Original Article

Preperitoneal postcesarean section bupivacaine analgesia: Comparison between dexamethasone and dexmedetomidine as adjuvants

ABSTRACT

Background: The peritoneal wound is frequently neglected during laparotomy. The preperitoneal local anesthetics and many adjuvants were effective for postcesarean analgesia. Analgesia may involve somatic and autonomic components. The preperitoneal bupivacaine and the promising adjuvants dexamethasone or dexmedetomidine were compared in this study.

Patients and Methods: Sixty patients subjected to a cesarean section (CS) under general anesthesia divided into two groups using a bolus of preperitoneal bupivacaine 0.7 mg/kg with either 1ug/kg dexmedetomidine (Group P) or 8 mg dexamethasone (Group D). The time to the first analgesic request was the primary outcome.

Results: There was a significantly prolonged time to the first analgesic request in the Group P than the Group D and less required preperitoneal injections in the Group P, also pain assessed by Numerical Rating Scale (NRS) was lower in the Group P than the Group D after 6 h postoperatively up to 24 h.

Conclusions: Dexmedetomidine provided better analgesia than dexamethasone as an adjuvant to preperitoneal bupivacaine post-CS.

Key words: Analgesia; cesarean section; dexamethasone; dexmedetomidine; preperitoneal

Introduction

Cesarean section (CS) delivery is one of the most common operative procedures performed worldwide.[1] Post-CS analgesia enhances early ambulance and mother's ability for breastfeeding and optimal care for her infant immediately postpartum.[2] Unexpectedly, the incidence of acute pain after CS is still high.[3] Post-CS pain treatment involves different strategies; the most challenging target is reducing opioid consumption that may be achieved by extended nerve blocks implementing the enhanced recovery protocols. Locoregional analgesia represents a component of the multimodal pain management approach that showed benefits after CS.[4] One of these techniques is the wound infiltration that showed the possibility to minimize the use of opioids post-CS.[5] Evidence-based data recommend the use of wound catheter local anesthetic (LA) infusions.[6]

The preperitoneal catheter technique is simple, where the surgeon directly places a multiorifice catheter at the end of the procedure. It is technically efficient with no failure rate,

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offers good analgesia with reduced opioids consumption; in addition, it can be used for several days even on ambulatory basis using portable pumps.[7]

Pain is a complex multifactorial phenomenon. Therefore, the combination of different analgesic techniques and medications acting on different target sites may offer excellent dynamic pain relief and reduced adverse effects.[8] Regional bupivacaine alone is short-lived.[9] Adjuvants may be used to prolong the LA analgesia.[10] Nonsteroidal anti-inflammatory (NSAID) utilization showed efficacy.[11] The administration of steroids was promising.[12] Dexmedetomidine perineural administration prolonged motor block by 87% and increased the time to the first analgesic request by 70% compared with LA alone.[13]

We proposed that preperitoneal dexamethasone and dexmedetomidine can extend post-CS bupivacaine analgesia.

Patients and Methods

This is a randomized double-blind study that was conducted on 60 patients scheduled for elective CS under general anesthesia through Pfannenstiel incision including different parity, presentation, body mass index, and American Society of Anesthesiologists status I-II. This study was approved by the institutional research board (code number R/16.03.90), and the Clinical Trials registry number is PACTR201701002007277.

Exclusion criteria were patient refusal, the patients with toxemia of pregnancy, antepartum hemorrhage, relevant drug allergy, drug abuse, psychiatric disorders, communication difficulties, and inability for peritoneal closure.

Using *a priori* G-power analysis with the time till the first analgesic request as the primary objective, based on 95% confidence interval, type 1 error protection of 0.05 and an effect size convention of 0.8 yield a total sample size of 56 (28 patients in each group) produced a power of 90%. However, we recruited sixty cases to overcome the possibility of drop out cases about 5% (thirty patients in each group).

All patients were evaluated for medical history, laboratory data, clinical physical, and airway examination, training for Numerical Rating Scale (NRS), consent signing, and preoperative hydration using 500 ml Ringer's solution.

