"A RANDOMISED CLINICAL TRIAL TO COMPARE THE EFFECTIVENESS BETWEEN BUPIVACAINE AND BUPIVACAINE-CLONIDINE COMBINATION IN BRACHIAL PLEXUS BLOCK BY SUPRACLAVICULAR APPROACH."

By

DR. MANJUNATH SHIVAPUJIMATH

Dissertation submitted to

BLDE UNIVERSITY, VIJAYAPUR, KARNATAKA.

In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE

IN

ANAESTHESIOLOGY

Under the guidance of

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2017

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ACKNOWLEDGEMENT

On completion of my post graduation journey and this scientific document, I would like to acknowledge the immense help received from my mentors in the department of anaesthesia.

With privilege and respect I would like to express my gratitude and indebtedness to my Guide, Professor and H.O.D **Dr. D. G. Talikoti** for his constant inspiration, extensive encouragement and loving support, which he rendered in pursuit of my post-graduate studies and in preparing this dissertation.

I am forever grateful to Professors **Dr.Vidya Patil** and **Dr.Vijayakumar T. K.** for their guidance and encouragement provided to me, to achieve new heights professionally over my course period.

I am grateful to Associate Profs. **Dr. R. R. Kusugal, Dr. Vijay Katti, Dr. Renuka, Dr.Nirmala** and **Dr.Shridevi** for their guidance, encouragement and inspiration.

I am thankful to **Dr. Shivanand L K, Dr. Basavaraj Patil**, **Dr. Prathiba, Dr. Ramesh, Dr. Santosh, Dr. Lalitha, Dr.Geetha, Dr.Mahendra, Dr.Sunil, Dr. Mala** and **Dr. Sharath** for their great help.

I am extremely thankful to Professor **Dr. S. P. Guggarigoudar**, Principal, of B.L.D.E.U'S Shri. B.M. Patil Medical College, Hospital and Research Centre, Vijayapur, for permitting me to utilize resources in completion of my work.

My thanks to one and all staff of Library, Anaesthesia Department and Hospital for their co-operation in my study.

I am thankful to colleagues **Dr. Abhishek, Dr. Santosh, Dr. Amansai, Dr. Tom George, Dr. Meghana, Dr. Vaishnu, Dr. Vikas, Dr. Vaibhav,**

Dr. Shishir, Dr. Danesh and **Dr. Yasaswani** for their advice, suggestions and co-operation in my journey.

I am thankful to the members of ethical committee BLDEU's Shri. B. M. Patil Medical College Hospital and Research Centre Vijayapur for permitting me to carry out this study.

I am thankful **Mr. Shahnawaz** for his help in statistical analysis.

I would also like to thank all my juniors for their help and co-operation.

I am deeply indebted to my parents for their blessings, which helped me to complete this dissertation.

Last but not the least; I convey my heartfelt gratitude to all my patients, without whose co-operation, this study would be incomplete.

Dr. Manjunath Shivapujimath

LIST OF ABBREVIATIONS USED

ASA -	American Society of Anaesthesiologist
BT -	Bleeding time
cm -	centimeter
CT -	Clotting Time
DBP -	Diastolic Blood Pressure
dl -	Deciliter
ECG -	Electrocardiogram
gm -	gram
HBsAg -	Hepatitis B Antigen
HIV -	Human Immunodeficiency Virus
HS -	Highly significant
Hrs -	Hours
IA -	Intra articular
IM -	Intramuscular
IV -	Intravenous
Kg -	Kilogram
LA -	Local Anaesthetic
µg -	Microgram
MAP -	Mean Arterial Pressure
Min -	Minutes
ml -	Milliliter

mm of Hg -	Millimeter of mercury
NS -	Not significant
RA -	Rescue analgesics
S.D. -	Standard Deviation
S.E. -	Standard Error
SBP -	Systolic Blood Pressure

ABSTRACT

Background and objectives : Adjuncts to local anaesthetics for brachial plexus block may enhance the quality and duration of analgesia. Clonidine, an Alpha-2 adrenergic agonist, is known to produce antinociception and enhance the effect of local anaesthetics when given epidurally, intrathecally or in various peripheral nerve blocks. The purpose of this study was to assess the effect of Clonidine added to brachial plexus block by supraclavicular approach.

Methods : A prospective, randomized, single blinded study was conducted on 100ASA I or II adult patients undergoing upper limb surgeries under supraclavicular brachial plexus block. Patients were randomly divided into two groups. Patients in Group B (n = 48) were administered 30mL of 0.375% Bupivacaine and Group BC (n= 48) were given 30mL of 0.375% Bupivacaine with Clonidine 1μg/kg. The onsettime and duration of sensory and motor blockade were recorded. Haemodynamic variables (i.e., heart rate, noninvasive blood pressure, oxygen saturation), sedations cores and rescue analgesic requirements were recorded for 24 hrs postoperatively.

Results : The onset of sensory and motor block was significantly faster in Group B Ccompared to Group B ($P < 0.05$). Rescue analgesic requirements were significantly less in Group BC compared to Group B ($P < 0.05$). Haemodynamics and sedations cores did not differ between groups in the post-operative period.

Conclusion: Clonidine (1μg/kg) in combination with 30mL of Bupivacaine (0.375%) hastened onset of sensory and motor block, and improved postoperative analgesia when used in brachial plexus block, without producing any adverse events.

Key Words : Clonidine, Bupivacaine, Sensory and motor block

INDEX

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

INTRODUCTION

Brachial plexus blocks provide a useful alternative to general anaesthesia for upper limb surgeries. They achieve near ideal operating conditions by producing complete muscular relaxation, maintaining stable intra-operative hemodynamics and the associated sympathetic block. The sympathetic block decreases post-operative pain, vasospasm, and edema.

Of various local anesthetics, Bupivacaine is used most frequently as it has a longer duration of action varying from 3 to 8 hours. However, there are many limiting factors like delayed onset, patchy or incomplete analgesia etc.

Various drugs like neostigmine, opioids, hyaluronidase, midazolam etc.[1-3] have been added to local anaesthetics in order to modify the block in terms of quick onset, good quality, prolonged duration and post-operative analgesia. But these presented with adverse systemic effects or doubtful efficacy.

Clonidine, an imidazoline alpha-2 adrenergic receptor agonist mainly used as an anti-hypertensive agent. Alpha-2 receptors mediate sedation, analgesia, and sympatholysis. Clonidine has been shown to be of benefit for use in central neuraxial blocks and other regional blocks by increasing the duration and intensity of pain relief[4-6] and also by decreasing the systemic and local inflammatory stress response.[7,8]. Clonidine produces this effect by modulating pain pathways through presynaptic alpha-2 adrenergic receptors. It also produces sedation through acting on pontine locus ceruleus where highest density of alpha-2 receptors are present. Neuraxial placement of Clonidine inhibits spinal substance P release and nociceptive neuron firirng produced by noxious stimulation.

So the present study is being undertaken in a randomized single blinded manner to evaluate the onset time, duration and analgesic efficacy of Clonidine-Bupivacaine combination compared to plain Bupivacaine (0.375%) for brachial plexus block by supraclavicular approach.

OBJECTIVES

The study of adding Clonidine (1µg/kg) to Bupivacaine (0.375%) in brachial plexus block for upper limb surgeries has the following objectives:

Primary Objectives :

To evaluate

1. Onset and duration of sensory & motor blockade.
2. Time for rescue analgesics in post-operative 24 hours.

Secondary objectives :

To evaluvate

Haemodynamic variables (HR, BP, Oxygen saturation) & Sedation score intra and post-operatively.

REVIEW OF LITERATURE

HISTORY OF BRACHIAL PLEXUS BLOCK[9]:

The first brachial plexus block was performed by William Stewart Halsted in 1885, less than a year after Koller demonstrated the anaesthetic properties of cocaine on the eye of patient.

Halsted exposed the roots surgically under local infiltration and injected each of them with a small amount of dilute Cocaine (0.1%) interneurally under direct vision. Only about 0.5 ml of local anesthetic was required to produce complete anaesthesia.

In 1897, Crile used a similar technique in which the plexus was exposed under local anesthesia. Just behind the sternomastoid muscle, cocaine was injected into the nerve trunks under direct vision which was done as a therapeutic measure in a 12 year old boy who developed tetanic spasms following a compound fracture of the forearm, later the technique was used to provide anesthesia for upper arm surgeries.

EVOLUTION OF SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK[10]:

In 1911-1912, KULENKAMPFF described the first percutaneous supraclavicular approach. He pointed out that above the clavicle the plexus lies under the skin as it passes over the first rib and accessible to a percutaneous technique. The midpoint of the clavicle and subclavian artery provided a constant landmark. Most frequently at the point where external jugular vein intersects the clavicle. He performed his first attempt on himself and used 5 ml of Novocaine, later he increased it to 10 ml and was able to obtain complete anaesthesia. Direction of the needle was backwards, inwards and downwards.

He emphasized that purpose of the technique was not to hit the rib but to find the trunks by eliciting paraesthesia. He said the rib just prevented pleural penetration. He used 4 cm needle.

LABAT in 1992 advocated an injection at three separate points which failed to elicit paraesthesia by Kulenkampff's method. First injection beneath the deep fascia in the direction of the first rib, second towards the chassaignac's tubercle and the third towards the lateral margin of the first rib behind the clavicle (5 ml with each injection).

In 1926, LIVINGSTON, carried out Kulenkampffs technique without the production of paraesthesia as soon as the deep cervical fascia had been penetrated. 30 ml of 2% procaine was injected. He wrote that the plexus and the artery are separated from the surrounding structures by a fascial investment.

In 1940, PATRICK chose to lay down a "wall of anaesthetic" through which the plexus must pass in its course over the first rib, where 60-70 ml of solution was being injected during 5-6 insertions. This technique become the "standard technique" of supraclavicular block, subsequently referred to by many as the "classical supraclavicular technique".

In 1942 KNIGHT modified Patrick's technique by making the three injections through three separate needle insertion, parallel to one another. For the first time he utilized a directly caudal direction of needle insertion.

In 1944, MURPHEY used a single injection technique and used lateral border of anterior scalene muscle as the landmark and direction of needle insertion caudal as with Knight's technique, not medial or dorsal, as with most other techniques.

In 1949, BONICA and MOORE utilized Kulenkampffs and Patrick's techniques and developed a technique where it begins with utilizing the classical landmarks and direction of needle insertion and demands a definite paraesthesia prior to first injection. Then continue as Patrick's technique and lay down a wall of anaesthetic solution by "walking the rib" and make multiple injections during each withdrawal of the needle. This was used over subsequent twenty years.

In 1958, LOOKMAN fully realised the potential of the sheath, who like Livingston realised on the fascial investment of the plexus. He carefully dissected the plexus and said that plexus lies in a closed compartment. He said this space lies between the anterior and middle scalene muscles and is pyramidal in shape, with its apex pointing upwards and medially towards the exit of the fourth cervical nerve. He did not verify the needle's proper placement within the space before injection. He admitted the tendency for the point of the needle to pass too posteriorly and hence to come to be within the substance of (or even behind) the middle scalene muscle.

FORTIN and TREMBLAY advocated the use of a short needle, which was long enough to reach the plexus but too short to reach the lung, in a attempt to minimize the threat of pneumothorax.

In 1964 WINNIE after numerous anatomical dissections showed that the relation of the plexus and the subclavian artery to the midpoint of the first rib is not constant. He showed that there is a constant relationship between the anterior and middle scalene muscles, the plexus and the first rib. The plexus between the two scalene muscles always insert on the first rib. He inserted needle between the two muscles, in the direction of the space between them. Once a paraesthesia is obtained, a single injection is made into the space.

K Sri Hyndavi, *et al* (2016) [11] conducted prospective, randomized double-blind placebo controlled study to evaluate the effect of Bupivacaine and Clonidine

combination of drugs with respect to the onset, duration of sensory and motor blockade and duration of analgesia in infra-clavicular brachial plexus block for elective upper limb orthopedic surgeries. 40 patients of American Society of Anaesthesiologists Grade I or II undergoing elective upper limb orthopedic procedures through Infra clavicular approach for brachial plexus block were randomly divided into two groups **Group C** received 30ml of 0.375%Bupivacaine and 0.4ml normal saline (n=20) **Group S** received 30ml of 0.375% Bupivacaine and (60μg) Clonidine (n=20) .Both the groups were compared for onset and duration of sensory and motor block, postoperative analgesia, level of sedation, sideeffects and complications. Analgesia duration was 753.2 ±109.6 min in group S (Clonidine) compared to 210.2 ± 32.min in group C (control). Onset time was shorter while duration of sensory and motor blockade were longer in group S(Clonidine) than group C(control) and the difference was statistically significant. No clinical significance was observed in hemodynamics. Ramsay Sedation Score(RSS) was higher in the group S(Clonidine) group. It was concluded that addition of small dose of Clonidine (60μg) to Bupivacaine shortens the onset time and prolongs the duration of sensory and motor blockade and duration of post operative analgesia significantly without any major side effects.

Sirohiya P. *et al* (2016)[12] conducted study to evaluate the effect of Bupivacaine Clonidine combination in supraclavicular brachial plexus block for upper limb surgeries. A randomized double-blind controlled trial was performed in 60 patients. **Group B (n=30)** patients received 25 mL 0.5% Bupivacaine and 0.2 mL of Saline, whereas **group C (n = 30)** received 25 mL 0.5% Bupivacaine and 0.2 mL (30 mcg) Clonidine through supraclavicular brachial plexus block. In both groups, differences between age, sex, ASA grades, weight, vital parameters were statistically

insignificant. Time of onset of sensory blockade and motor blockade were reduced in group C compared to Group B and were statistically significant. Duration of sensory and motor blockade were prolonged in group C compared to Group B and were statistically significant. Duration of post operative analgesia was prolonged in group C compared to Group B and were statistically significant. Sedation score of patients in group C were higher than those in group C intra-operatively and postoperatively. No clinically significant differences were observed in pulse rate, mean blood pressure and oxygen saturation. Due to its sedative properties, it can reduce patient anxiety and provide optimal intra-operative and postoperative patient comfort.

Audichya PC, Goyal S. (2016)[13] conducted study to compare the effect of Clonidine v/s placebo as adjuvant to lignocaine for brachial plexus block, by supraclavicular approach, for different upper limb surgeries. The present study was conducted in 50 patients of ASA I or II status in the age group of 18 – 50 years, under brachial plexus block by supraclavicular approach for various upper limb surgeries. Patients of both groups were assessed in terms of onset time of motor and sensory block, Perioperative hemodynamic status, Duration of post operative analgesia, Adverse effects of drugs if any etc. Data were analyzed using unpaired 't' test with p value <0.05 considered statistically significant. The mean time of onset of sensory and motor block was significantly lower in Group B compared to Group A. Mean duration of motor block and sensory block are significantly longer in Group B than in Group A. No incidence of nausea, vomiting, hypotension, tachycardia or bradycardia were observed in any group. They concluded that when Clonidine 150 μg is added to local anesthetic solution in supraclavicular brachial plexus block, it provides rapid onset of block, better analgesia, good hemodynamic stability and profound & longer analgesia without any adverse effects.

