

A Clinical Comparison Of Safety And Efficacy Of Levobupivacaine And Bupivacaine In Supraclavicular Brachial Plexus Block: A Prospective, Randomized, Double Blind, Clinical Trial

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ABSTRACT

AIMS AND OBJECTIVES: Bupivacaine in supraclavicular brachial plexus block is well known & very potent local anaesthetic but it is highly cardiotoxic and neurotoxic. It's recently introduced isomer levobupivacaine is proved to be less cardiotoxic and neurotoxic. The primary end points are the onset, peak and duration of sensory and motor block and duration of post operative analgesia, effect on hemodynamic variables & complications of drug. **MATERIAL AND METHODS:** After IRB approval & informed written consent from the patient, study was conducted in 120 patients of 20-50 years of either gender of ASA-I/II posted for elective upper limb orthopaedic surgeries for 2 years duration. Patients were randomized using sealed envelopes technique in 2 groups. (group B-30 ml 0.5% bupivacaine/ group L-30 ml 0.5% levobupivacaine). Primary study criteria include sensory and motor characteristics and post operative analgesia while hemodynamic variables and complications were included in secondary criteria. Inter group comparison of quantitative and qualitative data was done by Z test and Chi square test respectively. Statistical analysis was done by graph pad instat-3 software trial version. **RESULTS:** Demographic data were comparable in both the groups. The onset, peak and duration of sensory and motor blockade & duration of effective analgesia were comparable in both the groups. Vital parameters were within their clinical limit and comparable. **CONCLUSION:** It is to be concluded that bupivacaine and levobupivacaine are equally effective and safe.

Key words: Levobupivacaine, bupivacaine, supraclavicular brachial plexus block, sensory and motor block.

INTRODUCTION

Regional anaesthesia is a multifunctional, economical, reliable technique that provides ideal operative conditions without any sedation or systemic hemodynamic effects. It offers various advantages over general anaesthesia particularly in emergency situations, where the patients are not adequately starved, haemodynamically compromised or too ill to tolerate general anaesthesia. In addition, it provides excellent postoperative analgesia without any systemic side effects¹. Peripheral nerve block is cost effective anaesthetic technique used to

provide anaesthesia and analgesia without any airway manipulation and hemodynamic consequences. Local anaesthetic drugs have traditionally been used to provide anaesthesia and analgesia with regional block technique. Bupivacaine and lignocaine are well established local anaesthetics for brachial plexus block. Bupivacaine when used in high concentration or accidentally administered intravenously causes severe central nervous system and cardiovascular system toxicity. It has been linked to the R (+) isomer of bupivacaine². In 1980s, concern regarding this compound's adverse effect motivated researchers to investigate the mechanism underlying local anaesthetic-induced toxicity and to develop new, safer compound. As a result of these efforts, S (-) bupivacaine has been recognized as a lesser toxic compound as compared to R (+) enantiomer. It is less cardiovascular and central nervous system toxicity, makes levobupivacaine³ a less toxic substitute for

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bupivacaine. Levobupivacaine (S- 1- butyl-2- piperidylformo- 2', 6'- xylidide hydrochloride), the pure S(-) enantiomer of racemic bupivacaine, is a new long acting local anaesthetic that has been recently introduced in the clinical routine⁴⁻⁷. Interest in levobupivacaine raised after several cases of severe cardio-toxicity (including death) were reported where it was shown that the D isomer of bupivacaine had a higher potential for toxicity. This prompted us to evaluate the clinical profile of 0.5% isobaric levobupivacaine in supraclavicular brachial plexus block for upper limb orthopaedic surgeries and its clinical comparison with 0.5% isobaric racemic bupivacaine.

MATERIAL AND METHODS

After taking institutional review board approval (IRB no.435/2014) and written informed consent from the patients, this prospective, randomized, parallel group, double blind clinical trial was carried out in Department of Anaesthesiology, Government Medical College, Bhavnagar, Gujarat. Study was conducted between (years). After thorough preanaesthetic evaluation patients were included or excluded according to following criteria:

Table 1

INCLUSION CRITERIA	EXCLUSION CRITERIA
Age: 18 to 50 years. Gender: Either gender. Patients scheduled for elective upper limb orthopaedic surgery ASA physical status I and II.	Patients refusing consent. Contraindications to regional anaesthesia. Previous nerve injury. History of drug allergy. Patients on anticoagulants and with bleeding disorders. History of drug dependence/abuse. Any major systemic illness like diabetes mellitus, hypertension, IHD etc. Antenatal females and lactating mothers. Psychiatric illness. Uncooperative patients.

