Oxygen for Category II Intrauterine Fetal Resuscitation: a randomized, noninferiority trial

"O_2C_2 Trial"

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Specific Aims

Maternal oxygen administration for concerning fetal heart rate tracing (FHT) patterns is common practice on Labor and Delivery units in the United States. Despite the broad use of oxygen, it is unclear if this practice is beneficial for the fetus. Category II FHT, as defined by the National Institute of Child Health and Human Development (NICHD), is a broad class of FHT patterns that may suggest cord compression and/or placental insufficiency for which oxygen is most commonly administered. Although some animal and human studies have demonstrated that maternal hyperoxygenation can alleviate such fetal heart rate decelerations, this purported benefit has not been shown to translate into improved fetal outcomes, particularly in relation to acid-base status. In fact, some studies suggest harm with oxygen use due to lower umbilical artery pH and increased delivery room resuscitation or increased free radical activity. Given the indeterminate evidence for this ubiquitously employed resuscitation technique, there is an urgent need to further study the utility of maternal oxygen administration in labor for fetal benefit.

We propose a randomized controlled non-inferiority trial comparing oxygen to room air in patients with Category II FHT. Our central hypothesis is that room air alone is not inferior to oxygen administration with regard to neonatal acid-base status and FHT and may in fact, be a safer option for resuscitation due to less production of reactive oxygen species.

<u>Primary Aim</u>: Determine the effect of maternal oxygen administration for Category II FHT on arterial umbilical cord lactate.

Hypothesis: Room air, as a substitute for oxygen supplementation, is no different than oxygen in altering the acid-base status of the neonate as reflected in umbilical arterial (UA) lactate.

Fetal hypo-oxygenation, as reflected by decelerations in the FHT, results in metabolic acidosis due to a shift from aerobic to anaerobic metabolism in which lactate and hydrogen ion production significantly increase causing a decrease in pH. Elevated umbilical cord lactate has been shown to be a surrogate for fetal metabolic acidosis and resultant neonatal morbidity. The primary outcome will be umbilical arterial (UA) lactate, and secondary outcomes will be other components of a UA gas.

<u>Secondary Aim #1</u>: Characterize the effect of oxygen administration on fetal heart tracing patterns

Hypothesis: Oxygen administration will be associated with a rate of persistent Category II FHT that is not different from those exposed to room air.

Oxygen is typically administered in response to FHT interpretation. Hence, evaluating the effect of oxygen on subsequent FHT is pivotal to labor management. The primary outcome will be resolution of Category II FHT. We will also investigate the effect of oxygen administration on mode of delivery, particularly cesarean delivery for non-reassuring fetal status.

<u>Secondary Aim #2</u>: Evaluate the safety of oxygen administration by measuring reactive oxygen species (ROS) in maternal and neonatal blood.

Hypothesis: Oxygen administration will be associated with increased oxidative stress in maternal and neonatal cord blood as represented by malondialdehyde (MDA).

Over-oxygenation can result in free radical or ROS formation that have detrimental downstream effects. The presence of reactive oxygen species results in degradation of lipids in the cell membrane and resultant formation of malondialdehyde (MDA), which has been studied as a surrogate for oxidative stress.

Background/Significance

Maternal oxygen administration for fetal heart rate tracing (FHT) changes is a common practice on Labor and Delivery units in the Unites States. Despite the broad use of oxygen for intrauterine resuscitation of fetal heart rate decelerations, it is unclear if this practice is beneficial for the fetus. In a recent review of maternal oxygen administration in labor, Hamel et al[1] concluded that there is insufficient evidence for routine oxygen administration for intrauterine resuscitation and that such administration may even be harmful via production of free radicals. The 2012 Cochrane review evaluating maternal oxygen administration for fetal distress also found limited evidence to evaluate the effectiveness of oxygen for fetal distress.[2]

Category II FHT, as defined by the National Institute of Child Health and Human Development (NICHD)[3], is a broad class of FHT patterns which can include both variable and/or late decelerations, representing cord compression and placental insufficiency, respectively. These decelerations are often thought to be a reflection of fetal hypooxygenation. The underlying hypothesis for oxygen benefit and the primary motivation for generalized use in labor is to transfer oxygen to the fetus and therefore improve or reverse the perceived fetal hypooxygenation determined by the FHT.

