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A prospective randomized clinical study to compare the efficacy of 0.25% bupivacaine with clonidine and 0.25% levobupivacaine with clonidine in supraclavicular brachial plexus block for upper limb surgeries

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ABSTRACT

Introduction: Bupivacaine is an amide local anesthetic, available as a racemic mixture of Dextro and Levorotatory Isomers. Due to its rapid onset and longer duration of anesthesia, It is routinely preferred in various regional anesthetic techniques. However, it is associated with serious cardiovascular and neurological toxicity. Its pure S- enantiomer, Levobupivacaine having similar pharmacological profile is known to have lesser cardiovascular and CNS toxicity. Combining adjuvants like clonidine, a centrally acting partial alpha-2-adrenergic agonist to improve quality of anesthesia is common practice. Hence, the aim of our study is to compare efficacy and safety of 0.25% Levobupivacaine and 0.25% Bupivacaine when combined with clonidine in supraclavicular brachial plexus block for upper limb surgeries.

Materials and Methods: Eighty patients aged between 18 to 60 years with ASA physical status I-II, scheduled for elective upper limb surgeries under were randomized into two groups. Peripheral nerve stimulator guided Supraclavicular brachial plexus block was administered. Group BC received 30ml of 0.25% Bupivacaine plus 1µg/kg Clonidine and Group LC 30ml of 0.25% Levobupivacaine plus 1µg/kg Clonidine. The time of onset of sensory and motor block, duration of sensory and motor block, perioperative hemodynamic parameters, postoperative pain for 24hours and adverse effects were studied.

Results: Group LC had faster onset of sensory block (p= 0.014) as well as faster onset of motor block (p= 0.012) compared to group BC. However, durations of sensory block and motor block were statistically not significant in both the groups (p>0.05). Perioperative hemodynamic parameters and assessment of pain during 24 hours of post operative period were comparable and statistically not significant.

Conclusion: 1mcg/kg of clonidine used as an adjuvant to 30ml of 0.25% Levobupivacaine produces faster onset of sensory and motor block compared to 0.25% Bupivacaine in supraclavicular brachial plexus block. However, similar anesthetic efficacy in terms of duration of sensory and motor block, hemodynamics and postoperative analgesia were observed.

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1. Introduction

Clonidine, a selective Alpha 2 adrenergic agonist with some Alpha 1 agonist property has been commonly used as an adjuvant to local anaesthetics in various

regional techniques to extend the efficacy, postoperative analgesia, onset and duration of block. Various studies using clonidine as adjuvant have reported a significant improvement in anaesthetic efficacy on Bupivacaine^{1,2} as well as Levobupivacaine,^{3,4} although the efficacy and safety of both combinations have been proved individually, a parallel comparison between the two combinations do not

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arrive at a consensus.⁵

Considering the pharmacological profile of Bupivacaine, its clinical efficacy, long duration of action and favorable ratio of sensory to motor block, it is most frequently used among local anaesthetics for brachial plexus block. However, its major disadvantage is cardiotoxicity, primarily triggered by its dextrogyrous enantiomer.⁶

Levobupivacaine, a pure S-enantiomer of Bupivacaine has recently been introduced with a potentially reduced toxic profile compared to Bupivacaine⁷ Various pharmacokinetic, animal and clinical studies not only confirm the cardiac toxicity of racemic bupivacaine^{8–11} but experimental studies with Levobupivacaine also indicate lower cardiovascular depressant effect and central nervous toxicity.^{12,13}

Clinical trials comparing the anaesthetic efficacy of Levobupivacaine with Bupivacaine have shown mixed results, few studies suggest similar efficacy in peripheral¹⁴ and neuraxial^{15,16} nerve blocks and few suggest Levobupivacaine to be equipotent to Bupivacaine.¹⁷ Others observed variations in block characteristics where, the duration of motor blockade by levobupivacaine was shorter than that of racemic bupivacaine.^{18–21}

Supraclavicular brachial plexus block is limited by technical challenges, the proximity of brachial plexus to Subclavian artery and other large vessels suggest the potential for inadvertent intravascular injection or absorption. Owing to Bupivacaine's wide spread use, reports of severe irreversible cardiac and neurological toxic effects, including deaths from accidental intravascular injection,²² there is an immediate need to explore safer, efficient alternatives. Therefore, the purpose of this clinical study is to define and compare anesthetic efficacy and safety of 0.25% Levobupivacaine and 0.25% Bupivacaine when combined with 1mcg/kg clonidine in supraclavicular brachial plexus block for upper limb surgeries.

