The Effect of Intravenous Infusion of Tramadol-ondansetron on Recovery After Caesarean Section (TRON)

NCT05879536

Statistical Analysis Plan

Protocol Number: TRON

Version: 1.5

Date: 20/08/2024

Introduction

This Statistical Analysis Plan (SAP) outlines the statistical methods and procedures to be used for analyzing data from the study evaluating the non-inferiority of intravenous tramadol-ondansetron (TRON) compared to epidural analgesia (AL-EPI) in post-cesarean recovery.

Study Objectives

Primary Objective

- Evaluate the non-inferiority of TRON compared to AL-EPI in terms of global post-cesarean recovery.

Secondary Objectives

- Assess non-inferiority of TRON versus AL-EPI in acute post-cesarean pain control.
- Compare the incidence of adverse effects between TRON and AL-EPI.
- Evaluate the non-inferiority Of TRON compared to AL-EPI in the obstetric quality of recovery.
- Evaluate the incidence of chronic post-cesarean pain between TRON and AL-EPI.

Study Design

Prospective observational cohort study

Study Population

Inclusion Criteria:

- Patients over 18 years old undergoing cesarean section receiving any of the analgesic strategies studied.
- Consent to participate in the study.

Exclusion Criteria:

- Receiving an analgesic medication other than the one mentioned as "routine multimodal analgesia" (either as regular medication or for acute post-surgical pain)
- Medical history that determines the baseline data of the scales and data that we collect (pain or previous disabilities; addiction to drugs, alcohol or drugs; another disease that worsens the quality of life)
- Medical history that conditions the pharmacological effect (allergy, intolerance or atypical reaction to any of the drugs involved in its treatment or possible cross-reactions)
- Contraindication for neuraxial techniques (patient refusal, difficulty in understanding or communication, localized infection, increased intracranial pressure, or other medical criteria)
- Two or more previous caesarean sections
- Difficulty in understanding or communication
- Mother care will not be available to the newborn in the postpartum period for any reason

Endpoints

Primary

Recovery quality measured by the QoR-15 scale at 24 and 48 hours post-cesarean.

Secondary

- Pain levels measured by the Visual Analog Scale (VAS) every 4 hours for 48 hours.
- Adverse effects within 48 hours post-cesarean.
- Obstetric quality of recovery measured by the Obstetric Quality of Recovery-10 (ObsQoR-10).
- Incidence of chronic pain at 90 days post-cesarean measured by the Numerical Rating Scale (NRS).

Randomization and Blinding

This study does not involve randomization as it is observational. Blinding is not applicable.

Sample Size and Power Calculations

The minimum clinically important difference (MCID) of QoR-15 is 8 points, so we used it as the equivalence threshold. [Anesthesiology 2016 Jul;125(1):39-45]. We used data from previous analgesia studies using this tool with an expected mean of 120 points

with a standard deviation of 28.4. [Anesthesiology 2018; 128:598-608]. Therefore, we calculated that 312 patients are needed to conduct this non-inferiority study of tramadol-ondansetron perfusion with an alpha error of 0.05 and a statistical power of 0.8.

Data Collection and Management

Patient data will be collected at baseline, 24 hours, 48 hours, and 90 days post-cesarean. Data will be extracted from the hospital electronic health records.

Statistical Methods

A statistical analysis of the results obtained from the Quality of Recovery (QoR) 15 questionnaire will be conducted. The sequential Visual analog scale (VAS) pain sores, adverse effects, and the need for rescue medication will be analyzed. Additionally, the Obstetric Quality of Recovery-10 (ObsQoR-10) results will be analyzed to validate the Spanish-translated version and define the minimal clinically significant difference (MCID). Finally, the incidence of chronic postoperative pain will be studied by analyzing NRS results and medication use. A p-value of <0.05 is considered significant.

1. **QoR-15:** A mixed linear regression model will be fitted introducing the type of analgesia (TRON vs EPI) and the covariables considered in the model as fixed effects, with the patient as a random effect. The following covariables will be introduced in the model:
    - Weight of the newborn: quantitative variable in Kilograms
    - Breastfeeding: Yes or no
    - Duration of intervention: quantitative variable in minutes.
    - Previous caesarean section: Yes or no
    - Elective, urgent or emergency caesarean section.
    - Extended surgery: tubal sterilization or any other deviation from a standard caesarean section.
2. **Sequential VAS:** Scale from 0-10 repeated every 4 hours. It will also employ a mixed linear regression model, introducing the same covariables as mentioned in the previous section.
3. **ObsQoR-10:** A mixed linear regression model will be fitted introducing the same covariables as mentioned in the previous section.
4. **Adverse Effects:** Count of events as yes/no. A mixed Poisson regression model introducing the same covariables as mentioned in the previous section.

5. **Rescue Medication:** Count of events as yes/no. A mixed Poisson regression model introducing the same covariables as mentioned in the previous section
6. **Chronic Pain at 90 Days:** A Mixed logistic regression model introducing the same covariables as mentioned in the previous section.