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A comparative study of isobaric levobupivacaine 0.5% versus isobaric levobupivacaine 0.5% with 3mcg dexmeditomidine in spinal anaesthesia

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Abstract
Intrathecal α2 agonists prolong the duration of action of local anesthetics and reduce the required dose. Dexmedetomidine is an α2 receptor agonist and its α2/α1 selectivity is 8 times higher than that of clonidine. In this study, we aimed to investigate the effect of adding dexmedetomidine to intrathecal Isobaric levobupivacaine 0.5% on the onset time and duration of motor and sensory blocks. Patients were randomly assigned into two groups. Group L (n= 30) patients received 3 mL (15 mg) of 0.5% levobupivacaine +0.3 mL normal saline and Group LD (n= 30) patients received 3 mL (15 mg) of 0.5% levobupivacaine + 0.3 mL (3 µg) dexmedetomidine. Sensory block onset time, block reaching time to T10 dermatome, the most elevated dermatome level, two dermatome regression time, sensory block complete regression time as well as motor block onset time, reaching Bromage 3 and regressing to Bromage 0 were recorded. Sensory and motor block onset times were shorter in Group LD than in Group L ($p< 0.001$). The regression of the sensory block to S1 dermatome and Bromage 0 were longer in Group LD than Group L ($p< 0.001$). We conclude that intrathecal dexmedetomidine addition to Isobaric levobupivacaine 0.5%for spinal anaesthesia shortens sensory and motor block onset time and prolongs block duration without any significant adverse effects.

Keywords: Dexmedetomidine, isobaric levobupivacaine, spinal anaesthesia

Introduction
Spinal anaesthesia is a safe, reliable and inexpensive technique with the advantage of providing surgical anaesthesia and also extended pain relief in post operative period. It is also an effective treatment for acute operative pain and blunts autonomic, somatic and endocrine responses. Lower Limb surgeries are often done under regional anaesthesia. Till recently hyperbaric bupivacaine 0.5% was the only drug used for spinal anaesthesia after the discontinuation of lidocaine's intrathecal use. Bupivacaine is available as a racemic mixture of its enantiomers, dextrobupivacaine and levobupivacaine. It has been found that dextro enantiomer is the cause for cardiotoxicity and the levobupivacaine the pure S (-) enantiomer does not have the cardiotoxicity. Levobupivacaine has similar pharmacodynamic properties of racemic bupivacaine but a documented reduced central nervous system and cardiovascular toxicity [1].

In recent years levobupivacaine, the pure S (-) enantiomer of bupivacaine emerged as a safer alternative for regional anaesthesia than its racemic parent. Pharmacokinetics-Protein binding of levobupivacaine (97%) is more than that of racemic bupivacaine (95%). There is less free drug circulating in the plasma and acting on other tissues to cause adverse effects and toxicity. Studies have shown that while volumes of distribution and overall clearance of the two drugs are comparable, the clearance of unbound fraction of levobupivacaine is higher [2]. Levobupivacaine demonstrated lesser affinity and strength of inhibition of cardiac sodium channels *in vitro* animal tissue experiment studies.

It was also less potent in blocking cloned human heart potassium and sodium channels. Experiments in anaesthetized rats receiving arrthythmogenic intravenous levobupivacaine or dextrobupivacaine showed a less rapid blockage of the cell firing in the nucleus tractus solitarius after levobupivacaine than after dextrobupivacaine. Hence potential for cardiovascular and CNS toxicity is lower with levobupivacaine [3].

A sensory and motor blockade of similar characteristics and recovery over equal dosage ranges of levobupivacaine and bupivacaine was demonstrated in healthy volunteers and confirmed in surgical patients.

Sathitkarnmanee, Thepakorn *et al*. and Mantouvalou, M., *et al*. concluded that 15mg of levobupivacaine provides adequate sensory and motor block for abdominal surgeries. Smaller doses (5-10mg) are used in ambulatory/ day care surgery [4]. Spinal anesthesia with cocaine was initially produced inadvertently by Leonard J Corning, in 1885 and first used deliberately by August Bier, in 1898 [4].