Dr. Jyoti Vishnu Kale, Dr. Dhanashree Dongare, Dr. R. W. Naphade (2013)[14] conducted study on effect of Clonidine as an adjuvant in Bupivacaine for supraclavicular brachial plexus block: A randomized double-blind placebo controlled trial was conducted in 60 patients of American Society of Anesthesiologists Grade I or II status undergoing upper limb orthopedic procedures. Group C (n = 30) patients received 15 ml of 0.5% Bupivacaine and 10 ml of 2% lignocaine with adrenaline and 1 mcg/kg Clonidine, whereas group B (n = 30) received 15 ml of 0.5% Bupivacaine and 10 ml of 2% lignocaine with adrenaline through a supraclavicular approach for brachial plexus block. Onset and duration of both sensory and motor blocks and sedation score were studied in both the groups. All patients were observed and received injection tramadol 100mg. as soon as they complained of pain as rescue analgesic. It was concluded that addition of a small dose of Clonidine to local anaesthetic solution significantly prolonged the duration of analgesia without producing any clinically important adverse reaction. The time for rescue analgesia was also prolonged.

Sumanta Ghoshmaulik, *et al.* (2012) [15] conducted study on Clonidine as an adjuvant in axillary brachial plexus block for below elbow orthopedic surgeries. Seventy patients (ASA I or II) scheduled for below elbow orthopedic surgeries were randomly allocated in equal numbers to receive either 30 ml of 0.5% plain Bupivacaine with 150 mg (1 ml) of inj. Clonidine locally in the axillary sheath and 1 ml of normal saline (NS) subcutaneously (Group L) or 30 ml of 0.5% plain Bupivacaine with 1 ml of NS locally and 150 mg (1 ml) of inj. Clonidine subcutaneously (Group S). Standard monitoring of vital parameters was done. Duration of sensory and motor block, analgesia, hemodynamic changes, and any adverse effects were observed and recorded for different duration up to 24 and they concluded that compared to systemic

administration, local Clonidine as an adjuvant in axillary block resulted in significant prolongation of duration of sensory and motor blockade, and analgesia without any hemodynamic alteration, probably by locally mediated mechanism of action[1]

Shivinder Singh, Amitabh Aggarwal (2010)[16] conducted a randomized controlled double-blinded prospective study of the efficacy of Clonidine added to Bupivacaine as compared with Bupivacaine alone used in supraclavicular brachial plexus block for upper limb surgeries. In this prospective, randomized, double-blinded, controlled trial, two groups of 25 patients each were investigated using (i) 40 ml of Bupivacaine 0.25% plus 0.150 mg of Clonidine and (ii) 40 ml of Bupivacaine 0.25% plus 1 ml of NaCl 0.9, respectively. The onset of motor and sensory block and duration of sensory block were recorded along with monitoring of heart rate, non-invasive blood pressure, oxygen saturation and sedation. It was observed that addition of Clonidine to Bupivacaine resulted in faster onset of sensory block, longer duration of analgesia (as assessed by visual analogue score), prolongation of the motor block (as assessed by modified Lovett Rating Scale), prolongation of the duration of recovery of sensation and no association with any haemodynamic changes (heart rate and blood pressure), sedation or any other adverse effects. These findings suggest that Clonidine added to Bupivacaine is an attractive option for improving the quality and duration of supraclavicular brachial plexus block in upper limb surgeries.

Sumitha Chakraborty, *et al.(*2010)[17] conducted study on the effect of this combination in supraclavicular brachial plexus block for upper limb orthopedic procedures. A randomized double-blind placebo controlled trial was done with 70 patients of American Society of Anesthesiologists Grade I or II status undergoing upper limb orthopedic procedures. Group A (n = 35) patients received 25 ml of 0.5% Bupivacaine and 0.2 ml (30 mcg) Clonidine, whereas group B (n = 35) received 25 ml

of 0.5% Bupivacaine and 0.2 ml normal saline through a supraclavicular approach for brachial plexus block. Vital parameters were recorded 10 min prior to block placement and every 3 min thereafter till the end of the procedure. Onset and duration of both sensory and motor blocks and sedation score were recorded. All patients were observed in postanesthesia care unit and received tramadol injection as soon as they complained of pain as rescue analgesic. Duration of analgesia was taken as the time from placement of block till injection of rescue analgesic. It was concluded that Addition of a small dose of Clonidine to 0.5% Bupivacaine significantly prolonged the duration of analgesia without producing any clinically important adverse reactions other than sedation.

Jacques T. *et al* (2008)[18] conducted a randomized, double-blind, placebo-controlled study tested the hypothesis that 100 µg Clonidine added to 0.375% Bupivacaine would prolong the duration of analgesia from popliteal fossa nerve blockade. Ninety-nine patients scheduled for hospital admission after foot or ankle surgery entered this randomized, double-blind, placebo-controlled trial. Patients received a popliteal fossa block (nerve stimulator technique, via the posterior approach) using 30 mL 0.375% Bupivacaine, with epinephrine. Patients were randomized to receive no Clonidine, 100 µg Clonidine IM, or 100 µg Clonidine with Bupivacaine for the popliteal block. Patients also received a combined spinal epidural anesthetic, a saphenous nerve block, and postoperative IV patient controlled analgesia. The primary outcome was patient-reported duration of analgesia. Duration of analgesia was statistically longer in the block Clonidine group(18 ± 6 h for Clonidine with Bupivacaine vs 14 ± 7 h for IM Clonidine and 15 ± 7 h for control, P = 0.016 for control vs Clonidine with Bupivacaine). Pain scores, analgesic use, and side effects attributable to pain management were similar among groups. It was concluded that Clonidine

significantly prolongs the analgesic duration after popliteal fossa nerve blockade with Bupivacaine.

McCartney CJ, Duggan E, Apatu E.(2007)[19] conducted study to determine the benefit of adding Clonidine to peripheral nerve blocks. A systematic, qualitative review of double-blind randomized controlled trials on the benefit of Clonidine as an adjunct to peripheral nerve block was performed. Studies were identified by searching PubMed (www.ncbi.nlm.nih.gov/entrez) and EMBASE (www.embase.com) databases (July 1991 to October 2006) for terms related to Clonidine as an adjunct to peripheral nerve blocks. Studies were classified as supportive if the use of Clonidine demonstrated reduced pain and total analgesic consumption, or prolonged block duration versus negative if no difference was found. Twenty-seven studies were identified that met the inclusion criteria. Five studies included a systemic control group. The total number of patients reviewed was 1,385. The dose of Clonidine varied from 30 to 300 µg. Overall 15 studies supported the use of Clonidine as an adjunct to peripheral nerve blocks with 12 studies failing to show a benefit. Based on qualitative analysis, Clonidine appeared to prolong analgesia when added to intermediate-acting local anesthetics for peripheral nerve blocks. It was concluded that Clonidine improves duration of analgesia and anesthesia when used as an adjunct to intermediate-acting local anesthetics for peripheral nerve blocks. Side-effects appear to be limited at doses up to 150 µg.

Giovanni Cucchiaro, Arjunan Ganesh. (2007)[20] conducted study to evaluate the effects of Clonidine on the duration of sensory and motor block and analgesia time in children who underwent a variety of peripheral nerve blocks. It reviewed the regional anesthesia database that contains data on children who underwent an infraclavicular, lumbar plexus, femoral, fascia iliaca or sciatic nerve block for postoperative analgesia

at The Children's Hospital of Philadelphia between October 2002 and December 2005. Patients were prospectively followed after the nerve block. Two hundred fifteen patients (47%) received either Bupivacaine or ropivacaine local anesthetic (LA) and 220 (53%) a combination of local anesthetic and Clonidine (LAC). The duration of sensory block was significantly longer in the LAC (17.2 ± 5 h) compared with that in the LA group (13.2 ± 5 h) (P = 0.0001). The increase in duration was independent from the type of peripheral nerve block, local anesthetic used and operation performed. Themotor block duration was significantly longer in the LAC group (9.6 ± 5 vs 4.3 ± 4 h, P = 0.014). It was concluded that the addition of Clonidine to Bupivacaineand ropivacaine can extend sensory block by a few hours, and increase the incidence of motor blocks.

B.S.Sethi, Mary Samuel, Deepak Sreevatav (2007)[21] conducted study on Clonidine as adjuvant in spinal anaestheisa. Sixty adult patients belonging to ASA grade I and II, scheduled for gynaecological surgery under spinal anaesthesia were randomly divided into two groups. Clonidine group received Clonidine 1 μg.kg-1with 12.5 mg 0.5% Bupivacaine and the Control group receive dan identical volume of saline mixed with 12.5mg0.5% Bupivacaine.The maximum dose of Clonidine used was 70 μg. The mean time from injection to regression of the level of sensory analgesia by two segments was longer in the Clonidine group than in Control group (P<0.001). The duration of motor blockade was longer in Clonidine group than in Control group (P<0.05).There was also a significant difference in the duration of analgesia between the two groups (P<0.001). The rescue analgesia was required earlier in the Control group(mean 223 min) compared to the Clonidine group(mean614min). The number of injections of diclofenac in 24 hours was higher for Control group (mean2.66) than Clonidine group (mean 1.16) (P<0.05). The patients in the Clonidine group had a

significant fall in mean arterial pressure and heart rate and were more sedated than those in Control group, however, no therapeutic interventions needed. They concluded that addition of Clonidine to Bupivacaine in the dose of 1 **µ**g.kg-1 significantly increases the duration of spinal analgesia as compared to Bupivacaine alone with clinically insignificant influence on haemodynamic parameters and level of sedation.

D. Hutschala ,*et al* (2004)[22] conducted study on Seven healthy volunteers who underwent three brachial block procedures using Bupivacaine 0.25% 1µg/kg (=local analgesic) in a randomized, double-blind cross-over fashion: (a) *control treatment:* local analgesic with 0.9% sodium chloride solution for the block and an intramuscular injection of saline; (b) *intramuscular treatment:* local analgesic with 0.9% NaCl for block and an intramuscular injection of Clonidine 2 **µ**g kg^{-1} and (c) *block treatment:* local analgesic with Clonidine 2 **µ**g kg^{-1} for block and an intramuscular injection of saline. The onset and duration of complete blockade (sensory/motor/temperature) was evaluated in the four nerve regions of the hand and forearm. Additionally, sedation score, blood pressure, heart rate and plasma Clonidine concentrations were determined. The median duration of complete sensory blockade was 270 min (range 0–600) for block treatment compared to 0 min (range 0–480) for intramuscular treatment ($P< 0.05$) and 0 min (range 0–180) for control treatment ($P< 0.05$). Motor and temperature blockade exhibited similar results. Administration of Clonidine was associated with sedation and a decrease in heart rate and blood pressure independent of the route of administration. Plasma Clonidine concentrations were lower for block compared to the intramuscular treatment and it was concluded that the admixture of Clonidine to Bupivacaine plus epinephrine prolongs and enhances brachial plexus

blockade. Lower Clonidine plasma concentrations for block treatment strongly suggest a local effect.

I. Dobrydnjov, *et al* (2003)[23] did randomized double-blinded study to see whether the addition of small-dose Clonidine to small-dose Bupivacaine for spinal anesthesia prolonged the duration of postoperative analgesia and also provided a sufficient block duration that would be adequate for inguinalherniorrhaphy. They randomized 45 patients to 3 groups receiving intrathecal hyperbaric Bupivacaine 6 mg combined with saline (Group B), Clonidine 15 μg (Group BC15), or Clonidine 30 μg (Group BC30); all solutions were diluted with saline to 3 mL. The sensory block level was insufficient for surgery in five patients in Group B, and these patients were given general anesthesia. Patients in Groups BC15 and BC30 had a significantly higher spread of analgesia (two to four dermatomes) than those in Group B. Two-segment regression, return of S1 sensation, and regression of motor block were significantly longer in Group BC30 than in Group B. The addition of Clonidine 15 and 30 μg to Bupivacaine prolonged time to first analgesic request and decreased postoperative pain with minimal risk of hypotension. They concluded that Clonidine 15 μg with Bupivacaine 6 mg produced an effective spinal anesthesia and recommend this dose for inguinal herniorrhaphy, because it did not prolong the motor block.

Henri Iskandar, *et al* (2003)[24] conducted prospective double blind study to determine whether interscalene Clonidine induces analgesia for shoulder arthroscopy. Forty patients scheduled for shoulder arthroscopy were randomly divided into two groups. The interscalene group (n = 20) received Clonidine 150 μg in 15 mL of saline through the catheter and 1 mL of subcutaneous saline, and the systemic group (n = 20) received 15 mL of saline through the catheter and Clonidine 150 μg (1 mL) subcutaneously. All patients underwent general anesthesia for surgery. On completion

of arthroscopy, all patients received, via a patient-controlled analgesia, on demand a bolus of 8 mL of ropivacaine 0.2% through the catheter with a 1-h lockout period. Postoperative pain was measured every 4 h using the visual analog scale (VAS) for 24 h. Additional postoperative analgesia was available with parenteral nalbuphine if required until VAS < 3. VAS scores in the recovery room were significantly higher in the systemic groupcompared with the interscalene group (P< 0.0001). Analgesic duration was significantly longer in the interscalene group (P< 0.00001), and ropivacaine consumption was significantly less than in the systemic group (P< 0.0001). No significant difference was observed between groups for nalbuphine consumption. Side effects were comparable in the two groups. They concluded that Clonidine administered via an interscalene catheter enhanced analgesia compared with systemic administration.

Rashmi Madan, *et al* (2001)[25]conducted a study which assessed the dose-response relationship of Clonidine added to lidocaine in peribulbar block. Sixty patients undergoing cataract surgery were given peribulbar block with 7 mL of 2% lidocaine and hyaluronidase with either saline (Control) or Clonidine in 0.5-**μ**g/kg (0.5 Clon), 1.0-**μ**g/kg (1.0 Clon), or 1.5-**μ**g/kg (1.5 Clon) doses. The onset and duration of lid and globe akinesia, globe anesthesia and analgesia, postoperative analgesic requirement, and adverse effects (hypotension, bradycardia, hypoxia, sedation, and dizziness) were recorded. The success rate and onset of block were comparable in all groups. The duration of lid and globe akinesia, globe anesthesia and analgesia was significantly (P< 0.01) prolonged in patients receiving 1.0 and 1.5 **μ**g/kg Clonidine as compared with the Control group. Perioperative pain scores and analgesic requirement were significantly less in these groups. 0.5 **μ**g/kg Clonidine did not increase the duration of anesthesia and analgesia significantly. Hypotension and dizziness were observed more

in patients receiving 1.5 μg/kg Clonidine as compared with other groups. They concluded that 1.0 μg/kg Clonidine with a mixture of lidocaine (2%) significantly prolonged the duration of anesthesia and analgesia after peribulbar block with limited side effects.

Damien B, *et al*. (2000)[26]did a study on the efficacy of adding novel analgesic adjuncts to brachial plexus block, the goal of which is to prolong analgesic effect without the disadvantage of systemic side effects or prolonged motor block. Novel adjuncts studied to date include opioids, Clonidine, neostigmine, and tramadol. Twenty-four studies were reviewed and assessed by using specific inclusion criteria, and only those studies satisfying these criteria were included in the final assessment. Satisfactory studies were then assessed for inclusion of a systemic control group to determine peripheral effect, as opposed to possible systemic effect, of an adjunct administered peripherally. It was implicated that there is little evidence for the analgesic benefit of adding opioids to brachial plexus block. Clonidine appears to be beneficial in doses up to 150 μg. There are currently insufficient data with regard to neostigmine and tramadol to allow for further recommendations.

