

Investigating Effect of Olfactory Stimulation by Vanilla on the Rate of Apnea Attacks in Neonates with Apnea of Prematurity: A Randomized Clinical Trial

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Abstract

Background

Apnea of prematurity (AOP) is a developmental disorder that affects the premature newborns frequently. One of the new non-drug methods for controlling apnea attacks is olfactory stimulation. The aim of this study was to determine the effect of olfactory stimulation by vanilla on the rate of apnea attacks in neonates with AOP.

Materials and Methods: This study is a single-blind randomized clinical trial study. The study samples included a total of 40 premature neonates with AOP who were admitted to the neonatal Intensive care unit (NICU) of Shahid Sadoughi hospital in Yazd, Iran, in 2016 and were assigned randomly in experimental (n=20), and control (n=20) groups. The experimental group was exposed to cotton impregnated with 2ml of vanillin extract for 24 hours. The number of apnea attacks, heart rate, and arterial oxygen saturation (SaO₂) level were measured before, during and after intervention for three consecutive days. Data analysis was performed using statistical analysis in SPSS version 22.0 software.

Results: The results showed that there was no significant difference between the two groups in terms of mean number of apnea attacks ($p>0.05$). However, there was a significant difference between the experimental group on the first day (2.84 ± 1.25), and second day (1.63 ± 1.01) in terms of the mean number of attacks. Also, there was a significant difference between the mean heart rate and SaO₂ level in both the experimental and control groups ($p<0.05$).

Conclusion: At current study, olfactory stimulation by vanilla was not effective on reducing the number of apnea attacks in neonates with AOP.

Key Words: Apnea, Infants, Olfactory Stimulation, Randomized Clinical Trial, Vanilla.

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1- INTRODUCTION

Annually, 130 million neonates are born in the world, of which premature births make up 5.9% of births in developing countries, and 12.8% of births in the United States (1). Iran is also one of the areas with a high prevalence of preterm delivery, and premature neonates approximately account for 10% of births (2), and the risk of survival of high risk neonates, including the premature ones, has increased considering the advancement of perinatology in the last decade (3).

One of the most important problems in premature neonates is apnea of prematurity (AOP), which frequently occurs as a developmental disorder in premature neonates, especially neonates of lower gestational age (4), and its onset can lead to complications such as cyanosis, bradycardia, cerebral damage, decreased blood pressure, abnormal nerve development, decreased muscle tone and neurological complications; so that, AOP is a major concern for all the medical team members in the neonatal intensive care unit (NICU) (4, 5). Therefore, with the onset of apnea, various therapeutic approaches are used to control it, which includes two groups of drug and non-drug therapies (6).

Today, the combined use of non-drug and drug methods has been considered. In fact, simplicity, less costly, less complications, and ease of use of these methods have led the medical team members to focus on non-drug methods along with the methods of drug methods for apnea control, and different non-drug methods have been proposed over the past few years, and their effects on controlling apnea attacks have been studied (7-9). Olfactory stimulation is one of the new non-drug methods for controlling apnea attacks (4), and vanilla odor is the odor that can have controlling effect on apnea attacks with no side effects (10). Vanilla is medicinal plants from the family of *Orchis maculate* (11), which is

native to South and Central America, and Mexico; and uses air humidity as a source of nutrition (11, 12). This plant was first used by Marlier et al. (2005), who conducted a study on a group of 14 neonates with AOP and identified to be effective (4). Sadathosseini et al. also showed that pre-blood draw vanilla odor exposure could significantly reduce the duration of infant crying (13).

Williams et al. reported reduced respiratory distress level in newborns exposed to vanilla extract, one day before blood draw (14). Edraki et al., also studied the effect of vanilla odor on the prevention of apnea in premature neonates who still developed no AOP (10), and reported it can be effective, but there has been no experimental study on the effect of vanilla odor on premature neonates with AOP in Iran. Since NICU nurses play a significant role in the treatment of AOP, they can eliminate the need to invasive procedures to control the apnea by performing the related interventions (15); therefore, the present study was aimed to determine the effect of olfactory stimulation by vanilla on the number of apnea attacks in neonates with AOP.

