Intrathecal Bupivacaine – Dexmedetomidine Compared to Intrathecal Bupivacaine - Neostigmine in Elective Caesarian Section: A Randomized Controlled Trial

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Abstract

Background: Caesarean section (CS) is a common surgical procedure associated with moderate-to-severe postoperative pain, which can hinder recovery

Objectives: To evaluate the effects of adding neostigmine versus dexmedetomidine (DEX) to intrathecal hyperbaric bupivacaine 0.5% in CS

Patients and methods: A double-blind, randomized controlled trial was conducted on 54 parturients, aged 18 to 40 years, with a height range of 150 to 170 cm and a weight range of 70 to 110 kg, classified as ASA II, scheduled for elective CS under spinal anesthesia. Participants were randomly assigned to three equal groups. Patients received: 2 mL hyperbaric bupivacaine 0.5% plus 0.1 mL (10 µg) dexmedetomidine (DEX) and 0.1 mL saline 0.9% in group1 (D group).0.1mL (50 µg) neostigmine and 0.1 mL saline 0.9% in group2 (N group). 0.2 mL saline 0.9% in group3 (C group; control)

Results: The time to achieve Bromage 3 (D: 4.1 ± 2.1 min, N: 5.9 ± 2.1 min, C: 8.3 ± 2 min) ($p < 0.001$), time to reach T10 (D: 5.2 ± 2.1 min, N: 7 ± 1.7 min, C: 9.1 ± 1.9 min) ($p < 0.001$), time to reach T4 (D: 7.3 ± 1.7 min, N: 8.9 ± 1.7 min, C: 11.2 ± 2 min) ($p < 0.001$), and time to attain the maximum sensory level (D: 10.2 ± 1.9 min, N: 11.9 ± 1.8 min, C: 14.5 ± 2.2 min) ($p < 0.001$) were significantly shorter in the DEX group than in the neostigmine and control groups. The neostigmine group also showed a significant reduction compared to the control group. The regression times for sensory (D: 10.3 ± 1.5 min, N: 6.4 ± 1.8 min, C: 4.3 ± 0.7 min) ($p < 0.001$) and motor block (D: 8.9 ± 1.4 min, N: 5.1 ± 1.7 min, C: 2.8 ± 0.9 min) ($p < 0.001$) were significantly prolonged in the DEX group compared to the neostigmine and control groups. Additionally, the neostigmine group exhibited a longer regression time than the control group.

Conclusion: Dexmedetomidine provides more effective sensory and motor blockade characteristics than neostigmine when added to intrathecal bupivacaine during CS.

Keywords: Dexmedetomidine; Neostigmine; Bupivacaine; Intrathecal; Caesarean Section.

DOI: 10.21608/SVUIJM.2025.357051.2103

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Received: 6 February,2025.

Revised: 28 February, 2025.

Accepted: 2 March, 2025.

Published: 16 March, 2025

Cite this article as Reham Ali Abdelhaleem Abdelrahman, Tarek Mahmoud Fahmey Abdel-Barr, Mohammed Abdel-Kalek El-Sonbati, Ahmed Mossad Anwar Abeltawab. (2025). Intrathecal Bupivacaine – Dexmedetomidine Compared to Intrathecal Bupivacaine - Neostigmine in Elective Caesarian Section: A Randomized Controlled Trial. *SVU-International Journal of Medical Sciences*. Vol.8, Issue 1, pp: 576-585.

Introduction

Spinal anesthesia is a widely used neuraxial anesthetic technique for Caesarean sections (CS) due to its simplicity, rapid administration, effectiveness, and safe perioperative pain relief **(Parikh and Seetharamaiah, 2018).**

Although bupivacaine is the most commonly used local anesthetic for subarachnoid blocks, its duration of action is limited **(Alur et al., 2021).** Another concern is the perioperative hemodynamic stability. To enhance overall outcomes, patient satisfaction, and provide more controlled and prolonged pain management during elective CS, adjuvants are often combined with bupivacaine in intrathecal blocks **(Yoganarasimha et al., 2014; Mo et al., 2023; Sangkum et al., 2021).**

