Original Research

international lactation consultant association®

Journal of Human Lactation
2017, Vol. 33(2) 300–308

DOI: 10.1177/0890334417693225
journals.sagepub.com/home/jhl
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Analgesic Effect of Maternal Human Milk Odor on Premature Neonates: A Randomized Controlled Trial

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Abstract

Background: Two studies have demonstrated an analgesic effect of maternal milk odor in preterm neonates, without specifying the method of olfactory stimulation.

Research aim: This study aimed to assess the analgesic effect of maternal milk odor in preterm neonates by using a standardized method of olfactory stimulation.

Methods: This trial was prospective, randomized, controlled, double blinded, and centrally administered. The inclusion criteria for breastfed infants included being born between 30 and 36 weeks + 6 days gestational age and being less than 10 days postnatal age. There were two groups: (a) A maternal milk odor group underwent a venipuncture with a diffuser emitting their own mother's milk odor and (2) a control group underwent a venipuncture with an odorless diffuser. The primary outcome was the Premature Infant Pain Profile (PIPP) score, with secondary outcomes being the French scale of neonatal pain—Douleur Aiguë du Nouveau-né (DAN) scale—and crying duration. All neonates were given a dummy.

Results: Our study included 16 neonates in the maternal milk odor group and 17 in the control group. Neonates exposed to their own mother's milk odor had a significantly lower median PIPP score during venipuncture compared with the control group (6.3 [interquartile range (IQR) = 5-10] versus 12.0 [IQR = 7-13], $p = .03$). There was no significant difference between the DAN scores in the two groups ($p = .06$). Maternal milk odor significantly reduced crying duration after venipuncture (0 [IQR = 0-0] versus 0 [IQR = 0-18], $p = .04$).

Conclusion: Maternal milk odor has an analgesic effect on preterm neonates.

Keywords

breastfeeding, breastfeeding benefits, breast pain, human milk, human milk collection, infant behavior

Background

Preterm neonates are exposed to multiple painful and invasive procedures (Roofthooft, Simons, Anand, Tibboel, & van Dijk, 2014). Pain has noxious effects that include short- and long-term consequences (Grunau, Holsti, & Peters, 2006; Hohmeister, Demirakça, Zohsel, Flor, & Hermann, 2009). By recording cortical responses to pain using functional near-infrared spectroscopy (NIRS) in preterm neonates, a reduction can be observed in cerebral oxygenation in the somatosensory cortex in response to painful stimuli (Bartocci, Bergqvist, Lagercrantz, & Anand, 2006). Repeatedly painful procedures may have long-term effects on the hypothalamo-pituitary stress regulation system (Holsti, Weinberg, Whitfield, & Grunau, 2007). In both full-term and preterm neonates, this affects behavioral and physiological responses to pain and reduces the pain threshold (Taddio & Katz, 2005).

In neonatal intensive care units, pain prevention is an ethical and medical obligation that, despite international guidelines, is not yet sufficiently implemented (Committee on Fetus and Newborn & Section on Anesthesiology and Pain Medicine, 2016). Oral sucrose is an efficient and recommended pain prevention method in preterm neonates (Stevens, Yamada, Lee, & Ohlsson, 2013); however, a recent

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Date submitted: July 6, 2016; Date accepted: January 14, 2017.

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study casts doubt on its efficacy (Slater et al., 2010). Furthermore, the long-term effects of cumulative doses of oral sucrose are controversial and not well assessed (Harrison, Beggs, & Stevens, 2012; Holsti & Grunau, 2010). Pharmacologic analgesic treatments are available; however, a large number of experimental studies in animals have questioned their safety in neonates, particularly preterm neonates (Attarian et al., 2014; Dong & Anand, 2013). Various nonpharmacologic methods have also been put forward. These methods include breastfeeding, nonnutritive sucking, skin-to-skin care, positioning, swaddling, and various types of developmental care (Cignacco et al., 2007; Shah, Herbozo, Aliwalas, & Shah, 2012). These methods have shown relative efficacy, especially when used in combination. It can be difficult for preterm neonates to transfer milk at the breast successfully, which is a requirement for the analgesic effect of breastfeeding to be successful. The physical maternal presence can have an effect by maternal touch or maternal odor (Prasopkittikun & Tilokskulchai, 2003). Therefore, in this context, it is important to explore other analgesic methods.

