Infant Analgesia With a Combination of Breast Milk, Glucose, or Maternal Holding

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abstract

OBJECTIVES: We studied neonatal cortical brain response to 4 types of nonpharmacological analgesia (oral glucose, expressed breast milk, maternal holding plus oral glucose, breastfeeding). We aimed to assess the differential effect of oral solutions (glucose, breast milk) given alone or combined with the maternal-infant relationship (holding, breastfeeding).

METHODS: Eighty healthy term newborns undergoing a heel stick were randomly assigned to 4 parallel groups of 20 infants each: group 1, infants received a glucose solution on a changing table; group 2, infants received expressed breast milk on a changing table; group 3, infants received a glucose solution in their mothers' arms; and group 4, infants were breastfed by their mothers. Cortical activation in parietal, temporal, and frontal cortices was assessed by multichannel near-infrared spectroscopy. Pain expression was also evaluated.

RESULTS: Oral glucose alone or combined with maternal holding was associated with no cortical activation during heel stick. Expressed breast milk was associated with localized bilateral activation of somatosensory and motor cortices ($P < .01$). Breastfeeding was associated with extensive bilateral activation of somatomotor, somatosensory, and right parietal cortices ($P < .01$). Pain expression was lower with the maternal-infant relationship ($P = .007$).

CONCLUSIONS: Oral glucose, either alone or combined with maternal holding, appears to block or weaken cortical pain processing. Breast milk alone is associated with localized cortical activation. Breastfeeding is associated with extensive activation and may act by extending cortical processing. Maternal relationship, both combined with oral glucose and in breastfeeding, shows the greatest analgesic effect, although the neural patterns involved are distributed differently.

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Dr Bembich conceptualized and designed the study, acquired and analyzed the data, interpreted the data analysis, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Cont and Paviotti, Ms Causin, and Ms Marzari acquired the data, interpreted the data analysis, were involved in the writing of the manuscript, and critically reviewed the manuscript; Dr Demarini conceptualized and designed the study, interpreted the data analysis, was involved in the writing of the manuscript, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: The effect of oral sweet solutions on neonatal cortical response to a painful procedure has yielded conflicting results. No previous researchers have examined whether providing sweet solutions alone or combined with the maternal-infant relationship affects neonatal cortical response.

WHAT THIS STUDY ADDS: During heel stick, 4 analgesic methods (oral glucose, maternal expressed breast milk, maternal holding plus oral glucose, and breastfeeding) evoke different cortical patterns. Clinically, glucose and breast milk are more effective when combined with the maternal-infant relationship than when given alone.

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Nonpharmacological analgesia is commonly used in neonatal units during minor painful procedures, such as heel sticks. Several methods have been proven to be effective in decreasing neonatal pain expression from both a behavioral (eg, crying, facial expression, and fussiness) and physiologic (eg, heart rate) standpoint. Commonly used analgesics include sweet oral solutions,[1–5] swaddling,[6,7] breastfeeding,[8–10] skin-to-skin contact with the mother,[11,12] maternal holding,[13] and expressed breast milk.[14]

Nonpharmacological analgesia has also been studied by assessing the cerebral activity that is elicited by clinical nociceptive stimulation. Both EEG and near-infrared spectroscopy (NIRS) reveal that noxious stimuli are processed at high levels in the neonatal brain. An EEG can be used to detect event-related potential after noxious stimulation[15] and differentiate noxious from nonnoxious stimuli. A NIRS device is used to detect stimulus-associated cortical activation as increased levels of cortical oxyhemoglobin (HbO_2). NIRS has revealed that blood sampling can activate the neonatal somatosensory,[16,17] motor,[18] and prefrontal[19] areas starting in the 25th week of postmenstrual age.

