



RESEARCH ARTICLE

A COMPARATIVE STUDY OF 0.5% LEVOBUPIVACAINE WITH 0.5% BUPIVACAINE IN EPIDURAL ANAESTHESIA FOR LOWER ABDOMINAL AND LOWER LIMB SURGERIES

*Dr. Masaraddi Deepak K. and Dr. Talikoti, D.G.

Department of Anaesthesiology, BLDE University's Shri B.M. Patil Medical College, Hospital and Research Centre, Vijayapur, Karnataka, India

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*Corresponding author: Dr. Masaraddi Deepak K.

Department of Anaesthesiology, BLDE University's Shri B.M. Patil Medical College, Hospital and Research Centre, Vijayapur, Karnataka, India.

ABSTRACT

Background: Spinal and epidural anaesthesia are regional anaesthesia methods that are widely used, especially in lower abdominal and lower extremity operations. Bupivacaine is the widely used local anaesthetic in regional anaesthesia. Stereoisomers of the agent are being developed for use instead of the isomers, in order to avoid the toxic side effects of local anaesthetic agent. Bupivacaine is available in a commercial preparation as a racemic mixture (50:50) of its two enantiomers, Levo-Bupivacaine, S (-) isomer and Dextro-Bupivacaine, R (+) isomer. Several central nervous system and cardiovascular adverse reactions reported in the literature have been linked to the R (+) isomer of Bupivacaine.

Aim : To evaluate the clinical efficacy of 0.5% Levobupivacaine with 0.5% Bupivacaine in epidural anaesthesia without adjuvant medication in patients undergoing elective for lower abdominal and lower limb surgeries with respect to onset of action of sensory block, duration of analgesia, onset of action and duration of motor block, hemodynamic changes and side effects.

Materials and Methods: A prospective randomized clinical trial on 100 patients aged between 18-60 years scheduled for elective lower abdominal or lower limb surgery under epidural anesthesia belonging to ASA grade I and II were included in this study. All patients were randomly allocated into two groups. Group B (n=50) patients receiving 0.5% isobaric Bupivacaine 17 ml. Group L (n=50) patients receiving 0.5% isobaric Levobupivacaine 17ml. Following parameters observed - onset time of sensory block, highest level of sensory block, duration of sensory block, duration of sensory analgesia, onset time of motor block, degree of motor block, duration of motor block, hemodynamic changes and side effects such as hypotension, bradycardia, nausea, vomiting.

Results: Both groups are comparable with respect to age, sex, weight and duration of surgery. Group-L has similar onset time of sensory block and highest level of sensory block reached as compared to Group-B. Group-L has a longer duration of sensory block as compared to Group-B. Mean Time to two segment regression / Duration of sensory block in Group-L being 132.46 minutes and Group-B being 89.28 minutes. P-value=0.000. Group-L has longer duration of sensory analgesia as compared to Group-B. Mean Time of sensory analgesia in block in Group-L is 326.5 min and in Group-B is 284.42 min. P-value= 0.000. Group-L has a slower onset of motor block as compared to Group-B. Mean Time to onset of motor block in Group-L is 19.6 min and in Group-B is 17.74 min. P-value= 0.000. Group-L has shorter duration of motor block as compared to Group-B. Mean Duration of motor block in Group-L is 197.4 min and in Group-B is 203.3 min. P-value= 0.017. Group L has similar degree of motor blockade as compared to Group B. No statistical difference was found between Group-L and Group-B with respect to variability in systolic blood pressure, diastolic blood pressure, heart rate and oxygen saturation at various time intervals.

Conclusion: Levobupivacaine has a similar onset time and longer duration of sensory blockade and slower onset and shorter duration of motor blockade, with comparable quality of analgesia and hemodynamic parameters as compared with Bupivacaine. Owing to its better safety profile, Levobupivacaine is a good alternative to Bupivacaine.

