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ORIGINAL ARTICLE

Effect of mini-dose epidural dexmedetomidine in elective cesarean section using combined spinal–epidural anesthesia: a randomized double-blinded controlled study

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Abstract
Background Combined spinal–epidural anesthesia is commonly used for elective cesarean section. Our study aimed to evaluate the effect of adding dexmedetomidine to epidural bupivacaine and fentanyl in patients undergoing elective cesarean section using combined spinal–epidural anesthesia.
Methods Eighty healthy women at term were randomly assigned to two groups: a control group ($n = 40$; "Bup/Fen group") received combined spinal–epidural anesthesia with intrathecal hyperbaric bupivacaine 5 mg and an epidural mixture of 10 mL plain bupivacaine 0.25 % and fentanyl 50 μg, whereas the study group ($n = 40$; "Dex/Bup/Fen group") received 1 mL epidural dexmedetomidine 0.5 μg/kg in addition. The primary outcome measure was the difference between the groups in the supplementary fentanyl analgesic required. The quality of surgical anesthesia, incidences of hypotension and bradycardia, APGAR scores, intraoperative pain assessment, and onset of postoperative pain, sedation score, and side effects were recorded.
Results There was no statistically significant difference between the groups regarding block characteristics. Significantly less intraoperative and postoperative fentanyl were required by the Dex/Bup/Fen group ($P = 0.015$ and $P = 0.0011$, respectively). There was no statistically significant difference between the groups regarding sedation score or the incidences of hypotension, nausea and vomiting, dizziness, and pruritus.
Conclusions The addition of mini-dose epidural dexmedetomidine 0.5 μg/kg as a single injection to bupivacaine fentanyl in women undergoing elective cesarean section with combined spinal–epidural anesthesia improved intraoperative conditions and the quality of postoperative analgesia.

Keywords Dexmedetomidine · Combined spinal–epidural anesthesia

Introduction

Neuraxial anesthesia is the preferred choice for cesarean section since it allows the parturient to remain awake and participate in the birth of her baby whilst avoiding the risks of general anesthesia [1]. The main disadvantages of routine epidural anesthesia for cesarean delivery are the delayed onset of surgical anesthesia, sacral root block is difficult to achieve in about 25 % of cases, and muscle relaxation is not adequate, especially for the delivery of a large baby. Therefore, combined spinal–epidural (CSE) anesthesia for cesarean delivery has gained in popularity as it circumvents the drawbacks mentioned above [2, 3].

The current practice in obstetric anesthesia is to combine local anesthetics with adjuvant drugs in reduced doses to improve the quality of intraoperative and postoperative anesthesia, aid early ambulation and recovery from motor block, and reduce the incidence of associated side effects. Among the various agents employed are opioids and alpha-2 adrenergic agonists [4].

Dexmedetomidine is a highly selective α_2 agonist that provides some beneficial effects when administered

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through an epidural route: sedation, analgesia, anti-anxiety effects, and sympatholysis associated with hemodynamic stability [5, 6].

The purpose of the study reported in this paper was to evaluate the effect of adding mini-dose epidural dexmedetomidine to epidural bupivacaine fentanyl on the quality of intraoperative anesthesia and postoperative analgesia in women undergoing an elective cesarean section using the CSE technique.

Methods

The study was approved by the Investigational Review Board of the Faculty of Medicine, Tanta University; informed consent was obtained from all patients who participated in the study. This study is registered in the Pan African Clinical Trail Registry with the unique identification number PACTR201209000409253.

Eighty healthy 18- to 40-year-old parturients at term with an American Society of Anesthesiologists physical status of I or II (ASA I, II) were randomly allocated to two equal groups. The parturients were scheduled for elective cesarean section and wished to be conscious during cesarean delivery. Patients with pre-existing pregnancy-induced hypertension requiring treatment, hepatorenal or other end organ disease, twin pregnancy, placenta previa, placenta accreta and percreta, patients who had received an opioid agonist or agonist/antagonist in the preceding 6 h (or within 1 h if given intravenously), morbidly obese (BMI > 38 kg/m^2) patients, and those who were very short or very tall (<140 or >180 cm) were excluded from the study. Patients who were in active labor and those who were contraindicated for neuraxial block were also excluded.

A simple randomized double-blind design was used, with the patients, the anesthesiologist, and the medical assessors involved in patient care blinded to the management protocol and patient group allocations. Randomization was performed by generating random numbers that were placed in sealed envelopes. The operating theater nurse used the sealed envelopes to allocate each participating patient to one of the groups, and an independent anesthesiologist who did not participate in the study or data collection read the number contained in the envelope and prepared unlabeled syringes containing the study drugs.