2. Materials and Methods

After the approval by the Institutional Ethical Committee 80 patients aged between 18 to 60 years with ASA physical status I-II, scheduled for elective, upper limb surgeries under supraclavicular brachial plexus block were enrolled in this prospective, randomized, double blinded, comparative study, conducted between Jan 2014 to Mar 2017 in a 700 bedded tertiary care hospital. Patients aged 18 to 60 years of either sex belonging to ASA physical status I –II were included in the study, patients who refused consent for the study, patients with allergy to study drugs, patients with preexisting neurological deficits involving the brachial plexus, patients with bleeding disorders, patients on anticoagulant therapy and patients on adrenoceptor agonist or antagonist therapy were excluded from the study.

Patients enrolled in the study were randomly allocated to 2 groups of 40 each by computer generated random draw

method.

Study group BC- received 30ml of 0.25% Bupivacaine plus 1µg/kg Clonidine.

Study group LC- received 30ml of 0.25% Levobupivacaine plus 1µg/kg Clonidine.

All patients underwent pre anaesthetic evaluation and informed consent was obtained. Patients were kept nil orally overnight and premedicated with Tab. Ranitidine 150mg orally on the night before surgery. The study drugs were prepared by another anaesthesiologist not involved in the study and the Investigator anaesthesiologist performing the block was blinded to the study groups.

Before being shifted to operation room, an IV line with 18G IV cannula in the dorsum of hand of the patient was secured and the patients were started on ringer lactate solution half an hour before surgery.

In the operation room, patient was monitored using non invasive blood pressure (NIBP), peripheral oxygen saturation (SpO₂) and electrocardiography (ECG). The baseline blood pressure, mean arterial pressure, SpO₂ and heart rate were noted. Heart rate (HR), mean arterial blood pressure (MAP) and oxygen saturation (SpO₂) were monitored and recorded after the block every 5 minutes for 30 minutes followed by every 15 minutes for one hour and every 30 minutes until the end of surgery, Postoperatively, hemodynamic parameters HR, MAP, Systolic blood pressure (SBP), Diastolic blood pressure (DBP) were assessed every 15 minutes for 1 hour and every hourly for 8 hours and at 12th hour and 24th hour.

Peripheral nerve stimulator guided Supraclavicular brachial plexus block was performed in both the groups using a 22 Gauge, 2 inch, Insulated needle (Braun Stimuplex[®]) connected to a peripheral nerve stimulator (Inmed Technologies[®]). The location end point was a distal motor response with an output lower than 0.5 mA in the median nerve region and the study drugs were injected. During injection, negative aspiration was performed every 3ml to avoid inadvertent intravascular injection.

Sensory block was assessed by the pin prick method. Assessment of sensory block was done at each minute after completion of drug injection in the dermatomal areas corresponding to median nerve, radial nerve, ulnar nerve and musculocutaneous nerve till complete sensory blockade. Sensory onset was considered when there was a dull sensation to pin prick along the distribution of any of the above-mentioned nerves. Complete sensory block was considered when there was complete loss of sensation to pin prick

Sensory block was graded as-

Grade 0: Sharp pain felt

Grade 1: Analgesia, dull sensation felt

Grade 3: Anaesthesia, no sensation felt.

Assessment of motor block was carried out by the same observer every minute till complete motor blockade after



