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Study of Olfactory Stimulation with Lavender Essential Oil in Preterm Infants with Painful Radial Artery Blood Collection

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Abstract: ***Objectives:*** *To explore the effect of lavender essential oil olfactory stimulation as a non-pharmacological pain management strategy in preterm infants during radial artery blood collection.* ***Methods:*** *The 96 preterm infants from the neonatal intensive care unit (NICU) of a tertiary care hospital in China were randomly divided into two groups: the control group (n = 47) and the intervention group (n = 49). In the control group, conventional skin contact soothing measures were given before radial artery blood collection, while in the intervention group, lavender essential oil olfactory stimulation was implemented in addition to the control measures, i.e., a cotton swab with 3 drops of lavender essential oil was placed 2–3 cm away from the nasal cavity of the preterm infant for olfactory stimulation 3 min prior to radial artery blood collection. Caregivers used a cell phone camera to record the heart rate, oxygen saturation, and facial expressions of the preterm infant 3 minutes before, during, and after radial artery blood collection. Thereafter, the nursing staff collected saliva samples from the children for analyzing their salivary cortisol levels. The investigator and research assistant watched the videos independently and rated the pain level and calculated the crying duration for each infant.* ***Results:*** *The differences in pain scores, crying duration, and salivary cortisol concentration were statistically significant in the intervention group compared with the control group (P <0.001).* ***Conclusion:*** *Implementation of olfactory stimulation with lavender essential oil reduces pain scores, shortens cry duration, and reduces salivary cortisol concentrations in preterm infants during radial artery blood collection, effectively maintaining physiological stability and improving quality of care.*

Keywords: Pain, Prematurity, Aromatherapy, Lavender essential oil, Odor, Arterial blood collection**.**

1. Introduction

Pain is an unpleasant emotional-sensory experience associated with an actual or potential injury. It is defined as a fifth vital sign and as a nursing diagnosis that requires special attention and treatment in nursing practice and education. According to studies, hospitalized newborns are exposed to an average of 11.4 painful stimuli per day [1]. Newborns can detect, process, and respond to painful stimuli, making them more sensitive and vulnerable to pain compared to older children and adults [2]. Radial artery blood collection, a procedure that is mandatory for almost all hospitalized children, is the most painful, distressing, and recurring procedure subjected to children, and the prolonged and cumulative experience of pain affects the development of the nociceptive system, leading to an increased response to painful stimuli in the late neonatal period. Oral sucrose is commonly used in developing countries to relieve painful stimuli experienced by neonates as it releases endogenous opioids and -endorphins, thus reducing the transmission of pain signals to the central nervous system [3]. However, the sucrose dosage varies widely in clinical settings, with more than a 20-fold variation in neonatal care settings [4], and prolonged and repeated oral administration of sucrose to relieve painful stimuli may produce neurological side effects in preterm infants. According to Johnston et al., repeated use of sucrose water analgesia in <31-week-old infants may put the infants at risk of poor neurobehavioral development and physiological outcomes [5]; therefore, it is particularly important to explore alternative non-pharmacological pain management strategies to relieve pain in infants. The olfactory system of newborns is very mature and they show a remarkable ability to learn various smells within the first few days of life. Aromatherapy has been shown to reduce pain by creating a more pleasant environment, distracting from pain, and activating the endogenous opioid system to suppress pain impulses, thus modifying and altering pain perception [6]. Lavender essential oil is an aromatic essential oil that is used in aromatherapy and has been shown to have antifungal, muscle-relaxing, and analgesic properties. Moreover, it has been used successfully in studies such as peripheral IV placement in children and neonatal vaccinations. This study aimed to determine the effects of lavender essential oil olfactory stimulation in preterm infants subjected to painful radial artery blood collection.

2. Materials and Methods

2.1 Study Design

This randomized controlled trial was conducted in the neonatal intensive care unit (NICU) of a tertiary care hospital in China. An informed consent form was signed by the parents of each preterm infant before the trial began.

2.2 Patients

The study was conducted during Jan–Dec 2021 on preterm infants (32-37 weeks), with 1-min Apgar scores ≥7 at birth (stable condition). Infants with chromosomal abnormalities, craniofacial anomalies, and intracranial hemorrhage (grade III-IV); infants on mechanically assisted ventilation or oxygen;

infants subjected to sedation, analgesics, or muscle relaxants within 72 h; and infants requiring repeated punctures for unsuccessful primary blood collection were excluded from the study.