2- MATERIALS AND METHODS

The present study was a single-blind randomized clinical trial study which was conducted on all premature neonates with AOP disorder who were admitted to the NICU of Shahid Sadoughi hospital in centrally-located city of Iran, Yazd. A minimum number of 20 participants per each group were taken into consideration with regards to the 95% confidence interval (95% CI), power of 80%, and the standard deviation of 3.1 based on the number of apnea attacks reported by Edraki et al. (14), and also considering a one-unit change in the mean scores of apnea attacks between two groups.

$$n = (Z_{1-\alpha/2} + Z_{1-\beta})^2 \times 2S^2 / d^2$$

The inclusion criteria consisted of the neonates (1) aged less than 32 weeks, (2) weighed less than 2,000gr, (3) diagnosed with AOP by a neonatal specialist, (4) underwent treatment with methyl xanthine, and also (5) the neonates with at least one apnea attack for a period of 4-8 hours (peak effect) after receiving methyl xanthine. Except for the AOP, apnea attacks caused by other reasons including acute infections, congenital heart diseases, anemia (hemoglobin <10), sedation, hypoglycemia, hypocalcemia, cerebral hemorrhage larger than grade I, Periventricular leukomalacia (PVL), patent ductus arteriosus (PDA), chromosomal abnormalities, and brain disorders were dismissed in this study. The exclusion criteria included the neonates with three apnea attacks per hour or the neonates who required frequent ventilation with Ambo-Bag, continuous positive airway pressure (CPAP) or mechanical ventilation, the parents' dissatisfaction and the neonate's discharge or death.

The eligible study subjects were selected randomly. On the first day of study, the neonates were monitored for the number of apnea attacks as well as changes in oxygen saturation (SaO₂) and heart rate. On the second day, cotton balls soaked by 2 ml vanilla extract were placed in one corner of the incubator every 12 hours in the experimental group. To avoid any possible contact between the neonates' skin and vanilla-soaked balls, the cotton balls were placed away from the infants for approximately 20 cm. In order to preserve the study's blindness, cotton balls soaked with 2 ml of distilled water were placed 20 cm away from the neonates' heads in control group. The newborns were being monitored in both groups. On the third day, the neonates in both groups were monitored as did on the first day without any intervention to ensure that the ultimate changes were un-attributable to the neonates' normal growth. Also, the

incubator was placed at least one meter away from the neonates according to the standard considerations. The physiological parameters including SaO₂ and heart rate were examined by means of pulse oximetry. To do so, the device was plugged into the power outlet and the sensor probe was attached to the infant's foot so that the device displayed heart rate and SaO₂ on a monitor. The device being used in this study was standard portable device model A 520 manufactured by NOVAMETRIX USA, which was available in our clinical settings.

The changes in physiologic parameters were considered as apnea attack and recorded by researcher and assistant researcher whenever the SaO₂ less than 88% and heart rate less than 90 were observed (4). The olfactory stimulator in this study was prepared as follows: 0.64 gr vanilla extract (S3585211 from MERCK, Germany) was gradually added to 100 ml glycerol 85% (No. 49783 from MERCK, Germany) in the HotSter device (Heidolph, Germany MR 3001 k). Afterwards, transparent liquid of glycerin containing vanilla extract was obtained after being cooled in laboratory temperature for clinical purposes and was used as an olfactory stimulator after consulting with the neonatal specialist. The reason for the use of vanilla extract with the above-mentioned concentration was that previous studies attributed significant behavioral and physiological changes in the neonates following the application of this concentration (4, 10).

It is noteworthy that over the course of intervention, all routine preventive measures for apnea management including maintaining the proper position of neck to prevent neck flexion and airway obstruction, performing suction as needed to prevent the accumulation of discharge and obstruction of airway, and also Kangaroo mother care (KMC) (Once a day according to the wards care routine) were

taken in to consideration. The neonate's body temperature was maintained at 36.5 to 37.5 °C, and the incubator's temperature settings were changed if the body temperature decreased or increased. Over the course of study, the nurses' interventions following the occurrence of apnea attacks in the neonates of both groups included a gentle stimulating touch and the delivery of additional oxygen in the form of capping for treatment of apnea attacks. In case the apnea persisted and occurred more than 3 times per hour, the infant was supposed to be attached to the Nasal continuous positive airway pressure (NCPAP) and/or mechanical ventilation and excluded from the study. Accordingly, two neonates from the intervention group and one neonate from the control group were excluded from the study. The data were analyzed by SPSS software version 18.0 using descriptive statistics and Kolmogorov-Smirnov tests, independent t-test, paired t-test and Chi-square. P-value <0.05 was considered as significant.

