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Original Article

COMPARISON BETWEEN INTRATHECAL FENTANYL AND DEXMEDETOMIDINE AS AN ADJUVANT TO HYPERBARIC 0.5% LEVOBUPIVACAINE IN SUBARACHNOID BLOCK FOR CESAREAN SECTION: A PROSPECTIVE STUDY

(COMPARISON OF INTRATHECAL DEXMEDETOMIDINE AND FENTANYL WITH HYPERBARIC LEVOBUPIVACAINE)

Santanu Saha, Suman Chattopadhyay, Sagnik Datta, Debasish Bhar, Anusree Paul

Department of Anesthesiology, Midnapore Medical College

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Summary

Introduction: *The effect of dexmedetomidine and fentanyl as an adjuvant with hyperbaric levobupivacaine in cesarean section has not been evaluated adequately by researchers until now. The present study is designed to compare the effect of 5 mcg of dexmedetomidine and 25 mcg fentanyl when added to intrathecal 0.5% hyperbaric levobupivacaine for cesarean section.* ***Methods:*** *This randomized controlled trial was done with 105 parturient undergoing cesarean section under spinal anesthesia. Parturient were randomly divided into three groups. Group DL received 5 mcg of dexmedetomidine along with 1.8 ml of hyperbaric levobupivacaine intrathecally. Group FL and group NL received 25 mcg of fentanyl and 0.5 ml of normal saline respectively along with 0.5% hyperbaric levobupivacaine. The primary objective was to compare the duration of sensory and motor block among the groups. Comparing the onset time of sensory and motor block and time to first analgesic medication was considered a secondary objective.* ***Results:*** *Duration of sensory block was 138.14 ± 14.35 and 131.86 ± 7.85 min in group DL and FL ($P < 0.05$). Motor block duration was 250.2 ± 6.86 and 242.63 ± 4.71 min in group DL and FL respectively ($P < 0.05$). The time to first analgesic medication in group DL (273.43 ± 7.54 vs. 253.43 ± 6.52 min) was significantly prolonged compared to group FL ($P < 0.001$).* ***Conclusion:*** *A 5 mcg dose of dexmedetomidine when used as an adjuvant to intrathecal 0.5% hyperbaric levobupivacaine significantly prolongs the duration of sensory block, motor block, and the time to first analgesic medication compared to 25 mcg of fentanyl.*

Keywords: *anesthesia; spinal; adjuvants, anesthesia; caesarean section; dexmedetomidine; fentanyl; levobupivacaine*

Introduction

Recently, 0.5% hyperbaric levobupivacaine has been introduced commercially in clinical practice to substitute 0.5% hyperbaric bupivacaine. Studies have suggested that hyperbaric levobupivacaine is more predictable for sensory block level compared to isobaric levobupivacaine. It is also more effective for lower abdominal surgeries than isobaric levobupivacaine.[1]

Several studies compared the effect of intrathecal fentanyl and dexmedetomidine with 0.5% hyperbaric bupivacaine and 0.5% isobaric levobupivacaine in different types of surgery including lower segment caesarean section (LSCS).[2,3] Isobaric 0.5% levobupivacaine has been found to be safe in LSCS but no randomized clinical trial (RCT) has used hyperbaric 0.5% levobupivacaine in LSCS.[4]

Two RCTs have compared the effect of dexmedetomidine and fentanyl as adjuvant with hyperbaric levobupivacaine in non-pregnant patients for infraumbilical surgeries.[5,6] They observed that dexmedetomidine was superior to fentanyl in regards to the duration of block and post operative analgesia

In the present study, we have assumed that there would be no difference in the duration of block and time to first analgesic requirement among the groups. This is because no study is available compar-

Corresponding author: Debasish Bhar, Address: Baalajee Ganges, Flat D305, 105D Bidhan Nagar Road, Kolkata-700067, India, Phone number (91) 8617753967, Email: debasish77bhar@gmail.com

ing the effect of intrathecal dexmedetomidine and fentanyl when added to hyperbaric levobupivacaine for LSCS. So, null hypothesis was accepted for the proposed study. This study was designed to compare dexmedetomidine (5 mcg) and fentanyl (25 mcg) when added to 0.5% hyperbaric levobupivacaine (1.8 ml) in patients undergoing LSCS under SA.

