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Effect of the use of dexmedetomidine as a local anesthetic adjuvant to bupivacaine 0.125% in epidural labor analgesia: randomized controlled study

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Abstract

Background: Multiple methods exist for the management of pain during normal labor. Epidural analgesia has been reported to be an effective method in that perspective. The current study was conducted to evaluate the efficacy of dexmedetomidine as an adjuvant to local anesthetics in epidural analgesia for pregnant females presented for normal delivery. Sixty pregnant females were included in this prospective randomized study, and they were divided into two equal groups: control group which received bupivacaine alone and dexmedetomidine group that received bupivacaine with dexmedetomidine. The primary outcome was the onset of analgesia, while the secondary outcomes included the duration of analgesia, hemodynamic changes, labor progress, neonatal outcomes, and maternal complications.

Results: Dexmedetomidine group was associated with earlier onset of analgesia ($P < 0.001$), prolonged duration ($P < 0.001$), and lower need for top-up doses ($P < 0.001$) compared to control group. Also, sedation and maternal satisfaction were significantly better in the same group ($P = 0.001$, 0.025; respectively). Labor progress parameters and neonatal outcomes were comparable between the two groups. Dexmedetomidine group has lower heart rate and mean arterial blood pressure compared to the control group. Despite of dexmedetomidine group had higher incidence of hypotension and bradycardia, it was statistically insignificant when compared to control group.

Conclusions: Dexmedetomidine is a reliable and an effective adjuvant to the local anesthetics in epidural analgesia during normal delivery as it resulted in earlier onset and significant prolongation of the analgesic time with decrease in the top-up doses intake.

Trial registration: Pan African Clinical Trial Registry (PACTR201710002664704). Register on 3 October 2017.

Keywords: Epidural analgesia, Dexmedetomidine, Normal delivery

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Background

The majority of females who underwent normal labor have reported that this is one of the most painful life moments. If not well controlled, it can lead to serious consequences for both the mother and the baby (Li et al. 2020; Ali and Wahdan 2018; Keskin et al. 2003).

Multiple methods exist for the management of pain during normal labor including intravenous administration of opioids, neuraxial analgesia, inhaled anesthetics, and even alternative medicine (e.g., transcutaneous electrical nerve stimulation and acupuncture). However, there is a debate about the optimum method that should be used in these ladies as each of the previously described methods has its limitations in this group of population (Ali and Wahdan 2018; Whitburn et al. 2019).

A previous study has reported that epidural analgesia is the most efficacious method for managing labor pain; it can be customized for each pregnant woman to achieve painless labor (Lebovits et al. 2001). Nevertheless, multiple cons have been reported with that technique including motor blockade, hypotension, and prolongation of the second stage of labor (Okholm et al. 2014). Many clinical trials have been done to reduce these effects by choosing optimum local anesthetic concentration with adjuvant drugs.

Dexmedetomidine is a potent alpha-2 adrenergic receptor agonist that is known to have sedative, analgesic along with sympatholytic properties (Zhang et al. 2017). Previous studies have reported that the intrathecal administration of dexmedetomidine led to a significant prolongation of sensory blockage time during cesarean sections and hysteroscopic surgeries (Qi et al., 2016a, b).

This study was conducted to evaluate the efficacy of adding dexmedetomidine to bupivacaine in epidural analgesia in female presented for normal vaginal delivery.

Methods

This prospective randomized blinded study was conducted at the Obstetrics and Gynecology Department over 2 years starting from January 2018 to January 2020. The study was designed for primigravida parturient females aged from 21 to 30 years presented in active labor (cervical dilatation 3-5 cm) to our department, prepared for normal vaginal delivery, and requesting epidural labor analgesia.

The present study included cases with American Society of Anesthesiologists (ASA) (Knuf et al. 2018) class II, having a single pregnancy with vertex presentation, and gestational age > 37 weeks. On the contrary, multigravida or women presenting with mal-presentation, twin pregnancy, preeclampsia, uncontrolled systemic comorbidities (diabetes, renal, hepatic, or cardiac), bleeding diathesis, body mass index (BMI) more than 35 kg/m^2, or known allergy to any of the study drugs were excluded.