Dexmedetomidine (DEX), a selective alpha-2 adrenergic agonist, is widely used for sedation in mechanically ventilated patients in critical care settings **(Lewis et al., 2022).** It is also employed in various medical contexts to reduce anxiety and pain. When used as an adjuvant in spinal anesthesia, DEX has been shown to prolong block duration and enhance postoperative pain relief **(Shrestha et al., 2023; Kostroglou et al., 2021).**

Spinal neostigmine activates descending pain inhibition mechanisms through cholinergic interneurons, likely enhancing cholinergic tone during the postoperative period, making it highly effective in reducing somatic pain **(Si et al., 2023; Ahmadzade et al., 2023).**

Limited studies have directly compared the effects of neostigmine and DEX when administered during elective CS alongside intrathecal hyperbaric bupivacaine 0.5%. This study aims to compare the efficacy of intrathecal neostigmine versus DEX when added to hyperbaric bupivacaine 0.5% in CS.

Patients and methods

A randomized, controlled, double-blind trial was conducted on 54 ASA II females, aged 18 to 40 years, with a height range of 150 to 170 cm and a weight range of 70 to 110 kg, who were scheduled for elective CS under spinal anesthesia.

The study was approved by the Research Ethics Committee of Kasr Al-Aini Hospitals, Cairo University, Egypt (approval code: N11-G2-2015/M.Sc.) and was subsequently registered at clinicaltrials.gov (ID: NCT06055101). Written informed consent was obtained from all participants.

Exclusion criteria included emergency CS, known fetal anomalies, BMI > 35 kg/m², hemoglobin <10 g/dL, El-Ganzouri score ≥5, upper airway problems, hiatus hernia, obstructive sleep apnea, patient refusal, uncooperative patients, coagulation abnormalities, maternal diseases, obstetric complications, and severe hemodynamic instability.

Randomization and blinding

Participants were randomly assigned in a 1:1:1 ratio to three groups (18 patients per group) using a computer-generated randomization table. Allocation was concealed in sealed, opaque envelopes.

DEX Group: Received 0.1 mL (10 µg) of dexmedetomidine **(Nasr and Elokda, 2015)**, 0.1 mL of 0.9% saline, and 10 mg (2 mL) of hyperbaric bupivacaine.

Neostigmine Group: Received 0.1 mL (50 µg) of neostigmine **(Raghavan et al., 2016)**, 10 mg (2 mL) of hyperbaric bupivacaine, and 0.1 mL of 0.9% saline.

Control Group: Received 10 mg (2 mL) of hyperbaric bupivacaine and 0.2 mL of 0.9% saline.

All intraoperative data were recorded, while the study medication remained blinded to both the patient and the anesthesiologist administering the block.

Preoperatively, patients were evaluated to confirm eligibility based on

inclusion criteria and to exclude those meeting exclusion criteria.

Anesthesia Procedure

During the procedure, patients were positioned sitting, and a midline approach was used. A preload infusion of 8 mL/kg of 0.9% saline was administered over 10 minutes before performing a lumbar puncture at the L3-4 or L4-5 interspaces using a 25-gauge Quincke needle. Following intrathecal injection, patients were placed supine with left uterine displacement, and the bed's head was elevated by approximately 10 degrees. Oxygen was administered via a face mask at a rate of 4 L/min.

Assessment of Sensory and Motor Block

Sensory Block: Evaluated using the pinprick test and graded as follows:

2 = Complete block (no sensation/loss of touch)

1 = Partial block (diminished sensation/loss of pinprick sensation)

0 = No block (normal sensation)

The onset time of the sensory block was defined as the period from the injection of the study medication to complete sensory block. The time from intrathecal injection to achieving bilateral sensory block at T10 was assessed using a pinprick test from caudal to cephalic direction.

Motor Block: Assessed using the modified Bromage scale:

0 = Full mobility of the ankle, knee, and hip

1 = Mobility of the ankle and knee, but no hip movement

2 = Mobility of the ankle, but no movement in the hip or knee

3 = Complete motor block (no movement in the ankle, knee, or hip)

Hemodynamic Monitoring and Management

Mean arterial pressure (MAP) and heart rate (HR) were recorded every 3 minutes, with data collection at 10-minute intervals (T1-T6), using the spinal injection time as time zero (T0).

