Nitrous Oxide Analgesia for External Cephalic Version: A Randomized Control Trial

Study Protocol

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Investigational Protocol

Study title: Randomized Controlled Trial of Nitrous Oxide Analgesia in External Cephalic Version (ECV)

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Background and Purpose of the investigation:

Breech presentation occurs in 3% of pregnancies. The Term Breech Trial in 2000 demonstrated that planned cesarean delivery could reduce fetal morbidity and mortality compared to planned breech vaginal delivery[1]. As a result of these findings the incidence of cesarean delivery for breech presentation increased. In the U.S., nearly 90% of breech deliveries are performed by cesarean delivery[2]. It is recommended to offer external cephalic version (ECV), a maneuver to turn the fetus from breech to cephalic position, when possible to avoid cesarean delivery[2]. Although ECV is typically a brief procedure, it is associated with a moderate amount of pain[3]. The associated pain discourages some women from pursuing ECV and limits the ability of the obstetrician to perform this maneuver.

There is evidence that success of ECV is increased and pain is decreased when the procedure is performed under neuraxial anesthesia[4,5]. However, the use of neuraxial anesthesia for ECV remains controversial given the invasiveness of the procedure and associated risks. Risks may include maternal hypotension, post-dural puncture headache, urinary retention, pain at the injection site, meningitis, paresthesia, and weakness. In addition, post-procedure monitoring is required after a neuraxial anesthetic which may be considered excessive for this short procedure. At UNC, the standard of care is to offer no analgesia to the pregnant woman undergoing ECV.

Nitrous oxide is an ideal drug for use during ECV. Nitrous oxide provides analgesia, decreases the perception of pain, and has an anxiolytic effect. Some women find nitrous to be a satisfactory and effective agent for analgesia during labor[6]. It has a rapid onset and offset and is noninvasive. Pain during ECV is of relatively short duration, less than 5 minutes, and can easily be anticipated[3]. Nitrous oxide could be easily self-administered to treat the pain associated with ECV in much the same manner as it is commonly used to treat the pain associated with strong uterine contractions during labor. For these reasons, nitrous oxide may be an appropriate analgesic for patients undergoing ECV.

Worldwide, nitrous oxide is often used for labor analgesia and interest in nitrous oxide use continues to increase in the United States[6]. It has been estimated that nitrous oxide is used by approximately 50% to 75% of laboring women in the United Kingdom, and approximately 60% in Finland. Nitrous oxide is used and widely considered to be safe in many parts of the world including Canada, Australia, and New Zealand[7]. Use in the United States is currently estimated

to be <1% but with rapidly increasing interest. UNC is the third academic institution in the U.S. to offer self-administered inhaled nitrous oxide for labor analgesia.

In the context of obstetric analgesia, "nitrous oxide" refers to a half-and-half combination of oxygen and nitrous oxide gas, called by the trade name "Nitronox" (in the United States) and "Entonox" (in the United Kingdom). It is self-administered by the laboring woman using a face mask. It is generally administered beginning approximately 30 seconds before the onset of a strong contraction until the pain associated with contraction eases[7]. The Nitronox delivery system includes a demand valve which limits delivery of nitrous oxide to the inspiratory phase of ventilation. It also includes a scavenging system that collects expired gasses to minimize environmental exposure.

Nitrous oxide is the only commonly used inhaled labor analgesic in modern obstetric practice and has a long history of safe use. This is likely related to the ease of administration, lack of flammability, absence of pungent odor, minimal toxicity, minimal depression of the cardiovascular system, lack of effect on uterine contractility, and the fact that it does not trigger malignant hyperthermia[7].

In a systematic review of available literature in 2014, Likis notes that the most common maternal adverse effects are unpleasant side effects that affect tolerability (e.g., nausea, vomiting, dizziness, and drowsiness). Some of the above listed maternal adverse effects are common in laboring women regardless of whether analgesia is used[6]. We believe administration of nitrous oxide for ECV to be a safe practice with a favorable risk to benefit ratio. Confidence in the safety of this study is bolstered by the long history of safe administration to women in labor.