Scott S, Reuben, Neil Roy Connelly.(1999)[27] did a study to determine whether Clonidine added to an Intra-articular injection would result in an analgesic benefit. Fifty patients were randomly assigned to one of five groups that received Clonidine (either via the subcutaneous or IA route) or saline placebo with or without IA Bupivacaine, as follows: Group 1 received 30 mL of 0.25% Bupivacaine IA; Group 2 received 30 mL of 0.25% Bupivacaine with Clonidine (1 μg/kg) IA; Group 3 received 30 mL of 0.25% Bupivacaine IA and subcutaneous Clonidine (1 μg/kg); Group 4 received 30 mL of 0.25% Bupivacaine with epinephrine (5 μg/mL) IA; and Group 5 received Clonidine (1 μg/kg) in 30 mL of saline IA. The results of this study revealed

a significantdifference in analgesia from the IA administration of Clonidine. The group who received a combination of IA Bupivacaine and Clonidine had a significantly decreased need for oral postoperative analgesics and an increased analgesic duration ($P< 0.0001$). Theyconcluded that IA Clonidine improved comfort in patients undergoing knee arthroscopy.

H. Buerkle, *et al* (1999)[28] It has been demonstrated recently that in addition to its spinal analgesic actions, the alpha-2 adrenoreceptor agonist Clonidine also has peripheral analgesic activity. Few data are available regarding the antinociceptive effects of spinal vs peripherally delivered Clonidine in inflammatory pain. It has been studied by spinal (intrathecal = i.t.) and peripheral (intra-articular = i.a.) administration of Clonidine in the rat inflamed knee joint model. Thermal and mechanical antinociception was assessed in rats over 28 h using a modified Hargreaves box and von Frey hairs after induction of tonic persistent inflammatory pain by injection of a kaolin-carrageenan mixture into the right knee joint. Thirty minutes after injection of kaolin-carrageenan, Clonidine was administered via an i.t. catheter or by i.a. injection into the right inflamed knee joint or by subcutaneous injection (s.c.) (highest effective intra-articular dose). The specific site of action was assessed using the alpha-2 antagonist yohimbine i.t., i.a. or s.c. Clonidine i.t. resulted in thermal and mechanical antinociception during ongoing inflammation. Yohimbine inhibited the antinociceptive action of Clonidine at the site of delivery. This suggested that Clonidine produces potent thermal and mechanical antinociception regardless of the route of administration. However, chronic inflammatory processing appears to enhance the antinociceptive efficacy of the peripheral alpha-2 agonist.

Bernard JM, Macaire P. (1997)[29]did study on addition of Clonidine to local anesthetics can prolong pain relief after peripheral nerve block, a dose-range effect

has been determined. Fifty-six outpatients undergoing carpal tunnel release were randomly assigned to receive in a double-blind fashion 45 ml of a mixture containing either 400 mg lidocaine plus saline or 400 mg lidocaine plus 30, 90 or 300 **μ**g Clonidine for brachial plexus block. In each group (n = 14), blocks were evaluated at regular time intervals to determine sensory and motor functions in the five nerve regions of the hand and forearm. Also, adequacy of the block for surgery, postoperative pain intensity, and side effects were evaluated. Compared with saline, each dose of Clonidine reduced the onset time of sensory block and extended the field of adequate anesthesia. Ten minutes after injection, 30 **μ**g Clonidine was more effective than 90 **μ**g Clonidine in producing sensory blockade. Sedation occurred with Clonidine 30 and 300 **μ**g. Clonidine reduced the use of supplementary intravenous anesthetic agents for surgery and produced dose-dependent prolongation of analgesia, reaching a mean 770 min (range, 190-1440 min) for the largest dose. Clonidine also produced a dose-dependent decrease in systolic arterial pressure of up to -22.5% (range, -6.0 to -29.9%) of baseline. With Clonidine, 300 **μ**g, three patients had mean arterial pressure of < 55 mmHg; four patients had episodes of arterial oxyhemoglobin saturation of <90%, and two others were not discharged because of hypotension. This study suggested that a small dose of Clonidine enhances the quality of the peripheral blocks and limits the classical α_2- agonist side effects to sedation.

Singelyn F, Jean-Marie, Annie Robert.(1996)[30] did a study which assessed the minimum dose of Clonidine required to prolong the duration of both anesthesia and analgesia after axillary brachial plexus blockade. Eighty patients scheduled for elective hand surgery were divided into eight groups in a randomized,double-blind fashion. An axillary brachial plexus block was performed with 40 mL 1% mepivacaine plus 1:200,000 epinephrine. The control group received no Clonidine. In

the other groups, increasing doses of Clonidine (0.1, 0.2, 0.3, 0.4, 0.5, 1, and 1.5 micrograms/kg) were added to the local anesthetic solution. Onset time, duration of anesthesia and analgesia, postoperative pain score, intake of analgesics, and adverse effects were recorded. The eight groups were comparable in terms of onset time, postoperative pain score, and analgesic requirement. The minimum dose of Clonidine required to significantly prolong the duration of analgesia and anesthesia was, respectively, 0.1 and 0.5 microgram/kg. No side effects (sedation, drowsiness, bradycardia, arterial hypotension) were reported. They conclude that the dose of Clonidine required to prolong significantly the duration of both anesthesia and analgesia after axillary brachial plexus blockade is 0.5-1 microgram/kg and that, at this dose, Clonidine may be used without important reported side effects even in outpatients.

J. J. Lee, A. P. Rubin.(1994)[31] did a randomized, double-blind study in children undergoing elective orthopaedic surgery, which assessed the clinical value of combining Clonidine with Bupivacaine for caudal analgesia. Forty-six children, aged 1–10 yr, were allocated randomly to two equal groups to receive 0.25% Bupivacaine 1 ml kg^{-1} combined with either normal saline 1 ml (group A) or Clonidine 2 $\mu g\ kg^{-1}$ in normal saline 1 ml (group B). Mean (SD) duration of caudal analgesia for groups A and B were 5.2 (1.2) h and 9.8 (2.1) h, respectively ($P < 0.0001$). Group B required significantly less supplementary analgesia after operation ($P < 0.01$). There was no significant difference in the incidence of side effects between the two groups. The longer duration of sedation in group B (9.1 (2.5) h) resulted partly from the sedative effect of Clonidine and partly from the longer duration of analgesia provided by Clonidine. They concluded that, when added to Bupivacaine, Clonidine improves the efficacy of caudal analgesia in children.

Tsui BCH *et al,*[32] in 2008 conducted a case series on ultrasound guided supraclavicular block using a curvilinear probe in 104 day-case hand surgery patients and reported successful experience using ultrasound guidance and nerve stimulation during supraclavicular blockade. They concluded that the curvilinear probe enables a large field of view, adequate resolution in larger patients, and excellent needle visibility that allows access to the plexus while avoiding the pleura and subclavian artery.

Mehta SS *et al,*[33] in 2015 conducted a study titled "Comparative study of supraclavicular brachial plexus block by nerve stimulator versus ultrasound guided method". The study was conducted in 50 patients and divided into group A (n=25) and group B (n=25). Group A was given block with nerve stimulator and group B was given ultrasound guided block. Duration of block performance was 10±2.5 minutes in group A when compared to 6±1.5 minutes in group B. Mean onset time of sensory block was 9.64±1.14 minutes in group A when compared to 6.64±0.89 minutes in group B. Mean onset time of motor block was 12.18±1.48 minutes in group A when compared to 10.10±1.14 minutes in group B. In group B 15-25 ml of drug was required for successful block as compared to 20-35 ml for group A. One patient in group A has post operative pneumothorax and 5 patients required supplemental general anaesthesia as compared to no complications in group B and 2 patients required general anesthesia due to inadequate block in group B. They concluded that supraclavicular brachial plexus block using ultrasound guided method is an improved nerve block technique due to visualization of nerves with more success, decreased complication rate, faster onset and less time consuming as compared to nerve stimulator method but requires knowledge of sonoanatomy and skill to operate ultrasound machine.

Singh G *et al* (2014)[34] conducted a study titled "Comparison between conventional technique and ultrasound guided supraclavicular brachial plexus block in upper limb surgeries. Of the 60 patients included in the study they were divided into two groups of 30 patients each. Group 1 received ultrasound guided supraclavicular brachial plexus block. Group 2 received conventional supraclavicular brachial plexus block. Time taken for the procedure to administer a block in group 2 was 5.43 minutes where as using an ultrasound, time required for the same was 10.1 minutes($P<0.0001$). Onset of sensory block was 10.86±3.19 minutes in group 1 as compared to 11.6±2.45 minutes in group 2 ($P=0.32$). Onset of motor block was 14.56±3.85 as compared to 16.8±3.42 minutes in group 2($P=0.02$). Duration of sensory block was 397.9±67.3 minutes as compared to 352.22±87.5 minutes in group 2($P=0.03$).Duration of motor block was 343.44±60.8 minutes as compared to 305.19±60.1 minutes in group 2 ($P=0.02$). Block was successful in 90% in group 1 and 77.3% in group 2. Incidence of vessel puncture was 10% in group 2 compared to 3.33% in group 1($P=0.05$). They concluded that ultrasound guided supraclavicular brachial plexus block has more success rate and very few complications compared to block performed by conventional approach. Time taken for the block performed by ultrasound was longer than the conventional technique. Onset of sensory and motor blockade was little earlier by ultrasound technique. Duration of sensory and motor blockade was longer by ultrasound technique.

Hanumanthaiah D *et al* (2013)[35] conducted a study on ultrasound guided supraclavicular block and they concluded that recent renewed interest in ultrasound guided supraclavicular blocks may be due to easy image acquisition relating to superficial location of the brachial plexus at this level and identifying the pleura thus minimizing the risk of pneumothorax.

Rupera KB *et al* (2008)[36] conducted a study titled " Ultrasonography guided technique offer advantage over peripheral nerve stimulator guided technique in supraclavicular brachial plexus block''. The study was conducted among 60 patients suffering from chronic renal failure with ASA III scheduled for the creation of arterial-venous fistula. In group A (n=30) ultrasonography guided technique was used and in group B (n=30) peripheral nerve stimulation technique was used. Procedure time in group A was 4.55±0.74 minutes as compared to 5.71±0.92 minutes in group B ($p<0.0001$). Onset time for sensory block in group A was 2.97±0.72 minutes as compared to 3.63±0.76 minutes in group B ($p=0.002$). Onset time for motor block in group A was 4.55±0.78 minutes as compared to 5.13±0.71 minutes in group B ($p=0.007$). Time to achieve complete block in group A was 13.17±1.54 minutes as compared to 16.96±1.83 minutes in group B ($p<0.0001$). Duration of sensory block in group A was 5.29±0.82 hours as compared to 4.73±0.81 hours in group B ($p=0.015$). Duration of motor block was 5.05±0.67 hours in group A as compared to 4.58±0.73 hours in group B ($P=0.02$). No patients in group A had any complications while in group B, 3 patients had subclavian artery puncture and 1 had pneumothorax ($p<0.05$). They concluded that ultrasonography guided supraclavicular brachial plexus block is quick to perform, offers improved safety and accuracy in identifying the position of nerves to be blocked and of the structures. Wider availability of USG is likely to ensure even greater use in the future and will become gold standard for peripheral nerve blocks over the more conventional techniques.

Vincent WS *et al* (2003)[37] conducted a study on ultrasound guided supraclavicular brachial plexus block. Forty healthy outpatients received ultrasound-guided supraclavicular brachial plexus blocks for elective upper limb surgery. For the first 29 patients, a Toshiba Core Vision Pro unit equipped with a linear 8-MHz probe was

used. For the remaining 11 patients, a Philips ATL HDI 5000 SonoCT unit equipped with a linear 5-12 MHz probe, color Doppler, and compound imaging capability was used. They concluded that ultrasound guidance is clinically useful for supraclavicular brachial plexus block. It confers confidence and accuracy of needle placement for nerve localization and examines the pattern of local anesthetic spread.

ANATOMY OF BRACHIAL PLEXUS [9,38,39]

Knowledge of formation of brachial plexus and its ultimate cutaneous and muscular distribution is absolutely essential to the intelligent and effective use of brachial plexus anaesthesia for upper limb surgeries. Close familiarity with the vascular, muscular and fascial relationships of the plexus is equally essential to the mastery of various techniques, for it is these perineural structures which serve as the landmark by which needle may accurately locate the plexus percutaneously.

In its course from intervertebral foramina to the upper arm, the fibres are composed consecutively of roots, trunks, divisions, cords and terminal nerves.

FORMATION OF BRACHIAL PLEXUS :

Brachial plexus is formed by the union of ventral rami of lower four cervical nerves ($C_{5,6,7,8}$) and first thoracic nerve (T_1) with frequent contributions from C_4 or T_2.

When contribution from C_4 is large and from T_2 is lacking, the plexus appears to have a more cephaloid position and is termed "Prefixed". When contribution from T_2 is large and from C_4 is lacking, the plexus appears to have a caudal position and is termed "postfixed". Usually prefixed or postfixed positions are associated with the presence either of a cervical rib or of an anomalous first rib.

ROOTS :

Represent the anterior primary divisions of lower four cervical and first thoracic nerves. They emerge from the inter vertebral foramina and fuse above the first rib to form the trunks.

TRUNKS:

The roots combine above the first rib to form the three trunks of the plexus. C_5 and C_6 unite at the lateral border of the scalenus medius and form the "Upper trunk",

C_8 and T_1 unite behind the scalenus anterior to form "lower trunk" and C_7 continues as a sole contributor to the "middle trunk".

DIVISIONS :

As the trunks pass over the first rib and under the clavicle, each one of them divides into anterior and posterior divisions.

CORDS:

The fibres, as they emerge from under the clavicle, recombine to form three cords. The "lateral cord" is formed by anterior divisions of upper and middle trunks, lateral to the axillary artery. The anterior division of lower trunk descend medial to the axillary artery forming the "medial cord". The posterior divisions of all three trunks unite to form the "posterior cord", at first above and then behind the axillary artery.

The medial and lateral cords give rise to nerves that supply the flexor surface of upper extremity, while nerves arising from the posterior cord supply the extensor surface.

MAJOR TERMINAL NERVES :

Each of these cords gives off a branch that contributes to or become one of the major nerves to the upper extremity and then terminates as a major nerve. The lateral and median cords give off lateral and medial heads of the medial nerve and continue as major terminal nerves, the lateral cord terminating as musculocutaneous nerve and medial cord as ulnar nerve. Posterior cord gives off, axillary nerve as its major branch and then continues as the radial nerve.

In summary, conveniently it can be considered that brachial plexus begins with five nerves (C_5-T_1) and terminates in five nerves (Musculocutaneous, radial, axillary, median and ulnar nerves) with its intermediate portions displaying in sets of three, that is, three main trunks which divide into 2 sets of three, which reunite and give rise to three cords. These three cords give off three lateral branches before becoming the major terminal branches of the plexus.

