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# Assessment the effect of fentanyl and dexmedetomidine as adjuvant to epidural bupivacaine in parturients undergoing normal labor

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## Abstract

**Background**: Dexmedetomidine acts on the pre and post-synaptic sympathetic nerve terminal and central nervous system. It decreases the sympathetic outflow and norepinephrine release; therefore it leads to sedation, analgesia and hemodynamic effects. The aim of the study was to compare the effect of fentanyl and dexmedetomidine as adjuvant to epidural bupivacaine in parturients undergoing normal labor.

**Materials and methods**: The study included 170 parturients scheduled for epidural anesthesia for labor. The cases were classified randomly (by simple randomization) into two groups (n=85): Group D: The patients received 13 ml of 0.25% bupivacaine and 1μg/kg dexmedetomidine diluted in 2 ml saline. Group F: The patients received 13 ml of 0.25% bupivacaine and 1μg/kg fentanyl diluted in 2 ml saline.

**Results**: The dexmedetomidine shortened the onset and prolonged the duration of analgesia compared to fentanyl ($p<0.05$). Dexmedetomidine was associated with an increased incidence of maternal hypotension, bradycardia, motor block, and dry mouth ($p<0.05$), while the epidural fentanyl was associated with an increased incidence of maternal pruritus, nausea and vomiting, and respiratory depression ($p<0.05$). The incidence of shivering was lower in the dexmedetomidine group compared to fentanyl group ($p=0.003$).

**Conclusions**: The epidural dexmedetomidine has many advantages over the fentanyl, where it fastens the onset, prolongs the duration of analgesia, decreases the doses of bupivacaine and the incidence of pruritus, respiratory depression, nausea and vomiting. Also, it is associated with some disadvantages such as maternal hypotension, bradycardia and motor block.

**Keywords**: Dexmedetomidine, fentanyl, bupivacaine, epidural anesthesia, analgesia, labor

## Introduction

Epidural analgesia has been extensively used to provide pain relief during labor [1]. Labor pain and painful uterine contractions cause hyperventilation and high catecholamine levels, resulting in maternal and fetal hypoxemia [2]. Pain relief provides a comfort for the patients and attenuates the release of stress hormones [3]. Epidural bupivacaine is still the most widely used local anesthetic in obstetric analgesia [1]. Many drugs are added to bupivacaine to minimize its total dose and to prolong the analgesic effect [4].

Fentanyl has been used as an adjuvant for epidural local anesthetics during labor analgesia to achieve the desired anesthetic effect [5], and to decrease motor block of local anesthetics. However, the addition of opioid may increase the incidence of pruritus, urinary retention, nausea, vomiting and respiratory depression [6-8].

Dexmedetomidine is alpha-2 adrenergic agonists with analgesic properties which potentiate the epidural local anesthetic effects [9,10]. They act on both pre- and postsynaptic sympathetic nerve terminal and central nervous system, thereby decreasing the sympathetic outflow and nor-epinephrine release, causing sedative, anti-anxiety, analgesic, sympatholytic and hemodynamic effects [11-13]. The aim of the study was to compare the effect of fentanyl and dexmedetomidine as adjuvant to epidural bupivacaine in parturients undergoing labor.

## Outcome

The primary outcome was the adequacy of maternal analgesia

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throughout labor and the secondary outcome was the safety of the intervention. The safety was assessed by the occurrence of any adverse events to the parturient and fetus.

## Materials and methods

After obtaining informed consent and approval of local ethics and research committee in Aldar hospital, Almadinah Almonwarah, Saudi Arabia. A pilot study was done before starting this study to compare the effect of dexmedetomidine and fentanyl on the analgesic effect of epidural bupivacaine. The results of the pilot study showed that dexmedetomidine has a more analgesic effect than fentanyl and the requirement for a second dose local anesthetic was of 14.4% in dexmedetomidine group, and 32.5% in fentanyl group. Taking power 0.8 and alpha error 0.05, a minimum sample size of 85 patients was calculated for each group. 170 parturients with a full-term pregnancy were assessed in the study and scheduled for epidural anesthesia during labor. The inclusion criteria were full term pregnancy, active labor with cervical dilatation >4 cm, intact membrane, uterine contractions occurring at least every 5 minutes, normal cardiotocography (baseline fetal heart rate 120-160 bpm, baseline variability >5 beats/minute, the presence of accelerations). The exclusion criteria were coagulopathy, cardiac diseases, pregnancy-induced hypertension, the refusal the epidural anesthesia, accidental dural puncture, rapid progress of labor (delivery in less two hours of study period), and hypersensitivity to local anesthetic, dexmedetomidine or fentanyl.