Patients were randomly allocated using sealed envelopes into two groups according to the adjuvant used. During repositioning of the exteriorized uterus, the envelope is opened by an anesthetist not involved in the anesthetic management during surgery or postoperative assessments to prepare the study drugs in the anesthesia room next to the operating theatre. A mixture of 20 ml contains bupivacaine 0.7 mg/kg with the assigned adjuvant either:

- Group (P): Added 1 microgram (μg) /kg Dexmedetomidine (Precedex®, Hospira, Inc., Lake Forest, IL), or
- Group (D): Added 8 mg dexamethasone.

All participants received standardized general anesthesia, included induction of anesthesia with propofol (2 mg/kg), succinyl choline (1 mg/kg), and endotracheal intubation. Maintenance using atracurium and sevoflurane 1%–2% in 60% air in oxygen. Intravenous nalbuphine 0.3 mg/kg after delivery, maximum of 20 mg.

Before wound closure, the anesthetist will prepare an epidural catheter by doing perpendicular perforations in addition to the already present ones, using syringe needle one centimeter apart in a length suitable for the wound.

After the closure of the peritoneum, the obstetrician (single, experienced clinician) will insert the catheter on the peritoneum (under the transversalis fascia) through a Touhi needle few centimeters from the lower edge of the wound. A bolus of 10 mL saline solution is injected as a test, then the catheter is secured to the skin. After closure of the above layers till the skin, the blindly prepared mixture is injected through the bacterial filter before wound dressing to assess for any leakage.

On patient first request for analgesia, 20 ml bupivacaine 0.25% is injected through the preperitoneal catheter. After 20 min, pain is assessed by Numerical rating scale (NRS) from 0 to 10, with 10 as the worst pain. If NRS $\geq$4, a NSAID-ketorolac (Ketolac® Amriya. Alexandria) 30 mg intravenous is given. If pain still $\geq$3, nalbuphine 5 mg increments are given until NRS is $\leq$2. Then, preperitoneal injection to be repeated again if NRS is $\geq$4. The time to the first analgesic request, the number of preperitoneal injections, ketorolac and nalbuphine consumption were recorded within the first 24 h postoperatively. Mean arterial blood pressure, heart rate (HR), and (NRS) were assessed every 2 h for 12 h, then every 6 h till 24 h. The quality of sleep was assessed after 24 h using 0–10 visual analog scale, with 10 is the worst.

Side effects such as nausea, vomiting, and sedation were recorded through the first 24 h postoperatively. Anti-emetics; Metoclopramide 10 mg. If no response, Ondansetron 4 mg was given.

The incidence of wound infection through 2 weeks postoperatively was recorded.

Statistics analysis

The statistical analysis of data was done using Statistical Package for Social Science (SPSS Inc, Chicago, IL, USA) program version 16. To test the normality of data distribution, Shapiro–Wilk test was used. The unpaired Student's *t*-test was used for comparisons of parametric variables. For nonparametric data, the Mann–Whitney test was used. Chi-square test was used for qualitative data. Data are displayed as mean (± standard deviation) for parametric data, frequency, and proportion for nonparametric data. A difference in probability (*P*) <0.05 was considered statistically significant at a confidence interval 95%.

Results

A total of 60 patients were enrolled, allocated, and analyzed in this study. The peritoneum was closed successfully in all patients. There were no significant differences for patient's characteristics [Table 1].

Results showed a highly significant prolonged time to the first analgesic request in Group P in relation to Group D [Table 1]. During the first 24 h postoperatively, the number of preperitoneal required injections was significantly less in Group P [Table 1]; where three-quarters (74.2%) of the patients in Group P required one injection only [Figure 1], while 95% of patients in Group D required 2–3 injections. The quality of sleep was not different between the groups [Table 1].

Ketorolac and nalbuphine dose requirements were not different between the groups ($P > 0.05$), but most of the patients (two-thirds) required only 30 mg ketorolac in both groups. A quarter of the patients required no ketorolac of Group P, while a quarter required 60 mg dose of Group D [Figure 2].

It is observed that two-thirds (about 66%) of all the patients showed opioid free analgesia postoperatively [Figure 3].

