Clinical and Experimental Obstetrics & Gynecology

Original Research

Efficacy of intrathecally administered fentanyl versus dexmedetomidine for cesarean section: a double blinded, randomized clinical trial

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Background: Dexmedetomidine, a highly selective α_2 agonist has been studied in the past for its use as adjuvant to local anesthetics for spinal anesthesia. Fentanyl has also been used as a spinally administered adjuvant to various local anesthetics. The aim of this study was to investigate the duration of motor and sensory block along with the hemodynamic parameters, neonatal Apgar scores, postoperative analgesia and maternal satisfaction of overall anesthetic/analgesic regimen in parturients under ropivacaine 0.75% plus dexmedetomidine or fentanyl spinal anesthesia. *Methods*: Forty patients American Society Of Anesthesiology (ASA) I or II, scheduled for elective cesarean section were studied. Patients were randomly allocated to receive ropivacaine 0.75% 1.6–2 mL plus 10 μg fentanyl (Group F, n = 20) or ropivacaine 0.75% 1.6–2 mL plus 10 μg dexmedetomidine (Group D, n = 20), intrathecally. The primary outcome was duration of motor and sensory block. Secondary outcomes were:neonatal Apgar scores in the first and fifth minute, additional postoperative analgesia, time to first postoperative analgesic dose and maternal satisfaction of overall anesthesia and analgesia. *Results*: Patients in dexmedetomidine group (Group D) had prolonged duration of motor and sensory block when compared to patients in fentanyl group (Group F). Mean duration of motor block was significantly higher in Group D than in Group F (163.75 min versus 124.75 min respectively, p = 0.013). Regression of the sensory block to T_8 was significantly prolonged for Group D (158.50 min Group D versus 114.25 min in Group F, p = 0.021). Neonatal Apgar scores, additional postoperative analgesia, time to first postoperative analgesic dose and maternal satisfaction of overall anesthesia/analgesia process, did not statistically differ between the groups. *Conclusions*: Intrathecal dexmedetomidine is associated with prolonged motor and sensory block. Its profile is similar to fentanyl in terms of cardiovascular stability, sedation, Apgar scores, patient satisfaction and postoperative analgesia.

Keywords

Intrathecal dexmedetomidine; Elective cesarean section; Adjuvant

1. Introduction

Intrathecal local anesthetics with or without adjuvants are commonly used for elective cesarean section. Many drugs such as opioids, neostigmine, α_2 adrenergic agonists, ketamine, midazolam have been used as adjuvants to local anesthetics in ordertoimprove the quality of spinal anesthesia. Dexmedetomidine is eight times more specific and highly selective α_2 agonist than clonidine. Dexmedetomidine is metabolized in the liver and has a distribution half-life of 6 to 8 min. It is highly lipophilic and has, therefore, a high volume of distribution. When used intravenously, dexmedetomidine produces sedation with preserved respiratory drive. Both clonidine and dexmedetomidine have been extensively studied as adjuvants to spinal local anesthetics, but trials in the obstetric population are scarce, due to the demanding nature of obstetric anesthesia [1, 2].

This prospective, double blinded, randomized study explored whether intrathecal dexmedetomidine as adjuvant to ropivacaine 0.75% provided improved quality of anesthesia for cesarean section when compared to fentanyl. The primary outcome of this study was the duration of motor and sensory block. Secondary outcomes included neonatal Apgar scores in the first and fifth minute, additional postoperative analgesia, time to first postoperative analgesic dose and maternal satisfaction of overall anesthesia and analgesia.

2. Materials and methods

The regional Ethics Committee approved the study. Oral and written informed consent was obtained from all the patients. The study was carried out in accordance with the principles of the Helsinki Declarations.

Healthy parturients (ASA II), >37 weeks of gestation, scheduled for elective Cesarean section, under combined spinal epidural anesthesia were included. Exclusion criteria were: pre-eclampsia, eclampsia, Body Mass Index (BMI) >40, age <18 years, height <150 cm or height >180 cm, gestational diabetes, known cardiovascular disease of the mother, contraindication to neuraxial blockade. Enrolled patients were excluded from the study if spinal anesthesia was unsuccessful, if they had prolonged surgery >90 min or an estimated blood loss more than 500 mL. They were also excluded if they required second operation for postpartum hemorrhage.

