ORIGINAL ARTICLE

Efficacy of dexmedetomidine in combination with morphine for pain management in patients with cesarean section

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ABSTRACT

Background and Objective: Intraspinal morphine shows a high analgesic efficacy but may cause some adverse effects. Dexmedetomidine (Dex) improves anesthetic actions and reduces anesthesia-related adverse reactions. This study was aimed to observe the efficacy and safety of intravenous Dex combined with epidural morphine for pain management in patients after cesarean sections.

Methods: Eighty women undergoing cesarean sections were equally divided into two groups. Group A received Dex in combination with morphine and group B received morphine only. Participants in both groups were given morphine after cesarean sections. After delivery, women in the group A were given Dex, while participants in the group B were given physiological saline. Serum levels of cortisol, renin, and potassium were measured before anesthesia, immediately and 24 hours after cesarean sections, and the visual analog scale (VAS) and observer's assessment of alertness/sedation scale (OAA/S) scores were assessed at 4, 8, 12, and 24 hours after cesarean sections. In addition, post-operative adverse events and urine volume intraoperative and at 24-hour after cesarean section was measured.

Results: Lower serum levels of cortisol and renin were recorded in group A than group B immediately after cesarean sections ($p < 0.05$). VAS score was low in group A than group B at 12 and 24 hours after cesarean sections ($p < 0.05$); however, no significant differences were seen in the OAA/S score ($p > 0.05$). Lower frequency of shivering and nausea/vomiting was seen in group A than group B after cesarean sections, and increased urine volume intraoperatively and after 24 hours of cesarean sections was observed in group A than group B ($p < 0.05$).

Conclusion: Dex-morphine combination achieves a higher efficacy and lesser adverse events than morphine alone for post-cesarean analgesia.

Keywords: Cesarean section, analgesia, dexmedetomidine, morphine, efficacy, safety.

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Introduction

Epidural analgesia is a common choice for the pain management after caesarian section.[1] The incidence of insufficient analgesia after cesarean accounts for 50% even after multiple measures used to manage pain.[2,3] Effective pain management following cesarean section is required to control chronic pain and increased postpartum depression.[4,5] Intraspinal administration of morphine helps in achieving efficient and long duration of analgesia; however, this technique is associated with high incidence of adverse events, including nausea, vomiting, and pruritus.[6]

Dexmedetomidine (Dex), a highly selective α2-adrenergic receptor agonist, shows sedative, analgesic, anxiolytic, sympatholytic, and opioid-sparing actions properties. It plays a vital role in the improvement of anesthetic effect and prevention and alleviation of anesthesia-related adverse reactions.[7-9] Postoperative intravenous opioid-DEX combined with other pain controlling approaches lead to superior analgesia, opioid sparing, less side effects of opioids, fewer chills, and better patient satisfaction.[10] This research was conducted to observe the efficacy and adverse reactions of intravenous Dex combined with epidural morphine for pain management in women undergoing cesarean sections.

Methods

This single-center, randomized, controlled clinical trial was conducted at the Department of Anesthesiology, Jiangyin People's Hospital, China from April 2017 to October 2017 after

getting approval by the hospital Ethical Review Committee. A total of *n* = 80 singleton term pregnant women (aged; 20 to 40 years), undergoing selective cesarean sections were equally divided into two groups randomly: group A, who received Dex-morphine combination and group B, who received morphine only. All participants were selected according to the American Society of Anesthesiologists Physical Status Classification System.[11] Women with subarachnoid anesthesia, additional administration of local anesthetics through the epidural catheter, massive intraoperative hemorrhage and any other co-morbid conditions were excluded. Signed informed consent was taken from all the participants, following a detailed description of the potential risk and response management of the anesthesia. All procedures were performed by the well-trained and licensed anesthetists in accordance with the international and national guidelines.

All participants were fasted for 6 hours prior to cesarean sections. Peripheral venous access was established after transferring the women to operating room. Heart rate (HR), non-invasive blood pressure, and oxygen saturation were measured with an electrocardiogram monitor. Subarachnoid-epidural anesthesia was induced at the Lumbar (L2-L3) interspace in a left lateral decubitus position by subarachnoid administration with 1.8 ml 0.5% bupivacaine hydrochloride (batch no.: 74170402; Shanghai Harvest Pharmaceutical Co., Ltd.; Shanghai, China) followed by epidural catheterization 3 cm to a cephalad direction. The lying-in women were placed in a supine position, and the surgical table was turned to 15° of left lateral tilt. After the sensory block plane reached the Thoracic (T5-T6) level, cesarean section was performed via a transverse incision in the lower uterine segment, with intraoperative fluid administration of 500 ml of Lactated Ringer's Injection (batch no.: E17021503-2; Hunan Kelun Pharmaceutical Co., Ltd.; Yueyang, China) and Hetastarch injection (batch no.: 1703254; Nanjing Chia Tai Tianqing Pharmaceutical Co., Ltd.; Nanjing, China). All anesthesia procedures were induced by the same anesthetist.

