Original Article

Comparing the efficacy of different doses of intrathecal dexmedetomidine on hemodynamic parameters and block characteristics with ropivacaine spinal anesthesia for cesarean section: A double-blind, randomized clinical trial

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Abstract

Aims: This study aimed to assess the dose-related efficacy of intrathecal dexmedetomidine (DEX) on hemodynamic parameters and block characteristics following ropivacaine (ROP) spinal anesthesia (SA) for cesarean section (CS).

Methods: This was a double-blind trial conducted on four groups namely D2.5, D5, D7.5, and placebo. One hundred and twenty patients scheduled for nonemergency CS under SA were recruited and randomized into four groups. The first to fourth groups received 2.5 μg, 5 μg, and 7.5 μg of intrathecal DEX and 1.5 mL normal saline, respectively, in addition to ROP for SA. Blood pressure (BP), heart rate (HR), arterial blood saturation, sensory motor block, and pain score were recorded.

Results: The lowest BP/HR was observed in D7.5 group ($P < 0.05$). Moreover, the onset and duration of sensory motor block were shorter ($P = 0.0001$) and showed the lowest level of pain ($P = 0.0001$) in D7.5 group. Decrease in BP, HR, and pain score was observed with increasing dose of DEX, whereas the onset of sensory motor block and the time to achieve sensory motor block to ≥T6 declined with increasing the dose of DEX.

Conclusion: The 7.5-μg intrathecal DEX is recommended to use for stabling the hemodynamic parameters and block characteristics following ROP SA for CS. However, likely complications such as fall in both HR and BP should be taken into account simultaneously.

Key Words: Block characteristics, cesarean section, different doses of dexmedetomidine, hemodynamic parameters, intrathecal, neonatal Apgar score, ropivacaine, spinal anesthesia

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INTRODUCTION

Regional anesthesia remains the most common technique to numb the portion of body that will undergo the surgery.[1] Subarachnoid spinal anesthesia (SA) was first introduced by Bier in 1898[2] and has unique

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advantages such as fast onset of action, better patient comfort, less adjuvant required, and an excellent sensory motor block.[1] Stimulation of α-2 adrenergic receptor, including dexmedetomidine (DEX) in the spinal cord, can improve postoperative pain.[3-5]

DEX provides better postoperative analgesia and prolongs the duration of sensory motor block with minimal complications.[6] Several studies have been done on the effect of adding DEX to ropivacaine (ROP).[7,8] ROP is a fast acting agent with a rapid onset of action like lidocaine, and without reported lidocaine related side effects, such as pituitary syndrome. Hence, the evidences for using ROP is increasing. As the onset of action is faster in ROP than that of bupivacaine (BUP), this plays an important role in the consequences of anesthesia.[1] Given that cesarean section (CS) is associated with the lives of both pregnant women and their fetuses, a method that does not endanger mother's health should be used. Hence, intrathecal DEX can be administered to induce SA in women undergoing CS,[9] based on a study by He *et al*., which did not mention any serious complication when using it during CS.

Zhang *et al*. conducted a study using different doses of DEX as an adjuvant to BUP and reported that intrathecal DEX prolongs SA, although it increases the risk of bradycardia.[10] Several studies evaluated both intravenous and intrathecal DEX separately,[11-13] whereas some were focused on the use of different DEX doses as an adjuvant with local anesthetic in SA.[14]

However, because past studies have been explored only cases with no clear and definite results (such as analgesia). Moreover, recent studies did not assess the hemodynamic parameters and neonatal Apgar score at 1 and 5 min after DEX medication with ROP as an adjuvant. Therefore, we aimed to obtaining a dose of DEX as an adjuvant to ROP during SA for CS, with minimal hemodynamic changes, pain, harmful effects and provides more stable conditions during anesthesia in operating room. This study aimed to assess the dose-related efficacy of intrathecal DEX on hemodynamic parameters and block characteristics following ROP SA for CS.