Sample size was calculated based on the results of a previous trial conducted by Selim and his associates (Selim et al. 2012) which stated that at least 23 cases were required in each group to detect any significant change regarding sensory block onset of 3 min at an alpha value of 0.05 and a 95% study power. To counteract the possibility of the dropout cases, we included 30 cases in each group.

Before participating in the study, all cases were informed about the benefits and risks of epidural analgesia along with the medications used. A written informed consent was obtained after that. Also, the study was approved by the Local Ethical Committee (approval number 31725/08/17) and registered in Pan African Clinical Trial Registration (PACTR201710002664704).

The closed envelope opened after randomization with the computer-generated method. The included 60 women were equally allocated into two groups: control group (30 women) which received bupivacaine 0.125% (10 ml) in normal saline, and dexmedetomidine group (30 women) that received the same amount of bupivacaine in addition to dexmedetomidine 50 μg in normal saline as a loading dose (5 ml increments/5 min). This was followed by continuous infusion of bupivacaine 0.125% (at 10 ml/h rate) for both groups, which was stopped with full cervical dilatation. The epidural solutions were prepared by an anesthesiologist not included in the study. Moreover, all of the following were blinded to group allocation: the patient, the obstetrician, the neonatologist, and the obstetric ward nurse.

All of the included women (in an active second stage of labor with cervical dilatation of 3-5 cm) were commenced on Ringer's solution (500 ml) as a preload; then, routine baseline monitoring was established including blood pressure (non-invasive), electrocardiography, and pulse oximetry. Also, they were informed how to report their pain degree according to the visual analog scale (VAS) (0 for no pain felt at all, to 10 for the worst pain ever felt).

Later, they were placed in the sitting position with proper sterilization of the back, followed by local infiltration of the skin with underlying subcutaneous tissue overlying lumbar (L) 3-4 and L 4-5 intervertebral disc by lidocaine 2%. The epidural space was reached via an 18-gauge needle (Perifix®, Braun, Germany), and this was ensured using the loss of resistance to air technique. Next, aspiration was done to exclude the presence of blood or cerebrospinal fluid followed by injection of 3 ml of lidocaine 2% as a test dose. After that, a 20-gauge multi-orifice epidural catheter was introduced to about 4-5 cm depth. After securing the catheter over the back by plaster strips, the women were asked to lie in the left

lateral position to avoid compression of the inferior caval vein by the pregnant uterus. Injection of the study solution was performed only in between uterine contractions to decrease the risk of drug overspread in the epidural space.

The onset of analgesia was defined as the time needed to achieve a VAS ≤ 3 after injection, while the duration of analgesia was defined as time passing from the time of injection till the woman report a VAS > 3 or breakthrough pain. Both were managed by epidural injection of a top-up dose of bupivacaine 0.125% (5 ml). The top-up doses number were recorded.

The modified Bromage scale was used to assess the degree of motor block (Sari et al. 2015) before installation of the epidural catheter, every 15 min during the 1st hour after installation and then every 30 min till delivery. If Bromage score ≥ 2 was detected, bupivacaine infusion rate was decreased till achieving a score ≤ 1.

The sedation score was used to assess sedation level (Imani et al. 2011) at the same time intervals. This classification allocates patients as agitated, awake and calm, sleepy, mildly sedated, moderately sedated, and deeply sedated using a numerical scale from zero to five for each item respectively.

Both heart rate and arterial blood pressure were monitored and recorded before the installation of the epidural catheter, and 5, 15, 30, 45, and 60 min following its installation and then hourly till the end of delivery. Hypotension, defined as systolic blood pressure < 100 mmHg or a decrease in mean arterial pressure (MAP) > 30% compared to the baseline, and was managed by ephedrine (increment dose 10 mg) along with intravenous fluids. Bradycardia, defined as heart rate (HR) less than 60 beats/m, and was managed by intravenous 0.5 mg atropine.

