Original Research Article

COMPARATIVE STUDY OF THE EFFECTS OF DEXMEDETOMIDINE AND FENTANYL AS ADJUVANTS ON THE SPINAL BLOCK CHARACTERISTICS OF LEVOBUPIVACAINE IN INFRAUMBILICAL SURGERIES

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ABSTRACT

Background
There is little literature about the intrathecal use of dexmedetomidine with local anaesthetics in humans. Also, levobupivacaine is known to have lesser CNS and CVS side-effects than its racemic isomer. Fentanyl is a commonly used intrathecal adjuvant.

Aims
To compare and evaluate the efficacy of levobupivacaine alone, with dexmedetomidine and with fentanyl as adjuvants in spinal anaesthesia for providing adequate analgesia, hemodynamic stability and minimal sedation after infra-umbilical surgeries.

Methods
A total of 60 patients of ASA I-II of both sexes aged between 20 and 60 years were randomly allocated into three equal groups of 20 patients each. Group L received isobaric levobupivacaine 15 mg with normal saline as control; group LD received levobupivacaine 15 mg with 5 µg dexmedetomidine and group LF received 15 mg of levobupivacaine with 25 mcg of fentanyl, all made up to 4 ml after diluting with normal saline.

Results
The demographic profiles were comparable among the three groups. Dexmedetomidine showed early appearance of peak sensory level (5.72±1.05) and motor blockade (2.01±0.685), and early

reach T10 segments (2.253±0.69). S1 and Bromage 0 regression times were prolonged with dexmedetomidine (225.87±6.65, 194.75±4.17). Analgesic duration was also significantly prolonged with dexmedetomidine (250.33±8.92).

Conclusion

Adding dexmedetomidine as an adjuvant to levobupivacaine improves the duration of block and analgesia, resulting in early block achievement with minimal side effects.

Keywords: Dexmedetomidine, Fentanyl, Levobupivacaine, Intrathecal, Adjuvants.

INTRODUCTION

Spinal block is frequently used in different types of infra-umbilical surgery. Levobupivacaine, the pure S-enantiomer of racemic bupivacaine, is a new long-acting local anaesthetic used intrathecally with significantly decreased cardiovascular[1] and central nervous system[2] toxicity as compared to bupivacaine.

The use of intrathecal adjuvants has gained popularity with the goal of reducing the dose of local anesthetic, prolonging the block duration, improving the success rate, improving patient satisfaction, providing effective and adequate postoperative analgesia, and improving the recovery profile.

Administration of dexmedetomidine via an intrathecal or epidural route provides an analgesic effect in postoperative pain without severe sedation and a predictable haemodynamic decline (dose-dependently decreased arterial blood pressure and heart rate) in postsurgical patients coinciding with reductions in plasma catecholamines.[3]

Intrathecal use of opioids like fentanyl has been shown to have a synergistic analgesic effect on central neuraxial block[4,5,6] like alpha 2-agonists. Fentanyl in various doses (10, 20, 30, 40 µg) when used as adjuvants in spinal anaesthesia increases the duration of analgesia and reduces intraoperative nausea and vomiting.[7]

The purpose of this study remains to assess the intrathecal use of the less-toxic levobupivacaine alone, along with adjuvants like lipid soluble opioids like fentanyl and alpha 2-blockers like dexmedetomidine in intraoperative and post-operative analgesia, with an emphasis on the side effects profile of the drugs. The primary outcome parameter, however, remains the time to achieve the standard sensory block level of T10 using study drugs in elective infraumbilical surgeries.

MATERIALS AND METHODS

This prospective, randomized, double blind, open label, parallel group study included 120 patients of both sexes, aged between 20 and 60 years, undergoing lower abdominal and lower extremity surgeries under spinal anesthesia, following approval from the institutional ethical committee and informed written consent from the patients.

Exclusion criteria were patients with a history of uncontrolled or labile hypertension, allergy to the study drugs, opium addiction, being under treatment with sedative drugs, contraindication for spinal anaesthesia, failure of spinal block (need for intra-operative analgesia within the first 30

minutes), the need for general anaesthesia, and being obese (BMI >30 kg/m^2).