Till recently hyperbaric Bupivacaine 0.5% was the only drug used for spinal anaesthesia after the discontinuation of lidocaine's intrathecal use. Bupivacaine is available as a racemic mixture of its enantiomers, dextrobupivacaine and levobupivacaine. It has been found that dextro enantiomer is the cause for cardiotoxicity and the levobupivacaine the pure S (-) enantiomer does not have the cardiotoxicity. Levobupivacaine has similar pharmacodynamic properties of racemic bupivacaine but a documented reduced central nervous system and cardiovascular toxicity [5].

In recent years levobupivacaine, the pure S (-) enantiomer of bupivacaine emerged as a safer alternative for regional anaesthesia than its racemic parent. Though the duration of action of levobupivacaine is prolonged, it will not produce prolonged post-operative analgesia.

Uncontrolled post-operative pain may produce a range of detrimental acute and chronic effects. For this reason there has been in recent years, an increasing interest in the relief of post-operative pain by technique using local anesthestic agents with adjuvant for spinal anesthesia. Neuraxial adjuvants such as opiods and α_2-agonists are commonly used to improve perioperative analgesia.

Opioids and α_2-receptor agonists are important as neuraxial adjuvants not only to improve the quality of perioperative analgesia but also to minimize the local anesthetic dose, particularly in high-risk patients and in ambulatory procedures [6].

Dexmedetomidine is a α_2-adrenoceptor agonist that is approved as an intravenous sedative and coanalgesic drug. Its use is often associated with a decrease in heart rate and blood pressure. It has been proved that dexmedetomidine (5 µg) is associated with prolonged motor and sensory block, hemodynamic stability, and reduced demand for rescue analgesics when added to 12.5mg of hyperbaric bupivacaine in patients undergoing lower abdominal surgeries [6].

Neuraxial adjuvants such as opiods and α_2-agonists are commonly used to improve perioperative analgesia, but there is no studies available comparing the efficacy of dexmedetomidine added to levobupivacaine versus levobupivacaine alone for subarachnoid block in lower limb surgeries, therefore the current study was taken up.

Methodology

Sixty patients in the age group between 20 and 60 years belonging to ASA Grade-I and Grade-II posted for elective lower limb surgeries were grouped randomly into two groups (n=30). Randomization was done using simple sealed envelope technique. Based on outcome variables namely mean sensory and motor block time, significance detection of mean difference of 20 minutes, with 90% statistical power and 5% level of significance, the sample of 60 was adequate.

Group LF (n=30): Levobupivacaine 0.5% isobaric (3ml) with normal saline (0.3ml) (Total 3.3 ml).

Group LD (n=35): Levobupivacaine 0.5% isobaric (3ml) with Dexmedetomidine 3µg (0.3ml) (Total 3.3 ml).

Patients who were not willing to participate in the study, were excluded from the study.

At the time of Pre Anaesthetic Checkup, patient history were noted, general physical and systemic examination were carried out. They were explained, in their native language, the nature of the study and their initials were obtained on the Informed Consent Form. Patients were premedicated on the night before surgery with Pantoprazole 40mg and Alprazolam 0.5mg and also 90 min before surgery and were kept fasting overnight. After shifting to OT standard monitoring was carried using multiparameter monitor having pulse oximetry, ECG and NIBP. Intravenous access was obtained with 18 gauge cannula and were preloaded with Ringer lactate 500ml half an hour before spinal anaesthesia.

Patients were placed in right lateral position. Under strict aseptic precautions lumbar puncture was performed at the level of L3-L4 through a midline approach using 26 G Quincke spinal needle and study drug was injected after confirmation of needle tip in the subarachnoid space by free flow of CSF. Patients were made to lie down in supine posture immediately after spinal anaesthesia with 15^0 headup and supplementary oxygen was given with mask.

The following parameters were noted

- Onset of sensory blockade at T10 dermatome and onset of motor blockade motor blockade.
- Maximum level of sensory blockade attained and the time taken for the same.
- Maximum level of motor blockade attained and the time taken for the same.
- Total duration of sensory blockade and motor blockade.
- Sensory blockade was tested using Ice swab technique.
- Patients with inadequate or failed block were excluded from the study.
- Quality of motor blockade was assessed by modified Bromage scale.
- The time of first rescue analgesic requirement was noted.
- Total duration of surgery, analgesia and side effects were noted.
- All patients were monitored during the surgery and perioperative period employing multi parameter monitor which displays heart rate, blood pressure, ECG and SPO_2.