Hypotension (SBP <90 mmHg or a >20% decrease from baseline) was managed with IV ephedrine (10 mg increments) and additional Ringer's lactate.

Bradycardia (HR <50 bpm) was treated with IV atropine (0.5 mg).

SpO_2 was continuously monitored.

Intraoperative adverse effects (e.g., nausea, vomiting, pruritus, shivering) were documented.

Following sensory regression to the peak sensory dermatome and motor regression to Bromage 0, patients were discharged from the post-anesthesia care unit (PACU). Postoperative nausea and vomiting (PONV) were managed with IV ondansetron (4 mg).

Sedation and Pain Assessment

Sedation: Assessed using the modified Ramsay Sedation Score:

1 = Agitated, anxious, and restless

2 = Oriented, calm, and cooperative

3 = Responds to verbal commands

4 = Brisk response to loud noise or glabellar tap

5 = Slow response to loud noise or glabellar tap

6 = No response

Pain: Evaluated using the Visual Analog Scale (VAS) (1–10) every two hours in both the surgical ward and recovery area. A rescue analgesic was administered at a VAS score of 4. The analgesia duration was defined as the time from intrathecal injection to the first request for analgesia. The total analgesic dose required in the first 24 hours was recorded.

Sedation and VAS scores were measured at 15, 30, 45, and 60 minutes post-spinal injection, hourly for the next 8 hours, and again at 12 and 24 hours.

Sample size calculation

Sample size estimation was performed using G*Power 3.1.9.2 (Universitat Kiel,

Germany). A pilot study (n=5 per group) showed mean times to achieve T10 of 6.2 ± 1.7 min (DEX group), 7 ± 1.9 min (Neostigmine group), and 8.6 ± 1.81 min (Control group). Based on a group ratio of 1:1:1, 90% study power, a 95% confidence level, an effect size of 0.525, and an additional 3 cases per group to account for dropouts, the final sample size was determined to be 18 patients per group.

Statistical analysis

Statistical analysis was performed using SPSS version 27 (IBM©, Armonk, NY, USA). The normality of data distribution was assessed using histograms and the Shapiro-Wilk test.

Parametric quantitative data were analyzed using a one-way analysis of variance (ANOVA F-test), followed by Tukey's post hoc test when significant differences were found. Results were expressed as mean ± standard deviation (SD).

Non-parametric quantitative data were analyzed using the Kruskal-Wallis test and were presented as median and interquartile range (IQR).

Qualitative variables were compared using the chi-square test (χ^2) and were reported as frequencies and percentages (%).

A two-tailed p-value < 0.05 was considered statistically significant.

Results

In this study, 67 patients were assessed for eligibility. Of these, 9 parturients did not meet the inclusion criteria, and 4 parturients declined to participate. The remaining 54 patients were randomized into three groups (18 patients per group). Statistical analysis was conducted on all enrolled patients who completed the study and follow-up, as illustrated in (**Fig.1).**