There are concerns of potential neurotoxicity of nitrous oxide, but this finding is limited to animal studies and only when used in combination with other anesthetics. Nitrous oxide is transmitted via the placenta and is rapidly eliminated by the neonate after birth once breathing begins. No evidence exists to suggest altered neonatal outcomes associated with the use of nitrous oxide alone. Apgar scores in newborns whose mothers used nitrous oxide did not differ significantly from those of newborns whose mothers used other labor pain management methods or no analgesia[6].

Recently published literature has provided evidence that exposure of the immature animal brain to anesthetics during the period of rapid synaptogenesis triggers rapid neurodegeneration and causes significant long-term cognitive impairment[8]. However, nitrous oxide, by itself at subanesthetic concentrations, triggers little or no neuroapoptosis in the infant rat brain[9]. In our study, nitrous oxide will be delivered at 50%, which is an analgesic or subanesthetic concentration. In addition, no other analgesic or anesthetic agents will be administered in combination with nitrous oxide.

Nitrous oxide is classified as a Class C drug in pregnancy by the US FDA, "Risk cannot be ruled out. Either studies in animals have revealed adverse effects on the fetus (teratogenic or

embryocidal effects or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus." As discussed above, concerns about nitrous oxide induced neuroapoptosis are not applicable to this study. Nitrous oxide has been used safely in pregnancy for greater than 100 years, and many commonly used and widely accepted drugs are used for analgesia and anesthesia in the parturient that are also considered Class C. The class C rating of nitrous oxide is likely due to the absence of large randomized controlled studies in women.

As an example of a comparable Class C analgesic option in labor, other than an epidural, remifentanil has also been widely used and studied. In a meta-analysis of RCTs studying remifentanil for labor analgesia, remifentanil patient controlled analgesia was found to be safe and effective when compared with other analgesic options in labor[10]. In addition, remifentanil has been used and studied in the setting of ECV where it was found to reduce pain and increase patient satisfaction[11]. We do not routinely offer remifentanil for ECV at UNC Hospitals, but hope to show similar analgesic results with nitrous oxide.

The potential benefits of this study include increased patient satisfaction, decreased pain, increased success of ECV, and decreased cesarean section rate. In addition, after completion of this study, nitrous oxide analgesia may become more routinely used for ECV as well as other painful procedures such as epidural placement, peripheral intravenous access, arterial access, obstetric examinations etc. If effective, this study could also help other health care providers with the decision to use nitrous oxide for analgesia outside of the obstetric population in the future.

Study Design

Double blind randomized controlled trial

Subject Selection

Participants: Pregnant women with breech presentation at 37 weeks EGA who are scheduled to undergo external cephalic version.

Subjects eligible for study entry:

1. Female 18yo or greater
2. Scheduled to undergo ECV due to singleton breech presentation
3. Not scheduled to have spinal or epidural anesthesia during the ECV procedure
4. American Society of Anesthesiology (ASA) Physical Status 1, 2 or 3.
5. Able to provide informed consent and adhere to study protocol

A subject will not be eligible for the study if he/she meets any of the following criteria:

1. Current or historical evidence of any clinically significant disease or condition, especially cardiovascular or neurological conditions that, in the opinion of the Investigator, may

increase the risk of exposure to nitrous oxide or complicate the subject's postprocedural course.
2. Significant medical conditions or laboratory results that, in the opinion of the Investigator, indicate an increased vulnerability to study drugs and procedures.