At birth, the olfactory system of neonates, including preterms, is more mature than their other senses (Marlier, Gaugler, Astruc, & Messer, 2007). Preterm and full-term neonates can distinguish between different smells, including maternal milk odor, despite not having had any postnatal exposure (Marlier et al., 2007; Marlier & Schaal, 2005). From the first days of life, newborns are able to detect and recognize the odor of their mother's nipple as well as odors belonging to their mother's body and her human milk (Marlier & Schaal, 2005). Using NIRS monitoring, Bartocci et al. (2000) observed an olfactory cortex activation after olfactory stimulation in both full-term and preterm neonates. Maternal milk odor increased oxygenated blood flow in the orbito-frontal region to a greater extent than did formula milk odor (Aoyama et al., 2010). Several randomized studies have analyzed the calming effect of maternal milk odor in full-term neonates by recording the crying duration, grimacing, and motor activities during and after a painful event (Nishitani et al., 2009; Rattaz, Goubet, & Bullinger, 2005). In preterm neonates, a randomized study has also shown the calming effect of a familiar, vanilla-based odor after a painful stimulus (Goubet, Rattaz, Pierrat, Bullinger, & Lequien, 2003). The underlying mechanism sustaining the calming effect is not known accurately. Such studies in young rat pups attest to the link between opioids, pain, and familiar odors (Roth & Sullivan, 2003), but at this point we can only speculate about such a mechanism in human infants (Goubet et al., 2003). Effective nonpharmacologic pain intervention may elicit activation of neuropeptide systems, such as cholecystokinin (Cignacco et al., 2007). Cholecystokinin is an opioid-modulating substance that promotes stressor adaptability and can achieve an analgesic effect through the potentiation of opioid activity (Hebb, Poulin, Roach, Zacharko, & Drolet, 2005).

Key Messages

- Several studies have demonstrated an analgesic effect of maternal milk odor in preterm neonates without standardized olfactory stimulation.
- We used a standardized method of olfactory stimulation in preterm neonates. Maternal milk odor is found to have an analgesic effect, measured by the Premature Infant Pain Profile, during venipuncture.
- Olfactory stimulation by maternal milk could be used in pain prevention in neonatal intensive care units.

To our knowledge, there have been only two studies that have assessed the analgesic effect of maternal milk odor in preterm neonates (Badiee, Asghari, & Mohammadizadeh, 2013; Jebreili et al., 2015). Compared with formula milk odor (Badiee et al., 2013) or with vanilla odor (Jebreili et al., 2015), these studies demonstrate an analgesic effect of maternal milk odor. The olfactory stimulation in these studies was conducted using an unspecified amount of human milk on a filter paper or cotton ball. Our objective was to assess the analgesic effect of maternal milk odor in preterm neonates during a venipuncture by using a standardized method of olfactory stimulation.

Methods

Design

The trial was prospective, randomized, controlled, and double blinded. We used a randomized, double-blind, placebo-controlled design, which is the most appropriate design to demonstrate the efficacy of a new experimental intervention in accordance with the Levels of Evidence classification of the Evidence-Based Medicine Working Group (Oxford Centre for Evidence-Based Medicine, 2009). In the future, national and international recommendations could be updated based on our findings.

In both groups, the pain stimulus was a venipuncture. The participants were randomized into two groups. In the experimental "maternal milk odor" group, the venipuncture was performed on the neonate in the presence of a diffuser emitting the mother's milk odor. In the control group, the venipuncture was performed with an odorless diffuser. Computer-generated, randomized lists were provided by the Clinical Research Unit (KB) before the beginning of the study with a permuted randomization scheme (block size 4, randomization ratio 1:1).

This study was approved by the French Patient Protection Committee (No. IDRCB 2012-A00360-43, 20/09/2012) and

authorized by the French Agency for the Safety of Health Products (20/03/2012). The ClinicalTrials.gov identifier is NCT02381691.

Setting

This centrally administered trial was conducted in a level 3 maternity unit from Marseille in France and included neonates born between January 2013 and December 2014. In the study hospital, there are 2,500 live births per year, 8% of which are preterm births, and 70% are breastfeeding.

