Study Protocol and Statistical Analysis Plan

Efficacy and Safety of Dexmedetomidine Combined With Butorphanol Tartrate for Postoperative Analgesia and Breastfeeding in Cesarean Section

Registration number: NCT03065530

December 21, 2019

This study was registered at www.ClinicalTrials.gov (registration number: NCT03065530). The study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (Nanjing, Jiangsu province, China) and written consent was obtained from all participants. The study was conducted at The First Affiliated Hospital of Nanjing Medical University, Nanjing, China between February 2017 and October 2017.

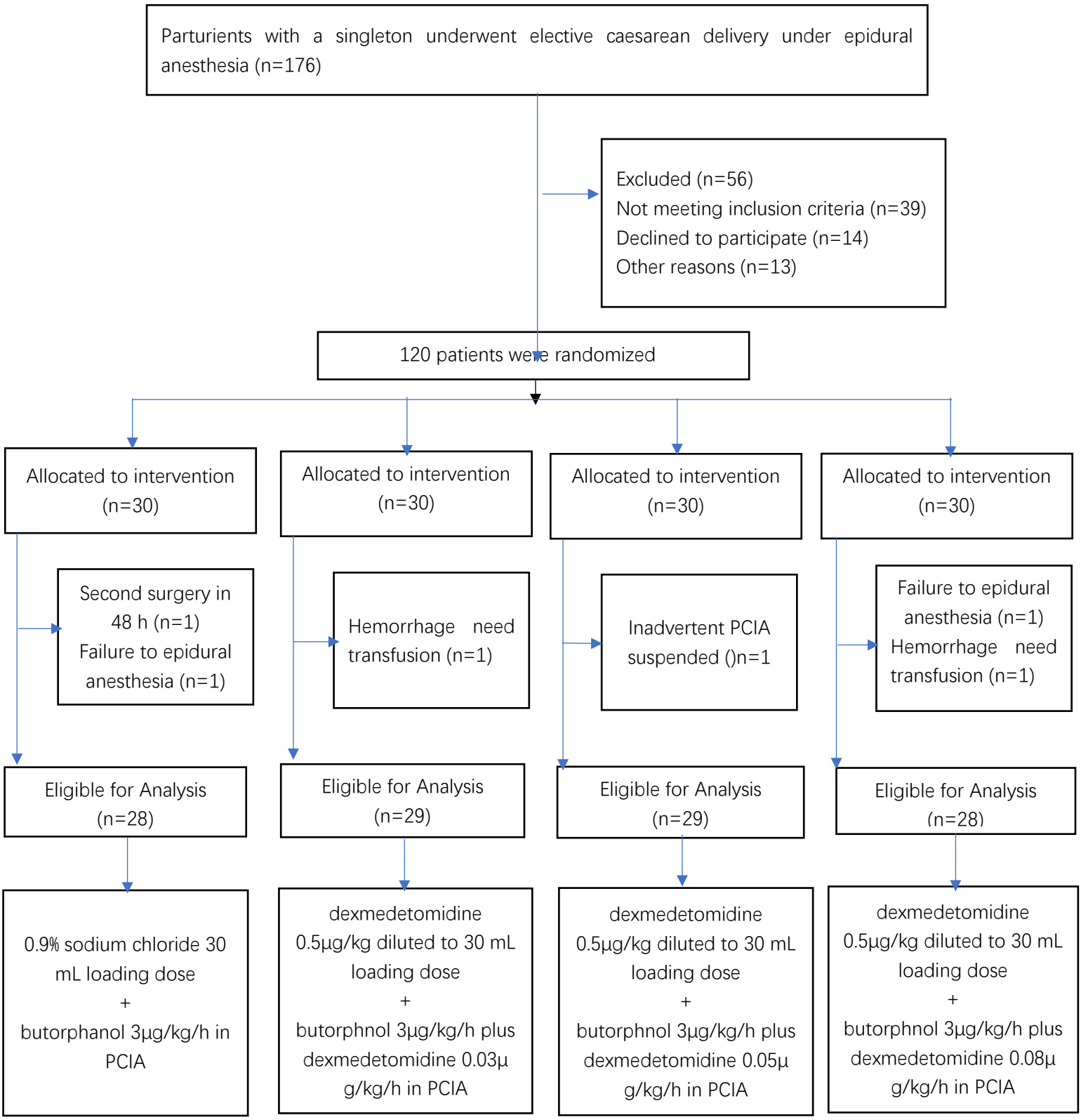
Patients were randomly allocated to one of four groups immediately after delivery of the newborn and cord clamping. Patients in group C received 30 ml 0.9% sodium chloride, whereas patients in group D1, D2, and D3 received 0.5 $\mu g \cdot kg^{-1}$ intravenous DEX diluted to 30 ml in 0.9% sodium chloride. Their PCIA protocol was programmed with 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ butorphanol in group C, while with 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ butorphanol combined with 0.03, 0.05, and 0.08 $\mu g \cdot kg^{-1} \cdot h^{-1}$ DEX in groups D1, D2, and D3, respectively. The settings for PCIA were a basal infusion at a rate of 2 $ml \cdot h^{-1}$ and 0.5 ml of boluses with a lock-out interval of 15 min (butorphanol and DEX in these PCIA protocols were calculated based on patient weight and infusion rate).