Objective

The primary outcome of the study was to compare the duration of sensory and motor block among the study groups. Secondary outcome was to compare the onset time of sensory and motor block and time to first rescue analgesic medication.

Methods

The trial started after obtaining approval from the Institutional Ethics Committee and registration in Clinical Trial Registry India, (CTRI/2023/04/051598 dated 13/04/2023). This prospective, double-blinded, randomized controlled trial (RCT) was carried out in a tertiary medical center over 12 months from May 2023 to April 2024 following the principles of the Declaration of Helsinki, 2013.

The sample size was calculated considering the duration of the sensory block as one of the primary outcomes. Based on a previous study by Basuni et al. the sample size was calculated.[7] In their study, the duration of sensory block in the dexmedetomidine and fentanyl groups was 73.9 ± 13.9 and 64.9 ± 11.3 min respectively. Accepting an alpha error of 5% (CI 95%) and power of the study of 80%, 32 subjects were needed in each group. Statistical analysis was done by OpenEpi version 3.01 (OpenEpi: Open-Source Epidemiologic Statistics for Public Health, Version. www.OpenEpi.com, updated 2013/04/06). To compensate for the losses and dropouts, we included an extra 10% of patients in each group. Finally, for each group, the calculated sample size was 35. The total study population was 105 parturient.

Initially, 116 parturient undergoing elective LSCS under SA were assessed for eligibility. Out of those assessed patients, 4 participants did not give consent, and 7 others did not meet the inclusion criteria (Fig. 1). Patient enrollment started after written informed consent was obtained from patients to participate in the study. Consent to use the patient data for research and educational purposes was also obtained.

Patients aged between 18 and 30 years, American Society of Anesthesiologists (ASA) class II, Body Mass Index (BMI) between 18.5 and 24, and gestational age ≥ 37 weeks were included in the study. Exclusion criteria were i) parturient with any coexisting medical disorder (cardiac, neurological, renal, hepatic, endocrine, or psychiatric disorder), ii) antepartum hemorrhage, iii) emergency cases, iv) multiple pregnancy, v) any contraindication for SA, vi) allergic to study drugs, vii) inadequate subarachnoid block (SAB) requiring additional analgesics or conversion to general anesthesia.

Randomization was done by randomizer.org software. Using this software numbers from one to 105 were randomly allocated to three groups. The numbers were concealed using 105 opaque sealed envelopes containing numbers one to 105. Patients were asked to select an envelope randomly. According to the number in the envelope, the patient was allocated to that group.

Group FL received 1.8 ml of 0.5% hyperbaric levobupivacaine with fentanyl 25 mcg (0.5 ml). Group DL received 1.8 ml of 0.5% hyperbaric levobupivacaine with 5 mcg of dexmedetomidine (prepared in 0.5 ml of normal saline). Only 0.5 ml of normal saline, along with the same dose of 0.5% hyperbaric levobupivacaine, was administered to Group NL. All participants received 2.3 ml of study drugs.

For double blinding purpose, all intrathecal study drugs were prepared under strict aseptic precautions by an anesthesiologist who followed the opaque sealed envelope technique and did not participate in the procedure of SAB or data collection. Another anesthesiologist, who performed the subarachnoid blocks, also collected data of the patients.

After proper pre-anesthetic check-up, parturient were taken to the operating room. Visual analogue scale [VAS] (10 point) scoring system for assessment of postoperative pain was explained during the pre-anesthetic check-up. No premedication was given. In the operating room, Ringer's lactate (RL) infusion was started with an 18G intravenous cannula. Baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate (RR), and peripheral arterial oxygen saturation (SpO2) were recorded. SAB was performed under