However, neurophysiological methods that were applied to neonatal nonpharmacological analgesia have yielded conflicting results. During nociceptive stimulation after sucrose administration, EEG revealed an attenuation of the electrical frontal response in 1 study[20] and no effect in another.[21] NIRS monitoring of cortical activity during a heel stick after oral glucose administration also revealed no activation in the parietal and frontal areas.[22] Moreover, the maternal–infant relationship, such as holding, during a heel stick has been associated with bilateral cortical activation in the somatosensory and inferior frontal regions.[23]

On the basis of previous studies, breast milk, glucose, and the maternal–infant relationship appear to be effective forms of nonpharmacological analgesia. Because >1 intervention may be applied simultaneously in clinical practice, the relative contribution and efficacy of the single analgesic components require further elucidation.

In this study, we focused on effective pain management by assessing the cortical and clinical responses to different combinations of nonpharmacological analgesic methods on procedural pain. We aimed to assess the relative analgesic effect of oral solutions (glucose and expressed breast milk) with and without the mother–infant relationship (maternal holding and breastfeeding) on cortical and clinical responses to a minor painful procedure (heel stick). We tested the hypothesis that the mother–infant relationship can improve the analgesic effect of oral solutions.

METHODS

Participants

The study was conducted in the nursery of the Institute for Maternal and Child Health–IRCCS "Burlo Garofolo"–Trieste (Italy). On the basis of previous multichannel NIRS studies on the cortical response to a heel stick when nonpharmacological analgesia is used,[22,23] a sample size of 20 newborns in each treatment group was considered to be appropriate to detect a functional activation of the cortex. We enrolled 80 healthy term newborns (gestational age: 37–42 weeks) who were undergoing a heel stick for metabolic screening on their third day of life (and who had started breastfeeding) in the study. Infants were randomly assigned to 1 of 4 nonpharmacological analgesia treatments: in group 1 (N = 20), the infants received 2 mL of oral glucose solution 2 minutes before the heel stick, which was performed on a changing table; in group 2 (N = 20), the infants received 2 mL of expressed breast milk 2 minutes before the heel stick, which was performed on a changing table; in group 3 (N = 20), infants were held in their mothers' arms throughout the procedure and received 2 mL of oral glucose solution 2 minutes before the heel stick; and in group 4 (N = 20), the infants were breastfed by their mothers 2 minutes before the heel stick and throughout the procedure. The bioethics committee of our institution approved the study, and informed consent was obtained from the infants' parents.

Multichannel NIRS Recording

A multichannel NIRS system allows for the assessment of cortical activation by continuously monitoring changes in hemoglobin concentration.[24] HbO_2 concentration has been shown to reflect cerebral blood flow, with an increase revealing cortical activation.[25] In an NIRS system, each pair of adjacent incident and detection NIRS light fibers (optodes) is used to define a single channel and measure vascular changes from the surface of the cerebral cortex.[26] By recording activation from multiple sites, multichannel NIRS allows for improved spatial resolution.[27]

We used the Hitachi ETG-100 optical tomography device (Hitachi, Ltd, Tokyo, Japan), which can be used to detect cortical activation from 24 channels by using 18 light emitters and detectors that are 1 mm in diameter and placed on the scalp. Hemodynamic variations are reported as millimolar-per-millimeter units (ie, the product of hemoglobin concentration changes expressed in millimolar units and the optical path length expressed in millimeters).

The optodes were arranged in two 3 × 3 patterns and positioned on the left and right sides of the newborn's head by using neoprene fiber holders, providing 12 channels on each hemisphere, with elastic bands keeping the fiber holders in place. The distance between adjacent emitters and detectors was set at 2.5 cm. Fiber holders were placed according to the international 10–20 EEG placement system.[28] The central optode of the inferior channel row of each holder was placed over T3 on the left temporal region and over T4 on the right temporal region (Fig 1), maintaining the central channel column of holders in both cases on the virtual line joining T3 with C3 (central left) and T4 with C4 (central right). Cortical activation was predominantly detected in the parietal, temporal, and posterior frontal areas of each hemisphere.

