

The Effects of Different Strategies on the Painful Procedure Management, and the Physiological Parameters in Preterm Infants: A Systematic Review

Samaneh Norooziasl¹, Alireza Ataei Nakhaei², *Farnaz Kalani-moghaddam³, Neda Dehghani⁴, Fatemeh Ahmadinezhad⁴

¹Assistant Professor of Pediatric Endocrinology, Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. ²Assistant Professor of Pediatrics, Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. ³Fellowship of Neonatology, Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. ⁴Department of Midwifery, Firoozabad Branch, Islamic Azad University, Firoozabad, Iran.

Abstract

Background: Since preterm infants are subjected to numerous painful and stressful procedures, various strategies reducing the effects during and after painful procedures are required; we aimed to review the effectiveness of the use of different strategies as a primary or adjunctive treatment on the painful procedures, and the physiological parameters in preterm infants.

Materials and Methods: In this systematic review, English databases such as PubMed, Scopus, ISI Web of Science, Cochrane Library and EMBASE were systematically searched without any time limitation up to February 2019. The search keywords were (Aromatherapy OR Olfactory OR Amniotic Fluid OR Milk or odor) AND (Pain OR Venipuncture).

Results: Finally, four articles were included. The first study conducted on four groups indicates that the pain profile score and the crying time slightly differed during and after the heel prick procedure. In the second study, having pricked the heel, the breast milk group in comparison with the formula milk group embodied the lower premature infant pain profile (PIPP) score. According to the third study, both the vanilla and the breast milk odors groups indicated soothing effects on the premature infants during sampling; and only the breast milk odor is the soothing factor affecting the infants after the sampling termination. The fourth study found that the infants, who were exposed to their own mother's milk odor, when compared with the control group, encompassed the lowest median PIPP score during venipuncture.

Conclusion: Amniotic fluid, the mother's milk, vanilla and the mother's odor were determined as reduction and enhancement factors affecting painful procedures and physiological parameters in preterm infants, respectively.

Key Words: Aromatherapy, Painful Procedure, Preterm Infants, Systematic Review.

*Please cite this article as Norooziasl S, Ataei Nakhaei A, Kalani-moghaddam F, Dehghani N, Dehghani N, Ahmadinezhad F. The Effects of Different Strategies on the Painful Procedure Management, and the Physiological Parameters in Preterm Infants: A Systematic Review. Int J Pediatr 2020; 8(5): 11251-259. DOI: 10.22038/IJP.2019.13981

*Corresponding Author:

Farnaz Kalani-moghaddam, MD, Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

Email: KalaniMF971@mums.ac.ir

Received date: Nov.20, 2019; Accepted date: Feb.12, 2020

1- INTRODUCTION

Pain is defined as an unpleasant somatic or visceral sensation associated with actual, potential, or perceived tissue damage (1). It has been well documented that pain is widely undertreated, especially in the pediatric population (2-4). Since newborn infants go through vital medical procedures, they repeatedly experience pain during their early life (5). According to the findings of the studies carried out on the short-term effects of the pain, disparate physiological and behavioral systems are under the influence of the pain. For instance, the cardiac rhythm increment, the plasma cortisol, the behavioral activity such as crying, facial expressions of pain, increased motor activity, and a decrease in oxygen levels, enumerated as physiological and behavioral systems (5). Given to both the detrimental short-term and the potential long-term effects of the pain, several methods were examined to relieve the pain during the painful venipuncture procedures (6, 7).

Although the usage of pharmacological and non-pharmacological methods is advantageous in pain treatment, the pharmacological procedures lost favor among people due to their side effects and have been replaced by alternative and complementary methods (8). For instance, a wide range of practices such as positioning, swaddling, shaking, holding on the lap, kangaroo care, massage, acupuncture, acupressure, Reiki, pacifiers, sweet solutions (sucrose, glucose), breastfeeding, maternal voice and smell, breast milk, singing a lullaby, aromatherapy, and familiar smells given to the infants, can have an effect on the painful procedure and the physiological parameters among infants (8). The prior studies indicated that the most developed sense at birth is the sense of smell helping the newborn infants recognize the odor of their mothers' nipples and suckle breast milk during their first days of life (9).

According to the Goubet et al.' research, the infants feel the pain probably becoming continuous and preceding the consequences. Nonetheless, sick infants' pain is still regularly inflicted in hospitals (5). Several identified strategies, which effectively relieve pain during painful venipuncture procedures, included Amniotic fluid, the mother's milk, vanilla and the mother's odor, etc. (5, 7-13). The aim of this study was to review the effectiveness of the use of different strategies as a primary or adjunctive treatment on the painful procedure, and the physiological parameters in preterm infants.

