

ORIGINAL RESEARCH

OBSTETRIC ANESTHESIA

Intrathecal bupivacaine-fentanyl vs. bupivacaine-dexmedetomidine for cesarean section: a randomized controlled trial

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Abstract

Background & objectives: Spinal anesthesia is the preferred technique for obstetric patients as it is economical, simple to perform, has a rapid onset and provides complete muscle relaxation. A variety of adjuvants have been used to enhance or prolong its effects. We compared the effects of dexmedetomidine and fentanyl on the onset and recovery times of sensory and motor blockade as well as on hemodynamics, postoperative complications and duration of postoperative analgesia in parturients undergoing lower segment cesarean section (LSCS).

Methodology: It was a prospective, double blind, randomized controlled trial. Sixty healthy parturients having cesarean delivery under spinal anesthesia were randomly divided into two equal groups. Group BD was given 10 mg bupivacaine plus 5 µg of dexmedetomidine and Group BF was given 10 mg bupivacaine plus 10 µg of fentanyl. Parturients was then observed for the onset and recovery times of sensorimotor blockade, hemodynamics, postoperative complications and postoperative analgesia.

Results: There was no statistically significant difference in the onset of sensorimotor block between the groups. The time to complete sensory and motor recovery was significantly prolonged in Group BD ($P = 0.01$ and $P = 0.0001$ respectively) as compared to Group BF. Both groups did not show significant differences in hemodynamic changes, but there was a reduction in systolic and diastolic blood pressures $\geq 20\%$ from baseline intraoperative. The VAS at 3 and 4 h postoperatively in the Group BD was significantly lower ($P = 0.02$ and $P = 0.01$ respectively). The incidence of complications was found comparable in two groups, except incidence of hypotension and nausea was more in the Group BD compared to Group BF ($P = 0.006$ and 0.002 respectively).

Conclusion: Although intrathecal dexmedetomidine prolongs the duration of sensory block, with comparable hemodynamic changes and good postoperative analgesia, prolonged motor block due to it, compared to intrathecal fentanyl, is not a desirable outcome particularly in short duration surgeries like LSCS, which can increase discharge time from post anesthesia care unit (PACU) to the ward.

Abbreviations: LSCS: lower segment cesarean section; PACU: post anesthesia care unit;

Key words: Anesthesia, Spinal; Analgesia, Obstetrical; Analgesics, Opioid; Anesthetics, Local; Dexmedetomidine; Double-Blind Method; Female; Humans; Pain Measurement; Pregnancy

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1. Introduction

Spinal anesthesia (SA) is the preferred technique for parturients undergoing lower segment cesarean section (LSCS).^{1,2} The addition of adjuvants with local anesthetic agents in SA has been in practice to improve the speed of onset and the duration of analgesia. The adjuvants also counteract the dose-dependent adverse effects of local anesthetics due to synergism.³ Several adjuvants like opioids, epinephrine, magnesium sulfate, midazolam, neostigmine, ketamine, dexmedetomidine, steroids, buprenorphine, clonidine, and anti-inflammatory drugs have been used as adjuvants with different doses of intrathecal bupivacaine.^{3,4,5}

Opioids have been commonly used as adjuvants to spinal local anesthetics to provide shorter onset and increased intensity and duration of the sensory and motor block, with minimal sympathetic block.^{6,7} However, opioids have been associated with side effects like itching, respiratory depression, nausea, vomiting or urinary retention, when used in a neuraxial block; therefore, search of an ideal non-opioid adjuvant continues.^{3,8}

Dexmedetomidine is a relatively newer highly selective alpha-2 adrenoceptor agonist agent that produces analgesic and sedative effects.⁹ It has also been used as an adjuvant in SA resulting in prolonged duration of block and improved postoperative analgesia without any associated hypotension or other adverse events.^{10,11} Low doses of bupivacaine with dexmedetomidine and fentanyl have been compared recently in parturients and concluded that dexmedetomidine provided better analgesia without significant effect on neonatal APGAR scores as compared with fentanyl.¹²

The primary objective of the study was to compare the onset and duration of sensory and motor blockade while secondary objectives were to compare the hemodynamics, maternal side effect profile and postoperative analgesia.