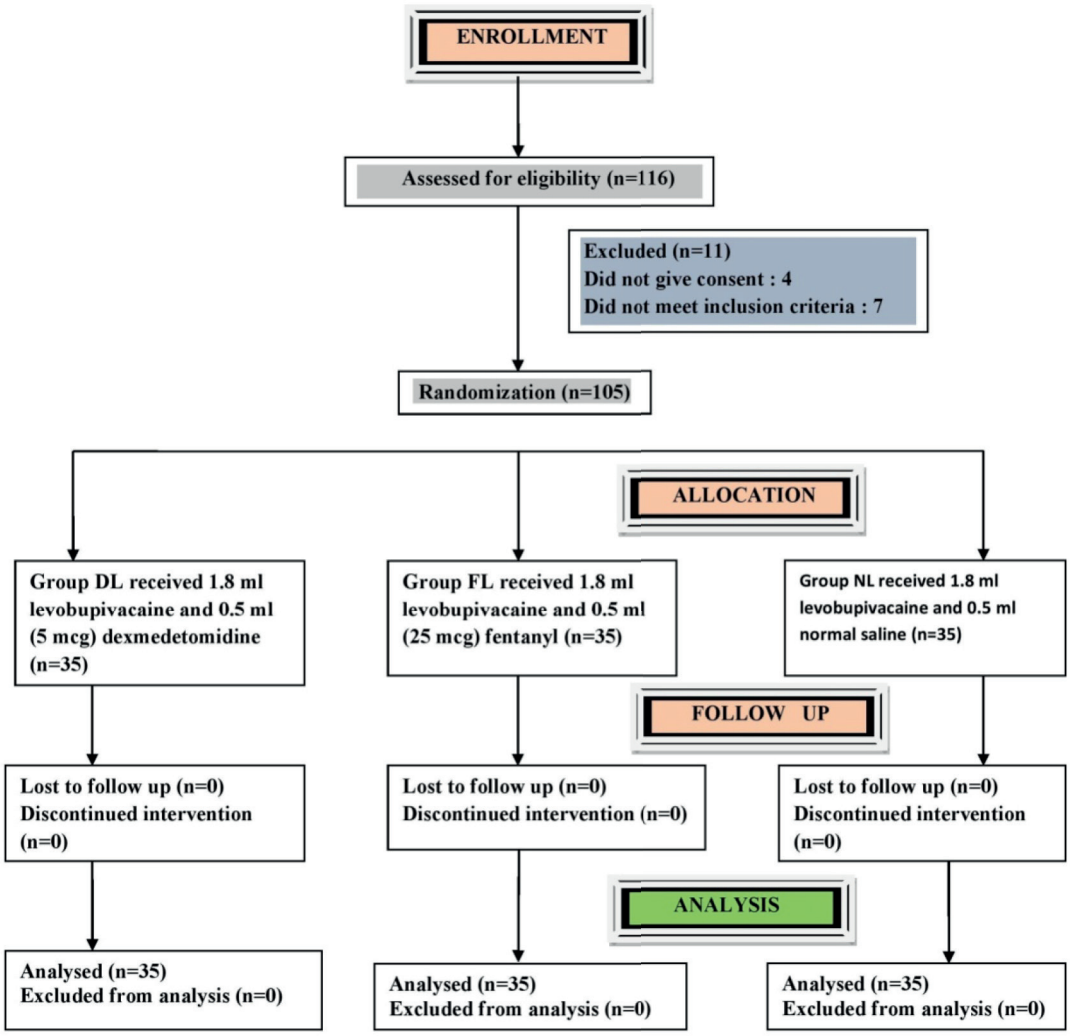

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) 2010 Flow Chart

strict aseptic conditions in sitting position at the level of L3-L4 or L4-L5 inter-vertebral space using a 26G Whitacre spinal needle after infiltrating the skin and subcutaneous tissue with 1 ml of 2% lignocaine. Immediately following the subarachnoid block, patients were placed in supine position with left lateral uterine displacement. Co-loading was done by 20 ml/kg of RL in the first 20 min followed by 10 ml/kg/hr.[8]

Intraoperative vitals (HR, SBP, DBP, MAP, RR, SpO_2) were recorded before SAB and thereafter at 2 min interval up to 10 min and then at 5 min interval till the completion of the surgery. Hypotension was defined as SBP < 100 mmHg or a reduction in SBP more than 20% from the baseline value. Norepinephrine 50 mcg intravenous bolus was used to treat hypotension.[9] Bradycardia (HR < 50 beats/min) was treated with 0.6 mg of intravenous atropine.[10] All the episodes of hypotension and bradycardia were noted.