METHODS

This was a double-blind, randomized clinical trial conducted on 120 patients of nonemergency CS undergoing under SA at one of the Arak governmental hospitals in Iran. The patients were recruited after obtaining written informed consent and verification of inclusion/exclusion criteria. The primary outcomes in this study were hemodynamic parameters and pain scores of patients after surgery. The secondary outcome was comparing the sensory block and motor block between the two groups.

Sample size calculation was conducted based on the results of other studies by considering power 80%, significant level 0.05, and mean difference between two groups (d = 2). According to these items, the minimum sample size for each group was estimated to be 30. Therefore, 120 patients were randomized into four groups. Figure 1 shows the consort chart of the study.

Inclusion criteria were age between 18 and 50 years, American Society of Anesthesiologists status II, and patients undergoing CS under SA. The exclusion criteria were patients with failed SA; those with a history of treatment with β-blockers, α2 agonists, and calcium channel blockers; those with cardiovascular problems, coagulation disorders, localized infection in the spinal cord, history of allergy to both DEX and ROP, arrhythmias, psychological problems, peripheral and central neuropathy, fetal distress, and signs of prelabor; multifetal pregnancies; and those with hypertension, preeclampsia, intrauterine growth restriction, polyhydramnios, and macrosomia.

All patients were hospitalized at least 1 day before surgery and were nil per oral for 8 h. After recording demographic data, the baseline heart rate (HR), and mean arterial pressure (MAP) assessed by noninvasive blood pressure (BP) monitoring, as well as arterial blood saturation (SaO_2), were measured and recorded for all patients. Then, patients were followed by administration of 10 mL/kg of crystalloid (ringer) in supine position on arrival to the operating room. Once the vital signs were recorded at baseline, the patients were split into four groups using block randomization. All patients were at modified supine position with the wedge kept below the right buttock. SA was performed by an anesthesiologist using a 25–26G Quincke needle at the L3/L4 or L4/L5 intervertebral space. We used ROP 0.5% (Molteni, Scandicci, Firenze, Italy) to induce SA for all patients[1] and prescribed DEX manufactured by Hospira company (Hospira, Lake Park, Illinois, US). The first group (D2.5) received 2.5 mL of intrathecal ROP 0.5% (12.5 mg) plus 2.5 μg of DEX (1.5 mL) (4 mL total volume); the second group (D5) received 2.5 mL of ROP 0.5% (12.5 mg) plus 5 μg of intrathecal DEX (1.5 mL) (4 mL total volume); the third group (D7.5) received 2.5 ml of ROP 0.5% (12.5 mg)