None of the parturients received any medication before the induction of anesthesia. On arrival to the operating room, a 20-gauge intravenous cannula was inserted into a peripheral vein on the arm, and five-lead electrocardiogram (ECG), noninvasive blood pressure (NIBP), and oxygen saturation on pulse oximetry (SpO_2) were continuously monitored. NIBP was measured every 2 min during the operation. The parturients were positioned in the lateral decubitus position with knees bent toward the chest and the epidural space was identified at the L2 to L3 interspace. After loss-of-resistance confirmed that the tip of the epidural needle was in the epidural space, the epidural catheter was inserted into the space and 3 ml 1.5% lidocaine combined with 5 $\mu g \cdot ml^{-1}$ epinephrine was administered via the epidural catheter as a test. All parturients were administered 0.75% ropivacaine with 2 $\mu g \cdot ml^{-1}$ fentanyl, and were in supine to the left lateral position. Surgery commenced when T4 to T6 sensory block was achieved.

Oxygen was administered at 5 $L \cdot min^{-1}$ via facemask, hypotension (systolic blood pressure [SBP] $\leq$ 90 mmHg or > 20% decline from baseline) was treated with

intravenous phenylephrine. Parturients received the “study drug” immediately, which was intravenously administered for 20 min when the umbilical cord was clamped. When the obstetrician closed the peritoneum, 50 mg flurbiprofen axetil and 10 mg azasetron hydrochloride was injected in every parturient as a loading dose. No other analgesics were administered post-cesarean section except the study drugs. Immediately after surgery, the PCIA pumps were attached at a rate of 2 $ml \cdot h^{-1}$, which was 0.5 ml per demand with lock-out intervals of 15 min, and the mother was transferred to the ward after a 1 h stay in the recovery room. NIBP was measured every 30 min for the first 6 h, and every 1 h until 48 h after the operation, with continuous HR and SpO_2 monitoring.

Side effects, such as hypotension (SBP < 90 mmHg), bradycardia (HR < 60 beasts/min), hypoxemia (SpO_2 < 90%), respiratory rate (RR, < 10 breaths/min, lasting > 10 min), and nausea and vomiting were recorded during the period starting from the end of surgery until 48 h after surgery. Respiratory depression was treated with oxygen and naloxone until RR reached >15 breaths/min. Severe nausea and vomiting were treated with azasetron or dexamethasone, whereas hypotension was treated with fluid loading, intravenous ephedrine or phenylephrine. Bradycardia was treated with atropine. Breast milk samples were collected on primary lactation (the start of which was from delivery to when > 5 ml of breast milk was expressed by massaging and compressing both breasts) for 48 h, and the time was also recorded. All samples were stored at -30°C. DEX levels in breast milk were quantified using high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) analysis and liquid-liquid extraction.


Parturients with a singleton underwent elective caesarean delivery under epidural anesthesia (n=176)
Excluded (n=56)
Not meeting inclusion criteria (n=39)
Declined to participate (n=14)
Other reasons (n=13)
120 patients were randomized
Allocated to intervention (n=30)
Allocated to intervention (n=30)
Allocated to intervention (n=30)
Allocated to intervention (n=30)
Second surgery in 48 h (n=1)
Failure to epidural anesthesia (n=1)
Hemorrhage need transfusion (n=1)
Inadvertent PCIA suspended ()n=1
Failure to epidural anesthesia (n=1)
Hemorrhage need transfusion (n=1)
Eligible for Analysis (n=28)
Eligible for Analysis (n=29)
Eligible for Analysis (n=29)
Eligible for Analysis (n=28)
0.9% sodium chloride 30 mL loading dose + butorphanol 3μg/kg/h in PCIA
dexmedetomidine 0.5μg/kg diluted to 30 mL loading dose + butorphnol 3μg/kg/h plus dexmedetomidine 0.03μg/kg/h in PCIA
dexmedetomidine 0.5μg/kg diluted to 30 mL loading dose + butorphnol 3μg/kg/h plus dexmedetomidine 0.05μg/kg/h in PCIA
dexmedetomidine 0.5μg/kg diluted to 30 mL loading dose + butorphnol 3μg/kg/h plus dexmedetomidine 0.08μg/kg/h in PCIA

Statistical Analysis Plan

The primary outcome was the VAS-R at 6 h after delivery. When designing the study, the sample size was calculated on the basis of an initial pilot study measuring VAS-R 6 h after surgery in 20 patients, and the standard deviation (SD) among the four groups was 1.4. The authors hypothesized that differences in VAS among the four groups and the SDs would be 15%. A power analysis suggested that 80% power would be required to detect differences at an α level of 0.05 (two-tailed), including 24 individuals per treatment group. Considering an anticipated attrition rate of 25%, 30 parturients were eventually recruited for each group. Secondary outcomes included VAS-M, VAS-C, RSS, RID, and satisfaction with analgesia after surgery.

GraphPad Prism version 7 (GraphPad, La Jolla, California, USA) was used to perform statistical analysis. Patient characteristics were analyzed using one-way analysis of variance (ANOVA). Patient satisfaction was analyzed using the chi-squared test and Kruskal-Wallis rank sum test. RID, VAS, and RSS were analyzed using the Kruskal-Wallis rank sum test. Dunn's multiple comparison tests were also used for multiple comparisons (post hoc test). $P < .05$ was considered to be statistically significant ($P<.0083$ was considered to be statistically significant when the post hoc test was used).