After delivery, continuous intravenous infusion of Dex (batch no.: 170831BP; Jiangsu Hengrui Medicine Co., Ltd.; Lianyugang, China) was given to the group A at a loading dose of 0.5 µg/kg and at a background infusion rate of 0.1 µg/(kg/hour) for 15 minutes, and the same volume of physiological saline was given in the group B by intravenous infusion for 15 minutes. Following cesarean sections, epidural administration of 2.5 mg morphine (batch no.: 161113-2 Northeast Pharmaceutical Group Co., Ltd.; Shenyang, China) was given to the participants in both groups, and patient-controlled analgesia (PCA) in the form of bolus dose (100 ml), continuous basal infusion (2 ml/hour), demand doses (1 ml), lockout interval, (30 minutes) was given followed by maintenance till 48 hours post-operation. Additional intravenous administration of tramadol (Batch no.: 00939F; Grünenthal GmbH; Aachen, Germany) at a dose of 2 ml/kg was given in case of incomplete analgesia. After 24 hours of cesarean sections, 400 mg tramadol was given to the participants in both groups for improving analgesia via disposable PCA pumps (Shanghai Bochuang Medical Instrument Co., Ltd.; Shanghai, China).

Serum levels of cortisol, renin, and potassium were measured immediately and 24 hours after cesarean sections. Pain was assessed by using a 10-point visual analog scale (VAS) scoring system at 4, 8, 12, and 24 hours after cesarean sections, where 0 represented no pain, and 10 indicated the worst imaginable pain.[12] The level of alertness in sedated women was tested at 4, 8, 12, and 24 hours after cesarean sections using a 5-point observer's assessment of alertness/sedation scale (OAA/S) scoring system, where 1: deep sleep/unconsciousness and no responses to mild prodding or shaking, 2: deep sedation but responses to mild prodding or shaking, 3: moderate sedation and responses to name spoken loudly or repeatedly, 4: mild sedation and lethargic responses to name spoken in a normal tone, and 5: completely awake and responses readily to name spoken in a normal tone.[13] Post-operative adverse events, including shivering, bradycardia (HR < 55 beats/minute), nausea, vomiting, pruritus, intraoperative, and 24-hour urine volume after cesarean sections were also recorded.

Statistical analysis

Statistical analysis was conducted using Statistical Package for the Social Sciences version 20.0 (SPSS, Inc.; Chicago, IL). All quantitative variables were measured as mean ± standard deviation (SD), and all categorical data were described as proportions. Student *t* test was used to compare the difference between the two groups. Chi-square test was used to compare the differences of proportions. A p value < 0.05 was considered as statistically significant.

Results

The age, height, body weight, intraoperative blood loss, and zduration of cesarean sections were comparable between the group A and group B ($p > 0.05$) (Table 1).

A lower VAS score was measured in group A than group B at 12 ($p = 0.037$) and 24 hours after cesarean sections ($p = 0.036$). OAA/S score was 3 in only 2 participants in group A at 4 hours after cesarean sections, 4 and greater scores were measured in other women at other time points; however, no significant differences were seen ($p > 0.05$) (Table 2).

Before induction of anesthesia, there were no significant differences between group A and group B in terms of serum cortisol or renin levels ($p > 0.05$); however, lower serum levels

Table 1. *Comparison of demographic and operative characteristics between groups (mean ± SD).*

Group	Age (years)	Height (cm)	Body weight (kg)	Intraoperative blood loss (ml)	Duration of cesarean section (minutes)
Dex-morphine combination group (A)	31 ± 4	160 ± 5	70 ± 7	283 ± 5	58 ± 5
Morphine group (B)	32 ± 5	160 ± 4	72 ± 11	278 ± 7	59 ± 6

