Egyptian Journal of Anaesthesia (2014) 30, 353–357

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Egyptian Journal of Anaesthesia

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Research Article

# Dexmedetomidine improves intraoperative conditions and quality of postoperative analgesia when added to epidural in elective cesarean section

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Received 12 February 2013; accepted 19 March 2014
Available online 26 April 2014

**KEYWORDS**

Combined spinal–epidural anesthesia;
Epidural dexmedetomidine;
Elective cesarean section

**Abstract** *Introduction:* This study was designed to evaluate the effect of adding dexmedetomidine to regular mixture of epidural drugs for pregnant women undergoing elective caesarian section with special emphasis on their sedative properties, ability to improve quality of intraoperative, postoperative analgesia and neonatal outcome.

*Methods:* Fifty women of ASA physical status I or II at term pregnancy were enrolled randomly to receive either plain bupivacaine plus fentanyl (BF group) or plain bupivacaine plus mixture of fentanyl and dexmedetomidine (DBF group). Incidence of hypotension, bradycardia, Apgar scores, intraoperative pain assessment, onset of postoperative pain, sedation scores and side effects were recorded.

*Results:* No difference in the times taken for block to reach T4 sensory level, to reach the highest level of sensory block and interval between first neuraxial injection and onset of surgery between the groups. Onset of postoperative pain was significantly delayed in the DBF group ($P = 0.001$), the need for supplementary fentanyl was significantly less in DBF group ($P = 0.03$), and no significant difference was obtained between both groups regarding neonatal Apgar scores as well as the incidence of hypotension, bradycardia, nausea, vomiting and duration of motor blockade between the groups. DBF group had significantly less incidence of shivering ($P = 0.03$).

*Conclusion:* Adding dexmedetomidine to regular mixture of epidural anesthetics in women undergoing elective cesarean section improved intraoperative conditions and quality of postoperative analgesia without maternal or neonatal significant side effects.



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Peer review under responsibility of Egyptian Society of Anesthesiologists.

1110-1849  http://dx.doi.org/10.1016/j.egja.2014.03.004

## 1. Introduction

Regional anesthesia is preferred for cesarean section since it allows a parturient to remain awake and participate in the birth of her baby while avoiding the risks of general anesthesia [1]. The combined spinal–epidural (CSE) technique is frequently used to provide anesthesia and analgesia for labor and delivery [2]. To improve the quality of intraoperative anesthesia, postoperative analgesia and aid early ambulation and recovery of motor block, several agents have been employed such as opioids and α-2 adrenergic agonist. Some recent placebo-controlled studies suggest that α-2 adrenergic agonist has both analgesic and sedative properties when used as an adjuvant in regional anesthesia [3–11].

Dexmedetomidine is a highly selective $\alpha_2$ adrenergic agonist with an affinity of eight times greater than clonidine. The dose equivalence of these drugs had not been studied before, but the observations of various studies have stated that the dose of clonidine is 1.5–2 times higher than dexmedetomidine when used in epidural route [12–17]. The anesthetic and the analgesic requirement get reduced by the use of these two adjuvants because of their analgesic properties and augmentation of local anesthetic effects as they cause hyperpolarization of nerve tissues by altering transmembrane potential and ion conductance at locus coeruleus in the brainstem [18–22]. The stable hemodynamics and the decreased oxygen demand due to enhanced sympatho-adrenal stability make them very useful pharmacologic agents [23,24].

The safety of the use of dexmedetomidine on neonatal outcome is a very important issue. Experimental study on acute exposure of rats to dexmedetomidine at the anticipated delivery time recorded the absence of any adverse effects on perinatal morphology of pups, their birth weight, crown-rump length, physical growth and postnatal behavioral performances and concluded that dexmedetomidine did not affect those parameters [25].

Others studied the transfer of clonidine and dexmedetomidine across the isolated perfused human placenta, and concluded that dexmedetomidine disappeared faster than clonidine from the maternal circulation, while even less dexmedetomidine was transported into the fetal circulation [26].

Some case reports concluded that dexmedetomidine had no harmful effects during cesarean delivery [27–29].

Our hypothesis was that the addition of dexmedetomidine to epidural bupivacaine and fentanyl could improve intraoperative anesthesia and postoperative analgesia in women undergoing elective cesarean section using a CSE technique without significant neonatal side effects.