Patients were divided into three groups, group L, group LD, and group LF, with forty patients in each group, using computer-generated random numbers. Patients were not given any medicine prior to surgery, and when they entered the operating room, multichannel monitors were attached. Non-invasive blood pressure, pulse oximetry, and an ECG were recorded. After preloading with 10 mL/kg Lactated Ringers solution and with the patient seated, a midline approach lumber puncture was carried out at the L3-L4 level with a 25-gauge Quincke spinal needle. Group LD (n = 40) received 15 mg of levobupivacaine with 5 µg of dexmedetomidine, Group LF (n = 40) received 15 mg of levobupivacaine with 25 mcg of fentanyl, and Group L (n = 40) received isobaric levobupivacaine (15 mg) with normal saline as a control. All of the mixtures were diluted to 4 ml using preservative-free normal saline. Patients were put in a supine position following an intrathecal injection.

Placement and an oxygen face mask were used to provide 2 L/min. The intraoperative data and study medication were unknown to the anesthesiologist who performed the block. The anesthesiologist recorded vital signs such as non-invasive blood pressure, heart rate, pulse oximetry (SpO2), and temperature every five minutes during the first twenty minutes of the procedure. Hemodynamic monitoring was then performed every ten minutes for the next hour, and then every thirty minutes until the end of the procedure. Finally, in the post-operative phase, vital signs were recorded every thirty minutes until rescue analgesia was administered.

A cold alcohol swab was used on both sides of the midclavicular line to measure the degree of sensory block. The modified Bromage scale was used to evaluate the motor block. In Bromage 0, the patient could move his or her hip, knee, and ankle; in Bromage 1, the patient could move the knee but not the hip; in Bromage 2, the patient could move the ankle but not the hip and knee; and in Bromage 3, the patient was unable to move any of the aforementioned limbs.

Prior to surgery, the duration required to achieve T10 dermatome sensory block, peak sensory level, and Bromage 3 motor block were noted. In the PACU (Post-Anaesthesia Care Unit), the regression times for sensory and motor blocks were noted. Time zero for all duration calculations was the spinal injection time. Following sensory regression to the S1 dermatome and motor block regression to Bromage 0, the patients were released from the PACU. The Ramsay Sedation Score was used to evaluate intraoperative sedation. A visual analogue pain scale with a range of 0 to 10 was used to assess postoperative pain in the PACU (0 being no pain and 10 being the most severe pain). There were reports of post-operative nausea, vomiting, and itching.

Statistical Analysis

We measured the rapidity of sensory block onset at T10 level using subarachnoid block techniques in minutes. If the true difference between the experimental and control means is 0.5 minutes, our study required 40 experimental subjects and 40 control subjects to reject the null hypothesis. The type I error probability associated with this test of the null hypothesis is 0.05.

Statistical analysis was done by Student's t-test, chi-square test, Fischer's exact test, ANOVA and other relevant tests as needed. A p-value < 0.05 was considered to be significant.

RESULTS

The demographic profiles of the patients in all three groups were similar in respect to age, gender, weight and ASA status.

We compared the spinal block characteristics among the three groups by applying the chi-square test, one-way ANOVA and Bonferroni's test. Regarding the onset of sensory block, the time it took to reach the highest level of sensory block, the time it took to reach T10, the time it took to reach Bromage-3 motor block, the mean regression time to S1 dermatome level, and the mean regression time to reach Bromage 0, we found that there were significant differences between all three groups. All these variables showed significance between group LF and group LD and significance between group LD and group L but no significance between group LF and group L (**Table 1**).

Time to reach peak sensory level (5.34±0.69 min), time to reach T10 (2.253±0.69 min) and time to reach Bromage 3 motor block (2.83±0.697 min) were least in the group LD (**Fig. 1**).

Regression time to S1 dermatome (227.76±7.29 min) and regression time to Bromage 0 (196.96±5.99 min) were maximum in group LD (**Fig. 2**).

The intraoperative mean Ramsay Sedation score showed significance between all three groups, with the group of LD patients having the highest mean score (2.48±0.51) (Table 2).