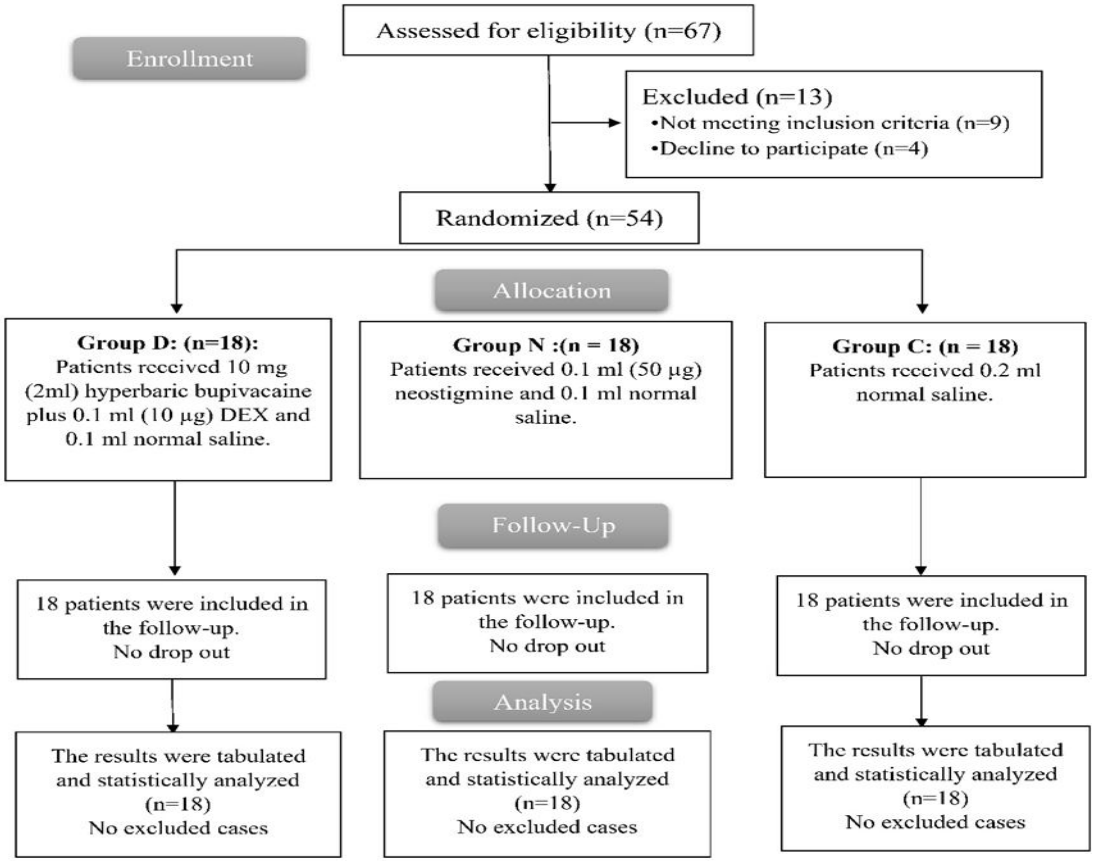

Fig.1. Consort Flow Chart Diagram

Demographic characteristics and medical history were comparable among the D, C, and N groups, as shown in **(Table.1).**

Table 1. Baseline participants characteristics of the studied groups

Variables		Group D (n=18)	Group N (n=18)	Group C (n=18)	p value
age (years)		30.4 ± 7.8	31.7 ± 5.1	29.2 ± 4.9	0.459#
weight (kg)		86.6 ± 10.6	93.1 ± 9.1	89.1 ± 7.5	0.114#
height (m)		1.62 ± 0.1	1.61 ± 0.1	1.6 ± 0.04	0.677#
BMI (kg/m^2)		33.1 ± 4.6	36 ± 4.7	34.7 ± 3.2	0.130#
smoking		1 (6%)	0 (0%)	0 (0%)	0.361##
medical history	**ITP**	1 (6%)	0 (0%)	0 (0%)	0.361##
	HTN	2 (11%)	1 (6%)	3 (17%)	0.570##
	DM	1 (6%)	1 (6%)	2 (11%)	0.763##
	BA	1 (6%)	1 (6%)	2 (11%)	
	Hypothyroidism	1 (6%)	0 (0%)	0 (0%)	0.361##

Data are presented as mean ± SD or frequency (%). ITP: Idiopathic thrombocytopenic purpura. HTN: Hypertension. BA: Bronchial asthma. BMI: Body mass index. DM: Diabetes mellitus. #: compared by ANOVA. ##: compared by chi square test. *statistically significant as p-value < 0.05

The time to achieve T10, time to reach Bromage 3 motor block, time to attain T4, and peak sensory level were significantly shorter in group D compared to groups N and C. Additionally, these times were significantly shorter in group N than in group C ($p < 0.05$). Similarly, the regression times for sensory and motor block were significantly prolonged in group D compared to groups N and C, and were significantly longer in group N than in group C ($p < 0.05$), as presented in **(Table .2).**