Patients were randomly allocated to one of the two groups of 60 patients each by distributing sealed envelopes.

Group B (n = 60) – Patients received 30 ml of 0.5% bupivacaine

Group L (n = 60) – Patient received 30 ml of 0.5% levobupivacaine

In preanaesthetic preparation room, standard monitoring for electrocardiogram (ECG), non-invasive blood pressure

(NIBP), pulse-oxymetry were established and baseline vital parameters including heart rate (HR), mean arterial blood pressure (MAP), peripheral arterial oxygen saturation (SpO2) were recorded. A 20G i.v. cannula was secured and Dextrose Normal Saline infusion was started. Injection Ondansetron 0.08 mg/kg was given as premedication 15 minutes before induction. The doctor performing the randomization prepared the drug in 3 separate 10 ml syringes labelled with patient's enrolment number as per the group assigned and handover to attending anaesthesiologist who is unaware about the content of the solution. Attending anaesthesiologist is responsible for performing the nerve block and effect assessment. In the operation theatre, supraclavicular brachial plexus block was performed with the aid of Nerve locator (B. BRAUN Company). After giving the position for supraclavicular brachial plexus block, a 22G 1.5inch insulated needle was introduced just lateral to subclavian artery pulsation 1 cm above clavicle and advanced medially, downward and backward. The current was initially set to deliver 1 mA at 2Hz stimulation frequency. The needle was advanced till we got contraction of forearm muscle up to 0.5 mA. Once the elicited motor response of forearm muscle was obtained, the injection of study drug was given after gentle aspiration. End of the injection was taken as time '0'. Immediately after the block, sensory and motor characteristics of blockade, hemodynamic variables, SpO2 were assessed at 1,3,5,10,15,30 minutes and then at hourly interval till offset of sensory and motor blockade and then at four hourly interval for 24 hours. Sensory and motor grading of block were assessed using the scale shown in table 2.

Table 2: Sensory and motor grading of block

GRADE	SENSORY	MOTOR
0	Normal sensation to pinprick	Normal movement of thumb
1	Dull response to pinprick	Decreased movement of thumb.
2	No response to pinprick	No movement of thumb

Post operatively, the time of first rescue analgesic required at visual analogue scale

(VAS) ≥ 4 and total doses of analgesic given in 24 hours was also noted. VAS score was taken after 2, 4,6,8,10,12,16,20,24 hours of giving the injection. Diclofenac sodium 75 mg i.v. was given as rescue analgesic whenever required (VAS ≥ 4). Any complication or adverse event was noted down. Bradycardia was defined as heart rate <60 /min and was treated by inj. atropine 0.6 mg i.v. Variation in mean arterial pressure 30% on either side of baseline was considered significant and was treated accordingly. The sensory and motor characteristics of the blockade were assessed as per the criteria mentioned below:

	Sensory Characteristics	Motor Characteristics	Duration Of Analgesia
Onset	Time duration from end of injection to dull response to pin prick.	time duration from end of injection to decreased thumb movement	time duration from onset of sensory block to first rescue analgesic requested by the patient at VAS ≥ 4
Peak	time duration from onset of sensory block to no response to pin prick	time duration from end of injection to complete abolition of thumb movement	
Duration	time duration from onset of sensory block to feeling of pin prick sensation	time duration from onset of motor block to reappearance of thumb movement	

Statistical Analysis : Considering the duration of analgesia as the main outcome measure of interest in this study with at least 10% efficacy shown by the treatment groups, minimum 60 patients were required per group with the permitted alpha error of 0.05 and beta error of 0.2. With permitted beta error of 0.2, the power of study stands out to be 80%. Data was summarized as mean \pm standard deviation and as percentage wherever required. Statistical analysis was done by Graph pad in Stat software version 3. Inter group comparison of the quantitative data was done using the standard error of difference between two means (t-test). Inter group comparison of qualitative data was done by chi square test. P value < 0.05 was considered as statistically significant.

