

# Comparison of the analgesic effect of inhaled lavender vs vanilla essential oil for neonatal frenotomy: a randomized clinical trial (NCT04867824)

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## Research Article

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# Abstract

**Background:** It is necessary to treat neonatal pain because it may have short and long-term adverse effects. Frenotomy is a painful procedure where sucking, a common strategy to relieve pain, cannot be used because the technique is performed on the tongue. In a previous randomized clinical trial, we demonstrated that inhaled lavender essential oil (LEO) reduced the signs of pain during neonatal frenotomy. We aimed to find out whether inhaled vanilla essential oil (VEO) is more effective in reducing pain during frenotomy than LEO.

**Methods:** Randomized clinical trial with neonates who underwent a frenotomy for type 3 tongue-ties between May and October 2021. Pain was assessed using pre and post-procedure heart rate (HR) and oxygen saturation (SatO<sub>2</sub>), crying time and NIPS score. Patients were randomized into “experimental” and “control” group. In both groups, we performed swaddling, administered oral sucrose, and let the newborn suck for two minutes. We placed a gauze pad with one drop of LEO (control group) or of VEO (experimental group) under the neonate’s nose for two minutes prior to and during the frenotomy.

**Results:** We enrolled 142 patients (71 per group). Both groups showed similar NIPS scores (2.02 vs 2.38) and crying times (15.3 vs 18.7 s). We observed no differences in HR increase or in SatO<sub>2</sub> decrease between both groups. We observed no side effects in either of the groups.

**Conclusions:** We observed no appreciable difference between LEO and VEO, therefore we cannot conclude which of them was more effective in treating pain in neonates who underwent a frenotomy.

## What Is Known

- Pain management is one of the most important goals of neonatal care as it can have long-term neurodevelopmental effects.
- Lavender essential oil can help relieve pain due to its sedative, antispasmodic and anticolic properties.

## What Is New

- Lavender and vanilla essential oils are safe, beneficial, easy to use and cheap in relieving pain in neonates who undergo a frenotomy for type 3 tongue-ties.

This clinical trial is registered with [www.clinicaltrials.gov](http://www.clinicaltrials.gov) with NCT04867824.

## Introduction

Neonates routinely undergo painful procedures such as blood sampling for the early diagnosis of inborn errors of metabolism. According to the International Association for the Study of Pain, “pain” is as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual

or potential tissue damage [1]. Over the last years, neonatal units have shown an increasing interest in studying neonatal pain. Historically, newborns were thought to have no pain due to the immaturity of their nervous system [2]. Evidence however demonstrated that newborns feel pain and may even have increased sensitivity to it and to its long-term negative effects due to this immaturity. Repeated, unrelieved pain can cause adverse physiologic effects in all systems, including the brain, potentially affecting long-term development [3]. This fact has driven development-based care, a model which promotes individualized care based on the observation of the neonates' behaviors and on the knowledge of their physical and family environment. Developmental care focuses on avoiding painful procedures such as blood sampling as much as possible, grouping interventions in order to minimally manipulate the newborn, and managing pain, either by administering analgesia, physically restraining the patient, or combining both [4]. It is important to recognize pain and relieve it because it may lead to hemodynamic instability, decreased oxygen saturation, and increased intracranial pressure [5]. Non-pharmacological pain relief interventions are important in neonatology due to the potential adverse effects of pharmacological treatments. They include: sensory stimulation (positioning or swaddling, vestibular action or rocking, aromatherapy, non-nutritive sucking, musical therapy), nutritive (oral sweet solutions) and maternal interventions (maternal odor and voice, breastfeeding, skin-to-skin contact) [3,4,6]. Oral sucrose solutions reduce the signs of pain but do not eliminate it, and this is why they should be used in combination with other non-pharmacological interventions [4,7-9]. Olfaction is essential for neonatal behavioral adaptation in many mammals, including humans [10]. Olfactory signals help the newborn baby localize and attach to the nipple at the first sucking bout [11]. Aromatherapy uses the healing effects of volatile essential oils in different ways and has been widely used for centuries in traditional and modern medicine as complementary therapy [3,12,13]. Aroma stimulates the olfactory bulb, anatomically close to the limbic system which is responsible for the emotions. Effects of essential oils on the limbic system lead to enkephalin, endorphin and serotonin release [14]. Lavender essential oil (LEO), of all the essential oils, has been studied most by healthcare professionals [15]. LEO may relieve pain [6,12,14] through inhibition of nociceptive stimuli by stimulating the olfactory system, inducing relaxation and stimulating endogenous opioids [4].