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INTRODUCTION

Regional anaesthesia with Spinal and Epidural anaesthesia is the most widely used anaesthesia techniques for lower abdominal and lower limb surgeries (Kleinman, 2002; Longo, 1999). Their advantages over general anaesthesia are (Michael, 2009) avoidance of poly pharmacy, avoidance of airway

manipulation and protection of airway reflexes, good motor and sensory blockade, better hemodynamic stability, lesser incidence of post operative nausea and vomiting and prolonged postoperative analgesia. The advantages of epidural anaesthesia (Collin, 1993) over spinal anaesthesia are extension of anaesthesia for prolonged duration of surgeries, prolonged post operative analgesia, better hemodynamic

stability and the incidence of post dural puncture headache is not there as the dura is not pierced. Bupivacaine is the widely used local anaesthetic in regional anaesthesia. Stereoisomers of the agent are being developed for use instead of the isomers, in order to avoid the toxic effects of local anaesthetic agents as much as possible. Bupivacaine is available in a commercial preparation as a racemic mixture (50:50) of its two enantiomers, Levo-Bupivacaine, S (-) isomer and Dextro-Bupivacaine, R (+) isomer. Several central nervous system and cardiovascular adverse reactions reported in the literature have been linked to the R (+) isomer of Bupivacaine. The levorotatory isomers were shown to have a safer pharmacological profile with less cardiotoxic and neurotoxic effects and it is attributed to its faster protein binding rate. S forms of the isomers are less toxic and provide longer lasting analgesia (Casati and Putzu, 2005; Foster and Markham, 2000). The pure S (-) enantiomers of Bupivacaine, i.e., Dextro-Bupivacaine and Levo-Bupivacaine were thus introduced into clinical anaesthesia practice. This study aims to compare the clinical efficacy of 0.5% Levo-Bupivacaine and 0.5% Bupivacaine without adjuvant medication in patients undergoing elective lower abdominal and lower limb surgeries under epidural anaesthesia with respect to the onset & highest level of sensory block, duration of sensory analgesia, onset, degree & duration of motor blockade, hemodynamic changes like heart rate, blood pressure, and oxygen saturation at various time intervals. Intraoperative and postoperative complications such as nausea, vomiting, hypotension, bradycardia and respiratory depression.

MATERIALS AND METHODS

This prospective randomized controlled trial was carried out at Shri B.M Patil Medical College; Vijayapur during the period from December 2015 to August 2017. This study was only undertaken on consenting patients after obtaining the ethical clearance from institutional ethical committee. The study population of 100 age and sex matched patients aged 18-60 years, scheduled for an elective lower abdominal or lower limb surgery belonging to ASA grade I and II were included in this study. They were randomly selected and divided by computer into two groups with 50 patients in each group. Study group L (n = 50) received 0.5% Levobupivacaine. Study group B (n = 50) - received 0.5% Bupivacaine. Result values were recorded using a preset Performa. Inclusion Criteria: Patients coming for elective surgeries in age group of 18-60 years of both sexes belonging to ASA grade I and II. Exclusion Criteria: Patient refusal, patient belonging to ASA grade III and IV, patients with infection at site of injection, coagulopathy, on anti coagulation treatment (INR >1.5), with congenital abnormalities of lower spine and meninges, with history of allergy to local anaesthetics, with uncorrected hypovolemia and obstetric patients.

Method of study

All pre-anaesthetic evaluation of the patients was performed by an anaesthesiologist a day before the surgery, assessing history and general condition of the patient, airway assessment by Mallampati grading, nutritional status, height and weight of the patient, Vital signs – heart rate, blood pressure, respiratory rate were recorded. A detailed examination of the cardiovascular system, Respiratory system and Central nervous system with examination of the spine was performed.

The following investigations were done in all patients

Urine (albumin, sugar, microscopy), hemoglobin, total count, differential count, platelet count, bleeding time, clotting time, HBsAg, HIV, blood urea, serum creatinine, ECG, chest x-ray (if required). All patients who belonged in the inclusion criteria, after giving a written informed valid consent were randomly allocated into the following groups.

Group B (n=50) -- patients receiving 0.5% isobaric Bupivacaine 17 ml.

Group L (n=50) -- patients receiving 0.5% isobaric Levobupivacaine 17ml.

In the operation theatre, a good peripheral intravenous access was secured using 18 gauge canula and patient was preloaded with 500ml Ringer Lactate solution. Multiparameter monitor was connected which records heart rate, non-invasive measurement of systolic blood pressure (SBP), diastolic blood pressure (DBP), continuous electrocardiogram (ECG) monitoring and arterial oxygen saturation (SpO₂). Baseline non invasive blood pressure, pulse rate, respiratory rate and SpO₂ were recorded. Premedication with Inj. Ondansetron 4mg i.v and Inj. Ranitidine 150mg i.v was given. Under all aseptic precautions using a sterile epidural kit and autoclaved epidural tray the 18g epidural catheter was secured in L3-L4 intervertebral space. After exclusion of blood/CSF in the epidural catheter with negative aspiration, 3ml of Lignocaine with Adrenaline 1:200,000 test dose was administered to exclude intrathecal or intravascular placement of the catheter. After 5 minutes of administering test dose, patients in group B received 0.5% isobaric Bupivacaine (17 ml) and group L received 0.5% isobaric Levobupivacaine (17 ml) epidurally.