Results

Table 1: Surgical Procedure

Surgery	Levobupivacaine		Levobupivacaine + dexmeditomidine	
	No	%	No	%
CRIF OF SOF RT	2	6.7	2	6.7
CRIF OF SOF LT	2	6.7	1	3.3
Implant Removal Femur RT	2	6.7	0	0.0
Implant Removal Femur LT	0	0.0	1	3.3
Skin grafting Lt leg	3	10.0	3	10.0

Tendon repair TA RT	2	6.7	3	10.0
RT partial patellectomy	2	6.7	2	6.7
Tendon repair TA LT	3	10.0	1	3.3
Above Knee Amputation RT	1	3.3	1	3.3
CRIF with Long PFN LT	0	0.0	1	3.3
CRIF with Long PFN RT	1	3.3	0	0.0
Left partial patellectomy	1	3.3	2	6.7
CRIF Tibial condyle RT	3	10.0	2	6.7
CRIF Tibial Condyle LT	1	3.3	2	6.7
CRIF IL nail Tibia LT	3	10.0	2	6.7
CRIF femur + Bone Grafting RT	1	3.3	2	6.7
CRIF femur + Bone Grafting LT	0	0.0	1	3.3
CRIF+ EF of Tibia LT	1	3.3	0	0.0
CRIF+ EF of Tibia RT	0	0.0	1	3.3
Implant Removal Tibia RT	1	3.3	1	3.3
Implant Removal Tibia LT	0	0.0	1	3.3
CRIF IL tibia RT	1	3.3	1	3.3
Total	30	100.0	30	100.0

Table 1 shows the various type of Lower Limb surgeries among the group

Table 2: Comparison of Mean Time for Onset of sensory block at T10 in mins

variables	Levobupivacaine	Levobupivacaine + dexmeditomidine	P value
1. Sensory block onset time(mins)	6.10±0.84	3.93±0.83	<0.001

Table 2 showing the mean time of onset of sensory blockade at T 10. In Group L it was 6.10±0.84mins and in Group LD it was 3.93±0.83. There was statistically significant difference between the two groups regarding the onset of sensory blockade ($p< 0.001$).

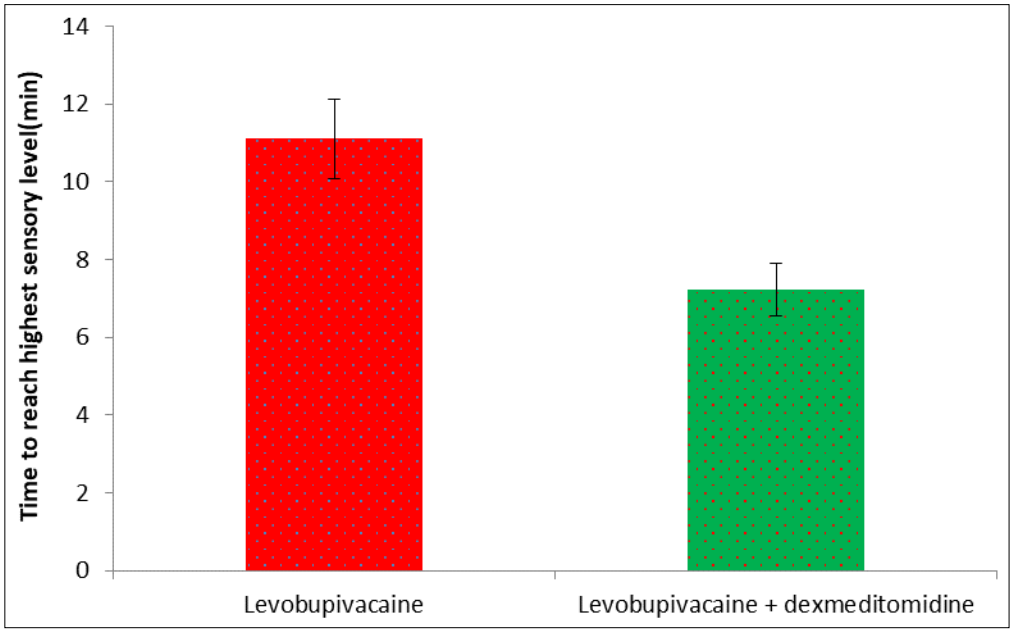

Fig 1: Comparison of Time for Maximum sensory block

The mean time taken for attaining the maximum sensory blockade. In Group L it was 11.10±1.03mins and in Group LD it was 7.23±0.68mins. There was statistically significant difference between the two groups ($p< 0.001$.).