Randomization

An independent statistician created a computer-generated, randomized treatment assignment list (simple randomization). Treatment allocations were placed in opaque and sealed envelopes and sequentially numbered from 1 to 80. Both procedures were masked to investigators. Participants were recruited by a neonatologist after a full technical and procedural explanation. Three hours before performing the heel stick, the assigned envelope was opened by an investigator, and the treatment allocation was revealed to the nurse who was in charge of the blood sampling and to the participant's mother. With this interval, the mothers who were allocated to group 2 were given sufficient time to express breast milk. Investigators, nurses, and mothers were not blinded to the treatment allocation.

Procedure

Infants who were allocated to group 1 and group 2 were placed on a changing table, and fibers were positioned on the scalp. A waiting period was allowed for the infant to get used to the equipment. Two minutes before starting the heel stick procedure, a 2-mL bolus of 20% oral glucose solution (group 1) or a 2-mL bolus of the mother's breast milk (group 2) was administered directly into the infant's mouth with a syringe.

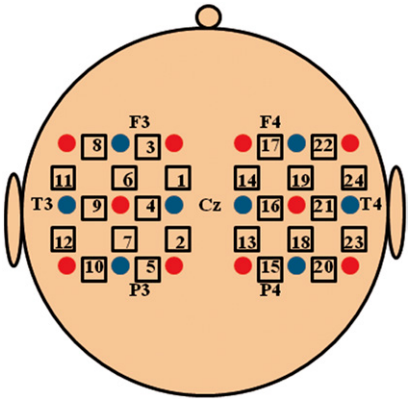

FIGURE 1
Schematic representation of optical fibers positioned on the left and right sides of the newborn's head. Red dots indicate near-infrared light emitters, and blue dots indicate near-infrared light detectors; numbered squares indicate channels. The international 10–20 EEG system reference points are also reported. F3, frontal left; F4, frontal right; P3, parietal left; P4, parietal right.

Infants in group 3 and group 4 were tested while in their mothers' arms (mother–infant relationship). Optical fibers were placed on the scalp, and a waiting period was allowed for the newborn to adapt. Two minutes before the heel stick procedure, a 2-mL bolus of 20% oral glucose solution was given directly into the infant's mouth with a syringe (group 3) or breastfeeding was started (group 4). The mothers were asked not to talk to their infants. Breastfeeding lasted at least until the heel stick procedure was completed.

NIRS data collection during the heel stick was performed as follows. After collecting baseline data for 10 seconds without any stimulation other than the nurse holding the infant's foot, the heel was disinfected. To avoid possible cortical activity associated with the disinfection stimulus,[25] an additional 25 seconds were allowed to elapse, and the heel stick was then performed without squeezing the heel. NIRS data were collected within 25 seconds of the painful stimulation.

Pain expression during the heel stick was assessed by using the Neonatal Infant Pain Scale (NIPS),[29] which is used to evaluate 6 pain signs (facial expression, crying, breathing pattern, arm and/or leg activity, and state of arousal) and score pain expression from 0 (no pain) to 7 (highest pain). NIPS scoring was performed by an investigator who was blinded to the NIRS data.

Data Analysis

We analyzed the increase in the HbO_2 concentration during the heel stick procedure as an index of cortical activation. Measures that were adopted to remove components of HbO_2 detection that were related to physiologic noise or movement have been described elsewhere.[30] Channels with poor signal because of interference were excluded from the statistical analysis.