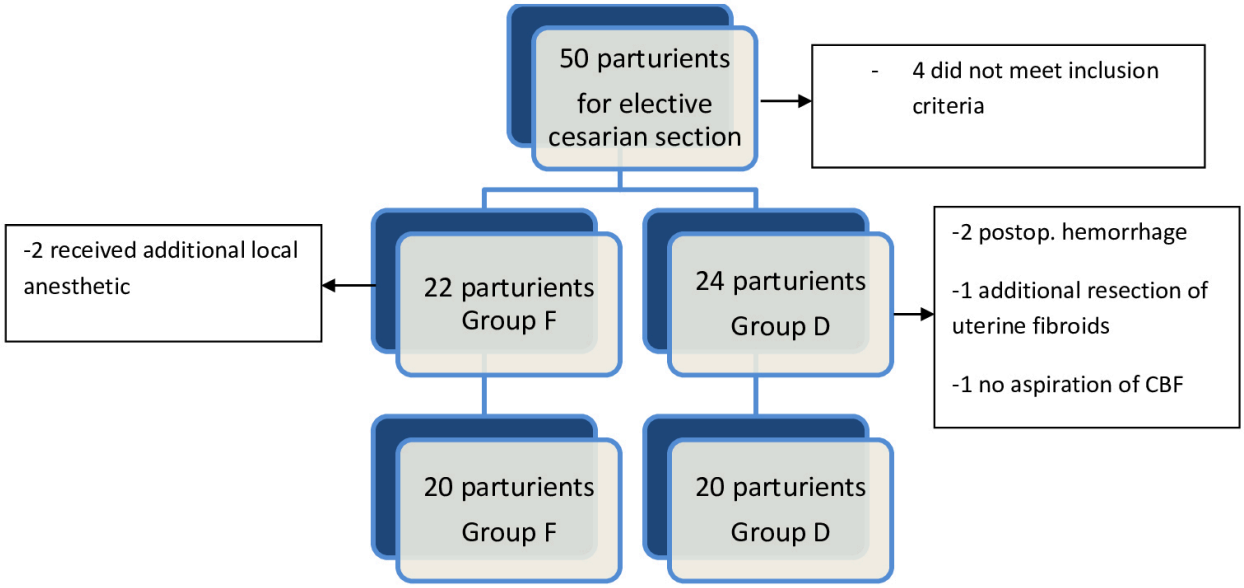

Fig. 1. Flow-chart of patient population. CBF, cerebrospinal fluid.

The trial was performed from 2015 to 2018 as a single-center, prospective, randomized, double blind controlled study. Sample size was calculated using G*Power version 3.1.9.7 (Faul F. University of Kiel, Kiel, Germany) and the following parameters: number of groups: 2, number of measurements: 9, correlation among repeated measures = 0.5, non-sphericity correction ε = 1, error α = 0.01, partial η^2 = 0.06, power = 99%). Minimum sample size per group was 20. The research staff (three Anesthesiologists with >10 years of experience in Obstetric Anesthesia) who enrolled the women and collected study data were blinded to group assignment. Group assignment was done at the time of enrolment by choosing an opaque serially numbered envelope. An independent Anesthesiologist, who was blinded to the injected drug, recorded all the parameters. The Obstetricians/Gynecologists were also blinded to anesthesia technique.

Forty-six parturients were randomly assigned to two groups of 23. Computer-generated random numbers were used for randomization of subjects. Parturients received 1.6–2.0 mL intrathecal ropivacaine 0.75% (Naropeine®, Astra Zeneca, Athens, Greece) plus 10 μg fentanyl (Group F) or 1.6–2.0 mL intrathecal ropivacaine 0.75% plus 10 μg dexmedetomidine (Dexdor® 100 μg/mL, Orion Pharma Ltd, Reading, United Kingdom) (Group D). Ropivacaine doses were decided at the anesthesiologists' judgement and the dose was based on the parturients' height. Dexmedetomidine dose was decided after a small pilot study which was based on recent literature [3].