- **Parameters observed:** Baseline pulse rate, noninvasive blood pressure, arterial oxygen saturation (SpO₂) and respiratory rate were recorded. "0" time is time of injection of epidural study anaesthetic drug (Levobupivacaine / Bupivacaine).
- **Onset time of sensory block:** The time interval between administration of drug into the epidural space and the absence of pain from pin prick at the T10 level was recorded as the onset time for sensory block.
- **Highest level of sensory block:** highest dermatome of sensory block reached.
- **Duration of sensory block:** Time to two-segment regression: time for regression of sensory block by two dermatomes from highest level of sensory block.
- **Duration of sensory analgesia:** The time interval between the administration of epidural block and the first requirement of supplementary analgesia will be noted.
- **Onset time of motor block:** The time interval between the administration of drug into epidural space and the patient's inability to lift the straight extended leg (Modified Bromage scale) was recorded as onset time for motor block.
- **Degree of motor block:** The degree of motor block was assessed by Modified Bromage scale.
- **Modified Bromage Scale2**
 - Able to raise leg straight, full flexion of knees and feet.

- Inability to raise leg, just able to flex knees, full flexion of feet.
- Unable to flex knees, but some flexion of feet possible.
- Unable to move legs or feet.
- Duration of motor block is taken as time between "0" time & time to complete regression of motor block.
- Haemodynamic changes: Patients were monitored for heart rate, blood pressure and oxygen saturation at 0, 2, 5, 15, 30, 60, 90, 120 and 180 minutes after administration of epidural block.
- Intra operative and post operative complications if any: such as nausea, vomiting, hypotension, bradycardia, respiratory depression, shivering will be looked for, recorded and treated accordingly.

Statistical analysis

After data collection, data entry was done in Excel.div. Data analysis was done with the help of SPSS Software ver 15 and Sigmaplot Ver 11.div. Quantitative data is presented with the help of Mean, SD and Median, and comparison between study groups is done by Unpaired or Mann-Whitney test as per results of normality test. Qualitative data is presented with the help of Frequency and Percentage table, association among study group is assessed with the help of Chi-Square test and Fisher's Exact Test. P value less than 0.05 is taken as significant level.

OBSERVATIONS AND RESULTS

Demographic Data: There were no significant differences in age, sex or weight of patients between the groups and patients were equally distributed among the different types of surgeries. Both the groups were comparable in terms of demographic profile and the duration of surgery (Table 1).

Table 1. Demographic Data

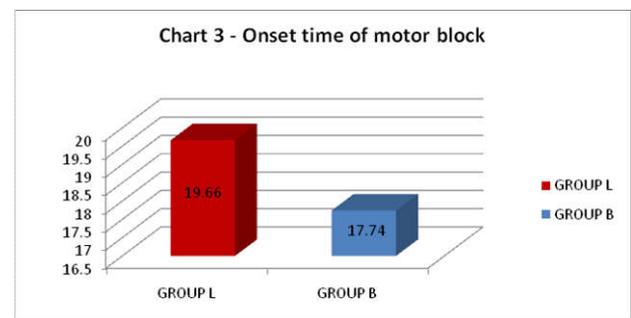
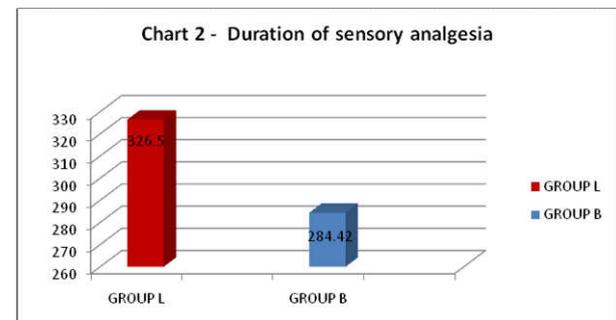
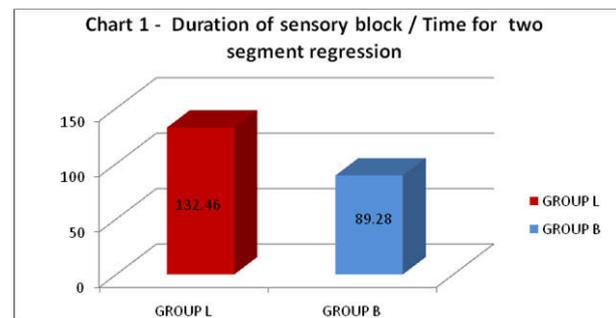
Demographic Profile	Group – L (n=50)		Group – B (n=50)		P Value
	Mean	SD	Mean	SD	
Age (in years)	40.56	11.22	40.28	10.73	0.899
Weight (in kg)	58.56	6.05	56.40	4.87	0.052
Duration of Surgery (in min)	105.6	10.52	109	11.65	0.129
Sex (no. of Male : Female patients)	31:19		31:19		1.000