Patients received oral ranitidine 150 mg the night before and on the morning of surgery. The second dose was given with oral metoclopramide 10 mg. In the operating theater, patients were monitored using electrocardiogram, a pulse oximeter, and a noninvasive blood pressure device. A fluid preload of 500 mL lactated Ringer's solution was given, and baseline blood pressure and heart rate were recorded in the left wedged supine position.

In the sitting position, CSE anesthesia was performed with a needle-through-needle technique at the L2–3 interspace using a midline approach (Epi-Star CSE, Maxi-Set, Kemen, Germany). The epidural space was located using loss of resistance to air with an 18-gauge Tuohy needle, and dural puncture was achieved with a 27-gauge pencil point needle. After confirmatory aspiration of cerebrospinal fluid, 1 mL of 0.5 % (5 mg) hyperbaric bupivacaine was injected intrathecally. The spinal needle was withdrawn and 12 mL of the study solution were administered via the epidural needle. This study solution was 10 mL 0.25 % plain bupivacaine and 1 mL 0.9 % sodium chloride plus 1 ml fentanyl 50 μg (for the Bup/Fen group) or 10 mL 0.25 % plain bupivacaine and 1 mL dexmedetomidine 0.5 μg/kg plus 1 ml fentanyl 50 μg (for the Dex/Bup/Fen group).

The highest level of sensory block (S_{max}) and the time taken to reach S_{max} were recorded. Sensory blockade was tested by pinprick on the midclavicular line bilaterally every minute during the first 5 min, and then every 5 min. Similarly, motor blockade of the lower extremities was assessed using the modified Bromage score [7]: BS0, full flexion of hip, knee, and ankle; BS1, impaired hip flexion; BS2, impaired hip and knee flexion; BS3, unable to flex hip, knee, or ankle. Complete motor block was defined as BS3. Time intervals from intrathecal injection to readiness for surgery, from skin incision to delivery, and from uterine incision to delivery were recorded.

Hypotension was defined as a fall in blood pressure of 20 % from pre-induction levels or a systolic blood pressure of <100 mmHg, and was treated immediately with 5 mg ephedrine by intravenous injection. Bradycardia was defined as a decrease in the heart rate to <50 beats/min, and was treated immediately with 0.5 mg atropine by intravenous injection.

Sedation was assessed using a 5-point numerical sedation scale (grade 0: fully awake, 1: calm, 2: awake on verbal command, 3: awake on gentle tactile stimulation, 4: awake on vigorous stimulation, and 5: unarousable).

Surgery was performed by one of two experienced obstetricians. They were blinded to the allocation group, and assessed muscle relaxation as poor, fair, good, or excellent.

Intraoperative and postoperative pain for the first 24 h were assessed on a 10-cm visual analog scale (VAS) in which 0 represented no pain and 10 represented the worst possible pain. The VAS was measured every 15 min during the intraoperative period and every 4 h during the postoperative period by an independent anesthesiologist who was unaware of the patient allocation group. All patients received 15 mg/kg i.v. acetaminophen every 6 h; the first dose was given before completion of surgery. If the patient complained of pain (defined as VAS > 4), intravenous

rescue fentanyl was given in 50-μg increments. Patients with VAS < 4 were given an acetaminophen infusion.

The primary outcome measure was difference between groups in the supplementary fentanyl analgesic required. Adverse effects such as hypotension, bradycardia, nausea and vomiting, and pruritus were also recorded during the 24 h immediately after the operation.

All neonates were evaluated by a pediatrician who was unaware of which patients were assigned to each group. APGAR scores at 1 and 5 min were recorded. The need for neonatal oxygen therapy was noted. Breastfeeding was prevented for the 24 h immediately after surgery.

Following surgery, patients were nursed in the post-anesthesia care unit (PACU). Recovery from motor block was defined as the time from the injection of epidural solution to BS0. The onset of postoperative pain, defined as the time from the completion of surgery to the onset of VAS > 4, was recorded.

Statistical analysis

Continuous data are presented as the mean (±SD). Parametric data were analyzed using Student's *t* test, while non-parametric data were analyzed using the Mann–Whitney *U* test and categorical data were assessed with the χ^2 test. A *P* value of <0.05 was considered significant. A sample size analysis was performed using the Epi Info 2002 software package created by the Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA).