Table 1: Patients demographic data in mean±standard deviation, and postoperative analgesia characteristics in median (range)

	Group P ($n=30$)	Group D ($n=30$)	*P*
Age (years)	28±9	28±10	0.890
BMI (kg/m^2)	29±4.8	28±4.5	0.590
Time to first request of analgesia (h)	7 (4-12)*	4 (2-8)	0.001
Number of preperitoneal injections	1 (0-2)*	3 (2-4)	0.001
Sleep quality (scale 0-10), 10 is worst	2 (0-4)	3 (2-4)	0.173

*Significant difference between Groups P and D. BMI: Body mass index

Pain scores (NRS) were significantly lower in Group P than Group D starting 6 h postoperatively up to 24 h [Figure 4]. In all patients, the mean pain scores ranged from 1.45 to 3.

Hemodynamically, the HR was significantly lower in Group P only in the first 6 h postoperatively, while the MBP showed no significant difference [Figure 5]

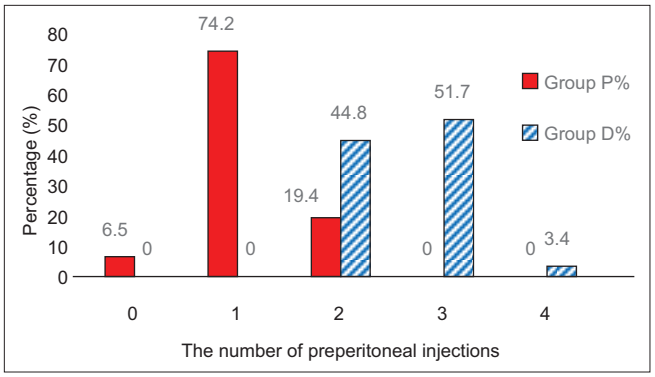

Figure 1: The frequencies of required preperitoneal injections in the first 24 h postoperatively

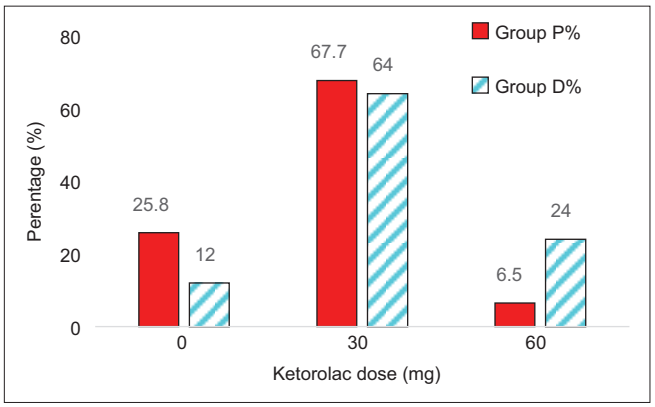

Figure 2: Ketorolac required dose frequencies in the first 24 h postoperatively

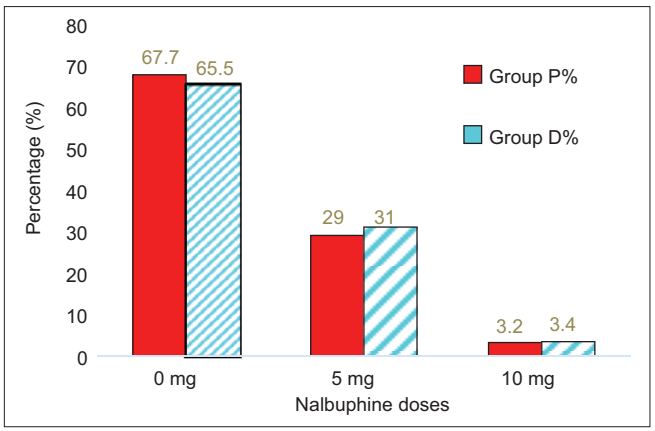

Figure 3: Dose requirements frequencies of nalbuphine in mg during the first 24 h postoperatively

