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Original Research Article

A Prospective, Randomized, Comparative Study of Effect of 0.5% Isobaric Levobupivacaine and 0.5 % Isobaric Levobupivacaine with Clonidine for Spinal Anaesthesia in Patients Undergoing Elective Lower Limb Orthopaedic Surgery

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Abstract

Background: In this study, we wanted to evaluate the sensory and motor blockade properties of intrathecal 0.5 % isobaric Levobupivacaine and 0.5 % isobaric Levobupivacaine with clonidine in patients undergoing elective lower limb orthopaedic surgery.

Methods: This was a hospital based prospective, randomized, comparative study conducted among 60 patients who were posted for elective lower limb orthopaedic surgeries in Apollo Speciality Hospital, Madurai, from December 2015 to June 2016 after obtaining clearance from Institutional Ethics Committee and written informed consent from the study participants.

Results: Statistically significant difference in prolonged duration of sensory block and also prolonged duration of analgesia was observed in LC group compared to LS group. The onset of sensory block at T10 was faster in LC group compared to LS group. Time to attain maximum sensory blockade was also quicker in the LC group than in LS group. Onset of motor blockade between LC group and LS group was statistically significant and the time for maximum motor block between LC group and LS group was statistically significant. The duration of motor block was statistically significant between the two groups.

Conclusion: 30 µg of clonidine as adjuvant along with 0.5 % isobaric levobupivacaine produces significant increase in duration of post-operative analgesia without producing significant haemodynamic changes.

Keywords: 0.5 % Isobaric Levobupivacaine, 0.5 % Isobaric Levobupivacaine with Clonidine, Spinal Anaesthesia, Patients, Elective Lower Limb Orthopaedic Surgery.

Introduction

Intrathecal anaesthesia and epidural anaesthesia are the most popular regional anaesthesia techniques used for lower limb orthopaedic surgeries. [1] Spinal anaesthesia is a safe, reliable, and inexpensive technique with the advantage of providing surgical anaesthesia and prolonged post-operative pain relief and it also blunts autonomic, somatic and endocrine response to surgical stimulus. [2] For decades, Lidocaine had been the local anaesthetic of choice for spinal anaesthesia. Its advantages are rapid onset of action and good motor block manifested as good muscle relaxation. Its use was limited by its short duration of action and has been implicated in transient neurologic symptoms and cauda equina syndrome following intrathecal injection. [3] Hence, lidocaine use as an intrathecal local anaesthetic has been stopped. Till recently, hyperbaric Bupivacaine 0.5 % was the only drug used for spinal anaesthesia in India after the discontinuation of Lidocaine. 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 (S-1butyl-2-piperidylformo-2', 6'-xylidide hydrochloride), 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. [4] Levobupivacaine has been introduced in India in 2012 and is available as 0.5 % isobaric preservative free 4 ml ampoules for intrathecal use. Not many studies have been done regarding its intrathecal route of administration. Hence, a study is required to know its effectiveness for spinal anaesthesia. It is known that a single injection of Levobupivacaine will not produce a prolonged duration of post-operative analgesia. Hence addition of a drug which can prolong the analgesic effect of Levobupivacaine will be required. Clonidine is a partial α2 agonist which has been used as an analgesic supplement through epidural and intrathecal routes along with local anaesthetics. [5] When combined with Bupivacaine for spinal anaesthesia, it has been found to prolong postoperative analgesia. [6] Clonidine in the dose of 1μg/kg body weight along with Bupivacaine has been found to prolong the post-operative analgesia but has produced significant perioperative hypotension and bradycardia. There are many reports regarding smaller doses of intrathecal Clonidine (15μg - 45μg) as supplement to local anaesthetic agents as this range of doses have been found to produce prolongation of post-operative analgesia with minimal cardiovascular complications. Hence, the study is required to see clonidine with levobupivacaine effects.