## 2. Methods

After approval by local research ethics committee, Informed consent was obtained from all patients participating in the study. Healthy (ASA I, II), 21–41 year old women at term were randomly allocated into two groups equally. Computer-generated simple random sampling procedure was used to allocate the subjects. Both nulliparous and multiparous women were included; all were scheduled for elective cesarean section. Exclusions criteria were twin pregnancy, placenta praevia, opioid agonist or agonist/antagonist administration in the preceding 6 h (or within 1 h if given intravenously), obesity (BMI > 38 kg/m$^2$), extremes of height (< 140 or > 180 cm), active labor, history of bleeding diathesis, history or the presence of cardiac, respiratory, hepatic and/or renal failures or those who had contraindications to neuraxial block.

The study drugs were prepared in unlabeled syringes by anesthesia technician not involved in the study who used the randomization protocol to assign participants to their respective groups. Patients were premedicated with 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 operation theater, a good intravenous access was secured and monitoring devices were attached such as electrocardiograph (ECG), pulse oximetry (SpO2), non-invasive blood pressure (NIBP), and respiratory rate. Baseline parameters were recorded. A fluid preload of 500 mL of lactated Ringer's solution was given and baseline blood pressure and heart rate were recorded in the right-wedged supine position. Oxygen at 6 L/min was administered via Hudson face mask.

In the sitting position, CSE anesthesia was performed using a needle-through-needle technique. The epidural space was located using loss of resistance to air with an 18-gauge Tuohy needle. The dural puncture at L3-4 level was achieved with 27-gauge pencil point needle. After confirmatory aspiration of cerebrospinal fluid, 2 mL of 0.5% hyperbaric bupivacaine was injected intrathecally. The spinal needle was withdrawn and a 20-gauge epidural catheter inserted 3–4 cm into the epidural space. The catheter was secured and the patient placed in the supine position with left uterine displacement. All then received 20 mL of study solution via the epidural catheter. This was either 10 mL 0.25% plain bupivacaine plus fentanyl 100 μg in 10 mL 0.9% sodium chloride (BF group) or 10 mL 0.25% plain bupivacaine plus mixture of fentanyl 100 μg and dexmedetomidine 1 μg/kg in 10 mL 0.9% sodium chloride (DBF group). Hypotension, defined as 20% fall in blood pressure from pre-induction levels or a systolic blood pressure lower than 100 mmHg, was treated immediately by intravenous injection of 5 mg ephedrine. The level of sensory block was assessed at 2-min intervals for 30 min after epidural injection using pinprick. The highest level of sensory block (S max) and time taken to reach S max were recorded. Motor block of the lower extremities was assessed at 5 min intervals for 30 min using the modified Bromage score (BS): 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, skin incision to delivery and uterine incision to delivery were recorded. Surgery was performed by one of two consultant surgeons of similar clinical experience, and they were blinded to the allocation group. Intraoperative and postoperative pain were assessed by 10-point verbal rating scale (VRS), in which 0 represented no pain and 10 represented worst possible pain. VRS was measured every 15 min intraoperative and every 4 h postoperatively by an anesthesiologist who was unaware of the patient allocation group. If women complained of pain (defined as VRS > 4), intravenous fentanyl was given in 50 μg increments. The requirement for supplementary analgesia was noted in different groups.

Sedation scores were recorded using five-point scale (1 = completely awake, 2 = awake but drowsy, 3 = asleep

but responsive to verbal commands, 4 = asleep but responsive to tactile stimulus, 5 = asleep and not responsive to any stimulus) [30], Just before the initiation of surgery and thereafter every 15 min during the surgical procedure. Adverse effects such as hypotension, nausea, vomiting and shivering were also recorded. All neonates were evaluated by a pediatrician who was unaware of group assignment. Apgar scores at 1 and 5 min and umbilical cord pH were recorded. The need for neonatal oxygen therapy was noted. Breastfeeding was prohibited for the first 24 h after cesarean delivery. Following surgery, patients were nursed in the postanesthesia care unit (PACU). Recovery from motor block was defined as time from injection of epidural solution to BS0. The onset of postoperative pain defined as the time from completion of surgery to onset of VAS > 4 was recorded.

### 3. Statistical analysis

Data are expressed as mean ± SD or frequency and percentages as appropriate. Unpaired student *t* tests were used to see statistical significance difference for interval variables and chi-square tests or Fisher's exact tests were performed for categorical variables between the groups. *P* value 0.05 (two tailed) was considered statistically significant level. SPSS 19.0 Statistical Package was used for the analysis.

### 4. Results

The demographic profiles of the patients in both the groups were comparable with regard to age, weight and height. The distribution as per ASA status was similar in both the groups and mean duration of surgery was comparable in both the groups ($P = 0.74$) (Table 1).

