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ORIGINAL RESEARCH

The Effectiveness and Safety of Intravenous Dexmedetomidine of Different Concentrations Combined with Butorphanol for Post-Caesarean Section Analgesia: A Randomized Controlled Trial

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Purpose: The present study aimed to determine the effectiveness of intravenous dexmedetomidine of different concentrations and to evaluate its maternal and neonatal safety when combined with butorphanol in parturients undergoing cesarean section.

Patients and Methods: A total of 114 parturients between 24 and 43 years of age, with singleton pregnancy who underwent elective cesarean section under epidural anesthesia, were randomly allocated to four groups: group C received 0.9% sodium chloride after delivery, followed by butorphanol (3 $\mu g \cdot kg^{-1} \cdot h^{-1}$); patients in groups D1, D2, and D3 received 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dexmedetomidine after delivery, followed by butorphanol (3 $\mu g \cdot kg^{-1} \cdot h^{-1}$) combined with dexmedetomidine 0.03, 0.05, and 0.08 $\mu g \cdot kg^{-1} \cdot h^{-1}$, respectively. The primary outcome was the visual analogue scale (VAS) score at 6 h after delivery when patients were at rest. Secondary outcome measures included VAS after delivery when patients were on movement and uterine cramping, Ramsay sedation scale (RSS), relative infant dose (RID) of dexmedetomidine, satisfaction with analgesia after surgery and symptoms of CNS depression in neonates.

Results: There were no significant differences in patient characteristics among the groups ($P > 0.05$). The VAS at all timepoints after delivery in groups D2 and D3 were significantly lower than in groups C and D1 ($P < 0.001$). RSS scores were clearly higher in group D3 than in the other three groups at 6 h and 12 h ($P < 0.0001$). RID in groups D1, D2, and D3 was 0.171%, 0.197%, and 0.370%, respectively. Compared with group D1, RID was higher in group D3 ($P = 0.0079$). Degree of satisfaction with analgesia was higher in groups D2 and D3 ($P < 0.005$).

Conclusion: Continuous intravenous infusion of 0.05 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dexmedetomidine combined with 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ butorphanol could be safely applied in healthy parturients with satisfactory analgesia after cesarean section without changes in sedation.

Keywords: cesarean section, dexmedetomidine, analgesia, relative infant dose, anesthesia

Introduction

Postoperative pain can exacerbate the body's stress response, which is induced by surgery, and adversely affect both endocrine and immune functions.[1] The intensity of acute postoperative pain is a predictor of chronic pain.[2] Several studies have demonstrated that inadequate postoperative pain management is associated with persistent pain, greater opioid use, delayed functional recovery, and increased postpartum depression.[3,4]

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The combination of different analgesics that act by different mechanisms (ie, multimodal analgesia) to enhance clinical outcome is a common strategy in pain management.[5] Butorphanol, a totally synthetic opioid, exerts partial agonist and antagonist activity at the μ-opioid receptor, and agonist activity at the κ-opioid receptor. In addition, κ-opioid receptor agonists have been suggested to be more effective in females than in males.[6] Dexmedetomidine (DEX) is a potent and highly selective α_2-adrenoreceptor (α_2-AR) agonist, exhibiting hypnotic, sedative, anxiolytic, sympatholytic, and analgesic properties.[7–9] Several studies have indicated that postoperative intravenous opioid-DEX combined with patient-controlled analgesia (PCIA) strategies lead to superior analgesia, significant opioid sparing, fewer opioid-related side effects, fewer chills, and greater overall patient satisfaction.[5,10,11] Furthermore, poor sleep quality is strongly associated with increased pain scores post-cesarean delivery,[12] while DEX could share similarities with natural sleep.[13] However, only a small number of studies have focused on the use of DEX in parturients.[14–17] Two previous studies investigated the safety of lactation with DEX; however, the sample sizes were small.[18,19] Nevertheless, the optimal dosage and safety of DEX used in combination with butorphanol for post-cesarean analgesia remain unclear.

The present prospective, randomized, double-blind controlled study was designed to investigate whether the administration of DEX could decrease postoperative pain intensity after delivery and during PCIA.

Patients and Methods

Ethics Approval

This study was registered at www.ClinicalTrials.gov (NCT03065530). The study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (Nanjing, Jiangsu province, China). Written consent was obtained from all participants and they were informed the purpose of this research. This study was conducted at The First Affiliated Hospital of Nanjing Medical University, Nanjing, China, between February and October 2017.