Aims and Objectives

- Comparison of Levobupivacaine 0.5 % isobaric (3 ml) with normal saline 0.5 ml and Levobupivacaine 0.5 % isobaric (3 ml) with Clonidine 30μg (in 0.5 ml normal saline) for spinal anaesthesia in patients undergoing elective lower limb orthopaedic surgeries.
- Onset and duration of sensory blockade.
- Maximum sensory blockade attained, and time taken for the same.
- Onset and duration of motor blockade.
- Quality of motor blockade and time taken for the maximum motor blockade.
- Duration of post-operative analgesia.
- Effectiveness of Levobupivacaine as an intrathecal local anaesthetic.
- Hemodynamic changes due to addition of Clonidine and any adverse effects like severe hypotension, bradycardia, respiratory depression.

Methods

This was a hospital based prospective, randomized, comparative study conducted among 60 patients who posted for elective lower limb orthopaedic surgeries in Apollo Speciality Hospital, Madurai, from December 2015 to June 2016 after obtaining clearance from Institutional Ethics Committee and written informed consent from the study participants.

The study population was randomly divided by using computer generated random number chart into two groups with 30 subjects in each group (n=30)

Group LS: Levobupivacaine 0.5% isobaric (3ml) with normal saline(0.5ml)- Total volume 3.5 ml.

Group LC: Levobupivacaine 0.5% isobaric (3ml) with clonidine 30µg (in 0.5 ml normal saline)-Total volume 3.5 ml.

Inclusion Criteria

Adult subjects of either sex, aged between 18 - 65 years belonging to ASA Class I and II scheduled for elective lower limb orthopaedic surgeries of duration less than 180 minutes were included in the study.

Exclusion Criteria

- Pregnancy.
- ASA class III and IV.
- Subjects posted for emergency surgeries.
- Subjects with body mass index more than 29.9 kg/m2
- Subjects shorter than 150 cm.

Statistical Methods

Descriptive statistics such as mean and standard deviation (SD) were used for continuous variables, median and range for non-normally distributed variables and categorical variables were summarized using percentages. All the variables are presented through tables. Student's t-test was used to test the statistical significance of the difference between two continuous variables like heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP). Chi-square test (χ^2 test) and Fisher's exact test were used. Data were entered into Microsoft Excel and analysed using Statistical Package for Social Science (SPSS) for Windows.

Results

Table 1: Demographic Distribution

		Study Group	Mean	Standard Deviation	P Value
Age		LS	37.27	9.403	0.337
		LC	34.93	9.251	
Age Distribution					
		Study Group			P Value
		LS	LC		
		Number of Patients	Number of Patients	Total Number of Patients	
Gender	Male	21	20	41	1.000
	female	9	10	19	
Total		30	30	60	
Sex Distribution					

There was no statistically significant difference in the age wise distribution of patients between groups. There was no statistically significant difference in the gender distribution of the patients between the groups.

Table 2: Time Taken to Attain Maximum Sensory Level (mins)

	Study Group	Mean	Standard Deviation	P Value
Sensory Onset at T10 (in min)	LS	6.60	3.900	0.000
	LC	3.53	1.525	
Time of Onset of Sensory Block at T10 (mins)				
	Study Group	**Mean**	**Standard Deviation**	**P Value**
Time for Max Sensory in mins	LS	12.37	5.301	0.003
	LC	9.00	2.729	

The mean time of onset of sensory blockade at T10 in Levobupivacaine 0.5 % with clonidine group is 3.53 ± 1.525 mins and in Levobupivacaine 0.5 % with saline group is 6.60 ± 3.90 mins. There was a statistically significant faster onset of sensory block in Levobupivacaine 0.5 % with clonidine group.

The mean time taken to attain maximum level of sensory blockade in Levobupivacaine 0.5 % with clonidine group is 9 ± 2.729 mins and in Levobupivacaine 0.5 % with saline group is 12.37 ± 5.301 mins.

There was a statistically significant faster onset of sensory block in Levobupivacaine 0.5 % with clonidine compared to Levobupivacaine 0.5 % with saline group.

Table 3: Duration of Analgesia (mins)

	Study Group	Mean	Standard Deviation	P Value
Duration of sensory block	LS	258.47	34.183	0.000
	LC	377.50	46.952	
Duration of Sensory Block (mins)				
	Study Group	**Mean**	**Standard Deviation**	**P Value**
Duration of analgesia (in mins)	LS	247.30	31.268	0.000
	LC	351.83	55.059	

Statistically significant duration of sensory block in Levobupivacaine with clonidine group compared to Levobupivacaine with saline group. Highly statistically significant difference was observed in duration of analgesia between groups LS and LC.