2.3 Randomization and Interventions

Patients were randomly assigned to the control group or the intervention group (lavender essential oil-treated group) using computer-generated random codes. Two experienced NICU specialist nurses performed the intervention. The investigator and research assistant were not involved in the intervention process.

Only appropriate skin-to-skin contact and gentle reassurances were given to the preterm infants of the control group during the radial artery blood collection procedure. In contrast, lavender essential oil (Plant Doctor brand of Chinese origin) olfactory stimulation was performed on the infants of the intervention group. For olfactory stimulation, 3 drops of lavender oil were placed on a cotton swab and the swab was placed 2–3 cm away from the preterm infant's nasal cavity 3 min prior to the radial artery blood collection. The nursing staff used a cell phone camera to record the heart rate, oxygen saturation, and facial expressions of the preterm infants 3 min before, during, and 3 min after the radial artery blood collection, respectively. Thereafter, the nursing staff collected saliva specimens from the children for examination. The investigator and research assistant watched the videos independently and rated the pain level and calculated the crying duration of each of the infants.

2.4 Observational Index

The pain was measured in preterm infants using the Preterm Infant Pain Inventory (PIPP), and the scale was developed jointly by the University of Toronto and McGill University in Canada. It consists of baseline (behavioral status and gestational age), physiological (transcutaneous oxygen saturation and heart rate), and behavioral (eye squeezing, frowning, and deepening of nasolabial folds) indicators. Each indicator was rated on a scale of 0–3, to give a total score of 21 (3 x 7), with 0–6 being mild pain, 7–12 being moderate pain, and 13–21 being severe pain and 0.769 as the Cronbach's coefficient for this scale [7].

The duration of crying (in seconds) was recorded from the beginning (the first sound heard) to the end (silence lasting at least 5 s).

After 5 min of blood collection, a swab was placed under the tongue of the infants to allow the saliva to flow out naturally.

The saliva was collected (50 μL) in a 15 mL centrifuge tube and 1 mL of saline was added. The samples were then centrifuged at 2000–3000 rpm for 20 min at 4 ℃, and the supernatant was carefully collected and stored in a -80 ℃ refrigerator for further examination. The specimens were thawed and centrifuged for 5–10 min, and cortisol was quantified using Rexin Human Salivary Cortisol (SC) Quantitative Assay Kit (ELISA). The detection range was 3–48 nmol/L, and the coefficients of variation (CV) within and between the groups were less than 15%.

2.5 Sample Size Estimation

The sample size was estimated with reference to the pain score in a double-blind randomized controlled study of metabolic screening for pain in preterm infants using heel sampling with lavender oil control by Usta [8[, and the PIPP pain score was selected as the primary outcome indicator. The average (mean ± SD) pain scores for the control and intervention groups were 5.73 ± 3.33 and 3.84 ± 2.18, respectively. The sample size was calculated using the PASS11 software and by taking $\alpha = 0.05$ (two-sided test) with a test efficacy of 85% (1-β). The results revealed a sample size of 82 cases, which was increased by 15% to 97 cases by considering the number of missed visits (n = 48 in the control group and n = 49 cases in the intervention group). One case was excluded from the control group due to a parental request to withdraw from the study, so the final study sample in this study was 47 and 49 in the control and the intervention groups, respectively.

2.6 Statistical Analysis

SPSS 23.0 statistical software was used for data analysis. Normal distribution data were expressed as mean ± SD, and the T-test was used for comparison between the groups, while non-normal distribution data were expressed as median and quartiles [M (P25, P75)], and the rank sum test was used for comparison between the groups. Count data were described as frequencies and percentages (%), and the 2 test was used for comparison between the groups. Differences were considered statistically significant at $P < 0.05$.

3. Results

3.1 General Demographic Characteristics of the Patients

A total of 96 preterm infants, 47 in the control group and 49 in the intervention group, were analyzed in the study. The gender, mode of delivery, gestational age, birth weight, 1-min Apgar score, and day of age between the two groups were comparable and not statistically significant (P >0.05). Table 1 shows the general demographic characteristics of the infants of the two groups.