All women eligible for the study were preloaded with 15 mL/kg Ringer's Lactate solution intravenously prior to spinal anesthesia and 500 mL hydroxyethyl starch (Voluven®, Fresenius Kabi Hellas, Athens, Greece) according to institutional guidelines. They were also pretreated with 4 mg intravenous ondasetron. No other analgesic or sedative agent was used during surgery. Basic monitoring probes (electrocardiography, non-invasive blood pressure, O_2 saturation) were applied. The parturients were placed in the lateral decubitus position and the epidural space was identified at the L_2 to L_3 interspace. After lumbar puncture with a 26-gauge pencil-point needle, the intrathecal drug was administered. The epidural catheter was placed as soon as the spinal needle was withdrawn and the parturients were immediately positioned supine with left lateral tilt. The operation started when the sensory block reached T_4 dermatome as determined by loss of sensation to pinprick.

Vital signs were continuously monitored but recorded as baseline, 1 min intervals until the fifth minute (starting from the administration of the intrarthecal drug) and every ten minutes thereafter until the end of the procedure. Vital signs were continuously recorded; only important anesthetic time-points have been included in Table 1, as all women remained practically hemodynamically stable after 25 min of intrathecal drug administration. Mean duration sensory block was recorded on regression to T_8, by evaluating warm/cold sensation. Motor block was assessed using the Bromage Scale (1: unable to remove feet or knees, 2: able to move feet only, 3: just able to move knees, 4: full flexion of knees and feet). Times from administration of the intrathecal drug to maximum motor blockade were recorded and mean duration of motor block overall was assessed by regression to Bromage 3. Hypotension (a decrease in systolic blood pressure of more than 30% from the baseline or a decrease below 90 mmHg) was treated with 10 to 15 mg ephedrine and bradycardia (heart rate <60 beats per minute) was treated with 0.5 mg atropine. The Apgar scores were evaluated at 1 and 5 min af-

Table 1. Variability of mean arterial pressure and heart rate between groups and time of first administration of analgesia.

	Group			
	Group F		Group D	
	Mean	Standard deviation	Mean	Standard deviation
Mean Arterial Pressure 1' (mmHg)	81.70	6.91	72.35	12.69
Mean Arterial Pressure 5' (mmHg)	80.85	5.82	78.90	5.68
Mean Arterial Pressure 15' (mmHg)	81.90	7.52	110.95	156.53
Mean Arterial Pressure 25' (mmHg)	75.10	9.19	73.10	11.12
Heart Rate 1' (bpm)	97.50	16.40	91.25	17.90
Heart Rate 5' (bpm)	94.35	17.25	86.75	14.39
Heart Rate 15' (bpm)	100.35	19.37	85.25	12.36
Heart Rate 25' (bpm)	100.95	12.31	92.95	26.62
1st administration of analgesia (min)	382.50	192.94	501.05	352.60

Bpm, beats per minute.

ter delivery. Women's satisfaction of the anesthetic/analgesic technique was also evaluated on the first postoperative day by a simple scale ranging from 0 (not satisfied at all) to 10 (very satisfied). Time to first postoperative analgesic administration was recorded and included paracetamol 500 mg t.i.d and subcutaneous morphine (1 mg/kg, according to ideal body weight) b.i.d.

Statistical analysis was performed using SPSS Software version 25 (IBM Corp, Armonk, NY, USA). The continuous variables were expressed in the form of mean value and standard deviation, while the discrete ones in frequency and relative frequency (%). The "Repeated Measures ANOVA" (RM-ANOVA) method was used to compare the variability of the studied variables with the univariate approach. The Two Independent Samples *T*-Test or the Mann-Withney Test (in case of violation of the assumptions of the parametric statistical criterion) was used to compare the mean values of two independent continuous variables. The Chi Square Test was used to test the relationship between two categorical variables. The significance level was set at 5%.