Sample

The inclusion criteria were neonates who were fed with their own mother's milk; born between 30 and 36 weeks + 6 days gestational age (GA); less than 10 days postnatal age; and hospitalized in neonatal units. The exclusion criteria were neonates who had a birth weight lower than the 5th percentile for GA according to Olsen curves (Olsen, Groveman, Lawson, Clark, & Zemel, 2010); were not clinically stable; had an interval of less than 48 hours of weaning from nasal continuous positive airway pressure; had been administered any analgesic or sedative drug in the past 48 hours; and had congenital anomalies or life-threatening diseases.

The number of participants required was calculated from the primary outcome, that is, the Premature Infant Pain Profile (PIPP) score difference between the two groups during the venipuncture. Our assumptions were based on Badiee and colleagues' (2013) study comparing the PIPP score between maternal milk odor and formula milk odor (mean difference = 4 points). We deliberately overestimated the expected difference between the two groups by 5 points, considering this difference to be more clinically significant. With a standard deviation set at 5, a power of 80%, and an alpha risk of 5%, we determined that a total of 15 participants per group was needed. Taking into account a refusal or exclusion rate of approximately 10%, we set the minimum number of participants to be included in each group at 16. Thirty-three neonates were included and randomly assigned to one of the two groups.

Measurement

The analgesic effect was rated using three different outcomes. The primary outcome measure was a clinical pain score, calculated by using an assessment tool, the Premature Infant Pain Profile, ascertained during the venipuncture. The PIPP is a score composed of seven items: three behavioral (brow bulge, eye squeeze, and nasolabial furrow); two physiological (heart rate and oxygen saturation); and two contextual (gestational age and behavioral state). The PIPP score is evaluated from 0 to 21. The higher the PIPP scores, the more intense the pain. The PIPP score is currently the most widely validated assessment tool for preterm neonates, with its advantage of taking the GA into account (Jonsdottir & Kristjansdottir, 2005). The secondary outcomes were the French scale of neonatal pain—Douleur Aiguë du Nouveau-né (DAN) scale—and crying duration. The DAN scale is composed of three items: facial expression, limb movements, and vocal expressions of pain (Carbajal, Paupe, Hoenn, Lenclen, & Olivier-Martin, 1997). The higher the DAN scores, the more intense the pain. The DAN scale is widely used in assessment pain in neonates (Modarres, Jazayeri, Rahnama, & Montazeri, 2013; Uyan, Bilgen, Topuzoğlu, Akman, & Ozek, 2008).

An air-flow odor diffuser was filled with 5 grams of a water-soluble polymer gel in the form of beads that absorbed and then slowly released an odor over time. The diffuser was placed under a hood with an air flow of 6 L/min and was manually switched on 3 minutes before the venipuncture and switched off 9 minutes after the completion of the procedure. A picture of the device is shown in Photograph 1. The type and quantity of maternal milk to be used were determined before the study by an olfactory test. During the olfactory test, an initial ratio of 1 ml maternal milk to 5 g weighted beads was gradually increased by 1-ml increments and placed in the diffuser. One expert's face was sprayed with a specific ratio at 5-min intervals and, based on established olfactory descriptors, the other five experts judged its intensity on a 1-5 scale. Each expert's perceptions concluded the following: 1 ml milk to 5g beads, no milk odor perceived; 5 ml milk to 5 g beads, two out of five perceived an intensity of two-fifths; and 6 ml milk to 5 g beads, all perceived the milk odor with variations in intensity. The "best nose" needed a 5 ml milk to 5 g beads ratio to perceive the milk odor with moderate intensity and good reproducibility. This test was then performed on five neonates, and two physicians calculated the scores using Brazelton's Neonatal Behavioral Assessment Scale (Lester, Tronick, & Brazelton, 2004). The scores had to indicate a significant neonate improvement and achieve a good interobserver agreement. This score was used only for the olfactory test before the study and not for the assessment of neonatal pain. This olfactory test enabled us to determine that, in the maternal milk group, we needed to add 5 ml of fresh milk from the neonate's mother.

Perinatal clinical data were collected from the medical records. The following data were collected from the video output: duration between the diffuser being switched on until 10 minutes after the venipuncture; duration of the venipuncture; number of needle pricks; the presence/absence of parents; and a quiet room (yes/no).

