A Comparison of Pre-oxygenation Techniques in Pregnant Patients Prior to a Cesarean Delivery - A Randomized Clinical Trial

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Study Protocol and Statistical Analysis

Study was approved by the University of British Columbia Children's and Women's Research Ethics Board

Inclusion criteria: healthy, term (≥ 36 weeks gestation), non-labouring parturients admitted for elective caesarean delivery or induction of labour

Exclusion criteria: ASA physical status 3 or above; any medical condition that could affect gas exchange; BMI ≥ 40 kg/m^2; known airway pathology; obstructed nasal airway; or unable to tolerate a tight-fitting facemask.

Microsoft Excel 2010 was used to generate a randomisation sequence with 1:1 allocation to either HFNO or control groups.

All patients were first placed in a 30-degree head up position using the Troop™ (Goal Medical, LLC, Eugene, OR, USA) elevation pillow and with a right lateral pelvic wedge to minimise aortocaval compression. A nose clip was applied and each patient was asked to breathe 21% oxygen at 12 $l.min^{-1}$ through a standardised mouthpiece using tidal volume breathing. The mouthpiece was connected to an anaesthetic circle system with a two-litre reservoir bag, heat moisture exchange filter and an oxygen analyser. At the end of 30 s, baseline values for oxygen saturation, respiratory rate, heart rate and EtO_2 were recorded.

Patients in the standard oxygen flow rate facemask group (control) were then pre-oxygenated with 100% oxygen, using tidal volume breathing and a tight-fitting facemask attached to a circle system, with an oxygen flow rate of 15 $l.min^{-1}$. End-tidal carbon dioxide waveform analysis was monitored to ensure a tight seal was achieved between the patient and the facemask. After 3 min, patients were asked to hold their breath for a few seconds and the nose clip was re-attached. The patients then exhaled fully and continued to breathe for several breaths via the mouthpiece (delivering 21% oxygen) to ensure the highest value for EtO_2 was measured.

Patients in the HFNO group were pre-oxygenated with 100% oxygen using tidal volume breathing and the Optiflow™ HFNO nasal high-flow cannula system (Fisher and Paykel Healthcare Ltd, Auckland, New Zealand). The oxygen flow rate was initially started at 30 $l.min^{-1}$and gradually increased to a maximum of 70 $l.min^{-1}$ over the first 30 s. If a patient did not tolerate the flow rate, it was

reduced to a level the patient could tolerate, typically 50–60 $l.min^{-1}$. Patients were specifically instructed to breathe via their nose with a closed mouth and the percentage of time this was achieved was recorded (0%, 25%, 50% or 100%). After 3 min, the patients were asked to hold their breath for a few seconds while the HFNO was quickly removed and the nose clip re-attached. The patients then exhaled fully and continued to breathe for several breaths via the mouthpiece (delivering 21% oxygen) to ensure the highest value for EtO_2 was measured.

Patients in both groups then underwent a washout period for up to 5 min until the EtO_2returned to within 10% of their baseline value. Once washout was completed, both groups repeated 30 s of tidal volume breathing followed by eight vital capacity breaths using their respective pre-oxygenation methods. During the initial 30 s of tidal volume breathing, the oxygen flow rate in the HFNO group was increased from 30 to 70 $l.min^{-1}$ and EtO_2 was measured at the conclusion of eight vital capacity breaths. The time taken to complete 30 s of tidal volume breathing and eight vital capacity breaths was also recorded.

Immediately after the study, patient satisfaction was assessed using a 5-category Likert scale for acceptability (acceptable, slightly acceptable, neutral, slightly unacceptable or unacceptable) and comfort (completely comfortable, slightly comfortable, neutral, slightly uncomfortable or completely uncomfortable).

Outcomes

The primary outcome was EtO_2 after pre-oxygenation, with factorial comparisons also being made between HFNO and standard flow rate facemask, and also between 3 min of tidal volume breathing and eight vital capacity breaths.

The Secondary outcomes were the proportion of patients achieving an $EtO_2 \geq 90\%$, percentage of time patients had their mouths closed during HFNO pre-oxygenation and tolerability (comfort and acceptability) of both pre-oxygenation techniques.

Sample Size Calculation

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The study sample size was determined based on a prior study demonstrating that the mean (SD) EtO_2 achieved following 3 min of pre-oxygenation in healthy, non-pregnant subjects with HFNO and facemask was 85.6% (6.4%) and 88.5% (6.2%), respectively. We initially powered the study for a non-inferiority comparison. The criterion for non-inferiority with respect to EtO_2 concentration achieved after 3 min was considered to have been met if the upper limit of a two-sided 95%CI for the absolute difference of EtO_2 concentration between groups was less than 10%. Using a non-inferiority design, assuming a non-inferiority margin of 10 and a standard deviation of 6.3, and that the HFNO group would have a mean approximately 3% lower than the control group, 26 patients (13 per group) were required to achieve a power of 90% with a type-1 error of 0.05. To account for attrition and study dropouts due to equipment errors (i.e. lack of a tight seal for waveform analysis), the sample size was increased to 40 (20 per group).

After patient recruitment we realised that as a physiological and not clinical study, a standard superiority design was more appropriate. Using a superiority analysis with 20 patients per group there would have been approximately 31% power to detect a difference in means of 3% with a standard deviation of 6.3. Consequently, data for primary outcomes were analysed using mixed-effects linear regression. Mixed-effects models take into account the repeated-measures aspect of the data and control for correlations among measurements from the same patient. To determine if there was a difference in how the treatment groups responded, we tested for an interaction term between group and time-point. If a significant interaction was found, we followed it up with pairwise tests of the estimated marginal means between the groups at each time-point (e.g. HFNO baseline vs. control baseline) using the Kenward–Roger method to estimate confidence intervals, and controlling for multiple comparisons using Tukey's method. The proportion of patients achieving an $EtO_2 \geq 90\%$, comfort and acceptability was compared using Fisher's exact test. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using RStudio version 1.0.153 (Integrated Development for R. RStudio, Inc., USA; **http://www.rstudio.com**) and R version 3.4.1, release date June 30, 2017 (The R Foundation for Statistical Computing, Austria).