### Anesthetic technique

In the labor ward, intravenous line G18 was inserted for all parturients and an infusion of 500 ml Ringer lactate solution was started. Monitors such as ECG, pulse oximetry, and blood pressure cuff were attached to the included parturients. Under complete sterilization and local anesthesia, an epidural set ( Perican® needle G18, catheter G27, B. Braun Melsungen AG Germany) was used. The epidural needle was inserted into the epidural space at the L3-4 or L4-5 interspace while the parturients were in the sitting position. The epidural space was identified using the loss of resistance to saline technique (1-2ml). A multiorifices epidural catheter was inserted 3 cm into the epidural space through the needle and secured. A test dose of 3 ml of 2% lidocaine was administered through the catheter after aspiration showed no blood or cerebrospinal fluid coming from the epidural catheter. The study medications were administered 6 minutes after the test dose. The cases were classified into two groups (each=85): Group D (dexmedetomidine group): The patients received 13 ml of 0.25% bupivacaine and 1µg/kg dexmedetomidine diluted in 2 ml saline. Group F (fentanyl group): The patients received 13 ml of 0.25% bupivacaine and 1µg/kg fentanyl diluted in 2 ml saline.

The sensory block was assessed by pin prick and cold application every 5 minutes until the onset of sensory block (The time from epidural injection to onset of analgesia) using a 3-point scale: 0=normal sensation, 1=loss of sensation of pin prick (analgesia), and 2=loss of sensation of touch (anesthesia). The motor block was assessed by Bromage three point score for the lower extremity (0-3), 0: no motor impairment (able to move the hip, knee, and ankle joints); 1: unable to raise either extended leg (able to move joints of knee and ankle); 2: unable to raise extended leg and flex knee (able to move the joint of ankle); 3; unable to move the knee and foot [**14**]. The pain relief was assessed by the pain verbal scale from 0 to 4(0: complete pain relief; 1: only slight pain; 2: a lot of pain relief, 3: little pain relief; 4: no pain relief) [**15**]. The level of sedation was assessed by a modified Wilson sedation scale from 1 to 4 [**16**]. Duration of analgesia was assessed by meassuring the time between onset of sensory block and a return of pain sensation. If the block was inadequate or the patient has a pain, another dose of study medication and local anesthetic was administered. The maternal hypotension (mean arterial blood pressure<20% of the baseline reading) was managed by the fluids administration, bolus doses of ephedrine (5-10mg) and left lateral tilting of the parturient. The bradycardia (heart rate <60 bpm) was managed with bolus doses of atropine (0.02 mg/kg). The monitors included the heart rate, maternal arterial blood pressure, arterial oxygen saturation, and fetal heart rate. The readings were recorded every 5 minutes for the first 30 minutes, then every 15 minutes until the end of the labor. The fetus was monitored by a continuous cardiotocography (Fetal Actoccardiograph, MT-516 EBISH-NISHI. SHBUYA-KU.TOKYO, Japan) before labor and by Apgar score and umbilical cord PH after labor. The umbilical cord blood sample was withdrawn by the pediatrician in the delivery or operative room.

### The statistical analysis

Data were statistically described in terms of range; mean± standard deviation (±SD), frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the study groups were done using Mann Whitney U test and one-way or two-way or repeated ANOVA for normally distributed variables. For comparing categorical data, Chi square ($c^2$) test was performed. Exact test was used instead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

## Results

**Figure 1** shows the CONSORT diagram for the flow of participants through each stage of the present study. All cases completed the study. There was no statistical difference regarding the demographic data, ASA class, parity, gestational and the