3- RESULTS

Finally, 18 premature infants in the control group and 19 premature infants in the intervention group participated in the study (**Figure.1**). The results of the Kolmogorov-Smirnov test showed that the data related to the variables studied exhibited a normal distribution. Therefore, necessary conditions for the use of parametric tests were met. Independent t-test showed that there was no significant difference between the mean age and weight of the experimental and control groups ($p < 0.05$). Chi-square test also showed that there was no significant difference between two groups in terms of the qualitative variable of gender, and type of delivery (normal and cesarean section) ($p < 0.05$) (**Tables 1 and 2**). Repeated measures ANOVA did not show a significant difference between the mean

number of apnea attacks in the experimental and control groups during the three days ($p = 142$) (**Table.2**). However, the intra-group study on the mean number of apnea attacks in the experimental group showed statistically significant difference ($p = 0.016$) during the three days, and showed a significant difference between the mean number of first-day apnea attacks with the second day ($p = 0.001$) based on LSD post-test (**Table.3**).

The results of repeated measures ANOVA showed a statistically significant difference between the mean heart rate of the experimental and control groups ($p = 0.001$). There was a statistically significant difference between the mean heart rate of the experimental and control groups using the LSD Test on the second day of study ($p = 0.001$). Intra group study showed that mean heart rate in the experimental group was significantly different during the three days ($p < 0.05$), and LSD post hoc test showed that there was a statistically significant difference between the mean heart rate of the first day and the second day ($p = 0.006$), and a statistically significant difference was also observed between the mean heart rate of the second day and the third day ($p = 0.001$) (**Table.3**).

The results of repeated measures ANOVA on mean SaO₂, showed a statistically significant difference between the mean SaO₂ of the experimental and control groups ($p = 0.001$), and there was a statistically significant difference between the mean SaO₂ in the experimental and control group on the second day of the study according to the LSD post hoc test ($p = 0.005$). The intra-group study showed a statistically significant difference ($P < 0.001$) between the first with second days and the second day with the third day in the experimental group in terms of the SaO₂ ($p = 0.001$) (**Table.3**).