Significantly activated channels during the heel stick were identified by using a 1-tailed Student's *t* test because there was only 1 direction of interest to test (HbO_2 increase). For every channel, the baseline was calculated as the mean relative HbO_2 changes in the 10 seconds before disinfection. The hemodynamic response that was associated with the painful stimulation was calculated as the mean change in HbO_2 concentration during the 25 seconds after the heel stick stimulation. Pain-associated cortical activity was assessed for each channel by using 1-tailed paired *t* tests that were used to compare the HbO_2 mean concentration changes during baseline and during the hemodynamic response. Analyses were performed separately for

TABLE 1 Baseline Demographic and Clinical Characteristics of Each Treatment Group ($N = 20$)

Baseline Characteristics	Group 1 (OGS)	Group 2 (EBM)	Group 3 (MH and OGS)	Group 4 (Breastfeeding)
Maternal age, y, mean (SD)	32.9 (4.2)	34.0 (5.6)	33.4 (5.7)	31.1 (4.0)
Cesarean delivery, *n* (%)	4 (20)	4 (25)	5 (25)	4 (20)
Gestational age, wk, mean (SD)	39.6 (1.1)	39.8 (1.3)	39.8 (1.2)	39.9 (1.2)
Birth wt, mean (SD)	3354.0 (431.8)	3155.5 (373.0)	3429.5 (477.1)	3298.3 (325.6)
Wt at assessment, mean (SD)	3255.0 (455.2)	3074.5 (300.0)	3278.5 (372.3)	3181.5 (299.6)
Male or female sex, respectively	9, 11	8, 12	9, 11	12, 8

EBM, expressed breast milk; MH, maternal holding; OGS, 20% oral glucose solution.

each group. A false discovery rate (FDR) approach was used to control for type I error in multiple testing situations ($q = 0.05$).[31]

We assessed the possible differences in pain expression intensity among the 4 groups using a nonparametric Kruskal-Wallis test to compare the NIPS scores that were exhibited by newborns in each of the groups during the heel stick. All analyses were performed by using SPSS version 13.0 for Windows (SPSS Inc, Chicago, IL).