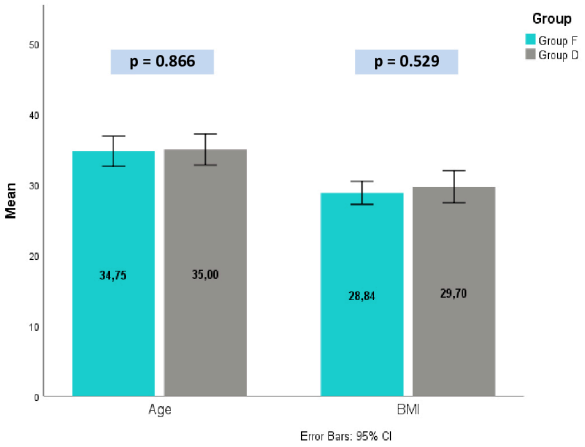

Fig. 2. Age and BMI (Body Mass Index) of the groups.

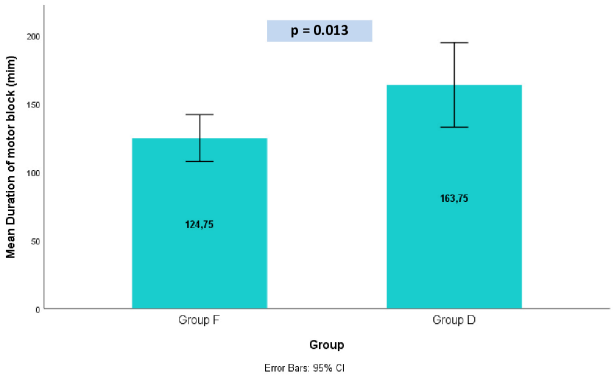

Fig. 3. Mean duration of motor block (min) of Groups F, D.

3. Results

Of the 46 parturients, six were excluded from the study. Two were in Group F: both of them received additional local anesthetic via the epidural catheter due to insufficient anesthesia. Four were in Group D: two underwent second operation for postpartum hemorrhage, one underwent myomectomy (uterine fibroids were a random intra-operative finding) in addition to cesarean section and in one there was no aspiration of cerebrospinal fluid. Forty parturients completed the study (Fig. 1).

There were no significant differences among groups in demographic data (Fig. 2), clinical characteristics and duration of surgery ($p > 0.05$). Mean duration of motor block was significantly higher in Group D than in Group F (163.75 min versus 124.75 min respectively, $p = 0.013$) (Fig. 3). Regression of the sensory block to T_8 was significantly prolonged for Group D (158.50 min Group D versus 114.25 min in Group F, $p = 0.021$) (Fig. 4).

Regarding hemodynamic variables measured during the intra-operative period, there were no significant differences between groups (Table 1). Additionally, there were no statistically significant differences in neonatal Apgar scores (first and fifth minute), need for additional postoperative analgesia and maternal satisfaction of overall anesthesia/analgesia

procedure (Figs. 5,6,7,8,9). Mean time to first postoperative analgesic dose was 382.5 min for Group F and 501 min for Group D; although prolonged for Group D, time did not statistically differ from Group F (p = 0.21, Table 1, Fig. 8). No significant difference in the onset of anesthesia or in the highest level of sensory block was observed.

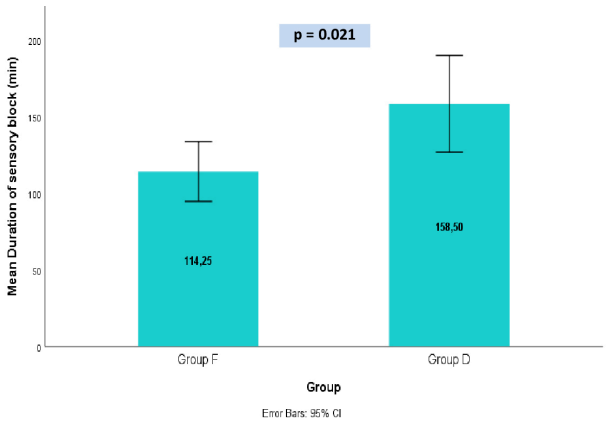

Fig. 4. Mean duration of sensory block (min) of Groups F, D.