Although some animal and human studies have demonstrated that maternal hyperoxygenation can alleviate fetal heart rate decelerations[4, 5] and increase fetal oxygen saturation[6-9], this purported benefit has not been shown to translate into improved fetal outcomes, particularly in relation to acid-base status. For example, a study in primates by Morishima et al demonstrated that maternal oxygen administration to those with acidotic hypoxic fetuses elevated fetal oxygen levels and eliminated late decelerations but did not correct acidosis.[10]

There are a limited number of clinical trials addressing maternal oxygen administration for fetal distress in labor. In 1995, Thorp et al conducted a randomized trial of oxygen versus room air in the second stage of labor, and found no benefit to oxygen exposure and in fact discovered that the oxygen group had a lower umbilical artery pH. This difference was theorized to be a result of fetoplacental vasoconstriction as a result of prolonged oxygen exposure.[11] Similarly, Nesterenko et al performed a trial of laboring women randomized to oxygen or room air and found that more infants in the oxygen group required delivery room resuscitation.[12] Excess oxygen exposure in this setting has also been linked with increased free radical activity. In a 2002 trial by Khaw et al,

women were randomized to oxygen or room air during cesarean delivery. There was no difference in umbilical artery pH between groups, however the oxygen exposed group had increased free radical activity in cord blood samples[8]. Studies such as these have prompted questioning of both the safety and the efficacy of oxygen for Category II FHT and highlight the urgent need for further investigation, particularly given its wide-spread use.

The primary objective of this study is to evaluate whether oxygen for intrauterine fetal resuscitation of Category II FHT affects fetal metabolic acid-base status as determined by umbilical cord lactate values. Secondary objectives include analysis of additional cord gas parameters used to predict neonatal wellbeing, changes to FHT patterns, and cord blood and maternal MDA as a marker of free radical activity. We hypothesize that room air exposure for Category II FHT in labor is no different from maternal oxygen administration with regard to fetal acid-base status.

Specific Aim 1: Determine the effect of maternal oxygen administration for Category II FHT on arterial umbilical cord lactate. Fetal hypooxygenation, as reflected by decelerations in the FHT, results in a metabolic acidosis due to a shift from aerobic to anaerobic metabolism in which lactate and hydrogen ion production significantly increases as a result of glucose breakdown and pyruvate conversion.[14] This rise in lactate results in decreased pH or an acidotic state. Elevated umbilical cord lactate has been shown to be a surrogate for metabolic acidosis in the fetus and is associated with neonatal morbidity.[15] It has also been shown to precede pH changes in the setting of hypooxygenation.[14, 16]

The theorized benefit of maternal oxygen administration is increase oxygen delivery to the fetus via the umbilical cord vein (Figure 1) resulting in prevention or reversal of anaerobic metabolism and a subsequent reflection in umbilical cord artery findings. This, however, has not been substantiated by evidence thus far. We hypothesize that room air, as a substitute for oxygen supplementation, is no different than oxygen in altering the acid-base status of the neonate as reflected in umbilical cord gas parameters. Secondary outcomes will be additional components of an umbilical artery gas.

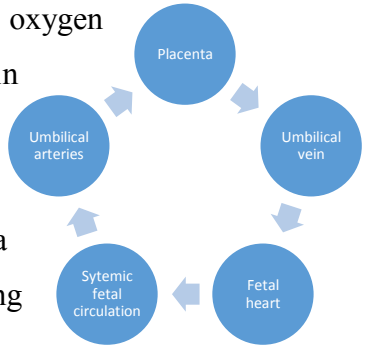

Figure 1: Fetoplacental circulation

Specific Aim 2: Characterize the effect of oxygen administration on fetal heart tracing patterns

In clinical practice, oxygen is administered to patients with Category II FHT in order to resuscitate potential fetal hypooxygenation that manifests as heart rate decelerations. Evidence thus far shows that Category II FHT are associated with a wide spectrum of neonatal outcomes and therefore do not uniformly reflect fetal acid-base status[19, 20]. Hence, evaluating the effect of oxygen on subsequent FHT categorization is pivotal to labor management. The outcome that will be investigated is rate of persistent Category II FHT after intervention. We will also evaluate the types and frequency of deceleration patterns present both pre and post intervention. We hypothesize that oxygen administration for Category II FHT will be associated with a rate of persistent Category II FHT that is not different from those exposed to room air.

Specific Aim 3: Evaluate the safety of oxygen administration by measuring reactive oxygen species in maternal and cord blood

In order to safely apply maternal oxygen administration for intrauterine fetal resuscitation, the risks of oxygen exposure must be further explored. Over-oxygenation can result in free radical formation, downstream effects of which include cell membrane and DNA damage and resultant carcinogenesis.[21] Although oxygen supplementation is often critical to resuscitation in most settings, studies evaluating hyperoxygenation in adults and animals have shown detrimental cardiac[22],pulmonary[23],and cerebral effects[24]. Over-oxygenation in neonates has been shown to be associated with bronchopulmonary dysplasia and retinopathy[1, 25]. Furthermore, reintroduction of oxygen after a period of hypooxygenation can result in adverse effects as the fetus and newborn lack robust antioxidant systems[1, 26].