2. Methodology

It was a prospective, double-blind, randomized controlled trial. The study protocol was approved by the Institutional Ethical Review Board of Dow University of Health Sciences and was registered with ClinicalTrials.gov (Identifier: NCT04095013). A total of 60 patients was calculated using Open Epi sample size

calculator with 30 parturients in each group with confidence level of 95% and power of 90%.

A written informed consent was obtained from sixty patients planned for elective LSCS with an American Society of Anesthesiologists (ASA) classification II, gestational age equal ≥ 35 weeks and BMI < 35 kg/m². The exclusion criteria were refusal to participate, pre-eclampsia, pregnancy induced hypertension, eclampsia, and any contraindication to SA.

Patients were selected by non-probability sampling technique and randomly divided into two groups having 30 patients: Group BF, to receive hyperbaric 0.5% bupivacaine 10 mg with fentanyl 10 μ g, or Group BD, to receive hyperbaric 0.5% bupivacaine 10 mg with dexmedetomidine 5 μ g, by opaque sealed envelope method performed by an independent anesthetist not involved in the treatment or follow up. Both study drugs were kept in the hospital pharmacy and provided before its use. The same anesthetist prepared the study drugs in syringes with identical appearance as follow:

For Group BD, 10 mg of 0.5% hyperbaric bupivacaine were taken in 3 ml disposable syringe. Dexmedetomidine, 200 μ g in 2 ml volume was drawn in 1 ml insulin syringe (100 units = 100 μ g) and 5 units (5 μ g) were added to bupivacaine syringe, making a total volume of 2.05 ml.

For Group BF, 10 mg of 0.5% hyperbaric bupivacaine were taken in 3 ml disposable syringe in a similar fashion. Fentanyl 10 μ g was added to bupivacaine syringe with the help of insulin syringe (100 units = 50 μ g fentanyl), making a total volume of 2.20 ml not making a significant volume difference.

The drug filled syringe was handed over to consultant anesthetist for intrathecal administration. All anesthetists involved in treatment and follow-up were blinded to the study protocols and the patient assignment until the completion of the analysis.

After receiving the patient in operating room, intravenous (IV) line was maintained with 18 G cannula and 10 ml/kg Ringer's lactate solution was started. Baseline vital signs were recorded after applying standard monitoring for heart rate, non-invasive blood pressure (NIBP), oxygen saturation (SpO₂), and respiratory rate. SA was administered in the sitting

Table 1: Demographic and surgical characteristics

Study variables	Group BF (n = 30)	Group BD (n = 30)	P-values
Weight (kg)	75.00 ± 11.54	67.20 ± 12.89	0.01*
Height (cm)	163.60 ± 19.14	177.00 ± 6.12	0.57
Gestational age (weeks)	39.97 ± 1.03	37.07 ± 2.65	0.08
Duration of surgery (min)	61.50 ± 14.47	64.53 ± 24.86	0.56
ASA status n (%)			0.31
II	29 (96.7%)	30 (100%)	
III	1 (3.3%)	0 (0%)	

Values are presented as mean ± SD or n (%). Use of independent sample t-test. P < 0.05 considered statistically significant.

position after standard aseptic measures at L4-L5 interspace with 25 G pencil point needle. Consultant anesthetist handed over the prepared drug-filled syringes and the end time of injection was recorded. The patient was placed in the supine position soon after SA with a left lateral tilt using a wedge. Hemodynamic parameters were recorded at baseline, immediately after spinal injection, and every 5 min thereafter until the delivery of the baby.

Spinal block characteristics were also recorded at different time points as follows: time till T10 dermatome level achieved, the time of maximum Bromage achieved, regression time to T10 dermatome, and the time of complete motor recovery.

The sensory block was checked using an ice pack in the mid-clavicular line on both sides every 30 sec. Motor block was assessed simultaneously every 30 sec using Bromage scale as follows: 0 = no motor loss, 1 = inability to flex the hip, 2 = inability to flex the knee, 3 = inability to flex the ankle. The time to reach a maximum Bromage scale was defined as the time to achieve a motor block of Bromage scale 3. Surgery was allowed to proceed once the desired sensory and motor blockage was achieved.

surgery, defined as the time interval from the skin incision to the end of dressing, was noted.

