Hindmilk for procedural pain in term neonates

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The aim of this study was to investigate whether repeated doses of hindmilk were effective for pain relief during routine heel stick in term neonates. Infants enrolled in this double-blind placebo-controlled study were randomly assigned to hindmilk, 12.5% sucrose and distilled water groups. Infants were given 1 ml of the test solution 1 minute prior to, immediately before and 1 minute after the heel stick. Pain responses were assessed by physiologic and behavioral parameters and also according to the Neonatal Facial Coding System (NFCS). There were significant reductions in crying time, duration of the first cry and tachycardia, time needed for return to baseline heart rate, and the average and 1- and 5-minute NFCS scores in the hindmilk group when compared with the distilled water group. When the hindmilk group was compared to the sucrose group, only the NFCS scores at 1 and 2 minutes reached statistical significance in favor of the sucrose group. Repeated dose hindmilk administration is an effective analgesic intervention in term newborns during heel stick. Although the analgesic effect of 12.5% sucrose is slightly superior, hindmilk may be considered as a physiologically suitable alternative to sucrose.

Key words: analgesia, heel stick, hindmilk, newborn, pain, breast milk.

The necessity of prevention and treatment of pain in newborns is emphasized, as the number of studies about long-term effects of neonatal pain increases[1]. Unfortunately, analgesic treatment for painful procedures by pharmacological and non-pharmacological methods is still unsatisfactory in newborns[2].

Breast milk is the preferred agent of antinociception in newborns when compared with other non-pharmacological methods, since it is readily available and has no potential side effects. The analgesic effects of breast milk have been investigated in a limited number of studies, and 1-2 ml of expressed breast milk was found to be ineffective for pain relief[3-5]. On the other hand, the analgesic effect of formula and its components (fat and protein) has been demonstrated in several studies[6-8]. In experimental studies, fat in the form of corn oil significantly increased pain thresholds in 10-day-old rats, an effect normalized by naltrexone pre-treatment, suggesting that antinociceptive actions of fat are probably opioid-mediated[9].

Breast milk is composed of foremilk and hindmilk, and the latter has been shown to have 2-3 times more fat content than foremilk[10-12]. We postulated that hindmilk might have a better analgesic effect than breast milk due to its higher fat content. We further hypothesized that prolonged orosensory stimulation by repeated doses may augment the analgesic effects of hindmilk, since the analgesic effects of milk are based on orosensory, orotactile and postgastric mechanisms.

In this study, the effect of repeated doses of hindmilk for simple procedural pain in newborns was investigated. The effect of hindmilk was also compared with that of sucrose, which is the most widely studied intervention as non-pharmacological analgesia in term neonates.

Material and Methods

We needed 16 babies in each group to achieve 80% power with $\alpha = 0.05$ to show a 10-second difference between the groups in terms of crying time. To increase the power to 90%, the estimated sample size was 22. We included 25 neonates in each group to cover potential problems related to video recording.

Seventy-five healthy full-term newborns delivered at Marmara University Hospital were enrolled. The Institutional Review Board approved the study and informed consent was obtained from parents of participating infants. Infants of <37 weeks gestational age, with birth weight <2500 g, age <48 hours or Apgar score <7 at 5 minutes, as well as infants with any congenital malformation, illness or receiving any medication were excluded.

A researcher not involved in the other steps of the study was responsible for randomization of infants by using sealed envelopes designating the intervention to be administered. Twenty-five envelopes for each study group were prepared and mixed. For each infant enrolled in the study, the next envelope from the pile was opened and the test solution was prepared in a covered syringe. Among the infants enrolled in the study, 5 infants were found to have hyperbilirubinemia necessitating phototherapy and 5 infants cried before the heel stick. These infants were excluded from the study and their envelopes were resealed and mixed with the remaining envelopes to be used for other infants.

Group 1 received hindmilk, Group 2 received 12.5% sucrose solution and Group 3 received distilled water. Hindmilk fraction of breast milk was defined as the milk collected subsequent to the first 2-3 minutes after flow began by complete breast emptying[10]. We used the creamatocrit technique to determine the fat concentration of hindmilk[13]. Fat concentration was calculated arithmetically from the formula: Fat (g/L) = (creamatocrit (%) – 0.59) / 0.146. Hindmilk was defined according to the literature[10].