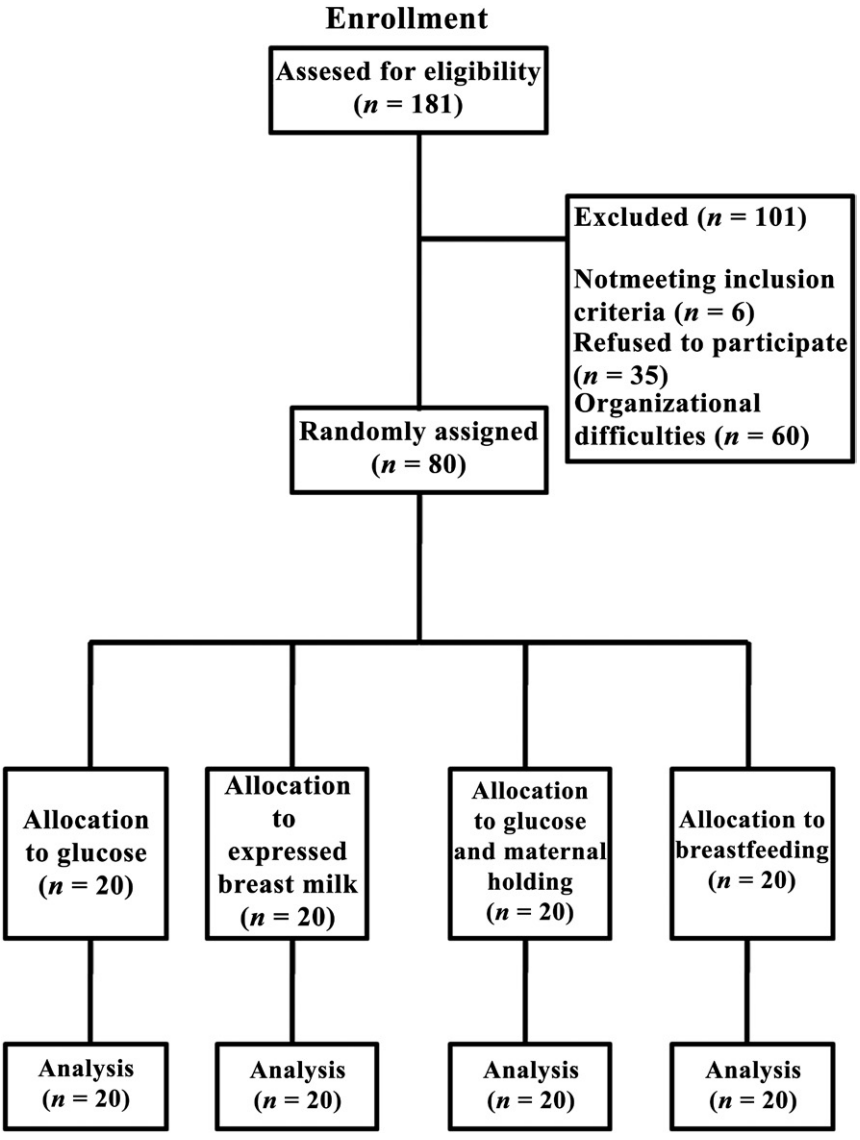

FIGURE 2
Consolidated Standards of Reporting Trials diagram showing participant flow through study stages.

RESULTS

Data were collected between November 2016 and May 2017. We show the participants' flow through each stage of the study in Fig 2. The baseline demographic and clinical characteristics of each treatment group are reported in Table 1.

In group 1, no channel passed the FDR threshold ($P < .05$). Thus, no significant cortical activation was detected in association with the heel stick after the administration of the oral glucose solution alone. The median NIPS score was 5.00 (interquartile range [IQR] 3.25–6.75).

In group 2, 4 channels passed the FDR threshold ($P < .05$). The administration of expressed breast milk before the heel stick induced significant activation in the left motor (channel 3, $t_{[18]} = -2.783$; $P = .006$) and somatosensory (channel 4, $t_{[18]} = -3.016$; $P = .0035$) cortical areas and, symmetrically, in the right motor (channel 17, $t_{[19]} = -3.120$; $P = .003$) and somatosensory areas (channel 16, $t_{[17]} = -3.170$; $P = .003$; Fig 3). The median NIPS score was 5.50 (IQR 2.00–7.00).

In group 3, no channel passed the FDR threshold ($P < .05$). No significant cortical activation was observed in association with a heel stick after oral glucose administration when the procedure was performed with the newborn in his or her mother's arms. The median NIPS score was 2.00 (IQR 1.00–5.00).

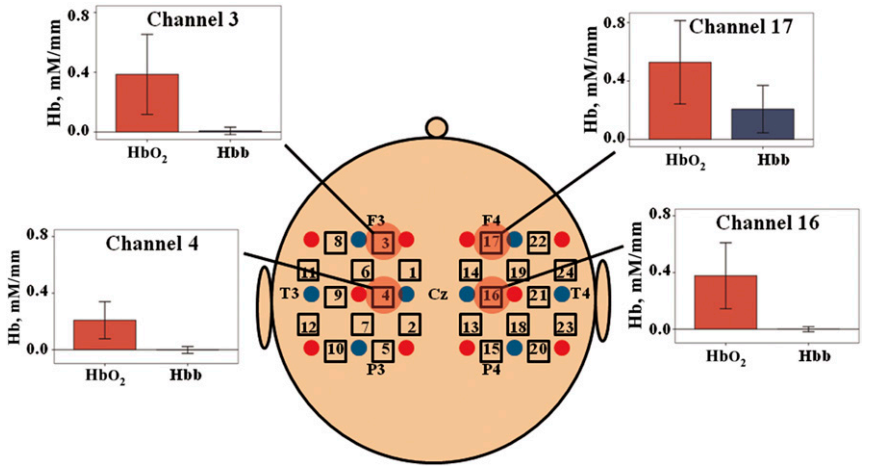

FIGURE 3

HbO_2 and deoxyhemoglobin mean variation in the 25 seconds after a heel stick observed in the 4 channels that were activated in newborns who were receiving expressed breast milk before the procedure. Channel positioning is reported on a schematic head. Mean hemoglobin variation (±2 SE), which is reported in millimolars per millimeters, is on the y-axis. F3, frontal left; F4, frontal right; Hb, hemoglobin; Hbb, deoxyhemoglobin; P3, parietal left; P4, parietal right.