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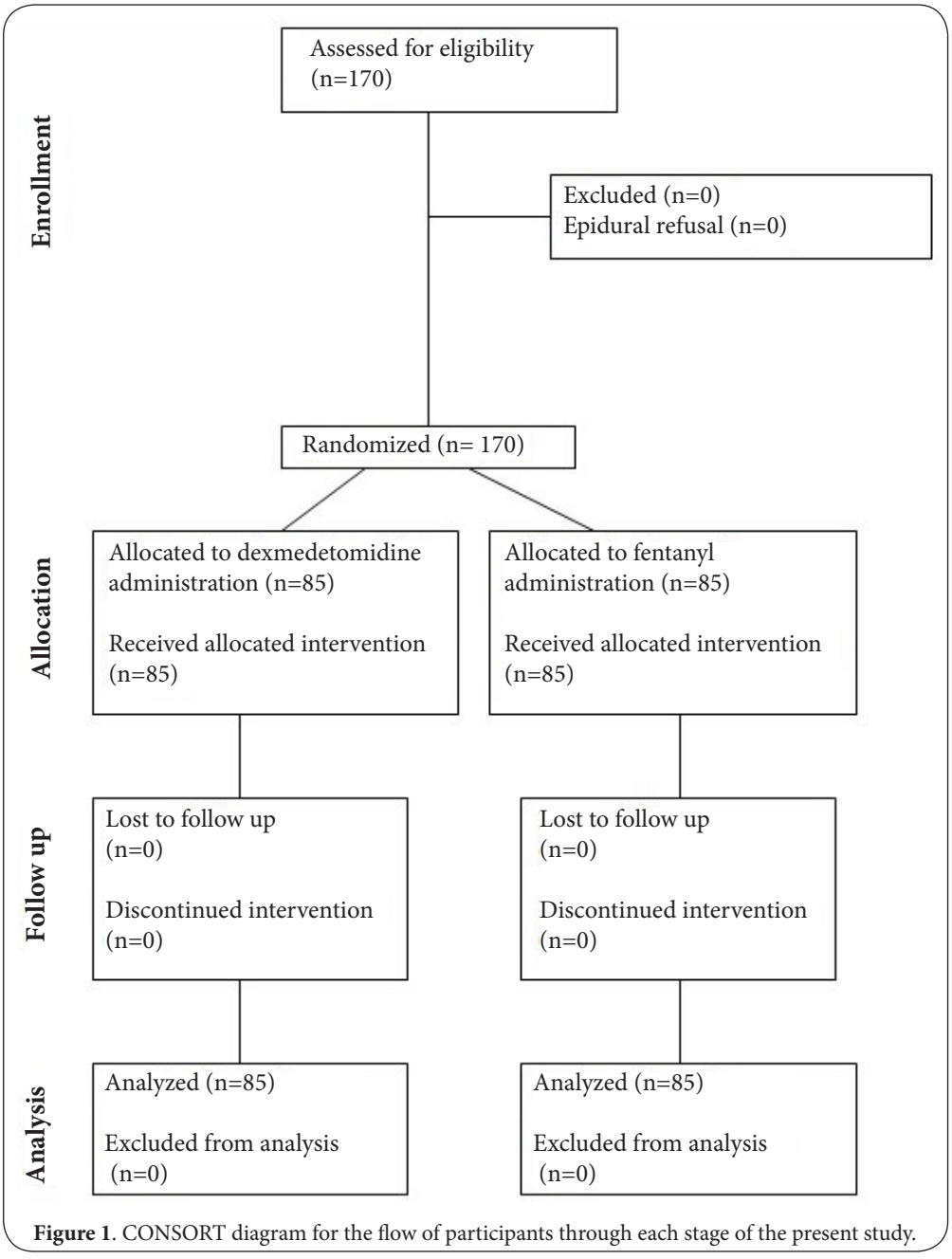


**Figure 1**. CONSORT diagram for the flow of participants through each stage of the present study.

degree of cervical dilatation (p>0.05) (**Table 1**).

**Table 2** shows the outcomes of epidural blocks. All parturients of both groups received a single dose of bupivacaine, but 12 cases in dexmedetomidine group and 28 cases in the fentanyl group required a second dose with statistical difference between the two groups (p=0.003). The onset of sensory block was earlier in the dexmedetomidine group more than the fentanyl group (p=0.011) and the duration of analgesia was longer in the dexmedetomidine group compared to the fentanyl group (p=0.001). The quality of pain relief was better in the dexmedetomidine group than the fentanyl group. The comparison of sensory block level between the two groups was insignificant (p>0.05). The incidence of motor block was higher in the dexmedetomidine group compared to the fentanyl group (p=0.004). The incidence of sedation was 9 patients in dexmedetomidine group and no sedation in the fentanyl group (p=0.002).