All babies were fed at least one hour before the procedure and each infant was taken into a quiet and warm room. Infants were undressed (wearing only a diaper) and connected to a vital signs monitor (Viridia, Hewlett-Packard, USA). Infants were lying on an examination table without being held or restrained during the entire procedure and data collection. After a short observation period, the baseline heart rate was recorded, and the behavioral state of the baby was noted as either quiet sleep, active sleep, quiet awake or active awake. Babies who cried during this period were excluded from the study. Infants in each group were given 1 ml of the test solution 1 minute prior to, immediately before and 1 minute after the heel stick, for a total of 3 ml. Test solutions were administered onto the anterior part of the tongue with a completely covered syringe. Infants were not allowed to suck the syringe tip. One minute after giving the first dose solution, the second dose was administered, and the heel prick was performed immediately by lancing the heel with a mechanical lancet (Glucotrend Soft Click, Germany). A nurse who was blinded to the groups performed all the heel pricks. Duration of blood sampling by means of gently squeezing the heel was limited to two minutes. One minute after the heel prick, the last dose of the solution was given. An independent researcher, who was not involved in the observations or analysis, administered the test solutions. The face and crying of the baby were recorded by a third person with a video camera prior to heel lancing, during blood sampling and for another 3 minutes after sampling was completed. The heart rate of the baby was recorded from the monitor every 10 seconds (Fig. 1).

A behavioral pain scale was applied according to the Neonatal Facial Coding System (NFCS) with nine discrete variables[14]. Infants were scored according to NFCS at 0, 1, 2, 3, 4, and 5 minutes by two researchers separately, and the arithmetical mean of each researcher's score at every time point was considered as the final score. The researchers were blind to the groups and utilized only the video recordings for scoring. Arithmetical mean of these six scores was calculated as 'average NFCS score' for each baby for providing information about the infants' facial expressions of pain throughout the study. Crying was noted as audible vocalization that lasted at least 5 seconds without a 20-second quiet interval. Crying time was defined as the duration of

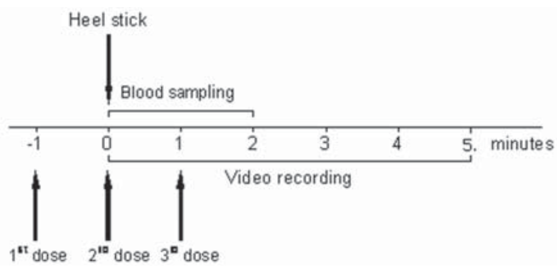

Fig. 1. Study timeline

crying within the 5-minute recording time, while the duration of the first cry was defined as audible distressed vocalizations with a continuous pattern before a quiet interval of 5 seconds soon after the painful stimulus. The percent change in heart rate was calculated from the difference between maximum and baseline heart rates. Two non-biased independent research assistants analyzed the results.

The statistical analysis was carried out with SPSS 11.0. The significance between the baseline characteristics among groups concerning sex, birth type and behavioral states was assessed by chi-square test. The significance between the groups regarding birth weight, gestational age, postnatal age, basal heart rate, crying time, duration of the first cry, percent change in heart rate, maximum heart rate, and mean pain scores at 0, 1, 2, 3, 4, 5 minutes and average score was assessed by Kruskal-Wallis test.

Results

The demographic features of the groups are shown in Table I. There were no significant differences between the groups in terms of sex, gestational age, postnatal age, birth type, basal heart rate, and behavioral states. Mean fat content of the breast milk samples used in the hindmilk group was 55.5 ± 8.84 g/L, which is well-adjusted to the limits defined in the literature[10]. Median crying time, duration of first cry and tachycardia, and time needed to return to baseline were longest in the distilled water group (Table II). These parameters were significantly shorter in the hindmilk group when compared with the distilled water group (p=0.022, p=0.008, p=0.009 and p=0.038, respectively), whereas no statistically significant differences were observed between the hindmilk and sucrose groups.

Maximum heart rate observed during the study period was highest in the distilled water group. Maximum heart rate in the hindmilk group was significantly lower when compared to the distilled water group (184 beat/minute vs. 196 beat/minute, p=0.031). There was a significant reduction in the average NFCS score (obtained from 6 scores throughout the study period), 1st minute NFCS score and 5th minute NFCS score in the hindmilk group compared to the distilled water group (p=0.006, p=0.017 and p=0.021, respectively) (Table III, Fig. 2). When the analgesic effect of hindmilk was compared to 12.5% sucrose, there was no statistically significant difference between the groups in the average NFCS scores and at 0, 3, 4, and 5 minutes. Crying time, duration of first cry and tachycardia, time needed for return to baseline, and percent change in heart rate were also not statistically different between the hindmilk

