

## Is Aromatherapy Effective for Apnea in Preterm Infants? A Systematic Review

Alireza Ataei Nakgaei<sup>1</sup>, Asma Javid<sup>2</sup>, Maryam Marefat<sup>3</sup>, Zahra Chichy<sup>3</sup>, Afra Alshahrestani<sup>3</sup>,  
\*Parisa Nazarpour<sup>4</sup>

<sup>1</sup>Associate Professor of Pediatrics, Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

<sup>2</sup>Firoozabadi Clinical Research Development Unit (FACRDU), Iran University of Medical Sciences (IUMS), Tehran, Iran.

<sup>3</sup>Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

<sup>4</sup>Department of Otorhinolaryngology, Head & Neck Surgery, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

### Abstract

**Background:** Apnea can be associated with many complications such as bradycardia, cyanosis, hypotension, hypotonia, hydrocephalus, neurologic complications, and even death. Pharmacological treatment is associated with many side effects. We aimed to investigate the effect of aromatherapy on Apnea in premature newborns.

**Materials and Methods:** An extensive search was done in databases of Medline, Embase, Scopus, Cochrane, and Web of Science until February 2019. Two independent researchers screened articles, in the next step, full texts of probably relevant articles were summarized and categorized based on the evaluated outcomes and overall effect size was presented.

**Results:** Three studies were included in the systematic review (including 110 preterm infants). Aromatherapy with breast milk odor not with vanilla odor, caused variability of premature infants' heart rate blood oxygen saturation during and after venipuncture. Calming effects were observed when preterm newborns were exposed to either vanilla or breast milk odors during venipuncture; however, only breast milk odors had a calming effect on subjects after sampling. Breast milk odor was more effective regarding calming effects on premature infants. Infants in olfactory stimulation with anise or cinnamon were discharged from hospital 3.4 days earlier than the control group ( $p = 0.12$ ). A subgroup analysis of subjects with a body weight of 2,000 grams or more showed a shorter hospitalization period. When compared by gender, better effect was observed in boys than girls with shorter hospitalization in NICU.

### Conclusion

Aromatherapy can be effective for apnea in preterm infants. Due to the small number of participants and low number of articles, the conclusion should be interpreted with caution.

**Key Words:** Aromatherapy, Apnea, Effect, Infants.

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### \*Corresponding Author:

Parisa Nazarpour (M.D), Department of Otorhinolaryngology, Head & Neck Surgery, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

Email: [nazarpourp941@mums.ac.ir](mailto:nazarpourp941@mums.ac.ir)

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## 1- INTRODUCTION

Premature is defined as less than 37 weeks of gestational age (1-3), increased mortality and morbidity due to respiratory immaturity and inefficient oral feeding performance (4, 5). Apnea is generally observed in premature infants (6, 7), the occurrence of the breath-holding spell for 20 seconds or more or a shorter pause, which can be associated with pallor, bradycardia (less than 100 bpm) or cyanosis (8), accounts for about 85% of infants with gestational age of  $\leq 34$  weeks (9). The developing brain may be damaged following Apnea, this can be associated with many complications such as bradycardia, cyanosis, hypotension, hypotonia, hydrocephalus, neurologic complications, and even death (10), brain damage (10-12) and prolonged hospitalization (13).

Continuous positive airway pressure and methylxanthine administration are the most common therapeutic strategies for Apnea (2). The recurrent apnea and need of mechanical ventilation within the first week of treatment are decreased with the aid of methylxanthines, such as aminophylline, theophylline and caffeine (9, 12, 14), but these are not completely useful (10). Additionally, some complications including irritability, tachycardia and sleeping disorders, may appear following the prescription of medicines used to treat apnea (2, 6).

For example, the blood flow in the brain is reduced by caffeine; the hypertension and thus cerebral hemorrhage occur due to doxapram (15); feeding intolerance and a rapid heart rate are the side effects of theophylline (14). Many health providers and researchers are interested in therapeutic approaches with less side effects such as aromatherapy. The aim of this study was to investigate the effect aromatherapy on Apnea in Premature Newborns.

## 2- MATERIALS AND METHODS

### 2-1. Strategy search

The present study was conducted based on the Cochran's guidelines. An extensive search, according to Mesh Terms, was performed on the Medline, Embase, Scopus, Cochrane, and Web of Science until February 10, 2019. The search query in Medline (via PubMed) is shown in **Table.1**. In addition, a manual search was conducted in Google motor engine, Google Scholar, and bibliography of related articles and reviews. Also, equivalent Persian keywords were searched in Iranian databases such as Irandoc, Magiran, Medlib, SID, and Barakatks.