RESULTS

Table 1: Patient Characteristics

Patient Characteristics	Group B (Mean \pm SD)	Group L (Mean \pm SD)	P Value
Age (Years)	31.88 \pm 5.64	32.8 \pm 7.82	0.46
Gender (M/F)	42/18	41/19	
Weight (Kg)	58.58 \pm 5.97	56.07 \pm 8.81	0.12
Height (cm)	159.92 \pm 4.47	158.95 \pm 7.74	0.46
ASA Physical Status (I/II)	50/10	51/9	
Duration of Surgery (min)	105.58 \pm 29.07	100.57 \pm 22.50	0.19

Inference: Patient characteristics in terms of age, sex, weight, height and ASA physical status were comparable among the two groups of patients. Duration of surgery was also comparable in the two groups. (P >0.05)

Figure 1: Demographic Profile Of Patients

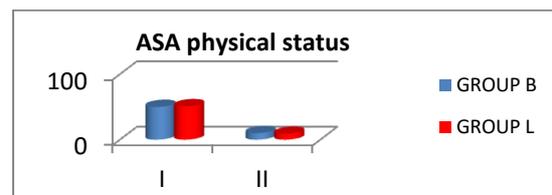
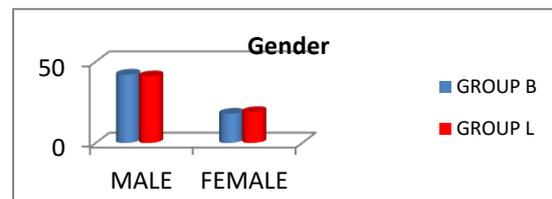
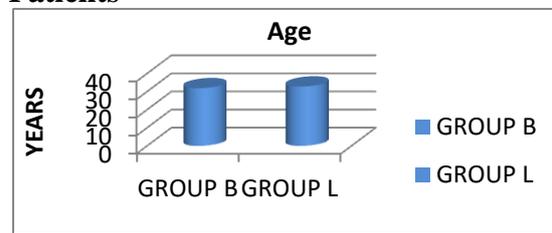
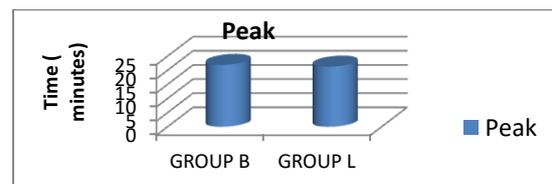
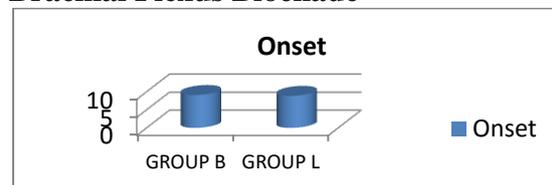
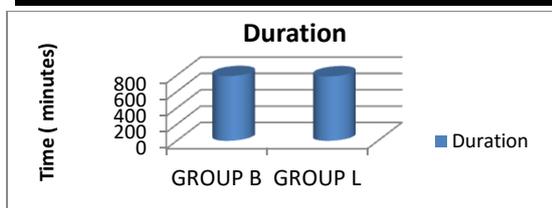


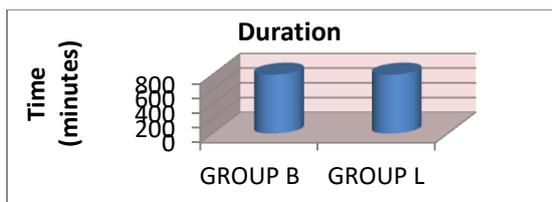
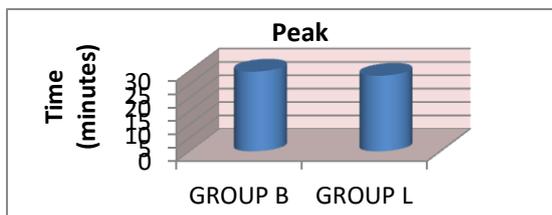
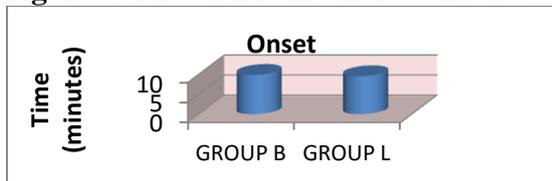
Figure 2: Sensory Characteristics Of Brachial Plexus Blockade