Sample size analysis

The sample size analysis performed using Epi Info 2002 indicated that 37 patients were needed per group to detect a between-group difference of at least 20 % in fentanyl consumption with a power of 80 %, α of 0.05, and an allocation ratio of 1:1 (based upon a pilot study).

Results

A total of 145 women were surveyed for their eligibility. Of these, 30 did not meet the inclusion criteria and 35 refused to participate in the study. The 80 remaining women were randomized into two equal groups (Fig. 1). The two groups had similar characteristics with regard to age, height, weight, parity, gestational age, and duration of surgery (Table 1).

There was no statistically significant difference between the groups in the time needed for the block to reach T4, the time interval between anesthesia and the onset of surgery, the time taken to reach the highest level of sensory black (S_{max}), the time from skin incision to delivery time, the time from uterine incision to delivery time, the time taken

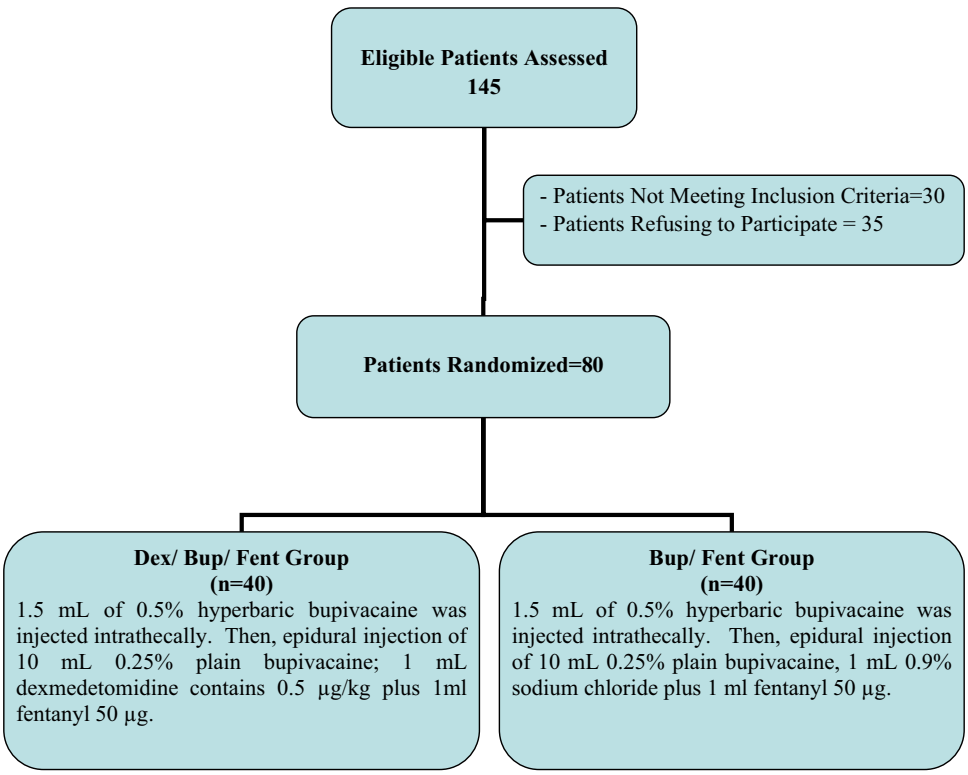

Fig. 1 Patient flow throughout the study

Table 1 Patient characteristics in both groups

	Dex/Bup/Fen group ($n = 40$)	Bup/Fen group ($n = 40$)	t value (from t test) or χ^2	P value
Age (years)	28.5 ± 5.7	26.9 ± 6.4	1.181	0.2413
Height (cm)	165 ± 14.8	162 ± 13.6	0.944	0.3481
Weight (kg)	87.4 ± 9.9	85.6 ± 2.1	1.125	0.2641
Parity: nulliparous/parous	10/30	11/29	0.06	0.799
Gestational age (week)	38.75 ± 0.1	38.6 ± 0.15	1.762	0.627
Duration of surgery (min)	50.4 ± 4.9	52.8 ± 6.2	1.921	0.584

Data are the mean ± standard deviation or number of patients (%)

Dex/Bup/Fen group dexmedetomidine/bupivacaine/fentanyl group, *Bup/Fen group* bupivacaine/fentanyl group