Patient Population

Parturients (>18 and <45 years of age) with a singleton pregnancy admitted to the authors' institute, who underwent elective cesarean delivery under epidural anesthesia, were recruited for this study between February and October 2017. Parturients who had successfully breastfed a previous infant and planned to breastfeed after this delivery were screened for eligibility. Patients who became pregnant by assisted reproductive technologies were excluded. Other major exclusion criteria included: lack of informed consent; pregnancy-induced hypertension syndrome; HELLP syndrome (hemolysis, elevated liver enzymes, and a low platelet count); hypertension; ischemic heart disease; long-term use of non-steroidal anti-inflammatory drugs (NSAIDs); addiction to alcohol, opioid(s), or sedative-hypnotics; psychiatric disorders; preoperative heart rate (HR) <50 beats/min with/without cardiac conduction or rhythm abnormalities; neuromuscular and endocrine diseases or allergic reactions to α_2-AR agonists; or any previous abdominal surgery. Individuals were excluded from the study if epidural anesthesia was unsuccessful, or blood transfusion for hemorrhage required a second operation or inadvertent PCIA was suspended. Parturients in whom surgery ended after 11:00 were excluded so as to not to disturb their rest. Before beginning the procedure, parturients were trained on how to use the PCIA pump and instructed on how to use the 10 cm visual analog scale (VAS: 0 = no pain, 10 = worst pain imaginable).

Randomization and Masking

A computer-generated randomization table was used to equally allocate parturients into 4 groups (n = 30 per group) before the study. A total of 120 subjects were divided into four groups, which were treated with group C, group D1, group D2 and group D3, respectively. The practice is as follows: (1) draw up in advance the serial number of 120 subjects is 1–120; (2) use Excel to generate random numbers; (3) stipulate that random numbers are arranged from small to large, the smallest is group C, then group D1, then group D2, and then group D3, divided into 4 groups, each group of 30 cases. A research nurse, who was not blinded to the study, opened opaque envelopes at the time of request for study, which concealed the group allocations in sequential number. The drugs for treatment were prepared by pharmacy staff who were also not involved in the study. After the research nurse obtained the intravenous solution and the PCIAs, the original contents were labelled "study drug". All other study staff, including parturients, obstetrician and anesthesiologist, were blinded to group allocation. To ensure patients and neonates safety, each had a treatment plan within the sealed envelope, which could guide emergency treatment if the experiment was terminated due to serious adverse events [eg, circulatory failure, severe respiratory depression, coma, or hemorrhage, among others. Symptoms of

CNS depression (eg, drowsiness, cyanosis, or difficult breathing, feeding, and latching) and paradoxical effects (eg, unusual excitement and irritability) in any neonates].

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 within 15 minutes, whereas patients in group D1, D2, and D3 received 0.5 $\mu g \cdot kg^{-1}$ intravenous DEX diluted to 30 mL with 0.9% sodium chloride within the same time. Based on the previous studies,[15,20–23] the 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] ≤90 mmHg or >20% decline from baseline) was treated with fluid loading, intravenous ephedrine or phenylephrine. When it comes to hypotension occurs with HR>50 bpm, a loading dose of 100 ～200 μg phenylephrine was considered as the first choice. The next dose was determined according to the patient's blood pressure response or other vasoconstrictor will be considered. Whereas hypotension with HR<50 bpm, 5～10 mg ephedrine was chosen for application. 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 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. After collection, colostrum samples were frozen at −30°C until used. The samples were then transported to the State Key Laboratory of Natural Medicines, Department of Natural Medicinal Chemistry, China Pharmaceutical University. Sample analysis was performed on an high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS /MS) system consisting of a SHIMADZU LC-20AD series HPLC system (Shimadzu, Tokyo, Japan) and an API 4000 triple quadrupole mass spectrometer (Applied Biosystems Sciex, Ont., Canada). A VP-ODS column (2.0 × 150 mm, 5 μm, Shimadzu, Tokyo, Japan) was used for separation. The mobile phase was composed of A (0.2% formic acid-water, *v/v*) and B (acetonitrile) at a flow rate of 0.3 mL/min with the following optimal gradient elution condition: 0–0.5 min, 10–10% B; 0.5–1.0 min, 10–90% B; 1.0–4.0 min, 90% B; 4.0–4.5 min 90–10% B; 4.5–6 min, 10% B. The column temperature was maintained at 35°C and the injection volume was 10 μL. The total time for each injection was 6.0 min. An aliquot of 1 mL of each colostrum sample was mixed with 20 μL of working internal standard solution (100 ng/mL of erlotinib solution). Diethyl ether (5 mL) was then added for liquid-liquid extraction. After vortexing for 5 min and centrifuging at 8000 rpm for 10 min, 4.8 mL of the supernatant was

transferred to a new tube and was evaporated to dryness at 50°C in a centrifugal vacuum evaporator (LABCONCO Corp., USA). The residue was then reconstituted in 100 μL mobile phase. After centrifuging at 14,000 rpm for 5 min, 10 μL of the supernatant was injected for HPLC–MS/MS analysis.[18]