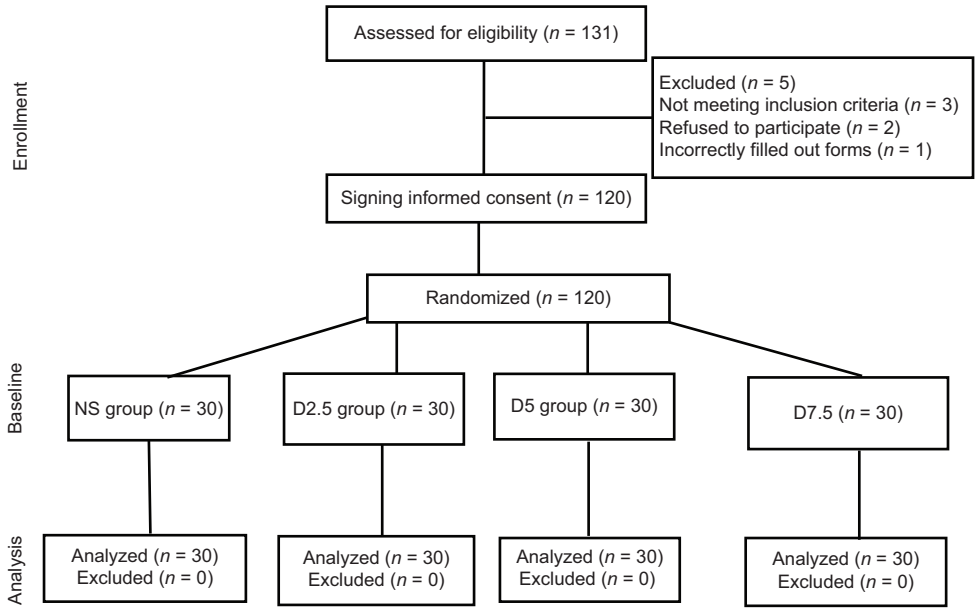

Figure 1: CONSORT diagram showing the flow of participants through each stage of a randomized trial

plus 7.5 µg of intrathecal DEX (1.5 mL) (4 mL total volume); and the fourth group; placebo (PBO) received 2.5 mL of ROP 0.5% (12.5 mg) with 1.5-mL distilled water (4-mL total volume).

The MAP, HR, and SaO_2 were recorded for all patients in the four groups by an anesthetist during surgery and recovery (every 5 min). Hypotension was defined as a 20% drop in mean BP, bradycardia <45 bpm, and SaO_2 of <92%. For each group, the sensory motor block to ≥T6 was measured and recorded by an anesthesiologist resident. The level of sensory block was assessed by means of a needle (pin prick method) every 1 min after anesthesia and that of motor block was also evaluated by the Bromage scale every 5 min.[12]

The surgery was allowed to start when the sensory motor block was assessed and the block to T6 target dermatome was achieved. Therefore, the surgery started after the T6 level was achieved in all patients. Pain scores using Visual Analogue Scale (VAS) scale were recorded by anesthesiologist resident at recovery and 1, 2, 4, 6, and 12 h after surgery, as follows: 0, the lowest; 10 the highest. If VAS >4, 0.5 mg/kg pethidine (meperidine) was administered at any time after surgery.[13] The time to achieve sensory block at T10 and Bromage score 0 or 1 was also recorded. In case of any complications, such as nausea, vomiting, bradycardia, hypotension, and dizziness, these side effects were recorded. The duration of CS was also recorded for all patients. The neonate Apgar score was recorded at 1 and 5 min.

It should be noted that the data were measured and recorded by an anesthesiologist who had no awareness of patient's medication in order to perform a double-blind study, and preparation of adjuvants was done by a nurse anesthetist for each group. In all cases, an anesthesiologist who was unaware of nature of drug in each syringe performed the SA.

Data analysis was conducted by SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, USA). The one-way analysis of variance was used to compare the hemodynamic variables (HR and BP), pain, sensory block, and motor block in four groups. Moreover, the *post hoc* Tukey test was used for binary comparison of groups. Comparing the trend of studied variables among different groups was assessed by analysis of variance for repeated measurements. In addition, Chi-square test was used to compare groups regarding the need for meperidine and side effects.

RESULTS

The CS patients (n = 120) under SA at Taleghani Hospital, Arak, Iran, were randomly assigned into four groups equally and each group included thirty patients. No statistically significant difference was observed in age and duration of surgery among the four groups ($P > 0.05$).

A significant difference was seen in BP among all patients [Table 1] from 35 to 75 min after the start of surgery ($P < 0.05$). The lowest BP was observed in

Table 1: Comparison of mean and standard deviation of mean of blood pressure (mmHg) in four groups