Data Collection

After obtaining signed consents by two legal representatives, the neonates were randomly assigned to one of the two treatment groups.

All the neonates were given a dummy. The use of a dummy was identical in the two groups, thus allowing the nonpharmacologic analgesic method of nonnutritive sucking in the control group. A unit professional nurse performed the venipuncture with a 20G needle while following a standardized procedure and was blinded to the allocation group. The venipuncture was for a therapeutic reason and not just for the study. To ensure blinding, only the chief professional nurse was aware of the neonates' group allocations and was able to distribute diffusers with 5 ml of maternal milk according to the randomization. The chief professional nurse was not present during venipuncture, which was done by the patient's professional nurse.

The neonates were filmed with a SONY® HDR-SR11 camcorder from the time the diffuser was switched on until 10 minutes after the venipuncture. The video was then viewed and analyzed by physicians blinded to the treatment group. Analysis was carried out independently by two teams, each composed of a senior and a junior physician.

The primary outcome was the PIPP score, ascertained during the venipuncture. The PIPP scores were also assessed before and 10 minutes after the venipuncture. Two teams, blinded to the patient group, analyzed these scores by viewing the patients' videos rather than during the venipuncture. Each team independently provided a score. The two teams defined the mean PIPP scores, and the interobserver reliability was calculated. The DAN scores were obtained using the same procedure as for the PIPP scores. For the PIPP score, we calculated the differences between the scores assessed before and during the venipuncture and the differences between the scores assessed during and after the venipuncture. These differences were then compared between the two groups. We then did the same for the DAN scores. Crying duration was registered during Phase 1, when the diffuser was switched on until the start of the venipuncture; Phase 2, while performing the venipuncture; and Phase 3, from the end of the venipuncture until the diffuser was switched off. Crying durations were analyzed and expressed as a percentage in each of the three phases.

Data Analysis

The intention-to-treat population (including all participants who were randomized and were at least evaluated at baseline) was used for the analysis. The normality of the parameters was estimated using the Shapiro test. The baseline parameters were presented per group. The PIPP score assessed during the venipuncture was compared between the two groups using the Mann–Whitney nonparametric test according to the variable distribution. The same procedure was performed for the PIPP and DAN scores assessed before and after the venipuncture. The crying duration/phase was compared between the two groups using the Mann–Whitney nonparametric test. For the PIPP score, we calculated the differences between the scores assessed before and during the venipuncture and the differences between the scores assessed during and after the venipuncture. These differences were then compared between the two groups. We then did the same for the DAN scores.

Results

Demographic Characteristics of the Sample

The primary endpoint was available for 16 in the maternal milk odor group and 17 in the control group. The flow chart is provided in Figure 1. The neonates' clinical characteristics are shown in Tables 1 and 2. There were 9 boys (56%) in the maternal milk odor group and 3 (35%) in the control group. The median gestational age was 32 weeks 4 days in the maternal milk odor group and 33 weeks 6 days in the control group. The median birth weight was 1,752 grams in the maternal milk odor group and 1,855 grams in the control group. The baseline age was 7 days in the maternal milk group and 6 days in the control group.

There were no significant differences regarding the data collected during venipuncture. Only one newborn in the maternal milk group had ventilatory support by nasal canula. The parents were present during two newborns' painful venipunctures. One newborn from the maternal milk group and four from the control group received two venipunctures. Other newborns received a single venipuncture. The median venipuncture was 258 seconds in the maternal milk group and 200 seconds in the control group (nonsignificant difference).

Differences Between Intervention and Control Groups

The median PIPP score assessed during the venipuncture was significantly higher in the control group compared with the maternal milk odor group, as illustrated in Figure 2 and Table 3.

The comparisons between the two groups of the PIPP scores after the venipuncture and of the DAN scores during and after the venipuncture did not differ significantly (see Table 3). During the venipuncture, lower DAN scores were found in the maternal milk odor group in comparison with the control group, but the differences were not statistically significant ($p = .06$) (see Figure 2). The comparisons of the differences in PIPP score before/during the venipuncture and during/after the venipuncture are shown in Figure 3; the same is shown for the DAN score. The control group showed significantly greater differences than the maternal milk odor group.