Cardiotocography was used for fetal heart rate monitoring. If any abnormalities were detected, the mother was asked to change her position to the left lateral one. Also, the mother was commenced on oxygen, intravenous fluids, while oxytocin was stopped. The neonatologist used 1- and 5-min Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score (Li et al. 2013) to assess the neonatal outcome.

The time needed for cervical dilatation, the duration of each stage of labor, and the mode of delivery were recorded. After 24 h of delivery, mother satisfaction was assessed with the five-point Likert's scale (Voutilainen et al. 2016) as follows: 1 for poor, 2 for fair, 3 for good, 4 for very good, and 5 for excellent satisfaction.

The primary outcome was the onset of analgesia, while the secondary outcomes include the duration of analgesia, hemodynamic changes, labor progress, neonatal outcomes, and maternal complications.

Statistical analysis

Data were entered, tabulated, and analyzed using Statistical Package for Social Science (SPSS) software, version 26.0 for Mac. After testing our data for normality by Kolmogorov-Smirnov and Shapiro-Wilk's tests, baseline characteristics were described as frequencies and percentages, mean values and standard deviations (SD), or median and range. For comparison of two independent groups of qualitative data, Chi-Square test (or Fisher's exact test) was applied. Besides, Mann-Whitney *U* test and independent-samples *t* test were used to compare two groups of non-parametric and parametric quantitative data respectively. *P* values < 0.05 were considered statistically significant for all of the used statistical tests.

Results

Sixty pregnant females were included in this study from eligible 72 pregnant females. They were allocated into two equal groups (Fig. 1). Patient's characteristics and the data of labor progress are illustrated in Table 1.

The dexmedetomidine group expressed a significantly earlier onset of analgesia when compared to controls (9.23 vs. 16.8 min; $P < 0.001$). Additionally, the duration of analgesia was more prolonged in the dexmedetomidine group (169.13 vs. 102.8 min in controls; $P < 0.001$). Also, the need for top-up doses was significantly decreased in the same group ($P < 0.001$). No significant difference was detected between the two groups regarding the Bromage scale ($P = 0.066$). The dexmedetomidine group showed significantly higher sedation score and patient satisfaction compared to the control group ($P = 0.001$, and 0.025; respectively) (Table 2).

As illustrated in Fig. 2, the dexmedetomidine group expressed significantly lower heart rates compared to the control group, starting from 15 min to 2 h. Also, the same group showed significantly lower mean arterial blood pressure starting from 15 min to 1 h.

When it comes to the neonatal outcomes and maternal complications, no significant difference was detected between both groups (Table 3).

Discussion

Epidural analgesia is a safe and efficacious technique in pain management during normal labor (Wang and Xu 2020). Multiple medications have been studied as adjuvants to prolong the local anesthetic duration of action with faster onset including opioids (Wang and Xu 2020), dexamethasone (Ali and Wahdan 2018), dexmedetomidine, and clonidine (El-Hennawy et al., 2009).

The epidural injection of alpha 2-agonists such as dexmedetomidine is associated with analgesic, sedative, anxiolytic along with sympatholytic effects (Mauro and Brandão 2004). Its analgesic effects are produced by depressing the release of C-fiber