All patients were monitored for complications like nausea, vomiting, bradycardia, hypotension, shivering, pruritus and respiratory distress. For nausea/vomiting patients were given metoclopramide 10 mg IV, pruritus was treated with diphenhydramine 25 mg, respiratory distress was managed with, supplemental oxygen and/or nebulization, shivering was treated with tramadol 30 mg. Atropine 0.5 mg was given if heart rate dropped < 50 beats /min. Hypotension, drop in mean blood pressure of ≥ 20% from the baseline, was managed with phenylephrine 50 µg or adrenaline 10 µg.

The time of delivery and the APGAR score of the baby, and any side effects were not part of the study.

Postoperative analgesia was ensured with tramadol 50 mg IV 6 hourly and acetaminophen infusion every 8 h. All patients were followed for postoperative pain assessment every hour for 4 h. The patient showing visual analog scale for pain > 3 points were given rescue analgesia with intravenous ketorolac 30mg, started standard analgesia as per hospital protocol and marked

Failure to achieve the desired sensory and motor blockage lead to conversion to general anesthesia (GA) and these patients were excluded from the study groups.

Postoperatively, patients were followed up for regression of block till T10 dermatome and time to complete motor recovery every half hourly using Bromage scale. The duration of

the end of pain scoring assessment for further hours.

Table 2: Comparison of spinal block characteristics between the study groups

Spinal block characteristics	Group BF	Group BD	P-values
Time (secs)			
Time till T10 dermatome level achieved (sec)	86.33 ± 32.58	103.23 ± 124.14	0.32
Time of maximum Bromage achieved (sec)	133.37 ± 72.23	124.17 ± 93.72	0.67
Regression time to T10 dermatome (min)	155 ± 40.6	205.7 ± 96.8	0.01*
Time of complete motor recovery (min)	199.4 ± 59.6	270.3 ± 84.1	0.0001*

Values presented as mean ± SD or n (%). Use of independent sample t-test. P < 0.05 is considered statistically significant; * Significant

Statistical analysis

Statistical analysis was performed using SPSS version 22. Chi-square test was used for analysis of the postoperative complications, the degree of motor block, and the sensory block level. Independent T-test was used for spinal

block characteristics, hemodynamics and pain scores. $P \leq 0.05$ was considered statistically significant.

3. Results

Sixty pregnant women were enrolled in our study and randomly assigned to two treatment groups. All 60 parturient completed the study. Demographic characteristics such as age, height, gestational age, matched in two groups. There were no significant differences in the duration of surgery and ASA status between the two groups (Table 1).

The spinal block characteristics are presented in (Table 2). In the Group BD, there was a significantly longer duration of analgesia than in the Group BF ($P = 0.01$) as shown by regression time to T10 dermatome (205.7 ± 96.8 vs 155 ± 40.6 min). A comparison of the time to complete motor recovery also showed a statistically significant difference between the study groups ($P = 0.0001$). The mean duration of motor block in the Group BD and Group BF was 270.3 ± 84.1 and 199.4 ± 59.6 min respectively. Hemodynamic parameters (SBP, DBP and HR) were comparable in both groups at different time periods; the systolic and diastolic blood pressure showed a reduction $> 20\%$ along the time in both groups.

A statistically significant difference was observed in both groups in SBP at 10 min and at 15 min ($P = 0.002$ and 0.02 respectively); Group BD had lower systolic blood pressures than Group BF while on other time points SBP was similar in both study groups ($P > 0.05$) (Figure 1a).