Table 2. Comparison of sensory and motor block characteristics in both Groups

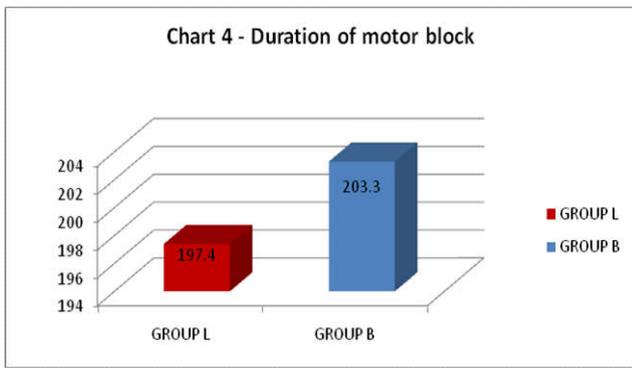
Parameters	Group – L (n=50)		Group – B (n=50)		P Value
	Mean	SD	Mean	SD	
Observed					
Onset time of sensory block (in min)	11.66	0.917	11.62	0.830	0.820
Duration of sensory block (in min)	132.46	10.74	89.28	4.75	0.000
Duration of sensory analgesia (in min)	326.5	6.64	284.42	7.18	0.000
Onset time of motor block (in min)	19.66	1.67	17.74	1.19	0.000
Duration of motor block (in min)	197.4	14.22	203.2	9.50	0.017

Onset Time of Sensory Block: Group-L has similar onset time of sensory block as compared to Group-B. Mean onset time to sensory block at T-10 in Group-L is 11.6 min and in Group-B is 11.62 min. P -value being P-value= 0.820 i.e. P-value<0.05 is not significant. Result calculated using Students Unpaired't' Test (Table2). Highest level Of Sensory block reached: In Group L T-6 level was reached in 29 patients (58%) , T-7 level was reached in 16 patients (32%) and T-10 level was reached in 5 patients (10%). In Group B T-6 level was reached in 31 patients (62%), T-7 level was reached in 15 patients (30%) and T-10 level was reached in 4 patients (8%).

Duration of Sensory Block: Group-L has slower regression of sensory block as compared to Group-B. Mean Time for two segment regression in Group-L is 132.46 min and in Group-B is 89.28 min. P -value is 0.000 i.e. P-value <0.05 is significant. Result calculated using Students Unpaired 't' Test (Table 2 & Chart 1). Duration Of Sensory Analgesia: Group-L has longer duration of sensory analgesia as compared to Group-B. Mean Time of sensory analgesia in block in Group-L is 326.5 min and in Group-B is 284.42 min. P -value is 0.000 i.e. P-value < 0.05 is significant. Result calculated using Students Unpaired't' Test (Table 2 & Chart 2).