Table 2. *Comparison of VAS and OAA/S scores between groups (mean ± SD).*

Group	Mean VAS score at different time points after cesarean section				Mean OAA/S score at different time points after cesarean section			
	4 hours	8 hours	12 hours	24 hours	4 hours	8 hours	12 hours	24 hours
Dex-morphine combination group (A)	0.9 ± 0.5	1.1 ± 0.6	2.0 ± 0.7*	2.1 ± 0.6*	4.4 ± 0.6	4.5 ± 0.5	4.6 ± 0.5	4.6 ± 0.5
Morphine group (B)	0.9 ± 0.4	1.2 ± 0.5	2.3 ± 0.6	2.4 ± 0.7	4.6 ± 0.5	4.6 ± 0.5	4.7 ± 0.5	4.7 ± 0.5

* $p < 0.05$ versus the morphine group (B).

of cortisol ($p = 0.041$) and renin ($p = 0.037$) were measured in group A after the completion of cesarean sections. We found no significant differences in the serum potassium level between the two groups before induction of anesthesia, immediately or 24 hours after cesarean sections ($p > 0.05$). Serum potassium level was lower than the normal range in three women 24 hours after cesarean sections, including two cases in the group A (3.3 and 3.4 mM) and one case in the group B (3.3 mM), and the serum potassium concentrations were significantly lower in both groups 24 hours after cesarean sections than before induction of anesthesia ($p= 0.026$) (Table 3).

During the analgesic treatment after cesarean sections, only one participant was presented with nausea/vomiting and four with pruritus in group A, while shivering (15%), nausea/vomiting (17.5%) and pruritus (17.5%) were seen more in group B. A lower incidence of shivering (0% *vs.* 15%, $p = 0.027$) and nausea/vomiting (2.5% *vs.* 17.5%, $p = 0.021$) was seen in group A than group B after cesarean sections. The intraoperative urine volume (205 ± 48 *vs.* 175 ± 44 ml, $p = 0.021$) and within 24 hours after cesarean sections (3,284 ± 730 *vs.* 2,644 ± 644 ml, $p = 0.019$) was high in group A than group B.

Discussion

Single epidural morphine administration is common and widely used for postoperative analgesia.[14-17]Epidural administration of sufentanil-morphine combinations improves the mother's ability to mobilize and interact with her newborn infant.[18] Epidural administration of morphine at a single dose of 3 mg /24 hours causes no respiratory depression and potential for catheter-related complications in patients undergoing cesarean sections.[19]Though, increased doses of morphine extend the duration and efficacy of post-cesarean analgesia but it may cause a rise in the post-cesarean side-effects, including nausea, vomiting and pruritus.[20] In the present study, tramadol at a dose of 2 ml/kg was given for improving analgesia in case of incomplete pain relief. Another study reported satisfactory post-cesarean analgesic efficacy by intravenous administration of tramadol at a continuous infusion dose of 10 g/L and an infusion rate of 2 ml/hour.[21] Since the analgesic efficacy attenuates remarkably 24 hours following single epidural administration of morphine, 400 mg tramadol was given by intravenous pumping 24 hours after cesarean sections. As an adjuvant for general and intraspinal anesthesia, the efficacy and safety of Dex have been extensively investigated in obstetric anesthesia and analgesia.[7-10] Extremely low Dex level is detected in breast milk, and its administration does not affect the time of colostrum development.[22] It has been shown that Dex may be used as an adjuvant for intravenous PCA and it does not increase the frequency of opioid-related respiratory depression, and also shows no marked impact on the spontaneous contraction of uterine smooth muscles. [23,24] Loading dose of Dex (0.5 µg/kg) followed by a continuous infusion rate of 0.4 µg/(kg/hour) is considered feasible and relatively safe.[25]

As an α2-adrenergic receptor agonist, Dex acts on the posterior horn of the spinal cord to exhibit an anti-nociceptor effect to reduce the responses to traumatic stimuli, and functions on peripheral and central nerves to exhibit an anti-sympathetic action.[8,9] Dex improves the analgesic efficacy of opioids and reduces the dose of opioids among patients undergoing hysterectomy.[26] In patients undergoing cesarean sections, combined administration of Dex, ropivacaine and sufentanil lowers the post-cesarean cortisol levels and achieves more satisfactory analgesic efficacy than those without Dex administration.[27] A lower VAS score found in group A than group B at 12 and 24 hours after cesarean sections ($p < 0.05$), suggests a synergistic effect caused by

Table 3. *Comparison of serum cortisol, renin and potassium concentrations between groups (mean ± SD).*

Group	Mean serum cortisol concentration (mg/l)			Mean serum renin concentration (ng/l)			Mean serum potassium level (mM)		
	Before anesthesia	Immediately post-surgery	24 hours post-surgery	Before anesthesia	Immediately post-surgery	24 hours post-surgery	Before anesthesia	Immediately post-surgery	24 hours post-surgery
Dex-morphine combination group	0.24 ± 0.07	0.32 ± 0.08*	0.20 ± 0.07*	33 ± 13	30 ± 11*	27 ± 12	3.92 ± 0.21	4.03 ± 0.22	3.73 ± 0.23**
Morphine group	0.25 ± 0.07	0.36 ± 0.08	0.24 ± 0.08	31 ± 14	36 ± 13	29 ± 13	3.91 ± 0.34	3.92 ± 0.24	3.71 ± 0.21**

* $p < 0.05$ versus the morphine group (B); ** $p < 0.05$ versus the level before anesthesia.