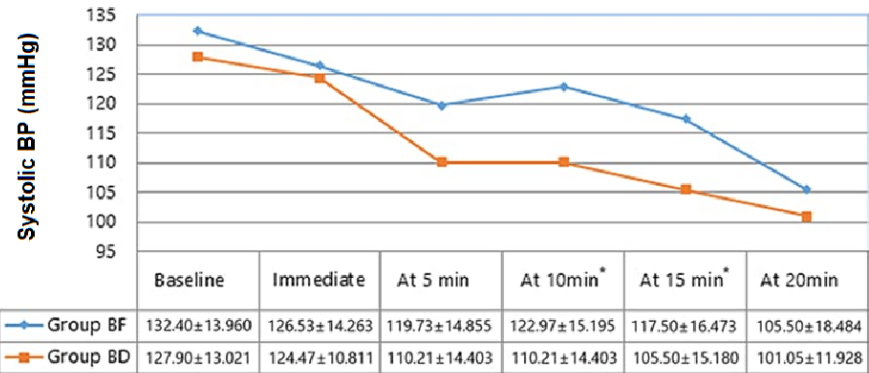


Figure1: Comparison of systolic blood pressure between the groups

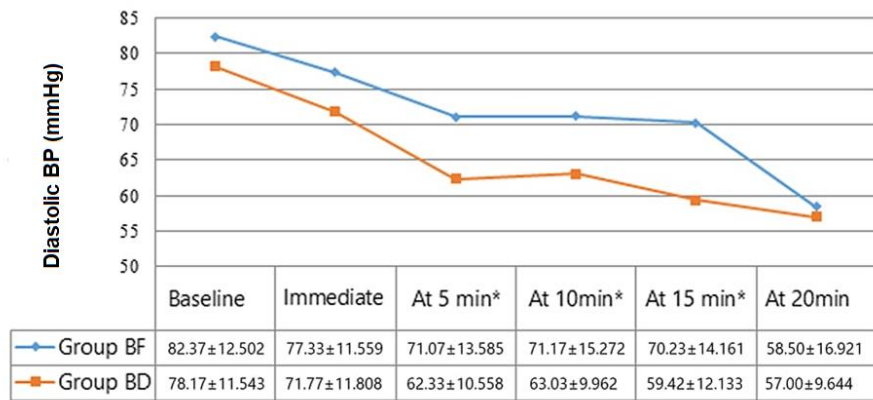


Figure 1-A: Comparison of diastolic blood pressure between both groups

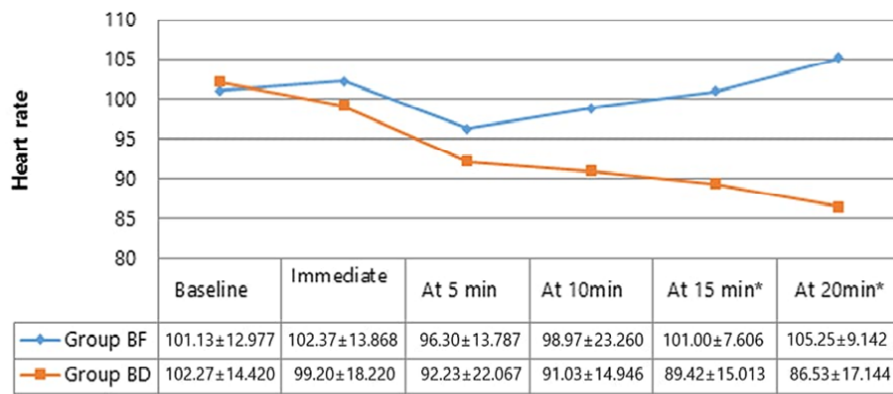


Figure 2: Comparative heart rates (beats/min) in two groups

$P < 0.05$ is considered statistically significant. * Significant

A statistically significant difference in diastolic blood pressure was observed at 5, 10 and 15 min ($P = 0.007$, 0.02 and 0.02 respectively) with lower diastolic pressures in Group BD than Group BF. At all other time points DBP was found equivalent in both study groups (Figure 1b).

Group BD showed statistically significant lower HR than Group BF at 15 and 20 min ($P = 0.01$, 0.04 respectively); on all other time points HR was found equivalent in both groups (Figure 2).