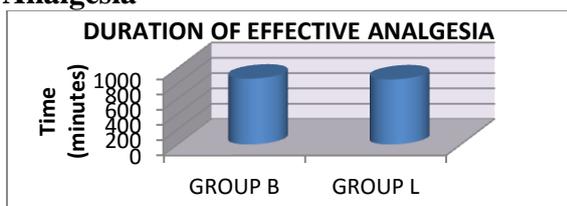
Inference: On comparison of group B with group L, the difference in mean time for onset, peak and duration of sensory blockade was not significant. (P>0.05)

Figure 3: Motor Block Characteristics



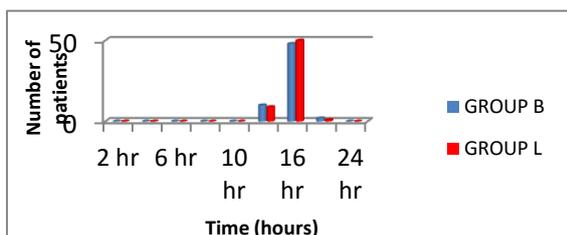
Inference: On comparison of group B with group L, the onset, peak and duration of motor blockade in both the groups were comparable. (P>0.05)

Figure 4: Duration Of Effective Analgesia



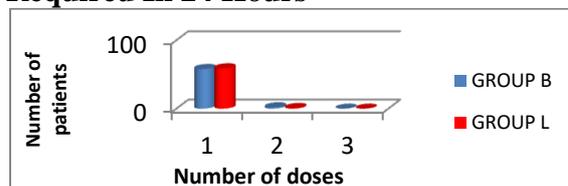
Inference: On comparison of group B with group L, the duration of effective analgesia was comparable in both the groups (P>0.05)

Figure 5: Time Of First Rescue Analgesics Required



Inference: On comparison of both the groups, there were no significant difference in the time of first rescue analgesic requirement after 12th, 16th and 20th hour in group B and group L.

Figure 6: Doses Of Rescue Analgesics Required In 24 Hours



Inference: The analgesic requirements of both the groups were similar. On comparison of group B with L, 58 patients required one injection of rescue analgesia, 2 patients required two injections and none required three injections while 59 patients in group L required only 1 injection and 1 patient required two injections in 24 hours. Hence there was no significant difference in total dose of rescue analgesics required in group L as compared to group B.

Figure 7: Changes In Heart Rate

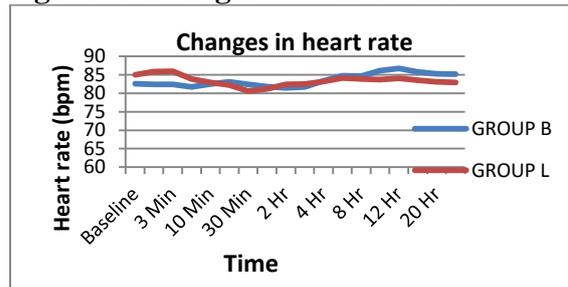


Figure 8: Changes In Mean Arterial Blood Pressure

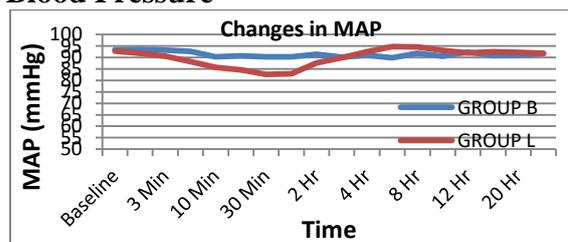


Figure 9: Changes In SpO2

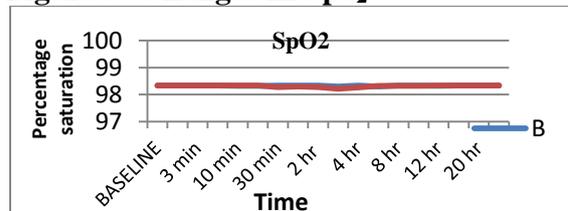


Table 2 Complications (Intra And Post Operative)