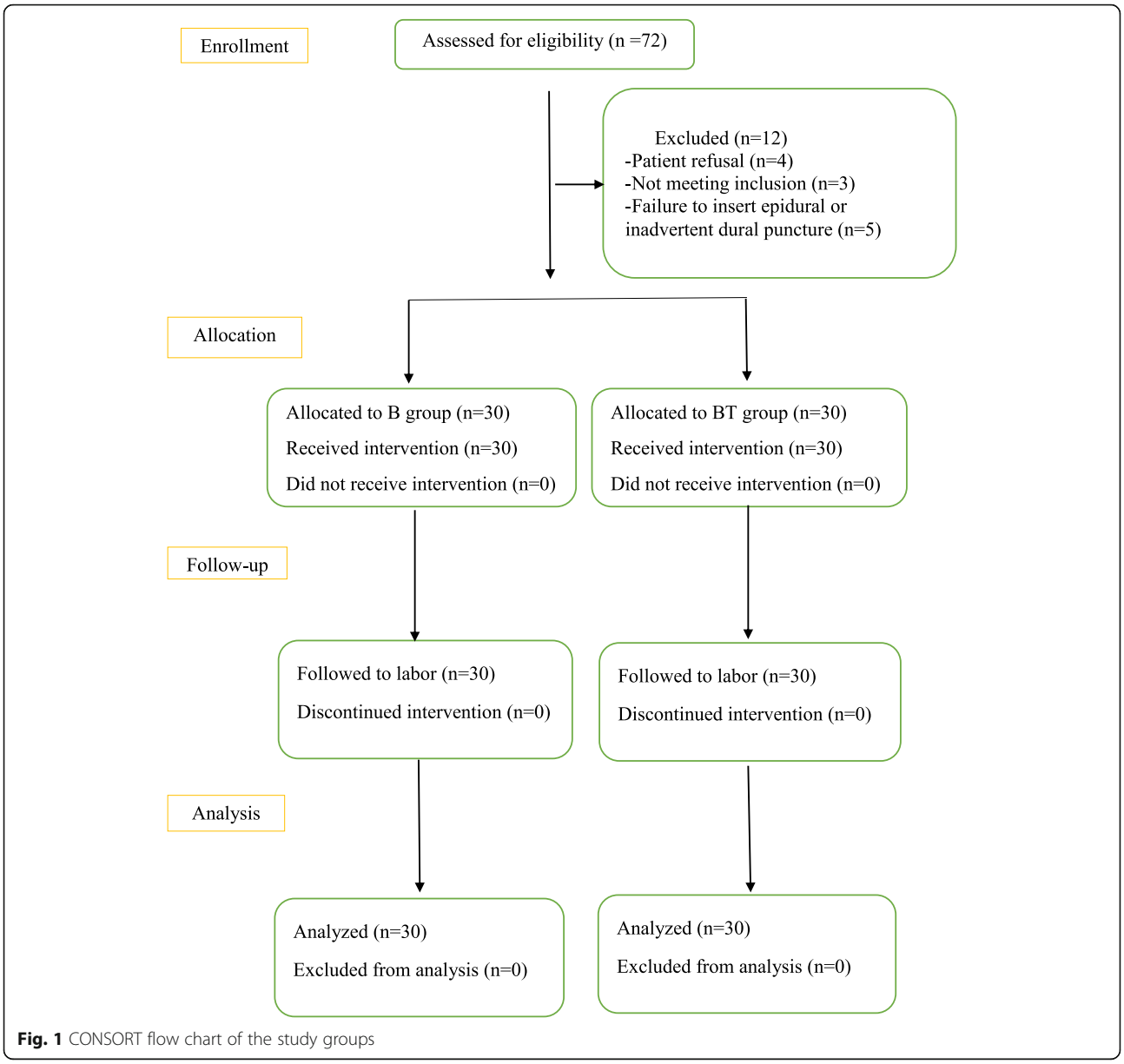

Fig. 1 CONSORT flow chart of the study groups

transmitters with postsynaptic dorsal horn neuron hyperpolarization through stimulation of alpha-2 adrenoceptors at the level of substantia gelatinosa of the dorsal horn. It enhances the analgesic properties when injected with local anesthetics (Shaikh and Mahesh 2016; Yoshitomi et al. 2008).