Table I. Demographic Features of the Study Groups

Groups	Hindmilk (n=25)	Sucrose (n=25)	Distilled Water (n=25)	P
Sex (n) Female/Male	15/10	15/10	16/9	0.11
Gestational Age (weeks)*	39.2 (37-41)	38.9 (37-41)	39.1 (38-41)	0.57
Postnatal Age (days)*	6.8 (5-10)	6.1 (4-9)	6.3 (4-8)	0.21
V/C	17/8	18/7	16/9	0.36
Birth Weight (gram)	3538 (2716-4160)	3232 (2590-4280)	3382 (2760-4290)	0.019
Basal HR (beats/minute)*	135 (102-166)	137 (105-167)	141 (110-165)	0.288
Behavioral state				
BS 1	8	12	12	1.1
BS 2	44	36	36	
BS 3	8	4	8	
BS 4	40	48	44	

* Median and minimum-maximum values are given in parentheses.
V/C: Vaginal/C-section. HR: Heart rate. BS: Behavioral State as %. 1: quiet sleepy, 2: quiet awake, 3: active sleepy, 4: active awake.

Table II. Median and IQR Values in Seconds for Crying Time, Duration of First Cry and Tachycardia and Recovery Time (Time Needed for Return to Baseline HR)

Group	Crying time	Duration of first cry	Duration of tachycardia	Recovery time
Distilled Water	229 (134.5-293)	100 (57.5-204)	190 (65-250)	300 (215-300)
Hindmilk	150 (60-230)*	49 (18.5-107.5)*	30 (0-165)*	190 (150-300)*
Sucrose	66 (16.5-173)*	22 (10-55)*	20 (0-100)*	150 (95-270)*

IQR: Interquartile range. HR: Heart rate.
*P<0.05 when compared to distilled water.

and sucrose groups. When compared with the hindmilk group, only the 1st and 2nd minute NFCS scores reached statistical significance in favor of the sucrose group (p=0.04, p=0.028, respectively). The median values for percent change in heart rate in the distilled water, hindmilk and sucrose groups were 37%, 35% and 30%, respectively (p=0.218).

Discussion

Early pain experiences may have various long-term effects on different neurodevelopmental parameters according to gestational and postnatal age[15,16]. For this reason, treatment of pain in neonates carries significance not only for acute effects of pain and ethical reasons, but also for ensuring normal neurodevelopment. However, even sucrose solutions, which are considered to be the gold standard of nonpharmacological methods for pain relief, may have negative effects on neurodevelopment in premature babies younger than 31 weeks of postconceptional age[17]. Sucrose solutions serve as a culture media for bacteria and may need to be prepared daily to avoid the risk of contamination if not easily available. Currently, there are no long-term neurodevelopmental follow-up studies for term infants receiving routine sucrose analgesia. Many clinicians have concerns regarding the solutions (need for daily preparation and contamination risk) and safety issues, especially in preterm infants. Therefore, more physiologic and low-risk methods for newborn analgesia are desired.

Administration of formula, skin-to-skin contact with the mother and breastfeeding before, during and after the procedure were reported as effective nonpharmacological and physiological interventions for heel stick in term and preterm neonates[6,18-22]. Administration of formula will introduce cow milk protein to the newborn in an early period when exclusive breast milk is recommended. Gray et al.[19] found that breastfeeding was effective in suppressing the behavioral and physiologic stress accompanying the heel stick procedure. Although the authors were not able to determine which component of breastfeeding had been more effective, they stated that it was unlikely that the analgesic effects of breastfeeding can be exclusively attributed to skin-to-skin contact. Analgesic effects of human milk isolated from other factors can only be tested by using expressed breast milk. This carries a special importance for infants whose mothers cannot or do not

Table III. Average NFCS Scores

Groups	Average NFCS scores		
	Median	IQR	Min-Max
Distilled Water	4.21	2.5-5.5	0.33-7.16
Hindmilk	2.69	1.24-4.4	0-7.16
Sucrose		1.96 0.25-3.6 0-6.3	
P		<0.001	

NFCS: Neonatal facial coding system. IQR: Interquartile range. Min-Max: Minimum and maximum values.

want to observe the painful interventions. In the limited number of studies done, 1-2 ml of expressed breast milk was found inadequate for pain relief[3-5]. In a recent study, 5 ml of expressed breast milk was found effective in reducing symptoms due to venipuncture in term newborns[23]. This suggests a dose-related antinociceptive effect for expressed breast milk.

Shide et al.[9] demonstrated earlier that corn oil had an analgesic effect. Fat increased the pain threshold of 10-day-old rats, an effect that was reversed by naltrexone. Therefore, fat content may contribute to the dose-related analgesic effect of breast milk.