**Table-1:** Search strategy for Medline (via PubMed).

```
("aromatherapy"[MeSH Terms] OR
"aromatherapy"[All Fields]) AND
Effectiveness[All Fields] AND ("apnoea"[All
Fields] OR "apnea"[MeSH Terms] OR
"apnea"[All Fields]) AND ("infant,
premature"[MeSH Terms] OR ("infant"[All
Fields] AND "premature"[All Fields]) OR
"premature infant"[All Fields] OR ("preterm"[All
Fields] AND "infants"[All Fields]) OR "preterm
infants"[All Fields])
```

### 2-2. Selection criteria

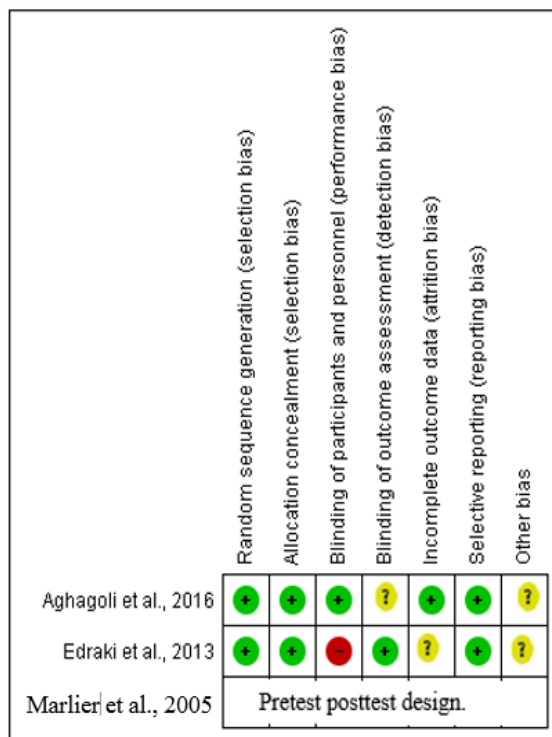
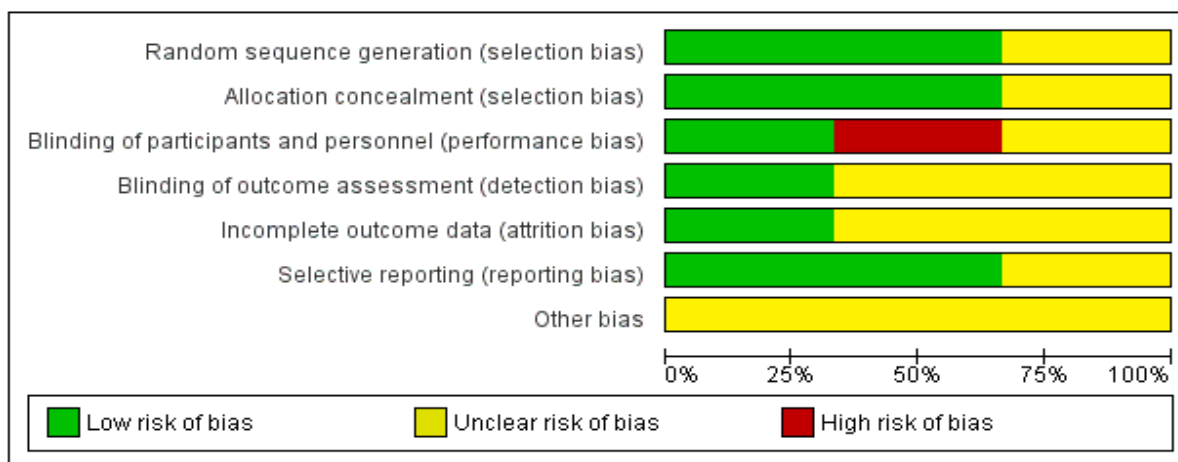
We included all clinical trials and pretest-posttest studies that evaluated the influence of aromatherapy on apnea, infants' response to pain during and after venipuncture, the switch from feeding tube to oral feeding. No time and language limitations were applied.

### 2-3. Quality Assessment and Data Extraction

After searching and eliminating some reports and duplicates, two independent authors read the titles and abstracts, and then relevant studies were selected. Any disagreement was solved by discussion among research team. Data related to the first author of article, year of publication,

location of study, type of study, design characteristic of subjects, number of subjects, duration and type of intervention and control, were recorded. The quality of the Clinical trial studies was assessed using Cochrane's proposed guidelines (16), STROBE checklist was used for pretest-posttest study (17). The risk of bias of the included studies was assessed by two authors independently using the criteria of the Cochrane Handbook for Systematic

Reviews of Interventions (Tarsilla, 2008) that evaluated: (a) random sequence generation; (b) allocation concealment; (c) blinding of participants and personnel; (d) blinding of outcome assessment; (e) incomplete outcome data; (f) selective reporting; and (g) other bias. In this assessment, each item was graded as 'low', 'high' or 'unclear' risk of bias (**Figure.1**) (10, 15, 18).