During the venipuncture, the crying duration during Phase 2 tended to be shorter in the maternal milk odor group than the control group (see Table 3). After the venipuncture, the crying duration during Phase 3 was significantly lower in the maternal milk odor group when compared with the control group (see Table 3).

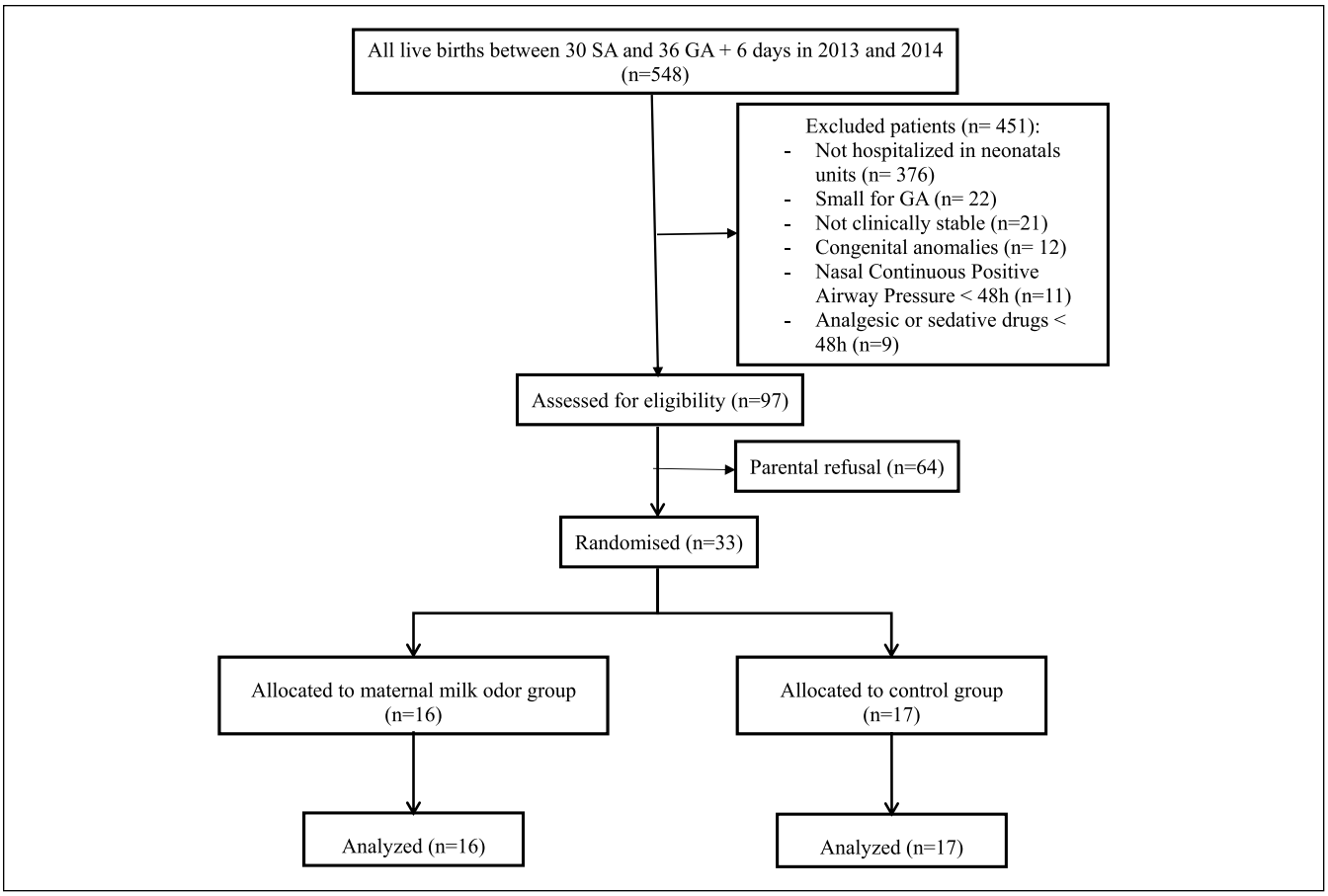

Figure 1. Sample selection flow chart. GA = gestational age.

Table 1. Clinical Characteristics of the Sample.