Variables	Group LF (mins)	Group LD (mins)	Group L (mins)	P-Value
Time to Peak Sensory	9.683±1.06 *	5.34±0.69 *	8.45±0.51 *	<0.000
Time to Reach T10	4.688±0.914 *	2.253±0.69 *#	4.72±0.54 #	<0.000
Time to Bromage 3	6.878±1.96 *	2.83±0.697 *#	6.39±0.54 #	<0.000
Regression to S1 Dermatome	202.066±9.36 *	227.76±7.29 *#	205.38±6.79 #	<0.000
Regression to Bromage 0	185.22±19.47 *	196.96±5.99 *#	185.15±8.09 #	<0.000
The significant pairs are shown by * and #, as assessed by Bonferroni's test.				

Table 1: Comparison of Subarachnoid Block Characteristics between the Three Groups

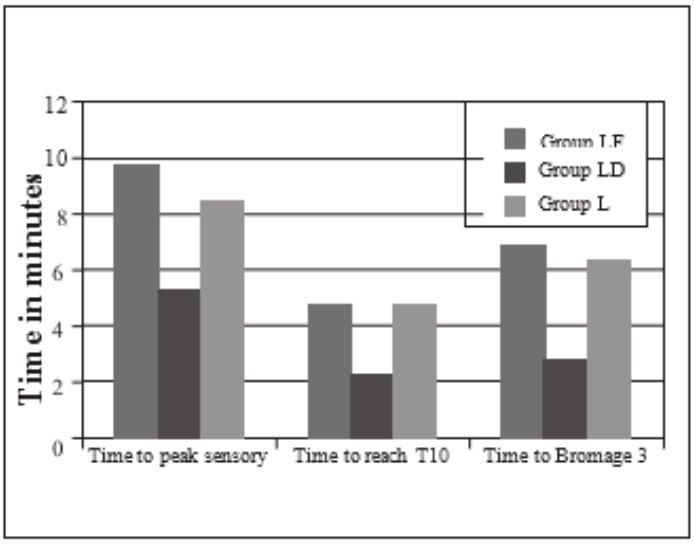

Figure 1: Comparison of Time to Reach Peak Sensory Level, T10 Sensory Level, Bromage 3 Motor Block (in min.)

Variables	Sedation Score	P-Value
Group LF	1.9±0.49*	<0.000
Group LD	2.48±0.51*	<0.000
Group L	1.43±0.50*	<0.000

Table 2: Comparison of Intraoperative Sedation using Ramsay Sedation Score

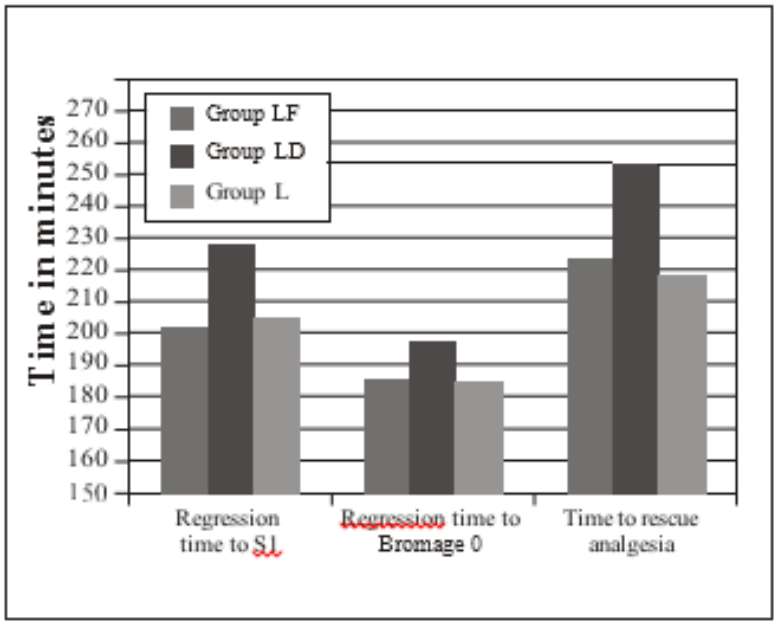

Figure 2: Comparison of Regression Time to S1 Dermatome, Regression Time to Bromage 0, Time to Administration of Rescue Analgesia (in min.)