**Fig.1:** Quality control of clinical trial studies.

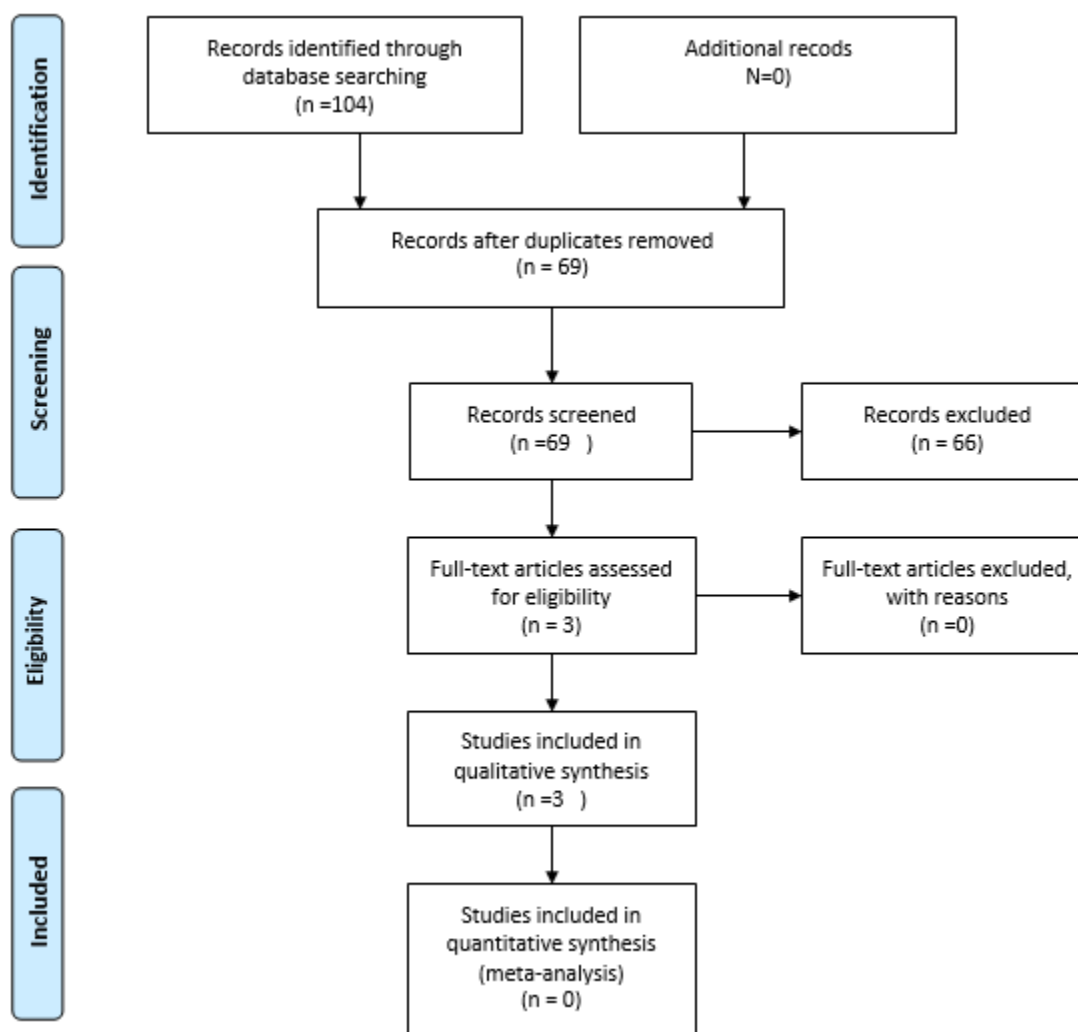
### 3- RESULTS

Three studies were included into systematic review. **Table.2** shows the baseline characteristics of studies included in our systematic review. Process of selecting the studies which were included in systematic review is shown in **Figure.2**. In the first study, Marlier et al., 2005 (18), conducted a before–after study without control group, 14 preterm infants with 24 to 28 gestational weeks with apnea despite caffeine and doxapram therapy. Odor was diffused during a 24 h period in the incubator. The mean number of total apneas decreased from 34.7 to 22.2, indicating a diminution of 36% ( $P < 0.001$ ). Frequency of apneas without bradycardia decreased from 17.9 to 10, indicating a diminution of 44% ( $P < 0.001$ ). Frequency of Apneas with severe bradycardia decreased from 8.2 to 4.5, indicating a diminution of 45% ( $P < 0.001$ ). However, frequency of apneas with moderate Bradycardia changed slightly from 8.6 to 7.9. Comparison between before and after was not significant ( $P > 0.05$ ). In a second study, Edraki et al. (10), conducted a