This study was conducted to evaluate the effectiveness of adding dexmedetomidine as a local anesthetic adjuvant in epidural analgesia for normal labor. Although the dose of dexmedetomidine as an epidural adjuvant ranged between 0.5 μg/kg and 1.5 μg/kg (Yousef et al. 2015, Zhao et al. 2017, Selim et al. 2012, Soni 2016) and it is known to cause dose–dependent bradycardia and hypotension, a relatively low fixed-dose (50 μg) was given to all the patients as their weights were within a narrow range to avoid exacerbation of maternal hypotension or bradycardia (Bharti et al. 2018; Alansary and Elbeialy 2019).

In the present study, the dexmedetomidine group reported significantly earlier onset of analgesia compared to the control group (9.23 vs. 16.8 min; $p < 0.001$). The duration of analgesia was more prolonged in the dexmedetomidine group (169.13 vs. 102.8 min; $p < 0.001$) than the control group without a significant change in motor block. Besides, the number of top-up doses was significantly decreased in the same group ($p < 0.001$).

Meta-analysis study conducted by Zhang et al. concluded that adding dexmedetomidine as an adjuvant to

Table 1 Patient characteristics and labor progress in the study groups

	Control group (*n* = 30)	Dexmedetomidine group (*n* = 30)	*P* value
Age (years)	24.10 ± 2.76	23.83 ± 2.65	0.704
Weight (kg)	83.40 ± 6.11	83.47 ± 9	0.973
Height (cm)	162.43 ± 5.62	163.23 ± 5.87	0.592
BMI (kg/m^2)	31.65 ± 2.29	31.27 ± 2.18	0.513
Gestational age (weeks)	37.30 ± 0.99	37.40 ± 1	0.699
Cervical dilatation (min)	4.63 ± 0.67	4.70 ± 0.75	0.718
Interval epidural till delivery (min)	268.90 ± 50.90	252.27 ± 42.21	0.174
Duration of 2nd stage (min)	35.50 ± 6.34	38.10 ± 5.97	*0.*107
Mode of delivery			
Operative assisted (*n*) (%)	3 (10%)	5 (16.7%)	0.448
Spontaneous (*n*) (%)	27 (90%)	25 (83.3%)	

Data presented as mean ± standard deviation or patient's number (percentage)
BMI body mass index

local anesthetics in epidural anesthesia resulted in significant prolongation of the analgesic duration with faster onset. This was in agreement with our results (Zhang et al. 2017).

Multiple studies (Kaur et al. 2014; Karhade et al. 2015; Sathyanarayana et al. 2016) have reported that adding dexmedetomidine in epidural anesthesia provides a marked reduction in time to experience sensory and motor block, prolonged duration of the block, and decrease the analgesic requirements. Yang et al. (2020), Hanoura et al. (2013), Mo et al. (2017), and Yousef et al. (2015) have performed their studies on pregnant females undergoing cesarean section and concluded that adding dexmedetomidine potentiates the effect of local anesthetics in epidural anesthesia with minimal maternal side effects. These were in concordance with the results of the present study.

Furthermore, Jun et al. (2018) in their study comparing the effect of adding dexmedetomidine 0.5 μg/ml to ropivacaine 0.1% in epidural labor analgesia concluded that dexmedetomidine group has a better analgesic effect than ropivacaine group. Also, Zhao et al. (2017) combined dexmedetomidine 0.5 μg/kg with ropivacaine 0.125% in epidural analgesia on females undergoing normal labor and they reported a reduction of the feeling of pain without motor block. However, both of these studies differ from the current study as they used ropivacaine and also a different dose of dexmedetomidine.

Moreover, Zhang et al. (2019) demonstrated in their study the effects of dexmedetomidine 0.25 μg/ml and sufentanil 0.25 μg/ml added to ropivacaine 0.1% for epidural labor analgesia. They demonstrated that dexmedetomidine results in a faster onset of analgesia with lower VAS and reduced local anesthetics requirements.