CONSORT 2010 Flow Diagram

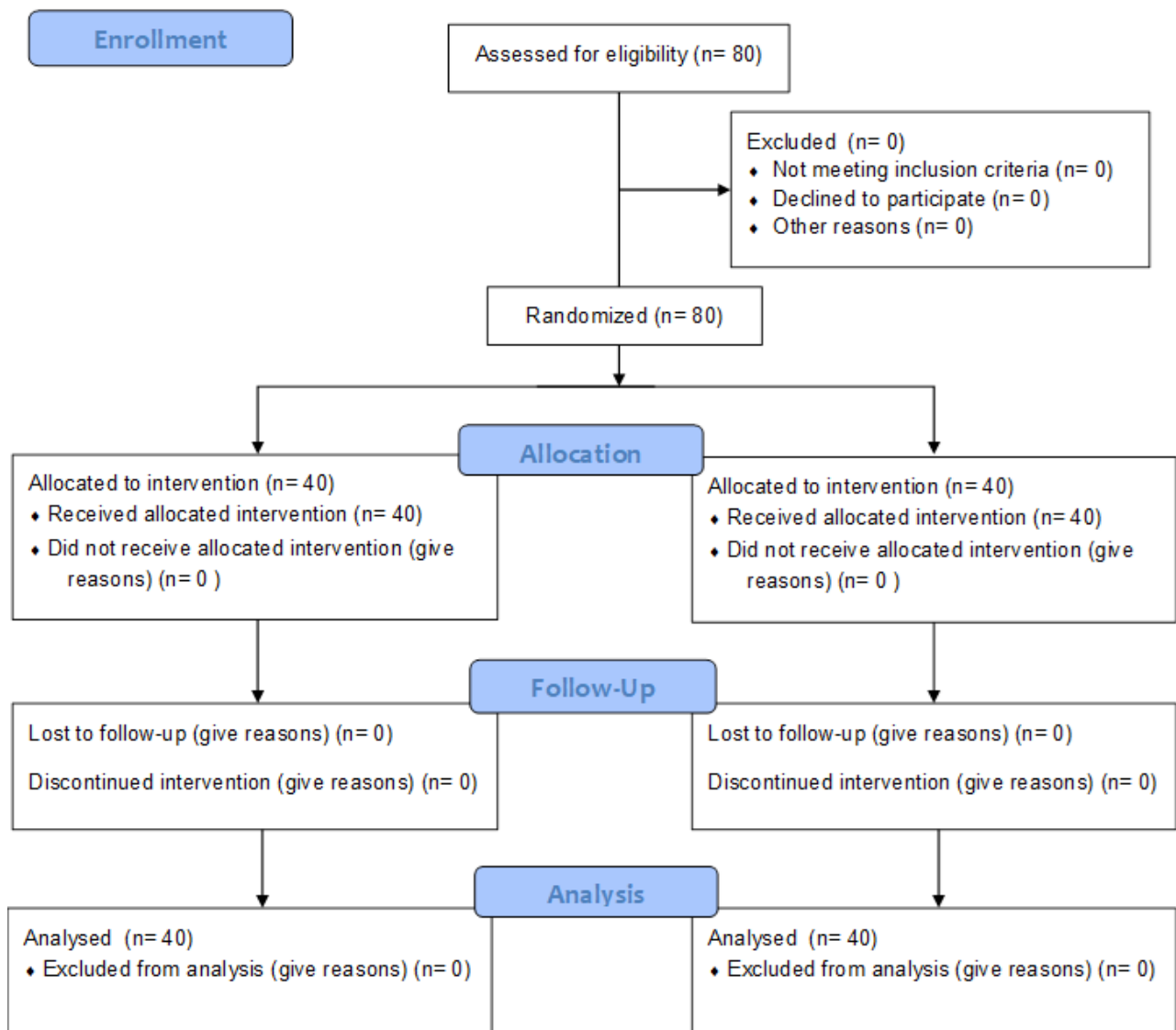


Diagram 1: Consort diagram of the study

drug injection. Onset of motor blockade was considered when there was complete motor blockade.(Grade 2). Motor block will be determined according to a modified Bromage scale for upper extremities on a 3-point scale.²³

Grade 0: Normal motor function with full flexion and extension of elbow, wrist and fingers.

Grade 1: Decreased motor strength with ability to move the fingers only

Grade 2: Complete motor block with inability to move the finger

Inadequate sensory and motor blockade beyond 30mins following the infiltration was considered as unsuccessful block.

Postoperatively, patients were evaluated every 30 mins until the sensory and motor blocks returned to normal. Postoperatively quality of analgesia was evaluated with visual analogue scale from 0 to 10 where 0 defines no pain and 10 defines worst pain ever suffered, every 30min until VAS>5.

Visual analog scale*

Pain Intensity Word Scale

0 No pain

1-2 Least pain

3-4 Mild pain

5-6 Moderate pain

7-8 Severe pain

9-10 Excruciating pain

The rescue analgesia was given at VAS>5 in the form of inj. Diclofenac sodium 75mg iv.