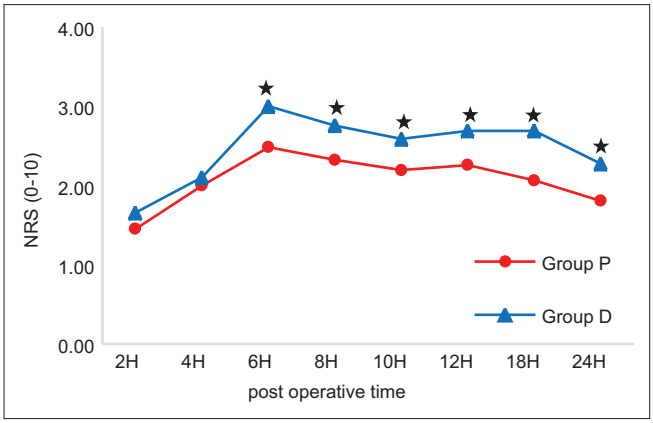

Figure 4: The mean numerical pain rating scale (NRS) in the first 24 h postoperatively. *Significant difference between Group P and D. *P* < 0.05

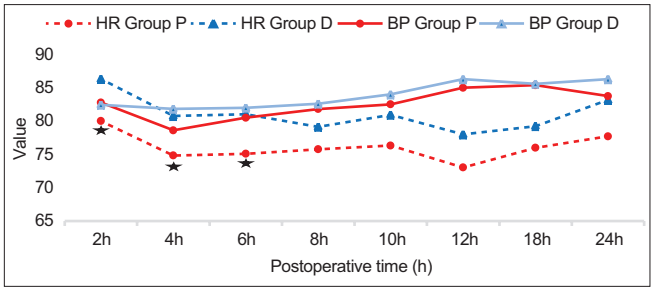

Figure 5: The mean heart rate in beat/min. and the mean arterial blood pressure in mmHg during the first 24 h postoperatively. *Significant HR difference between Group P and D. *P* < 0.05

There was no significant difference ($P = 0.76$) in the incidence of vomiting between Group P (13.9%) and Group D (10.3%) or doses of antiemetics. Sedation was minimal in both groups. There is no reported wound infection.

Discussion

This study showed an effective postcesarean preperitoneal analgesia that was superior using dexmedetomidine (P) than dexamethasone (D) as an adjuvant. Only few studies recently reported improved analgesia after preperitoneal LA with dexamethasone[14] as well as dexmedetomidine.[15] Preperitoneal bupivacaine provided also effective analgesia and enhanced postoperative recovery.[16] Although preperitoneal analgesia is a promising simple technique, yet there is conflicting reports about its efficacy.[7] The explanation of this conflict may be related to single injection rather than infusion,[17] and the suprafascial rather than the more effective subfascial preperitoneal position between transversalis fascia and the peritoneum,[11] and it may also be related to the dose.[18]

The peritoneal contribution to preperitoneal analgesia

The exact mechanism of preperitoneal analgesia is not defined. Both somatic and visceral anti-nociceptive effects may be implicated. LA in the preperitoneal space act locally on specific peritoneal pain receptors,[19] blocking afferents of the fascia and the peritoneum thus reducing pain, hyperalgesia, and diaphragmatic dysfunction.[20]

Anatomically, the abdominal nerves communicate extensively, encroaching medially to enter the rectus sheath through the lateral margin of the linea semilunaris, then approach the posterior surface of rectus abdominis as a plexus that run craniocaudally around the deep inferior epigastric artery. Below the semicircular line of Douglas, the rectus sheath is deficient, leaving the rectus muscle in direct contact with the fascia transversalis and the peritoneum.[21] When a contrast medium is injected preperitoneally, it remained in the space between transversalis fascia and peritoneum.[11] The parietal peritoneum and overlying muscles are innervated by the segmental spinal nerves from T7 to L1.[22] The visceral peritoneum is innervated by the vagus nerves and sympathetic fibers. Its stimulation mediates poorly localized discomfort and profound reflex autonomic and emotional reactions.[23] Visceral sensations reach the brain mostly through afferent vagal fibers.[24]

Indeed, the peritoneum is an active organ, not a passive container.[25] If the peritoneum is manipulated during laparotomy, it reacts by initiating acute local and systemic inflammatory response involving various mediators that act directly on the vagal afferents mediating pain.[26] Furthermore, these mediators induce peripheral and central sensitizations contributing to pain and hyperalgesia.[27]