Outcome Measures

Pain was evaluated using the VAS at rest (VAS-R), movement (VAS-M), and during uterine cramping (VAS-C). VAS-R was assessed when the patient was supine, VAS-M was assessed when patients changed from supine to lateral position, and VAS-C was assessed when the patient required oxytocin after surgery in supine position. Sedation was assessed using the Ramsay sedation scale (RSS) as follows: 1, Awake; agitated or restless or both; 2, Awake; cooperative, oriented, and tranquil; 3, Awake but responds to commands only; 4, Asleep; brisk response to light glabellar tap or loud auditory stimulus; 5, Asleep; sluggish response to light glabellar tap or loud auditory stimulus; and 6, Asleep; no response to glabellar tap or loud auditory stimulus.[24] The degree of satisfaction (0, very satisfied; 1, satisfied; 2, moderately satisfied; and 3, not satisfied) was evaluated 48 h after surgery. VAS and RSS were recorded at 6, 12, 24 and 48 h after surgery. The dose (infant) in $mg \cdot kg^{-1}$ was calculated by multiplying the concentration of the drug in breast milk by the volume of breast milk consumed daily (approximately 150 $mL \cdot kg^{-1}$). Relative infant dose (RID) = dose (infant, $mg \cdot kg^{-1} \cdot day^{-1}$)/ dose (mother, $mg \cdot kg^{-1} \cdot day^{-1}$) $\mu g \cdot kg^{-1} \cdot h^{-1}$. Detailed results of this study have been uploaded to ClinicalTrials.gov PRS (www.ClinicalTrials.gov, registration number: NCT03065530). The other way is that data made available to all interested researchers upon request (The Ethics Committee of The First Affiliated Hospital of Nanjing Medical University).

Statistical Analysis

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) and STATA version 15.1 (Stata Corp, USA) were used to perform statistical analysis. All continuous data that were normally distributed are reported as means and standard deviation (SD). Continuous covariates were assessed for normality using the Shapiro–Wilk test (STATA version 15.1), if the test indicated a P value>0.05, then the data were normally distributed. 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). $P < 0.05$ was considered to be statistically significant (P<0.0083 was considered to be statistically significant when the post hoc test was used).

Results

Between February and October 2017, a total of 120 patients were recruited for this study; 6 parturients withdrew from among all four groups. The flow of the study participants is shown in Figure 1. Ultimately, 114 patients completed the study. Patient characteristics showed no significant differences between the 4 groups (Table 1).

The VAS-R after delivery in groups D2 and D3 were significantly lower than in groups C and D1 at 6 h ($P <$ 0.001), and at 12 and 24 h ($P < 0.0001$). At 48 h, VAS-R in group D3 was lower than groups C and D1 ($P = 0.002$ and 0.004, respectively). There were no differences between groups C and D1, nor groups D2 and D3 at all timepoints (Figure 2A).

There were no significant differences in VAS-M and VAS-C between groups C and D1 at all time-points. At 6 and 24 h, VAS-M in group D2 ($P < 0.001$) and group D3 ($P < 0.0001$) was lower than in groups C and D1. Moreover, VAS-M in group D3 was lower than in group D2 at 12 h ($P = 0.0007$) (Figure 2B). When uterine cramping occurred, the VAS-C in group D3 was lower than in groups C and D1 ($P < 0.0001$) (Figure 2C).