In our service we perform painful techniques following administration of oral sucrose, performing swaddling, and allowing neonates to breastfeed or suck, which helps prevent crying. However, these measures are not enough during frenotomies because they are performed in the mouth and patients cannot suck during the procedure. We have a high prevalence of neonatal ankyloglossia (32.5%) in our center, for which frenotomy is a common treatment [16]. In a former clinical trial (NCT04877392), we compared the use of common pain control strategies (swaddling, administration of oral sucrose, and suck for two minutes prior to the procedure) with the use of those plus inhaled LEO, and observed that signs of pain (duration of crying and NIPS score) were lower in the experimental group. From that moment on, we have routinely used inhaled LEO when performing a frenotomy [17]. Other authors have observed the benefits of using vanilla (*Vanilla fragrans*) essential oil (VEO) for pain control in neonates [18,19]. The aim of this study was to demonstrate if the use of inhaled VEO was more effective than inhaled LEO (*Lavandula angustifolia ssp angustifolia*) in reducing signs of pain during frenotomy in

healthy, full-term neonates. Our hypothesis was that signs of pain (mostly crying time and NIPS score) would be lower in the experimental group than in the control group. We chose LEO and VEO because these are the fragrances for which more studies have been performed in neonates and infants [3,4,6,12,17,19-27]. As far as we know, there are no previous studies which have analyzed the potential benefit of LEO vs VEO to relieve pain in neonatal frenotomy.

## Patients And Methods

We conducted a blinded randomized clinical trial (registered at <https://clinicaltrials.gov> with the identifier NCT04867824, under the title “The Use of Lavender vs Vanilla Essential Oil as Complementary Analgesia for Frenotomy in Healthy Newborns”). Our hospital Ethics Committee (CEIm-PSMAR) reviewed and approved this study on May 4, 2021 (approval number: 2021/9731/I). This study was conducted according to the ethics code of the Barcelona Medical Association and the principles of the Helsinki-Fortaleza Declaration 2013.

This study was conducted at the neonatal unit of a tertiary care hospital in Barcelona, Spain, which experiences approximately 1,400 births per year from a multiethnic population with Spanish, Pakistani and Bangladeshi being the most frequent nationalities of our patients [28]. We have high breastfeeding rates: around 85% at discharge from the maternity ward (86.8% in 2018) [16], 82% at the age of three months, and 54% at the age of six months. We assess for the presence of ankyloglossia as part of the routine neonatal evaluation and classify it based on Coryllos’s criteria [29] and the Hazelbaker tool [30]. A lingual frenulum is symptomatic if it scores eight points or less in appearance and/or 11 points or less in function according to Hazelbaker. Advice and help with positioning and attachment for breastfeeding is provided to all the mothers by lactation support providers.

During the study period, if we identified a symptomatic patient with a type 3 tongue-tie which affected breastfeeding, we offered the patient's parents to participate. We chose type 3 tongue-ties because they are the most common in our population [16] and, due to their anatomical features (thick and submucosal), they seem to make breastfeeding more difficult. Patients were enrolled if their parents agreed to and signed a written informed consent prior to the procedure, then they were allocated into the experimental or the control group by simple random sampling using the program OxMAR (Online Minimization and Randomization for Clinical Trials) [31]. Prior to recruitment, we generated a list of 142 numbers, where each number was randomized to either the “VEO” or “control (LEO)” group. Patients were enrolled in numerical order and assigned into the pre-determined group. The group into which a patient had been enrolled was not known by the attending personnel until the moment of performing the frenotomy.

To perform the frenotomy, the neonate was taken to the neonatal unit and monitored with a pulse-oximeter (COVIDIEN Nellcor Portable SpO<sub>2</sub> Patient Monitoring System PM10N, Covidien Ireland Limited, IDA Business & Technology Park, Tullamore, Ireland) before, during and after the procedure. For both groups we swaddled, administered 1 mL of oral sucrose, and let the newborn suck for two minutes prior