One of the primary markers of oxidative stress studied in the literature is malondialdehyde (MDA). The presence of reactive oxygen species results in degradation of lipids and resultant formation of MDA[27]which then modifies endogenous proteins. MDA levels, therefore, have been studied as a surrogate for oxidative stress.[28-32] (Figure 2)

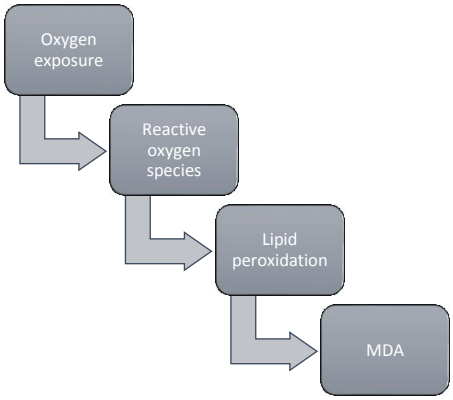

Figure 2: Pathway of oxidative stress

Increased MDA levels in the neonate may be consequential and have been associated with morbidity including hyperbilirubinemia[33] and hypoxic-ischemic encephalopathy[34].There is also evidence that MDA can be transplacentally transported and thus, both mother and fetus are at risk for downstream effects.[35]

Prior studies have evaluated the relationship between maternal oxygen administration in labor and markers of free radical formation[8, 12] with mixed results. We hypothesize that maternal hyperoxygenation for Category II FHT is associated with increased oxidative stress in the mother and fetus. We will measure MDA in maternal and neonatal cord blood samples as a gage for oxidative stress and to assess the relationship between oxygen administration and subsequent free radical formation.

Significant and Potential Impact

Current practice on our Labor and Delivery is maternal oxygen administration in the presence of Category II FHT for the duration of labor. This practice is unproven in benefit thus far and in fact, some studies suggest harm[11, 12]. Although it may improve fetal oxygenation, evidence thus far does not show an improvement in fetal acid-base status which ultimately correlates with neonatal outcomes. Our study has the potential to create a paradigm shift in intrauterine fetal resuscitation and has significant clinical implications for the fetus and mother. No prior clinical trials in this setting have used cord lactate as a primary outcome. Umbilical cord lactate is an established marker of asphyxia and predictor of neonatal morbidity[14] and serves as a useful assessment of the benefit, or lack thereof, of oxygen for fetal resuscitation. Prior studies have mainly evaluated cord pH as the primary outcome which not only falls behind lactate as a predictor of neonatal outcomes, but also does not serve as an accurate reflection of the degree of metabolic acidosis that may be present due to hypooxygenation[17]. Furthermore, previous trials addressing oxygen administration for similar indications have not employed a similar three-pronged approach to evaluating outcomes via neonatal acid-base status, FHT patterns, and free radical activity. If our stated hypothesis is proven, room air may be an equally efficacious, safer, and cost saving alternative to oxygen. Additionally, it would pave the way for further investigation into the most effective strategies for intrauterine fetal resuscitation.

Strategy

The aim of this study is to compare maternal oxygen administration to room air for intrauterine resuscitation of Category II FHT in relation to cord gas parameters, FHT patterns, and oxidative stress in the fetus and mother. The study will be a prospective, randomized non inferiority trial to be conducted at Barnes Jewish Hospital. Current practice at our institution for intrauterine fetal resuscitation of Category II FHT include any of the combination of (1) oxygen administration via nonrebreather face mask at 10L/min (FiO2 approximately 0.80)[36] continued for the duration of labor (2) intravenous fluid bolus (3) maternal repositioning (4) discontinuation of oxytocin. We hypothesize that room air for Category II FHT will be no different than oxygen administration in reducing the degree of fetal metabolic acidosis. This study will include term, singleton patients admitted to Labor& Delivery for spontaneous labor or labor induction. Multiples, fetal anomalies, Category III FHT, umbilical artery doppler abnormalities and preterm pregnancies will be excluded. Additionally, women will be excluded if oxygen is required for maternal indications such as hypooxygenation or cardiopulmonary disease. Our primary objective will be umbilical cord lactate. Secondary objectives include additional cord gas parameters including umbilical artery pH, umbilical artery base deficit, and umbilical vein oxygen saturation; FHT categorization and deceleration patterns; maternal and umbilical cord blood measurement of malondialdehyde.