Table 3: Maximum level of sensory blockade attained

Sensory level	Group LF (Number of patients)	Group LD (Number of patients)	p-value
T6	30	30	1

Table 3 shows the maximum level of sensory block attained by the patients in both the groups. All the patients in both the groups attained a block of T6 level with no statistically significant difference between the two groups (p=1).

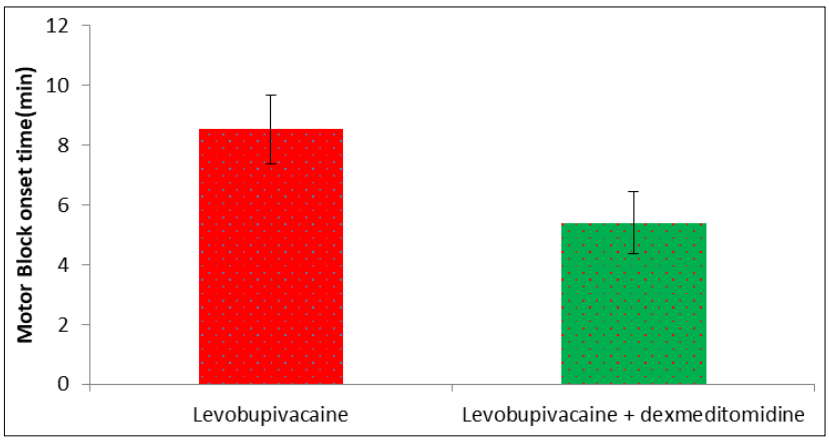

Fig 2: Comparison of Mean Time for Onset of motor block in minutes

The mean time taken for onset of motor blockade. In Group L it was 8.53±1.14mins and in Group LD it was 5.40±1.04mins. There w statistically significant difference between the two groups ($p< 0.001$).

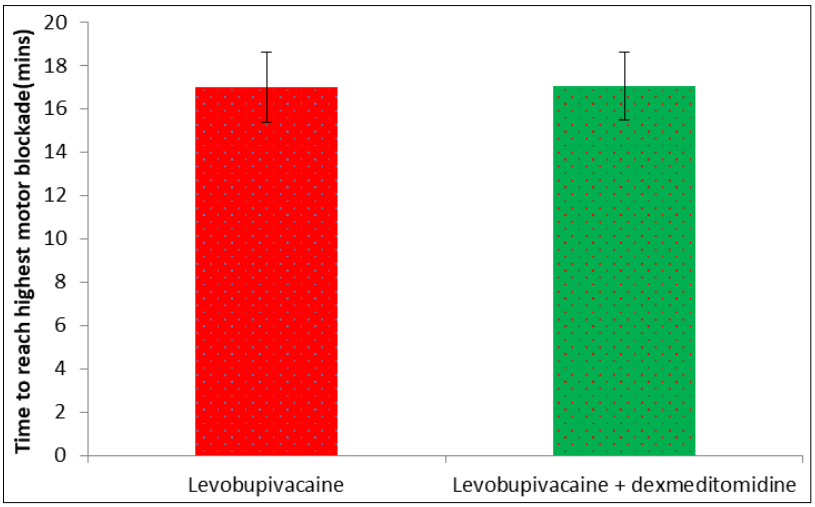

Fig 3: Comparison of Time for Maximum motor block

The mean time taken for attaining the maximum motor blockade. In Group L it was17.00±1.62mins and in Group LD it was 17.03±1.56mins. There was no statistically significant difference between the two groups (p=0.936).