Dex administration in combination with epidural morphine increasing the analgesic efficacy of morphine.

Surgical trauma may lead to activation of stress responses, and cortisol is a sensitive parameter for stress responses.[28,29] Activation of the renin-angiotensin-aldosterone system is an important mechanism in stress responses.[30] Opioid peptides are remarkably affecting the release of hypothalamic regulatory peptides, and morphine is reported to reduce stress responses through inhibiting the release of hormone by the adrenocorticotropic hormone. [31,32] Dex exhibits a sedative action by targeting the locus coeruleus in the central nervous system, thereby alleviating anxiety and tension, and also suppresses the release of injury-sensory neurotransmitters and the conduction of nerve fiber impulses, thereby reducing stress responses.[7] This may be a possible explanation for the low serum levels of cortisol and renin following Dex administration observed in the present study.

Shivering and nausea/vomiting are common intraoperative complications.[33] In pregnant women undergoing cesarean sections, shivering is more likely to occur due to an elevated basal metabolic rate at the late-stage of pregnancy, increased blood circulation, vascular dilation caused by oxytocin administration after delivery and loss of plenty of amnionic fluids.[34] In the current study, a significantly lower incidence of shivering was observed in group A than group B ($p < 0.05$), which may be associated with the suppressing effect of Dex on the thermoregulatory center to reduce the shivering threshold and the blockade of thermal conduction via spinal cord.[35] During the cesarean section, intravenous pumping of Dex at a loading dose after cutting the umbilical cord was reported to reduce the incidence of nausea/vomiting within 24 hours after the cesarean section, which is almost in agreement with the findings of the present study.[36]

Dex has a dose-dependent diuretic activity but does not affect serum potassium concentrations in patients receiving general anesthesia, which may be associated with the inhibition of the sympathetic nervous system on kidney, alleviation of vasopressin in renal tubules, and elevated secretion of natriuretic peptides.[37] In the current study, increased urine volume in group A in both intraoperative and within 24 hours after cesarean sections was reported ($p < 0.05$), suggesting the intraoperative and postoperative diuretic actions of Dex in patients undergoing intraspinal anesthesia. Patients receiving cesarean sections are likely to develop hypopotassemia because of preoperative fasting, postoperative potassium-free fluids infusion and postpartum sweating due to pain and tension. The current study did not show any significant differences in serum levels of potassium between group A and group B before induction of anesthesia, immediately or 24 hours after cesarean sections ($p > 0.05$), indicating that administration of Dex during and

after cesarean sections may increase the urine volume but not affect serum potassium levels remarkably.

Conclusion

Intravenous administration of Dex combined with morphine for post-cesarean analgesia is efficacious in alleviating stress responses in women and leads to minimal analgesia-related adverse events thus achieving better quality of life for both newborn and the mothers in the post-natal period.

Limitations of the study

The current study has some limitations. First, this was a single-center randomized, controlled clinical trial. Further multi-center trials recruiting more participants to validate the findings from this study need to be conducted. Second, present study could not differentiate that lower cortisol and renin serum levels seen in group A after cesarean sections were either because of Dex alone or Dex-morphine combination. Further studies to unravel the mechanism underlying reduced cortisol and renin following Dex administration are required.

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List of Abbreviations

Dex	Dexmedetomidine
HR	Heart rate
OAA/S	Observer assessment of alertness/sedation scale
PCA	Patient-controlled analgesia
SD	Standard deviation
VAS	Visual analog scale

Conflict of interest

None to declare.

Grant support and financial disclosure

None to disclose.

Ethical approval

This study was approved by the Ethics Committee of the Jiangyin People's Hospital, China vide Approval No. 2017-022 dated 01-03-2017. This study was registered in Chinese Clinical Trial Registry (ChiCTR-IOR-17010423).

Author's contribution

The author takes full responsibility of conception, design, drafting and approval of the final version of the manuscript to be published.

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