Consent will be obtained at time of admission to Labor & Delivery. Randomization to either the oxygen group or room air group will be performed when the patient is in active labor (defined as regular contractions and $\geq$ 6cmcervical dilation) and develops Category II FHT necessitating intrauterine resuscitation as determined by the care provider team (Figure 3). This will be performed via a computer-generated randomization sequence in a 1:1 ratio. Patients randomized to the oxygen group will receive the above stated current management of oxygen via nonrebreather face mask at 10L/min and "per-protocol" defined as receiving the mask for at least 90% of the remaining duration of labor including during cesarean delivery. Patients randomized to the room air group will not receive oxygen for Category II FHT unless otherwise required for maternal indications. Alternative and/or additional intrauterine resuscitation techniques for both groups (i.e. fluid bolus, maternal repositioning, and discontinuation of oxytocin) will be left to

the discretion of the medical team. The initial 6 patients consented and randomized will be part of a compliance run-in with the same protocol as above.

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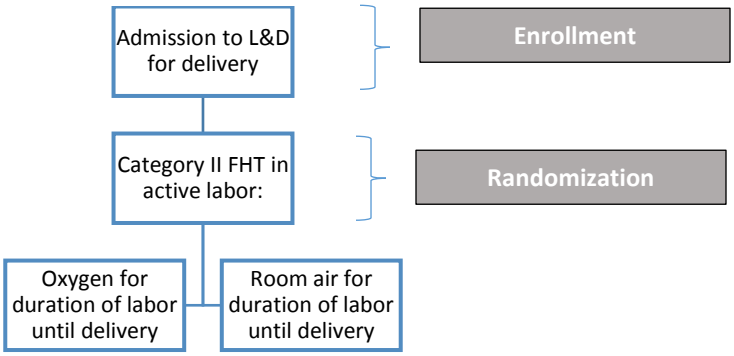

Figure 3: Flow diagram for randomization and treatment groups
L&D: Labor and Delivery FHT: fetal heart tracing

Specific Aim 1: Determine the effect of maternal oxygen administration for Category II FHT on neonatal cord gas parameters

After delivery of the infant, a segment of the umbilical cord will be removed with immediate collection of umbilical artery and vein samples by trained providers. These samples will be sent to the hospital laboratory for routine cord gas measurements as is universally practiced on our Labor and Delivery unit.

Specific Aim 2: Characterize the effect of oxygen administration on fetal heart tracing patterns

The patient's primary nurse will document the time at which intervention is initiated. A blinded investigator will then retrospectively assess FHT categorization and deceleration patterns both pre and post intervention.

Specific Aim 3: Evaluate the safety of oxygen administration by measuring ROS in maternal and neonatal blood

We will be measuring serum MDA in both cord and maternal blood as a marker of oxidative stress. MDA is a byproduct of lipid peroxidation, which occurs as a result of oxidative stress. Measurement of Thiobarbituric Acid Reactive Substances (TBARS) is a commonly used assay

for quantifying MDA[30 37] This assay is performed by fluorometrically measuring the MDA-TBA complex formed in plasma or serum by the reaction of MDA and TBA.

Upon delivery of the infant, an additional sample of umbilical artery blood will be collected for this analysis. An optional sample of maternal blood will also be drawn within 60 minutes of delivery. Both blood samples will be centrifuged to collect plasma which will then be stored at -80◦C until the TBARS assay is performed.

Data Collection

The patient's primary nurse will perform real-time documentation of oxygen initiation, any disruption in intervention, administration of amnioinfusion and additional resuscitation techniques performed (number of times patient is repositioned, total intravenous fluids, discontinuation of oxytocin). Study staff will collect data from medical records on:

1) Antepartum history:
    - **a.** Demographic data: Maternal age, race
    - **b.** Obstetric history: parity, prior cesarean, gestational age at delivery
    - **c.** Medical history: BMI at initial prenatal visit, diabetes, chronic hypertension, severe anemia (Hemoglobin <7), tobacco use, illicit drug use
    - **d.** Prenatal course: diagnosis of hypertensive disorders, gestational diabetes, abruption, intrauterine growth restriction, oligohydramnios
2) Intrapartum data:
    - **a.** Indication for admission/induction
    - **b.** Oxytocin (duration, total received dose)
    - **c.** Analgesia
    - **d.** Duration of labor (first and second stage)
    - **e.** Diagnosis of chorioamnionitis
    - **f.** Mode of delivery
    - **g.** Indication for cesarean
    - **h.** Electronic fetal monitoring
3) Neonatal course:
    - **a.** APGARs
    - **b.** Neonatal weight

c. Admission to special care nursery (SCN) or neonatal intensive care unit (NICU)

d. Duration of admission to SCN or NICU

e. Diagnosis of any of the following: hypoxic ischemic encephalopathy, respiratory distress syndrome, oxygen requirement, requirement of hypothermia therapy, seizures, sepsis or suspected sepsis, neonatal death