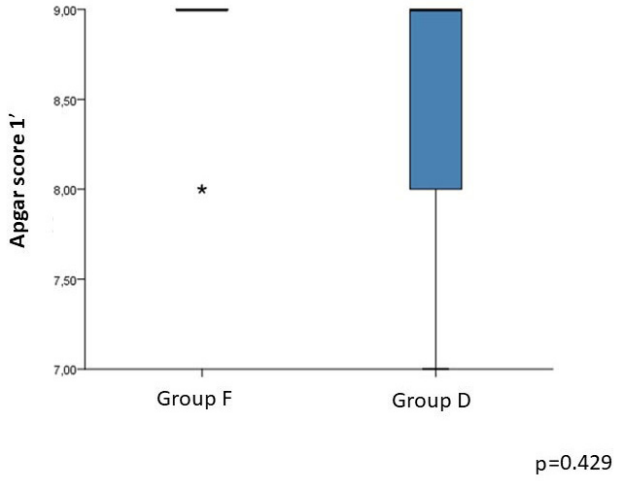

Fig. 5. Apgar scores 1' of neonates of Groups F, D.

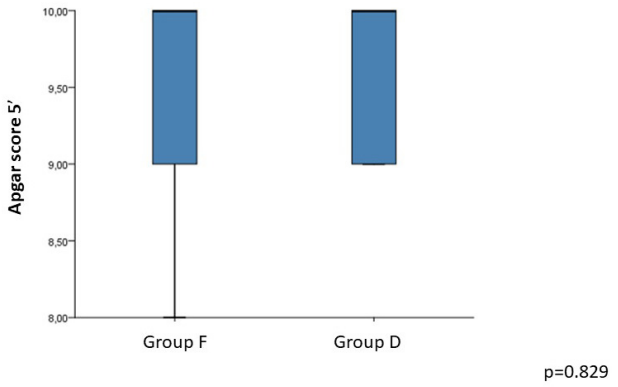

Fig. 6. Apgar scores 5' of neonates of Groups F, D.

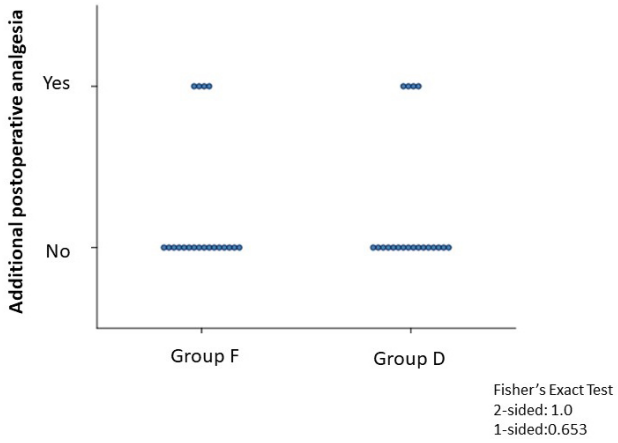

Fig. 7. Additional postoperative analgesia for Groups F, D.

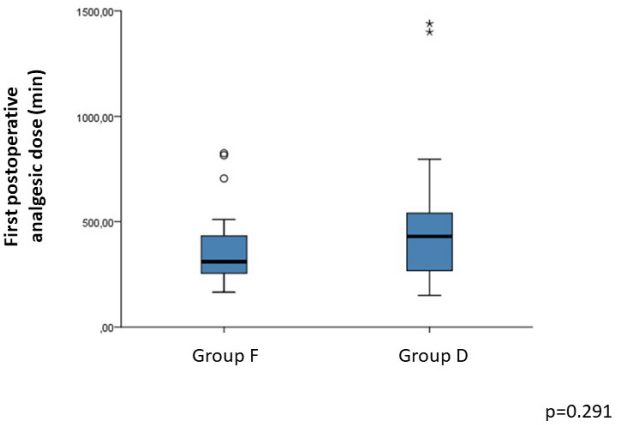

Fig. 8. Time to first postoperative analgesic dose in minutes for Groups F, D.