Variables	Time to Rescue Analgesia	P-Value
Group LF	224.037 ± 14.64*	<0.000
Group LD	253.20 ± 9.70*	<0.000
Group L	218.47 ± 5.91*	<0.000
p value between LF and L =0.065 (significant), p value between LF and LD <0.001 (very significant), p value between LD and L <0.001 (very significant).		

Table 3: Comparison of Time to Rescue Analgesia across Three Groups

Variables	VAS (0 hrs.)	VAS (4 hrs.)	VAS (8 hrs.)	VAS (16 hrs.)	P-Value
Group LF	0.6±0.496*	4.05±0.96*	4.08±0.62*	3.9±0.714*	<0.001
Group LD	0.53±0.51#	2.55±0.68*	2.9±0.55*	3.08±0.57*	<0.001
Group L	1.35±0.77*#	3.25±0.54*	3.05±0.75*	3.03±0.97*	<0.001

Table 4: Comparison of Postoperative Analgesia (using Visual Analogue Score)

Variables	Group LF	Group LD	Group L	P-Value
Nausea/Vomiting	10(25%)	7(17.5%)	10(25%)	0.324
Pruritus	14(35%)	3(7.5%)	2(5%)	0.042
Bradycardia	9(22.5%)	12(30%)	12(30%)	0.449
Hypotension	13(32.5%)	15(37.5%)	13(32.5%)	0.166

Table 5: Comparison of the Incidences of Adverse Effects between the Groups

There were notable variations in the average time it took to administer rescue analgesia among the three groups. Specifically, group LD had a considerably longer mean time after surgery before the patient requested rescue analgesics. (2.481±0.51) (**Table 3**) (**Fig. 2**).

The mean post-operative VAS score at 0 hr. (just when the operation ends) showed significance between group LF and L and between group LD and L. In all the post-operative hours following that, group LD showed a significantly lower mean VAS score (**Table 4**).

By using the Pearson chi-square test to compare the incidences of different side effects in each group, we discovered that, although it was statistically not significant [p-value = 0.324 (<0.05)], the incidence of nausea and vomiting was higher in groups LF and L (25% in each) than in group LD (17.5%). Compared to groups LF (22.5% and 32.5%) and L (30% and 32.5%), group LD had a greater incidence of bradycardia and hypotension (30% and 37.5%, respectively). However, these differences were not statistically significant (p-values of 0.166 and 0.449 for bradycardia and hypotension, respectively). This study found that the incidence of pruritus following intrathecal fentanyl administration was 35%, which is statistically significant when compared to 7.5% in the case of intrathecal dexmedetomidine and 5% in the case of using simple levobupivacaine.

Comparison of intra- and post-operative heart rate, systolic and diastolic blood pressure, and SpO2 showed no significant difference between the three groups in our study.

DISCUSSION

Spinal anesthesia is frequently used for lower abdominal procedures. This approach is widely used because of its benefits, which include quick patient turnover, low cost, and an awake patient. The primary drawbacks of this method are complaints about its short duration of effect and inability to provide persistent postoperative analgesia. Hence, spinal anesthetic compounds are frequently employed to extend the subarachnoid block's duration. Opioids and local anesthetics have a strong synergistic effect. They offer superior analgesia with less medication needed.

In recent years, levobupivacaine, the pure S (–) enantiomer of bupivacaine, has emerged as a safer alternative for regional anaesthesia than its racemic parent bupivacaine and demonstrated less affinity and strength of depressant effects on myocardial and central nervous vital centers in pharmacodynamic studies, and a superior pharmacokinetic profile. Reports of toxicity with levobupivacaine are scarce.

There has been recent doubt about the two medications' equipotency; nonetheless, levobupivacaine has the benefit of causing less motor block. Levobupivacaine works pharmacologically by blocking sodium channels in neurons in a reversible manner. The anesthesia's progression generally correlates with the diameter, myelination, and conduction velocity of the impacted nerve fibers. Levobupivacaine's primary binding site is the alpha1 glycoprotein. Levobupivacaine binds to proteins 97% more than racemic bupivacaine (95%). In plasma, less than 3% of the medication is free to circulate. The drug's free component may operate on other tissues, resulting in toxic manifestations and unfavorable side effects. It therefore has lower frequencies of toxicity under typical circumstances.