The RSS of group D3 was obviously increased at 6 and 12 h after surgery (P<0.0001) (Figure 2D). In addition, the RIDs of neonate in all patients were far <10%. There were no differences in RID between groups D1 and D2, nor

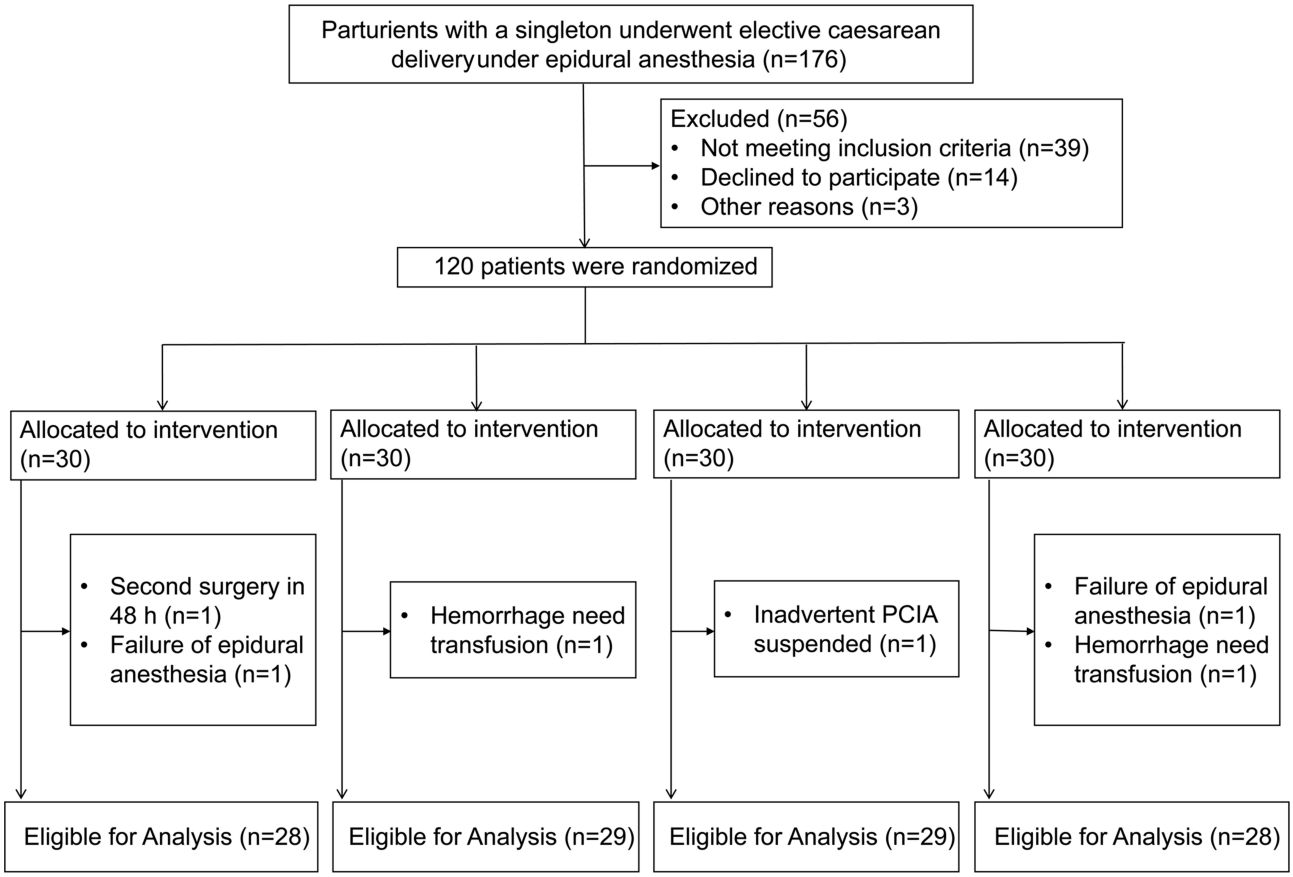

Figure 1 Flow chart of study.
Abbreviations: DEX, dexmedetomidine; PCIA, patient-controlled intravenous analgesia.

groups D2 and D3. Compared with group D1, the RID in group D3 was clearly higher ($P = 0.0079$) (Figure 3).

The incidence of "over-satisfied" (ie, satisfied and very satisfied) patients was significantly higher in groups D2 and D3 than in groups C and D1 ($P < 0.005$) (Figure 4). During the 48 h after surgery, one patient in group C, D2 and D3, and two patients in group D1 experienced nausea, but there were no significant differences in nausea, nor vomiting recorded in any of the four groups. Side effects, such as hypotension, bradycardia and hypoxemia were not observed in parturients. Symptoms of CNS depression (eg, drowsiness, cyanosis, or difficult breathing, feeding, and latching) and paradoxical effects (eg, unusual excitement and irritability) were also not observed in any neonates.