**Table 3** shows the obstetric and fetal outcomes. There was no significant difference regarding the progress of labor, spontaneous labor, assisted labor, cesarean section, Apgar score, and the umbilical cord PH.

**Figures 2** and **3** shows the changes in the maternal heart

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**Table 1. Demographic data of the parturients (data are presented as mean±SD, number).**

| Variables | Group D (n=85) | Group F (n=85) | P-value |
|---|---|---|---|
| Age(year) | 25.92±4.60 | 26.24±4.99 | 0.664 |
| Weight(kg) | 79.42±13.17 | 77.80±11.48 | 0.393 |
| Height (cm) | 167.51±7.35 | 165.74± 7.18 | 0.114 |
| ASA I | 41 | 37 | 0.707 |
| II | 44 | 48 | 0.736 |
| Parity | 1.80±1.40 | 2.12±1.51 | 0.182 |
| Gestational age(week) | 38.15±1.14 | 38.22±1.11 | 0.685 |
| Cervical dilatation(cm) | 5.23±1.17 | 5.18±1.12 | 0.776 |

ASA: American Society of Anesthesiologists physical status classification system
Group D: Dexmedetomidine group, Group F: Fentanyl group

**Table 2. Outcomes of the epidural block (data are presented as mean±SD, number).**

| Variables | Group D (n=85) | Group F (n=85) | P-value |
|---|---|---|---|
| Single dose of bupivacaine | All patients | All patients | 0.999 |
| Second dose of bupivacaine | 12 | 28 | 0.003 |
| Onset of analgesia (min) | 6.55±1.87 | 10.70±2.12 | 0.011 |
| Duration of analgesia (min) | 314.54± 38.41 | 240.63± 25.74 | 0.001 |
| **Pain verbal scale** | | | |
| 0 | 58 | 45 | 0.041 |
| 1 | 13 | 4 | 0.021 |
| 2 | 2 | 8 | 0.050 |
| 3 | 9 | 12 | 0.484 |
| 4 | 3 | 16 | 0.002 |
| **Sensory block level** | | | |
| T5 | 24 | 29 | 0.407 |
| T6 | 21 | 25 | 0.489 |
| T7-T10 | 40 | 31 | 0.161 |
| Motor block | 14 | 3 | 0.004 |
| Sedation | 9 | 0 | 0.002 |

Group D: Dexmedetomidine group, Group F: Fentanyl group

**Table 3. Obstetric and fetal outcomes (data are presented as mean±SD, number).**

| Variables | Group D (n=85) | Group F (n=85) | P-value |
|---|---|---|---|
| Progress of labor (cm/hr) | 1.69±0.45 | 1.73±0.48 | 0.575 |
| Spontaneous delivery | 68 | 70 | 0.694 |
| Assisted delivery | 4 | 3 | 0.699 |
| **Cesarean delivery** | | | |
| Total number | 13 | 12 | 0.828 |
| Failure of progress | 10 | 7 | 0.443 |
| Fetal distress | 3 | 5 | 0.468 |
| Birth weight(kg) | 3.24±0.45 | 3.19±0.49 | 0.489 |
| **Apgar score** | | | |
| at 1 minute | 7.82±0.72 | 7.77±0.84 | 0.677 |
| at 5 minute | 9.42±0.50 | 9.44±0.43 | 0.780 |
| Umbilical cord PH >7.2 | 83 | 82 | 0.649 |
| Umbilical cord PH | 7.28±0.06 | 7.27±0.04 | 0.203 |

Group D: Dexmedetomidine group, Group F: Fentanyl group

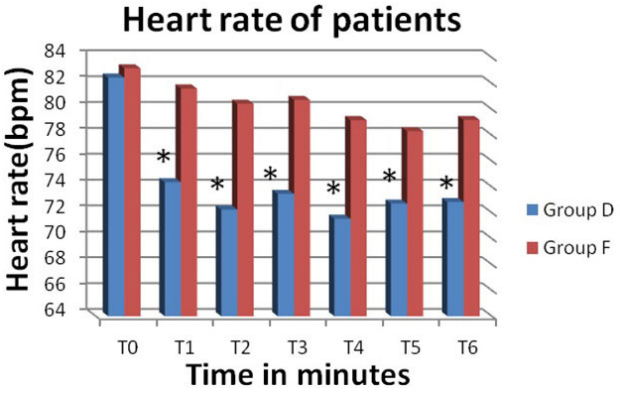


**Figure 2. Maternal heart rate of patients.**
Group D: Dexmedetomidine group, Group F: Fentanyl group
T0: Readings before study medication, T1: Readings 15 minutes after study medication administration, T2: Readings 30 minutes after study medication administration, T3: Readings 60 minutes after study medication administration, T4: Readings 90 minutes after study medication administration, T5: Readings 120 minutes after study medication administration, T6: Readings 5 minutes before labor.
*P<0.05 significant comparison between the two groups.