Table 1: General demographic characteristics of the preterm infants in the control and intervention groups

Group	Gender		Delivery method		Gestational age (Weeks)	Birth weigh t (Kg)	1-min Apgar score	Postnatal age (d)
	Male	Female	Vaginal delivery	Cesarean delivery				
Control group n = 47	24	23	40	7	34.4(33.0, 35.5)	2.12(1.85,2. 43)	9(8, 9)	6(5, 7)
Intervention group n = 49	30	19	39	10	35.2(33.4, 36.1)	2.14(1.96, 2.35)	9(8, 9)	6(5, 7)
χ2/Z	$\chi^2 = 1.006$		$\chi^2 = 0.122$		Z = 1.589	Z = 0.286	Z = 0.615	Z = 0.004
P	0.316		0.727		0.112	0.775	0.538	0.997

3.2 Comparison of Observed Indicators between the Two Groups of Preterm Infants

The pain score of the intervention group was 6.57 ± 1.15, which was significantly lower than that of the control group (8.65 ± 2.57; t = 5.093 and *P* <0.001). Moreover, the crying duration of the intervention group was 63.00 ± 9.38 s, which was significantly lower than that of the control group (73.25 ± 8.86 s; t = 5.500 and *P* <0.001). Lastly, the salivary cortisol concentration of the intervention group was 4.09 (3.60, 4.63), which was significantly lower than that of the control group [5.43 (4.91, 6.03); Z = 6.373 and *P* <0.001]. The pain scores, crying time, and salivary cortisol concentrations of the two groups are shown in Table 2, Figure 1, Figure 2, and Figure 3.

Table 2: Comparison of the pain scores, crying duration, and salivary cortisol concentrations of the preterm infants in the control and intervention groups

Group	Pain score	Crying duration (s)	Salivary cortisol concentration nmol/L; M(P25, P75)
Control group n = 47	8.65 ± 2.57	73.25 ± 8.86	5.43(4.91, 6.03)
Intervention group n = 49	6.57 ± 1.15	63.00 ± 9.38	4.09(3.60, 4.63)
t/Z	T = 5.093	T = 5.500	Z = 6.373
P	＜0.001	＜0.001	＜0.001

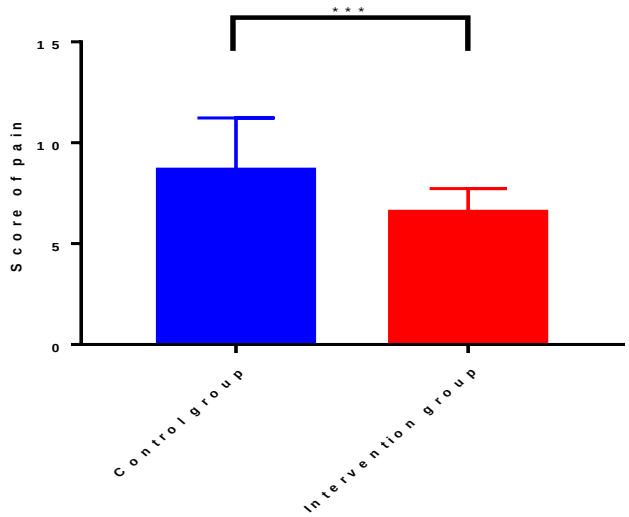

Figure 1: Comparison of the PIPP pain scores of the preterm infants in the control and intervention groups. ****p* <0.001.

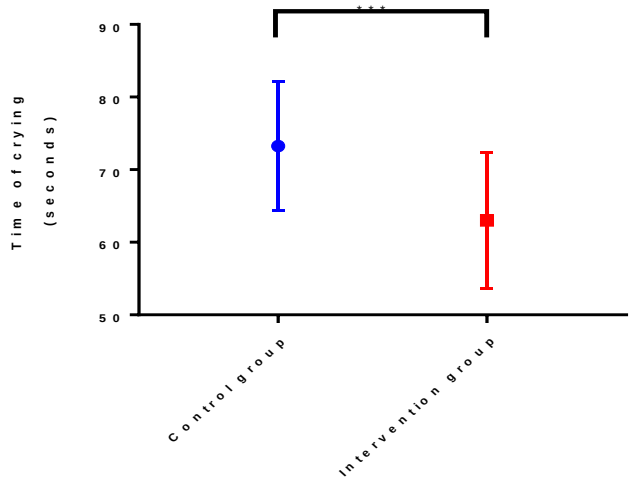

Figure 2: Comparison of the crying duration of the preterm infants in the control and intervention groups. ****p* <0.001.