Table 1 Patient Characteristics in the Four Groups: Group C: Control Group, Group D1: DEX Injected with 0.03μg·kg^{-1}·h^{-1} in PCIA, Group D2: DEX Injected with 0.05μg·kg^{-1}·h^{-1} in PCIA and Group D3: DEX Injected with 0.08μg·kg^{-1}·h^{-1} in PCIA

	Group C (n=28)	Group D1 (n=29)	Group D2 (n=29)	Group D3 (n=28)	P value
Age (years)	31.8±3.5	31.4±3.7	32.1±4.2	31.1±3.4	0.7816
Height (cm)	161.7±3.7	160.0±4.3	160.7±4.6	161.2±4.0	0.4872
Weight (kg)	73.6±5.8	72.9±8.5	74.5±8.0	72.2±7.5	0.6837
Gestational period (weeks)	39.1±0.8	38.9±1.0	38.9±1.0	38.7±0.8	0.6483
Duration of operation (min)	59.8±7.8	61.1±6.1	61.5±7.1	61.5±7.7	0.7863
Baseline of SpO_2 (%)	98.6±0.8	98.5±0.6	98.6±079	98.5±0.8	0.9589
Baseline of SBP (mmHg)	114.9±8.4	113.7±11.3	111.4±8.2	113.2±8.7	0.5604
Baseline of HR (bpm)	77.7±4.5	76.6±5.6	75.4±4.0	77.0±4.8	0.3208

Note: Data are expressed as mean (SD).
Abbreviations: SBP, systolic blood pressure; SpO_2, pulse oxygen saturation; DEX, dexmedetomidine; PCIA, patient-controlled intravenous analgesia.