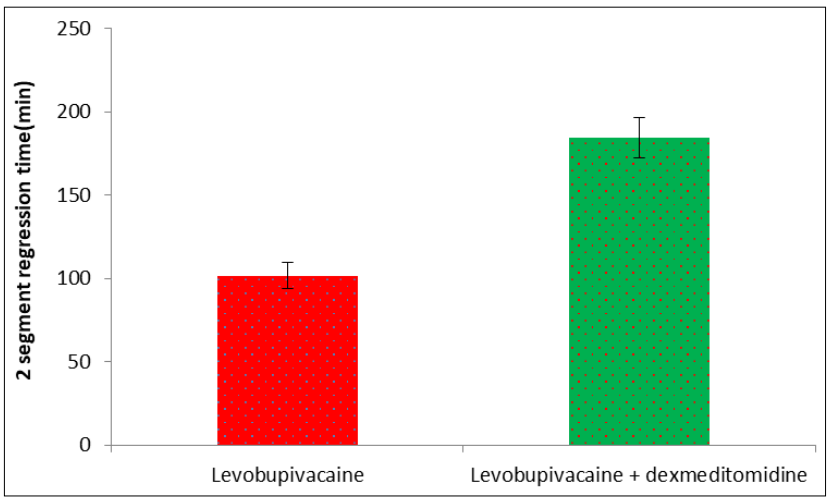

Fig 4: Comparison of 2 Segment Regression time in minutes

The comparison of Two Segment Regression Time in Group L it was 101.67±7.81min and in Group LD it was 184.67±12.03 min. There was statistically strongly significant difference in two segment Regression time in Minutes.

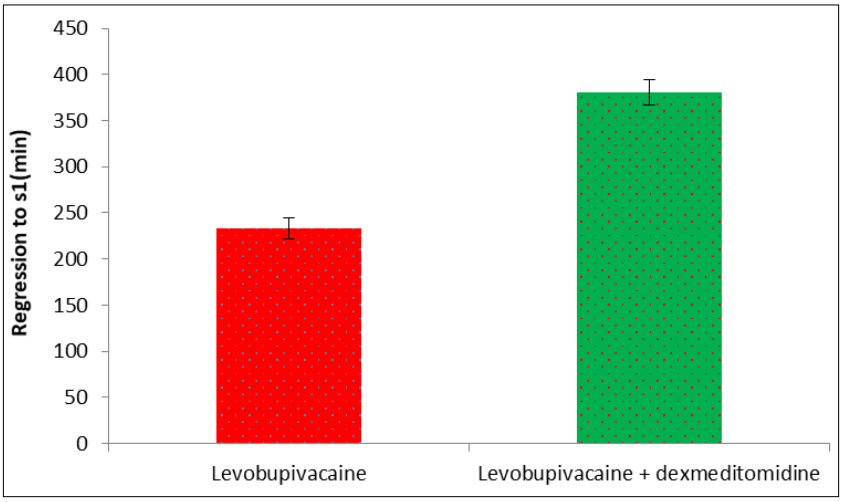

Fig 5: Comparison of mean duration of sensory block in minutes (Regression time to S1)

The comparison of mean duration of sensory block in minutes. In Group L it was 233.00±11.03 min and in Group LD it was 380.83±14.09 min. There was statistically strongly significant difference in the mean duration of sensory block (p=<0.001).

Discussion

In present study the mean time taken for onset of sensory block at T10 was 6.10±0.84mins in Group L and 3.93±0.83mins in Group LD. There was statistically significant difference in the mean time taken for onset of sensory blockade between the two groups (p< 0.001). Similarly Esmaoglu *et al.* [7], found statistically significant difference in the time taken for onset of sensory blockade between Levobupivacaine and 3µg dexmedetomidine along with Isobaric levobupivacaine (Group L-5.2 ±0.7min, Group LD 3.1± 0.7mins. P>0.001)

The mean time taken for maximum sensory blockade in the present study was 11.10±1.03min in Group L and in 7.23±0.68min Group LD. There was statistically significant difference (p< 0.001) in the mean time taken for maximum sensory blockade. Esmaoglu *et al.* [7], found statistically significant difference in the mean time taken for maximum sensory blockade between Levobupivacaine and 3µg dexmedetomidine along with Isobaric levobupivacaine (Group L 13.4±5.8min Group LD 8.3±3.3min.P>0.001)

In our study the maximum level of sensory blockade achieved was T6. All the patients in both the groups had attained T6 level of block. There was no statistical significant difference in the maximum level of sensory blockade. Similarly Esmaoglu *et al.* [7] observed statistically no significant difference between group L (T 8.6±1.0) and group LD (T 8.2±2.0) P=0.340.