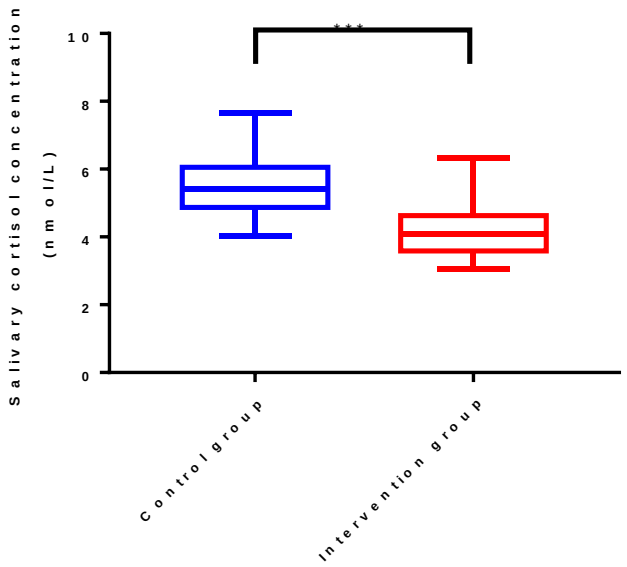

Figure 3: Comparison of the salivary cortisol concentrations of the preterm infants in the control and intervention groups. ****p* <0.001.

4. Discussion

Although advances in NICU management have significantly improved preterm birth survival rates, the extent and scope of environmental exposures and necessary medical interventions may alter the normal development of the immature nervous system. Studies have shown that pain has physical, behavioral, and cognitive consequences, such as impaired brain development and effects on subcortical structures and white matter [9]. Furthermore, pain affects the development of the immature brain by blocking myelin formation, with preterm infants being the most susceptible age group. Therefore, exploring effective pain interventions to alleviate painful stimuli experienced by preterm infants may not only improve the quality of care but also reduce short- and long-term pain-induced complications in these infants. Olfactory genes form the largest gene family in humans and play an important role in memory, taste, defense, and sensory integration. During 28 weeks of intrauterine life and 35 weeks of postmenstrual age (PMA), the olfactory system matures rapidly and continues to gain experience and produce physiological changes throughout the infant's life span [10]. Therefore, the olfactory input function is gaining popularity among scholars for applications in pain control research.

Lavender oil is botanical aromatic oil known for its calming and soothing effects. In the UK, the use of aromatherapy has been adopted as part of holistic care. Inhalation aromatherapy is a technique that uses essential oils for inhalation to reduce pain, relieve stress and depression, and improve vital signs [11]. Lavender essential oil olfactory stimulation has been studied with satisfactory results in adult hemodialysis patients with painful arteriovenous fistula punctures, in children with indwelling intravenous catheters, and pediatric dental treatment but has not been adequately studied for pain control in preterm infants [12-14]. In this study, the lavender essential oil was used for olfactory stimulation in preterm infants to determine its effects on pain relief during radial artery blood collection. The results in Table 2 reveal that the olfactory stimulation of lavender essential oil was effective in reducing pain scores during radial artery blood collection in preterm

infants, consistent with the findings of Usta et al [11]. The pain-relieving effects of lavender essential oil are attributed to the presence of linalyl acetate and linalool. Linalool inhibits the release of acetylcholine and alters the function of ion channels at the neuromuscular junction, thus acting as a sedative. Furthermore, the glutamine and cholinergic systems play a role in lavender oil analgesia when the lavender odor molecules are absorbed and converted into nerve impulses in the olfactory bulb, amygdala, and limbic system [15]. Lavender essential oil odor stimulates a positive physiological effect via the olfactory system, and the intervention is simple, easy, safe, and effective, warranting further clinical study.

Since preterm infants are unable to express their emotions verbally, crying is a specific emotional manifestation of their response to nociception when subjected to painful stimuli. Although there are individual differences and crying duration cannot be used as a standard for measuring pain intensity, it is still believed that this index can be used as one of the reference indicators for evaluating nociception. The results in Table 2 show that olfactory stimulation with lavender essential oil shortens the duration of crying in preterm infants during radial artery blood collection, similar to the results reported by Vaziri et al [16]. Lavender essential oil is a known aromatic essence that improves mood, reduces anxiety, and increases sedation by stimulating the autonomic nervous system parasympathetically post inhalation. In animal studies, inhalation of essential oils has been shown to stimulate the production of endorphins and norepinephrine in the bloodstream and produce pharmacological effects [17]. In addition chemicals in essential oils can bind to the receptors in the olfactory bulb and affect the limbic system, which is the emotional center of the brain, ultimately affecting pain perception [18]. The soothing ability of lavender essential oil also prevents an increase in heart rate and maintains stable blood oxygen saturation, allowing for a quicker return to a calm state, thus reducing crying duration [19]. According to the theory of sensory gating, when the preterm infant's brain is deficient in sensory gating and the central inhibition is weakened, the infant is more likely to pay attention to pain-related stimuli. A large amount of nociceptive information is transmitted to the brain through the "medial thalamus-prefrontal cortex" bottom-up transmission pathway, resulting in pain information overload and pain sensitivity, and failure to take effective pain relief measures will have a negative long-term impact on infants. Lavender essential oil olfactory stimulation creates a familiar and comfortable odor environment and soothes the neuromuscular system so that the premature infants subjected to painful stimuli are distracted from the stimulus, thereby reducing the pain sensitivity and pain memory and affecting the pain information sent from the brain, which in turn regulates the pain gate switch and raises the pain threshold.

