STUDY TITLE: Effectiveness of Clonidine, Dexmedetomidine, and Fentanyl Adjuncts for Labor Epidural Analgesia: A randomized controlled trial (CLASSIER)

IRB: STUDY22030095

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Study Protocol: 10 MAY 2022

*** Title of study:**

Effectiveness of Clonidine, Dexmedetomidine, and Fentanyl Adjuncts for Labor Epidural Analgesia: A Randomized Controlled Trial

*** Short title:**

CLASSIER Trial

*** Brief description:**

The purpose of this trial is to compare the effectiveness of labor analgesia with clonidine, dexmedetomidine, or fentanyl (usual care) adjuncts.

Study Aims

Research Key Question:

Does the addition of dexmedetomidine to a ropivacaine solution used for epidural labor analgesia initiation, improve epidural labor analgesia when compared with a solution combining clonidine with ropivacaine, or a solution combining fentanyl with ropivacaine?

Hypotheses:

We hypothesize that the addition of dexmedetomidine to a ropivacaine solution used for epidural perfusion in labor analgesia improves epidural labor analgesia as evaluated by Visual Analogue Scores at various time points after epidural initiation compared with a solution combining clonidine with ropivacaine and fentanyl with ropivacaine.

1. Background:

In the current practice, the standardized epidural solution that is used in the labor analgesia protocol combines a local anesthetic with an opioid. The addition of opioids as adjuvants to local anesthetics has many advantages as they increase the quality of the epidural block. They also act by reducing the local anesthetic total dose which results in lower incidence of motor block and assisted vaginal delivery.

The addition of opioids to the local anesthetic solution used for epidural perfusion has become a standard of practice in North America. Although the literature advocates for this practice, a small proportion of patients may benefit from a different approach.

Patients with chronic pain and chronic opioid consumption are at risk of developing opioid tolerance defined as the use of the oral morphine equivalent of greater than or equal to 60 mg a day for 7 days or longer. 5 Another population that could possibly benefit from this approach are parturient that are diagnosed with an opioid use disorder. These patients often develop opioid tolerance requiring higher dosage to address acute pain. Experts' consensus advocates for a multimodal approach in this population. Moreover, some patients are consuming medication to treat opioid use disorders such as buprenorphine and methadone. These medications have an impact on the pharmacokinetics of opioids and alter their effect on the human body.

Tailoring the approach to labor pain management in the population of parturient that are at risk for complex pain management is the cornerstone to an individualized approach, leading to optimal care. This approach may be achieved by substituting the opioid in the epidural solution with another adjuvant. For example, clonidine is an alpha-2-adrenergic agonist that has been extensively studied in the context of neuraxial anesthesia and analgesia

Addition of clonidine to the epidural solution for postoperative analgesia has been studied widely in orthopedic and general surgery procedures. It offers a dose-sparing action of local anesthetics while increasing the duration of sensory blockade. It is also widely used for post-operative pain management after various pediatric surgical procedures and has shown a reassuring safety profile in this population. A systematic review and meta-analysis evaluated the effects of neuraxial clonidine added to local anesthetics in women admitted for caesarean section under neuraxial anesthesia. Their conclusions show that intrathecal clonidine reduced 24 h morphine consumption and prolonged time to first analgesic request.

Neuraxial clonidine increased the incidence of intraoperative hypotension defined as a 20% reduction from the pre-anesthetic baseline systolic blood pressure. This augmentation of the intraoperative hypotension episodes did not translate into an augmentation of treatment with vasopressors such as ephedrine, which leads us to think that this hypotension was not clinically significant. Moreover, the usage of neuraxial clonidine did not negatively impact neonatal umbilical artery pH or Apgar scores.

Clonidine added to ropivacaine for labor epidural analgesia has shown to provide a longer duration of analgesia and a reduction of the total ropivacaine dose over the first 4 hours. It has been extensively studied for the initiation and maintenance of epidural analgesia in laboring women. The literature regarding the addition of clonidine to the local anesthetic solution perfused in epidural for labor shows an increased the quality of analgesia while reducing the need for rescue supplementation.

It has also shown to prolong the duration of analgesia offered by a bupivacaine bolus after the initiation of epidural analgesia. Moreover, the addition of clonidine shortened the onset of analgesia and showed a decrease in the local anesthetic consumption in laboring patients.

Dexmedetomidine is an alpha-2-agonist that has a greater affinity for the alpha-receptor. It is about 8 times more selective towards this receptor. It is currently used in obstetric anesthesia for multimodal labor analgesia, post cesarean delivery analgesia and postoperative shivering. Some studies have also found a benefit in the quality of analgesia offered by dexmedetomidine when compared to opioids as adjuvants to epidural.

A meta-analysis of randomized controlled trials reviewed the effects of epidural dexmedetomidine as an adjuvant to local anesthetics for labor analgesia. Nine studies were included in the qualitative synthesis presented in this meta-analysis. The group arrived to the conclusion that “epidural dexmedetomidine has the potential to offer a better analgesic effect than placebo, similar labor pain control to opioids, and has no definite adverse effects on the parturient or fetus, but more high-quality studies are needed to confirm these conclusions.”