2- MATERIALS AND METHODS

2-1. Search strategy

To conduct this systematic review, the English databases such as Medline (via PubMed), Scopus, ISI Web of Science, Cochrane Library and EMBASE were searched systematically without any time limitation up to February 10, 2019. The search keywords included (Aromatherapy OR Olfactory OR Amniotic fluid OR milk OR odor) AND (Pain OR Venipuncture). At first, two researchers separately inspected the titles and abstracts of the articles. Then, the articles with the relevant subjects were extracted and the full-text articles were scrutinized. Ultimately, the articles meeting the inclusion criteria were assessed in terms of quality.

2-2. Eligibility criteria

Participants, interventions, comparators, and outcomes (PICO) used to formulate the review objective and inclusion criteria (14). **Participant:** Preterm infants. **Interventions:** All clinical trials assessed the effect of aromatherapy through amniotic fluid, the mother's milk, vanilla and the mother's odor on painful procedures, and the physiological parameters in the preterm infants.

Comparators: Treatment vs. control group, treatment vs. different types of treatment, before vs. after treatment. **Outcome:** Primary outcomes include amniotic fluid, the mother's milk, vanilla and the mother's odor; secondary outcomes include the physiological parameters in preterm infants.

2-3. Data extraction

Table-1: General characteristics of the included trials in the systematic review.

Author, Year, Country, Reference	Type of design	Intervention /control	Number of subjects	Main result
Küçük Alemdar et al., 2017, Turkey, (7)	Randomized controlled experimental	Amniotic fluid: 21, mother's milk: 22, mother's odor: 20, control group: 22	85	Amniotic fluid, the mother's milk, and the mother's odor during painful procedures were not efficacious in the preterm infants.
Badiee et al., 2013, Iran, (10)	Double blind randomized clinical trial	Mother's milk poured on a filter paper, placed near the nose of the infant from 3 minutes prior to and up to 9 minutes after heel prick for blood	50	Having the heel pricked, the premature infant pain profile (PIPP) score in the breast milk group in comparison with the formula milk group was observed as a noteworthy low point.
Baudesson de Chanville et al., 2017, French, (11)	Prospective, randomized, controlled, double blinded	Maternal milk odor/ an odorless diffuser	33	A significantly lower median Premature Infant Pain Profile (PIPP) score during the venipuncture belongs to the group which was under the exposure of their own mother's milk odor compared to the control group [(6.3 (IQR) = 5-10 versus 12.0 (IQR = 7-13), p = 0.03)].
Mahnaz Jebreili et al., 2015, Iran, (12)	Randomized controlled trial	Breastmilk odor and the familiar vanilla odor, respectively, 5 minutes before the start of sampling to 30 seconds after the end of sampling	135	Although according to the statistical analyses, both vanilla and the breast milk odors soothed the pain in the premature infants during the sampling, only the breast milk odor was identified as a soothing factor on the infants and remaining after the sampling.

IQR: Interquartile range.

2-4. Included studies

Randomized controlled trials (RCT), clinical studies both randomized and nonrandomized either retrospective or prospective. Due to the limited number of published RCT in the literature, other types of clinical studies were included. According to the inclusion criteria, they are required to examine the effect of

A table devised to extract the data embodies the subsequent variables: the first author of the article, the year of publication, the type of the study, the presence of blinding, the design feature and the quantity of the subjects, the length and type of intervention and control group (**Table.1**).

aromatherapy on apnea, the infants' reaction to pain during and after venipuncture, and the alternation from the feeding tube to oral feeding. Pilot, preliminary and case report studies were not included due to limited sample size and higher risk of bias. Studies publish in English up to Feb 2019.

2-6. Study selection

Database search was done for possible studies, abstracts of the studies were screened for identification of eligible studies, full text articles were obtained and assessed and a final list of included studies was made. This process was done independently and in duplication by two reviewers and any disagreement was resolved by the third reviewer.

2-7. Quality assessment of articles

The Jadad scale (15) was used to assess the quality of the articles found in the search. This scale comprised of five items in the following areas: randomization, method of randomization, blinding, method of blinding, and dropouts and withdrawals. The scores of this tool range between zero and five (**Table.2**).

Table-2: Quality Assessment using Jadad scale (15).