Mean of BP at postoperative time (min)	Group, mean±SD				*P*
	D2.5	D5	D7.5	PBO	
Baseline	90.83±8.59	91.06±8.56	91.00±8.58	91.16±8.33	0.999
5	89.80±8.72	89.73±8.43	90.13±8.66	90.46±8.23	0.986
10	88.43±8.60	88.66±8.35	87.50±8.91	90.33±8.15	0.632
15	87.93±8.48	88.06±8.02	86.90±8.69	90.26±8.10	0.461
20	87.550±8.59	87.70±7.83	86.36±8.48	90.03±8.04	0.376
25	87.13±8.34	87.06±7.49	85.56±8.32	90.16±7.98	0.166
30	86.43±8.33	86.56±7.30	85.0±8.15	90.23±8.0	0.075
35	86.06±7.97	86.13±7.07	84.30±8.06	90.16±8.01	0.032
40	86.36±7.77	85.60±6.63	83.56±7.83	90.16±7.92	0.009
45	86.33±7.71	85.36±6.47	83.20±7.80	90.13±7.97	0.005
50	86.70±7.68	85.83±6.13	82.90±7.79	90.10±7.84	0.003
55	87.0±7.49	86.26±5.95	82.66±7.77	90.13±7.89	0.002
60	87.20±7.32	86.50±5.86	82.40±7.64	89.96±7.60	0.001
65	87.40±7.25	86.76±5.64	82.66±7.44	90.06±7.82	0.001
70	87.60±7.14	87.10±5.47	82.93±7.06	90.03±7.98	0.002
75	88.10±6.82	87.50±5.23	83.46±6.41	89.86±7.42	0.002

SD: Standard deviation, PBO: Placebo, BP: Blood pressure

D7.5 group. The groups who used DEX had the lowest and highest BP in D7.5 and D2.5 groups, respectively. Overall, the PBO group had the highest BP. The repeated measurement analysis of variance showed a significant difference in decreasing trend of BP among groups. Moreover, the DEX group showed decreasing effect on BP, whereas in PBO group, this effect was not observed [Figure 2].

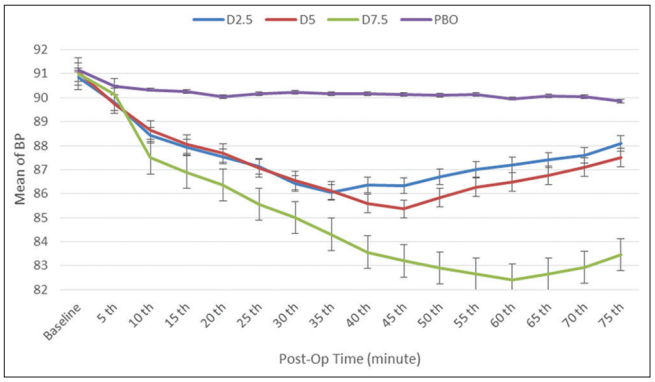

Figure 2: The trend comparison in mean of blood pressure in the four studied groups

Based on Table 2, all patients had a statistically significant difference in HR from 35 to 75 min after the start of surgery ($P < 0.05$), whereas the lowest HR was observed in D7.5 group. The groups who used DEX had the lowest and highest HR in D7.5 and D2.5 groups, respectively, and the PBO group overall had the highest HR. The decreasing trend of HR was statistically significant in D7.5 ($P < 0.001$) bases on repeated measurement analysis of variance [Figure 3], but in other groups, it was not statistically significant ($P > 0.05$).

Based on Table 3, all patients showed significant differences in sensory block onset, the time to achieve sensory block to ≥T6, the time to achieve sensory block to T12/L1, and wearing off of sensory block ($P = 0.0001$). The onset of sensory block after SA and the time to achieve sensory block to ≥T6 were shorter in D7.5 group than that in other groups. The time to achieve sensory block to T12/L1 and wearing off of sensory block were lower in D2.5 group than those in other groups of DEX, but not that in PBO group. Moreover, based on Table 3, significant differences were observed in the onset of motor block after SA, the time to achieve motor block to ≥T6, the time to achieve Bromage 0 or 1, and wearing off of motor block among the four groups ($P = 0.0001$). The onset of block after SA and time to achieve motor block to ≥T6 were shorter in D7.5 group than that in other groups. The time to achieve Bromage 0 or 1 and wearing off of motor block were shorter in D2.5 group than that in other groups, but not in PBO group.