Table 3. Characteristics of intrathecal block of the compared groups

Variables	Group D (n=18)	Group N (n=18)	Group C (n=18)	p value	Post hock
Time to reach T10 (min)	5.2 ± 2.1	7 ± 1.7	9.1 ± 1.9	**<0.001***	**p1=0.019* p2<0.001* p3=0.006***
Time to reach Bromage 3 motor block (min)	4.1 ± 2.1	5.9 ± 2.1	8.3 ± 2	**<0.001***	**p1=0.02* p2<0.001* p3=0.003***
Time to reach T4 (min)	7.3 ± 1.7	8.9 ± 1.7	11.2 ± 2	**<0.001***	**p1=0.034* p2<0.001* p3<0.001***
Peak sensory level (min)	10.2 ± 1.9	11.9 ± 1.8	14.5 ± 2.2	**<0.001***	**p1=0.023* p2<0.001* p3<0.001***
Regression time for motor block (h)	8.9 ± 1.4	5.1 ± 1.7	2.8 ± 0.9	**<0.001***	**p1<0.001* p2<0.001* p3<0.001***

The regression time for sensory (h)	10.3 ± 1.5	6.4 ± 1.8	4.3 ± 0.7	**<0.001***	**p1<0.001* p2<0.001* p3<0.001***

Data are presented as mean ± SD and compared with ANOVA (F) test with post hoc test (Tukey). *statistically significant as p-value <0.05.p1: p value between group D and group N. p2: pvalue between group N and group C. p3: p value between group D and group C.

At T0, T1, T2, T5, and T6, mean arterial pressure (MAP) and heart rate (HR) were comparable among the groups. However, at T3 and T4, both MAP and HR were significantly lower in group D compared to groups C and N, and in group N compared to group C ($p < 0.05$), as demonstrated in **(Fig. 2 and Fig.3).**

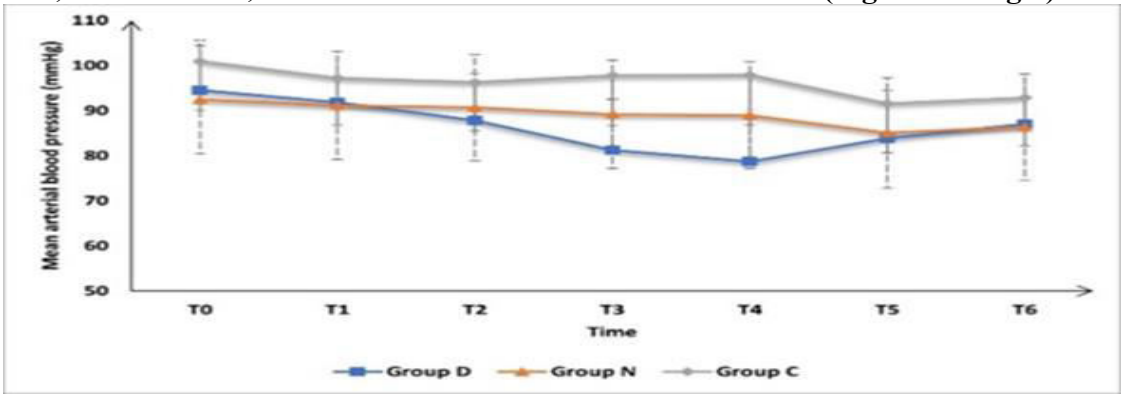

Fig.2. Mean arterial blood pressure in the studied groups at different time points
T1: at 10min, T2: at 20min, T3: at 30min, T4: at 40min, T5: at 50min, T6: at 60min.