to the procedure. The control group had a 7 x 7 cm gauze pad with one drop of 100% pure LEO (Pranarôm España S.L.) placed 2 cm under their nose for two minutes prior to starting the frenotomy and for the duration of the procedure; whereas in the experimental group the drop on the gauze pad was of 100% pure VEO (Pranarôm España S.L.) instead. The bottles of both LEO and VEO have a dropper that always dispenses the same amount of oil per drop. We did not start the procedure until the patients were calm and had a NIPS score of 0. Frenotomy was performed by one of the three staff neonatologists by placing a sterile groove director under the tongue holding the frenulum in place with visualization of tongue base and frenulum, then snipping the frenulum with a blunt tip scissor along the underside of the tongue to its base just proximal to the genioglossus muscle until a full release was achieved [29]. We assessed pain by means of crying time and the highest Neonatal Infant Pain Scale (NIPS) score in the five minutes post procedure, and whether there was an increase in heart rate (HR) and decrease in oxygen saturation (SatO<sub>2</sub>). NIPS evaluates facial expression, crying, breathing pattern, arm and leg position, and state of arousal on a scale from 0 to 7, where 0-2 means no pain to mild pain, 3-4 mild to moderate pain, and >4 severe pain [32]. A blinded neonatologist who did not perform the frenotomy evaluated vital signs through the screen of the pulse-oximeter, NIPS score and crying time from a neighboring room through a glass, for which he/she could not smell or see which oil was being used. Vital signs, whether the baby cried or not, the seconds crying lasted, and the post procedure NIPS score were recorded on a data collection sheet. If a neonate cried, the attending staff who performed the frenotomy provided calming techniques such as holding, swaddling, and sucking regardless of which essential oil was being used. These persons were not blinded. Once the procedure was completed, we removed the gauze pad and returned the neonate to the mother for breastfeeding.

Calculation of sample size: In an exploratory preliminary study prior to the intervention, we observed a mean (SD) crying time of 19.80 (21.14) seconds. We used this data as our baseline. In order to detect a difference of 10 seconds in crying time, we calculated that we needed a sample size of 71 patients per group to be able to draw conclusions with a confidence interval (CI) 95% and a power of 80%. We used crying time to calculate sample size because it is an objective way to measure pain, whereas NIPS could be more person-specific.

The observer recorded demographic (sex, gestational age, birth weight, age in hours at the time of frenotomy) and clinical data (HR and SatO<sub>2</sub> before, during, and after the procedure, whether the patient cried or not during the procedure, length of crying time in seconds, presence of side effects during the procedure (apnea, desaturation, others) and highest NIPS score within the first five minutes after the procedure) on a data collection sheet. The primary outcome was difference in crying time between the experimental and the control group, and secondary outcomes were: difference of NIPS score, HR and SatO<sub>2</sub> pre and post-procedure between the experimental and the control group. Participants' confidentiality was maintained because neither the name nor the medical record number were recorded on the data collection sheet.

Statistical analysis: Quantitative variables are described using the mean, standard deviation, and 95% CI; the experimental and the control groups were compared with a Student's t test. Qualitative variables are

presented in percentages and compared using Fisher's exact test. We compared NIPS scores between both groups using the Wilcoxon rank-sum (Mann-Whitney) test. Statistical significance was set for a  $p < .05$ . To perform statistical analyses we used STATA version 16.1 (StataCorp, College Station, TX, USA).

## Results

We enrolled 142 patients until we reached 71 patients in each group from a total of 155 potential candidates between May 10, 2021 and October 9, 2021. Thirteen were excluded for the following reasons: eight parents refused to participate in the study, there was a language barrier with four parents, and one was isolated due to maternal COVID-19 infection. There was no follow up period therefore we did not lose any participants to follow up. All the patients were analyzed for the primary and secondary outcomes. We included 77 male (54.2%) and 65 female (45.8%) newborns. Globally, mean (SD) gestational age was  $39^{6/7}$  ( $1^{1/7}$ ) weeks, and mean (SD) birth weight, 3328.58 (488.04) g. The mean (SD) age at the time of the procedure was 43.0 (32.9) hours. Table 1 shows the demographic characteristics of both groups. There were no differences between the two groups in terms of sex, birth weight, gestational age, or age at the moment of the frenotomy.

Mean (SD) HR pre-procedure was 125.4 (17.3) bpm, and post-procedure 155.3 (16.8) bpm; mean (SD) HR increase was 29.9 (15.6) bpm. Mean (SD) SatO<sub>2</sub> pre-procedure was 99.3 (1.2) %, and post-procedure, 96.4 (3.1) %; mean (SD) SatO<sub>2</sub> decrease was 2.9 (3.0) %. 140 patients cried (99.3%) with a mean (SD) crying time of 17.0 (19.5) seconds. Mean (SD) NIPS score was 2.20 (1.05). There were no differences between the two groups in terms of baseline HR. There were statistically different baseline SatO<sub>2</sub> that had no clinical significance. Table 2 presents the outcomes of the experimental group and the control group.