Study Procedures:

Potential subjects will be identified as they are scheduled to undergo ECV at the UNC Department of Obstetrics and Gynecology. Subjects will be enrolled in the study by one of the study investigators. Details of the study will be reviewed with potential subjects and those wishing to enroll in the study will be consented for the study by one of the study investigators. Once enrolled participants will be randomized to receive either a mixture of 50% nitrous oxide in 50% oxygen or 100% oxygen, both of which will be delivered via the Nitronox apparatus. Demographic variables will be recorded for each participant at the time they are enrolled in the study (weight, BMI, age, ethnicity, gestational age, parity, placentation, breech position, hx of previous cesarean delivery, hx of previous ECV)

The Nitronox apparatus will be set up to deliver either 50% nitrous oxide in 50% oxygen or 100% oxygen by an anesthesia provider covering labor and delivery who is not involved in the study. The Nitronox device will be covered to prevent participants, study investigators and obstetricians performing the procedure from knowing whether nitrous oxide is being delivered. Nitrous oxide is odorless and colorless, so in that way is indistinguishable from oxygen.

Participants will be prepared for ECV according to current protocols for ECV at UNC. IV access will be obtained and tocolytic agents will be given according to current practice and protocols. Monitoring of maternal and fetal vital signs will be done according to current protocols.

Immediately before an ECV attempt participants will breathe through the facemask of the Nitronox device for 30 seconds and will then be free to use the device ad lib during the ECV attempt. Immediately following each attempt, while fetal monitoring is occurring, the participants will be asked to rate their maximum pain score (0-10) during the previous attempt. They will also be asked to rate their current level of anxiety (0-10). This process will be repeated for any further ECV attempts.

At conclusion of all ECV attempts, while fetal monitoring is occurring, the participants will be asked to rate their current level of pain (0-10), their satisfaction with the procedure (0-10) and about any side effects they experienced (nausea, vomiting, dizziness, headache, other). Participants will continue to be monitored on labor and delivery as current protocol dictates, typically 30 minutes of maternal and fetal monitoring if there are no complications and fetal status is reassuring.

Following the procedure, the obstetrician who performed the procedure will be asked to rate how difficult they felt it was to perform the procedure (1-10) and to rate how much they felt the analgesic provided assisted in performing the procedure (1-10). They will also be asked to

indicate whether they thought the patient was in the treatment or placebo arm of the study. This will be recorded to address the adequacy of blinding.

Outcomes that will be recorded following the procedure include whether the procedure was successful, the number of attempts performed, complications associated with the procedure (maternal hypotension, fetal bradycardia transient/persistent, emergent cesarean delivery, cord prolapse, placental abruption, other), eventual mode of delivery, indication for cesarean delivery if performed and analgesic/anesthetic used for delivery if any.

All study variables will be assessed and recorded by one of the study investigators to ensure consistency in data collection.

Study outcome evaluation:
A suite of preliminary tabular and graphical investigations will be conducted prior to quantitative analyses to provide a thorough understanding of the data. These investigations will include:
a. Descriptive statistics, with histograms and boxplots on continuous variables
b. Frequency distributions on discrete variables
c. Correlations among potential model predictors and covariates to reveal potential variable multicolinearity problems.

In addition to the information compiled from the preliminary investigations described above, Chi-square tests of association for the outcome variables of interest and principle predictors will be conducted to reveal important relationships and justifications for more robust analyses.

The primary outcome of the study is pain experienced during ECV. The null hypothesis of this outcome is that there is no difference in pain scores between patients who use a mixture of 50% nitrous oxide and 50% oxygen during ECV (treatment group) compared to those that use oxygen only during ECV (placebo group). Pain scores during each ECV attempt will be recorded for each participant. For those participants who have more than one attempt these scores will be averaged to obtain a single score for the entire procedure. A student t-test will then be performed to evaluate the null hypothesis of no difference in pain scores between the treatment vs placebo groups. A difference in pain score of 2 (Scale: 0-10) is considered clinically significant. Based on a mean pain score difference of 2 and an average standard deviation of 2.5 for the treatment and placebo groups, a statistical power of 80% is expected. Consideration will be given to categorizing the patients into “Low”, “Moderate” and “Severe” pain score categories along clinical guidelines to further assess the impact of analgesia on pain severity. Where feasible, both p-values and confidence intervals for odds ratios from logistic regression and/or parameter estimates from general linear modeling will be reported.