Variable	Total (*N* = 33)	Maternal milk odor group (*n* = 16)	Control group (*n* = 17)	*p*[a]
Male	15 (45)	9 (56)	6 (35)	0.23
Gestational diabetes	6 (18)	4 (25)	2 (12)	0.40
Antenatal corticotherapy	23 (69)	11 (69)	12 (71)	1
Twin	14 (42)	7 (43)	7 (41)	0.88
Inborn[b]	30 (91)	14 (87)	16 (94)	0.60
Cesarean section	23 (69)	12 (75)	11 (65)	0.71
Small for gestational age	4 (12)	1 (6)	3 (17)	0.46
5 min Apgar < 7	1 (3)	0 (0)	1 (6)	1
Surfactant therapy	8 (24)	5 (31)	3 (17)	0.44
Type of enteral feeding				0.61
Maternal milk only	15 (46)	8 (50)	7 (41)	
Maternal + formula feeding	18 (54)	8 (50)	10 (59)	
Mode enteral feeding				0.06
Nasogastric tube, no breastfeeding	13 (39)	9 (56)	4 (23)	
Breastfeeding ± tube feeding	20 (60)	7 (44)	13 (76)	

Note. *N* = 33.
[a]Comparison between maternal milk odor group and control group.
[b]Inborn refers to being born in the facility where data are collected as opposed to being transferred in.

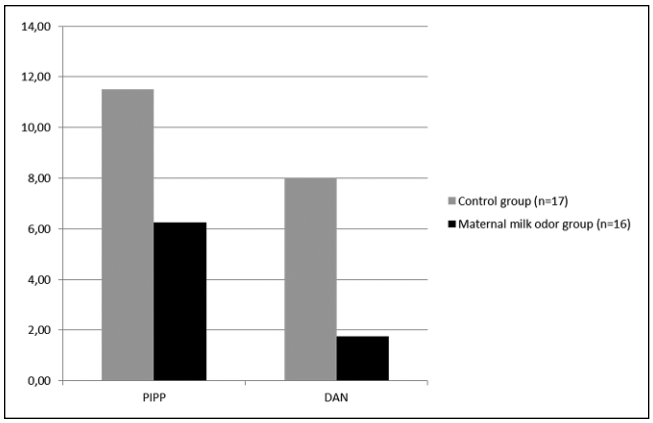

Figure 2. Median Premature Infant Pain Profile (PIPP) and Douleur Aigue du Nouveau-né (DAN, French scale of neonatal pain) scores assessed during the venipuncture. $p < .05$, Mann–Whitney test.

Discussion

Using an odor diffuser is unique and, to our knowledge, has not been used to date to stimulate the olfactory responses in preterm neonates. We provide an alternate explanation for the current findings. Previous studies on the analgesic effect of human milk, before the start of our study, did not use validated assessment tools for neonates and have shown no efficacy during the painful stimulus. We describe the study limitations and identify areas that need further study. Then, we suggest possible applications to lactation practice.

Clear behavioral response to smell can be recorded in preterm infants starting from approximately 29 weeks' gestational age. In human fetuses, certain conditioning events may happen in utero that may subsequently account for the newborns' suckling behavior. In addition, these events may possibly account for the previously reported soothing effect of amniotic fluid and other maternal odors (Lagercrantz & Changeux, 2010). Furthermore, the olfactory system may provide a path to manipulate respiration in sleep and have an effect on the autonomic nervous system (Arzi et al., 2010).