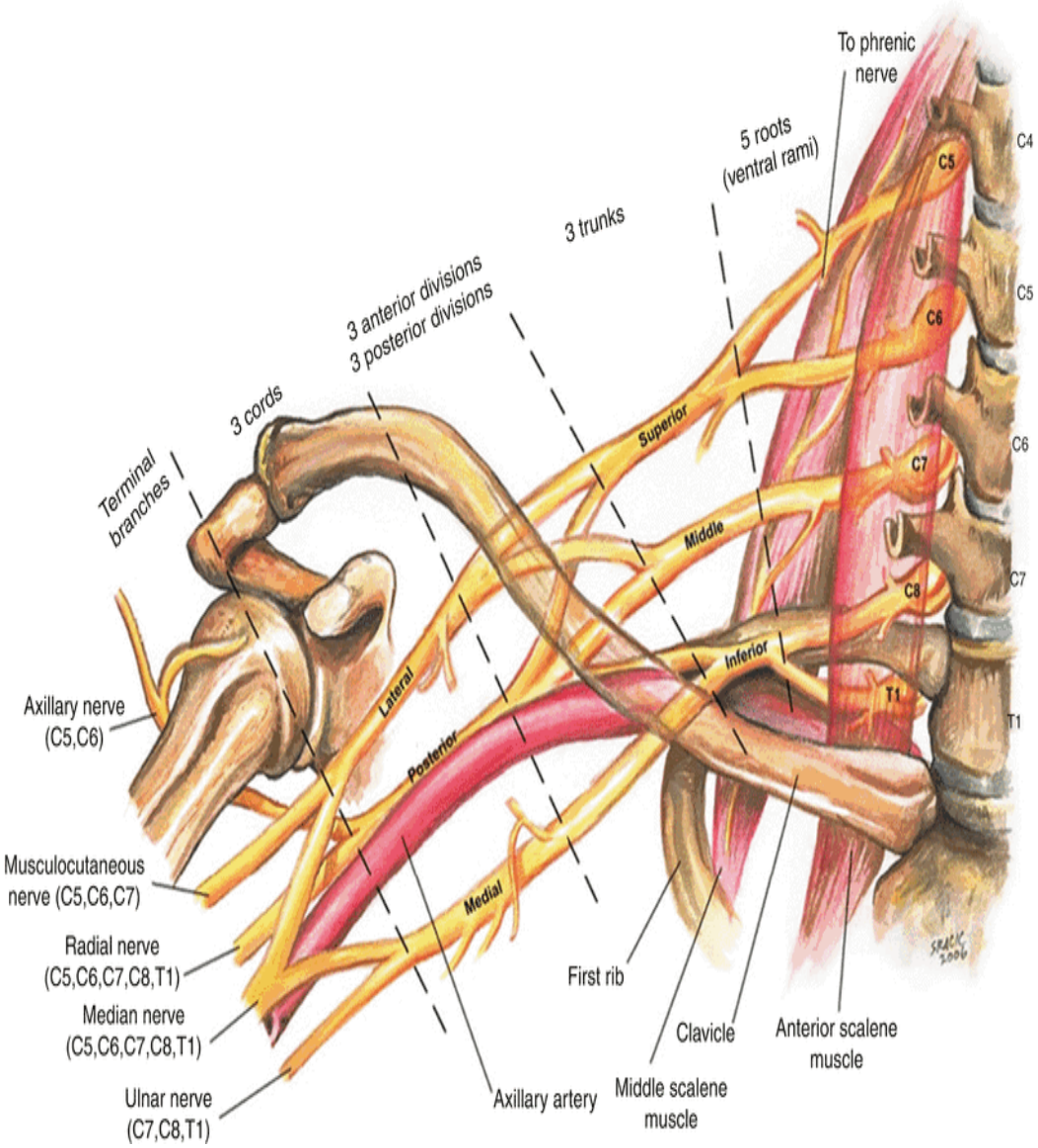


Fig.1 : FORMATION OF BRACHEAL PLEXUS

DISTRIBUTION OF BRACHIAL PLEXUS :

These are divided into those that arise above the clavicle - the supraclavicular branches and those that arise below it, the infraclavicular branches.

Supraclavicular branches :

From roots :

1. Nerves to scaleni and longus colli - $C_{5,6,7,8}$
2. Branch to phrenic nerve - C_5
3. Dorsal scapular nerve - C_5
4. Long thoracic nerve – $C_{5,6,(7)}$

From trunks :

1. Nerve to subclavius – $C_{5,6}$
2. suprascapular nerve - $C_{5,6,}$

Infraclavicular branches : They branch from cords but their fibres may betracked back to spinal nerves.

Lateral cord :

1. Lateral pectoral nerve - $C_{5,6,7}$
2. Musculocutaneous nerve – $C_{5,6,7}$
3. Lateral root of median nerve - $C_{5.6,7}$

Medial cord :

1. Medial pectoral nerve – C_8, T_1
2. Medial cutaneous nerve of forearm – C_8, T_1
3. Ulnar nerve-C_7, T_1
4. Medial root of median nerve-C_8, T_1
5. Medial cutaneous nerve of arm – C_8, T_1

Posterior cord :

1. Upper subscapular nerve - $C_{5,6}$
2. Thoracodorsal nerve – $C_{6,7,8}$
3. Lower subscapular nerve - $C_{5,6}$
4. Axillary nerve - $C_{5,6}$
5. Radial nerve — $C_{5,6,7,8,}T_1$

SYMPATHETIC CONTRIBUTION TO BRACHIAL PLEXUS :

The segmental preganglionic sympathetic contributions are variable, but generally extend more caudal. The highest contribution is usually T_2 with T_1 contributing only rarely, while lowest may be as far as T_8, T_9 or even T_{10}.The post ganglionic contributions are from grey rami communicants from the sympathetic chain.

RELATIONS OF BRACHIAL PLEXUS :

In its passage from the cervical transverse processes to the first rib, the plexus is "sandwiched" between the anterior and middle scalene muscles and invested in the fascia of those two muscles.

The 'interfascial comaprtment', along with subclavian artery which crosses the first rib immediately in front of the trunks. Artery is close to the scalenus anterior and the plexus close to the scalenus medius. Subclavian vein is separated from the artery by the scalenus anterior. The fascia covering the muscles is derived from the perivertebral fascia, which splits to invest these muscles and rejoins again at their lateral margins to form an enclosed space, the interscalene space. As the plexus cross the first rib, the three trunks are 'stacked' one on top of the other vertically. Not infrequently, the inferior trunk gets trapped behind and even beneath the subclavian artery above the rib, during embryologic development.

This may be reason why local anaesthetics injected via the interscalene technique sometimes fail to provide anaesthesia in the distribution of the ulnar nerve, which may be buried deep within inferior trunk behind or beneath the subclavian artery. After crossing the first rib, they the split to form 2 divisions and the cords and subclavian artery becomes the axillary artery. Above the clavicle, the axillary artery lies central to the three cords, in the axilla the lateral and posterior cords are lateral to the first part of the axillary artery, the medial cord being behind it. Around the second part of the artery, they are related according to their names. In the lower axilla, cords divide into nerves for the upper limb. In passing over the first rib under the clavicle, the subclavian vein also becomes the axillary vein and its relationship with the neurovascular bundle changes. Above the first rib the subclavian vein does not lie within the neurovascular bundle, it is separated by the insertion of scalenus anterior. As it passes over the first rib, becoming the axillary vein it joins the neurovascular bundle so that parts of the plexus are sandwiched between artery and vein. As all the three enter the axilla, they invaginate the perivertebral fascia at the lateral margins of the anterior and medial scalene muscles, carrying this fascial investment of the neurovascular bundle into the axilla as the axillary fascia, an extension of the perivertebral or scalene fascia forming the axillary perivascular space, a tubular extension of the interscalene space. In its course through the axilla and upper arm the fascia of the surrounding muscles contribute to the axillary sheath, making it thick and tough, providing the 'fascial click' to the anaesthetic while entering the sheath. It is important to note that major terminal nerves leave the sheath high in the axilla under cover of perctoralis minor muscle.

The musculocutaneous nerve enters the substance of coracobrachialis and continues down within this muscle. The axillary nerve also leaves the sheath immediately after arising from the posterior cord. The interocostobrachial nerve

travels parallel to but outside the axillary sheath and medial cutaneous nerve of the arm runs similarly but occasionally it may remain within the sheath.

THE BRACHIAL PLEXUS SHEATH

Volume of the sheath : 42ml.

Shape of the sheath : Cylindrical to conical - Wide proximally and narrow distally.

Length : 8-10cms long.

- The connective tissue of the prevertebral fascia and the anterior and middle scalenes envelopes the brachial plexus as well as the subclavian and axillary artery in a neurovascular "sheath".
- The tissue is densely organized as it leaves the deep cervical fascia proximally, but becomes more loosely arranged distally. The sheath blends with the fascia of the biceps and brachialis muscle distally.
- Anatomic dissection, histologic examination and CT scanning after injection of radio contrast into the sheath demonstrate the existence of connective tissue septae which extend inward from the fascia surrounding the sheath. The thin velamentous connective tissue septae frequently adhere to nerves and vessels leaving no free space between layers and compartmentalizing the components of the sheath.

Anesthetic implications :

Because of these connective tissue septae, anaesthesia might be complete and rapid in onset in some nerves, but delayed and incomplete or completely absent in others. The incidence of partial block is an exception rather than the rule, so septae apparently are of little clinical significance as the local anaesthetic can percolate through them.

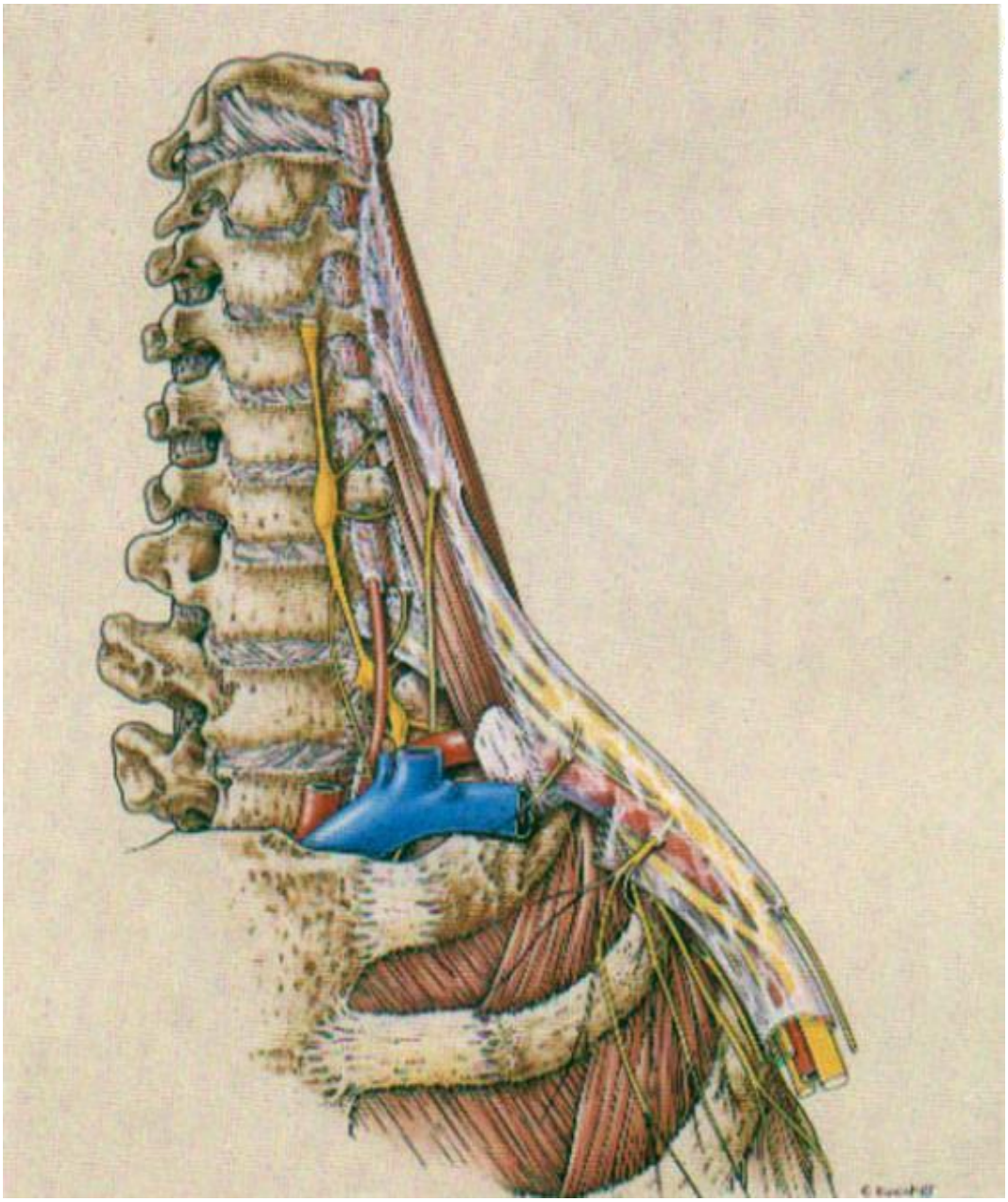


Fig 2 : Sheath around the brachial plexus

SONOANATOMY OF BRACHIAL PLEXUS [40]

The brachial plexus in supraclavicular area is scanned using a high frequency 5-14 MHz linear ultrasound probe held in an oblique plane, (coronal or sagittal) which scans both in longitudinal and horizontal direction.

The subclavian artery is a prominent landmark identified immediately superior to first rib as a pulsatile hypoechoic tennis ball like image on ultrasound. The first rib appears as a bright hyperechoic rim with a drop out bony acoustic shadow. The brachial plexus normally appears superior, supero-lateral or superomedial to subclavian artery as multiple hypoechoic ovals/circles, often described as a honeycomb pattern or "bunch of grapes". The brachial plexus may acquire a triangular, linear or vertical (or oblique) arrangement of trunks/division/cords around subclavian artery in supraclavicular region on ultrasound scan.

The pleura is seen as a hyperechoic line at same level as more "shiny" than the rib. Pleura moves and shines more with breathing. The hyperechoic pleural shadow does not have a drop out acoustic shadow, which differentiates it from the rib shadow. The scalenus anterior and medius muscles appear as hypoechoic structures on ultrasound scan and can be followed commencing from their origin to the point of insertion on first rib. The phrenic nerve lies on anterior surface of scalenus anterior from C4-7 level in neck. The long thoracic and dorsal scapular nerves pass through middle scalene muscle and may appear as "holes" or hypoechoic structures. Often part of brachial plexus passes through scalenus anterior or medius muscles and is seen as small round or oval hyperechoic or hypoechoic structures.

The thyrocervical trunk and transverse cervical artery often appear similar to nerve trunks on ultrasound scan. The pulsations of smaller arteries or branches are easily masked by the strong pulsations of subclavian artery. These vessels may fall in nerve block needle trajectory or course along or through the brachial plexus. This poses a threat of vascular injury, hematoma formation or inadvertent intra-vascular injection. Color Doppler may help in differentiation of brachial plexus from arteries by demonstrating color enhancement. Thus ideally the proposed nerve block needle trajectory should be routinely scanned with Color Flow Doppler. In addition, veins are collapsible and may be identified by applying and releasing pressure with help of ultrasound probe while scanning.

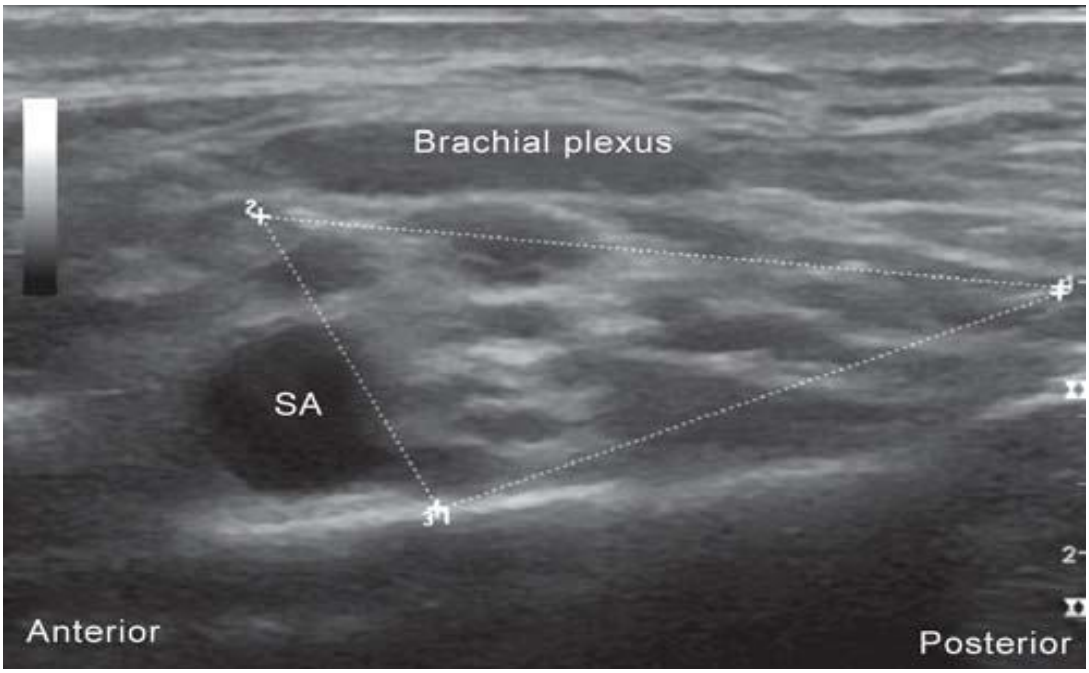


Fig. 3a: Supraclavicular brachial plexus arranged in triangular pattern. Plexus is seen as rounded to oblong hypoechoic structures surrounded by hyperechoic rim. Subclavian artery (SA) is seen as large rounded hypoechoic structure which is pulsatile in real time.