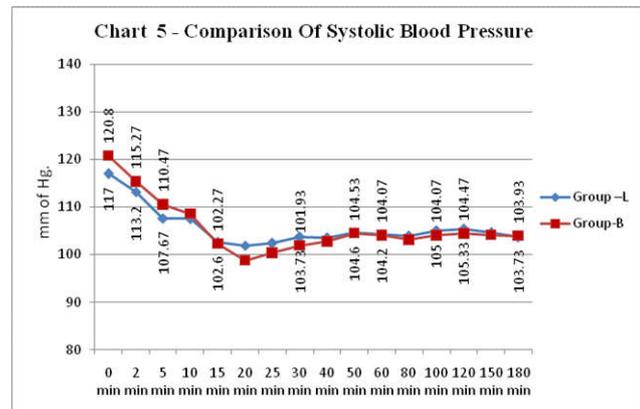
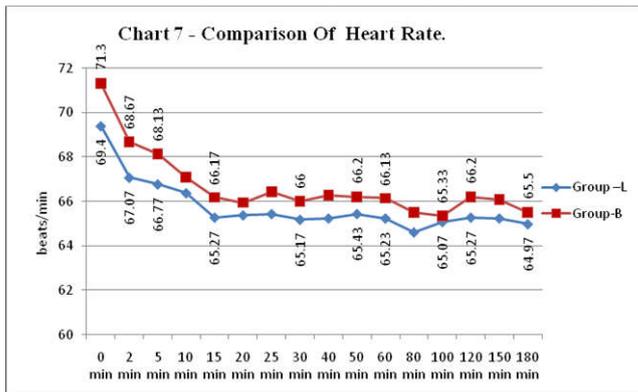
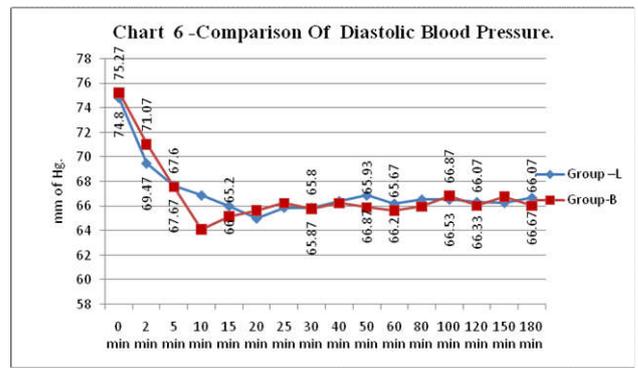
This is statistically not significant as P-value is 0.1 i.e. P-value>0.05. Result calculated using Students Unpaired't' Test (Table 2).



Onset Time Of Motor Block: Group-L has a slower onset time of motor block as compared to Group-B. Mean Time to onset of motor block in Group-L is 19.6 min and in Group-B is 17.74 min. P -value is 0.000 i.e. P-value < 0.05 is significant. Result calculated using Students Unpaired 't' Test (Table 2 & Chart 3). Degree of Motor Block: Assessed by Modified Bromage Scale. In Group L MBS 3 was reached in 38 patients (76%), MBS 2 was reached in 12 patients (24%). In Group B MBS 3 was reached in 40 patients (80%), MBS 2 was reached in 10 patients (20%). This is statistically is not significant as P-value is 0.633 i.e. P-value > 0.05. Result calculated using Students Unpaired 't' Test.

Duration of Motor Block

Group-L has shorter duration of motor block as compared to Group-B. Mean Duration of motor block in Group-L is 197.4 min and in Group-B is 203.3 min. P -value. P-value is 0.017 i.e. P-value < 0.05 is significant. Result calculated using Students Unpaired 't' Test (Table 2 & Chart 4). Hemodynamic Changes: There is no difference between Group-L and Group-B with respect to variability in systolic blood pressure, diastolic blood pressure, heart rate and oxygen saturation at various time intervals. P-value is >0.05 at all time intervals and is not significant. Result calculated using Students Unpaired 't' Test. Spo2 < 95% is defined as hypoxia & treated with supplemental O2 via face mask . In our study oxygen saturation was found > 95% in both the groups at all intervals, so none of the patient required oxygen masks. (Chart 5, 6, 7)



Complications

Hypotension was seen in 7 cases (14%) and Bradycardia in 2 cases (4%) of Group-L. Hypotension was seen in 12 cases (24%) and Bradycardia in 1 case (2%) of Group-B. Hypotension and bradycardia were not significant. P-value=1.000 i.e. P-value>0.05.

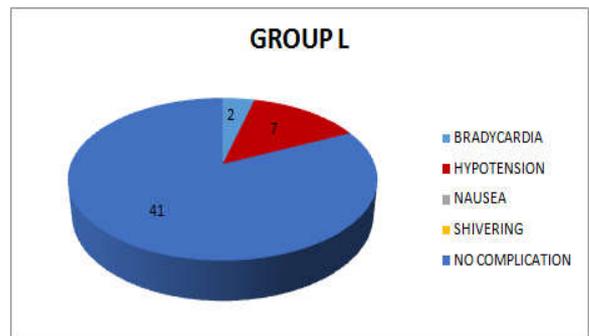
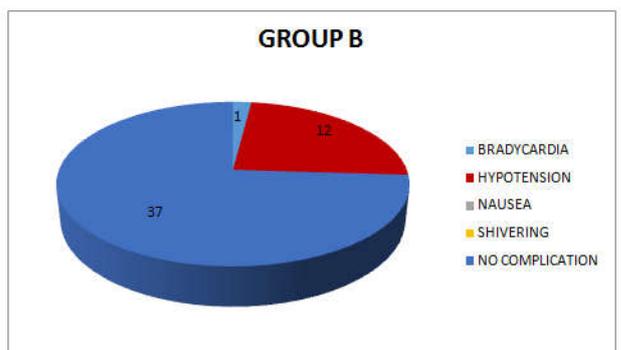