The highest level of sensory block was determined in the mid-clavicular line bilaterally by checking insensitivity to pinprick sensation. The sensory block was tested with a blunt 25G needle every 2 min till the maximum block height was achieved. The onset time of sensory block was noted. The time required for maximum sensory block was also recorded. The highest level of sensory block was assessed after spinal anesthesia and then at every 15 min interval postoperatively till two-segment regression of sensory block. This was recorded as the duration of the sensory block.

Motor block was assessed every 2 min after administration of SA with Bromage motor blockade score (1- Unable to move feet or knee, 2- Able to move feet only, 3- Just able to move knees, 4- full flexion of knees and feet).[11] The onset time of the

motor block was noted as the time at which Bromage score 3 was achieved after SA. The time to achieve maximum motor block (Bromage score 1) was also recorded. The time to reach the minimum motor block (Bromage score 4) was noted postoperatively as the duration of the motor block. Surgery was started after maximum sensory and motor block were achieved.

Inj. Oxytocin 10 U was administered intravenously over 10 min after the delivery of the baby. If needed carboprost 250 mcg was administered intramuscularly.[12]

The quality of post-operative analgesia was assessed by using VAS score every 15 min after the operation. When patient complained of VAS ≥ 4, 100 mg tramadol hydrochloride was administered intramuscularly. The time to first analgesic requirement from the onset time of sensory block was recorded. Post-operative vitals were recorded every hour for 3 hours.

Neonatal wellbeing was assessed by Apgar score at 1 min and 5 min after delivery. Incidence of bradycardia, tachycardia, hypotension, dry mouth, sedation, or any other complications were recorded.

Continuous variables were expressed as mean ± standard deviation (SD). For parametric data Student's t-test and one-way analysis of variance (ANOVA) test were used when comparing two groups and three groups respectively. The chi-square test was used for categorical data which was expressed in percentage and 95% confidence interval (CI). The subgroup analysis was done using post-hoc analysis to determine the relationship between variables depending on the initial results generated. STATISTICA version 9 (StatSoft, Inc. Tulsa, OK, USA) was used for all statistical tests.

Results

All the groups were comparable regarding age, height, weight, BMI, and duration of surgery (Table 1).

From Table 2 it can be concluded that the onset time of sensory and motor block was significantly reduced in group DL and FL when compared to group NL ($P < 0.001$). No significant difference was observed between group DL and NL regarding the onset of sensory block (Group DL vs FL: 0.270) and motor block (Group DL vs FL: 0.345). A similar result was recorded when the time to achieve maximum height of sensory block (Group DL vs FL: 0.068) and time to achieve complete motor block were compared (Group DL vs FL: 0.093). (Table 2)

From Table 2 it can be also concluded that the duration of sensory and motor block was significantly prolonged in group DL compared to all other groups ($P < 0.001$). Time to first analgesic medication was also significantly prolonged in group DL compared to group FL and NL ($P < 0.001$). Duration of sensory block, motor block, and time to first analgesic requirement was significantly longer in group FL compared to group NL ($P < 0.001$). (Table 2)

From Table 3 it is evident that the height of the block was comparable among the groups (P 0.483). No significant difference in heart rate was observed among the groups in the intra operative and post-operative period ($P > 0.05$). On the other hand, SBP, DBP and MAP were significantly lower in group DL in the first 10 min after spinal anesthesia, compared to other groups. (Table 4) Respiratory rate and oxygen saturation (SpO_2) were comparable among the study groups. Apgar score at 1 min and 5 min among the groups were also similar without any statistical difference. From Table 5 it can be observed that the incidence of adverse effect was comparable among the groups ($P > 0.05$).