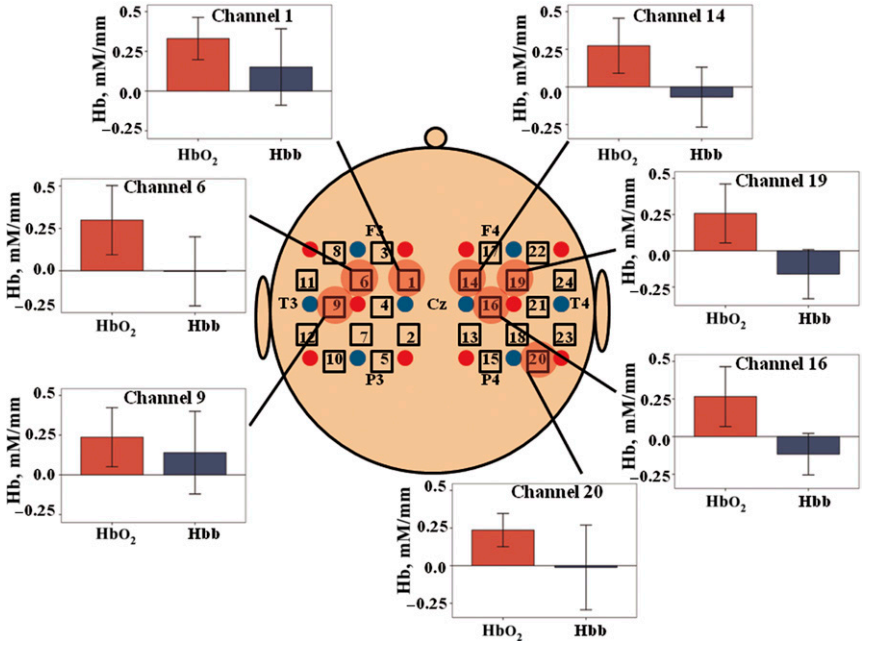

FIGURE 4

HbO_2 and deoxyhemoglobin mean variation in the 25 seconds after a heel stick observed in the 7 channels that were activated in newborns who were breastfed before and throughout the procedure. Channel positioning is reported on a schematic head. Mean hemoglobin variation (±2 SE), which is reported in millimolars per millimeters, is on the y-axis. F3, frontal left; F4, frontal right; Hb, hemoglobin; Hbb, deoxyhemoglobin; P3, parietal left; P4, parietal right.

In group 4, 7 channels passed the FDR threshold ($P < .05$), revealing bilateral, diffused activation of the neonatal cortex associated with a heel stick procedure that was performed during breastfeeding. The following areas were activated: left-superior sensorimotor cortex (channel 1, $t_{[19]} = -4.436$; $P < .001$), left somatosensory cortex (channel 6, $t_{[16]} = -2.843$ [$P = .006$]; channel 9, $t_{[18]} = -2.387$ [$P = .014$]), right-superior sensorimotor cortex (channel 14, $t_{[19]} = -2.821$; $P = .0055$), right somatosensory cortex (channel 16, $t_{[19]} = -2.576$ [$P = .0095$]; channel 19, $t_{[19]} = -2.657$ [$P = .008$]), and right-posterior parietal cortex (channel 20, $t_{[16]} = -3.888$; $P < .001$; Fig 4). The median NIPS score was 2.50 (IQR 1.00–4.75).