Chart 8. Complications in Group L



Other complications like nausea or shivering were not observed in any patients of Group-L or Group-B. (Chart 8, 9)

DISCUSSION

Regional anaesthesia has many advantages like consciousness of the patient, early awareness of complications owing to the ongoing cooperation of the patient, protection of the airway reflexes, better hemodynamic stability compared to general anaesthesia, while it has the disadvantages of late onset of its effects and possible development of motor block (Levobupivacaine, 2000).

This method is preferred by anaesthesiologists, especially in patients who suffer from respiratory system problems. (Ouellette and Ouelette, 1995) Epidural anesthesia followed by epidural postoperative analgesia is also preferred for high-risk cardiac patients (Burke *et al.*, 1999). Bupivacaine is a long-acting local anesthetic from the amino-amide subgroup, which is frequently used in local infiltration and epidural and spinal anesthesia. Although it has been safely used in all types of regional applications for many years, fatal cardiotoxic effects may be seen following accidental intravascular injection (Atalay *et al.*, 2010; Reiz *et al.*, 1986). An important cause of cardiovascular side effects is Bupivacaine leaving sodium channels slowly. Therefore, local anesthetics with similar actions to Bupivacaine, but with fewer effects on the cardiovascular system, have been needed.

Levobupivacaine is an S (-) enantiomer of racemic Bupivacaine. The affinity of the S (-) isomer to the cardiac sodium channel in the inactive state is lower than that of the R (+) isomer (Marx, 1984; Aberg, 1972). In the studies conducted, Levobupivacaine has been demonstrated to present similar pharmacokinetic characteristics to Bupivacaine and to be less cardiotoxicity. Levobupivacaine is considered a good alternative to Bupivacaine, because of its lower side effects on the cardiovascular and central nervous system (Luduena *et al.*, 1972; Foster and Markham, 2000). Equal doses of Levobupivacaine and Bupivacaine (17 mL of 0.5%) provide similar onset of sensory block (8-30 min), maximum cephalic spread (T6-T7) and duration of analgesia (4-6 hours). Though, the onset of motor block is delayed with Levobupivacaine (Casati *et al.*, 2003) it is less dense as compared to Bupivacaine but with a similar duration. (Van *et al.*, 1998; Cox *et al.*, 1998; Casati *et al.*, 2003). Higher concentration of Levobupivacaine (i.e., 0.75% vs. 0.5%) provides a longer duration of sensory and motor block without any increase in the incidence of adverse side effects (Kopacz *et al.*, 2000).

An increase in both volume and concentration of Levobupivacaine is however associated with a higher incidence of hypotension (82%) and delayed block regression (Fesih Kara *et al.*, 2013). The incidence of hypotension is similar when either Levobupivacaine or Bupivacaine is used for epidural anesthesia for cesarean section (Senard *et al.*, 2004). So a study was conducted by us, to compare the clinical profile of Levobupivacaine and Bupivacaine when administered epidurally. Onset Time of Sensory Block: Group-L has similar onset of sensory block as compared to Group-B. Mean onset time to sensory block at T-10 in Group-L is 11.6 min and In Group-B is 11.62 min. P-value= 0.820. In a study done by Fesih Kara *et al* in 2013 (Kopacz *et al.*, 2000), Time of sensory block to reach T6 in Group L and Group B is 24.54±2.27 min and 23.97±1.485 min respectively. Onset was similar with Levobupivacaine and Bupivacaine.

Highest level of Sensory block reached

Group L has similar highest level of sensory block reached as compared with Group B p value 0.1 Cox *et al.* (1998) (Van *et al.*, 1998), Kopacz and Allen (2000) (Casati *et al.*, 2003) and Fesih Kara *et al.* (2013) (Kopacz *et al.*, 2000) also found no significant difference between the two groups with respect to peak block height attained, which is similar to our study.