Analysis of variance showed a significant difference in pain score [Table 4] among the four groups at 1, 2, 4, 6, and 12 h after the starting of surgery ($P < 0.001$). The least and highest levels of pain were observed in D7.5 and PBO groups. The increasing trend of pain was significant in PBO group ($P < 0.001$) bases on repeated measurement analysis of variance [Figure 4], but in other groups did not significant ($P > 0.05$). In addition, a significant difference was observed in need for meperidine among the four groups ($P < 0.001$). The need for meperidine was reported in 33.33% (10 patients) of patients in PBO group, whereas there was no need in DEX groups. Moreover, the patients in all groups did not have significant difference in complications (bradycardia and hypotension) and neonatal Apgar score ($P > 0.05$).

Table 2: Comparison of mean and standard deviation of heart rate (beats/min) in four groups

Mean of HR at postoperative time (min)	Group, mean±SD				*P*
	D2.5	D5	D7.5	PBO	
Baseline	90.43±8.72	90.50±8.67	90.46±8.45	90.20±8.63	0.999
5	89.78±8.78	89.53±8.68	88.63±8.48	90.0±8.50	0.938
10	88.50±8.38	89.0±8.27	87.63±7.62	89.93±8.39	0.743
15	88.03±8.16	88.43±7.79	87.16±7.28	89.76±8.35	0.642
20	87.60±7.73	87.90±7.40	86.26±6.80	89.63±7.96	0.384
25	87.16±7.56	87.33±6.82	85.40±6.58	89.70±7.99	0.156
30	86.80±0.7.28	87.06±6.44	85.03±6.31	89.80±8.33	0.083
35	86.86±7.20	86.86±6.15	84.16±5.97	89.76±8.07	0.023
40	87.10±6.95	86.56±5.82	83.30±5.83	89.76±8.13	0.004
45	86.83±6.63	86.00±5.45	83.76±5.56	89.70±7.96	0.001
50	87.30±6.24	86.40±5.28	82.56±5.3	89.80±8.11	<0.001
55	87.53±6.17	86.73±5.19	82.33±5.15	89.70±7.94	<0.001
60	87.60±6.06	87.06±4.87	82.26±4.92	89.66±7.87	<0.001
65	87.96±5.84	87.43±4.95	82.43±4.68	89.93±8.39	<0.001
70	88.40±5.72	87.86±4.86	82.66±4.54	89.33±7.8	<0.001
75	88.83±5.58	88.13±4.75	82.86±4.47	89.40±7.65	<0.001

SD: Standard deviation, PBO: Placebo, HR: Heart rate

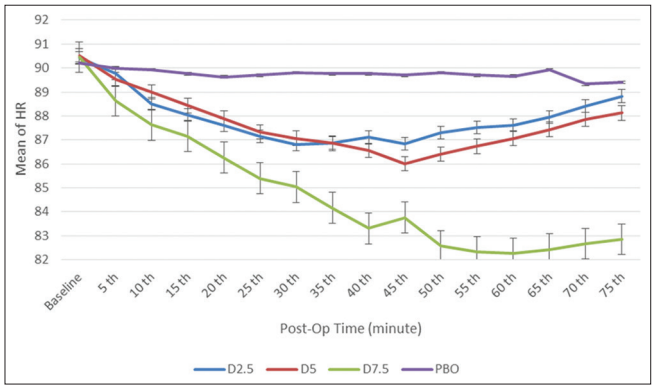

Figure 3: The trend comparison in mean of heart rate in the four studied groups

DISCUSSION

This study aimed to compare the dose-related efficacy of intrathecal DEX on hemodynamic parameters, block characteristics, and neonatal Apgar score following ROP SA in CS. The DEX groups had the lowest and highest BP and HR in D7.5 and D2.5 groups, respectively. The onset of sensory block after SA and the time to achieve sensory block to ≥T6 were shorter in D7.5 group than those in other groups. The onset of block after SA and the time to achieve motor block to ≥T6 were shorter in D7.5 group than those in other groups. While the least level of pain was observed in D7.5 group, the highest was observed in PBO group.