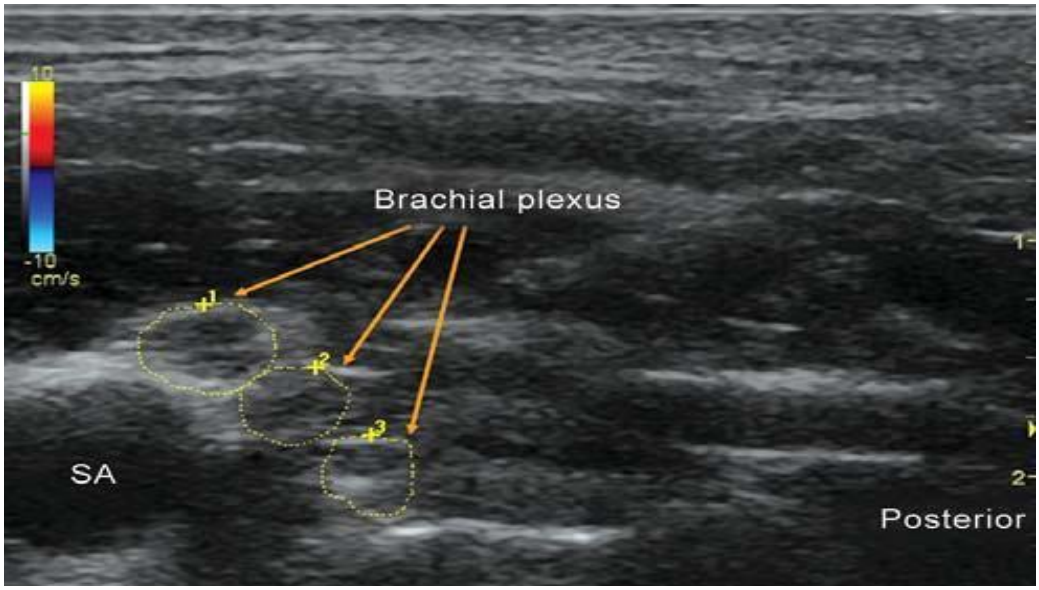


Fig. 3b: Supraclavicular brachial plexus arranged as vertical/obliquelyarranged circles. Plexus is seen as hypoechoic round structure

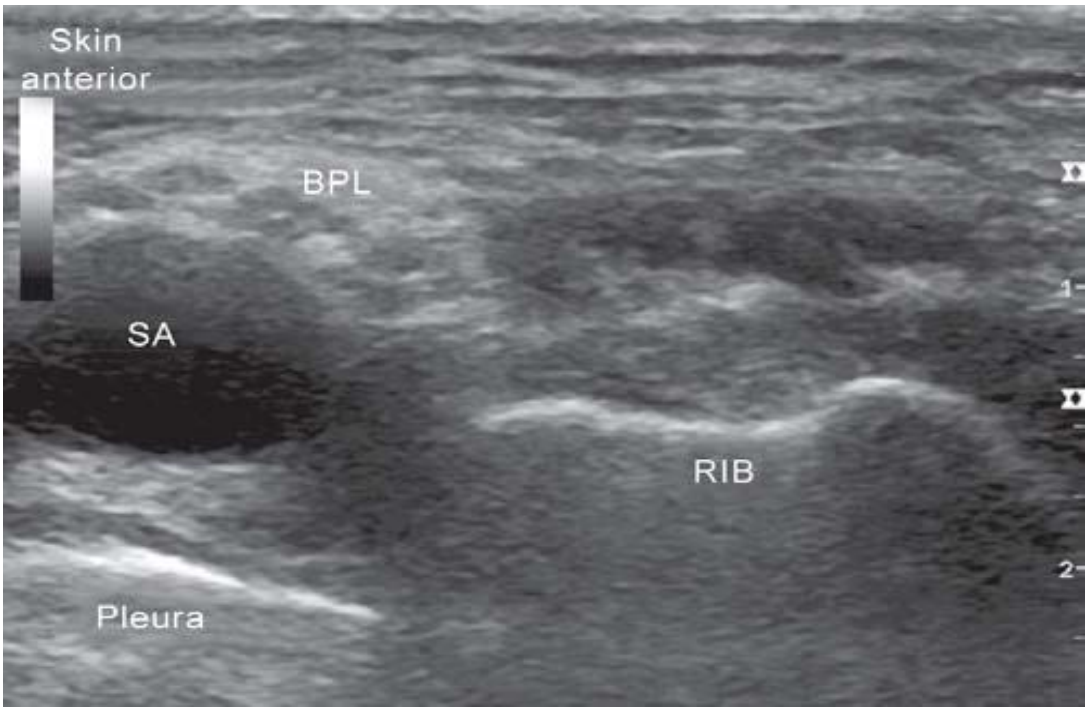


Fig. 3c: Showing pleura and rib. Rib is seen as linear hyperechoic area with acoustic shadowing, pleura is visualised as hyperechoic structure without acoustic shadow. SA, subclavian artery; BPL, brachial plexus.

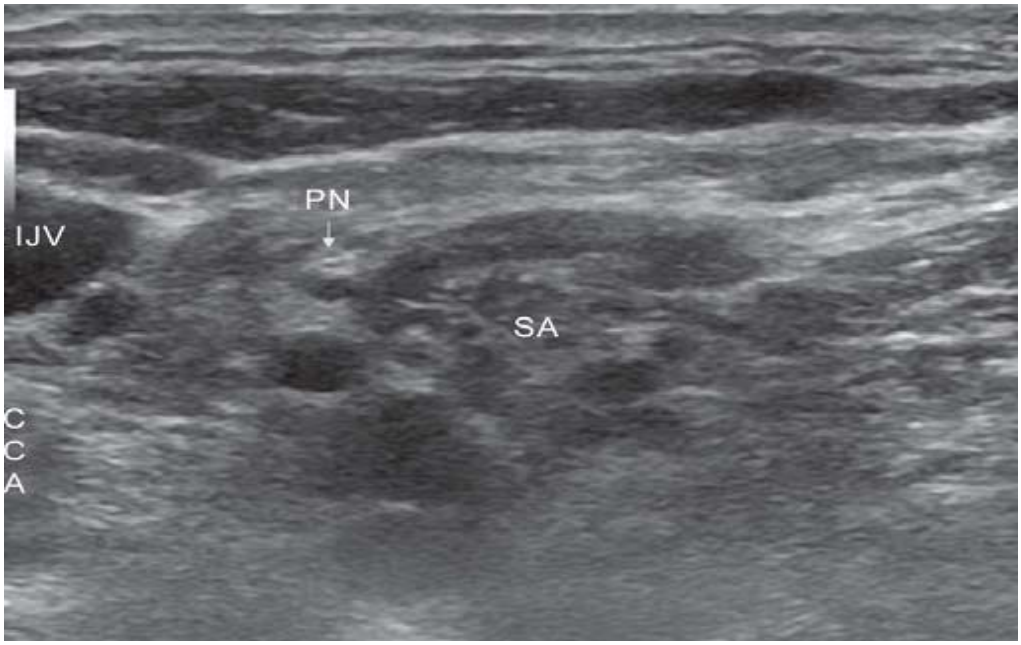


Fig. 3d: Showing phrenic nerve (PN) as hyperechoic structure on anterior surface of scalenus anterior (SA) muscle. IJV, internal jugular vein; CCA, common carotid artery

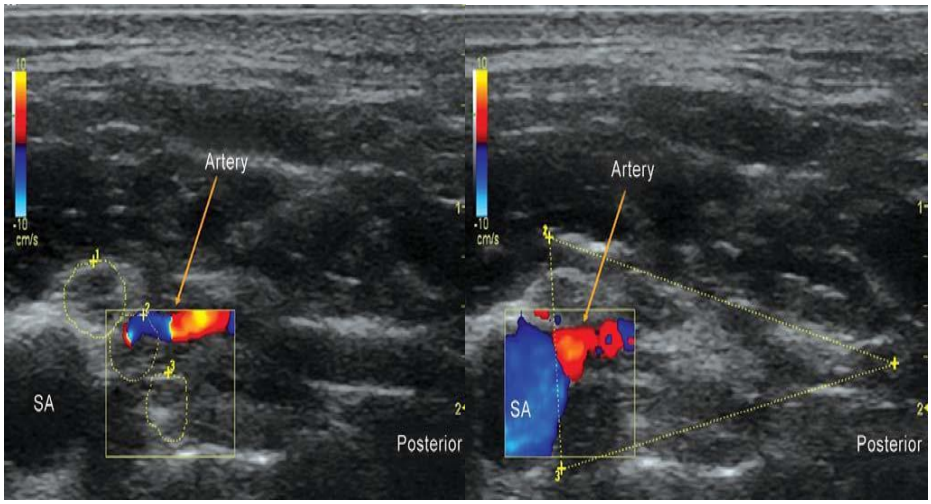


Fig 3e: Showing a branch of subclavian artery coursing through brachial plexus on colour doppler. SA, subclavian artery

INDICATIONS

Supraclavicular brachial plexus block produces rapid, reliable anaesthesia for surgical procedures of upper extremity.

Areas blocked are – Arm, forearm and hand except area over tip of shoulder (C3,C4) and inner aspect of upper arm (T2, intercostobrachial nerve).

CONTRAINDICATIONS

- General – patient refusal, allergy, disorder of hemostasis, preexisting neurologic deficit, respiratory failure, infection at site.
- Specific-particular stature(short neck, stiff neck)
- Associated disease – goiter.
- Radiotherapy sequel, past history of cervical node resection, contralateral recurrent laryngeal nerve palsy.

LOCAL ANESTHETIC MECHANISMS IN NERVE BLOCKADE

Impulse blockade by local anaesthetics may be summarized by the following chronology:

- Solutions of local anaesthetic are deposited near the nerve. Removal of free drug molecules away from this locus is a function of tissue binding, removal by the circulation, and local hydrolysis of amino-ester anaesthetics. The net result is penetration of the nerve sheath by the remaining free drug molecules.
- Local anaesthetic molecules then permeate the nerve's axon membranes and reside there and in the axoplasm. The speed and extent of these processes depend on a particular drug's pKa and on the lipophilicity of its base and cation species.

- Binding of local anesthetic to sites on voltage-gated Na^+ channels prevents opening of the channels by inhibiting the conformational changes that underlie channel activation. Local anesthetics bind in the channel's pore and also occlude the path of Na^+ ions.
- During onset or recovery from local anesthesia, impulse blockade is incomplete and partially blocked fibers are further inhibited by repetitive stimulation, which produces an additional use-dependent blinding to Na^+ channels.
- One local anesthetic binding site on the Na^+ channel may be sufficient to account for the drug's resting (tonic) and use-dependent (phasic) actions. Access to this site may potentially involve multiple pathways, but for clinical local anesthetics, the primary route is the hydrophobic approach from within the axon membrane.
- The clinically observed rates of onset and recovery from blockade are governed by the relatively slow diffusion of local anesthetic molecule into and out of the whole nerve, not by their much faster binding and dissociation from ion channels. A clinically effective block that may last for hours can be accomplished with local anesthetic drugs that dissociate from Na^+ channels in a few seconds.

COMPLICATIONS[41]

Vascular puncture

Internal jugular vein may be punctured at skin wheal infiltration. Simple digital compression is required before continuing, the likelihood of arterial puncture implies not to pinpoint behind and too medial from mid clavicle. Best is to withdraw and redirect the needle when perceiving artery pulsation at the needle tip.

Pleural puncture

The most significant complication of supraclavicular approach for blocking brachial plexus is development of pneumothorax. The incidence of pneumothorax is one percent with this technique and much higher in inexperienced hands. A pneumothorax must be suspected when there is dyspnea, cough or pleuritic chest pain but the diagnosis can be confirmed only by chest x-ray.

Phrenic nerve block

Phrenic nerve block occurs in 40-60% of patient because of spread of local anaesthetic to the anterior surface of anterior scalene muscle. The effect is avoided if anaesthetic is deposited deep on the middle trunk on division or cord. This is rarely symptomatic. Radiographic confirmation may be obtained.

Recurrent laryngeal nerve block

It causes transient dysphonia, occurs in 1% of case and only on the right side because recurrent laryngeal nerve loops around the subclavian artery on the right side and arch of aorta on the left.

Nerve damage or neuritis

It results from the needle trauma or faulty positioning of anaesthetised arm preoperatively. Other remote causes include excessive tourniquet time, concentrated solution with vasoconstrictor and susceptible host tissue.[42]

Horner's syndrome

It consists of ptosis, miosis, anhydrosis and enophthalmos. It usually follows stellate ganglion block. It is found in 10% of cases, after interscalene block.

Toxic reaction to drug

It is likely to occur if there is over dosage of drug or inadvertent intravascular injection is made, but can be avoided with proper negative aspiration test before drug injection.

PHARMACOLOGY OF BUPIVACAINE [43,44,45,46,47]

Local Anaesthetic Drugs :

Local anaesthetics are drugs that produce reversible conduction blockade of impulses along central and peripheral nerve pathways after regional anaesthesia. With progressive increase in concentrations of local anaesthetics the transmission of autonomic, somatic sensory and somatic motor impulses are interrupted producing autonomic nervous system blockade, sensory anaesthesia, and skeletal muscle paralysis in the area innervated by the affected nerve. Removal of the local anaesthetic is followed by spontaneous and complete return of nerve conductions, with no evidence of structural damage to nerve fibres.

Local anaesthetics have similar configuration. They have one aromatic lipophilic part (Benzene ring) and one hydrophilic part (quaternary ring) connected by an intermediate ring either ester (-COO-) or an amide (-NHCO-).

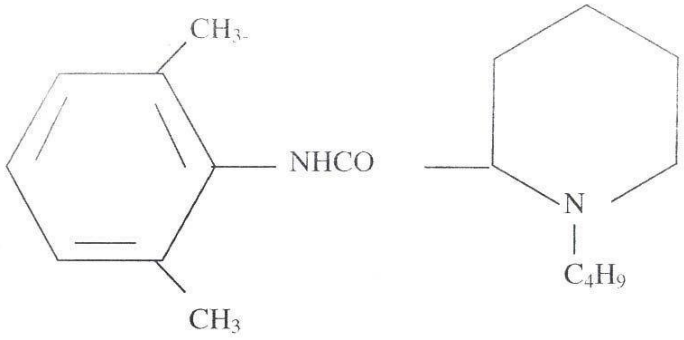
BUPIVACAINE :

Source : Bupivacaine, a synthetic drug, was prepared by A.F. Ekenstam in 1957.