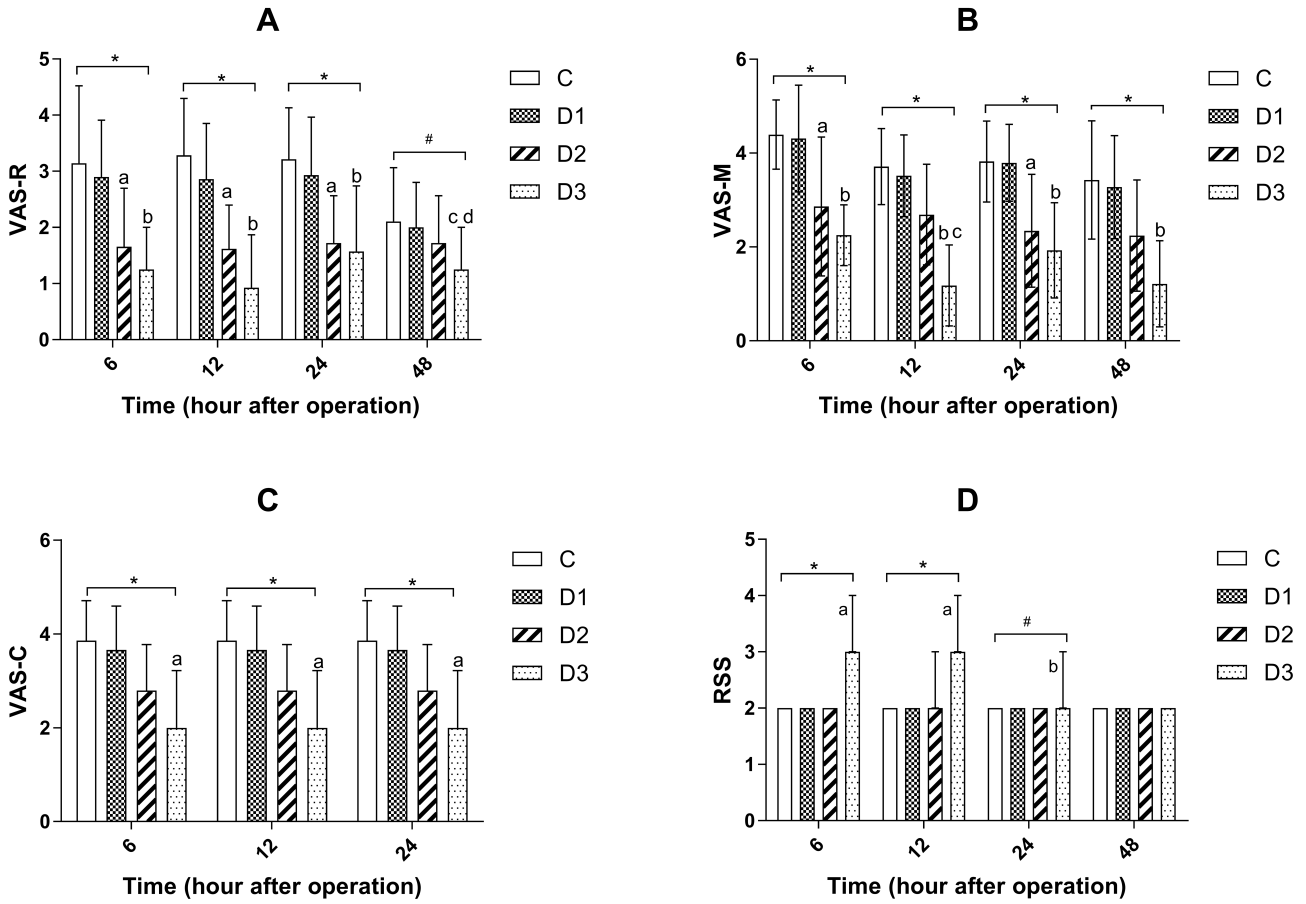

Figure 2 Group (**C**) control group, group D1: DEX injected with 0.03 μg·kg^{-1}·h^{-1} in PCIA, group D2: DEX injected with 0.05 μg·kg^{-1}·h^{-1} in PCIA and group D3: DEX injected with 0.08 μg·kg^{-1}·h^{-1} in PCIA. (**A**): Postoperative VAS-R in the four groups. Data are expressed as mean (SD). *P < 0.0001 means there were significant differences between the 4 groups, #P = 0.0010 means the differences between the 4 groups. [a]Means Group D2 vs groups C and D1 (adjusted P < 0.001). [b]Means group D3 vs groups C and D1 (adjusted P < 0.001). Adjusted [c]P = 0.002, group D3 vs group C, adjusted [d]P = 0.004, group D3 vs group D1. (**B**): Postoperative VAS-M in the four groups. Data are expressed as mean (SD). *P < 0.0001 means there were significant differences between the 4 groups. [a]Means group D2 vs groups C and D1 (adjusted P < 0.001). [b]Means group D3 vs groups C and D1 (adjusted P < 0.001). [c]Means group D2 vs group D3 (adjusted P < 0.001). (**C**): Postoperative VAS-C in the four groups. Data are expressed as mean (SD). *P < 0.0001 means there were significant differences between the 4 groups. [a]Means group D3 vs groups C and D1 (adjusted P < 0.001). (**D**): RSS in the four groups, Data are expressed as median (inter-quartile range) *P < 0.0001 means that there were significant differences among the 4 groups, #P = 0.0200 means the differences between the 4 groups. [a]Means significant differences, group D3 vs groups C, D1 and D2 (adjusted P < 0.0001), [b] means significant differences, group D3 vs group C (adjusted P = 0.0145).

Abbreviations: DEX, dexmedetomidine; RSS, ramsay sedation scale; VAS-R, visual analog scale at rest; VAS-M, visual analog scale at movement; VAS-C, visual analog scale at uterine cramping.

Discussion

The major findings of this prospective study were that intravenous injection of a loading dose of DEX after delivery, followed by continuous intravenous infusion of DEX along with butorphanol in PCIA, led not only to pain reduction (according to VAS) at rest, movement and uterine cramping, but also enhanced the analgesic effect and improved maternal satisfaction. We also found that RIDs were far below 10%, suggesting that there was no central nervous system (CNS) depression observed in neonates after maternal DEX intravenous infusion.[25,26]

The considerable pharmacological action of DEX is due to the excitement of α_2-ARs. DEX can activate presynaptic α_2-ARs, inhibit norepinephrine release through a negative feedback mechanism, and stop pain signal transduction. The unique "conscious sedation" of DEX is primarily associated with the nucleus coeruleus in the brain. When compared with remifentanil, it has superior properties, particularly in wake-up sedation, mild analgesia,[27] and a lower risk for respiratory depression. In this study, as an adjuvant to opioids, DEX exhibited enhanced analgesia and improved maternal satisfaction after cesarean section. The loading dose of 0.5 μg·kg^{-1} was chosen during cesarean section under epidural anesthesia, which proved to be beneficial to parturients.[15,21,28] We then administered 0.03, 0.05, and 0.08 μg·kg^{-1}·h^{-1} DEX to determine the dose-dependent