Discussion

In the present study, the duration of sensory and motor block was significantly prolonged in the dexmedetomidine and fentanyl group compared to the normal saline group. There was a statistically significant difference in the duration of sensory and motor block between dexmedetomidine and fentanyl group indicating prolongation with dexmedetomidine ($P < 0.05$). The time to first analgesic requirement was significantly longer in the dexmedetomidine group compared to fentanyl and normal saline group ($P < 0.001$).

Hyperbaric bupivacaine has been the local anesthetic of choice for SAB despite it's highly cardiotoxic profile. Levobupivacaine on the other hand demonstrated less affinity and depressant effects on the heart and central nervous system in previous studies.[13] The incidence of toxicity with levobupivacaine is uncommon. Toxic symptoms, if occur occasionally with levobupivacaine are usually manageable without any incidence of mortality.[13,14]

Table 1. Demographic Profile

	Group DL (n = 35)	Group FL (n = 35)	Group NL (n = 35)	*P* value
Age (yrs)	22.11 ± 2.94	22.89 ± 3.34	22.31 ± 3.14	0.579
Weight (kg)	61.17 ± 3.49	61.60 ± 2.55	62.00 ± 2.12	0.473
Height (cm)	161.60 ± 4.20	162.89 ± 3.65	163.17 ± 2.99	0.172
BMI (kg/m^2)	23.37 ± 0.54	23.19 ± 0.43	23.29 ± 0.44	0.277
Duration of surgery (min)	37.49 ± 6.43	37.63 ± 4.83	37.91 ± 4.85	0.946

Group DL: Intrathecal dexmedetomidine-levobupivacaine, Group FL: Intrathecal fentanyl-levobupivacaine, Group NL: Intrathecal normal saline-levobupivacaine, BMI: Body mass index

Table 2. Block characteristics:

Duration in min	Group DL (n = 35)	Group FL (n = 35)	Group NL (n = 35)	p value
Onset time of Sensory Block	2.31 ± 0.62	2.49 ± 0.65	4.94 ± 0.71	Group DL vs FL: 0.270 Group FL vs NL: **<0.001** Group DL vs NL: **<0.001** Overall: **<0.001**
Onset time of Motor Block	3.11 ± 0.67	3.29 ± 0.81	5.86 ± 0.93	Group DL vs FL: 0.345 Group FL vs NL: **<0.001** Group DL vs NL: **<0.001** Overall: **<0.001**
Time to achieve maximum sensory block	6.20 ± 0.67	6.51 ± 0.73	8.43 ± 0.60	Group DL vs FL: 0.068 Group FL vs NL: **<0.001** Group DL vs NL: **<0.001** Overall: **<0.001**
Time to achieve complete motor block	6.26 ± 0.65	6.54 ± 0.73	8.54 ± 0.55	Group DL vs FL: 0.093 Group FL vs NL: **<0.001** Group DL vs NL: **<0.001** Overall: **<0.001**
Duration of sensory block (Time for two segment regression)	138.14 ± 14.35	131.86 ± 7.85	77.71 ± 6.80	Group DL vs FL: **0.028** Group FL vs NL: **<0.001** Group DL vs NL: **<0.001** Overall: **<0.001**
Duration of motor block	250.20 ± 6.86	242.63 ± 4.71	189.17 ± 7.27	Group DL vs FL: **<0.001** Group FL vs NL: **<0.001** Group DL vs NL: **<0.001** Overall: **<0.001**
Time to first analgesic medication	273.43 ± 7.54	253.43 ± 6.52	199.71 ± 7.92	Group DL vs FL: **<0.001** Group FL vs NL: **<0.001** Group DL vs NL: **<0.001** Overall: **<0.001**

Group DL: Intrathecal dexmedetomidine-levobupivacaine, Group FL: Intrathecal fentanyl-levobupivacaine, Group NL: Intrathecal normal saline-levobupivacaine

As there is a lack of data on the dosage of 0.5% hyperbaric levobupivacaine used for cesarean section, a dose of 0.5% hyperbaric bupivacaine (2 ml) used by Sun Y et al [15], Li Z et al [16] and Khosravi F et al [17] was used as a reference in the present study. We have used an even smaller dose of levobupivacaine (1.8 ml) in our study to avoid a higher spread of spinal block because the average weight and height of the parturient registered in this institute is low. This is due to the prevalence of lower average height and weight of parturient in this region of the country.[18]