There were no differences between the experimental group and the control group in terms of HR increase, SatO<sub>2</sub> decrease, crying time, or NIPS scores. Almost all patients cried in both groups. We observed no adverse effects with the use of LEO or VEO.

With the results obtained, the power of our study to detect significant differences in crying time between the experimental and the control group with the use of VEO vs LEO was 86.5%.

## Discussion

Goubet conducted the first study of aromatherapy with neonates in 2003 [33]. Aromatherapy has been used to treat pain in infants, showing an objective improvement in neonatal pain scale scores, decreased heart rate, shorter crying time, and prevention of decreased oxygen saturation [3,4,6,12,17,20]. The main aromas used in neonatology are lavender, vanilla, amniotic fluid and human milk [3,34].

LEO may alter the perception of pain by inhibiting nociceptive stimuli by means of stimulating the olfactory system and inducing relaxation, providing a pleasant environment, distracting the mind from the pain, and stimulating endogenous opioids [4]. Its sedative, antidepressant, as well as antispasmodic

and anticolic properties make it capable of relieving the symptoms of pain [6,12]. Inhaled LEO has demonstrated benefits in reducing pain during neonatal blood sampling, heel puncture [4,6,20] and vaccination at the age of two months [21].

Several studies concluded that the use of a familiar odor (mainly breast milk, but also vanillin, present in VEO) helps to reduce agitation, apneas, and stress and adverse effects of neonatal pain [27,35,36]. Vanillin seems to be hedonically pleasant for full-term and preterm neonates, seems to influence pain reaction, and may even be analgesic, especially if the infant has been previously exposed to its odor [26,27,33,37]. We did not sensitize neonates with the aroma of VEO because we performed the frenotomy when it was indicated, and thus there was no time to sensitize them prior to the procedure. Goubet observed that VEO has soothing effects on premature neonates during venipuncture but not during heel stick [33], whereas some authors have observed that it is effective in full-term neonates during heel stick [19,26,37], venipuncture [18] and arterial puncture [38]. Sadathosseini observed that crying lasted significantly less and that variation in SatO<sub>2</sub> was lower when the odor of VEO was familiar [38]. Other studies have found no effects of VEO in soothing pain in full-term infants if the patients have not been previously exposed to this odor [24]. Neshat et al. found no differences on prematures' heart rate and SatO<sub>2</sub> during venipuncture even though the neonates had been previously familiarized with VEO [23].

To the best of our knowledge, this is the first study to evaluate the effect of inhaled LEO vs VEO as pain relief during neonatal frenotomy. In a previous clinical trial, which we conducted, we observed a significant decrease in crying time and NIPS scores in the LEO exposed group when compared to the control group and traditional pain control measures [17]. When planning this clinical trial, we chose VEO because it is the second most used aroma (apart from breastmilk) in neonatology. In this study, we observed no difference in crying time or the NIPS scores between the LEO and VEO groups. Thus, we can assume that VEO is as effective as LEO in treating neonatal pain during frenotomy. Given the high power of our study (86.5%), we consider our results reliable.

None of the prior aromatherapy studies performed in infants have described any side effects, for instance nausea, vomiting or chills [22,25,27,38]. In keeping in line with them, we also have observed no side effects from its use. Therefore, we conclude that using inhaled LEO and VEO for frenotomy is safe. Our study is easily reproducible.

One positive note is that the use of inhaled essential oils is cheap. A 10-mL bottle of Pranarôm LEO or VEO costs \$7.60 US, and contains approximately 200 drops. We used one drop per patient, which represents approximately \$0.04 US.

We acknowledge that the study has limitations. The team who performed the frenotomies was not blinded, primarily because the smell of LEO and VEO is too obvious to ignore. However, the person who recorded the data was blinded, as described in the "Patients and methods" section. Some candidates (8.39%) were not eligible to participate primarily because eight parents did not consent and four parents had language barrier issues for which they were not offered to participate. Another limitation is that more

than one person performed the frenotomies, for which the technique could have minimal variations, however, all three staff neonatologists have similar experience and training.

## Conclusions

In conclusion, we observed no differences in the signs of pain between the experimental and the control group. For this reason, we cannot conclude that LEO or VEO are more effective in treating pain in the neonates who underwent a frenotomy for type 3 tongue-ties. We observed no side effects from its use.