Authors, Reference	Randomization			Blinding			Report of dropping out
	Mention randomization	Appropriate method	Inappropriate Method	Mention blinding	Appropriate method	Inappropriate method	
Küçük Alemdar et al., 2017, Turkey, (7)	😊	😊	😡	😡	😡	😐	😊
Badiee et al., 2013, Iran, (10)	😊	😊	😡	😊	😡	😡	😊
Baudesson de Chanville et al., 2017, French, (11)	😊	😊	😡	😊	😊	😡	😊
Mahnaz Jebreili et al., 2015, Iran, (12)	😊	😊	😡	😡	😐	😡	😊

😊 : Yes; 😡 : No; 😐 : Unclear.

3- RESULTS

After the electronic search of the prespecified databases with the preset search terms and limits, 5,862 studies were identified in the first phase of screening. After screening the abstracts 5,858 studies were excluded for multiple reasons including but not limited to study type, study population, age, duplicates, etc. Finally, four articles were included in the study (7, 10-12). PRISMA flow diagram was used to show the process of study selection (**Figure.1**). First, Küçük Alemdar et al. conducted a study on 85 preterm infants enrolled into the study based on the inclusion criteria. Infants were sorted into three groups i.e., the amniotic fluid, the mother's milk, the mother's odor. The last one (the mother's odor) was taken as the control group. The groups have a slight difference with respect to the crying time during the painful procedures ($p>0.05$). The control group, the mother's odor group, the mother's milk group, and the

amniotic fluid group exhibited the lowest scores, respectively. The amniotic fluid, the mother's milk, and the mother's odor during painful procedures were not efficacious in the preterm infants (7). Second, Badiee investigated on the 50 preterm infants aged between 32 and 37 weeks of gestation who were randomly included into two groups. During the pricking of the heel, the formula milk odor and the breast milk odor were applied for the first and second groups, respectively; 3 to 9 minutes after the heel blood sampling, a filter paper embodying either the formula or the breast milk was placed adjacent to the infant's nose. Having the heel pricked, the premature infant pain profile (PIPP) score in the breast milk group in comparison with the formula milk group was observed as a noteworthy low point. In addition, the increment level of salivary cortisol was observed in the formula milk group in spite of the breast milk group result (25.3 nmol/L compared to 17.7

nmol/L ($p < 0.001$). Breast milk odor is known for its anodyne effect on preterm infants as well as being a safe method to use for alleviating pain (10). Jebreili et al. randomly selected 135 preterm infants and distributed them into three groups, namely, the control group, the vanilla odor group, and the breast milk odor group. The infants in the breast milk group and those in the vanilla group were exposed to breast milk odor and vanilla odor respectively from 5 minutes before the start of sampling up to 30 seconds after sampling. Although according to the statistical analyses, both the vanilla and the breast milk odors soothed the pain in premature infants during sampling, only the breast milk odor was identified as a soothing factor affecting the infants and remaining after sampling. The breast milk odor rather than

the vanilla odor has more soothing effects on premature infants (12). The trial implemented by Audrey Baudesson de Chanville was characterized as a prospective, randomized, controlled, and double blind trial, and conducted on 32 infants aged 30 to 36 weeks. There were two groups: (a) a control group experienced a venipuncture with a diffuser with no odor and (b) a mother's milk odor group went through a venipuncture with a diffuser emanating their own mother's milk odor. A significantly lower median Premature Infant Pain Profile (PIPP) score during the venipuncture belongs to the group which was under the exposure of their own mother's milk odor compared to the control group [6.3 (IQR) = 5-10 vs. 12.0 (IQR) = 7-13, $p = 0.03$] (11).