rate and mean arterial blood pressure in the patients of the two groups. The heart rate decreased significantly in the dexmedetomidine group with minimal changes in the fentanyl group (P>0.05). Also the mean arterial blood pressure decreased significantly in the dexmedetomidine group compared to the fentanyl group (P>0.05).

**Table 4** shows that the incidence of maternal hypotension, bradycardia and dry mouth was higher in the dexmedetomidine group than the fentanyl group and the comparison was significant (p<0.05). The incidence of pruritus, respiratory depression, nausea and vomiting was lower in the dexmedetomidine group than the fentanyl group and the difference was significant (p<0.05). The incidence of the headache, urine retention and shivering between the two groups was insignificant (p>0.05). The incidence of fetal distress (fetal heart rate<100bpm) between the two groups was insignificant (p=0.468).

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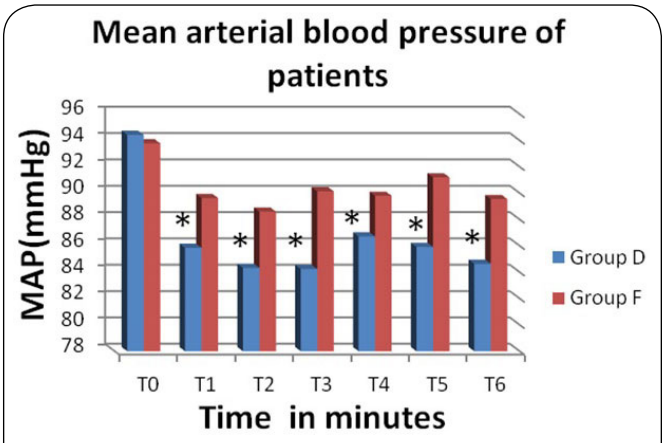


**Figure 3. Maternal mean arterial blood pressure of patients.**
MAP: Mean arterial blood pressure of patients
Group D: Dexmedetomidine group, Group F: Fentanyl group
T0: Readings before study medication, T1: Readings 15 minutes after study medication administration, T2: Readings 30 minutes after study medication administration, T3: Readings 60 minutes after study medication administration, T4: Readings 90 minutes after study medication administration, T5: Readings 120 minutes after study medication administration, T6: Readings 5 minutes before labor.
*P<0.05 significant comparison between the two groups.

**Table 4. Complications of the epidural block (data are presented as number).**

| Complication | Group D (n=85) | Group F (n=85) | P-value |
|---|---|---|---|
| Maternal hypotension (Decrease in MAP >20%) | 15 | 6 | 0.035 |
| Maternal bradycardia (Heart rate<60 bpm) | 14 | 4 | 0.012 |
| Fetal heart rate <100 bpm | 3 | 5 | 0.468 |
| Nausea and vomiting | 5 | 15 | 0.017 |
| Dry mouth | 14 | 3 | 0.004 |
| Pruritis | 0 | 8 | 0.003 |
| Headache | 4 | 3 | 0.699 |
| Respiratory depression | 0 | 5 | 0.023 |
| Urine retention | 0 | 3 | 0.080 |
| Shivering | 3 | 15 | 0.003 |

## Discussion

The present study showed that the addition of dexmedetomidine to epidural bupivacaine fastens the onset of analgesia and prolongs the duration of analgesia. The quality of analgesia was better with dexmedetomidine group compared to fentanyl group; therefore the incidence of the required second dose of bupivacaine was lower the dexmedetomidine group compared to the fentanyl group. These findings correlate with the result of Selim et al [17]. They reported that the dexmedetomidine shortened the onset with analgesia of bupivacaine and also prolonged the duration of analgesia compared to the addition of fentanyl to the epidural bupivacaine in women undergoing labor and other studies showed the same results [9,18-21].