## Abbreviations

HR: heart rate; LEO: Lavender Essential Oil; NIPS: Neonatal Infant Pain Scale; SatO<sub>2</sub>: oxygen saturation; VEO: Vanilla Essential Oil.

## Declarations

**Ethics approval and consent to participate:** Our Ethics Committee approved the study (reference number: 2021/9731/I), which was conducted in accordance with the Declaration of Helsinki. Consent to participate: Yes.

**Consent for publication:** N/A.

**Availability of data and materials:** Our database is accessible from the authors upon request.

**Competing interests:** We declare that we have no conflicts of interest to disclose.

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### Authors' contributions:

Dr. SM designed the study, collected data, analyzed the results, and drafted the initial manuscript.

Dr. MF designed the study, analyzed the results, and drafted the initial manuscript.

Ms. RL reviewed the literature and helped draft the initial manuscript.

Drs. JC, JG and ML collected data, and helped draft the initial manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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### **Compliance with Ethical Statements**

**Conflict of Interest:** The authors declare that they have no conflict of interest. This research was not sponsored.

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**Ethical approval:** Our hospital Ethics Committee approved this study (reference number: 2021/9731/I), which was conducted in accordance with the Declaration of Helsinki.

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## Tables

**Table 1.** Demographic characteristics of the experimental group and the control group.

Variables	Experimental group (VEO) <i>n</i> = 71 (%)	Control group (LEO) <i>n</i> = 71 (%)	<i>P</i> value
Male newborn	38 (53.5)	39 (54.9)	>0.99 <sup>a</sup>
Birth weight (grams) (mean, SD)	3277.97 (494.71)	3379.20 (479.41)	0.217 <sup>b</sup>
Gestational age (weeks) (mean, SD)	39 <sup>6/7</sup> (1 <sup>1/7</sup> )	39 <sup>6/7</sup> (1 <sup>2/7</sup> )	0.909 <sup>b</sup>
Age at frenotomy (hours) (mean, SD)	43.6 (31.1)	42.4 (34.8)	0.819 <sup>b</sup>

<sup>a</sup>Fisher's exact test, <sup>b</sup>Student's t-test, <sup>c</sup>Wilcoxon rank-sum (Mann-Whitney). LEO: Lavender Essential Oil, VEO: Vanilla Essential Oil.

**Table 2.** Outcomes of the experimental group and the control group. Control group is the reference.

Variables	Experimental group <i>n</i> = 71 (%)	Control group <i>n</i> = 71 (%)	<i>P</i> value	95% CI <sup>d</sup>
Heart rate (bpm)				
pre-procedure (mean, SD)	125.1 (13.1)	125.8 (17.3)	0.781 <sup>b</sup>	-5.83 to +4.39
post-procedure (mean, SD)	155.8 (16.5)	154.9 (17.2)	0.762 <sup>b</sup>	-4.74 to +6.46
Increase in heart rate post-procedure (bpm) (mean, SD)	31.3 (16.1)	30.6 (15.5)	0.549 <sup>b</sup>	-3.62 to +6.77
Oxygen saturation (%)				
pre-procedure (mean, SD)	99.1 (1.5)	99.6 (0.9)	<b>0.024<sup>b</sup></b>	-0.87 to -0.06
post-procedure (mean, SD)	96.1 (3.3)	96.7 (2.9)	0.277 <sup>b</sup>	-1.62 to +0.47
Decrease in oxygen saturation post-procedure (%) (mean, SD)	2.3 (2.7)	2.4 (2.9)	0.826 <sup>b</sup>	-1.13 to +0.90
Crying (yes, %)	71 (100%)	70 (98.6%)	>0.99 <sup>a</sup>	-
Crying (seconds) (mean, SD)	15.3 (16.5)	18.7 (22.0)	0.297 <sup>b</sup>	-9.88 to +3.04
Presence of adverse effects (yes, %)	0 (0.0%)	0 (0.0%)	-	-
NIPS score (mean, SD) (range)	2.02 (0.97) (1-4)	2.38 (1.11) (0-4)	0.114 <sup>c</sup>	-0.63 to +0.07

<sup>a</sup>Fisher's exact test, <sup>b</sup>Student's t-test; <sup>c</sup>Wilcoxon rank-sum (Mann-Whitney) test; <sup>d</sup>95% CI: 95% confidence interval of the difference between the experimental and the control group.