Chemistry : The molecular weight of the chloride salt is 325 and that of the base form is 288. It has a melting point of 258°C. Solutions containing epinephrine have a pH of about 3.5.

The chemical name is l-n-butyl-DL-piperidine-2 carboxylic acid-2,6 dimethylamilide hydrochloride.

The molecular formula is $C_{18}N_2OH_{28}HCl$.



Chemical structure

Physiochemical properties :

1) **Solubility :** The base is sparingly soluble, but the hydrochloride is readily soluble in water.
2) **Stability and sterilization :** Bupivacaine is highly stable and can with stand repeated autoclaving.
3) **pH of saturated solution :** 5.2
4) **Specific gravity :** 1.021 at 37°C
5) **Melting point:** 247-258°C

Anaesthetic properties:

Potency:

Bupivacaine is approximately three to four times more potent than Lidocaine. The duration of action for local anaesthesia is two to three times longer than Lidocaine.

Anaesthetic index :

Bupivacaine's anesthetic index is 3.0 to 4.0.

Mechanism of action :

It is similar to that of any other local anaesthetics. The primary action of local anaesthetics is on the cell membrane of the axon, on which it produces electrical stabilization. The large transient increase in permeability to sodium ions necessary for

propagation of the impulse is prevented. Thus the resting membrane potential is maintained and depolarization in response to stimulation is inhibited.

The mechanism by which local anaesthetics block sodium conductance is as follows :

a) Local anaesthetics in the cationic form act on the receptors within the sodium channels, on the cell membrane and block it. The local anaesthetic can reach the sodium channel either via the lipophilic pathway directly across the lipid membrane, or via the axoplasmic opening. This mechanism accounts for 90% of the nerve blocking effects of amide local anaesthetics.

b) The second mechanism of action is by membrane expansion. This is a non specific action in contrast to the more specific drug receptor interaction.

Dosage and preparation available :

The dosage of Bupivacaine depends on :

- Area to be anaesthetized
- The vascularity of the tissue to be blocked
- The number of neuronal segments to be blocked
- Individual tolerance
- Technique of local anaesthesia

Available concentration :

- 0.25%, 0.5%.
- 0.25% and 0.5% soluble in isotonic saline
- 0.5% solution in 8% dextrose - Hyperbaric

These doses may be repeated in 3-4 hours but 400mg is the maximum dose in 24 hours. The addition of vasoconstrictor produces a very slight increase in the duration of action. However the peak blood level is significantly reduced, there by minimizing the systemic toxicity.

Table A : Dosage and concentration of Bupivacaine in various blocks

Type of block	Concentration	Dosage in ml	Dosage in mg
Local infiltration	0.25-0.5%	5-20ml	Upto 175mg
Brachial plexus block	0.25-0.5%	20-40ml	75-225mg
Intercostal nerve block	0.25-0.5%	3-5ml	15-20mg per each
Epidural block	0.25-0.5%	15-20ml	50-200mg
Caudal block	0.25-0.5%	15-30ml	75-15mg
Subarachnoid block	0.5%	2-4ml	10-20mg

ACTIONS :

Central nervous system:

Overdose of Bupivacaine produces light headedness and dizziness followed by visual and auditory disturbances such as difficult to focus andtinnitus. Disorientation and drowsiness can also occur. Shivering, muscular tremors and tremors of muscles of face and distal part of extremities can occur.

Ultimately generalized convulsions of tonic clonic nature occurs. Further increase in doses causes respiratory arrest.

Since Bupivacaine is a potent drug, smaller doses can cause rapid onset of toxic symptoms when compared to other drugs.

Autonomic nervous system:

Bupivacaine does not inhibit the Noradrenaline uptake and hence has no sympathetic potentiating effect. Myelinated preganglionic beta fibres have a faster conduction time and are more sensitive to the action of local anaesthetics including Bupivacaine. Involvement of preganglionic sympathetic fibres is the cause of widespread vasodilatation and consequent hypotension that occurs is epidural and

paravertebral block. When used for conduction blockade, all local anaesthetics particularly Bupivacaine produce higher incidence of sensory than motor fibres blockade.

Neuro-muscular junctions :

Bupivacaine like other local anaesthetics can block motor nerves if present in sufficient concentration but has no effect on the neuromuscular junction as such.

Cardiovascular system:

The primary cardiac electro physiologic effect of local anaesthetic is a decrease in the maximum rate of depolarization in the purkinje fibres and ventricular muscle. This is due to a decrease in the availability of sodium channels. Action potential duration and the effective refractory period is also decreased. The depression of rapid phase of depolarization (V-max) in purkinge

fibres and ventricular muscle by Bupivacaine is far greater compared to Lignocaine. Also the rate of recovery of block is slower with Bupivacaine. Therefore there is incomplete restoration of V-max between action potential particularly at higher heart rates. Therefore, Bupivacaine is highly arrythmogenic. The cardiac contractility is reduced, this is by blocking the calcium transport.

Low concentration of Bupivacaine produces vasoconstriction while higher doses causes vasodilatation.

Respiratory system:

Respiratory depression may be caused if excessive plasma level is reached which in turn results in depression of medullary respiratory center. Respiratory depression may also be caused by paralysis of respiratory muscles as may occur in high spinal or total spinal anaesthesia.

Toxicity :

The toxic plasma concentration is set at 4-5 µg/ml. Maximum plasma concentration rarely approach toxic levels. Non specific local irritant effects on nerve tissue have been noted in human subjects. No evidence of permanent damage has been found in clinical dosage. There is no alteration is blood picture or methaemoglobin formation due to this drug.

Pharmacokinetics :

Bupivacaine can be detected in the blood within 5 minutes of infiltration or following either epidural or intercostal nerve blocks. Plasma levels are related to the total dose administered. Peak levels of 0.14 to 1.18 µg/ml were found within 5 minutes to 2 hours after the administration of anaesthesia and they gradually declined to 0.1 to 0.34 µg/ml by 4 hours.

Plasma binding :

In plasma, drug binds avidly with protein (l- acid glycoprotein) to the extent of 70-95%. The rank order of protein binding for this and its homologues is-Bupivacaine Mepivacaine Lidocaine. Conversely, the unbound active fraction is one seventh that of Lidocaine and one fifth that of Mepivacaine.

Metabolism - elimination :

Because Bupivacaine is an amide, the liver is the primary site of metabolism. The drug is metabolized partly by N-dealkylation primarily to pipecolyloxylidine. N-disbutyl-Bupivacaine and 4-hydroxy-Bupivacaine are also formed. It crosses the placental barrier as any other local anaesthetic by passive diffusion, but the lowest level of placental diffusion is reported for this drug (umbilical vein/maternal ratio is 0.31 to 0.44). The high protein binding capacity of the agent is probably the reason why less diffusion occurs across the placenta. No effects on fetus have been noted.

Pharmacodynamics :

The onset of action of Bupivacaine is between 4 and 6 minutes and maximum anaesthesia is obtained between 15 and 20 minutes. The duration of anaesthesia varies according to the type of block, the average duration for peridural block is about 3.5-5 hours, for nerve blocks, it is about 5 to 6 hours.

About 10% of drug is excreted unchanged in urine within 24 hours; 5% excreted as pipecolyloxylidine. Glucoronide conjugate is also excreted.

Adverse reactions :

Adverse reactions occur with excessive plasma levels which may be due to overdose, inadvertent IV injections or slow metabolic degradation. These manifest by effects on CNS and CVS. The CNS effects are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurring of vision or tremors following drowsiness, convulsions unconsciousness and probably respiratory arrest.

Other effects may be nausea, vomiting, chills, constriction of pupils and tinnitus. The CVS manifestation include myocardial depression, hypotension and cardiac arrest, in obstetrics fetal bradycardia may occur. Allergic reactions include urticaria, bronchospasm and hypotension.

Treatment of adverse reaction :

Treatment is mainly symptomatic. One should be prepared to maintain circulation and to support ventilation with oxygen or controlled ventilation, if required, supportive treatment with IV fluids and vasopressors restore the cardiovascular stability, convulsions may be controlled with Diazepam (0.1-0.2 mg/kg) or Thiopentone (2-3 mg/kg) or a muscle relaxant and controlled ventilation with oxygen. Corticosteroids, if allergic reactions are suspected. Treatment of

ventricular fibrillation and tachycardia by Amiodarone (5mg/kg iv) or defibrillation (2-6 joule/kg).

Cardiovascular collapse / CNS ratio :

The CC/CNS dose ratio for Bupivacaine is 3.7±0.5 or findings indicating that 3 times drug was required to induce irreversible cardiovascular collapse as was needed to produce convulsions. It has also been suggested that some of the enhanced cardiac toxicity of Bupivacaine is due to greater myocardial uptake.

Role of additives :

1. Adrenaline Onset time reduced and duration prolonged.
2. Sodium bicarbonate : onset time reduced and duration variable.
3. Clonidine : Onset time reduced and duration prolonged.
4. Hyaluronidase : Onset time reduced and duration variable.
5. Opioids: Onset time reduced and duration prolonged. Reports controversial.
6. Midazolam : Onset time reduced and duration prolonged.

LEVOBUPIVACAINE[48]:

It is the S- enantiomer of Bupivacaine. Compared to Bupivacaine, it is associated with less vasodilatation and has a longer duration of action. It is approximately 13 % less potent (by molarity) than racemic Bupivacaine. Levobupivacaine, a single enantiomer of Bupivacaine, has recently been introduced as a new long-acting local anaesthetic with a potentially reduced toxicity compared with Bupivacaine. Numerous preclinical and clinical studies have compared levobupivacaine with Bupivacaine and in most studies there is evidence that levobupivacaine is less toxic. Advantages for levobupivacaine are seen on cardiac sodium and potassium channels, on isolated animal hearts and in whole animals, anaesthetised or awake. In particular the intravascular dose of levobupivacaine

required to cause lethality in animals is consistently higher compared with Bupivacaine. In awake sheep, for example, almost 78% more levobupivacaine was required to cause death. In contrast, in anaesthetised dogs no differences were seen in the incidence of spontaneous or electrical stimulation- induced ventricular tachycardia and fibrillations among animals exposed to levobupivacaine or Bupivacaine. The reversibility of levobupivacaine-induced cardiotoxicity has also been assessed. Levobupivacaine was found to cause smaller changes in indices of cardiac contractility and the QTc interval of the electrocardiogram and also to have less depressant effect on the electroencephalogram. Assuming that levobupivacaine has the same local anaesthetic potency as Bupivacaine, then, all things being equal, it is difficult to argue that levobupivacaine should not displace Bupivacaine as the long-acting local anaesthetic of choice. It would appear, however, that levobupivacaine has not yet significantly displaced Bupivacaine from the markets in which it is sold. This may be due to a lack of perceived safety benefit and/or consideration of the additional costs that are associated with switching to levobupivacaine, which is approximately 57% more expensive than Bupivacaine. With the continued clinical use of levobupivacaine the database available to make comparisons will increase and this may allow cost-benefit arguments to be made more forcefully for levobupivacaine in the future.

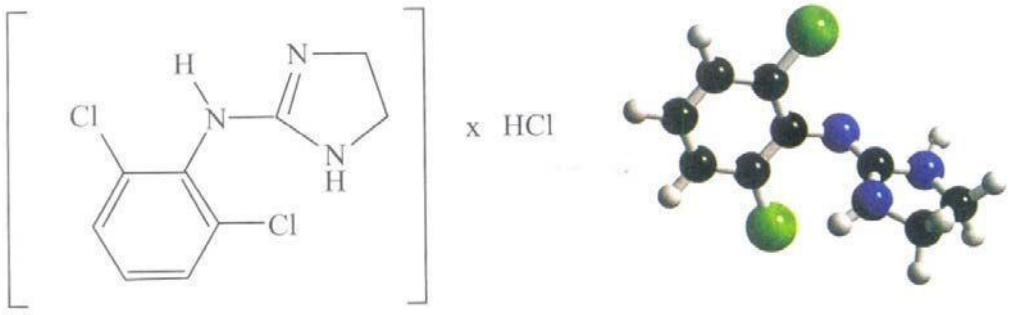
CLONIDINE - ITS PLACE IN ANESTHESIA [49,50,51,52,]

History and Chemistry:

Clonidine hydrochloride, an imidazoline derivative was originally developed as a nasal decongestant and vasoconstrictor. Its hypotensive and bradycardia effects were first appreciated in 1962. It is a centrally acting adrenergic agonist that lowers blood pressure by decreasing basal sympathetic nervous system activity. It was introduced first in Europe in 1966 and subsequently in the U.S. for use as an antihypertensive agent.

Clonidine hydrochloride is an imidazoline derivative and exists as a mesomeric compound. The chemical name is 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride. The following is the structural formula: $C_9H_9C_{12}N_3$ HCl.

Structure:



The molecular weight of Clonidine is 266.56. Clonidine hydrochloride is an odorless, bitter, white, crystalline substance soluble in water and alcohol.

It was introduced in the early 1960's as a nasal decongestant. It was during its use a nasal decongestant that the anti hypertensive property of the drug was found out. Subsequently more insight into the pharmacological properties has led to its use in clinical anaesthetic practice as well.

Mechanism of action:

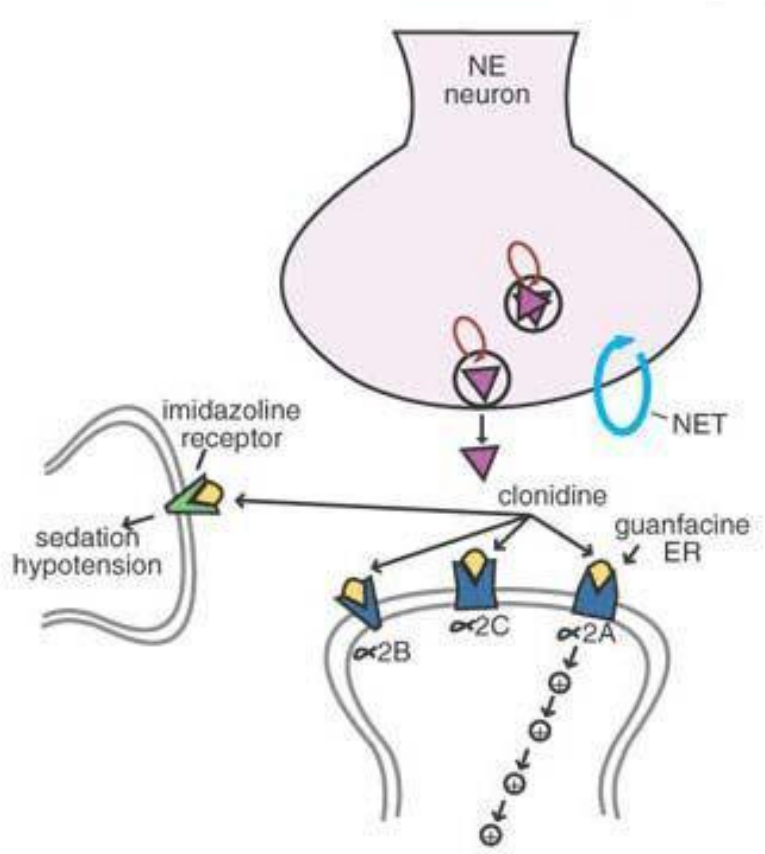


Fig 4: Mechanism of action of Clonidine

Alpha-2 adrenergic agonists produce clinical effects by binding to alpha-2 receptors of which there are 3 subtypes: alpha-2a, alpha-2b and alpha-2c. Alpha-2a receptors mediate sedation, analgesia and sympatholysis. Alpha-2b receptors mediate vasoconstriction and possibly anti-shivering mechanisms. The startle response reflects activation of alpha-2c receptors and it is the response of mind and body to a sudden unexpected stimulus, such as a flash of light, a loud noise (acoustic startle reflex), or a quick movement near the face. In human beings, the reaction includes physical movement away from the stimulus, a contraction of the muscles of the arms and legs, blinking and it also includes blood pressure, respiration, and breathing changes.