Table 2 Block characteristics of both groups

	Dex/Bup/Fen group $n = 40$	Bup/Fen group $n = 40$	χ^2 test or t test	
			t or χ^2	P value
Block characteristics				
Time to reach sensory block (min)	5.4 ± 1.4	5.8 ± 1.2	1.372	0.174
Time to reach S_{max} (min)	7.5 ± 1.5	8.1 ± 1.7	1.674	0.098
Time to readiness for surgery (min)	6.4 ± 1.3	7.5 ± 1.6	3.375	0.12
Time from skin incision to delivery time (min)	9.2 ± 3.7	9.9 ± 3.4	1.845	0.945
Time from uterine incision to delivery time (min)	1.34 ± 0.57	1.46 ± 0.32	2.273	0.872
Time to recovery from motor block (min)	148 ± 36	133.5 ± 40	1.801	0.075
Grade of muscle relaxation				
Excellent	23 (57.5 %)	25 (62.5 %)	0.238	0.8878
Good	12 (30 %)	11 (27.5 %)		
Fair	5 (12.5 %)	4 (10 %)		

Data are the mean ± standard deviation or number of patients (%)

Dex/Bup/Fen Group dexmedetomidine/bupivacaine/fentanyl group, *Bup/Fen group* bupivacaine/fentanyl group

to recover from motor block, or the grade of muscle relaxation (Table 2).

The intraoperative fentanyl requirement was significantly lower in the Dex/Bup/Fen group: two women required fentanyl supplementation in comparison to 11 patients in the Bup/Fen group ($P = 0.015$). The postoperative fentanyl requirement was significantly lower in the Dex/Bup/Fent group: four women required fentanyl supplementation compared to 18 patients in Bup/Fent group ($P = 0011$). The total fentanyl requirement was significantly lower in the Dex/Bup/Fent group. The mean total fentanyl requirement was significantly lower in the Dex/Bup/Fent group (12 ± 3.5 μg) than in the Bup/Fent group (56.25 ± 14.6 μg) ($P = 001$). The mean time to first rescue fentanyl administration was 185 ± 47 min in the Bup/Fent group and 435 ± 68 min in the Dex/Bup/Fen group ($P = 0.003$) (Table 3).

There was no statistically significant difference between the groups regarding sedation score: a higher number of patients were rated grade 0 in the Bup/Fent group, while a higher number of patients were rated grade 1 on the sedation scale in the Dex/Bup/Fent group, but these differences were not statistically significant ($P = 0.125$) (Table 4).

There was no statistically significant difference between the groups regarding the incidences of hypotension, nausea and vomiting, dizziness, and pruritus (Table 5).

There was no statistically significant difference between the groups in neonatal outcome regarding APGAR scores at 1 and 5 min.

Discussion

Patients who received epidural dexmedetomidine in addition to a standardized CSE dosage regimen achieved better intraoperative conditions in addition to better postoperative analgesia. The use of this novel mini-dose of dexmedetomidine has a double benefit: it allows

Table 3 Supplementary analgesia in both groups

Supplementary fentanyl	Dex/Bup/Fen group ($n = 40$)	Bup/Fen group ($n = 40$)	χ^2 or t test	
			χ^2 or t	P value
Intraoperative fentanyl consumption, number (%)	2 (5 %)	11 (27.5 %)	5.878	0.015
Postoperative fentanyl consumption, number (%)	4 (10 %)	18 (45 %)	10.596	0.0011
Total fentanyl consumption, number (%)	5 (12.5 %)	22 (55 %)	16.16	0.001
Mean total fentanyl usage (μg)	12 ± 3.5	56.25 ± 14.6	10.215	<0.001
Time to first rescue fentanyl administration, mean value (min)	435 ± 68	185 ± 47	9.452	0.003

Data are the mean ± standard deviation or number of patients (%)

Dex/Bup/Fen group dexmedetomidine/bupivacaine/fentanyl group, *Bup/Fen group* bupivacaine/fentanyl group

Table 4 Intraoperative sedation scores in both groups

Intraoperative sedation score	Dex/Bup/Fen group ($n = 40$)	Bup/Fen group ($n = 40$)
Grade 0	8 (20 %)	17 (42.5 %)
Grade 1	25 (62.5 %)	19 (47.5 %)
Grade 2	4 (10 %)	2 (5 %)
Grade 3	3 (7.5 %)	2 (5 %)
Grade 4	0	0
Grade 5	0	0
p	0.125	

Data are number of patients (%)

Dex/Bup/Fen group dexmedetomidine/bupivacaine/fentanyl group, *Bup/Fen group* bupivacaine/fentanyl group

hemodynamic instability such as hypotension and bradycardia produced by a large dose of dexmedetomidine or a prolonged motor blockade to be avoided, and it provides prolonged postoperative analgesia without producing intense sedation.