2.1. Statistical analysis

The sample size was calculated based on a similar pilot study conducted in our tertiary care hospital on 12 patients where an effect size of 0.626 was obtained, considering $\alpha=0.05$ and $\beta=0.20$ sample size was determined with a power of study at 80% & confidence interval at 95% to detect a projected difference of 20% in duration of postoperative analgesia between the groups, a sample size of 39.35 in each group was required. Thus, we planned to conduct study on 80 patients, randomized in to two groups of 40 each. Statistical software SPSS 15.0, MedCalc 9.0.1 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs and tables. Descriptive, inferential statistical analysis has been carried out in the study. Results on continuous measurements are presented as Mean \pm SD and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two groups. P value of less than

0.05 was suggestive of significance.

3. Results

On comparing the demographic data, no statistical significance ($p>0.05$) was observed in demographic data which included physical characteristics weight, height, gender distribution, ASA physical status distribution and duration of surgery as describes in Table 1.

The mean time of onset of sensory block in Group BC was 16.29 ± 0.85 min and 15.73 ± 1.14 min in group LC, which was statistically significant ($p=0.014$). And the mean time of onset of motor block in group LC was 17.93 ± 0.71 min, which was shorter than group BC 18.33 ± 0.69 min and statistically significant with $p=0.012$. as shown in .

The duration of sensory block which was defined in our study as the time from sensory onset of the block to the request for rescue analgesic or VAS >5. It was similar in both group BC and group LC with $p= 0.725$. (Table 2). The mean duration of motor block in Group trBC and Group LC were 473.23 ± 11.42 minutes and 478.78 ± 19.44 minutes respectively and p value suggested no significant difference ($p=0.124$) as shown in Table 2.

Perioperative Hemodynamic parameters Heart rate (HR) Systolic blood pressure (SBP), Diastolic blood pressure (DBP), mean arterial pressure (MAP) and peripheral oxygen saturation (SpO₂) in both the groups are shown in Figures 1 and 2 they were comparable and statistically insignificant ($P>0.05$).

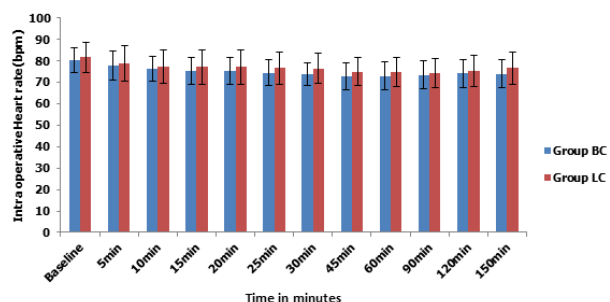


Fig. 1: Intraoperative heart rates at various time intervals between the study groups

Assessment of pain done during 24 hours of post-operative period at an interval of 15 minutes for the first one hour and hourly thereafter for eight hours and at time intervals of 12 hours and 24 hours using the visual analog scale were statistically insignificant however, pain scores were 0 for the first four hours in both the groups, the highest score was achieved at 8 hours in both the groups which was statistically not significant (Figure 3) Hypotension was defined in our study as a fall in mean arterial pressure below 30% of baseline was seen in three patients in Group BC and four patients in Group LC which is statistically insignificant

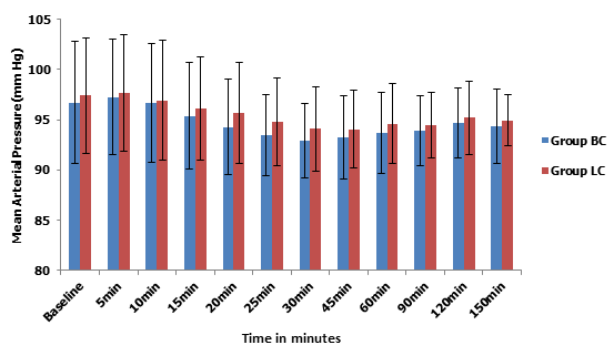
Table 1: Comparison of demography, ASA status, duration of surgery and physical characteristics between the two groups

Baseline characteristics	Group BC	Group LC	P value
Age (years)	37.18±12.68	41.32±11.89	0.135
Height (cm)	168.20±7.03	167.70±6.10	0.735
Weight (kg)	67.45±6.24	65.60±5.67	0.169
Gender: Male:Female (percentage)	84.5% : 15.5%	82.5% : 17.5%	1.004
ASA I : ASA II (percentage)	85% : 15%	77.5% : 22.5%	0.390
Duration of Surgery	121.50±22.48	114.75±22.42	0.183