The NIPS scores for clinical pain expression differed significantly among the 4 groups ($\chi^2_{(3)} = 12.194$; $P = .007$). We performed a post hoc analysis comparing NIPS scores among the 4 groups using a nonparametric Mann–Whitney *U* test. The following comparisons were significant: (1) breastfeeding (group 4) was associated with a lower NIPS score (ie, induced a higher degree of analgesia) when compared with oral glucose (group 1, $z = 2.900$; $P = .004$), (2) maternal holding plus oral glucose (group 3) yielded a lower NIPS score than oral glucose alone (group 1, $z = 2.567$; $P = .010$), (3) breastfeeding (group 4) was associated with a lower NIPS score compared with expressed breast milk (group 2, $z = 2.226$; $P = .026$), and (4) maternal holding plus oral glucose (group 3) resulted in a lower NIPS score compared with expressed breast milk (group 2, $z = 2.094$; $P = .038$). The other comparisons were not significant (Table 2). No adverse events were observed.

DISCUSSION

We aimed to assess the effect of different nonpharmacological analgesic interventions on neonatal responses to a minor painful procedure (heel stick). We assessed both brain cortical response (by multichannel NIRS) and clinical response (using the NIPS).

The administration of a 20% oral glucose solution did not result in significant cortical activation during heel sticks either alone or combined with maternal holding. The median

TABLE 2 Comparison of the NIPS Score Observed in Each Analgesic Group With That Observed in Each of the Others

Comparison[a]	Median Score	*z*	*P*
OGS versus expressed breast milk	5.00 vs 5.50	0.014	.99
OGS versus maternal holding plus OGS	5.00 vs 2.00	2.567	.01*
OGS versus breastfeeding	5.00 vs 2.50	2.900	.004*
Expressed breast milk versus maternal holding plus OGS	5.50 vs 2.00	2.094	.038*
Expressed breast milk versus breastfeeding	5.50 vs 2.50	2.226	.026*
Maternal holding plus OGS versus breastfeeding	2.00 vs 2.50	0.055	.97

OGS, 20% oral glucose solution.

[a] Nonparametric Mann–Whitney U test.

* $P < .05$.

NIPS score was higher when the oral glucose was administered alone. From a neurophysiological standpoint, Slater et al[21] found sucrose analgesia to have no effect on newborn nociceptive cerebral processing. However, the study was performed by using EEG and recording cerebral activity from the vertex (Cz point of the international 10–20 EEG placement system). From a clinical standpoint, sucrose decreased pain scores. Glucose is also recognized as being clinically effective in decreasing pain scores during heel sticks.[4]

The mechanism of action of oral glucose analgesia in newborns is not yet fully understood. Authors of animal studies have indicated that orally administered sweet solutions can be used to activate the brainstem structures that are involved in descending pain modulation, such as the periaqueductal gray matter or the nucleus raphe magnus, with no involvement of the forebrain.[32] This process could be mediated by taste sensation[33] because the ascending pathway for taste has its first relay in the brainstem (rostral nucleus tractus solitarius).[32] Clinically, the effect is rapid, occurring in <2 minutes.[34] The analgesic effect of oral glucose could be due to a weakening of pain cortical processing[20,22] as has already been observed in adults with a functional MRI (fMRI).[35]

The analgesic effects of breastfeeding and expressed breast milk, which was administered by using a syringe while the infant lay on a changing table, were examined separately.

To our knowledge, this is the first study in which the neonatal cortical response to expressed breast milk analgesia was assessed. Contrary to glucose administration, breast milk administration did not appear to weaken cortical processing, but it was associated with the bilateral activation of the motor and somatosensory areas. Authors of a previous fMRI study showed that the bilateral activation of such areas was associated with pinprick stimulation in newborn infants.[36] Clinically, the median NIPS score that was found in the expressed breast milk group was the highest, meaning that this was the least effective of the 4 methods.

We did not study the effect of maternal holding alone because it is already known to be clinically beneficial for term infants.[37] Regarding neurophysiological aspects, we have previously shown that maternal holding alone during a heel stick is associated with bilateral somatosensory and right-inferior frontal cortex activation.[23] In addition, the use of skin-to-skin contact may provide some degree of pain relief as assessed by using pain scores[38] and 2-channel NIRS scores.[39] In our study, no cortical activation was observed when oral glucose was combined with maternal holding. Our results support our hypothesis that sweet solutions weaken somatosensory cortical processing in general rather than nociceptive processing alone.