The present study showed that the incidence of side effects such as the motor block, hypotension, bradycardia, sedation, and dry mouth was higher in the dexmedetomidine group than the fentanyl group. These findings correlate with the study of Selim et al [17]. The study showed that the incidence of maternal hypotension and bradycardia was higher in the dexmedetomidine group than the fentanyl group. A meta-anaylsis of 16 studies showed that the most side effects of neuraxial dexmedetomidine were hypotension, bradycardia, and sedation [22]. Another metanaylsis study showed that the dexmedetomidine is associated with a significant requirement to phenylephrine or atropine to manage the hypotension and bradycardia compared to the control group (p<0.0001) [23]. Hanoura et al., [18] evaluated the effect of fentanyl or fentanyl plus dexmedetomidine to the combined spinal-epidural anesthesia for cesarean section. The study showed no significant difference regarding the Apgar scores, the incidence of hypotension, bradycardia, nausea, vomiting, and duration of motor blockade and Salgado et al., [19] found no significant side effect related to the dexmedetomidine to the epidural ropivacaine in patients undergoing hernia repair or varicose vein surgery. But Gupta k et al., [20] found no significant difference in the hemodynamics between the epidural dexmedetomidine–levobupivacaine (0.5%) and fentanyl-levobupivacaine (0.5%) in patients undergoing vaginal hysterectomy and the same result was shown in patients undergoing cesarean section with combined spinal-epidural anesthesia [24]. The side effects such as pruritus, respiratory depression, nausea and vomiting were lower in the dexmedetomidine group than the fentanyl group and other studies documented the same results [9,17,20]. The present study showed no difference in the incidence of shivering between the two groups, but Hanoura et al., [18] found the incidence of shivering was lower in the dexmedetomidine group compared to fentanyl group (p=0.03).

Although the systemic maternal effect of dexmedetomidine such as hypotension and bradycardia, there was no effect on the fetus as reflected by the Apgar score and the umbilical PH. Ala-Kokko et al., [25] showed that the fetus is protected as the placenta minimizes the crossing of dexmedetomidine to the fetus [25] and if there is any uteroplacental transfer, it doesn't affect the fetus [26-28]. Palanisamy et al., [28] used intravenous dexmedetomidine as an adjunct to opioid-based PCA and general anesthesia for the labor analgesia and cesarean section in a parturients with favorable maternal and neonatal outcome and the same result were reported by Abu-Halaweh et al [27].

On the other hand, Konaki et al., [29] demonstrated that 10 $\mu$g of dexmedetomidine HCl produces moderate to severe demyelination of spinal cord white matter in rabbits following epidural administration. They postulate that low pH of

4.5-7.0 of dexmedetomidine is responsible for injury to the myelin sheath; however clonidine with similar pH (5-7) does not produce neurotoxic side effects [30-32].

The present study and other studies showed the perineural addition of dexmedetomidine to bupivacaine, prolongs the duration of sensory block, motor block, and analgesia, in addition to the decreased requirement to postoperative analgesia. These findings can be explained by the following mechanisms. Dexmedetomidine produces vasoconstriction around the injection site and decreases the absorption of local anesthetics [22], induces local analgesic substances such as enkephalin-like substances [23], decreases the release of proinflammatory mediators [24], increases the release of anti-inflammatory cytokines and modulates the impulse propagation through neurons as a result of interaction with axonal ion channels or receptors [25].

## Conclusions

The epidural dexmedetomidine has many advantages over the fentanyl, where it fastens the onset, prolongs the duration of analgesia, decreases the doses of bupivacaine and the incidence of pruritus, respiratory depression, nausea, and vomiting. Also, it is associated with some disadvantages such as maternal hypotension, bradycardia and motor block. Therefore other studies are recommended to determine the proper dose of epidural dexmedetomidine that does not affect the maternal hemodynamics undergoing labor.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

| Authors' contributions | RS | GZ |
|---|---|---|
| Research concept and design | ✓ | ✓ |
| Collection and/or assembly of data | ✓ | -- |
| Data analysis and interpretation | ✓ | ✓ |
| Writing the article | ✓ | ✓ |
| Critical revision of the article | ✓ | ✓ |
| Final approval of article | ✓ | ✓ |
| Statistical analysis | -- | -- |

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