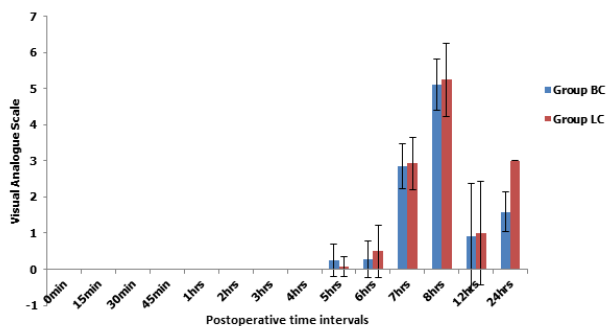
Table 2: Comparison of block characteristics in both groups

Block Characteristics	Group BC	Group LC	P Value
Onset of Sensory block (min)	16.29±0.85	15.73±1.14	0.014*
Onset of Motor block (min)	18.33±0.69	17.93±0.71	0.012*
Duration of Motor block (min)	473.23±11.42	478.78±19.44	0.124
Duration of Sensory block (min)	572.68±12.97	573.85±16.55	0.725

*indicates significant statistical difference at P<0.05

**Fig. 2:** Intra operative mean arterial pressure (MAP) between the study groups

(p=1.000) shown in Figure 3. Supraclavicular block given with peripheral nerve stimulator guidance was successful in all patients and no other complications such as Bradycardia, Hypoxaemia or major adverse events were observed in our study.

**Fig. 3:** Comparison of visual analogue scale (VAS) pain scores between the two groups

4. Discussion

Supraclavicular brachial plexus block is an effective, time tested regional anesthetic technique for surgeries of upper extremities. It is not only an excellent alternative, but also offers several perioperative advantages over general anesthesia such as early ambulation, reduced stress response, provides optimal postoperative analgesia and reduces the incidence of postoperative nausea and vomiting, leading to satisfactory patient acceptance and improved clinical outcomes.²⁴

Since, supraclavicular brachial plexus block requires larger volumes of local anesthetic, it is associated with the risk of local anesthetic systemic toxicity,²⁵ efforts were made in our study to lower the concentration of our study drugs to 0.25% bupivacaine and 0.25% levobupivacaine and compare anesthetic efficacy and safety when combined with 1 mcg/kg clonidine.

The central actions of clonidine are mediated through α_2 adrenoceptors, situated at locus coeruleus and dorsal horn of spinal cord. There have been four proposed mechanisms for the action of clonidine in peripheral nerve blocks which are: centrally mediated analgesia, α_2 β adrenoceptor-mediated vasoconstrictive effects, attenuation of inflammatory response and direct action on peripheral nerve.²⁶

Study conducted by Dalle et al,²⁷ proposed that clonidine, by enhancing activity-dependent hyperpolarisation generated by the Na/K pump during repetitive stimulation, increases the threshold for initiating the action potential causing slowing or blockage of conduction.

Kosugi et al.²⁸ examined the effects of various adrenoceptor agonists including dexmedetomidine, tetracaine, oxymetazoline and clonidine, and also an α_2 adrenoceptor antagonist (atipamezole) concluded

Table 3: Rate of complications both study groups with p=1.000 (Chi Square Test)

Complications	Group BC		Group LC	
	No	%	No	%
No	37	92.5	36	90.0
Yes	3	7.5	4	10.0
Total	40	100.0	40	100.0

that compound action potentials were inhibited by α_2 adrenoceptor agents so that they are able to block nerve conduction.

Various clinical studies clearly show the benefit of adding clonidine as an adjuvant to local anesthetics meta-analysis by Popping et al.²⁹ who reviewed 20 randomized placebo-controlled trials published between 1992-2006, studying the efficacy of adding clonidine to peripheral single-injection nerve or plexus blocks in 1,054 patients, where 573 received clonidine studies involved plexus (14 brachial, 1 cervical) and nerve blocks (2 sciatic/femoral, 1 mid humeral, 1 ilioinguinal/iliohypogastric, 1 ankle) and found that clonidine extended average block duration by approximately 2 hours, providing approximately 100 additional minutes of analgesia with long-acting local anesthetics.

A 2015 systematic qualitative review conducted by Kirksey et al,³⁰ on 61 randomized clinical trials and meta-analyses published between 1990 and 2014 also conclude that clonidine prolongs the duration of analgesia after peripheral nerve blocks. They also reported increased sedation, hemodynamic and systemic side effects, such as hypotension and bradycardia with higher doses and recommended a maximum dose of 150mcg.