Breastfeeding was associated with extensive cortical activity involving the bilateral somatomotor and somatosensory cortices and the right-posterior parietal cortex. Clinically, the NIPS score was lower in the breastfeeding group than in both the glucose and the expressed breast milk administration groups. With our results, we confirm a possible role of multisensory somatic stimulation (tactile, proprioceptive, and thermal) in breastfeeding analgesia.[22] Interestingly, in adults, the right-posterior–superior-temporal sulcus was identified as a region that mediates the translation of tactile stimuli into positive and socially relevant interpersonal touch.[40] Although NIRS scores cannot match the spatial resolution of fMRIs, it is worth noting that this area is located in close proximity to the right-posterior cortex, which we found became activated during breastfeeding. We speculate that this process might also occur in breastfed newborns.

From a clinical standpoint, both maternal holding plus oral glucose and breastfeeding were shown to be more effective in reducing NIPS scores than either oral glucose or expressed breast milk alone. As hypothesized, maternal relation improved the analgesic effects of both oral solutions. Clinically, maternal holding is already known to improve sweet oral solution analgesia.[12,41] Breast milk has been reported to reduce behavioral pain expression when compared with a placebo or massage,[10] whereas breastfeeding has repeatedly been shown to be an effective analgesic.[8–10,42] Taken together,

these findings reveal that the main analgesic factor in breastfeeding is the relational experience rather than the breast milk itself.

Cortical processing does not appear to be necessary for analgesia to be effective. Maternal holding plus glucose revealed a stronger analgesic effect than glucose solution alone; however, no cortical activation was observed with either method during the heel stick, revealing that the neurobiological basis of the effect is probably subcortical.[43] Conversely, maternal holding plus glucose and breastfeeding revealed no significant differences in terms of clinical analgesic effectiveness (as assessed with NIPS), but only breastfeeding resulted in extensive cortical activation. In addition, breastfeeding also revealed a greater clinical analgesic effect than expressed breast milk alone. Therefore, we speculate that somatic sensations that are processed by the cortex, such as sucking activity and socially relevant tactile stimulations, [40] might be important components of breastfeeding analgesia.

Our study has several limitations, including the following: (1) A functional assessment with NIRS is limited to the cerebral cortex, and the spatial resolution cannot match that of an fMRI. However, NIRS is relatively insensitive to movement artifacts and can be used at the bedside. (2) Our sample size was limited; therefore, our results need to be confirmed in a larger sample. (3) And although the NIPS evaluation was performed by an expert nurse who was blinded to the NIRS results, newborn pain expressions were not video recorded and scored in a separate session.

CONCLUSIONS

Each combination of a painful procedure and the analgesic method used might constitute a specific complex experience for newborns because of the recruitment of differently distributed neural patterns. These are, presumably, not limited to the cerebral cortex and thus need to be investigated in greater depth. Discrepancies exist between the clinical and neurophysiological assessments of nociceptive interventions. Therefore, a multidimensional approach (eg, behavioral, physiologic, neurophysiological, and hormonal) seems to be more appropriate than neurophysiological methods alone to achieve a comprehensive assessment of analgesic effectiveness. Although the current study has limitations, our results support our hypothesis that the maternal relationship may provide more effective analgesia than oral solutions alone. In our study, the difference in analgesic effectiveness between breastfeeding and glucose plus holding is minimal. Considering that breastfeeding is based on the natural and unique primary relationship between the mother and her newborn and entails no additional costs, breastfeeding should be considered as the preferred nonpharmacological analgesic method during minor painful procedures in infants who are clinically able to breastfeed.

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ABBREVIATIONS

FDR: false discovery rate
fMRI: functional MRI
HbO_2: oxyhemoglobin
IQR: interquartile range
NIPS: Neonatal Infant Pain Scale
NIRS: near-infrared spectroscopy

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