When an organism is stimulated by a stressor, the hypothalamic-pituitary-adrenal axis is activated and cortisol is released. Cortisol concentrations have been used as an objective indicator of pain and stress levels and to assess the effectiveness of pain relief measures. The results in Table 2 show that olfactory stimulation with lavender essential oil reduces salivary cortisol concentrations in preterm infants after radial artery blood collection, similar to the findings of Ghaderi et al [20]. The endocrine system of preterm infants is relatively well developed and can release cortisol when stimulated by pain, resulting in changes in plasma and salivary cortisol concentrations, consequently generating physiological and biochemical changes. Salivary cortisol is derived from the passive transport of free cortisol from the blood to the saliva via glandular vesicle diffusion, and it can accurately reflect the dynamic changes in the level of serum-free cortisol to an extent. Therefore, salivary cortisol was used as an indicator of the plasma cortisol as a reflection of the stress level of preterm infants in response to painful stimuli from radial artery blood collection. However, in this study, salivary cortisol samples were collected 5 min after the pain intervention, and there were no multiple time points for comparative testing. Therefore, it was not possible to determine whether salivary cortisol levels continued to differ significantly between the two groups of preterm infants at multiple time points, thus proving the efficacy of lavender essential oil odor stimulation on pain intervention in preterm infants, necessitating further studies.

5. Conclusions

Lavender essential oil olfactory stimulation is effective in relieving pain during radial artery blood collection in preterm infants. It is also safe to use at low concentrations and does not produce adverse effects. The intervention protocol is simple and easy to implement, with high nurse compliance, and is appropriate in the clinical context. Further multicenter and intervention studies on preterm infants suffering from different pain stimuli are required to establish lavender essential oil olfactory stimulation as a clinical non-pharmacological pain management tool.

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Author Contributions

DX and TL contributed equally to this Study. DX and TL designed this study. YL and ZH conducted the experiments and data analysis. NM anf LH prepared all the figures and tables. JW and TH wrote the manuscript. All authors reviewed and approved the final manuscript.

Conflicts of Interest

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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References

[1] Roofthooft DW, Simons SH, Anand KJ, Tibboel D, van Dijk M. Eight years later, are we still hurting newborn infants? NEONATOLOGY. [Journal Article; Observational Study]. 2014 2014-01-20;105(3):218-26.

[2] Boggini T, Pozzoli S, Schiavolin P, Erario R, Mosca F, Brambilla P, et al. Cumulative procedural pain and brain development in very preterm infants: A systematic review of clinical and preclinical studies. Neurosci Biobehav Rev. [Journal Article; Review; Systematic Review]. 2021 2021-04-01;123:320-36.

[3] Razaghi N, Aemmi SZ, Sadat HA, Boskabadi H, Mohebbi T, Ramezani M. The effectiveness of familiar olfactory stimulation with lavender scent and glucose on the pain of blood sampling in term neonates: A randomized controlled clinical trial. COMPLEMENT THER MED. [Journal Article; Randomized Controlled Trial]. 2020 2020-03-01;49:102289.

[4] Stevens B, Yamada J, Campbell-Yeo M, Gibbins S, Harrison D, Dionne K, et al. The minimally effective dose of sucrose for procedural pain relief in neonates: a randomized controlled trial. BMC PEDIATR. [Journal Article; Multicenter Study; Randomized Controlled Trial; Research Support, Non-U.S. Gov't]. 2018 2018-02-23; 18(1):85.

