Effectiveness of Clonidine and Dexmedetomidine Adjuncts for Labor Epidural Analgesia Initiation: A Randomized Double-Blind Fentanyl-Controlled Non-Inferiority Trial (The CLASSIER Trial)

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

Hypothesis
The hypothesis is that clonidine (Group C) and dexmedetomidine (Group D) are non-inferior to fentanyl (Group F) (usual care) as adjuncts for epidural labor analgesia.

The null hypothesis is that clonidine and dexmedetomidine are inferior to fentanyl as adjuncts for epidural labor analgesia.

Background
Labor pain is the worst pain that most women will experience in their lifetime, and poorly treated labor pain is associated with depression, birth trauma, and risk for cesarean delivery and its attendant lifetime morbidities. Currently, standard evidence-based epidural labor analgesia protocols combine lipophilic opioids with local anesthetics to increase analgesia quality, reducing side effects of plain local anesthesia solutions alone: hypotension, motor block, and instrumental vaginal delivery. However, some patients such as those with complex pain (e.g., chronic pain, opioid use disorder, OUD), often experience pain that is more difficult to treat. Further, they may desire complete opioid avoidance due to interference with treatment goals (both severe pain and opioid exposure risks return to use and resultant overdose death) or postpartum drug screening. There is a critical need for viable alternatives to opioid exposure for effective pain management in this population. Clonidine and dexmedetomidine are two alpha-2-adrenergic agonists that have been studied in the context of neuraxial analgesia and have demonstrated benefits, but head-to-head comparisons with the current standard, opioids, are lacking. This lack of comparative data leaves patients and clinicians ill equipped to identify appropriate opioid alternatives in labor analgesia. The CLASSIER trial will compare the effectiveness of these adjuvants against the current standard of epidural fentanyl. The results of this investigation will be definitive evidence regarding viable alternatives to opioids as adjuvants for epidural analgesia, maximizing analgesia while continuing to limit side effects. CLASSIER will engender future trials aimed at furthering individualized pain management strategies in special populations.

Pain Outcome
Pain intensity scores were measured by 0-10 numeric rating scale (NRS) where 0 is no pain and 10 is the worst imaginable. Scores were measured at baseline (immediately before the intervention), 5-, 10-, 15-, 30-, 60-, 90-, 120-minutes after the intervention. The first 30 minutes of analgesia was considered for the primary outcome, as we judged this period to be a clinically relevant time when anesthesia clinicians are most intensely involved in the initial labor analgesia encounter and clinical judgements are being made about labor analgesia effectiveness. The totality of the pain experience over the first 30 minutes was assessed using Area Under the Curve (AUC) (Cappelleri 2009). AUC was calculated by the trapezoidal rule (AUC = AUC + (X[i]-X[i−1])*((Y[i]+Y[i−1])/2), where X is the number of time intervals since intervention, and Y is the reported NRS pain score) using the 5-, 10-, 15-, 30-minute pain ratings.

Exploratory Analyses
We will perform two exploratory analyses. First, we will assess the noninferiority of the outcome of the totality of the pain experience over the first 120 minutes using AUC, PI-AUC_{120} between the 3 groups. Second, we will compare the primary outcome PI-AUC_{30} between dexmedetomidine and clonidine groups to explore noninferiority between clonidine and dexmedetomidine as adjuncts.

Statistical Analysis Plan
Descriptive statistics will be calculated for demographic variables. Normally distributed data will be expressed as mean (standard deviation [SD]) while non-parametrically distributed data will be reported as median (interquartile range [IQR]), and categorical variables will be summarized as counts and percentages. Box plots and histograms will be used to evaluate the normality of data distribution. Absolute standardized difference (ASD) will be determined to identify any imbalance for baseline characteristics between groups.

The primary outcome (pain intensity burden AUC in first 30 minutes, PI-AUC_{30}) will be analyzed using noninferiority testing. The noninferiority margin (δ) will be defined as 10% of the PI-AUC_{30} in the control (fentanyl) group.

A conventional 1-sided 95% confidence interval (CI) will be constructed using normal distribution assumptions. Analysis will be by intent to treat. Assessments of any protocol violation will be reported. Treatment assignments will be evaluated against treatments received, and a sub-analysis of intention-to-treat analysis will be done if there are any study participants who did not receive their allocated intervention.

Sample Size Calculation

The primary outcome is pain intensity burden measured by area under the curve (AUC) for the first 30 minutes after initiation of epidural labor analgesia, PI-AUC_{30}. A 1-sided P value of 0.05 was considered statistically significant for the primary outcome. If the confidence interval (CI) for mean differences of PI-AUC_{30} between groups (Group D and Group F and between Group C and Group F) lie above the lower limit of $-\delta$ with $P < 0.05$, then we define Group D and Group C as noninferior to Group F.

We hypothesized that there would be no differences between the 3 groups in this noninferiority trial (Hida E 2018). We considered that up to 10% difference in pain burden (AUC) would not be clinically important. Therefore, the noninferiority margin was chosen based on a 10% difference in pain burden (AUC) between groups. We planned *a priori* to declare noninferiority of the dexmedetomidine or clonidine groups compared to the fentanyl groups if the upper bound of the 1-sided 95% confidence interval (CI) of the difference in rates of analgesia between groups (specifically: fentanyl - dexmedetomidine, clonidine - dexmedetomidine) was less than 10%. Using a 1-sided α level of 0.05, 2-sample noninferiority test, 23 patients were required in each group (total n=69) to achieve at least power of 80%.

Statistical analyses will be completed using PASS 23.0.2 (Kaysville, UT), Stata SE 17.0 (College Station, TX), and SAS 9.4M8 (Cary, NC).

References

Hida E, Tango T. Design and analysis of a 3-arm noninferiority trial with a prespecified margin for the hazard ratio. Pharm Stat. 2018 Sep;17(5):489-503. doi: 10.1002/pst.1875. Epub 2018 Jul 9. PMID: 29984524.

Cappelleri JC, Bushmakin AG, Zlateva G, Sadosky A. Pain responder analysis: use of area under the curve to enhance interpretation of clinical trial results. Pain Pract. 2009 Sep-Oct;9(5):348-53. doi: 10.1111/j.1533-2500.2009.00293.x. Epub 2009 Jun 22. PMID: 19549060.