Clonidine is a centrally acting selective partial adrenergic agonist (alpha-2: alpha-1=220:1). Alpha-2 receptors are found densely in the pontine locus coeruleus which is an important source of sympathetic nervous system innervation of the forebrain and a vital modulator of vigilance. The sedative effects evoked by alpha-2 agonists most likely reflect inhibition of this nucleus. Clonidine also stimulates alpha-2 adrenergic inhibitory neurons in the medullary vasomotor centre. As a result, there is a decrease in the sympathetic nervous system outflow from the central nervous system (CNS) to the peripheral tissues. This causes central and peripheral attenuation of sympathetic outflow and central activation of non-adrenergic imidazoline preferring receptors. Decreased sympathetic nervous system activity is manifested as peripheral vasodilatation and a decrease in systolic blood pressure, heart rate and cardiac output. The ability of Clonidine to modify the potassium channels in the CNS and thereby hyperpolarize the cell membranes may be the mechanism for profound decrease in anaesthetic requirements produced by Clonidine. Neuraxial placement of Clonidine inhibits spinal substance P release and nociceptive neuron firing produced by the noxious stimulation. Alpha-2 afferent terminals are situated centrally and peripherally, in the superficial laminae of the spinal cord and several brain stem nuclei. This suggests that Clonidine's analgesic effects are more pronounced after neuraxial administration. Clonidine synchronously decreases the cold response threshold while slightly increasing the sweating threshold thus suggesting that it acts on the central thermoregulatory system rather than preventing shivering peripherally.

Pharmacological effects:

Intravenous Clonidine can cause a transient rise in blood pressure due to its ability to cause vasoconstriction via an alpha-2 agonist effect on vascular smooth muscle of skin and mucosa. This is followed by a decreased blood pressure due

presumably to activation of CNS alpha-2 receptors, resulting in a decreased central outflow of impulses in the sympathetic nervous system, although this is an area of intense current research interest, and some evidence suggests that different mechanisms may be more important. Some of the antihypertensive effect of Clonidine may also be due to diminished release of Norepinephrine at sympathetic postganglionic nerve terminals due to activation of presynaptic alpha-2 receptors.

Pharmacokinetics:

Clonidine is well absorbed orally, and is nearly 100% bioavailable. The mean half life of the drug in plasma is about 12 hours. It is excreted in an unchanged form by the kidney, and its half life can increase dramatically in the presence of impaired renal function. A transdermal delivery system is available in which the drug is released at a constant rate for about a week. Three or four days are required to achieve steady state concentrations.

Side Effects

1. **Body as a Whole :** Weakness, about 10 in 100 patients; fatigue, about 4in 100; headache and withdrawal syndrome each about 1 in 100. Also

reported were pallor; a weakly positive Coombs' test; increased sensitivity to alcohol; and fever.

2. **Cardiovascular :** Orthostatic symptoms, about 3 in 100 patients; palpitations and tachycardia, and bradycardia, each about 5 in 1000. Syncope, Raynaud's phenomenon, congestive heart failure, and electrocardiographic abnormalities (i.e., sinus node arrest, junctional bradycardia, high degree AV block and arrhythmias) have been reported rarely. Rare cases of sinus bradycardia and atrioventricular block have been reported, both with and without the use of concomitant digitalis.

3. **Central Nervous System :** Nervousness and agitation, about 3 in 100patients; mental depression, about 1 in 100 and insomnia, about 5 in 1000. Other behavioral changes, vivid dreams or nightmares, restlessness, anxiety, visual and auditory hallucinations and delirium have rarely been reported.
4. **Dermatological :** Rash, about 1 in 100 patients; pruritus, about 7 in1000; angioneurotic edema and urticaria, about 5 in 1000; alopecia, about 2 in 1000.
5. **Gastrointestinal :** Nausea and vomiting, about 5 in 100 patients; anorexia and malaise, each about 1 in 100; mild transient abnormalities in liver function tests, about 1 in 100; hepatitis, parotitis, constipation, pseudo-obstruction, and abdominal pain, rarely.
6. **Genitourinary :** Decreased sexual activity, impotence and loss of libido, about 3 in 100 patients; nocturia, about 1 in 100; difficulty in micturition, about 2 in 1000; urinary retention, about 1 in 1000.
7. **Hematologic :** Thrombocytopenia, rarely.
8. **Metabolic :** Weight gain, about 1 in 100 patients; gynecomastia, about 1in 1000; transient elevation of blood glucose or serum creatine phosphokinase, rarely.
9. **Musculoskeletal :** Muscle or joint pain, about 6 in 1000 and leg cramps, about 3 in 1000.
10. **Oro-otolaryngeal :** Dryness of the nasal mucosa was rarely reported.
11. **Ophthalmologic:** Dryness of eyes, burning of the eyes and blurred vision were reported.

Drug Interactions :

Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs. If a patient receiving Clonidine hydrochloride is also taking tricyclic antidepressants, the hypotensive effect of Clonidine may be reduced, necessitating an increase in the Clonidine dose.

Due to a potential for additive effects such as bradycardia and AV block, caution is warranted in patients receiving Clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction, e.g., digitalis, calcium channel blockers and beta-blockers.

Amitriptyline in combination with Clonidine enhances the manifestation of corneal lesions in rats (see Toxicology).

Toxicology :

In several studies with oral Clonidine hydrochloride, a dose-dependent increase in the incidence and severity of spontaneous retinal degeneration was seen in albino rats treated for six months or longer. Tissue distribution studies in dogs and monkeys showed a concentration of Clonidine in the choroid.

In view of the retinal degeneration seen in rats, eye examinations were performed during clinical trials in 908 patients before, and periodically after, the start of Clonidine therapy. In 353 of these 908 patients, the eye examinations were carried out over periods of 24 months or longer. Except for some dryness of the eyes, no drug-related abnormal ophthalmological findings were recorded and, according to specialized tests such as electroretinography and macular dazzle, retinal function was unchanged.

In combination with amitriptyline, Clonidine hydrochloride administration led to the development of corneal lesions in rats within 5 days.

Carcinogenesis, Mutagenesis, Impairment of Fertility :

Chronic dietary administration of Clonidine was not carcinogenic to rats (132 weeks) or mice (78 weeks) dosed, respectively, at up to 46 or 70 times the maximum recommended daily human dose as mg/kg (9 or 6 times the MRDHD on a mg/m^2 basis). There was no evidence of genotoxicity in the Ames test for mutagenicity or mouse micronucleus test for clastogenicity.

Fertility of male or female rats was unaffected by Clonidine doses as high as 150 mcg/kg (approximately 3 times MRDHD). In a separate experiment, fertility of female rats appeared to be affected at dose levels of 500 to 2000 mcg/kg (10 to 40 times the oral MRDHD on an mg/kg basis; 2 to 8times the MRDHD on an mg/m^2 basis.)

Over dosage :

Hypertension may develop early and may be followed by hypotension, bradycardia, respiratory depression, hypothermia, drowsiness, decreased or absent reflexes, weakness, irritability and miosis. The frequency of CNS depression may be higher in children than adults. Large overdoses may result in reversible cardiac conduction defects or dysrhythmias, apnea, coma and seizures. Signs and symptoms of overdose generally occur within 30 minutes to two hours after exposure. As little as 0.1 mg of Clonidine has produced signs of toxicity in children.

Antidote:

There is no specific antidote for Clonidine over dosage. Clonidine over dosage may result in the rapid development of CNS depression; therefore, induction of vomiting with ipecac syrup is not recommended. Gastric lavage may be indicated following recent and/or large ingestions. Administration of activated charcoal and/or a cathartic may be beneficial. Supportive care may include atropine sulfate for

bradycardia, intravenous fluids and/or vasopressor agents for hypotension and vasodilators for hypertension. Naloxone may be a useful adjunct for the management of Clonidine-induced respiratory depression, hypotension and/or coma; blood pressure should be monitored since the administration of naloxone has occasionally resulted in paradoxical hypertension. Tolazoline administration has yielded inconsistent results and is not recommended as first-line therapy. Dialysis is not likely to significantly enhance the elimination of Clonidine.

Available forms:

Clonidine is available as tablets, injections and transdermal patches as in table.

Table – B : Available formulations of Clonidine

Formulations	Generic / Brand	Available Dosage/ Strength
Oral tablets	Clonidine tablets	0.1, 0.2 and 0.3 mg
Transdermal patches	Clonidne-TTS(Catapress)	0.1, 0.2 and 0.3g 3 mg/ 24hrs.
Combination tablets	Clonidine and chlorthalidone	0.1, 0.2 or 0.3 mg Clonidine+15mg chlorthalidone.
Injection	Cloneon , Duraclon	500, 150, 100 mcg/ml

Table – C : Various roots and doses of Clonidine

Route	Dose
Intranasal	2-4 mcg/kg
Intramuscular	2mcg/kg
Oral	4-5 mcg/kg
Rectal	2.5-5 mcg/kg with atropine 40 mcg/kg
Intravevous	1-2 mcg/kg bolus or 0.18-3.16 mcg/kg/hr infusion.
Caudal anesthetic adjuvant	1-2 mcg/kg
Spinal anesthetic adjuvant	1-2 mcg/kg
Epidural anesthetic adjuvant	00.0625% Bupivacaine with fentanyl 1 mcg/ml and Clonidine 0.6 mcg/ml
Sciatic block	0.2% Ropivacaine 0.4mg/kg/hr with Clonidine 0.12 mcg/kg/hr infusion.

Anaesthetic use of Clonidine:

The anaesthetic use of an alpha-2 adrenergic receptor agonist has been of considerable and prolonged interest over the last 20 years. Clonidine is the archetype of this class of drugs. Though it is not the most selective acting drug, its use in anesthetics is getting familiar by the day. The different sedative, haemodynamic and analgesic action of the drug is however confusing. Presently there is a plethora of evidence available to us describing its use in clinical anaesthetic purpose. Based on this evidence it might be prudent to argue that it is a valuable agent available in the anaesthetic armamentarium.

1. Premedication:

Clonidine causes sedation by stimulation of the locus ceruleus, a nucleus of the medulla involved in the sleep wake cycle. Sedation is by the stimulation of specific alpha-2 receptors coupled with a G protein, leading to cell membrane hyperpolarisation. The sedative effect can be useful when Clonidine is used as a premedicant. In addition it also has an anaesthesia- sparing effect. Alpha-2 adrenergic agonists reduce the dose of intravenous hypnotics and also reduce the MAC of the volatile anaesthetic agents. Clonidine has been recommended in doses of e in doses of 4 mcg/kg orally or intranasally and in doses of 5µg/kg rectally provides adequate sedation. Routine atropine administration along with Clonidine negates the adverse effects like bradycardia and hypotension.

However, one needs to cautious with the dosages of the IV induction agents when Clonidine has been used as a premedicant. Their dosages need to be reduced. Otherwise there is a propensity for the increased incidence of hypotension after induction and increased incidence of bradycardia during anaesthesia.

Its use as a premedicant is particularly useful in certain subgroup of patients like

a. Drug addicts and alcoholics who give problems like withdrawal symptoms and risk of increased sympathetic activity especially in cocaine users.
b. Chronic pain and palliative care patients who often receive large doses of opioids and therefore have large perioperative opioid needs. This can be reduced with Clonidine premedication.
c. Hypertensive patients who are particularly vulnerable to blood pressure swings. Premedication with Clonidine is useful, though very underutilized means of reducing the haemodynamic hyperactivity.

2. Control of haemodynamic response:

The haemodynamic effects of alpha-2 adrenergic agonists are both central and peripheral. Stimulation of the peripheral sub endothelial receptor causes vasoconstriction. This action is however transient.

However, stimulation of the alpha -2 adrenergic receptors of the neurons in the nucleus tractus solitarius causes inhibition of the nucleus of the sympathetic neurons in the medulla. By this mechanism, alpha adrenergic agonists reduce the tonic activity of the baroreflex, decreasing atrial pressure and causing bradycardia. It is interesting to note that the phasic activity of the baroreflex is preserved or perhaps even improved, so that any decrease in arterial pressure is followed by a significant increase in heart rate. In addition alpha-2 adrenergic agonists depress presynaptic sympathetic neurons in the lateral horn of the thoracic spinal cord. It should be noted here that this effect is reversed by the local administration of cholinesterase inhibitor neostigmine. It is a result of this modality of action that intrathecal administration of Clonidine causes more profound hypotension than after intravenous administration. Hypotension and bradycardia caused by Clonidine need to be reversed by fluids, vasoconstrictors (eg: Phenylephrine) and atropine respectively. Large doses may be needed.

Clonidine prevents hypertension and tachycardia during laryngoscopy and intubation as well as during surgical stimulation. During recovery from anaesthesia Clonidine also prevents tachycardia and hypertension, decrease the incidence of shivering and reduce VO_2 to control postoperative shivering it is given in 50mcg doses. Doses up to 150mcg have been reported to control postoperative shivering in 90% of patients within 5 minutes. Patients undergoing cardiac surgery and vascular surgery have superior control of haemodynamics and reduced incidence of myocardial

ischemia in patients who have been pretreated with Clonidine. Patients with coronary artery disease undergoing major vascular surgical procedures, Clonidine has been found to decrease both morbidity and mortality.

3. Postoperative analgesia and Regional Anaesthesia :

Alpha -2 adrenergic agonists inhibit transmission of nociceptive stimuli in the dorsal horn of the spinal cord. Their effects mimic that of noradrenalin released by the inhibitory descending pathways. Noradrenalin inhibits the evoked activity of the wide dynamic range neurons and causes analgesia in laboratory animals. Clonidine increases the analgesic effect of opiates and interacts with cholinergic neurons to do so. They augment local anaesthetic blockade and prolong duration.

A. Central Neuraxis Blocks:

a. **Epidural:** Because of its action in the spinal cord, Clonidine has been given both intrathecally as well epidurally. If used as a sole agent to produce epidural analgesia large doses (up to 2 - 3000 mcg/ day) are needed to produce long term analgesia. At these doses significant sedation, bradycardia, hypotension are common. Thus its use as a sole is not popular at all. It is used more commonly as a combination with opioids and or local anesthetics to provide good to excellent analgesia with minimal side effects. The dose in combination with other agents is limited to 10 - 15 mcg / hour.

b. **Spinal:** Compared to morphine, intrathecal Clonidine produces analgesia of shorter duration but without the associated risk of respiratory depression or urinary retention. In association with local anesthetics the maximum dose of intrathecal Clonidine is 1-2 mcg/ kg. Giving Clonidine with local

anesthetics improves the quality and duration of the block, minimizes the tourniquet pain during lower limb surgery, and prevents shivering.

c. **Caudal:** Caudal Clonidine combined with local anesthetics inchildren potentially very useful and increases the duration of anaesthesia and analgesia by a factor of 2 or 3 without haemodynamic side effects. The dosage recommended in the caudalroute is 1-2 mcg / kg.

Epidural Clonidine has also been suggested for use in labour analgesia. Clonidine has been given alone or in combination with sufentanil and Bupivacaine. Clonidine does cross the placental barrier but no adverse events have been documented in the newborns. To avoid hypotension and bradycardia in the foetus as well, the recommended dose of Clonidine has been suggested as 100 mcg during labour.