[5] Johnston CC, Filion F, Snider L, Majnemer A, Limperopoulos C, Walker CD, et al. Routine sucrose analgesia during the first week of life in neonates younger than 31 weeks' postconceptional age. PEDIATRICS. [Clinical Trial; Journal Article; Multicenter Study; Randomized Controlled Trial; Research Support, Non-U.S. Gov't]. 2002 2002-09-01; 110(3):523-8.

[6] Sadathosseini AS, Negarandeh R, Movahedi Z. The effect of a familiar scent on the behavioral and physiological pain responses in neonates. PAIN MANAG NURS. [Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't]. 2013 2013-12-01;14(4):e196-203.

[7] Stevens B, Johnston C, Petryshen P, Taddio A. Premature Infant Pain Profile: Development and Initial Validation. The Clinical journal of pain. 1996 1996-01-01; 12(1):13-22.

[8] Usta C, Tanyeri-Bayraktar B, Bayraktar S. Pain Control with Lavender Oil in Premature Infants: A Double-Blind Randomized Controlled Study. J Altern Complement Med. [Journal Article; Randomized Controlled Trial]. 2021 2021-02-01;27(2):136-41.

[9] Gursul D, Hartley C, Slater R. Nociception and the neonatal brain. Semin Fetal Neonatal Med. [Journal Article; Research Support, Non-U.S. Gov't; Review]. 2019 2019-08-01;24(4):101016.

[10] Davidson J, Ruthazer R, Maron JL. Optimal Timing to Utilize Olfactory Stimulation with Maternal Breast Milk to Improve Oral Feeding Skills in the Premature Newborn. BREASTFEED MED. [Journal Article; Randomized Controlled Trial]. 2019 2019-05-01; 14(4):230-5.

[11] Farrar AJ, Farrar FC. Clinical Aromatherapy. Nurs Clin North Am. [Journal Article; Review]. 2020 2020-12-01; 55(4):489-504.

[12] Şahin S, Tokgöz B, Demir G. Effect of Lavender Aromatherapy On Arteriovenous Fistula Puncture Pain and the Level of State and Trait Anxiety in Hemodialysis Patients: A Randomized Controlled Trial. PAIN MANAG NURS. [Journal Article; Randomized Controlled Trial]. 2021 2021-08-01;22(4):509-15.

[13] Bikmoradi A, Khaleghverdi M, Seddighi I, Moradkhani S, Soltanian A, Cheraghi F. Effect of inhalation aromatherapy with lavender essence on pain associated with intravenous catheter insertion in preschool children: A quasi-experimental study. Complement Ther Clin Pract. [Journal Article]. 2017 2017-08-01;28:85-91.

[14] Arslan I, Aydinoglu S, Karan NB. Can lavender oil inhalation help to overcome dental anxiety and pain in children? A randomized clinical trial. EUR J PEDIATR. [Journal Article; Randomized Controlled Trial]. 2020 2020-06-01;179(6):985-92.

[15] Silva BL, Emanuelli T, Souza DO, Elisabetsky E. Effects of linalool on glutamate release and uptake in mouse cortical synaptosomes. NEUROCHEM RES. [Journal Article; Research Support, Non-U.S. Gov't]. 2001 2001-03-01;26(3):191-4.

[16] Vaziri F, Khosropoor M, Hidari M, Pourahmad S, Morshed BB, Saki F. The Effect of Aromatherapy by Lavender Oil on Infant Vaccination Pain: a Double Blind Randomized Controlled Trial. J Caring Sci. [Journal Article]. 2019 2019-03-01;8(1):17-21.

[17] Perry N, Perry E. Aromatherapy in the management of psychiatric disorders: clinical and neuropharmacological perspectives. CNS DRUGS. [Journal Article; Research Support, Non-U.S. Gov't; Review]. 2006 2006-01-20; 20(4):257-80.

[18] Johnson AJ. Cognitive facilitation following intentional odor exposure. Sensors (Basel). [Journal Article; Review]. 2011 2011-01-20;11(5):5469-88.

[19] Akcan E, Polat S. Comparative Effect of the Smells of Amniotic Fluid, Breast Milk, and Lavender on Newborns' Pain During Heel Lance. BREASTFEED MED. [Journal Article]. 2016 2016-08-01;11(6):309-14.

[20] Ghaderi F, Solhjou N. The effects of lavender aromatherapy on stress and pain perception in children during dental treatment: A randomized clinical trial. Complement Ther Clin Pract. [Journal Article; Randomized Controlled Trial]. 2020 2020-08-01; 40:101182.