Table 4: Duration of Motor Block (mins)

	Study Group	Mean	Standard Deviation	P Value
Time for max motor block (in mins)	LS	9.97	3.996	0.002
	LC	7.43	1.695	
Time Taken to Attain Maximum Motor Block (mins)				
	Study Group	**Mean**	**Standard Deviation**	**P Value**
Duration of Motor Block (in mins)	LS	220.07	31.643	0.001
	LC	244.43	19.880	

Time taken to attain maximum motor block (mins) shows statistically significant difference between group LS and group LC.

Duration of motor block (mins) shows statistically significant difference between group LS and group LC.

Discussion

Type of Surgeries Selected for the Study

It has been found that isobaric local anaesthetics are ideal for surgeries below T10 level of block and high volumes are required for surgeries above T10. Hence, in

our study all the patients selected were for lower limb orthopaedic surgeries requiring a blockade below T10. [7]

Demographic Features

In our study, 60 patients belonging to American Society of Anaesthesiologists (ASA) physical status class I and II posted for elective lower limb orthopaedic surgeries were divided into two groups of 30. There was no significant difference regarding the age, gender, body weight and height between two groups. There was no significant difference regarding type of surgical procedures and also mean duration of surgeries among the two groups.

Sensory Block

Onset of Sensory Block at T_{10}

In our study, onset of sensory block is defined as time taken from the completion of the injection of the study drug till the patient does not feel the pin prick at T10 level. Sensory block in the present study was tested using loss of sensation to pin prick as used by Van Kleef et al. [8] The choice of this method, instead of others (such as loss of sensation to ice, pain perception, tetanic twitch or chemical irritation with capsaicin), was based on Hocking's study which proved the reliability and easy application of the pin prick method. [9]

In our study, the mean time for onset of sensory block in group LS was 6.60 ± 3.90 minutes and in group LC was 3.53 ± 1.525 minutes.

There was a statistically highly significant difference (p = 0.000) with group LC having the least time of onset of sensory block.

Our study compares with the study done by Saxena H et al. [10] who also found significant difference in the onset of sensory block between the control (hyperbaric Bupivacaine 0.5 %) and Clonidine 30 µg group.

In the study conducted by Yadava AS et al. 30 µg of Clonidine along with 15 mg of Bupivacaine (heavy), the authors did not find any significant difference between the 30 µg of Clonidine and the control group regarding the sensory onset. In their study, proper definition for the onset of sensory block has not been given and the loss of sensation for pin prick taken at a particular dermatomal level has not been clearly defined. This probably explains why it differs from our study.

Our study also does not compare with the study conducted by Agarwal D et al. [11] who had compared 15 µg and 30 µg of Clonidine with hyperbaric Bupivacaine and found no significant difference regarding the onset of sensory block at T10 level in both the Clonidine groups and control group. This is probably due to the technique that was being used in their study was combined spinal-epidural technique and because of introduction of epidural catheter before spinal anaesthesia, producing an epidural volume expansion effect (EVE) hastening the onset of sensory block.

Time for Maximum Level of Sensory Block

In our study, the time taken for maximum level of sensory block in the LS group 12.37 ± 5.3 and LC groups were 9 ± 2.7 minutes, this is statistically significant (p = 0.003).

Our study does not correspond to the study conducted by Sagiroglu G et al. Thakur A et al. [12] and Saxena H et al. In the study conducted by Sagiroglu G et al. where 15 µg and 30 µg of Clonidine was compared with the control, the local anaesthetic used was 12 mg of Ropivacaine and body weight of patients was > 70 kg and height was > 167 cm. In all the three groups because of the different Local anaesthetic agent and higher body weight and height compared to the patients (mean height 158 cm and weight 56 kg) in our study may be the reason for the difference in the results. In the study done by Thakur A et al. the technique used was unilateral spinal

anaesthesia and also the drug used was 0.5 % hyperbaric Bupivacaine 11mg (2.2 ml) and the total volume of the study drugs was 2.4 ml compared to 3.5 ml in our study, hence the difference in the results.