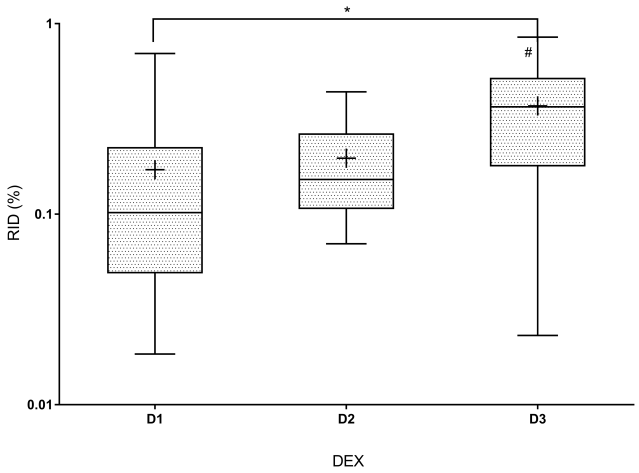

Figure 3 RID in the three groups: group D1: DEX injected with 0.03 μg·kg^{-1}·h^{-1} in PCIA, group D2: DEX injected with 0.05 μg·kg^{-1}·h^{-1} in PCIA and group D3: DEX injected with 0.08 μg·kg^{-1}·h^{-1} in PCIA. Data are expressed as median (interquartile range). *P = 0.0092 means there were significant differences between the 3 groups. Adjusted $^{\#}P$ = 0.0079 means group D3 vs group D1.
Abbreviations: DEX, dexmedetomidine; RID, relative infant dose.

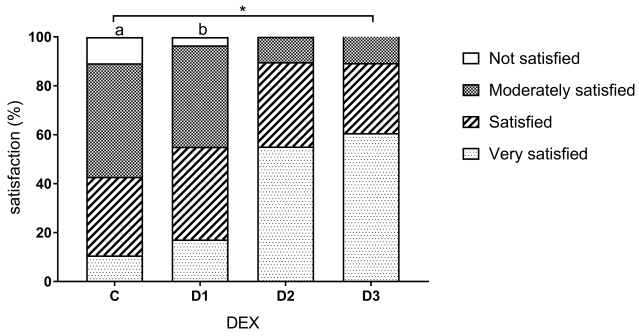

Figure 4 Comparison of patient satisfaction among the four groups: group C control group, group D1: DEX injected with 0.03 μg·kg^{-1}·h^{-1} in PCIA, group D2: DEX injected with 0.05 μg·kg^{-1}·h^{-1} in PCIA and group D3: DEX injected with 0.08 μg·kg^{-1}·h^{-1} in PCIA. *P < 0.0001 means there were significant difference between the 4 groups.; [a] means significant differences, group C compared with groups D2 and D3 (adjusted P < 0.0001); [b] means significant differences, group D1 compared with groups D2 and D3 (adjusted P < 0.005).
Abbreviation: DEX, dexmedetomidine.

effect and optimal dosage in analgesic management along with PCIA.[29]

Postoperative pain and side effects of analgesic treatment, in particular those of opioids, need to be minimized. Uterine cramping pain is distinct from incision pain in both pathophysiological mechanism and pharmacological responses to analgesic agents; thus, making post-cesarean pain generally different from other postoperative pains.[22] Studies have shown that butorphanol can also relieve visceral pain, but butorphanol reduces visceral pain in a dose-dependent manner.[30,31] Furthermore, there were insufficient evidence to make conclusions regarding the effectiveness of opioids at relieving pain from uterine cramping.[32] Previous studies have found that DEX is effective in controlling visceral pain.[33,34] In our study, when uterine cramping occurred, the VAS-C in group D3 was lower than in groups C and D1. We thought that DEX as an adjuvant combined with butorphanol, with an infusion rate of 0.08 μg·kg^{-1}·h^{-1} seems to play a role in inhibiting visceral pain, and had the potential benefits of reducing the side effects of high-dose butorphanol.