In LSCS, previous studies with hyperbaric bupivacaine have used dexmedetomidine (5 mcg) and fentanyl (25 mcg) in the same dose as in the present study.[15-17] Studies using 0.5% hyperbaric

Table 3. Height of sensory block

Highest level of Sensory block	Group DL (n = 35)	Group FL (n = 35)	Group NL (n = 35)	*P* value
T4	13 (37.14%)	11 (31.4%)	6 (17.14%)	Group DL vs FL: 0.964 Group FL vs NL: 0.445 Group DL vs NL: 0.164 Overall: 0.483
T5	10 (28.57%)	9 (25.7%)	7 (20%)	
T6	8 (22.85%)	10 (28.57%)	12 (34.28%)	
T7	3 (8.57%)	4 (11.4%)	7 (20%)	
T8	1 (2.8%)	1 (2.8%)	3 (8.57%)	

Group DL: Intrathecal dexmedetomidine-levobupivacaine, Group FL: Intrathecal fentanyl-levobupivacaine, Group NL: Intrathecal normal saline-levobupivacaine.

Table 4. Perioperative Mean Arterial Pressure:

Mean Arterial Pressure (MAP)	Group DL (n = 35)	Group FL (n = 35)	Group NL (n = 35)	*P* value
MAP Prior SAB	82.86 ± 4.74	81.14 ± 5.99	81.11 ± 4.39	0.217
MAP Post SAB	76.69 ± 6.85	77.83 ± 5.01	79.46 ± 5.15	0.208
2 min	70.83 ± 3.69	72.77 ± 3.59	75.17 ± 5.74	Group DL vs FL: **0.031** Group FL vs NL: **0.043** Group DL vs NL: **<0.001** Overall: **<0.001**
4 min	70.64 ± 2.65	73.32 ± 2.74	75.22 ± 4.63	Group DL vs FL: **0.015** Group FL vs NL: **0.024** Group DL vs NL: **<0.001** Overall: **<0.001**
6 min	69.97 ± 2.71	71.66 ± 3.37	73.43 ± 3.68	Group DL vs FL: **0.026** Group FL vs NL: **0.042** Group DL vs NL: **<0.001** Overall: **0.001**
8 min	68.54 ± 3.44	72.51 ± 3.68	74.31 ± 4.11	Group DL vs FL: **0.011** Group FL vs NL: **0.034** Group DL vs NL: **<0.001** Overall: **<0.001**
10 min	70.91 ± 4.07	73.14 ± 4.58	75.03 ± 2.66	Group DL vs FL: **0.038** Group FL vs NL: **0.042** Group DL vs NL: **<0.001** Overall: **<0.001**
15 min	75.03 ± 4.27	75.29 ± 4.03	75.60 ± 2.11	0.621
20 min	75.23 ± 3.80	75.77 ± 4.58	76.34 ± 2.01	0.466
25 min	76.43 ± 4.51	76.83 ± 3.57	77.29 ± 2.50	0.860
30 min	76.77 ± 4.66	77.14 ± 3.95	77.63 ± 2.73	0.626
40 min	77.09 ± 4.31	77.63 ± 2.73	78.11 ± 2.80	0.789
50 min	78.60 ± 3.88	77.66 ± 3.24	77.26 ± 2.60	0.228
60 min	78.23 ± 4.18	77.43 ± 3.42	76.66 ± 3.03	0.199
Post OP 1 hour	79.63 ± 4.72	78.69 ± 3.96	77.83 ± 3.34	0.187
Post OP 2 hour	78.66 ± 4.21	77.26 ± 3.92	76.97 ± 3.57	0.169
Post OP 3 hour	78.86 ± 3.94	77.63 ± 3.35	77.11 ± 3.98	0.152

Group DL: Intrathecal dexmedetomidine-levobupivacaine, Group FL: Intrathecal fentanyl-levobupivacaine, Group NL: Intrathecal normal saline-levobupivacaine.