The results of this study showed that the sedation score was significantly higher in the dexmedetomidine group compared to the control group. Epidural dexmedetomidine possesses its sedative property through activation of the spinal cord α_2 receptors leading to inhibition of the release of norepinephrine in the locus coeruleus, adding to its systemic absorption due to higher lipid solubility. This property has a great advantage as the patient can be easily aroused so they can participate in the normal delivery process and at the same

Table 2 Analgesic properties, Bromage scale, sedation, and patient satisfaction in the study groups

	Control group (*n* = 30)	Dexmedetomidine group (*n* = 30)	*P* value
Onset of analgesia (min)	16.80 ± 4.66	9.23 ± 3.01	< 0.001*
Duration of analgesia (min)	102.80 ± 23.20	169.13 ± 29.07	< 0.001*
Number of top up doses	2 (2-3)	1 (1-2)	< 0.001*
Maximal Bromage scale	1 (0-1)	1 (1-1)	*0.*066
Sedation score	1 (1-1)	1 (1-2)	0.001*
Patient satisfaction	4 (4-4)	4 (4-5)	0.025*

Data presented as mean ± standard deviation or median (range)
**P* value < 0.05 (significant value)

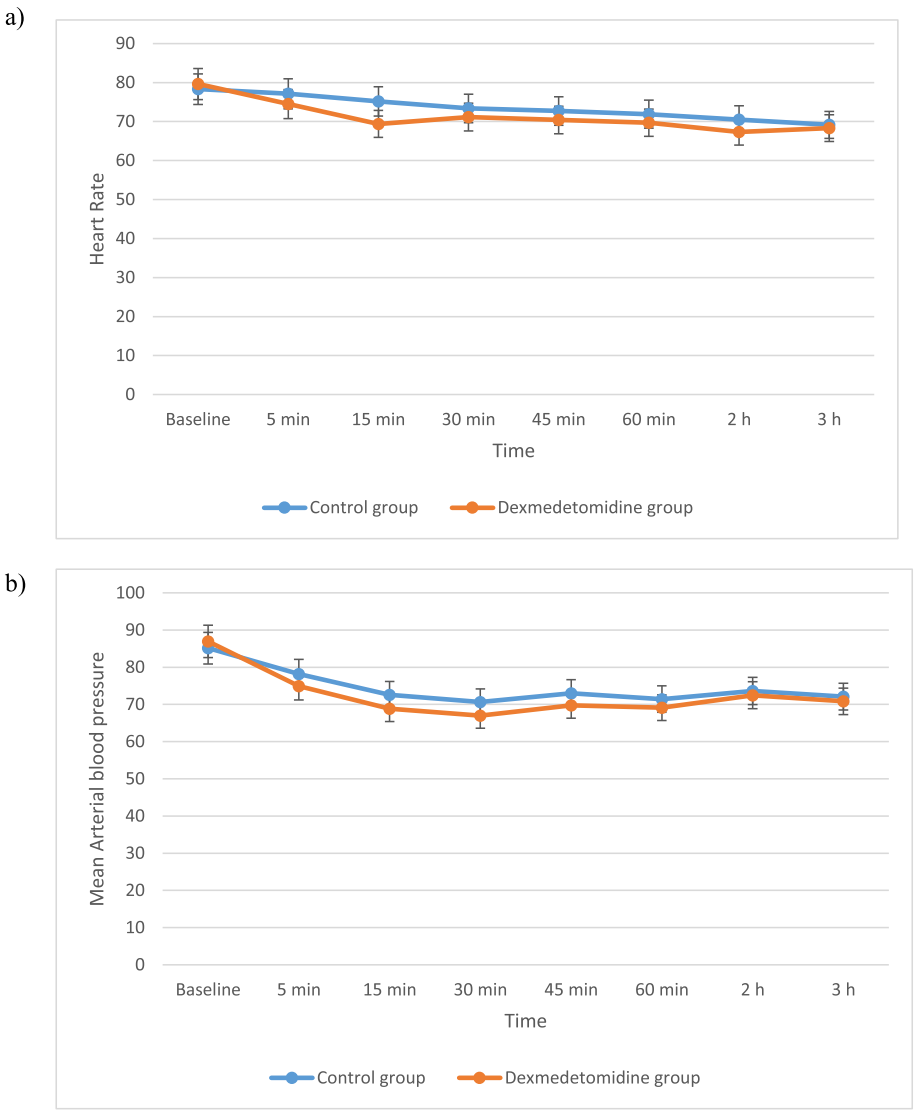

Fig. 2 **a** Heart rate in the study groups. **b** Mean arterial blood pressure in the study groups