Our study compared with the study done by Kulkarni S et al. using 45 µg of Clonidine, found significant difference in the time to attain maximum sensory block in Clonidine group (4 ± 3.2 minutes) compared to control group (9.5 ± 4 minutes). The time for maximum sensory block was 4 ± 3.2 minutes which was much less than Clonidine 30 µg of our group (9.08 minutes) which was due to the higher dose of Clonidine (45 µg) used in their study.

Our study also does not compare with Agarwal D et al. and Kock DM et al. [13] studies as they did not find any significant difference in the time for maximum sensory level of block.

As in the above two studies, the technique used was combined spinal-epidural technique.

Maximum Level of Sensory Block

In our study, the mean level of sensory block there was no statistically significant difference in the maximum level of blockade attained between groups. Our study corresponds with Dobrydnjov I et al. Prabha P et al.[14] and Kock DM et al. who also did not find any statistically significant difference in the maximum level of sensory block.

Time for two Segment Sensory Regression

In our study, time for 2 segment sensory regression in control group and Clonidine 30 µg groups were 95.63 minutes and 100.37 minutes respectively which was statistically not significant. Our study corresponds to the study conducted by Agarwal D et al and Kock DM et al.

Duration of Sensory Block

In our study, the duration of sensory block taken as regression to S_1 was 258.47 minutes, 377.50 minutes LS group and LC group respectively. This is statistically highly significant. Our study compares with the studies conducted by Sagiroglu G et al. and Thakur A et al.

Prabha P et al., Dobrydnjov I et al. and Kock DM et al. have also found prolonged duration of sensory block in 30 µg Clonidine group compared with control group.

Duration of Analgesia

Our study compares with the studies conducted by Anastasslou E et al.,[15] Dobrydnjov I et al., Thakur A et al. Yadava AS et al., Prabha P et al., Saxena H et al. and Agarwal D et al. who also found statistically significant difference in the duration of analgesia. In all these studies, there was a statistically significant prolongation of analgesia in Clonidine groups as in our study.

In our study, the duration of analgesia in group LC was 351.8 ± 55.05 minutes which was statistically highly significant compared to group LS which was 247.3 ± 31.26 minutes.

Our study was compared with the study done by Yadava AS et al. with the duration of analgesia with Clonidine group, (387 minutes compared to control group of 204 minutes) which was statistically highly significant. In the above study by Yadava AS et al. the local anaesthetic agent used was Bupivacaine 15 mg which was similar as in our study of Levobupivacaine 15 mg.

Dobrydnjov I et al. in their study found that the duration of analgesia with 15 µg Clonidine - 274 minutes, compared to control – 171 minutes, was statistically highly significant though the dose of Bupivacaine used in their study was 6 mg of Bupivacaine (Heavy). This is because the technique used in their study was selective spinal anaesthesia (unilateral spinal anaesthesia) and hence the small dose of the drug used, with patients kept in

lateral position for a minimum of 15 minutes before turning to supine posture.

In our study, the duration of analgesia with Clonidine 30 µg (351 minutes) was statistically highly significant compared to control (247 minutes). Similar results have been obtained by Dobrydnjov I et al. and Thakur A et al., Yadava AS et al., Prabha P et al., Saxena H et al., Chandrashekarappa K et al. and Agarwal D et al.

The duration of analgesia with 30 µg of Clonidine with our study (351 minutes) compares with the study done by Yadava AS et al. (387 minutes) and Chandrashekarappa K et al. (320 minutes).

In the studies conducted by Thakur A et al., Prabha P et al., Saxena H et al. and Agarwal D et al. the duration of analgesia with 30 µg Clonidine is much less compared to our study. The reasons for this difference are the smaller dose of local anaesthetic used and technique was combined spinal epidural in Agarwal D et al.

The duration of analgesia was less in study conducted by Saxena et al. compared to our study because of lesser dose of Bupivacaine used (13.5 mg). In contrast to our study in the study done by Prabha P et al. the duration of analgesia was much less which was due to the use of only 6 mg of Bupivacaine (Heavy).