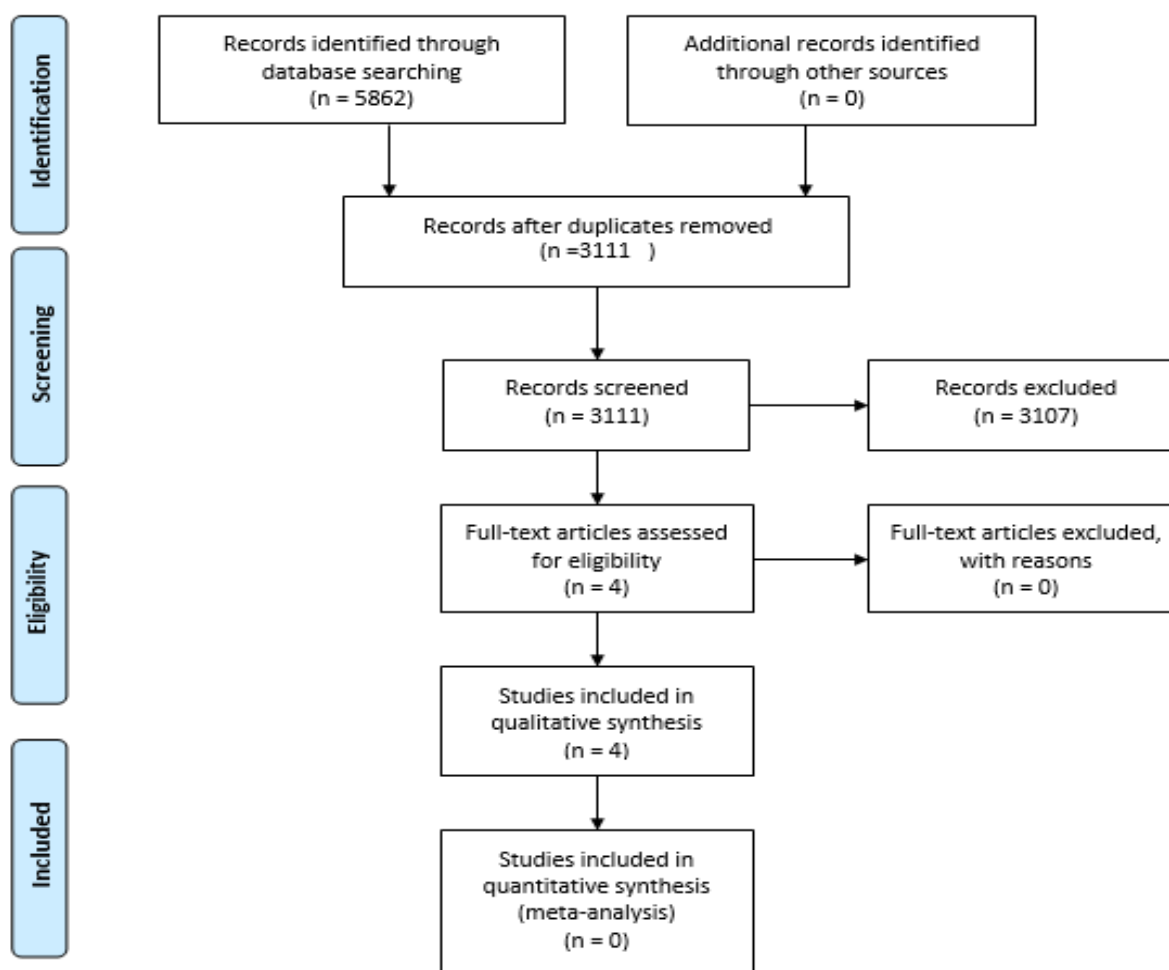


Fig.1: PRISMA flowchart.

4- DISCUSSION

Almost all neonates have blood tests for newborn screening in their first days of life, and preterm or sick hospitalized infants may require repeated invasive needle-related procedures for medical monitoring over the course of their hospitalization (16-19). Generally, pediatric pain management remains a huge challenge to all health care providers in primary, acute and other settings in the world (20). In addition, infants depend on others to recognize, to assess and to treat pain and discomfort. The situation for the preterm infant is more complex than that of the full term infant, since they often require intensive or high dependency care for many weeks, and their immature stage of neuromotor development may minimize the external manifestations of distress (21-25). In NICU, according to babies' responses, it does not seem appropriate to subject the infants to negative olfactory stimuli such as strong perfumes or scented aftershave, alcohol, cleaning chemicals, alcohol-based hand rubs, and oral remedies. These odors should be minimized in favor of fragrances with a positive stimulus, such as substances related to breastfeeding or those with the mother's smell (7).