Table 2 shows that the time needed for the block to reach T4, highest level of sensory block (S max), time interval between anesthesia and onset of surgery and recovery from motor blockade were not significant statistically. The onset of postoperative pain was significantly delayed in the DBF group ($P = 0.001$).

In DBF group all women did not need any supplementary analgesic throughout the operation while in the DF group 6 patients needed supplementary fentanyl ($P = 0.03$) for complaining intraoperative pain or discomfort (defined as VRS > 4).

The postoperative analgesic requirement was significantly reduced in DBF group compared to DF group ($P = 0.01$). Shivering also was significantly reduced in DBF group compared to DF group ($P = 0.03$). Incidence of hypotension, bradycardia, nausea, vomiting, dizziness and pruritus were not significant between the groups (Table 3). There were also no significant differences in neonatal outcomes in both groups.

Sedation scores were significantly higher in DBF group ($P = 0.001$) (Table 4).

### 5. Discussion

Our study emphasized that the addition of dexmedetomidine 1 μg/kg to a standardized CSE dosage regimen (bupivacaine and fentanyl) achieved better intraoperative conditions; improved analgesia and provided good sedation level, prolonged postoperative analgesia and lower incidence of shivering than those who received only bupivacaine and fentanyl.

Epidural dexmedetomidine in dose of 1 μg/kg did not cause significant hemodynamic effects and did not affect neonatal outcome. Dexmedetomidine as adjuvant to bupivacaine and fentanyl achieved better sedation, as forty percent of the patients had sedation in score 3 and were arousable by gentle tactile stimulation compared to no patients in BF group. Sixty percent of the patients remained awake but calm in BF group compared to sixteen percent in DBF group who were equally cooperative and calm. Overall sedation scores were statistically more in dexmedetomidine group (DBF group).

Our data support the previous studies that used dexmedetomidine as additive to regional anesthetics; Salgado et al., in a double blind study conducted in 40 patients undergoing hernia repair or varicose vein surgery; concluded that adding dexmedetomidine 1 μg/kg to epidural ropivacaine increases sensory and motor block duration and prolongs postoperative analgesia, without causing hemodynamic instability [11].

Bajwa et al., compared dexmedetomidine 1.5 μg/kg versus clonidine 2 μg/kg as an additive to epidural ropivacaine in patients scheduled for vaginal hysterectomy. They observed that dexmedetomidine is a better adjuvant than clonidine in terms of intraoperative and postoperative analgesia, patient's satisfaction and cardio-respiratory effects [31].

El-Hennawy et al., compared dexmedetomidine versus clonidine as additive to caudal bupivacaine in children aged

**Table 1** Patients demographic and clinical characteristics.

| | DBF No-25 | BF No-25 | *P* value |
|---|---|---|---|
| Age (years) | 29.8 ± 4.6 | 28.8 ± 4.9 | 0.47 |
| Height (cm) | 167 ± 4.9 | 168.5 ± 4.2 | 0.30 |
| Weight (kg) | 74.6 ± 8 | 75 ± 7.7 | 0.94 |
| Baseline MBP (mmHg) | 74.8 ± 7.9 | 73.8 ± 6.5 | 0.63 |
| Heart rate (beats/min) | 83.2 ± 7.6 | 80.7 ± 9 | 0.30 |
| Duration of surgery (min) | 49 ± 8 | 48 ± 8.5 | 0.63 |
| ASA I/II | 19/6 | 18/7 | 0.74 |

MBP: mean blood pressure, DBF: (dexmedetomidine, bupivacaine and fentanyl group), BF: (bupivacaine and fentanyl group).

**Table 2** Block characteristics.

| | DBF (No-25) | BF (No-25) | *P* value |
|---|---|---|---|
| *Block characteristics* | | | |
| Time to reach sensory block (min) | 7.2 ± 1.8 | 7.6 ± 1.7 | 0.42 |
| Time to S max (min) | 9.1 ± 1.4 | 9.4 ± 1.7 | 0.50 |
| Time to ready for surgery (min) | 7.6 ± 2.1 | 8.1 ± 2.1 | 0.40 |
| Recovery of motor block (min) | 126.7 ± 29 | 115.6 ± 27 | 0.17 |
| Onset of postoperative pain (min) | 321 ± 19 | 174 ± 15.7 | 0.001* |
| *Highest level of sensory block* | | | |
| T4 | 10 (40%) | 11 (44%) | |
| T3 | 11 (44%) | 11 (44%) | |
| T2 | 4 (16%) | 3 (12%) | 0.91 |

Data are mean ± standard deviation. DBF: (dexmedetomidine, bupivacaine and fentanyl group), BF: (bupivacaine and fentanyl group).
* Statistically significant.