Table 5. Complications and adverse events:

Adverse Reactions (No. of episodes)	Group DL (n = 35) Percentage (CI95)	Group FL (n = 35) Percentage (CI95)	Group NL (n = 35) Percentage (CI95)	*P* value
Nausea	8.57% (0-17.8)	14.8% (2.6-25.8)	5.7% (0-13.4)	0.493
Vomiting	5.7% (0-13.4)	8.57% (0-17.8)	2.85% (0-8.3)	0.607
Shivering	8.57% (0-17.8)	11.4% (0.8-21.9)	5.7% (0-0.13)	0.717
Pruritus	0	8.57% (0-17.8)	0	0.050
Bradycardia	0	0	0	--
Hypertension	0	0	0	--

Group DL: Intrathecal dexmedetomidine-levobupivacaine, Group FL: Intrathecal fentanyl-levobupivacaine, Group NL: Intrathecal normal saline-levobupivacaine.

levobupivacaine for infra-umbilical surgeries have also compared dexmedetomidine with fentanyl in doses of 5 mcg and 25 mcg respectively.[5,6]

Dexmedetomidine when administered intrathecally binds with alpha2 adrenergic receptor at pre-synaptic C fibers and decreases the release of neurotransmitters from C fibers. It also hyper-polarizes post-synaptic dorsal horn neurons. Both these mechanisms are responsible for the increased duration of block and postoperative analgesia.[2]

On the other hand, intrathecal fentanyl acts on Laminae I and II of the dorsal horn. It activates G-protein-linked pre- and postsynaptic opioid receptors which reduce the release of glutamate and substance P from presynaptic C fibers, resulting in antinociception.[19,20]

In the present study the duration of sensory and motor block was more in the dexmedetomidine group compared to other groups. Our observation is in agreement with the previous studies comparing similar doses of dexmedetomidine and fentanyl as adjuvants using hyperbaric levobupivacaine in infra-umbilical surgery.[5,6] Similar observation was recorded when the same dose of dexmedetomidine and fentanyl were used with hyperbaric bupivacaine in SA for lower abdominal surgery.[21-23]

Though the difference between fentanyl and dexmedetomidine regarding the duration of sensory and motor block was statistically significant in the present study, the actual difference was less than 10 min. Previous studies with non-pregnant patients comparing dexmedetomidine with fentanyl observed a greater difference in duration.[5,6,21-23] This contrast in observation in the present study may be either due to a lower dose of levobupivacaine used in the present study (1.8 ml) or due to the premixed adjuvant with hyperbaric levobupivacaine. A previous study suggests that sequential administration of adjuvant and local anesthetic intrathecally has increased the duration of block.[24]

Results showed that the time to first rescue analgesic was 273.43 min in the dexmedetomidine group. The duration of analgesia in the dexmedetomidine group was significantly longer in comparison with the fentanyl group. Jain S et al had similar observation while using 5 mcg dexmedetomidine along with 2 ml of hyperbaric levobupivacaine.[5] They had post-operative analgesia of 259.4 min while using dexmedetomidine as adjuvant and it was significantly longer than the fentanyl group. Studies with 0.5% hyperbaric bupivacaine in LSCS also described prolongation of postoperative analgesia in the dexmedetomidine group compared to the fentanyl group when similar doses were used.[15-17]

There was no significant difference regarding the onset of block between dexmedetomidine and fentanyl group which is comparable with the previous trial using a similar dose of dexmedetomidine and fentanyl with hyperbaric levobupivacaine.[5]

The present study is not free from limitations. The requirement of analgesic and VAS score in the first 24 hours were not compared. Future studies with different doses of dexmedetomidine and sequential administration of local anesthetic and adjuvant may be planned. Subarachnoid block administered in lateral position instead of sitting position may obtain different results.

Conclusion

It can be concluded from the present study that intrathecal 5 mcg of dexmedetomidine when used

as an adjuvant with 0.5% hyperbaric levobupivacaine significantly prolongs the duration of sensory block, motor block, and the time to first analgesic requirement compared to 25 mcg fentanyl.

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