COMPLICATION	GROUP B	%	GROUP L	%
Nausea/vomiting	0	0	0	0
Hypotension	0	0	0	0
Bradycardia	0	0	0	0
Shivering	0	0	0	0

Pneumothorax	0	0	0	0
Surgical emphysema	0	0	0	0
Respiratory depression	0	0	0	0

Inference: No complication was observed in both the groups throughout the study period.

DISCUSSION

Regional anaesthesia has more to offer in orthopaedic surgery than in any other surgical specialty, either alone or as part of an anaesthetic sequence. With regional anaesthesia there are better preservation of mental functions, intact pharyngeal, laryngeal reflexes, thus reducing the risk of aspiration, also ensures a decreased stress response and airway manipulation^{1,2} in patients. It also provides excellent post-operative analgesia without undue sedation thus facilitating early mobilization and discharge. Supraclavicular brachial plexus block is a popular technique for upper limb surgery. This block is performed at the level of the brachial plexus trunk where almost the entire sensory, motor, and sympathetic innervations of the upper extremity are carried in just three nerve structures (trunks) confined to a very small surface area. As a result, brachial plexus blockade by supraclavicular route provides rapid onset, predictable and dense anaesthesia along with its high success rate and less complications as compared to interscalene block. But brachial plexus is a potential territory for absorption of local anaesthetics. Currently bupivacaine is the most commonly used local anaesthetic worldwide due to its longer duration of action, but the problem with bupivacaine is its high cardiovascular toxicity. Levobupivacaine is S (-) enantiomer of racemic bupivacaine. It has various advantages⁸⁻¹¹ over bupivacaine. The affinity of S (-) isomer to the cardiac sodium channel in the inactive state is lower than that of R (-) isomer and its faster protein binding rate suggest a lower degree of cardiovascular toxicity and also possess higher convulsive threshold. This shows that levobupivacaine can be considered as a good alternative to bupivacaine. Mean time of onset (9.1 ± 1.19 min vs. 8.87 ± 1.11 min), peak (21.9 ± 1.49 min vs. $21.28 \pm$

1.84 min) and duration (791 ± 28.45 min vs. 787.75 ± 27.56 min) of sensory blockade was as mentioned earlier in group B and group L respectively. ($P>0.05$) Cox et al.¹² evaluated the dose of 0.4mg/kg of 0.25% and 0.5% levobupivacaine and 0.5% racemic bupivacaine in patients undergoing elective hand surgeries and they did not observed statistically significant differences in the latency of sensorial blockade between the groups. So, the results of our study are comparable to this study. Baskan S. et al.¹³ compared 0.25% levobupivacaine and 0.25% bupivacaine for posterior approach interscalene brachial plexus block in sixty adult patients undergoing open or closed shoulder surgery. They concluded that 0.25% levobupivacaine and 0.25% bupivacaine have similar sensory block onset times and qualities when used in posterior approach interscalene brachial plexus block. So, the results of our study are comparable to this study. Mean time of onset (9.83 ± 1.34 min vs. 9.5 ± 1.07 min), peak (29.77 ± 2.17 min vs. 28.23 ± 2.82 min) and duration (821.5 ± 25.83 min vs. 816.83 ± 29.24 min) of motor blockade was as mentioned earlier in group B and group L respectively. ($P>0.05$) In literature, other studies found similar results as we found in present study. Cox et al.¹² evaluated the dose of 0.4mg/kg of 0.25% and 0.5% levobupivacaine and 0.5% racemic bupivacaine in patients undergoing elective hand surgeries and they did not observed stastically significant differences in the onset, peak and duration of motor blockade between the groups. The results of this study are comparable to our study. Pedro et al.¹⁴ compared the anaesthetic efficacy of levobupivacaine in brachial plexus block with racemic bupivacaine using the perivascular subclavian approach and statistical differences in latency, failure rate and degree of motor blockade. The results are similar to our study. Baskan S. et al.¹³ compared 0.25% levobupivacaine and 0.25% bupivacaine for posterior approach interscalene brachial plexus block in sixty adult patients undergoing open or closed shoulder surgery. They concluded that 0.25% levobupivacaine and 0.25% bupivacaine have similar motor block onset