The duration of analgesia was less in study conducted by Thakur A et al. because of lesser dose of Bupivacaine used.

Onset of Motor Block

In our study, time required for onset of motor block is statistically not significant between two groups. Same result has been obtained by Yadava AS et al.

Our study does not compare with the study conducted by Saxena H et al. who has found a significant difference regarding the onset of motor blockade with the control group (7.4 minutes) compared with Clonidine 15µg group (2.67 minutes) and Clonidine 30 µg group (2.3 minutes). However, they have not defined the onset of motor block in their methodology.

Time for Maximum Motor Blockade

In our study, the time for achieving maximum motor blockade was 9.47 min and 7.43 min in control group and 30 µg group respectively and this is statistically significant.

Our study does not correspond with Sagiroglu G et al., Thakur A et al., Agarwal D et al. who did not find any statistically significant difference between control and Clonidine groups.

In the study conducted by Sagiroglu G et al. there was a clinically significant difference between the control group (16 minutes) and Clonidine 30 µg (11 minutes), but it was not statistically significant.

Grade of Motor Blockade

In our study, 25 patients in control group, 29 patients in Clonidine 30 µg group developed Bromage 3 motor blockade. This is statistically not significant but clinically significant. Similar observations have been made in the studies conducted by Sagiroglu G et al. and Yadava AS et al.

Our study does not correspond to the study conducted by Kock DM et al. They found statistically significant difference between control and Clonidine groups. However, in the Clonidine groups, significant motor blockade has been obtained when Clonidine 75 µg was used in comparison with 45 µg and 15 µg. This difference is due to use of higher dose of Clonidine in the above study.

Our study does not correspond with the study conducted by Kulkarni S et al. who also found statistically significant higher level of blockade with the Clonidine groups. Even in this study 45 µg Clonidine has been used which is higher than 30 µg used in our study.

Intrathecal Clonidine alone, even in doses up to 450 µg, has not been found to induce motor blockade or weakness in contrast to

intrathecal Clonidine combined with local anaesthetics, which significantly potentiates the intensity of the motor block. The explanation for this could be due to α_2 adreno receptor induced cellular modification in the ventral horn of the spinal cord which facilitates the local anaesthetic action, and these effects seem to be dose related. Hence in the studies using higher doses of Clonidine, more intense motor blockade has been observed.

Duration of Motor Block

In our study, the duration of motor block was 220.07 min and 244.43 min in control group and Clonidine group respectively which was significant statistically.

In our study there is a statistically significant difference regarding the duration of motor blockade in Clonidine 30 µg group compared to control group. Our study compares with the studies done by Dobrydnjov I et al. Agarwal D et al. Sagiroglu G et al. Thakur A et al and Prabha P et al.

Haemodynamic Changes

In our study, there was no significant difference among the two groups regarding number of patients developing bradycardia and hypotension. Similar hemodynamic changes were observed in the studies conducted by Yadava AS et al. Agarwal D et al. Sagiroglu G et al. and Prabha P et al., where the dose of Clonidine used was not > 30 µg.

In the study conducted by Kock DM et al. The mean arterial pressure (MAP) was significantly lower (p-value = 0.05) in patients where Clonidine more than 30 µg was used, i.e. 45 µg and 75 µg. The authors observed that a small dose of intrathecal Clonidine is not usually associated with systemic side effects such as bradycardia and hypotension. Higher doses produce sympatholysis and reduce arterial blood pressure through effects at specific brain stem nuclei and on sympathetic preganglionic neurons in the spinal cord.

Conclusion

It has been found that 30 µg of Clonidine when used along with 0.5 % isobaric Levobupivacaine intrathecally produced long duration post-operative analgesia and produced prolonged sensory block compared to the control. It has been found that 30µg of Clonidine as adjuvant has produced faster onset and prolonged duration of sensory block and also significantly reduced motor onset and prolonged motor blockade compared to levobupivacaine with saline. Addition of Clonidine did not produce any significant haemodynamic changes compared to control group. It is concluded that 30 µg of Clonidine as adjuvant along with 0.5 % isobaric Levobupivacaine produces significant increase in duration of post-operative analgesia without producing significant haemodynamic changes.

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