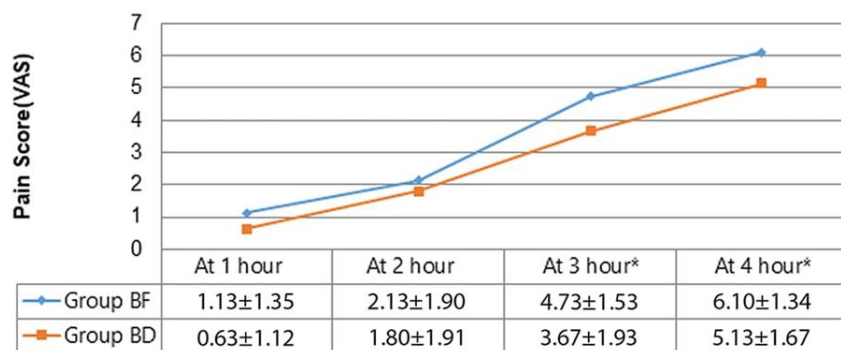


Figure 3: Comparative postoperative VAS scores in the groups

*P < 0.05 is considered statistically significant. * Significant*

Table 3: Comparison of postoperative complications

Complication	Group BD	Group BF	P value
Nausea	26.7	0	0.002*
Vomiting	10	3.3	0.61
Pruritis	0	0	NA
Respiratory distress	0	0	NA
Shivering	6.7	16.7	0.23
Bradycardia	10	13.3	0.69
Hypotension	30	3.3	0.006*

Data presented as number and percentage. Use of chi-square test.

*P < 0.05 is considered statistically significant. * Significant*

The pain score was measured at the 1st, 2nd, 3rd and 4th hours of arrival in the PACU in the postoperative period (Figure 3). VAS scores were found to be similar between the two groups at 1 and 2 h. However, pain scores differed significantly between the two groups at 3rd and 4th hours postoperatively. Average pain scores were 4.73 ± 1.53 and 3.67 ± 1.93 ($P = 0.02$) at the 3rd hour, while 6.10 ± 1.34 and 5.13 ± 1.67 ($P = 0.01$) at the 4th hour in the Group BF and Group BD respectively.

The incidence of the postoperative complications (Table 3) such as vomiting, pruritus, respiratory depression, shivering, bradycardia was comparable in the groups; however, hypotension and nausea were higher in the Group BD compared to the Group BF ($P = 0.006$ and 0.002 respectively). Post-operative pruritus and respiratory distress did not occur in any patient of the study groups.

4. Discussion

SA is the most common anesthesia modality used for LSCS. Bupivacaine is the most widely used drug for SA, but it has its limitations.¹³ The current study compared the effects of adding fentanyl and dexmedetomidine as

adjuvants to 10 mg of 0.5% hyperbaric bupivacaine for SA, on the block characteristics. We found no difference

in onset of sensory and motor blockade between the two groups. The same results were noticed by Ibrahim et al. and Rajni et al, when adding dexmedetomidine (10 µg) or sufentanyl (10 µg) with bupivacaine (0.5%, 10 mg) in SA for elective LSCS.^{14,15}

The regression time of sensory blockade to T10 dermatome was significantly increased with the dexmedetomidine group (approximately 50 min). Although it is undesirable to have prolonged motor block, prolonged sensory block benefits patient satisfaction and overall recovery. Dexmedetomidine is especially useful in surgeries expected to continue for long duration, or the duration of the surgery is unpredictable.

Contradictory to current study

Tawfiq et al. found shorter onset of motor and sensory block in the dexmedetomidine group when he compared with fentanyl in doses 10 µg and 20 µg, respectively, with 10 mg hyperbaric 0.5% bupivacaine for LSCS, but they found significant increase in duration of sensory and motor block in dexmedetomidine group which goes along with the current study.¹⁶ Qi X et al. noticed results like Tawfiq et al. with quicker onset and longer sensory motor blockade when they compared 5 µg dexmedetomidine with 100 µg morphine in bupivacaine 2 ml 0.5% (originally 0.75%) in cesarean sections.¹⁷ A similar action was observed by Al-Mustafa et al. when dexmedetomidine was used in urological procedures.¹⁸