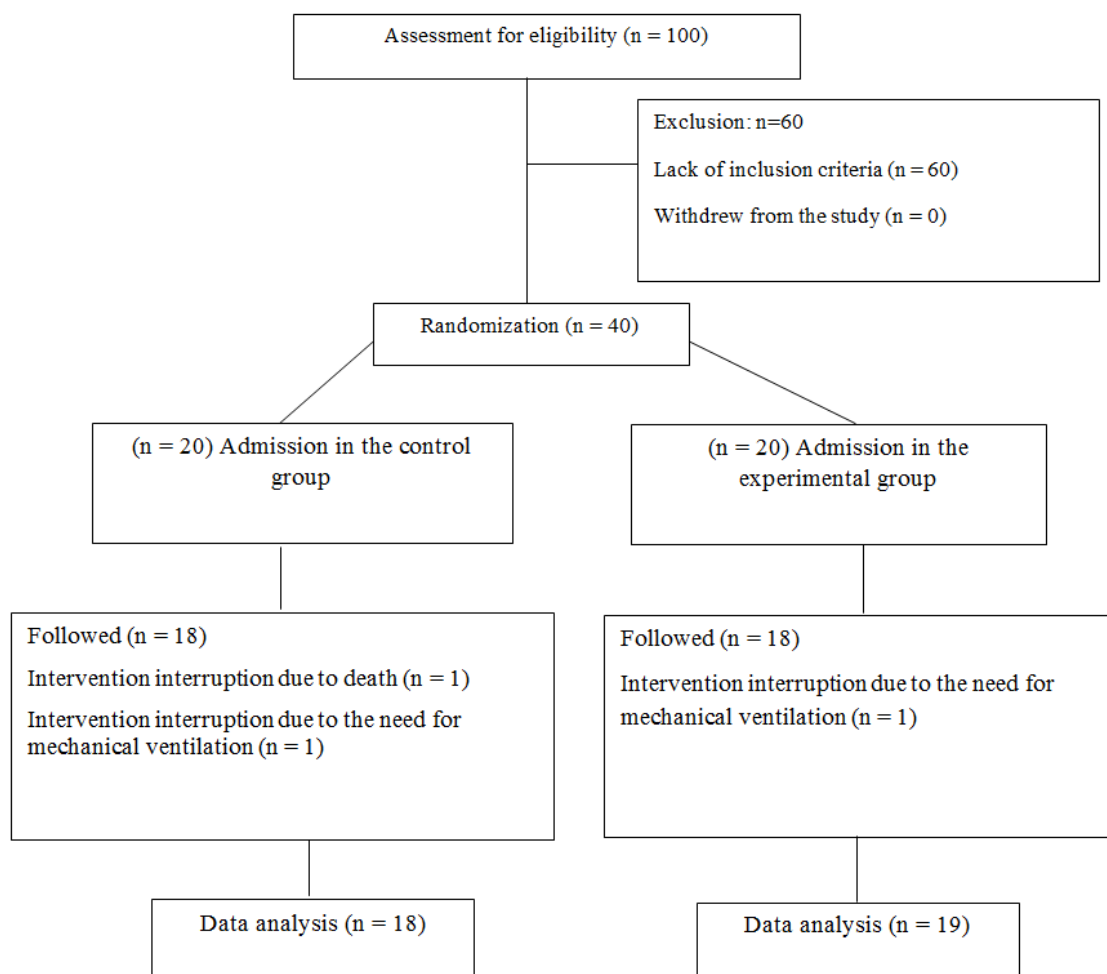


Fig.1: The flowchart of present study.

Table-1: The comparison of the individual characteristics of the studied samples

Demographic information		Experimental group		Control group		P-vale
		Mean ± SD		Mean ± SD		
Gestational Age (week)		29.26 ± 1.72		28.94 ± 1.73		0.408
Age (day)		5 ± 6.86		4.88 ± 2.31		0.8
Weight (gr)		986.31 ± 162.76		996.66 ± 186.200		0.8
Variables		Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	P-value
Gender	Girl	10	52.6	11	61.1	0.873
	Boy	9	47.4	9	0.50	
Type of Labor	NVD	9	47.4	9	0.50	0.604
	Cesarean	10	52.6	9	0.50	

NVD: normal vaginal delivery; SD: standard deviation.

Table-2: Comparison of mean apnea attacks in two groups of test and control during three days

Day	Mean \pm SD of apnea in the experimental group	Mean \pm SD deviation of apnea in the control group	P- value
First day	2.84 \pm 1.25	2.67 \pm 0.97	0.016
Second day	1.63 \pm 1.01	2.39 \pm 1.72	
Third day	2.37 \pm 1.67	2.33 \pm 0.90	

SD: standard deviation.

Table-3: The comparison of mean of apnea attacks, heart rate and arterial oxygen saturation in two groups during three days

Group	Stage examined	Mean \pm SD of apnea attacks	P- value	Mean \pm SD of the heart rate	P- value	Mean \pm SD of the Spo ₂	P- value
Experimental	First day with the second day	1.2 \pm 1.35	0.001	3.5 \pm 4.3	0.006	5.81 \pm 6.9	0.001
	First day with the third day	0.47 \pm 2.06	0.33	1.6 \pm 6.09	0.31	1.47 \pm 4.8	0.19
	Second day with the third day	0.73 \pm 1.75	0.08	6.5 \pm 2.7	0.001	7.28 \pm 3.5	0.001
Control	First day with the second day	0.27 \pm 1.5	0.45	1.3 \pm 5.8	0.07	0.66 \pm 12.04	0.73
	First day with the third day	0.33 \pm 0.90	0.13	2.3 \pm 7.3	0.20	2.44 \pm 8.5	0.95
	Second two with the third day	0.056 \pm 1.3	0.84	1.29 \pm 7.4	0.73	1.78 \pm 9.1	0.55

SD: standard deviation.