randomized controlled trial. In this study, 36 premature infants were randomized and allocated into control and intervention groups. The intervention group was exposed to saturated vanillin solution and the control group received no treatment. The presence of apnea was significantly lower in intervention group compared to control group for the first, second, and fourth day of the study ( $P < 0.05$ ) but not the third and fifth day of the study ( $P > 0.05$ ). Aghagoli et al. (15), assessed the effect of aromatherapy with Rosa Damascenes in Apnea in a randomized clinical trial (RCTs). 60 preterm neonates were randomized into two groups to inhale Rosa damascenes distillate or distilled water besides the routine treatment. In intervention group, two drops of 10% Rosa damascenes distillate were dripped on cotton in second day at 6 AM then it was repeated at 9 AM, 12 PM, 15 PM and 18 PM. The number of apnea attacks showed a significant decrease in intervention group than control in first, second, third and sum of three days ( $P < 0.05$ ).

**Table-2:** Characteristics of five studies included in our systematic review.

Author, Year, Location, (Reference)	Design	Intervention	Control	Characteristics of subjects	Number of subjects (Int. / Cont.)	Duration
Edraki et al. 2013, Iran (10)	Clinical trial	2 ml of 2% saturated solution of vanillin	Routine care	Premature infants that were born before 36 weeks of gestation	18/18	24 hours
Marlier, 2005, France (18)	Pre and posttest design	Pleasant odors	Post-treatment control	Born at 24 to 28 gestational weeks	14 preterm newborns	24 hours
Aghagoli et al. 2016, Iran, (15)	Clinical trial	2 drops of 10% Rosa damascenes distillate on the pad eye + the routine treatment.	Distilled water + routine treatment.	Gestational age ( $31.4 \pm 1.4$ ) weeks and birth weight $1321 \pm 178$ grams	30/30	Four times per 12 hours (9 AM, 12PM, 15 PM and 18 PM).



**Fig.2:** PRISMA flowchart of present study.

#### 4- DISCUSSION

Apnea of prematurity is one of the most common diagnoses in the Neonatal Intensive Care Unit (NICU) (8). It is occurred in 80% of neonates less than 1000 g and in 25% of them that are less than 2500 g (15). Apnea can be associated with many complications such as bradycardia, cyanosis, hypotension, hypotonia, hydrocephalus, neurologic complications, and even death (10), brain damage (10-12) and prolonged hospitalization (13). Widely used treatments for apnea include aminophylline, theophylline and caffeine doxapram (9, 12, 14), but these are not

completely useful (10) and are associated with complications, and irritability, tachycardia and sleeping disorders cerebral hemorrhage, intolerance and a rapid heart rate are the side effects of theophylline (14). Therefore, it is important that a comprehensive review on the effect of aromatherapy on Apnea in premature newborns be done. Marlier et al. (18) showed that aromatherapy with vanilla in premature neonates that have gestational age 24-28 weeks was effective on the apnea occurrence at the second day after intervention compared to the first and third days. Three mechanisms have been suggested for the impacts of vanillin. First,

the respiratory center in the brain is influenced directly or indirectly by vanillin that is penetrated into the blood flow to reach brain via nasal mucosa or nerves in olfactory system. Second, orbitofrontal blood flow is increased by vanillin, which can be explored by near-infrared spectroscopy. Third, infantile stress can be attenuated by vanillin (2). Accordingly, the stressed-induced apnea may be reduced by the vanillin, highlighting the importance of further research on the treatment regimen of apnea with the fewest complications (10).

The pharmaceutical effects with *Rosa damascenes* include antibacterial, antioxidant, antitussive, hypnotic, and relaxant effect, hypnotic, sedative, and anticonvulsive effects alleviate anxiety and promote relaxation (decreasing pain), and has dilation effect on respiratory airways. In Aghagoli et al.'s study, the number of apnea attacks showed a significant decrease (15). Nevertheless, physiological and psychological improvement can be achieved by plant-derived aromatic essential oils, which is called aromatherapy (19). In this way, inhalation, digestion or massage are used for the oils to penetrate into the body (19, 20).