Also, most studies^{5,31,32} used between 0.5 to 1.5 $\mu\text{g}/\text{kg}$ of clonidine, with higher doses associated with hemodynamic and systemic adverse effects such as sedation, bradycardia and hypotension. Hence, we limited the dose of clonidine to 1 mcg/kg, well within the range of clonidine's clinical effectiveness.

Anesthetic efficacy of adding clonidine to a concentration of 0.25% bupivacaine is well established. Suchismitha et al³³ who studied the efficacy of 150mcg clonidine added to 40 ml of 0.25% bupivacaine in 60 patients reporting a faster onset of action, longer duration of sensory block devoid of systemic adverse effects. Similarly, Kulkarni A et al³⁴ who studied effects of adding 75 mcg of clonidine to 25 ml of 0.25% bupivacaine for supraclavicular brachial plexus blocks in 60 patients, also hypothesized similar prolongations in duration of analgesia and motor blocks. Randomized control trail by Paliwal et al³⁵ on 60 patients, comparing the effects of buprenorphine and clonidine added to 40 ml of 0.25% bupivacaine not only report similar block characteristics but also recommend clonidine over buprenorphine due to associated adverse effects of nausea, vomiting and sedation. In our study the Group BC that received 0.25% Bupivacaine with 1mcg/kg

clonidine had complete sensory onset and duration at 16.29 ± 0.85 min and 572.68 ± 12.97 with motor onset and duration at 18.33 ± 0.69 min and 473.23 ± 11.42 min.

G Karthik et al³⁶ and F Wilson et al⁴ compared the effects of adding of clonidine to 0.5% levobupivacaine reported a prolonged sensory and motor block durations.

Similarly, Cox et al.³⁷ compared 0.5% with 0.25% levobupivacaine for supraclavicular block and also reported that a dose of 0.25% levobupivacaine was efficacious in producing surgical anesthesia, but had a slower onset with no significant differences in duration of sensory and motor blocks. In another clinical trial by C. L. Burlacu et al³ who used clonidine as an adjuvant with a low dose 0.25% levobupivacaine also found reported similar findings.

Assessment of block characteristics in our study revealed Group LC to have statistically significant shorter onset of complete sensory block ($p=0.014$) and motor block ($p=0.012$) compared to Group BC these findings were comparable to Hutschala et al³⁸ and Swamy et al³⁹ who reported shorter analgesic durations of 270minutes and 289 ± 62 minutes with 0.25% levobupivacaine and clonidine. On the contrary, J Eldejam and colleagues² reported a longer duration of analgesia lasting 994.2 minutes. Randomized control trails similar to the present study by Cox et al.³⁷ and Burlacu et al.,³ as well as studies that compared efficacy of clonidine with higher concentrations of levobupivacaine by Duma et al⁵ and Lisananti et al⁴⁰ found no meaningful difference with respect to block characteristics. Hemodynamic parameters that were monitored in our study HR, SBP, DBP, MAP and SpO2 during the perioperative periods were comparable and statistically not significant. There were no major adverse events in either groups were noted during the course of study, however transient, episodes of hypotension (MAP less than 30% baseline as defined by our study) was observed in three patients in the BC group and four patients in the LC group during the intraoperative period, which was managed with IV injection of ephedrine in 6 mg boluses and crystalloid fluids, the complication rates of 7% and 10% observed in our study was not only statistically insignificant but it was likely to also be confounded by factors such as intraoperative blood loss or tourniquet release. Assessment of pain was done using the visual analogue scores where, it was 0 till 4 hours in both the groups and were highest at 8th hour when rescue analgesics 75 mg Diclofenac sodium IV was given, In postoperative period of 24 hrs 32% patients of Group BC required only one rescue analgesic and 67.5%

of patient required two rescue analgesic dosages. In Group LC 37.5% of patients required only one rescue analgesic and 62.5% of patient required two rescue analgesic dosages which were comparable in both groups.

5. Conclusion

From our prospective randomized clinical study we conclude, 1mcg/kg of clonidine used as an adjuvant to 30 ml 0.25% Levobupivacaine in supraclavicular brachial plexus block produces faster sensory and motor onset with similar anesthetic efficacy in terms of block duration, hemodynamics and postoperative analgesia compared to 30ml 0.25% Bupivacaine. Considering the greater toxicity potential and the cardiovascular effects of the racemic Bupivacaine, Levobupivacaine seems to be an excellent and safe alternative.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare no conflict of interest.

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