Secondary outcomes of the study include patient anxiety experienced during the ECV procedure, pain scores following the ECV procedure, patient satisfaction with ECV procedure, side effects experienced and OB providers ratings of ease of procedure.

We will be recording whether the ECV procedures are successful and whether any complications occur as a result of the ECV procedure, but given that our study is powered to evaluate patient pain and not these outcomes we do not expect to see any differences. Previous studies have shown that analgesia alone does not alter success rates of ECV, this includes a previous study that used nitrous oxide during ECV.

Complications of ECV are very rare. Given that nitrous oxide has been demonstrated to be safe for labor analgesia, a similar patient population to ours, we do not anticipate that we would be able to detect any differences in complications in this patient population. These variables are being recorded for completeness.

Several variables known to influence the effectiveness of ECV (BMI, age, ethnicity, gestational age, parity, placentation, type of breech position, amniotic fluid level, tocolytic used, history of prior c-section) are being recorded for each participant. We are also recording whether participants have previously undergone ECV with a prior pregnancy since this could influence their expectations of this procedure. These variables will be analyzed using chi-square or fisher exact test to ensure that there are no differences in these variables between the treatment and placebo groups.

Either a general linear model or a logistic model will be employed to assess the effect of the main effects, interactions, and appropriate covariates on the primary outcomes of interest. Selected covariates and potential confounders will be included in a “forward” regression model and subsequently retained in the final model only if found to explain a significant amount of the variability in the outcome. Candidate covariates include patient anxiety during the ECV procedure, patient satisfaction, ECV success and history of previous ECV.

All data will be recorded during one interaction with the participants and will not require participants to be contacted following the ECV procedure. Because of this the likelihood of missing data and drop out is extremely low.

The only area where we might expect to have missing data is for delivery information and type of anesthetic used for delivery since not all patients who have an ECV at UNC actually deliver at UNC. However, this data is included on the data sheet only because we are curious to know whether involvement in the study might influence participants to try nitrous oxide for labor analgesia. The use of nitrous oxide for labor, while common worldwide, remains uncommon in the United States. Many women who present in labor have actually never heard of the use of nitrous oxide for labor analgesia. We also have parturients who come to UNC to deliver specifically because we offer nitrous oxide for labor analgesia. It would be interesting to know whether our contact with them through the consent process may inform them of and potentially lead them to consider use of nitrous oxide for labor analgesia.

Power analysis:
A power analysis to determine the sample size required to see a difference in pain score of 2 between the groups was performed which yielded the needed sample size of 50. This analysis

was based on pain scores from previous studies on pain during ECV in the setting of no analgesia as well as use of nitrous oxide or remifentanil for treatment of pain (Burgos et al, Fok et al, Munoz et al).

Normal Distribution α=0.05	
Mean Difference	2
Standard Deviation	2.4
Total Sample Size	50
Number of Sides	2
Power	0.823

Lognormal Distribution α=0.05	
Group 1 Geometric Mean	4.5
Group 2 Geometric Mean	6.5
Coefficient of Variation	0.45
Total Sample Size	50
Number of Sides	2
Power	0.843

Data handling:

At the time of enrollment in the study each participant will be assigned a unique study ID number. A spreadsheet that links the patient's study ID number with the patient's name and medical record number will be kept on a secure department server that only the investigators will have password protected access to. The remainder of study data will be coded and information regarding an individual patient will only be linked to their study ID number. Study ID numbers will be recorded on each data collection sheet. Data from the data collection sheets will then be entered into a database for analysis. In this way a coded hard copy of data for each participant will exist that does not include any patient names or medical record numbers, but will allow to ensure the integrity of the data within the database. All coded data will be entered into a Microsoft excel spreadsheet by one of the study investigators. This will be a password protected file to ensure that data cannot be manipulated by anyone other than the study investigators. Data analysis will be performed as described above by the study investigators with assistance from a consulting statistician as needed. The consulting statistician will not have access to any patient identifiable data, but would solely be working with the coded data.

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