Nishitani et al. (2009) explored the calming effect of maternal milk odor in full-term neonates. They analyzed three outcome measures: crying and grimacing duration and motor activity. These authors found a significant decrease in the crying duration after a heel stick but found no effect during the painful stimulus. Rattaz et al. (2005) have also shown a significant decrease in crying duration after a heel stick in full-term neonates exposed to the odor of their mother's own milk, after the nociceptive stimulation. In contrast, our study also seems to have an efficacy during nociceptive stimulation. Badiee et al. (2013) analyzed the analgesic effect of maternal milk odor in preterm neonates using the PIPP score as a primary outcome measure, with a heel stick as the pain stimulus. The neonates were randomized into two groups, with the first group exposed to maternal milk odor and the second to a formula milk odor. As in our study, they observed a significant decrease in the PIPP score during the pain stimulus (mean [standard deviation] 5.4 [1.9] in the human milk group vs. 9 [3.1] in the formula milk group). Their PIPP values were lower than ours, but they used a heel stick. They also analyzed crying duration as a secondary outcome measure, which was significantly decreased in the human milk group. Our study has an advantage of using a diffuser with a known and standardized quantity of human milk. In their study, the olfactory stimulation was performed with a filter paper without specifying the quantity. Jebreili et al. (2015) assessed the analgesic effect of maternal milk odor in preterm neonates using the PIPP score as a primary outcome measure, as did we and Badiee et al. Their pain stimulus was a venipuncture. The neonates were randomized into three groups, with a control group, a group exposed to human milk odor, and another to a vanilla odor. There were 135 patients who showed significant reduction in the PIPP score (mean [standard deviation] 7.31 [2.52] in the human milk odor group, 9.21 [2.78] in the vanilla odor group, and 10.61 [2.60] in the control group). Their PIPP value was similar to ours. As in the Badiee et al. study, the olfactory stimulation was performed with a cotton ball without specifying the quantity.

The strength of our study also includes a double-blind method, the use of a control group, a randomization of the neonates into two groups, and the use of two teams of observers to conduct independent analysis of the videos.

A limitation of the study is that several parents refused to participate, thus explaining the low number of participants. In addition, this is a single-center study and, therefore, has a possible bias as it relates to the recruitment center. Our study was limited by the fact that it was a pain assessment based on a clinical and behavioral scale. Many studies have shown the effect of oral administration of sugar as a newborn analgesic, as measured by behavioral scores of pain assessment (Stevens et al., 2013). These scores are dependent on the observer. Slater et al. (2010) undertook a randomized, controlled trial of sucrose analgesia using electroencephalography as a specific nociceptive brain activity to directly measure the infants' pain. Nociceptive brain activity after a heel lance did not differ significantly between infants who received sucrose and those who received sterile water, whereas the PIPP score was significantly lower in infants given sucrose. A pain assessment using a specific nociceptive brain activity might probably have been a better measurement, but the electrography installation disturbed neonates and changed their behavioral state. In the maternal milk odor group, the majority of neonates were tube fed rather than breastfed and had less direct oropharyngeal contact with maternal milk. This limited their contact and demonstrates that an analgesic effect exists even without previous exposure. Marlier and Schaal (2005) also showed that neonates were more attracted to maternal milk odor than to formula milk odor, and this preference was independent of any postnatal exposure. Newborns

Table 2. Clinical Characteristics of the Sample.

	Median (IQR)			
Variable	Total (*N* = 33)	Maternal milk odor group (*n* = 16)	Control group (*n* = 17)	*p*[a]
Gestational age (weeks)	33.2 (31.6-34.1)	32.4 (30.9-34)	33.6 (32.7-34.6)	.06
Birth weight (grams)	1790 (1647-1947)	1752 (1528-2070)	1855 (1670-1937)	.23
Corrected age (weeks)	34.1 (32.8-35)	33.2 (32-34.8)	34.3 (34-35.6)	.07
Age at inclusion (days)	6 (6-8)	7 (6-8)	6 (6-8)	.3

Note. *N* = 33. IQR = interquartile range.
[a]Comparison between maternal milk odor group and control group.