The findings of the first study indicate that the pain profile score and the cry duration approximately correspond to each other for the four groups during, and after the heel prick procedure (7). Following the heel prick, the premature infant pain profile (PIPP) score was much lower in the breast milk group compared to the formula milk group in the second study. Moreover, despite of the breast- milk group result, the formula milk group indicated significant growth in the level of salivary cortisol (10). In the third study, the statistical analyses corroborate the soothing effect of not only the vanilla but also the breast milk odors on the premature infants during the sampling. Nevertheless, the breast milk

odor has been known to have a soothing effect on the infants after the end of sampling. When comparing vanilla odor and breast milk odor, the second one has the critical component in soothing the pain of the premature infants (12). In the fourth study, a significantly lower median Premature Infant Pain Profile (PIPP) score during the venipuncture belongs to the group, which was under the exposure of their own mother's milk odor compared to the control group (11). In the Küçük Alemdar et al.'s study, mother's milk, amniotic fluid and mother's odor during the heel prick procedure were closer in their results to each other. Nonetheless, the mother's milk group encompasses the lowest PIPP score during the procedure due to the low quantity of the infants in each group. Furthermore, all of the smells used belonged to the mothers, consequently, the PIPP scores of the infants in the experimental group, were alike but lower than the control group (7).

Following the heel prick, the premature infant pain profile (PIPP) score was much lower in the breast milk group compared to the formula milk group in the second study (5.4 compared to 9 with $p < 0.001$). Moreover, despite the breast milk group result, the formula milk group indicated a significant growth in the level of salivary cortisol (25.3 nmol/L compared to 17.7 nmol/L ($p < 0.001$)) (10). Breast milk odor is known for its anodyne effect on preterm infants as well as being a safe method to use for alleviating pain (10). In the follow-up study carried out by Nishitani et al. (9), 48 preterm infants were involved and the results indicate that the infants who were exposed to the smell of breast milk during the heel prick blood sampling experience, had a lower level of pain than those exposed to either formula milk smell or milk of other mammals. It is indicated that the salivary cortisol in the control group was significantly higher than those who were exposed to the smell of the breast

(with a small sample size). First, it is possible that mother's milk has pharmacological features and subsequently has direct effects on respiratory centers. Second, a supplementary element organizing an individual's psychological and physiologic states was determined to be the mere presence of a pleasant odor in the environment (26). Nasal mucosa has been known for its absorptive capacity for decades. The chemical amalgamations randomly traverse the nasal mucosa, enter the blood stream by way of the micro capillary channels, and finally reach the cerebral structures. It is noteworthy that the olfactory pathway demands a lower dosage of pharmacological material than is generally necessary in their administration through the intravenous or enteral routes. The olfactory pathway makes up a more direct route to the brain centers in comparison with the other conventional routes utilized by the physicians. It is a route attracting future studies (26).

Infants from the smell of non-maternal breast milk reportedly distinguish smell of maternal breast milk. They can sense the amniotic smell and the aroma of the mother; however, breastfeeding is more attractive, special, effective and important for infants. The baby's head rotates spontaneously toward the mother's breast a few minutes after delivery, and indicates a positive behavior when exposed to breast milk, possibly due to the odor of breast milk (13). Neonatal pain and crying can be positively affected by the smell of their mother's breast milk. Studies document that infant stress and pain can be alleviated only through the smell of their mother's breast milk. Decreased oxygen saturation and increased heart rate caused by invasive measures in the neonates can be prevented through the smell of their mothers' breast milk more than any other odor (10). Schaal et al. suggested that infants' behavioral responses are influenced by a variety of odors during pregnancy (27). In a study of

Goubet et al., the results showed that familiar odors could be beneficial for the infant. The exposure of non-nutritive preterm to breast milk odor while feeding through tubes resulted in increased sucking activity (5). Accordingly, it is recommended that physicians or researchers should consider the mentioned direct intervention in infants, especially preterm infants.

4-1. Limitations of the study

In the Küçük Alemdar et al. opinion, the limitation was defined as considering the amniotic fluid only obtained from the infants born by cesarean section as inclusion criteria; since it is problematic (7). Another limitation originates from the absence of blindness because the assessment of pain was implemented through watching videos. It was easily understood which group they belonged to, as the Ookie doll and gauze sponge were set adjacent to the infants' noses during the assessment of the pain and were recognizable in the videos. However, separate video recordings of the groups were viewed by one NICU nurse who was not engaged in the research, the leading researcher checked the pain, and the researcher's observations after the procedure.

5- CONCLUSION

Pain management in pediatric patients should be given a high priority by all health care professionals through advocating for optimal use of comforting strategies that reduce pain distress during painful procedures. Some findings emphasize the analgesic effect on some neonatal functions, including crying, waking and gestures, by other odors emitted by the mother, and most importantly the odor of breast milk being the most preferred option. The definitive conclusion about the analgesic effect of breast milk on infants needs research that is more comprehensive.

6- CONFLICT OF INTEREST: None.

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