Effect of Vanilla on Hypoxic Intermittent Events in Premature Infants

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1. OBJECTIVES AND HYPOTHESIS

1.1. Main objective

The main objective of the study is to assess whether exposure to vanilla odor decreases the number of intermittent hypoxia events in preterm infants born between 32^0 and 33^6 weeks and reaching near term-equivalent age. A hypoxic event is defined as a desaturation < 90% with a decrease in oxygen saturation (SpO_2) ≥ 5% compared to preceding SpO_2, for a duration ≥ 5 seconds (Rhein et al. 2014).

1.2. Secondary objectives

Secondary objectives are to determine the effect of vanilla odor further by measuring the percentage of recording time spent with a SpO_2 < 80%, the percentage of recording time spent with a SpO_2 < 90%, the bradycardia index (number per hour), the percentage of recording time spent in periodic breathing, as well as the effect on heart and respiratory rate variability. In addition, we aim to gather preliminary results on the effect of vanilla odor on the states of alertness.

1.3. Hypothesis

We hypothesize that vanilla odor stimulates the cardiorespiratory centers, and especially decreases periodic breathing and arterial oxygenation oscillations in preterm infants at near-term-equivalent age.

2. METHODS

2.1. Study design

To fulfill our main objective, a randomized, controlled, unblinded, balanced cross-over study will be performed.

2.2. Study population and patient sample

The study population will be preterm infants born between 32^0 and 33^6 weeks and hospitalized in the neonatal care unit at the University of Sherbrooke Hospital Center, with a postnatal age of 3 to 4 weeks, i.e., close to a term-equivalent age.

2.2.1. Patient sample

We will study a convenience sample. Preterm infants in the neonatal care unit will be included in chronological order of their birth.
The sample size has been computed with the help of Mrs Marie-Pierre Lapointe-Garant, biostatistician at the University of Sherbrooke Hospital Research Center using the *nQuery* software. Literature data suggest that an average of 4 periodic breathing epochs per hour is expected in the population under study (Martin et al, 2011). A sample of 17 patients is therefore necessary to detect a difference of 33% between conditions, with a power of 80% and an α error of 0.05. Accordingly, we aim to include 30 preterm infants to get 20 technically valid recordings. If necessary, we will continue patient recruitment to reach 20 valid recordings. We believe that the latter can be obtained within a 2-year period. This number is based on data from the neonatal care unit at the University of Sherbrooke Hospital Center showing that 51 and 59 preterm infants were born between 32^0 and 33^6 weeks in 2012 and 2013 respectively.

2.2.1.1. <u>Inclusion criteria</u>

- Birth between 32 and 33^6 weeks of gestational age
- Postnatal age between 3 and 4 weeks
- Absence of any respiratory support or supplemental oxygen
- Clinically stable for a minimum of 48 hours prior to inclusion
- Obtention of parental consent.

2.2.1.2. <u>Exclusion criteria:</u>

- Any respiratory condition (e.g., pneumonia or bronchopulmonary dysplasia) other than apnea of prematurity
- Intraventricular hemorrhage grade 3 or 4, or periventricular leukomalacia;
- Chromosomal anomalies
- Congenital malformation susceptible to lead to cardiorespiratory or neurological complications

- Parental refusal
- Significant clinical deterioration during the study period.

* Note that caffeine treatment is not an exclusion criterion.

2.3. Measuring instruments

Our polysomnography equipment will allow recording electrocardiographic activity (ECG), SpO_2 (Masimo oximeter), and thoracic and abdominal respiratory movements (respiratory inductance plethysmography, *Respitrace*). Preliminary observations will be collected for electroencephalographic activity and eye movements (states of alertness). No invasive sensor will be used for the study.

2.4. Vanilla odorization

As reported in past studies by Marlier L et al (2005), and Edraki M et al (2013), we will use 2 mL of a 2% vanillin solution to odorize the infant environment. The vanilla solution will be spread on the infant's bib, both on the shoulders and the superior part of the thorax. According to results from the two past studies cited above, a single application at the beginning of the study will be sufficient.
Following recordings, we will retrospectively check in the infant's medical record whether any unexpected event has occurred during and within 24 hours after the odorization period, to detect any side-effect potentially related to vanilla odor exposure.

2.5. Conduct of the study

2.5.1. Data collection

Following patient recruitment, medical history taking, and physical examination, all included preterm infants will undergo two nocturnal continuous recordings of ECG, SpO_2 and respiratory movements between 9:00 pm and 9:00 am. The two 12-hour recordings will be performed at 48-hour interval—i.e., with a 24-hour wash-out period—, one in the control condition, and the other under vanilla odor exposure, in a random order and in a balanced fashion.

2.5.2. Polysomnographic recordings

In addition, two 3-hour polysomnographic recordings will be performed on the morning following the 12-hour recordings above in a convenience subsample of 10 to 15 of the infants —depending on the availability of the research personnel—. These additional recordings will allow gathering preliminary results on the potential effect of vanilla odor on sleep-wakefulness cycles.

2.6. Data analysis

2.6.1. Variables

In agreement with our main research question, we will compute the 90% and 80% desaturation indices per hour from the two 12-hour nocturnal recordings. We will also compute the percentage of the recording time spent with SpO_2 < 80%, the percentage of the recording time spent with SpO_2 < 90%, the percentage of the recording time spent in periodic breathing and the bradycardia index per hour.
Finally, a corollary study will be performed by a physiology doctoral student under the direction of Jean-Paul Praud to assess the effect of vanilla odor on heart and respiratory rate variability. This assessment will be performed on the 12-hour recordings and will not require any additional intervention on the preterm infants.

2.6.2. Definitions

- States of alertness: the usual electrophysiological and behavioral criteria will be used to recognize wakefulness, NREM and REM sleep (Anders et al, 1984; Grigg-Damberger M et al, 2007).
- Central apneas will be defined by the absence of both nasal airflow and respiratory movements for at least two respiratory cycles, if a desaturation ≥ 3% or an arousal is present, or for 20 seconds in the absence of desaturation or arousal (Nunez J et al, 2011; Henderson-Smart DJ et al, 1986).
- Periodic breathing: an epoch of periodic breathing will be defined by the presence of at least three central apneas with a duration ≥ 3 seconds, with a maximum of 20 seconds of normal respiration between two apneas (Brockmann PE et al, 2013).
- Desaturation: a desaturation will be defined as a decrease in SpO_2 below 90% and of at least 5% compared to the preceding SpO_2, for a duration > 5 seconds (Rhein et al, 2014).
- Bradycardia: a bradycardia will be defined as a decrease of at least 33% in heart rate for ≥ 5 seconds (Poets et al, 1993).

2.7. Statistical analysis

Statistical analysis of the results has been elaborated with Mrs Marie-Pierre Lapointe-Garant, biostatistician at the University of Sherbrooke Hospital Research Center. For each continuous quantitative variable, the normality of the distribution will be first confirmed with the *Shapiro-Wilks* test. Then, a mixed model will be designed with the SPSS software and used under close supervision of Mrs Lapointe-Garant.

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