not effective for neonatal pain relief; however, larger volumes may present better effects, possibly due to the combination of several mechanisms. Studies exploring the combination of EBM with other interventions such as skin-to-skin contact or sucking are required to verify synergic or addictive effects of these interventions.

There was low incidence of AEs that are commonly related to prematurity and difficulties in coordinating sucking, swallowing, and breathing. All events were benign and self-limited with no requirement of professional intervention. Therefore, glucose and EBM are safe interventions for neonates undergoing minor painful procedures.

CONCLUSIONS

To our knowledge, this is the first RCT investigating pain relief interventions specifically in late preterm infants. Although the results of the hypothesis testing were inconclusive, PIPP scores and crying time indicate poorer effects of EBM compared with 25% glucose during heel lances. Analgesic properties of EBM should be further investigated considering different volumes, administrations, and combinations with other pain relief strategies.

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