The current study results showed that the aromatherapy effect with *Rosa damascena* distillate is effective on the apnea attacks, heart pulse rate, and significance of fetal arterial oxygen saturation (SpO<sub>2</sub>) in premature neonates besides the routine treatment comparing to control group that only received the routine treatment with distilled water (15).

#### 4-1. Limitations of the study

This study investigated the effect of vanillin on only one type of apnea, i.e. idiopathic apnea of prematurity in the newborns. Therefore, further studies are suggested to be performed in order to determine the effectiveness of this non-pharmacological method on different types

of apnea and also for improving its evidence-based practice. One of the limitations of this study was the small number of participants.

#### 5- CONCLUSION

Aromatherapy can be effective for apnea in preterm infants. Due to the small number of participants and low number of articles, the conclusion should be interpreted with caution.

**6- CONFLICT OF INTEREST:** None.

#### 7- REFERENCES

1. Uddin SG, Martin JA. Preterm Birth and Low Birth Weight by Source of Payment for the Delivery: New Data from the Birth Certificate Sally C. Curtin, MA Marie E. Thoma, PhD MHS.
2. Zlotkin S, Casselman C. Percentile estimates of reference values for total protein and albumin in sera of premature infants (less than 37 weeks of gestation). *Clinical Chemistry*. 1987;33(3):411-3.
3. Adams LM, Emery JR, Clark SJ, Carlton EI, Nelson JC. Reference ranges for newer thyroid function tests in premature infants. *The Journal of pediatrics*. 1995;126(1):122-7.
4. Neshat H, Jebreili M, Seyyedrasouli A, Ghojazade M, Hosseini MB, Hamishehkar H. Effects of breast milk and vanilla odors on premature neonate's heart rate and blood oxygen saturation during and after venipuncture. *Pediatrics & Neonatology*. 2016;57(3):225-31.
5. Nau J. Prematurity, a fight never won. *Revue medicale suisse*. 2012;8(336):818.
6. Miller HC, Behrle FC, Smull NW. Severe apnea and irregular respiratory rhythms among premature infants: A clinical and laboratory study. *Pediatrics*. 1959;23(4):676-85.
7. Miller M, Martin R. Apnea of prematurity. *Clinics in perinatology*. 1992;19(4):789-808.
8. Eichenwald EC. Apnea of prematurity. *Pediatrics*. 2016;137(1):e20153757.

9. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Caffeine therapy for apnea of prematurity. *New England Journal of Medicine*. 2006;354(20):2112-21.
10. Edraki M, Pourpoulad H, Kargar M, Pishva N, Zare N, Montaseri H. Olfactory stimulation by vanillin prevents apnea in premature newborn infants. *Iranian journal of pediatrics*. 2013;23(3):261.
11. Sagi E, Eyal F, Alpan G, Patz D, Arad I. Idiopathic apnoea of prematurity treated with doxapram and aminophylline. *Archives of disease in childhood*. 1984;59(3):281-3.
12. Pillekamp F, Hermann C, Keller T, Von Gontard A, Kribs A, Roth B. Factors influencing apnea and bradycardia of prematurity—implications for neurodevelopment. *Neonatology*. 2007;91(3):155-61.
13. Eichenwald EC, Aina A, Stark AR. Apnea frequently persists beyond term gestation in infants delivered at 24 to 28 weeks. *Pediatrics*. 1997;100(3):354-9.
14. Henderson-Smart DJ, Steer PA. Methylxanthine treatment for apnea in preterm infants. *Cochrane Database Syst Rev*. 2001;(3):CD000140.
15. Aghagoli S, Salimi A, Salimi M, Ghazavi Z, Marofi M, Mohammadbeigi A. Aromatherapy with rosa damascenes in apnea, bradycardia and Spo2 of preterm infants; a randomized clinical trial. *International Journal of Pediatrics*. 2016;4(6):1911-8.
16. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj*. 2011;343:d5928.
17. STROBE Statement. Available at: <https://www.strobe-statement.org/index.php?id=available-checklists>
18. Marlier L, Gaugler C, Messer J. Olfactory stimulation prevents apnea in premature newborns. *Pediatrics*. 2005;115(1):83-8.
19. O'Flaherty L-A, van Dijk M, Albertyn R, Millar A, Rode H. Aromatherapy massage seems to enhance relaxation in children with burns: an observational pilot study. *Burns*. 2012;38(6):840-5.
20. Cooke B, Ernst E. Aromatherapy: a systematic review. *Br J Gen Pract*. 2000;50(455):493-6.