**Table 3** Incidence of side effects.

| | DBF (No-25) | BF (No-25) | *P* value |
|---|---|---|---|
| *Incidence of side effects* | | | |
| Hypotension | 4 (16%) | 3 (12%) | 0.68 |
| Bradycardia | 1 (4%) | 0 | 0.32 |
| Nausea and vomiting | 1 (4%) | 2 (8%) | 0.55 |
| Intraoperative pain or discomfort | 0 | 6 (24%) | 0.03* |
| Postoperative pain | 3 (12%) | 12 (48%) | 0.01* |
| Shivering | 1 (4%) | 8 (32%) | 0.03* |
| Pruritus | 1(4%) | 1 (4%) | 1.00 |
| Dizziness | 0 | 0 | – |
| Respiratory depression | 0 | 0 | – |
| *Supplementary fentanyl* | | | |
| Intraoperative requirement | 0 | 6 (24%) | 0.03* |
| Postoperative requirement | 3 (12%) | 12 (48%) | 0.01* |

Data are number (%). DBF: (dexmedetomidine, bupivacaine and fentanyl group), BF: (bupivacaine and fentanyl group).
* Statistically significant.

**Table 4** Comparison of intra-operative sedation scores in patients of group DBF and group BF.

| Sedation scores during surgery | DBF (No-25) | BF (No-25) | *P* value |
|---|---|---|---|
| 1 | 4 (16%) | 15 (60%) | |
| 2 | 11 (44%) | 10 (40%) | |
| 3 | 10 (40%) | 0 | 0.001* |

Data are number (%). DBF: (dexmedetomidine, bupivacaine and fentanyl group), BF: (bupivacaine and fentanyl group).
* Statistically significant.

6 months–6 years undergoing lower abdominal surgeries and concluded that both drugs significantly improve postoperative analgesia [10].

Antishivering mechanism of dexmedetomidine had been studied but not extensively. In the present study, we obtained satisfactory results in the prevention of shivering in patients who were administered with dexmedetomidine as only one patient out of total 25 suffered an episode of shivering. The α-2 receptor agonists are known to prevent shivering to a moderate extent without any associated respiratory depression as with other antishivering drugs such as meperidine, dexmedetomidine reduces shivering by lowering vasoconstriction and shivering thresholds [32].

Kanazi et al., investigated the effect of adding a small dose of 3 μg of intrathecal dexmedetomidine to 12 mg bupivacaine and found a significant prolongation of sensory and motor block as compared to bupivacaine alone [33]. In dissimilarity to our study, we failed to demonstrate a statistically significant change in sensory and motor block time.

On the other hand Konaki et al., demonstrated that 10 mcg of dexmedetomidine HCl produces moderate to severe demyelination of spinal cord white matter in rabbits following epidural administration. They postulate that the low pH of 4.5–7.0 of dexmedetomidine is responsible for the injury to the myelin sheath [34]. However clonidine with similar pH (5–7) does not exert neurotoxic side effects [35–37].

To our knowledge, there is no previous study on using dexmedetomidine during cesarean section had not been addressed apart from only individual case reports; Neumann et al., used dexmedetomidine to facilitate awake fiberoptic endotracheal intubation for patient with spinal muscular atrophy 10 min before cesarean delivery and found no serious neonatal effects were detected [27]. Similarly, Palanisamy et al., used intravenous dexmedetomidine successfully as an adjunct to opioid-based PCA and general anesthesia for cesarean delivery in a parturient with a tethered spinal cord, and they achieved favorable maternal and neonatal outcome [28]. Also, others used intravenous dexmedetomidine infusion for labor analgesia in patient with preeclampsia without significant neonatal side effects [29].

The limitations of this study were the relatively small number of patients included and lack of follow up of patients till time of discharge from hospital. The strengths of this study were performance of the surgical procedure by two consultants with the same experiences in a single center and postoperative data collected by single blinded investigator.

## 6. Conclusion

Addition of dexmedetomidine 1 μg/kg to an epidural bupivacaine/fentanyl combination in patients undergoing elective cesarean section using the CSE technique improves the intraoperative conditions; provides good sedation level and improves the quality of postoperative analgesia without significant maternal or neonatal side effects.

## Conflict of interest

No conflict of interest.

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