In our study the time taken for two segment regression was 101.67±7.81 mins in Group L and 184.67±12.03 mins in Group LD. There was a statistically highly significant increase in the duration of two segment regression in Group LD (p=<0.001). Similarly in the study conducted by Esmaoglu *et al.* [7] there was statistically significant difference between two groups in two segment regression time (Group L-83.0±18.9, Group LD-125.3±22.8 P< 0.001). In the study conducted by Eid HEA *et al.* [8] there was statistically significant difference between two groups in two segment regression time Group N-76.9±26.8mins (Hyperbaric Bupivacaine 15mg), GroupD10-103±28.7mins where dexmedetomidine 10µg added to bupivacaine, Group D15 200.6±30.9mins where dexmedetomidine 15µg added to bupivacaine.

The time taken for regression of sensory block to S1 in the present study was 233.00±11.03mins in Group L and 380.83±14.09mins in Group LD. It was highly significant increase in the meantime taken for regression of sensory block to S1 in Group LD (p=<0.001), Similarly in the study conducted by Esmaoglu *et al.* [7] there was statistically significant difference between two groups in the time taken for regression to S1 segment(Group L-226.6±26.4mins, Group LD-356.3±35.2mins P< 0.001). In the study conducted by Al –Mustafa MM *et al.* [9] there was statistically significant difference between two groups in the time taken for regression to S1 segment (Group N-165.5±32.9mins (Isobaric Bupivacaine 12.5mg), Group D10-302.9±36.7mins where dexmedetomidine 10µg added to bupivacaine, Group D5 246.43±25.7mins where dexmedetomidine 5µg added to bupivacaine.

The mean duration of time at which rescue analgesic required in present study was 237.67±23.44mins in Group L and 429±18.45 mins Group LD. There was a highly significant increase in the duration of analgesia in Group LD (p=<0.001). similarly in a study conducted by Gupta R *et al.* [10] the time for rescue analgesia in control group (Isobaric Ropivacaine 0.75% 15mg) was 241.7± 21.7 min and in group D it was 478.4±20.9min (Dexmedetomidine 5µg was added to ropivacaine).

In a study conducted by Hala EA Eid *et al.* [8] shown significant prolongation of the duration of spinal blockade by Intrathecal administration of dexmedetomidine as an adjunct to hyperbaric bupivacaine. Patients in the groups that received dexmedetomidine had reduced postoperative pain scores and a longer analgesic duration than those who received spinal bupivacaine alone. This effect appears to be dose dependent and more pronounced with the dose of 15 µg. Fifteen µg dexmedetomidine but not 10 µg was associated with lower 24-hours analgesic requirements and desirable level of sedation.

In our study the mean time for onset of motor block was 8.53±1.14min in Group L and 5.40±1.04 in Group LD. There was statistically significant difference in the mean time for onset of motor blockade in the two groups (p< 0.001). similarly in a study conducted by Esmaoglu *et al.* [7] reported that mean time taken for onset of motor blockade was 3.5±1.5min in group L and 1.7±0.6min in group LD (P< 0.001).

The mean time taken for maximum motor blockade in our study was 17.00±1.62 mins in Group L and 17.03±1.56mins in Group LD. There was no statistically significant difference in the time taken for maximum motor blockade in the two groups (p=0.936). The grade of motor blockade in the study groups did not differ. Both the groups had a motor blockade of Bromage grade 3. similarly in a study conducted by Esmaoglu *et al*. [7] reported that mean time for maximum motor blockade was 3.5±1.5min in group L and 1.7±0.6min in group LD (*P*< 0.001).

In our study the mean duration of motor blockade (Regression time to bromage 0) was 220.17±12.7 mins in Group L and322.17±15.01mins in Group LD. There was a statistically highly significant increase in the duration of motor blockade in Group LD (*p*=<0.001). Similarly in the study conducted by Esmaoglu *et al*. [7] there was statistically significant difference between two groups in the time taken for regression to bromage 0(Group L-201.0±26.9mins, Group LD-332.0±36.7mins *P*< 0.001). In the study conducted by Al-Mustafa MM *et al*. [9] there was statistically significant difference between two groups in the time taken for regression to Bromage scale 0 (Group N-140.1±32.3mins (Isobaric Bupivacaine 12.5mg), GroupD10-338.9±44.8mins where dexmeditomidine 10µg added to bupivacaine, Group D5 277.1±23.2 mins where dexmeditomidine 5µg added to bupivacaine.

Conclusion

Dexmedetomidine when used as an adjuvant with levobupivacaine offers better quality and prolonged postoperative analgesia and motor block as compared to levobupivacaine alone.

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