4- DISCUSSION

The results of this study showed that apnea attacks were not significantly different in the experimental and control groups during the three days of study, but the number of apnea attacks in the first and second days showed a significant difference in the experimental group, indicating that exposing the premature neonate to the vanilla odor could reduce the number of apnea attacks. These results are consistent with the findings obtained by Marlier et al. who reported that premature neonates did not respond to doxapram and caffeine and were treated with vanillin saturated solution, they showed that incubator indoor air

aromatization with vanilla odor is effective on the apnea treatment (4). In fact, because of medicinal properties, vanilla has direct or indirect effects on respiratory centers (16); it can enter the bloodstream through the small capillaries and into the brain after passing through the mucous membrane (17); and it is also effective in facilitating the physiological-psychological adaptation of premature neonates with an external environment (4). The findings on the mean of heart rate showed that there was a significant difference between the mean heart rate of the two experimental and control groups on the first day of the study with the second day and the second day with the third day. In fact, heart rate was less decreased after exposing the

infant to vanilla odor on the second day of the study, and reducing the number of attacks on apnea. Marlier et al. also showed that the heart rate of the premature neonates was stable in the presence of vanilla odor (4). Edraki et al. also reported a significant difference between the control and experimental groups in terms of the mean neonatal heart rate, so that the experimental group exposed to vanilla odor had higher heart rate (10). In the study by Aghauli et al., the neonates from the intervention group who were exposed to the scent of rose had significantly fewer episodes of bradycardia compared with the control group (18); and the findings of the mentioned studies were consistent with the findings of the present study. However, it was not consistent with the findings of Sadathosseini et al. who showed that there is no statistically significant difference between three groups, the familiar odor (vanilla), the unusual odor and the control group, in terms of heart rate after insertion, and removal of the needle (13).

It seems that the difference between the results of this study and the present study, can be due to the different conditions of the two studies (the painful procedure for neonates in Sadathosseini's study), and the different duration of exposure with vanilla odor (in the Sadathosseini's study, infants exposed to vanilla odor for 9 hours, but in the present study, this time was 24 hours) (13). Another finding of the present study was the difference in mean SaO₂ between the two study groups on the second day of the study; indicating a higher oxygen saturation of vanilla-exposed neonates. There was also a statistically significant difference between the amounts of SaO₂ in the experimental group on the first day with the second day, and the second day with the third day. In fact, the experimental group neonates who were exposed to vanilla odor on the second day, have less SaO₂ than the control group and had less hypoxia and a more stable

respiratory state. Bartocci et al. conducted a study titled "Activation of the olfactory cortex caused by olfaction stimulation in neonates in the United States" and confirmed the foregoing; this research showed that the binding capacity of hemoglobin to oxygen in newborns exposed to the vanilla odor increases significantly (19). The findings Zeraati et al.'s study which was conducted to investigate the effect of multi-sensory stimulation on SaO₂ during the examination of the eyes in premature neonates, also showed that multi-sensory stimulation (sensory, hearing, taste stimulation by vanilla odor) causes less reduction in the amount of SaO₂ (20), but Sadathosseini et al. who compared the SaO₂ level in newborns after insertion of the needle into the skin in the three study groups (vanilla odor stimulation, non-familiar odor stimulation and control group), did not show any significant difference, but the SaO₂ of neonates in vanilla odor stimulation group (exposed to vanilla odor for 9 hours before blood draw), immediately after removing the needle from the skin, was significantly higher than that of the other two groups (13). The difference between the results of this study and the present study on the assessing the effect of vanilla odor on the amount of SaO₂ seems to be related to the intervention duration, so that as the duration of a soothing sensory intervention is prolonged, the sedative and analgesic effects of that intervention also increase (21, 22), thus provides more opportunity for the infant to modify his/her physiological system changes (13).

4-1. Limitations of the study

A significant limitation of this study was the small sample size, as well as short exposure to vanilla odor. Therefore, similar studies are recommended by prolonging the duration of the intervention and the larger sample size.

5- CONCLUSION

These findings are important because olfactory stimulation by vanilla could affect the onset of apnea in premature newborns with AOP, and following the reduction in the number of apnea attacks, elevated SaO₂ and heart rate. Generally, the findings suggest the positive effect of vanilla stimulation on the physiologic status of the infant. Considering that this intervention is an easy and inexpensive intervention and is not time-consuming for nurses, it can be considered as one of the effective non-drug method to control neonatal apnea attacks.

6- CONFLICT OF INTEREST: None.