Our study showed that increasing dose of DEX decreased BP and HR, and the onset of sensory motor block and the time to achieve sensory-motor block to ≥T6 decreased by increasing the dose of DEX. However, an increased dose of DEX increases the time to achieve sensory block to T12/L1 and wearing off of sensory block, as well as the time to achieve Bromage 0 or 1 and wearing off of motor block, while this decreased BP and HR. A study by Naithani *et al*. assessed the dose-dependent effect of intrathecal DEX on ROP in SA for abdominal hysterectomy to evaluate the level and severity of block and concluded that similar block characteristic and postoperative analgesia were produced by both doses (3 μg vs. 5 μg) of DEX. However, more hypotension and sedation were seen in group receiving dose of 5-μg DEX as compared to the other group.[15] The difference in block characteristics can be due to the greater number of samples and use of different doses in our study.

We compare different doses of DEX and found that the lowest BP/HR was observed in D7.5 group and the onset and duration of sensory-motor block were shorter in this group compared to that of other groups. A meta-analysis study by Zhang *et al*. at 2016 assessed the dose-related effects of intrathecal DEX in SA. That study showed a high dose of DEX was considered to be 5–15 μg, whereas low dose was 2–5 μg. Comparison of sensory block in low-and high-dose DEX was found 36.06 min and a significant correlation was seen. Significant differences were observed in reduced duration of first sign of sensory-motor block and in increased duration of motor block. High-dose DEX increased the duration of analgesia and decreased postoperative anesthetic consumption, though, the risk of bradycardia was increased in high-dose DEX. Finally, they reported that the dose of intrathecal DEX prolongs SA, although, it increases the risk of bradycardia at the same time.[10] Their results were consistent with our study, but no bradycardia and other complications here were observed. In addition, another similar study, by Singh *et al*., compared two different doses of intrathecal DEX as an adjuvant with ROP in lower abdominal surgery and

Table 3: Comparison of mean and standard deviation of sensory block and motor block in four groups

Time (min)	Mean±SD				*P*
	D2.5	D5	D7.5	PBO	
Sensory block					
Onset of sensory block after SA (min)	5.36±0.718	4.33±0.758	2.83±0.746	7.27±0.739	<0.001
The time to achieve sensory block to T12/L1 and wearing off of sensory block	120.67±5.86	132.43±5.56	141.17±6.11	101.10±5.040	<0.001
Time to achieve motor block to ≥T6 (using pin prick test every 1 min)	6.37±0.718	5.33±0.758	3.80±0.714	8.266±0.739	<0.001
Motor block					
Onset of motor block after SA	9.33±0.711	8.33±0.758	6.80±0.714	11.266±0.739	<0.001
Time to achieve motor block to ≥T6 (Bromage Grade 3) (min)	11.333±0.711	10.33±0.758	8.80±0.714	13.266±0.739	<0.001
Time to achieve Bromage 0 or 1 and wearing off of motor block	134.30±5.873	148.60±6.066	163.13±5.99	119.90±6.098	<0.001

SD: Standard deviation, PBO: Placebo, SA: Spinal anesthesia

Table 4: Comparison of mean and standard deviation of pain in the four studied groups