Al-Ghaneem et al. compared 5 µg dexmedetomidine with 25 µg fentanyl in 0.5% isobaric bupivacaine 12 mg for gynecological procedures and found the regression time to zero Bromage exactly the same as current study findings. Although Al-Ghaneem et al. didn't observed side effects associated with the drugs used, their comparison suggests using a low dose of fentanyl to avoid unnecessary drug administration, which avoids complications associated with high dosage.¹⁹

The hemodynamic fluctuation is a common finding in obstetric population after SA. Patients in Group BD had

decrease in HR from baseline at 15 and 20 min, this finding is comparable to that of Rahimzadeh et al.¹⁸ In contrast Y Sun et al. compared intrathecal bupivacaine alone with bupivacaine-fentanyl and bupivacaine-dexmedetomidine in LSCS and found equal incidence of hypotension in all groups, comprehending that there was little influence of the adjuvants on its occurrence.²⁰

Al-Ghanem et al. and Abdelhamid et al. demonstrated a significant decrease in HR and mean arterial blood pressure.^{19,21} However, Sushruth et al. in their study on elective LSCS comparing 5 µg dexmedetomidine in 9 mg hyperbaric bupivacaine with saline group found no difference in hemodynamic parameters.²²

There was no clinically significant difference in SpO₂ and respiratory rate between the groups, and no case of respiratory depression was recorded, as found in many other studies.^{17,20,22,23}

No case of pruritus was noticed in both groups in our study. The results agreed with other studies for the dexmedetomidine group only, although Rajni et al. and X Qi et al. found pruritus in fentanyl, and more prominently in morphine group respectively.^{15,17} While Z. Li et al. found equal incidence of pruritus when he compared intrathecal bupivacaine with fentanyl, dexmedetomidine and clonidine as adjuvants in cesarean sections.²³

The current study found the incidence of nausea and vomiting in the dexmedetomidine group in comparison to fentanyl, the results are contrary to other studies where more nausea and vomiting was noticed with opioids.^{17,23} However, Nasser et al. found equal incidence of nausea and vomiting when he compared bupivacaine with dexmedetomidine and bupivacaine with saline intrathecally.²⁴

In this study, it was seen that adding 5 µg of dexmedetomidine provided better and prolonged analgesia specially at 3rd and 4th postoperative hours. Many studies have shown analgesic effects of dexmedetomidine. Xiaofei Qi in their study on elective sections found similar analgesic profile of dexmedetomidine with morphine.¹⁷

The number of patients with severe pain was doubled in fentanyl group in comparison to dexmedetomidine group in our study, but the occurrence of moderate pain was almost equal in both groups. Like our study, Xia Q et al. found statistically significant reduced pain scores at 4th hour in the dexmedetomidine group compared with morphine.¹⁷ Yong-Hong Bi et al. also found that VAS for pain at 6 h after LSCS was higher in bupivacaine group alone in comparison to bupivacaine with 3 µg or 5 µg of dexmedetomidine group.²⁵

5. Limitations

The present study had some limitations. One, the sample size was small. Large sample size and multicenter studies may further assess the safety of dexmedetomidine. Second, dexmedetomidine was used in only a single dose of 5 µg. Third, there was no control group, which could have allowed true comparisons with or without the study adjuvants. Fourth, the effects on neonatal outcomes were not evaluated.

Therefore, larger randomized, controlled studies with different doses of dexmedetomidine and fentanyl are required. Neonatal outcome needs to be evaluated in all drug comparisons used in the parturients.

6. Conclusion

The use of fentanyl and dexmedetomidine as adjuvants to hyperbaric 0.5% bupivacaine 10 mg for spinal anesthesia in parturients undergoing elective lower segment cesarean section is comparable in terms of the onset of sensory and motor block characteristics and hemodynamic responses. Dexmedetomidine provided prolonged duration of anesthesia and better postoperative pain relief as compared to fentanyl. However, the prolonged motor blockade may increase the length of PACU stay.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

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9. Conflict of interest

The study utilized the available resources of the departments of anesthesiology, and no external or industry funding was involved.

10. Authors' contribution

SU, AN: Concept, Manuscript editing

AM: Conduct of study, Manuscript writing

MS: Manuscript writing

SZF: Critical review, Editing

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