4. Discussion

To our knowledge, this is the first study assessing the efficacy of dexmedetomidine as adjuvant to ropivacaine for elective cesarean sections. Gupta *et al.* [4] found that 5 μg of intrathecal dexmedetomidine as adjuvant to bupivacaine, is associated with prolonged motor and sensory block, hemodynamic stability and reduced demand for rescue analgesics in 24 hours as compared to fentanyl. Similarly, in the present study, time to first postoperative analgesic dose was prolonged for parturients that received dexmedetomidine, but not in a statistically significant way (p = 0.291). Both Qi *et al.* [5] and Kamal *et al.* [6] concluded that dexmedetomidine prolonged sensory and motor block without significantly increasing side effects. The present study is in accordance with their results. Mean duration of motor and sensory block was prolonged for women in Group D (163.75 and 158.5 min respectively). Motor and sensory blockade was

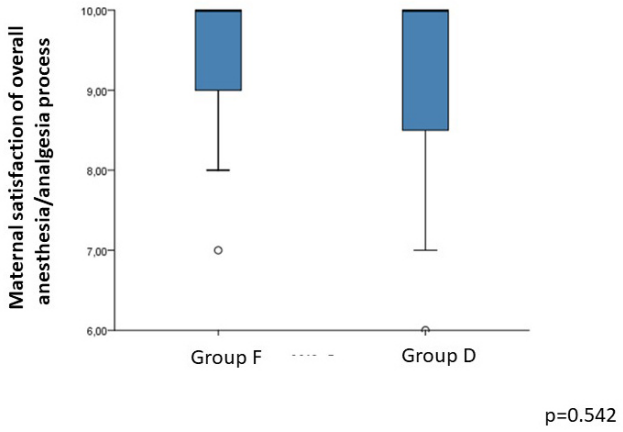

Fig. 9. Maternal satisfaction of overall anesthesia/analgesia process for Groups F, D.

prolonged for women who received intrathecal dexmedetomidine; these were the only results of the present study that met statistically significant levels ($p = 0.013$ and $p = 0.021$ respectively/Figs. 3,4). Dexmedetomidine has been found to be safe for the neonates when administered intrathecally [7]. Its safety has also been demonstrated even when administered in larger doses [8, 9] (e.g., as intravenous continuous infusions along with remifentanil or fentanyl for labor). In the present study, Apgar scores did not differ between the groups; however, the results fell short of meeting the statistically significant p value of 0.05.

Only a few studies with dexmedetomidine as adjuvant to local anesthetics for cesarean sections have been published so far [2, 4–6]. In some countries the intrathecal use of dexmedetomidine for obstetric anesthesia is still off-label. The usual dose of intrathecal dexmedetomidine, in these studies, was 5 μg and the local anesthetic used was bupivacaine 0.5%. Only Sun *et al.* [2] administered 10 μg of intrathecal dexmedetomidine as adjuvant to bupivacaine. Similarly to the above-mentioned studies, the addition of 10 μg of intrathecal dexmedetomidine significantly prolonged the mean duration of sensory and motor block. It appears however that ropivacaine 0.75% has a more favourable profile for the parturient when combined with dexmedetomidine. Although in accordance with the results published by Qi *et al.* [5] and Kamal*et al.* [6], as far as sensory block prolongation with dexmedetomidine is concerned, it should be noted that in our study, sensory block lasted fewer minutes. Similarly, mean duration of motor block was shorter for the dexmedetomidine-ropivacaine group (163.75 min) when compared to dexmedetomidine-bupivacaine groups (e.g., motor regression time of 226 $\pm$ 40.51 min by Qi *et al.* [5], 265.42 min by Kamal *et al.* [6]).

In the present study, it is also worth mentioning that the addition of 10 μg of intrathecal dexmedetomidine was not associated with remarkable adverse effects (or hemodynamic instability. This is illustrated by the Apgar scores and the positive feedback we received from women when asked of their experience regarding anesthesia/analgesia. Mean time to first administration of postoperative analgesic dose was 501.05 $\pm$ 352.60 min; significantly longer than times reported by previous authors.