In addition, having an awake parturient able to have skin-to-skin contact with her newborn soon after delivery is recommended in several hospitals, also the American Academy of Pediatrics. We here surmised that appropriate sedation may improve the comfort of the parturient receiving intervertebral anesthesia and skin-to-skin will not be affected. A large proportion of women scheduled for cesarean section experience poor-quality sleep before surgery, in which poor sleep quality significantly increased the risk for severe peak pain upon movement.[12] One study found that DEX exhibited a hypercapnic arousal phenomenon similar to what has been described during natural sleep. The characteristic of mimic natural sleep caused that DEX clinically considered apart from other sedatives, such as gamma-aminobutyric acid-related sedation, including propofol and benzodiazepines.[13] Adequate sedation without respiratory depression reduced the pain after cesarean section. However, with 0.08 μg·kg^{-1}·h^{-1} DEX infusion, the mothers' RSS was significantly higher (RSS > 3) than the other three groups at 6 h and 12 h after surgery. Over-sedation could attenuate mother's ability to interact with infants. In fact, it is not uncommon for mothers to fall asleep while feeding their infants. The American Academy of Pediatrics believe that a mother falling asleep can increases the risk of Sudden infant death syndrome (SIDS).[35,36] Breastfeeding appears to have an independent protective effect against SIDS.[37] Therefore, we speculated that this higher dose of DEX was not beneficial for baby care and lactation, because over-sedation could attenuate the mother's ability for interaction with infants.

On the other hand, due to CNS depression that often occurs (up to 24%) in breastfed infants when mothers use drugs, such as codeine, morphine, oxycodone and benzodiazepines, CNS depression in neonates should be closely considered when the safety of DEX intravenous infusion is assessed during puerperium medication.[38,39] In this study, symptoms of CNS depression (eg, drowsiness, cyanosis, or difficult breathing, feeding, and latching) and paradoxical effects (eg, unusual excitement and irritability) were not observed in any neonates, regardless of group. None of the

patients experienced high blood pressure, lower blood pressure, bradycardia, respiration depression, or hypoxemia. Even in the 0.08 $\mu g \cdot kg^{-1} \cdot h^{-1}$ group with several cases, in which RSS > 3, no one required naloxone, atropine, ephedrine, or phenylephrine treatment.

We then further measured the RID of DEX to evaluate the safety of DEX during breastfeeding of the infants by mothers who received the DEX infusion for post-cesarean analgesia. Several studies have demonstrated that breastfeeding and breast milk are superior to formula in immediate and long-term health. Cesarean section is believed to expose neonates to significantly more medication. The majority of medications are relatively safe for breastfeeding mothers; however, the safety of many newer medications used during and after cesarean section has not yet been studied. DEX is one such example of these newer medications. The RID provides an estimate of the weight-normalized dose relative to the mother's dose, which is more meaningful to clinicians.[25] In general, a RID < 10% is considered to be acceptable in a healthy postnatal infant, a RID>25% may have a therapeutic effect on the infant if absorbed, which may be unacceptable.[26] In our study, we found that all RIDs were in the safe range. The oral bioavailability of drug(s) in breastfeeding mothers should also be considered. Given that DEX demonstrates an oral bioavailability value of 16%, the DEX concentration in the neonate plasma absorbed from DEX-containing breast milk should be especially low.[40]

There were several limitations to our study. Oral analgesics (such as NSAIDs) are usually used as part of a multimodal analgesia regimen for post-cesarean section. In our study, no other narcotics were administered for post-cesarean section. When the obstetrician closed the peritoneum, only 50 mg flurbiprofen axetil was injected in every parturient as a loading dose, which was probably insufficient, and even lacked remediation. A further limitation of the current study was that we did not include nulliparous women because we needed to collected breast milk to calculate the RID for DEX. We selected parous parturients, who had a successful breastfeed experience to minimize variability, which could possibly influence breastfeeding. Although we cannot conclude that intravenous DEX has no effect on breastfeed in primipara, theoretically, in pharmacodynamics and pharmacokinetics, it would be unlikely to occur according the results of our study. Thirdly, simple random is not optimal for this study, Stratified Blocked Randomization is more appropriate. This is the deficiency of this study. Finally, the present study lacked a standardized scale for evaluating infant CNS function and relied simply on clinical observation; as such, further research is warranted.

Conclusion

Continuous intravenous infusion of a high dose of DEX combined with butorphanol in PCIA not only enhanced analgesic effect and reduced VAS score but also improved parturient satisfaction compared with butorphanol PCIA alone. Maternal DEX used during cesarean delivery was safe for the breastfed neonate. In terms of consideration of maternal analgesia efficiency and lactation, and safety of the neonate, a 0.5 $\mu g \cdot kg^{-1}$ loading dose with 0.05 $\mu g \cdot kg^{-1} \cdot h^{-1}$ intravenous infusion of DEX in PCIA should be considered as an optimal regimen for post-cesarean section analgesia.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

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