Pain	Group, mean±SD				*P*
	D2.5	D5	D7.5	PBO	
Recovery	0.500±0.508	0.366±0.490	0.133±0.345	0.810±0.402	0.078
1 h postoperative	0.500±0.508	0.366±0.490	0.133±0.345	1.633±0.490	<0.001
2 h postoperative	0.500±0.508	0.366±0.490	0.133±0.345	2.533±0.628	<0.001
4 h postoperative	1.500±0.508	1.166±0.379	1.033±0.182	3.33±0.606	<0.001
6 h postoperative	1.866±0.345	1.733±0.520	1.300±0.466	3.733±0.639	<0.001
12 h postoperative	2.733±0.449	2.033±0.319	1.866±0.434	4.933±0.784	<0.001

SD: Standard deviation, PBO: Placebo

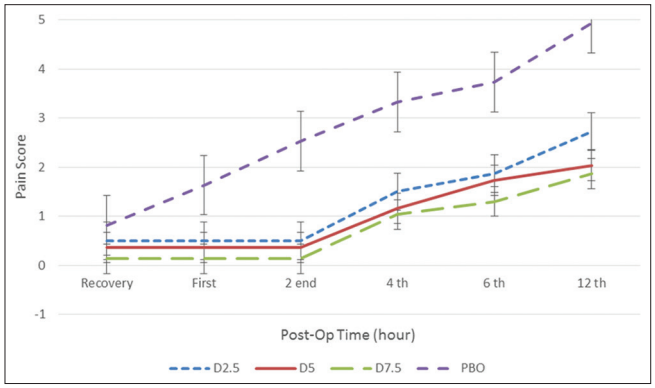

Figure 4: The trend comparison in mean of pain in the four studied groups

showed that the duration of block was higher in 10 μg DEX than that in control group. Sensory motor block was more in dose of DEX than the other two groups. Hemodynamic parameters were stable in three groups. They showed that 10 μg DEX could increase the duration of analgesia without any untoward side effects,[14] whose study results were consistent with ours. Moreover, another study by Sun *et al*. in 2015 conducted to evaluating intrathecal BUP alone, BUP-fentanyl, and BUP-DEX and showed that no significant difference was observed in neonatal Apgar score among their three groups. They reported that DEX-BUP can improve pain management and prolong the sensory motor block,[16] whose results were consistent with those in our study.

Based on our results, DEX is related to prolongation of sensory motor block. Similar studies were consistent with our study.[17-19] The Shaikh and Dattatri's study was aimed at comparing different doses of DEX plus BUP during abdominal surgery, in which significant differences were observed in the duration of sensory block for 10 μg DEX and in Bromage scale 3 motor block for 5 μg DEX. DEX prolongs the sensory motor block.[19] Moreover, Al-Mustafa *et al*. conducted a study which aimed to assess the efficiency of adding DEX to BUP for SA in urological procedures. The duration of sensory motor block was prolonged in 10 μg DEX group, whereas the time to achieve the block was lower. They stated that the dose is effective on the effect on the block.[18] In another similar study, the study by Gupta *et al*. assessed the effect of three different doses of intrathecal DEX (2.5 μg, 5 μg, and 10 μg) on subarachnoid block characteristics in elective lower abdominal and lower limb surgeries and showed that a group with a dose of 10 μg DEX had earlier onset and better and higher block characteristic value than those of other two groups.[17]

This study could assess the dose ranging of intrathecal DEX on hemodynamic parameters and block characteristics following ROP SA in mothers who were referred for CS. However, mothers with higher dose of DEX need to more care and we have exposed to low number of nurse and personnel for care taking.

CONCLUSION

The intrathecal DEX with dose of 7.5 μg is recommended to be used on hemodynamic parameters and block

characteristics following ROP SA for CS. Increased dose of DEX decreased BP, HR, the onset of sensory motor block, and time to achieve sensory motor block to ≥T6. However, the time to achieve sensory block to T12/L1 and wearing off of sensory block, the time to achieve Bromage score of 0 or 1, and wearing off of motor block are related to the dose of DEX administered. Moreover, the pain was reduced in patients after surgery (up to 12 h) with increase in intrathecal dose of DEX.

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Conflicts of interest

There are no conflicts of interest.

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