Duration of sensory block

Group-L has a longer duration of sensory block as compared to Group-B. Mean Time to two segment regression / Duration of sensory block in Group-L being 132.46 minutes and Group-B being 89.28 minutes. P-value=0.000. Group-L has longer duration of sensory analgesia as compared to Group-B. Mean Time of sensory analgesia in block in Group-L is 326.5 min and in Group-B is 284.42 min P-value= 0.000. In a study done by Kopacz *et al* in 2000 (Casati *et al.*, 2003), Time to complete regression (Duration) of sensory block was significantly longer with Levobupivacaine (550.6 ± 87.6 min) than Bupivacaine (505.9 ± 71.1 min) (P = 0.016). It is in contrast to our study. Time to onset of motor block: Group-L has a slower onset of motor block as compared to Group-B, which is in accordance to our hypothesis that onset of motor block is delayed with Levobupivacaine as compared to Bupivacaine. Mean Time to onset of motor block in Group-L is 19.6 min and in Group-B is 17.74 min. P-value= 0.000. Cox CR *et al* (1998) (Van *et al.*, 1998), Fesih Kara *et al.* (2013) (Kopacz *et al.*, 2000); found in their study that Onset of motor block was similar with Levobupivacaine and Bupivacaine. In a study by, Kopacz *et al.* (2000) (Casati *et al.*, 2003), slower onset of motor block was found with Levobupivacaine as compared to Bupivacaine, as seen in our study, but in our study we found this difference to be statistically significant.

Duration of motor block

Group-L has shorter duration of motor block as compared to Group-B. Mean Duration of motor block in Group-L is 197.4 min and in Group-B is 203.3 min. P-value= 0.017. In a study by, Aasim *et al.* (2014) (Bergamaschi *et al.*, 2005), Fesih Kara *et al.* (2013) (Kopacz *et al.*, 2000), Kopacz *et al.* (2000) (Casati *et al.*, 2003); Duration of of motor block was similar in both Levobupivacaine and Bupivacaine groups.

Degree of motor block

Group L has similar degree of motor blockade as compared to Group B. P-value = 0.633

Hemodynamic Changes

In our study we observed that, there is no difference between Group-L and Group-B with respect to variability in systolic blood pressure, diastolic blood pressure and heart rate at various time intervals, which is in accordance with our hypothesis. P-value is not significant. P value = P-value>0.05 at various time intervals. In a study done by Fesih Kara *et al* in 2013 (Kopacz *et al.*, 2000), No statistically significant difference was found between the Levobupivacaine and Bupivacaine groups in terms of heart rate, noninvasive systolic artery pressure, diastolic artery pressure (P > 0.05).

Oxygen saturation at various time intervals

Spo₂ < 95% is defined as hypoxia & treated with supplemental oxygen via face mask. In our study oxygen saturation was found > 95% in both the groups at all time intervals.

Complications

Hypotension was seen in 7 cases (14%) and Bradycardia in 2 cases (4%) of Group-L. Hypotension was seen in 12 cases (24%) and Bradycardia in 1 case (2%) of Group-B. Hypotension and bradycardia were not significant. P-value=1.000 i.e. P-value>0.05. Other complications like

nausea or shivering were not observed in any patients of Group-L or Group-B (Chart 8, 9). In a study done by Aasim in 2014 (Bergamaschi *et al.*, 2005), Bradycardia was seen in 2 patients in Bupivacaine group and 1 patient in Levobupivacaine group. Hypotension was observed in 12% patients of Levobupivacaine group and 20% patients of Bupivacaine group. No significant difference between the two groups.

Conclusion

We conclude from our study that epidurally administered isobaric 0.5% Levobupivacaine has a similar onset and longer duration of sensory blockade and slower onset and shorter duration of motor blockade with comparable hemodynamic parameters as with epidurally administered isobaric 0.5% Bupivacaine. Owing to its better safety profile, Levobupivacaine is a good alternative to Bupivacaine. Also, levobupivacaine is a good alternative to bupivacaine, for surgeries requiring early mobilisation or shorter duration of motor block.