When administered I.V., fentanyl is 100 times more potent than morphine, but it is only four times more potent when administered intrathecally. This 25-fold decrease in the dose potency of intrathecal fentanyl relative to morphine is explained by the greater exposure of the spinal cord to morphine than to fentanyl. It is a more lipophilic opioid and has little rostral spread, causing less respiratory depression when compared to morphine, which has greater rostral CSF spread.

Intrathecal fentanyl produces selective spinal analgesia, which is the blockage of pain without significant sympathetic and motor block. This improves hemodynamic stability during spinal anesthesia and permits early ambulation. Intrathecal fentanyl prolongs the duration of spinal analgesia; however, this effect is independent of dosage.

Seewal R, Shende D, Kashyap L, Mohan V, et al. found that intrathecal fentanyl and bupivacaine produced analgesia that was significantly longer and of higher quality compared to intrathecal bupivacaine alone. However, the author did not observe any additional increase in analgesia duration when the dose of fentanyl was increased from 10 µg to 20, 30, or 40 µg.[7]

Elizabeth A. Hamber, M.D., and Christopher M. Viscomi, M.D., et al., in a review article, found that a dose of 20–30 μg of fentanyl as an adjunct to spinal anaesthesia produces faster block onset time, improved intraoperative analgesia, and a decreased incidence of intraoperative hypotension and shivering in obstetric patients.[8] In the present study, we used 25 micrograms of fentanyl to supplement spinal levobupivacaine (15 mg) based on the previous studies.

Dexmedetomidine is an alpha-2 adrenoreceptor agonist that is highly selective (more selective than clonidine). It is approved as an intravenous sedative and pain reliever. When combined with spinal bupivacaine, intrathecal dexmedetomidine makes the sensory block last longer by raising the voltage of post-synaptic dorsal horn neurons and stopping the release of C-fiber transmitters. When α2-adrenoreceptor agonists bind to motor neurons in the dorsal horn of the spinal cord, they may make the motor block last longer. Researchers have discovered that intrathecal 2-receptor agonists exhibit antinociceptive effects on both visceral and somatic pain.

When combined with hyperbaric bupivacaine (12 mg), 3 micrograms of dexmedetomidine and 30 micrograms of clonidine are equipotent intrathecally in patients having urological procedures, according to research by Kanazi G.E., Aouad M.T., Khoury S.I. Rabbour, et al. The same author also found that, compared to bupivacaine alone, dexmedetomidine and clonidine significantly cause sensory and motor block to begin earlier and last longer without causing major adverse effects.[9] The present study compared the effects of intrathecal levobupivacaine (15 mg) alone and fentanyl (25 micrograms) on subarachnoid block characteristics, hemodynamic response, intraoperative and postoperative analgesia and sedation, and adverse effects. Based on the aforementioned findings, we supplemented spinal levobupivacaine (15 mg) with 5 micrograms of dexmedetomidine.

Firstly, we compared the spinal block characteristics among the three groups and noticed that there was significant difference between all three groups in the time to reach the highest level of sensory block (group LF = 9.683±1.06 min, group LD = 5.34±0.69 min, group L = 8.45±0.51; p-value <0.001 i.e., very significant). Time to reach T10 (group LF = 4.688±0.914, group LD = 2.253±0.69, group L = 4.72±0.54)**,** time to reach Bromage-3 motor block (group LF = 6.878±1.96, group LD = 2.83±0.697, group L = 6.39±0.54), the mean regression time to S_1 dermatome level (group LF = 202.066±9.36**,** group LD = 227.76±7.29, group L = 205.38±6.79) and also the mean regression time to reach Bromage 0 (group LF = 185.22±19.47, group LD = 196.96±5.99, group L = 185.15±8.09). All these variables showed significance between group LF and group LD and significance between group LD and group L but no significance between group LF and group L.