The prevention of neuron sensitization by multimodal analgesia reduces postsurgical pain,[28] an effect that may extend after stopping LA "preventive analgesia."[29] That may explain extended lower pain scores in Group P in this study 24 h postoperatively. Therefore, local preperitoneal or intraperitoneal chemical afferentectomy may serve to block vagal afferents thus reducing sensitization.[30,31] Consequently, that may contribute to enhanced patients recovery,[31] where the somatic and peritoneal abdominal wounds predispose to autonomic disturbance, catabolic response, fatigue, anorexia, and disturbed sleep rhythm postoperatively.[24]

Pharmacologic contribution to preperitoneal analgesia

In addition to block of nociception, LAs possess also a systemic anti-inflammatory effect,[30] and block the visceral sensitization at medullar neurons.[32] Glucocorticoids[33] as well as dexmedetomidine[34] provide also an anti-inflammatory effect.

The exact mechanism of topical dexmedetomidine (P) analgesia is not well understood. It may extend the duration of LA by local vasoconstriction through an action on $\alpha 2$ adrenoreceptors subtypes.[35] Peripheral $\alpha 2$ receptors are expressed on peripheral sensory neurons and are involved in peripheral analgesia.[36] Dexmedetomidine (P) alone did not provide a significant sensory or motor blockade, but potentiates LA action about 75%, due to blockade of the hyperpolarization-activated cation (I_h) current, not through $\alpha 2$ action.[37] Similar to clonidine, (P) peripheral analgesia may be through release of an encephalin-like substance.[38]

Comparison with other analgesia modalities

Different modalities of post-CS analgesia were applied, but opioids still the gold standard, tranversus abdominis plane (TAP) block is the most investigated, while wound infiltration requires further evaluation.[39] Intrathecal morphine efficiently reduces post-CS pain but involves numerous side effects.[40]

Comparative to other regional analgesic techniques for laparotomy, the epidural is the gold standard but may not be the first choice post-CS owing to possible delayed ambulation of mothers.[41] Furthermore, it may be associated with hypotension, urine retention, inadequate distribution, and epidural hematoma.[42] Particularly with the presence of contraindications to epidural, the preperitoneal analgesia became an interesting alternative with equivalent pain control and lower complications.[43]

Post-CS analgesia using TAP block may be equally effective with wound infiltration,[44] but lacking visceral effects and may be associated with possible visceral damage and high-plasma concentration of LA.[45]

In agreement with other investigators,[5] applying multimodal analgesia and preperitoneal technique in this study are associated with beneficially opioid-free analgesia in about two-thirds of patients.

Preperitoneal technique

We used multiorifice epidural catheter where the standard catheter is not available in our country. The preperitoneal infusion was not applied in this study because the high pressure pumps also not available, and for comparison between adjuvants as reflected by the time to the first analgesic request. The extended effects due to adjuvants may preclude infusion.

There is no standard preperitoneal regimen. In this study, we used 20 ml bupivacaine 0.25% provided a median pain scores ranged 1.45–3. No patients had score zero also using 0.25% bupivacaine at 6 ml/h.[16] Ozturk *et al*. recorded a score zero using 0.2% ropivacaine at 10 ml/h.[46]

Despite the promising preperitoneal analgesia, a limitation raised, where the required peritoneal closure may be associated with more pain and adhesions compared to non-peritoneal closure.[47] When closure is difficult, alternatively, the preperitoneal tunneled catheter technique can be used.[48]

Our results revealed mild bradycardia in the Group P for the first 6 h compared with Group D. That may correlate with longer analgesia in the Group P, where the first request for analgesia was after 7 h or may be a systemic (P) action. No hypotension or bradycardia was evident using dexmedetomidine in Ayse *et al*. study in spite of using 2 mcg/kg but in hysterectomy patients.[15]

Conclusions

This study showed that dexmedetomidine provided better analgesia than dexamethasone as an adjuvant to preperitoneal bupivacaine post-CS. Implementing this technique, opioid-free analgesia could be achieved in two-thirds of patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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