times and qualities when used in posterior approach interscalene brachial plexus block. So, the results of our study are comparable to this study. The mean duration of effective analgesia was 860.67 ± 28.75 min vs 851.42 ± 32.05 min in group B and group L respectively. ($P > 0.05$). D'Ambrosio et al.¹⁵ did not find any difference regarding postoperative analgesia need with levobupivacaine and bupivacaine. Liisanantti et al.¹⁶ found that first postoperative analgesia was similar in both the levobupivacaine and bupivacaine group Our results are comparable to these studies. Fusun Eroglu et al.¹⁷ compared between levobupivacaine and bupivacaine in axillary brachial plexus block on thirty five ASA physical status I-II patients, aged 18 to 70 years scheduled for upper limb surgery. They evaluated sensorial block onset time, duration of sensorial block and first analgesic requirement time in each of the groups. They concluded that levobupivacaine may be preferred for its rapid sensorial and motor onset time. So, our results are not comparable with this study. This contrary result may be due to low concentration (0.375%) of the drug used with more volume (40ml) and adjuvant (10 mg morphine). Postoperative VAS and rescue analgesia requirement were similar in both the groups. Post operative VAS values in the study of D'Ambrosio et al.¹⁵ were similar. Cenik Ilham et al.¹⁸ also concluded that the difference in postoperative VAS score was not significant in clinical practice since the scores were below 3. So, the results of our study are comparable with both the studies. Heart rate and mean arterial pressure were stable and comparable to baseline. Mean arterial pressure of both the groups showed statistically significant different results sometimes, but it seems to be by-chance. Despite some studies providing evidence that levobupivacaine is less cardiotoxic and neurotoxic than bupivacaine¹⁹⁻²³, we found no differences between both agents for hemodynamic and incidence of side effects. We used nerve locator to localize brachial plexus. This is a better technique than blind approach as the local anaesthetic and the study drug is deposited in close proximity

of neurons. The deposition of drug close to the neuron bundles is the prime requirement while studying the effect of any drug. Still better technique for localization of brachial plexus is its identification by ultrasonography. Ultrasound guided blocks bypass the electrical stimulation and at the same time provide visual identification of nerve bundles. We did not use ultrasonography because of the non-availability of equipment in the operation theatre. To conclude, both levobupivacaine and bupivacaine are equally efficacious with regards of sensory and motor blockade without potential harm.

REFERENCES

1. Damien B, Murphy, Collin JL McCartney, Vincent W.S. Chan. Novel analgesic adjuncts for Brachial plexus block: A Systematic Review. *Anaesthesia Analgesia* 2000;90:1122-8
2. Zapata-Sudo, Gisele MD, PhD; Trachez, Margerete M. MD, PhD; Sudo, Roberto T. MD, PhD, and; Nelson, Thomas E. PhD is Comparative Cardiotoxicity of S (-) and R(+) Bupivacaine Related to Enantiomer-Selective Inhibition of L-Type Ca²⁺ Channels. February 2001-volume 92-Issue 2- pp 496 – 501.
3. Aberg G. Toxicological local anaesthetic effect of optically isomers of two local anaesthetic compounds. *Act Pharmacol Toxicol (Copenh)* 1972;31:237- 86
4. Burke D, Bannister J. Left handed local anaesthetics. *Curr anaesth Crit Care*. 1999; 10:262-9.
5. Mcleod GA, Burke D, Levobupivacaine: *Anaesthesia* 2002; 57:200.
6. Foster RH, Markham A. Levobupivacaine A review its pharmacology and use as a local anaesthetic. *Drugs* 200; 59:551-79
7. Ivani G, Borghi B. Van Oven H. Levobupivacaine *Menerva Anaesthesiol*. 2001 ; 67 suppl.1:20-3
8. Y.F.Huang, M.E.Pryor, L.E.Mather, and B.T.Veering, "Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep," *Anaesthesia and*