Data and Safety Monitoring Plan

In addition to principle investigator review of adverse events, a data and safety monitoring board (DSMB) will be established. This board will have three individuals (Dr. Collen McNicholas, Dr. Omar Young, Dr. Emily Fishman) not directly involved in the study. The DSMB will meet once 50% of participants have been recruited to review any adverse neonatal or maternal events among the study cohort and determining safety of continuing the study to completion. The DSMB will receive a report of any severe and/or non-severe adverse neonatal outcomes within 72 hours of occurrence. Reportable severe adverse neonatal outcomes include intrapartum stillbirth and neonatal death. Reportable non-severe adverse neonatal outcomes include need for hypothermia protocol, seizures, and prolonged NICU stay >72 hours.

Statistical Analysis

Intention-to-treat (primary analysis) and per protocol analyses will be performed. Chi-squared and Fisher's exact tests will be used to compare categorical variables as appropriate. Continuous variables will initially be assessed for distribution pattern via the Kolmogorov-Smirnov test. Normally distributed variables will be compared using Student's t-tests and non-normally distributed variables will be analyzed with the Mann-Whitney U test. These analyses will be supplemented by multivariable logistic regressions to adjust for confounders.

Tests with $p < 0.05$ will be considered statistically significant. Analyses will be performed using Stata (Stata Corp., College Station, TX).

For the primary outcome of lactate, 95% confidence intervals (CI) will be calculated for the mean cord lactate levels in each group. Comparison of the 95% CI in each group will then determine non-inferiority or inferiority.

Additional interaction analyses for the primary outcome will be performed for the following subgroups:

1) Presence of chronic medical conditions (hypertensive disorder, diabetes)

    a. Patients with hypertensive disorders (chronic hypertension, gestational hypertension, preeclampsia)
    b. Patients with diabetes mellitus (gestational diabetes, T1DM, T2DM)
2) Recurrent late decelerations pre intervention
3) Recurrent variable decelerations pre intervention
4) Prolonged deceleration pre intervention
5) Fetal tachycardia pre intervention
6) Fetuses with intrauterine growth restriction
7) Chorioamnionitis
8) Within oxygen group: Duration of oxygen exposure
    a. <50% of total duration of active labor (onset of active labor to delivery)
    b. >50% of total duration of active labor (onset of active labor to delivery)

Odds ratios and 95% CI will be calculated for the secondary outcome of persistent Category II FHT. Kaplan-Meir analyses will be performed for fetal monitoring analyses.
For the outcome of maternal and cord blood MDA, a fetal MDA will be calculated by subtracting umbilical artery MDA from maternal MDA for each sample. The calculated mean fetal MDA and maternal MDA values will then be compared between groups using either Student t test or Mann Whitney U test.

Sample size analysis

A review of previously collected data from our institution of 5182 term singleton pregnancies revealed a mean cord lactate of 3.5±1.6 mmol/L in women with Category II FHT within 30 minutes of delivery. All of these deliveries were managed using our current protocol of routine oxygen administration for Category II FHT. Given the normal mean lactate seen in our population of patients with Category II FHT, a noninferiority approach was selected to test our hypothesis that room air is not inferior to oxygen administration in treating Category II FHT. A total sample size of 98 patients will be needed to detect a non-inferiority margin of 30% with 90% power, using a one-sided two-sample t-test (alpha 0.025). To accommodate a 15% drop out/cross over rate, a total of 114 patients will be needed. We plan on performing an initial compliance run-in of 6 patients making the total enrollment 120 patients. Data analysis will only be performed on the 114 patients enrolled after the initial 6 patients enrolled/randomized in the compliance run-in/pilot. Previous studies have shown an increased risk for neonatal morbidity with cord lactate cut-offs ranging from 3.2-6.0[14, 15, 38-41]. The margin of noninferiority was

therefore set at a lactate cut-off of 4.5, above which there is a clear association with neonatal morbidity.

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