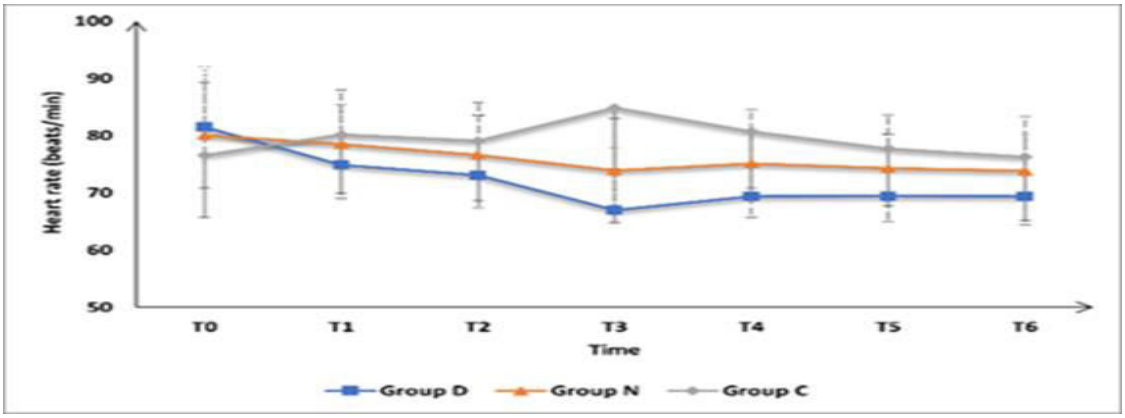

Fig.3. Heart rate in the studied groups at different time points
T1: at 10min, T2: at 20min, T3: at 30min, T4: at 40min, T5: at 50min, T6: at 60min.

The VAS score was comparable among the groups at 2h, 12h, and 24h. However, at 4h and 6h, it was significantly lower in group D compared to groups C and N, and in group N compared to group C ($p < 0.05$). At 8h, the VAS score was significantly lower in group D than in groups N and C ($p < 0.05$) but remained comparable between groups N and C. The Ramsay sedation score at 4h, 6h, 8h, 12h, and 24h was comparable among the three groups. However, at PACU and 2h, it was significantly higher in group D than in groups N and C ($p < 0.05$) but remained comparable between groups N and C, as presented in **(Table.3).**

Table 3. VAS score and Ramsay sedation score of the compared groups

Variables	Group D (n=18)	Group N (n=18)	Group C (n=18)	p value	Post hock
	VAS score				
PACU	0(0 - 0)	0(0 - 0)	0(0 - 0)	---	
2h	0(0 - 0)	0(0 - 0)	0(0 - 0)	0.138	
4h	1(1 - 1)	2(1.25 - 3.75)	3(2 - 6)	**<0.001***	**p1=0.008* p2<0.001* p3=0.019***
6h	1.5(1 - 2.75)	3(2 - 5)	6(3 - 7)	**<0.001***	**p1=0.046* p2<0.001* p3=0.029***
8h	2(1 - 4)	3(2 - 5.75)	3(3 - 6)	**0.004***	**p1=0.044* p2<0.001*** p3=0.193
12h	3(2 - 5)	4(4 - 5)	4(4 - 5)	0.209	
24h	4(4 - 5)	4(4 - 5)	4(4 - 4.75)	0.615	
	Ramsay sedation score				
PACU	3(3 - 4)	2(2 - 3)	2(2 - 2)	<0.001	**p1=0.044 p2<0.001*** p3=0.090
2h	3(3 - 3)	2(2 - 3)	2(2 - 2)	<0.001	**p1<0.001* p2<0.001*** p3=0.090
4h	2(2 - 2)	2(2 - 2)	2(2 - 2)	0.052	
6h	2(2 - 2)	2(2 - 2)	2(1.25 - 2)	0.084	
8h	2(2 - 2)	2(2 - 2)	2(1.25 - 2)	0.232	
12h	2(2 - 2)	2(2 - 2)	2(1 - 2)	0.417	
24h	2(1 - 2)	2(1.25 - 2)	2(1 - 2)	0.777	

Data are presented as frequency (%). PACU: Post-Anesthesia Care Unit. VAS: visual analogue scale. p1: p value between group D and group N. p2: p value between group N and group C. p3: p value between group D and group C. *statistically significant as p-value <0.05

The need for ephedrine, additional Ringer's solution, and atropine, as well as APGAR scores at 1 min and 5 min, and the incidence of adverse events (including PONV, pruritus, shivering, and headache), were comparable among the three groups, as presented in (**Table 4).**

Table 4. Need for ephedrine, additional ringer and atropine during block, APGAR and adverse events of the compared groups

Variables	Group D (n=18)	Group N (n=18)	Group C (n=18)	p value
Need for ephedrine	8 (44%)	4 (22%)	5 (28%)	0.328#
Need for additional ringer	18 (100%)	15 (83%)	17 (94%)	0.151#
Need for atropine	0 (0%)	1 (6%)	0 (0%)	0.361#
APGAR at 1min	8.1 ± 1.5	7.3 ± 1.4	7.1 ± 1	0.061##
APGAR at 5min	8.5 ± 1.3	7.9 ± 1.5	7.5 ± 1.3	0.095##