The present study has several limitations: there is no control group and the dose of ropivacaine 0.75% ranged from 1.6–2 mL according to the decision of the anesthesiologist involved. As the child-bearing age advances in Europe, further studies are needed to ensure the safety and efficacy of dexmedetomidine as adjuvant to local anesthetic, in parturients with co-existing disease such as: hypertension, preeclampsia, eclampsia and complex neurologic syndromes.

5. Conclusions

In conlusion, it appears that the addition of 10 μg of dexmedetomidine to 1.6–2 mL of ropivacaine 0.75% significantly prolongs the mean duration of sensory and motor block in elective cesarean sections. Patients on dexmedetomidine remained pain-free longer postoperatively. Given the hemodynamic stability and the lack of adverse effects in the parturient, 10 μg of additional dexmedetomidine intrathecally might be useful in cases where, further surgical manipulations are about to take place during the cesarean section, such as tubal ligation or excision of uterine fibroids.

Abbreviations

t.i.d, three times daily; b.i.d, twice daily.

Author contributions

AT and AM conceived and designed the project. TM and KT did the data collection, data analysis and interpretation, ATG drafted the article and performed its critical revision. All authors approved the final version of the manuscript to be published.

Ethics approval and consent to participate

Ethics approval was obtained from Aretaieion University Hospital Ethics Committee (approval no 17896). Oral and written consent was obtained from all patients and is kept in their medical records.

Acknowledgment

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Conflict of interest

The authors declare no conflict of interest.

References

[1] Nair A, Sriprakash K. Dexmedetomidine in pregnancy: Review of literature and possible use. Journal of Obstetric Anaesthesia and Critical Care. 2013; 3: 3–6.

[2] Sun S, Wang J, Bao N, Chen Y, Wang J. Comparison of dexmedetomidine and fentanyl as local anesthetic adjuvants in

spinal anesthesia: a systematic review and meta-analysis of randomized controlled trials. Drug Design, Development and Therapy. 2017; 11: 3413–3424.
[3] Khosravi F, Sharifi M, Jarineshin H. Comparative Study of Fentanyl vs Dexmedetomidine as Adjuvants to Intrathecal Bupivacaine in Cesarean Section: A Randomized, Double-Blind Clinical Trial. Journal of Pain Research. 2020; 13: 2475–2482.
[4] Gupta R VR, Bogra J, Kohli M, Raman R, Kushwaha J. A comparative study of intrathecal dexmedetomidine and fentanyl as adjuvants to bupivacaine. Journal of Anaesthesiology Clinical Pharmacology. 2011; 27: 339–343.
[5] Qi X, Chen D, Li G, Huang X, Li Y, Wang X, *et al.* Comparison of Intrathecal Dexmedetomidine with Morphine as Adjuvants in Cesarean Sections. Biological and Pharmaceutical Bulletin. 2016; 39: 1455–1460.
[6] Kamal M IJ, Saaed A, Zayed M, Magdy M. Comparison of intrathecal dexmedetomidine and fentanyl as asjuvants to levobupivacaine in parturients undergoing elective cesarean sections. The Medical Journal of Cairo University. 2017; 85: 593–600.
[7] Wang C, Liu S, Han C, Yu M, Hu Y, Liu C. Effect and placental transfer of dexmedetomidine during caesarean section under epidural anaesthesia. Journal of International Medical Research. 2017; 45: 964–972.
[8] Nie Y, Liu Y, Luo Q, Huang S. Effect of dexmedetomidine combined with sufentanil for post-caesarean section intravenous analgesia: a randomised, placebo-controlled study. European Journal of Anaesthesiology. 2014; 31: 197–203.
[9] Abdalla W, Ammar MA, Tharwat AI. Combination of dexmedetomidine and remifentanil for labor analgesia: A double-blinded, randomized, controlled study. Saudi Journal of Anaesthesia. 2015; 9: 433–438.