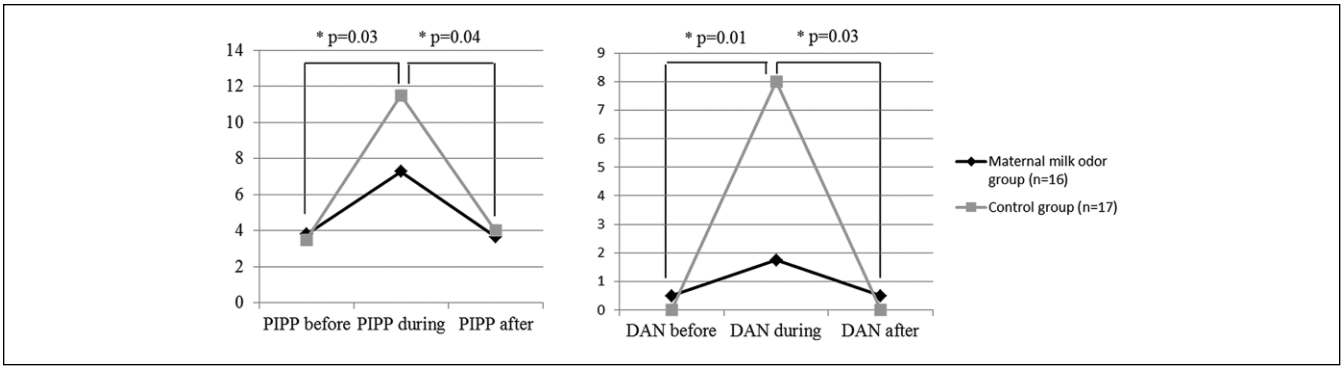

Figure 3. Median Premature Infant Pain Profile (PIPP) and Douleur Aigue du Nouveau-né (DAN, French scale of neonatal pain) scores before, during, and after venipuncture. $p < .05$, Mann–Whitney test.

Table 3. Comparison of Primary and Secondary Outcomes.

	Maternal milk odor group (*n* = 16)		Control group (*n* = 17)		
Variable	Median (IQR)	*M* (*SD*)	Median (IQR)	*M* (*SD*)	*p*
PIPP during venipuncture	6.3 (5-10)	7.28 (3.0)	12 (7-13)	10 (3.5)	.03[a]
PIPP after venipuncture	3.5 (3-4)	3.6 (1.1)	4 (3-4)	3.5 (1.0)	.91
DAN during venipuncture	1.75 (1.12-6)	3.3 (3.1)	8 (1.25-9.25)	6 (3.7)	.06
DAN after venipuncture	0.5 (0-0.5)	0.4 (0.6)	0 (0-1.25)	0.5 (0.8)	.31
Crying duration Phase 2 (%)	0 (0-0.14)	9.4 (16.7)	0.21 (0-0.47)	29.7 (32.1)	.06
Crying duration Phase 3 (%)	0 (0-0)	0.17 (0.6)	0 (0-0.18)	9.7 (17.3)	.04[a]

Note. *N* = 33. DAN = Douleur Aigue du Nouveau-né (French scale of neonatal pain); IQR = interquartile range; PIPP = Premature Infant Pain Profile. Phase 2: while performing the venipuncture; Phase 3: from the completion of the venipuncture until the diffuser was turned off.
[a]$p < .05$, Mann–Whitney test.

showed no conditioning or tolerance to their own mother's milk odor. Indeed, the perception of the maternal odor does not decrease with increasing age of the newborn. Although it is difficult for parents to witness any painful stimulus of their neonates, their physical presence during the venipuncture can have a synergic analgesic effect with maternal milk odor. In our study, parents were invited to be in attendance, but there were only two infants who had their parents present.

Olfactory stimulation using maternal milk odor could have other clinical implications in neonatal medicine in addition to pain prevention. This is also true for an olfactory stimulation with a pleasant vanilla-based odor, and it could be integrated into developmental care of preterm neonates (Rattaz et al., 2005). Last, olfactory stimulation may have a maturational effect on the autonomic nervous system and might be useful in developmental care, so we can consider this as an area for further study.

Therefore, from a clinical perspective, the odor of the mother's own milk had an analgesic effect on her preterm neonate. Maternal milk odor may be used for pain prevention to reduce the pain threshold.

Conclusion

In conclusion, compared with a control group, maternal milk odor has an analgesic effect on preterm neonates during venipuncture, using the PIPP, with a standardized method of olfactory stimulation. Maternal milk odor should be suggested as a nonpharmacologic pain prevention method in neonatal units.

Acknowledgments

The authors would like to thank the parents for allowing their infants to participate in the study, as well as the nursing staff and the nurse supervisor for her valued help. Their additional thanks go to the person and the society who helped them with the diffuser.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by institutional grants from the French 2013 Appel d'Offre Recherche Clinique Assistance Publique, Hôpitaux de Marseille. The sponsor was represented by Assistance Publique, Hôpitaux de Marseille, France, whose role was to control the appropriateness of ethical and legal considerations. Aroma Therapeutics provided materials and technical and scientific support for this study.

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