Adverse events	**PONV**	2 (11%)	4 (22%)	5 (28%)	0.450[#]
	Pruritus	0 (0%)	0 (0%)	1 (6%)	0.361[#]
	Shivering	1 (6%)	3 (17%)	4 (22%)	0.358[#]
	Headache	2 (11%)	4 (22%)	2 (11%)	0.556[#]

Data are presented as frequency (%). PONV: Postoperative nausea and vomiting. [#]: compared by chi square test. [##]: compared by ANOVA. *statistically significant as p-value <0.05

Discussion

The co-administration of adjuvants with local anesthetics enhances the effectiveness of perineural blocks while reducing the cumulative dose of local anesthetics required. This, in turn, minimizes the risk of local anesthetic toxicity and prolongs the duration of sensory and motor blocks **(Krishna et al., 2020; Swain et al., 2017; Bao et al., 2022; Fernández et al., 2023).**

In our study, both the DEX and neostigmine groups achieved the peak sensory level, Bromage 3, T10, and T4 significantly faster than the control group. Additionally, these groups experienced delayed sensory and motor block regression times compared to controls. MAP and HR were significantly lower at T3 and T4 in the DEX and neostigmine groups than in the control group. Similarly, VAS scores at 4 and 6 hours were significantly lower in the DEX and neostigmine groups than in the control group. The Ramsay sedation score at PACU and 2 hours was also significantly higher in these groups compared to the control group. Among these, DEX demonstrated superior efficacy over neostigmine.

APGAR scores at 1 and 5 minutes, the incidence of adverse events, and the need for ephedrine, additional Ringer's solution, and atropine were comparable among the three groups.

Our findings align with those of **Tilkar et al. (2022)**, who reported delayed sensory and motor block regression and lower VAS scores in the DEX group compared to controls. Similarly, a meta-analysis by **Liu et al. (2019)**, which included six studies with 494 female patients, demonstrated that DEX led to an earlier peak sensory level compared to controls, while differences in PONV, pruritus, and the need for ephedrine, Ringer's solution, and atropine were statistically insignificant.

Our results are also consistent with **Singh et al. (2017)**, who found that following lower limb surgeries, the time to reach T10 was faster in the DEX group compared to both the neostigmine and control groups. The neostigmine group also reached T10 faster than the control group. Additionally, sedation scores were higher in the DEX group compared to both the neostigmine and control groups. However, shivering and the need for ephedrine, additional Ringer's solution, and atropine were comparable across all groups. PONV was more frequent in the neostigmine group than in both the control and DEX groups, whereas pruritus and headache were absent in all patients. The difference in findings between studies could be attributed to variations in anesthetic techniques, such as the use of general anesthesia.

Additionally, **Sun et al. (2015)** reported that the peak sensory level was achieved earlier in the DEX group compared to controls and that VAS scores were significantly lower with DEX. APGAR scores at 1 and 5 minutes were also comparable between the DEX and control groups.

Conversely, our findings contrast with those of **Tilkar et al. (2022)**, who found no significant differences in peak sensory level, HR and MAP changes, or sedation scores between the DEX and control groups. **Saha et al. (2022)** highlighted that intrathecally administered α2-adrenoceptor agonists exert a dose-dependent sedative effect. The lower

DEX dose (5 µg) used in their study may explain the differences in results.

Similarly, our findings are in agreement with **Sathyamoorthy et al. (2016)**, who observed that following a total abdominal hysterectomy, VAS scores at 4 hours were lower in the neostigmine group compared to controls. The Ramsay sedation score at PACU was comparable between the neostigmine and control groups, but the sedation score at 2 hours was significantly higher in the neostigmine group. Additionally, MAP was lower at T3 and T4 in the neostigmine group compared to controls. The use of general anesthesia in their study may account for differences in findings.

Limitations: This study was conducted at a single center with a relatively small sample size

Conclusion

For cesarean section, DEX is superior to neostigmine, and neostigmine is superior to the control in enhancing intrathecal hyperbaric bupivacaine 0.5% sensory and motor blocks without increasing the incidence of adverse events. Further studies comparing other adjuvants and alternative anesthetic techniques are recommended.

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