REFERENCES

- Aasim, S. A., Syamasundara Rao, B. and Nagaraj Gajagouni, 2014. "A Comparative study of 0.5% Levobupivacaine and 0.5% Racemic Bupivacaine in Epidural Anaesthesia for Lower Limb Surgeries". *Journal of Evidence based Medicine and Healthcare*, Volume 1, Issue 15, December 15, Page: 1874-1881.
- Aberg, G. 1972. Toxicological and local anaesthetic effects of optically active isomers of two local anaesthetic compounds. *Acta Pharmacol Toxicol.*, 31: 273-86.
- Atalay, C., Dağlı, C., Bayram, E., Alici, HA., Erdem, AF., Keleş, MS. *et al.*, 2010. Effects of three different methods of anesthesia on the release of brain natriuretic peptid in patients with cardiac risk undergoing lower extremity surgery. *Turk J Med Sci.*, 40: 405-14.
- Bergamaschi, F., Balle, V R., Gomes, ME., *et al.*, 2005. Levobupivacaine Versus Bupivacaine in Epidural Anesthesia for Cesarean Section. Comparative Study. *Rev Bras Anestesiol.*, 55: 6: 606 -613
- Burke, D., Kennedy, S. and Bannister, J. 1999. Spinal anaesthesia with 0.5% S(-)-Bupivacaine for elective lower limb surgery. *Region Anaesth Pain Med.*, 24: 519-23.
- Casati, A., Putzu, M., Bupivacaine, Levobupivacaine and Ropivacaine, are they clinically different? *Best Practice and Research Clinical Anaesthesiology* 2005; 19:247-68.
- Casati, A., Santorsola, R., Aldegheri, G., Ravasi, F., Fanelli, G., Berti, M., Frascini, G. and Torri, G. 2003. Vita-Salute University of Milano-Department of Anesthesiology, IRCCS H SanRaffaele, Milan, Italy. Intraoperative epidural anesthesia and postoperative analgesia with Levobupivacaine for major orthopedic surgery: a double-blind, randomized comparison of racemic Bupivacaine, Levobupivacaine and Ropivacaine. *J Clin Anesth.*, 15(2):126-31.
- Collin, VJ. 1993. Principles of anesthesiology. 3rd ed. Philadelphia: Lea and Febiger;
- Cox, CR., Faccenda, KA., Gilhooly, C., Bannister, J., Scott, NB. and Morrison, LM. 1998. Extradural S(-)-Bupivacaine: comparison with racemic RS-Bupivacaine. *Br J Anaesth.*, 80(3):289-93.
- Fesih Kara, Husnu Kursad, Mine Celik, Aysenur Dostbil, Ilker Ince, Ahmet Faruk Giren *et al.*, 2013. Comparison of the effects of epidural 0.5% Bupivacaine and 0.5% Levobupivacaine administration on anesthesia quality, side effect incidence, and analgesia requirement times in hip and lower extremity surgery. *Turkey Turk J Med Sci.*, 43:580-585.
- Foster, RH. and Markham, A. 2000. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. *Drugs.*, 59 (3) ; 551-579.
- Foster, RH. and Markham, A. 2000. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. *Drugs.*, 59: 531-79.
- Kleinman, W. 2002. Regional anesthesia and pain management: spinal, epidural and caudal blocks. In: Morgan GE, Mikhail MS, Murray MJ, editors. *Clinical Anesthesiology*. 3rd ed. Los Angeles: Appleton & Lange; p. 253-82.
- Kopacz, Dan J. MD., Allen, Hugh W. MD. and Thompson, Gale E. MD. 2000. A Comparison of Epidural Levobupivacaine 0.75% with Racemic Bupivacaine for Lower Abdominal Surgery. *Anesthesia & Analgesia* . 90(3):642-648.
- Longo, S. 1999. Postdural puncture: implications and complications. *Curr Opin Anaesth*, 12: 271-5.
- Ludueno, FP., Bogado, EF. and Tullar, BF. 1972. Optical isomers of Mepivacaine and Bupivacaine. *Arch Int Pharmacodyn Ther.*, 200: 359-69.
- Marx, GF. 1984. Cardiotoxicity of local anesthetics - the plot thickens. *Anesthesiology*, 60: 3-5.
- Michael, J. 2009. Cousins. Neural blockade in clinical anesthesia and pain medicine. 4th ed. Philadelphia: Lippincott Williams and Wilkins;
- Ouellette, SM. and Ouelette, R. 1995. Regional anesthesia: is it safer? *CRNA.*, 6: 70-8.
- Reiz S, Nath S. Cardiotoxicity of local anaesthetic agents. *Br J Anaesth* 1986; 58: 736-46.
- Senard, M., Kaba, A., Jacquemin, MJ., Maquoi, LM., Geortay, MP., Honoré, PD., *et al.*, 2004. Epidural Levobupivacaine 0.1% or Ropivacaine 0.1% combined with morphine provides comparable analgesia after abdominal surgery. *Anesth Analg.*, 98:389-94.
- Van, F., Rolan, PE., Brennan, N. and Gennery, B. 1998. Differential effects of levo- and racemic Bupivacaine on the EEG in volunteers. *Regional Anesth Pain Med Suppl.*, 23: 48.