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8- REFERENCES

1. Rezaeian M, Goujani R, Sheikh Fathollahi M, Vaziri Nejad R, Manshori A, Razi S. A Comparative Study on Prevalence of Preterm Birth and Low Birth Weight in Iranians and Afghans Races in Rafsanjan NIK-Nafs Hospital in 2011-2012. *Journal of Rafsanjan University of Medical Sciences*. 2014;13(1):67-82. (In Persian)
2. Momeni F, Hakimjavadi M, Gholamali lavasani M, Haghshenas M. The Effect of Music Therapy (Lullabies) on Infants' Physiological and Growth Parameters.

Middle Eastern Journal of Disability Studies. 2015;5(0):242-50. (In Persian)

3. boskabadi H, Bagheri F, Askari Hosseini Z. Developmental Disorders in Preterm Neonates during the First Two Years of Life Using the Ages and Stages Questionnaire. *Journal of Babol University Of Medical Sciences*. 2016;18(2):7-13. (In Persian)
4. Marlier L, Gaugler C, Messer J. Olfactory stimulation prevents apnea in premature newborns. *Pediatrics*. 2005;115(1):83-8.
5. Hamedi A, Akhlaghi F. A survey of multiple births in Mashad. *Iranian Journal of Pediatrics*. 2002;12(4):46-8. (In Persian)
6. Bissonnette JM, Hohimer AR, Knopp SJ. Effect of hypoxia on expiratory muscle activity in fetal sheep. *Respiratory physiology & neurobiology*. 2010;171(2):110-4.
7. Heimler R, Langlois J, Hodel D, Nelin L, Sasidharan P. Effect of positioning on the breathing pattern of preterm infants. *Archives of disease in childhood*. 1992;67(3):312-4.
8. Jenni OG, von Siebenthal K, Wolf M, Keel M, Duc G, Bucher HU. Effect of nursing in the head elevated tilt position (15) on the incidence of bradycardic and hypoxemic episodes in preterm infants. *Pediatrics*. 1997;100(4):62-5.
9. Kianifar H, Ahanchian H, Grover Z, Jafari S, Noorbakhsh Z, Khakshour A, et al. Synbiotic in the management of infantile colic: A randomised controlled trial. *Journal of Paediatrics and Child Health* 2014; 50(10):801-5.
10. Edraki M, Pourpulad 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.(In Persian)
11. Bythrow JD, editor *Vanilla as a medicinal plant*. *Seminars in integrative medicine*; 2005: Elsevier.
12. Prince RC, Gunson DE. Just plain vanilla? *Trends in biochemical sciences*. 1994;19(12):52

13. Sadathosseini A, Ngarandeh R, Mehran A, Movahedi Z. Effect of familiar olfactory stimulus on responses to blood sampling pain in neonates. *Scientific Journal of Hamadan University of Medical Sciences and Health Services*. 2011;18:10-9. (In Persian)
14. M W .Soothe Babies with Familiar Smells. *Developmental and Behavioral Pediatrics*. 2005;26:86-92
15. Eichenwald EC. Apnea of prematurity. *Pediatrics*. 2016;137(1):e20153757.
16. Fletcher AJ, Edwards LD, Fox AW, Stonier P. *Principles and practice of pharmaceutical medicine*: Wiley Online Library; 2002.102-10.
17. Pagliaro LA, Pagliaro AM. *Problems in pediatric drug therapy*: American Pharmaceutical Association; 2002.
18. Aghagoli S, Salimi A, Salimi M, Ghazavi Z, Marofi M, Mohammadbeigi A. Aromatherapy with Rosa Damascenes in Apnea, Bradycardia and Spo2 of Preterm olfactory stimulus on responses to blood sampling pain in neonates. *Scientific Journal of Hamadan University of Medical Sciences and Health Services*. 2011;18:10-9. (In Persian)
19. Bartocci M, Winberg J, Ruggiero C, Bergqvist LL, Serra G ,Lagercrantz H. Activation of olfactory cortex in newborn infants after odor stimulation: a functional near-infrared spectroscopy study. *Pediatric Research*. 2000; 48(1):18-23.
20. Zeraati H, Shahinfar J, Vashani HB, Reyhani T. Effect of Multisensory Stimulation on Pain of Eye Examination in Preterm Infants. *Anesthesiology and Pain Medicine*. 2017;7(1): e42561.
21. Castral TC, Warnock F, Leite AM, Haas VJ, Scochi CG. The effects of skin-to-skin contact during acute pain in preterm newborns. *European Journal of Pain*. 2008;12(4): 464-71.