Although epidural fentanyl produces lower incidences of side effects such as respiratory depression, urinary retention, and nausea and vomiting, the rapidity of its analgesic effect and its relatively short duration of action necessitate the use of patient-controlled epidural analgesia, which is not always suitable in certain circumstances, such as low economic status and for poorly educated and uncooperative patients. There is an unmet need for the use of alternative drugs to fentanyl, or its use in combination with an alpha-2 adrenergic agonist [8, 9].

Alpha-2 adrenergic agonists and opioids act through different mechanisms, so a combination of them will produce synergistic analgesic effects without increasing the drawbacks associated with opioid use [10]. Because the analgesic effect of alpha-2 adrenergic agonists is mostly mediated at spinal level, neuraxial administration is preferred for dexmedetomidine [11, 12]. A previous study demonstrated enhanced anesthetic action due to vasoconstriction around the site of injection, resulting in delayed absorption of the local anesthetic and consequently a prolonged duration of action, or the direct inhibition of peripheral neuronal activity [13]. Konacki et al. [14] experimentally observed a potential neurotoxic effect of epidural dexmedetomidine in the form of demyelinization of oligodendrocytes in the white matter, which could be explained by the tenfold greater dose of epidural dexmedetomidine (5 μg/kg) used in their study than in ours (0.5 μg/kg). The dose applied in our study was previously used without any recorded side effects [15]. However, dexmedetomidine is highly lipophilic, so it is retained in the placental tissue and a minimal amount is transferred to the fetus, leading to a small risk to the fetus [16].

Table 5 Incidences of various side effects in both groups

	Dex/Bup/Fen group ($n = 40$) (%)	Bup/Fen group ($n = 40$) (%)	χ^2 test	
			χ^2	P value
Hypotension	10 (25)	8 (20)	0.287	0.592
Bradycardia	7 (17.5)	5 (12.5)	0.392	0.531
Nausea and vomiting	3 (7.5)	4 (10)	0.157	0.692
Pruritus	3 (7.5)	2 (5)	0.213	0.644
Dizziness	2 (5)	1(2.5)	0.346	0.556

Data are number of patients (%)

Dex/Bup/Fen group dexmedetomidine/bupivacaine/fentanyl group, *Bup/Fen group* bupivacaine/fentanyl group

The use of epidural dexmedetomidine in combination with local anesthetic prolongs the durations of both sensory and motor blockade and postoperative analgesia [17]. The use of epidural dexmedetomidine in conjunction with general anesthesia reduces intraoperative anesthetic requirements and improves oxygenation [18].

Various clinical studies [8, 18] have used the epidural administration of dexmedetomidine in higher doses ranging from 1 to 2 μg/kg. These high doses had a beneficial effect in the form of enhanced local anesthetic action and improved intraoperative and postoperative analgesia, but they also had unwanted side effects in the form of prolonged motor block, bradycardia, and hypotension.

The use of epidural dexmedetomidine [18] produced early sensory blockade and complete motor blockade with prolonged postoperative analgesia in patients undergoing abdominal and lower limb surgeries. Bajwa et al. [8] observed that epidural dexmedetomidine resulted in earlier onset of sensory analgesia, excellent motor blockade, and prolonged postoperative analgesia in patients who underwent vaginal hysterectomy.

Jain et al. [19] demonstrated that the use of epidural dexmedetomidine prolongs the duration of analgesia and decreases the requirement for rescue analgesic in patients undergoing lower-limb orthopedic surgery.

Epidural dexmedetomidine was used to achieve an intraoperative reduction of hemodynamics in previous studies [8, 19]. These studies used up to fourfold high doses of dexmedetomidine 2 μg/kg and consequently demonstrated decreases in mean arterial blood pressure and heart rate, in contrast to the small dose of epidural dexmedetomidine used in our study (0.5 μg/kg), which maintained patient hemodynamic stability.

There has been much debate regarding problems with breastfeeding after epidural anesthesia. Unfortunately, there are no published studies on the safety of breastfeeding after epidural dexmedetomidine when used as an adjunct in labor analgesia, so we decided that breastfeeding should be avoided during the 24 h immediately after surgery [20].

Conclusion

The addition of mini-dose epidural dexmedetomidine 0.5 μg/kg as a single injection to bupivacaine fentanyl in women undergoing elective cesarean section with combined spinal–epidural anesthesia improved intraoperative conditions and the quality of postoperative analgesia.

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Conflict of interest All authors declare that they have no conflict of interest.

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