Khalifa F.A. Ibrahim conducted an investigation to determine the impact of combining intrathecal hyperbaric bupivacaine with either sufentanil or dexmedetomidine. He concluded that intrathecal 5 mcg dexmedetomidine, when given to 2 ml of 0.5% hyperbaric bupivacaine, results in a longer-lasting sensory and motor block than 5 mcg sufentanil. [10]

The results obtained in this present study also comply with a study conducted by Rajni Gupta, Reetu Verma, Jaishri Bogra, *et al.*, on hyperbaric bupivacaine with dexmedetomidine and

fentanyl as adjuvants where patients in the D group had significantly longer sensory and motor block times than patients in the F group. The mean time to sensory regression to S1 and to modified Bromage 0 was significantly higher in group D than in group F.[11]

Also H.Dobrucali, N.A Efe, G.U. Sivrikaya, M. Bektas *et al.*, obtained a shorter onset time for sensory and motor block in group LD compared to group L but the difference was found to be statistically insignificant ($p>0.05$) whereas in our study the difference was found to be statistically significant ($p<0.05$). The motor block duration was significantly longer in their study, as well as in ours in group LD than in the other two groups. In group LD, the peak level of sensory block was significantly higher than in the other two groups.[12]

Cuvas O, Basar H, Yeygel A, et al. found that group LF experienced a motor block for a shorter period of time than group L ($p = 0.001$). In our study, there was no significant difference in the duration of motor blockade between groups LF and L (group LF = 185.22±19.47 and group L = 185.15±8.09).

This apparent discrepancy may be due to the larger amount of fentanyl used in our study (25 micrograms vs. 15 micrograms).[13]

No patients needed extra painkillers during surgery. Group LD had a significantly higher intraoperative mean sedation score than the other two groups, as determined by the Ramsay sedation score. On comparison of the time to demand rescue analgesia, the three groups in our study showed significant differences, with the maximum time to demand rescue analgesia found in group LD patients (group LF = 224.037±14.64, group LD = 253.20±9.70, group L = 218.47±5.91).

In this investigation, there was no statistically significant difference between the two groups' means for heart rate or systolic and diastolic blood pressure. Khalifa F.A. Ibrahim found a similar result in a study she did to see how intrathecal hyperbaric bupivacaine plus sufentanil or dexmedetomidine affected pain after surgery in people who had an inguinal hernia repaired.

The post-operative VAS scores at 4, 8, and 16 hours after surgery showed significant intergroup differences. These results were similar to those found by Rajni Gupta, Reetu Verma, Jaishri Bogra, et al., who discovered that the group that received dexmedetomidine along with hyperbaric bupivacaine needed less pain relief than the group that received fentanyl. Group LD had the lowest score (2.55±0.68, 2.9±0.55, 3.08±0.57). [11]

There was found to be no significant difference ($p > 0.05$) with respect to the adverse effects like nausea and vomiting, bradycardia and hypotension between the three groups, except for pruritus, which was significantly higher in the group receiving fentanyl (35%) as an intrathecal adjuvant ($p<0.05$). With respect to the incidence of side effects in the intra operative period, the incidence of hypotension was greater in the LD group (37.5%) but was statistically insignificant. The incidence of bradycardia was found to be the same in groups LD and L (30%) and greater than in group LF, but still the difference was found to be statistically insignificant. The incidence of nausea and vomiting was equal in groups LF and L (25%) and greater than in group LD (17.5%), but the difference here too was statistically insignificant.

Similarly, Seewal R., Shende D., Kashyap L., Mohan V., et al. supported this fact. In

lower abdominal surgeries, researchers investigated how different doses of fentanyl added intrathecally to 0.5% hyperbaric bupivacaine affected perioperative analgesia and subarachnoid block characteristics. They found that adding fentanyl at different doses (10, 20, 30, 40, and so on) to intrathecal bupivacaine significantly reduces somatic and visceral pain and lengthens the time it takes for sensory block to resolve. However, at higher doses, intrathecal fentanyl can cause nausea, vomiting, and pruritus.[12]

CONCLUSION

To conclude, dexmedetomidine (5 micrograms) seems to be a better alternative to fentanyl (25 micrograms) when mixed with intrathecal isobaric 0.5% levobupivacaine (15 milligrams). This is because it provides longer-lasting and similar hemodynamic stability, better pain relief and sedation after surgery, and fewer side effects.

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