The calming and analgesic effects of hindmilk have been investigated in two studies[24, 25]. Barr et al.[24] found that hindmilk had a calming effect on spontaneously crying infants. In their study comparing the analgesics effects of 2 ml of hindmilk, foremilk and placebo, Uyan et al.[25] noticed that hindmilk appeared to have an analgesic effect slightly superior to foremilk, although this did not reach statistical significance.

In our study, repeated doses of hindmilk had an obvious improving effect on all of the physiologic and behavioral parameters of pain perception. Among the significantly ameliorated behavioral parameters, both crying time and duration of the first cry were revealed to be sensitive methods for assessment of pain and analgesia in the literature[14,26]. Facial expression is also considered as one of the most specific and reliable indicators of pain in neonates[14]. Repeated doses of hindmilk caused a reduction in NFCS scores throughout the study, and at the 1st and 5th minute time points, this reduction reached statistical significance. We assumed the significant reduction in the average NFCS score is a more reliable parameter because it shows the overall effect of test solutions from the beginning to the end of the study.

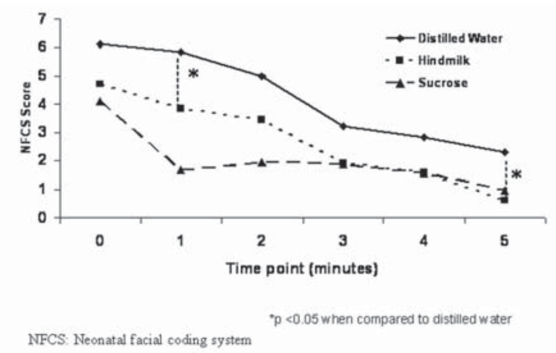

Fig. 2. NFCS scores at different time points

Following a tissue-damaging stimulus in newborns, it has been demonstrated that increase in heart rate parallels the intensity of pain[27]. Maximum heart rate observed during the study, duration of tachycardia and time needed for return to baseline (recovery time) were significantly reduced with hindmilk.

With these data, it appears that administration of repeated doses of hindmilk is an effective intervention for pain relief during heel stick in term neonates. Hindmilk had comparable analgesic effects with 12.5% sucrose solution when given in repeated doses. There were no statistically significant differences between the hindmilk and sucrose groups in any of the physiological parameters and in most of the behavioral parameters. In fact, sucrose solution was found to be significantly more effective only at the 1st and 2nd minute NFCS scores (Fig. 2). This effect of sucrose probably originates from the early starting sweetness effect of sucrose solutions. Positive effects of hindmilk on the NFCS scores became more evident towards the end of the observation period. At the 5th minute, we noticed that the hindmilk group had lower NFCS scores when compared to the sucrose group.

One could possibly argue the comparison of analgesic effects of hindmilk with 12.5% sucrose solution. The International Evidence-Based Group for Neonatal Pain, in its consensus statement, recommends using sucrose in concentrations between 12-24% with pacifier two minutes before the heel stick procedure[28]. In the metaanalysis of Stevens et al.[29] in 2004, sucrose was found to be safe and effective for reducing procedural pain from single painful events such as heel lance and venipuncture. However, the authors noted the inconsistency in the dose of sucrose that was effective, ranging between 0.012 g to 0.12 g. Therefore, they could not identify an optimal dose to be used in preterm and/or term infants. They also addressed the need for investigation of the use of repeated administrations of sucrose in neonates. Johnston et al.[30] investigated the efficacy of repeated versus single dose sucrose to decrease pain from routine heel stick procedures in preterm neonates. In that study, 0.05 ml of 24% sucrose solution was administered three times. The repeated dose group had lower Premature Infant Pain Profile (PIPP) scores than the single dose group.

In our study, a total amount of 3 ml of 12.5% sucrose solution was administered to the infants in a repeated fashion, which augments the analgesic effect. Thus, using 12.5% sucrose solution versus hindmilk should not confound the results of this study.

In this study, the analgesic effect of expressed breast milk was maximized by using the hindmilk fraction, as well as by prolonging orosensory stimulation utilizing repeated doses and also by increasing the total dose administered. Use of prolonged orosensory stimulation may be difficult to perform without a second caregiver, which may be noted as a limitation to this method. Effective combination of hindmilk and prolonged orosensory stimulation for increasing the analgesic effect of breast milk needs to be further investigated, especially in premature infants who are the most vulnerable group for short- and long-term side effects of sucrose solutions and in whom non-pharmacological methods such as skin-to-skin contact and breastfeeding are not always convenient.

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