- Analgesia, vol. 86, no. 4, pp.797-804,1998.
9. Luduena FP, Bogado EF, Tullar BF. Optical isomers of mepivacaine and bupivacaine. *Arch Int Pharmacodyn Ther* 1972; 200:359-69.
 10. C.Valenzuela, D.J.Snyders, P.B.Bennett, J.Tamargo and L.M.Hondeghem, "Stereoselective block of cardiac sodium channels by bupivacaine in guineapig ventricular myocytes," *Circulation*, vol. 92, no.10, pp. 3014-3024,1995.
 11. S.G. Morrison, J.J.Dominguez, P.Frascarolo, and S.Reiz, "A comparison of the electrocardiographic cardiotoxic effects of racemic bupivacaine, levobupivacaine, and ropivacaine in anaesthetized swine," *Anaesthesia and Analgesia*, vol. 90, no. 6, pp. 1308-1314, 2000.
 12. Baskan S, Taspinar V, Ozdogan L, Gulsoy KY, Erk G, Dikmen B, Gogus N. "Comparison of 0.25% levobupivacaine and 0.25% bupivacaine for posterior approach interscalene brachial plexus block" *J Anaesth*. 2010 Feb; 24(1):38- 42.
 13. Pedro JR, Mathias LA, Gozzani JL, Pedro FS, Rittes JS. "supraclavicular brachial plexus block: a comparative clinical study between bupivacaine and levobupivacaine". *Rev Bras Anaesthesiol* 2009 Nov-Dec; 59 (6): 665-73.
 14. D'Ambrosio A, De Negri P, Damato A, Cavalluzzo A, Borghi B. S(-) bupivacaine (levobupivacaine)in peripheral blocks: preliminary results. *Minerva Anesthesiol* 2001; 67(9 Suppl 1):37-43.
 15. Liissanantti O, Luukkonen J, Rosenberg PH. High dose bupivacaine, levobupivacaine and ropivacaine in axillary brachial plexus block. *Acta Anaesthesiol Scand* 2004; 48(5):601-606.
 16. Füsün Eroğlu, Berit Gökçe Ceylan, Sinem Sarı Ak, Mehmet Topal, Tolga Atay, Lütfi Yavuz. Comparative study of two agents in axillary brachial plexus block: Bupivacaine vs. Levobupivacaine. *Smyrna Tıp Dergisi* – 27 –33
 17. Cenk İlham, Elif Bombasi, Serhan Yurtlu, Serhan Colakoglu. Efficiency of levobupivacaine and bupivacaine for supraclavicular block: a randomized double blind comparative study. *Rev Bras Anesthesiol*. 2014;64(3):177-182
 18. Luduena FP, Bogado EF, Tullar BF. Optical isomers of mepivacaine and bupivacaine. *Arch Int Pharmacodyn Ther* 1972; 200:359-69.
 19. 20.Bardsley, R. Gristwood, H. Baker, N. Watson, and W. Nimmo, "A comparison of the cardiovascular effects of levobupivacaine and racbupivacaine following intravenous administration to healthy volunteers," *The British Journal of Clinical Pharmacology*, vol. 46, no. 3, pp. 245-249, 1998.
 20. C.Valenzuela, D.J.Snyders, P.B.Bennett, J.Tamargo and L.M.Hondeghem, "Stereoselective block of cardiac sodium channels by bupivacaine in guineapig ventricular myocytes," *Circulation*, vol. 92, no.10, pp. 3014-3024,1995.
 21. R.W.Gristwood, "Cardiac and CNS toxicity of levobupivacaine strength of evidence for advantage over bupivacaine: strength of evidence for advantage over bupivacaine," *Drug Safety*, vol. 25, no. 3, pp. 153-163, 2002.
 22. S.G. Morrison, J.J.Dominguez, P.Frascarolo, and S.Reiz, "A comparison of the electrocardiographic cardiotoxic effects of racemic bupivacaine, levobupivacaine, and ropivacaine