Table 3 Neonatal outcomes and maternal complications in the study groups

		Control group (n = 30)	Dexmedetomidine group (n = 30)	P value
Neonatal outcomes	Apgar 1 min	8.10 ± 0.92	8.17 ± 0.91	0.779
	Apgar 5 min	9.37 ± 0.67	9.43 ± 0.63	0.692
	Fetal weight (kg)	3.19 ± 0.24	3.22 ± 0.27	0.611
Maternal complications	Bradycardia	5 (16.7%)	10 (33.3%)	0.136
	Hypotension	8 (26.7%)	12 (40%)	0.273
	Respiratory depression	0	0	-

Data presented as mean ± standard deviation or patient number (percentage)
*P value < 0.05 (significant variable)

time decreases maternal anxiety (Zhang et al. 2017). Whatever the sedation score used, many studies have reported the same results (Zhao et al. 2017; 2019; Cheng et al. 2019).

The mean arterial blood pressure and the heart rates were significantly lower in the dexmedetomidine group than the control group; these were of no clinical significance from our point of view as the values were within the normal range and the adverse effects as hypotension and bradycardia were statistically insignificant. Zhao et al. (2017), and Jun et al. (Jun et al. 2018) reported the same results. The decreased value of both parameters could be explained by a better analgesic response in the dexmedetomidine group along with decreased sympathetic outflow as an action of the drug itself (Carollo et al. 2008).

The motor block did not show any significant difference between the two groups, and it did not affect the mode of delivery. The use of low concentration of bupivacaine (0.125%) seems to provide satisfactory analgesia with a Bromage scale of a median value (Li et al. 2020; Rodríguez-Ramón et al. 2015). Adding low dose of dexmedetomidine (50 μg) does not appear to affect the motor block.

As the dexmedetomidine group reported better analgesic efficacy and better sedation score compared to the control group, it was reasonable to report a significant improvement in patient satisfaction with dexmedetomidine administration.

Regarding the labor progress and Apgar score, our results were in line with other studies (Jun et al. 2018; Zhao et al. 2017; Wangping and Ming 2017) that negated any significant difference between the two groups.

One of the limitations in this study is that dexmedetomidine was used as an equal dose (50 μg); for all the patients, it would be more accurate if we use a dose according to the patient's weight. Additionally, we did not measure the umbilical cord pH used for the assessment of fetal outcomes.

Conclusions

Overall, dexmedetomidine appears to be a reliable and effective adjuvant to the local anesthetics in epidural analgesia during normal delivery as it resulted in earlier onset and significant prolongation of the analgesic time with decrease in the top-up doses intake. In addition, no significant adverse effects were noted either on mother or fetus.

Abbreviations

APGAR score: Appearance, Pulse, Grimace, Activity and Respiration score; ASA: American Society of Anesthesiologists; BMI: Body Mass Index; HR: Heart Rate; L: Lumbar; MAP: Mean Arterial Pressure; SD: Standard Deviation; SPSS: Statistical Package for Social Science; VAS: Visual Analog Scale

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Not applicable.

Authors' contributions

MEA contributed in the idea and the design of work. RFM and MMAA contributed to the literature search, analysis, and interpretation of data. RFM and MEA contributed in the manuscript preparation, editing, and review. HL contributed in the follow-up of the progress of labor, fetal monitoring, delivery of the fetus, and collecting the data for interpretation. All the authors have read and approved the final submitted manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Local Ethical Committee of Tanta University (approval number 31725/08/17) and Pan African Clinical Trial Registration (PACTR201710002664704). A written informed consent was obtained from the participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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