The usage of dexmedetomidine as an adjuvant to epidural during labor has been a subject of great interest in the last few years. Zhao and al. performed a RCT with 80 laboring patients that received an epidural with low concentration of epidural ropivacaine (0.125%) alone or combined with dexmedetomidine (0.5 mg/kg) as bolus. This anesthetic regimen that included dexmedetomidine reduced the pain scores at most time intervals evaluated after epidural initiation. It is also reassuring to see that other outcome such as the duration of the first and second stage of labor, the rate of instrumental delivery and cesarean section, Apgar scores, umbilical artery pH, maternal motor blockade scores, intensity of maternal sedation, and the incidence of maternal complications did not show significant difference between the two studied groups. Selim and al. carried out a study where they evaluated the impact of dexmedetomidine as an adjunct to bupivacaine compared to a standard fentanyl – bupivacaine solution. They aimed to explore uterine artery pulsatility index and umbilical artery pulsatility index during uterine contractions and relaxations. They were able to show that the bupivacaine – dexmedetomidine group had a shorter onset of analgesia and an increased duration of analgesia. Their analysis of the uterine artery pulsatility index and umbilical artery pulsatility index showed that dexmedetomidine did not induce any deleterious effects of uteroplacental circulation or neonatal outcomes.

Zhang and al. did show that the combination of dexmedetomidine with ropivacaine for labor analgesia offered similar sensory block when compared to a control group that received a ropivacaine only solution. Moreover, the duration of the first and second stage of labor, the mode of delivery and the Apgar scores and umbilical arterial pH after birth were similar between both groups. Finally, side effects such as hypotension, bradycardia and pruritus were also similar between both cohorts.

Dexmedetomidine has been used as an adjuvant to epidural in various surgical interventions. It has also been compared to clonidine to evaluate the benefits of this novel molecule compared to clonidine which has been on the market for a few decades. Dexmedetomidine is a better neuraxial adjuvant

compared to clonidine since it provides early onset of sensory analgesia superior intraoperative analgesia, a prolonged postoperative analgesia while offering stability of the cardiorespiratory parameters.

The intrathecal administration of dexmedetomidine in a cohort of patients admitted for lower limb surgery is associated with prolonged sensory and motor block, hemodynamic stability, and a reduction in the consumption of rescue analgesics in 24h period as compared to clonidine, fentanyl, or bupivacaine alone. When comparing dexmedetomidine to clonidine as adjuvants to local anesthetics in labor analgesia, it seems that both molecules offer an excellent quality of analgesia and a great safety profile. However, dexmedetomidine has shown a faster onset of analgesia a prolonged analgesia and a decrease in the time to achieve maximal analgesia.

2. Significance/Rationale: (Why is the question worth pursuing? Will it reduce complications or costs, improve outcome, change practice?)

This study is significant because it can potentially alternative non-opioid adjunctive agents for epidural labor analgesia. The opioid crisis in the United States has translated to an increasing number of pregnant women requiring care for labor and delivery. These trends have resulted in new questions about alternative epidural analgesia adjuncts besides lipophilic opioids (e.g., fentanyl and sufentanil) because: 1) many people with OUD desire to avoid opioids in all formulations and routes of administration; and 2) epidural fentanyl or sufentanil administration for labor can potentially interfere with the accuracy of urine drug screening in the postpartum period.

Regarding the scope of the problem: A retrospective study evaluated the incidence of maternal opiate usage using a database that compiled information from 7.4 million discharges in 44 states. It shows that the maternal consumption of opioids has increased nearly fivefold in a 9-year observation period (2000-2009)57 while others report prevalence of opioid use disorder during pregnancy Increasing by 127% from 1998 to 2011. 58 It is estimated that 4.5% of pregnant women aged 15–44 years are using illicit or prescription opioid medications, which emphasizes the importance of this issue.

Tailoring the approach to labor pain management in the population of parturient that are at risk for complex pain management is the cornerstone to an individualized approach, leading to optimal care. This approach may potentially be achieved by substituting the opioid in the epidural solution with another adjuvant such as clonidine or dexmedetomidine, two alpha2-adrenergic agonists.

Some existing literature suggests that dexmedetomidine and clonidine are adjuncts to local anesthetics that offer a faster onset and a better quality of analgesia for patients requiring labor analgesia. Further studies are required to precise the dosage and regimens in a population of laboring patients.

Study Design

Total number of subjects to be enrolled at this site:

400 (200 Mothers and their infants (200))

Describe and explain the study design:

- This study is designed as a randomized, parallel arm, controlled trial in 3 groups allocated in a 1:1:1 ratio

Describe the primary and secondary study endpoints:

Primary outcomes

Pain as defined by Numeric Rating Score (NRS) (0-10 where 0 is no pain and 10 Is the worst Imaginable) at 30 minutes after initiation of epidural analgesia

Secondary outcomes

0-10 pain scores, obstetric outcomes related to delivery details; hemodynamic outcomes; patient reported scales of symptoms and ratings including nausea, vomiting, shivering, pruritus, satisfaction; fetal and newborn outcomes.

Duration of an individual subject's active participation:

Approximately 24 hours (duration of labor). Study participation ends 10 minutes after delivery (for the newborn Apgar)

Inclusion criteria

1. >/ = 18 years
2. ASA Physical Status 2 or 3
3. Term pregnancy [> 37 gestational weeks]
4. Planning epidural labor analgesia
5. Singleton pregnancy
6. Vertex presentation
7. Planned vaginal delivery

Exclusion criteria

1. Pre-eclampsia with or without severe features
2. New initiation of antihypertensive agent within 24 hours prior to enrollment
3. Uncontrolled systemic comorbidities [i.e., diabetes, hepatic, renal or cardiac]
4. Known or suspected fetal abnomalies
5. Allergy to study agents
6. Contra-indication to neuraxial anesthesia
7. Inability to communicate or to participate in study procedures
8. Current beta blocker therapy