B. Peripheral Nerve Blocks:

Clonidine is commonly used as an adjuvant to local anesthetics in peripheral nerve blocks where it prolongs the duration of anaesthesia as well analgesia. This effect is obtained at relatively small doses (2 - 3 mcg/kg) which obviously reduce the risks of side effects. Adding Clonidine gives very good quality of analgesia after lower limb surgery with the duration of analgesia lasting beyond 24 hours.

The quality of intravenous regional anaesthesia (IVRA) or Bier's block produced by Lignocaine is improved by the addition of Clonidine. Addition of 150 mcg Clonidine has been found to enhance the tolerance of the tourniquet.

Intraarticular analgesia has also been shown to be improved with Clonidine. The results are similar to the ones found with intraarticular morphine.

Clonidine thus has wide applications as an adjunct to local anesthetics in peripheral regional blocks.

Other uses are:

1.Prevention of emergence agitation:

In children who were given Clonidine had less perioperative sympathetic stimulation and postoperative pain as compared to children who were given midazolam .

2. Decreasing Minimum Alveolar Concentration (MAC) of sevoflurane:

Studies have found that oral Clonidine 4 mcg/kg given 105 minutes before induction decreased MAC values of sevoflurane for LMA insertion. The combination of Clonidine and nitrous oxide lessened the MAC of sevoflurane more than that achieved by either drug alone .

3. Postoperative nausea and vomiting (PONV):

Studies has shown that premedication with 4mcg/kg of oral Clonidine 105 minutes before paediatric strabismus surgery enhances the antiemetic effect of propofol when compared with oral midazolam 0.4 mg/kg . Both oral and caudal Clonidine has been reported to reduce the incidence of postoperative vomiting in children.

4. Controlled hypotension:

In adolescents aged 10 – 16 years, oral Clonidine 5 mcg/kg on the night before surgery and 90 minutes before a major oromaxillofacial surgery reduced the dose of anaesthetics, analgesics, hypotensive agents and provided faster recovery from anaesthesia. It also reduced the fluctuations in blood pressure and heart rate perioperatively.

6. In cardiovascular surgery:

Intravenous Clonidine 0.18 to 3.16 mcg/kg/hr was found to be an effective analgesic, sedative and it ensured haemodynamic stability by decreasing withdrawal symptoms like CNS hyperactivation, hypertension, tachycardia and fever following surgery to correct congenital heart defects in infants aged 0–24 months. There was an age related

normalized profile of the haemodynamic parameters with a reduction in heart rate and mean arterial pressure from the upper norm to the mean within 24 hours. In no case, was there a fall in blood pressure which required additional therapy to reach the target blood pressure.

7. Post operative shivering:

Clonidine is effective in treating post operative shivering in children. In a study Clonidine prevented postoperative shivering when compared to midazolam. Extrapolation from adult data revealed that a dose of 1.5 mcg/kg is required to stop shivering in 5 minutes after drug administration.

8. Daycare Surgery:

Oral Clonidine premedication and new safer local anaesthetics like ropivacaine and levobupivacaine with adjunvants like Clonidine or ketamine for regional blocks and single caudal shots prolong analgesia with minimal side effects.

9. Attenuation of response to tracheal intubation and extubation:

It was found that children premedicated with rectal Clonidine 2.5 mcg/kg did not have a rise in neuropeptide Y, a marker of major adrenergic activation during tracheal intubation, compared to those who received midazolam 300 mcg/kg. It was also found that oral Clonidine 4 mcg/kg given 105 minutes before induction attenuated hemodynamic changes associated with tracheal extubation.

9. Anaesthetic sparing effect:

Oral Clonidine premedication at a dose of 2-4 mcg/kg decreases the dose of intravenous barbiturate required for induction of anaesthesia and also reduces halothane requirement for maintenance of anaesthesia.

10. Treatment of spasticity:

Clonidine is used in children diagnosed with cerebral palsy or traumatic brain injury.

Contraindications to the use of Clonidine:

1. Hypovolemia,
2. A-V block,
3. Prolonged P-R interval and
4. Spontaneous bradycardia.

METHODOLOGY

SOURCE OF DATA:

The present study was carried out in the Department of Anaesthesiology, B.L.D.E. University's Shri B.M Patil Medical College, Hospital and Research Centre, Vijayapur. The study was conducted after obtaining clearance from ethical committee of institution. Informed consent was taken from all patients who participated within the study.

METHOD OF COLLECTION OF DATA:

Study Design: Randomized clinical trial.

Study Period: One and half year from December 2014 to June 2016.

Sample Size: At 5% level of significance and power of 80%; anticipated mean difference of onset of sensory blockade between two comparison groups = 1.9 min and anticipated standard deviation is 3.9 min .

Using the formula

$$n = \frac{(Z_\alpha + Z_\beta)^2 \times 2 \times SD^2}{MD^2}$$

the total sample size is 48 + 48 = 96

where,

Z_α - Z statistic for α level of confidence

Z_β – Z statistic for β level of confidence

SD – Standard deviation

MD – Mean deviation

Inclusion criteria :

- ASA Class I & II
- Age between 20 to 60 years.

Exclusion criteria :

- Patients belonging to ASA Class III & IV.
- Known cause of hypersensitive reaction to Clonidine.
- Patients with medical complications like severe anemia, severe hypovolemia, shock, septicemia.
- Abnormal BT, CT or on anticoagulant therapy.
- Local infection at the site of proposed puncture for supraclavicular block.

Investigations Required :

- Hb%, TC, DC, BT, CT.
- Urine routine
- RBS, Blood urea and serum creatinine
- Chest x-ray, ECG
- HIV, HBsAg

Preliminaries :

- Written informed consent.
- Intravenous access with a 20 guage I.V cannula on the contralateral upper limb under aseptic techniques.

Randomization :

A prospective, randomized, single blinded study was undertaken. 96 patients posted for upper limb surgeries under supraclavicular block were randomly divided into 2 groups, each containing 48 patients by computer generated randomization number.

- Control group - Group-B: Received 30 ml Bupivacaine (0.375%)
- Study group - Group BC: Received 30 ml of mixture of Bupivacaine (0.375%) and Clonidine (1μ/kg).

Equipments :

SonoSite M Turbo Ultrasound Machine

a) For the procedure :

A portable tray covered with sterile towels containing :

- Sterile syringes - one 20ml and one 10ml.
- Hypodermic needles of 5 cm length, 22 G.
- Bowl containing Povidone iodine and spirit.
- Sponge holding forceps.
- Towels and towel clips.
- Sterile gauze pieces.

b) For emergency resuscitation :

- The anaesthesia machine, emergency oxygen source (E type cylinders), pipeline O_2 supply, working laryngoscopes, appropriate size endotracheal tubes and connectors.
- Working suction apparatus with suction catheter.
- Oropharyngeal airways.
- Intravenous fluids.
- Drugs : Thiopentone, Diazepam, Succinylcholine, Hydrocortisone, Atropine, Adrenaline, Aminophylline, Mephenteramine, Calcium gluconate and Sodium bicarbonate.

c) Monitors :

- Pulse oximeter.
- Non invasive blood pressure monitor by sphygmomanometer on the opposite upper limb.

PROCEDURE: After the patient was taken on the operating table, intravenous access secured in the upper limb opposite to that undergoing surgery with a large bore i.v. cannula. Standard multi parameter monitor, ECG, pulse oximeter, non invasive blood pressure were connected and monitored in all the patients.

POSITIONING: Patient was placed in supine position with the head turned away from the side to be blocked. Arm to be anaesthetized adducted and extended towards the ipsilateral knee as far as possible which will depress the clavicle slightly and allow better access to the structures of the anterolateral neck. Also, a slight elevation of the head of the bed is often more comfortable for the patient and allows for better drainage and less prominence of the neck veins.

IMAGE ACQUISITION: With the patient in proper position the supraclavicular area is aseptically prepared and draped and a linear 38-mm, high frequency 10-15 MHz transducer is placed firmly over the supraclavicular fossa in the coronal oblique plane to obtain the best possible transverse view of the subclavian artery and brachial plexus. Nerves in the supraclavicular region appear hypo-echoic and are round or oval. The brachial plexus is located lateral and superficial to the pulsatile subclavian artery and superficial to the first rib. The subclavian artery is identified first, subclavian vein lies more medially. The first rib is identified as a hyper-echoic structure lying deep to the vessels, and giving a bony shadow. The brachial plexus is consistently found lateral and superficial to the subclavian artery and above the first rib.

NEEDLE PLACEMENT: For the in plane approach (lateral to medial) a 5 cm 22G insulated block needle is inserted under sterile conditions on the outer (lateral) end of the ultrasound transducer (5-12 or 6-13 MHz) after skin local anaesthetic infiltration. The brachial plexus is identified as a compact group of nerves, sometimes compared to a 'bunch of grapes', located over the first rib, lateral and superficial to the subclavain artery. The rib and pleura are identified before needle insertions. The needle is advanced along the long axis of the transducer in the same plane as the ultrasound beam.

This way the needle shaft and tip can be visualized in real time as the needle is advanced towards the target nerves. The identity of the nerves may be confirmed by electrical stimulation if desired. Useful stimulation endpoints for surgery proximal to elbow are biceps and triceps twitches; hand muscle twitches are more appropriate for surgery distal to the elbow. After negative aspiration for blood, 30 ml of respective local anaesthetic drug was injected depending on whether patient is allotted to either of group B or BC so as to cause hydro dissection of the planes around the plexus. Local anaesthetic spread is observed during injection and the needle repositioned to ensure distribution around all the nerve trunks and divisions within the plexus sheath. No sign of local anaesthetic spread may indicate intravascular injection and so care must be taken when this occurs to re-identify the needle tip before further local anaesthetic injection.

In plane (medial to lateral) approach may also be used based on user comfort. Inj. Bupivacaine 0.25% 5ml will be given to block intercostobrachial nerve (T_2) to avoid tourniquet pain.

Onset of sensory blockade, onset of motor blockade, duration of sensory blockade, duration of motor blockade and any adverse effects were noted.

Sensory block was evaluated by temperature testing using spirit soaked cotton on skin dermatomes C_4 to T_2 where as motor block was assessed by asking the patient to adduct the shoulder and flex the forearm against gravity.

Onset of sensory block was defined as the time elapsed between injection of drug and complete loss of cold perception of the hand, while onset of motor blockade was defined as the time elapsed from injection of drug to complete motor block.

Fig 5 : Drugs used for study.

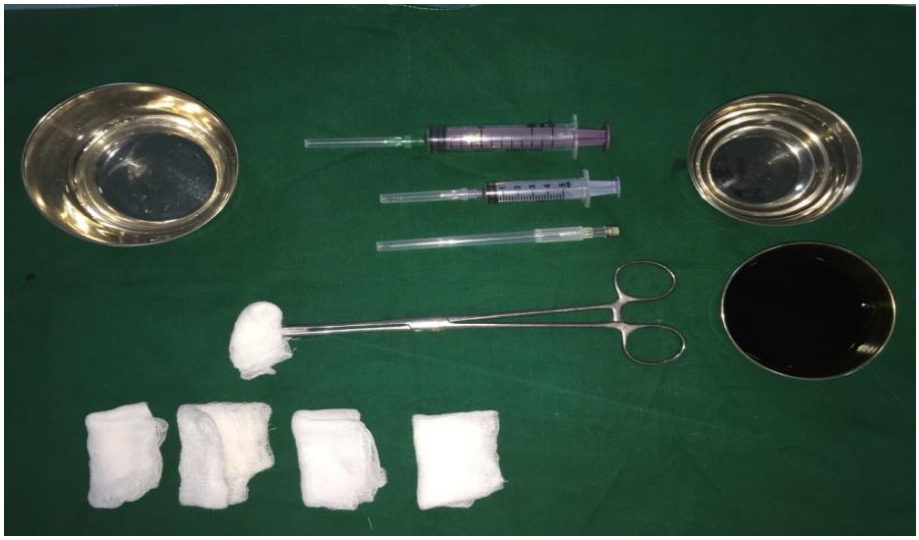


Fig 6 : Sterile tray containing drug and equipments.

Fig 7 : SonoSite M-Turbo Ultrasound Machine

Fig 8: Position of the patient used for usg guided brachial plexus block

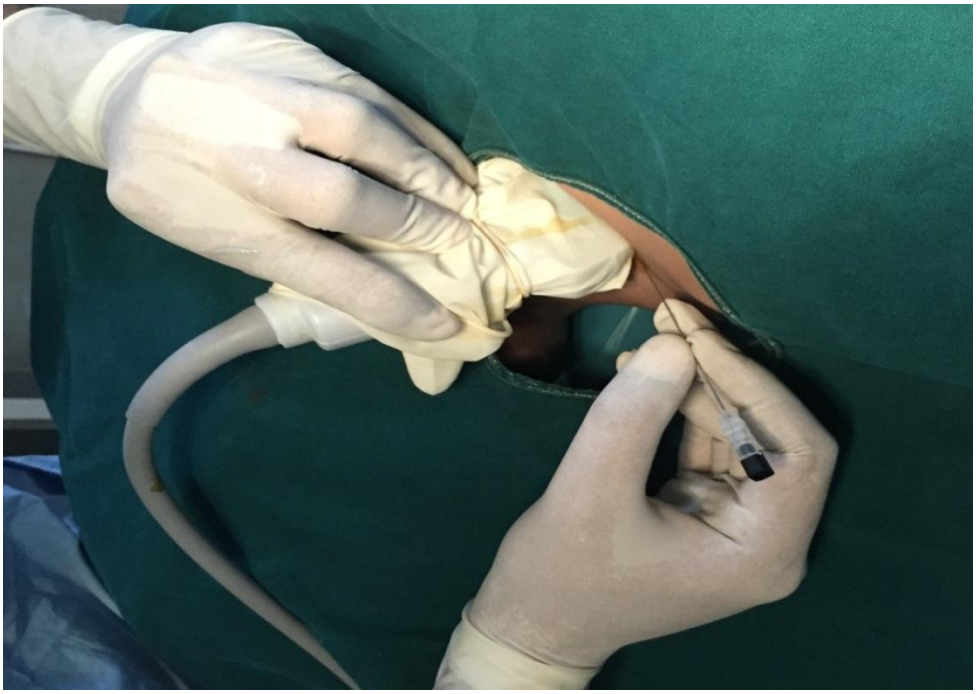


Fig. 9: Ultrasound probe placed in oblique coronal plane and needle insertion.

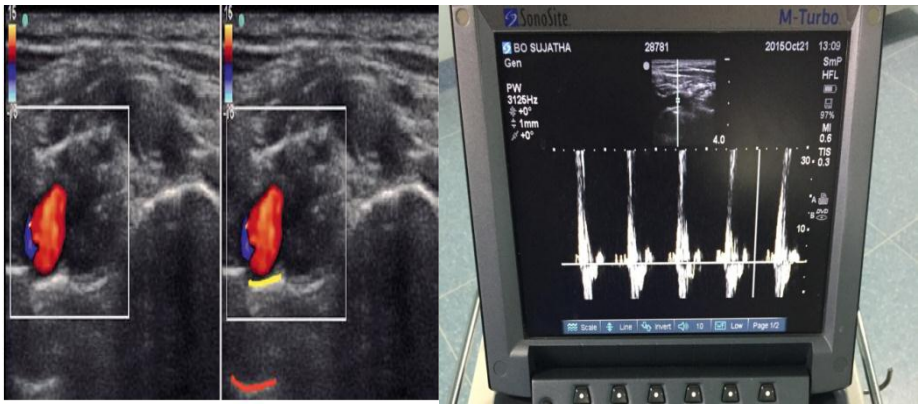


Fig.10: Doppler for identification of vessels. Indicated for both initial identification of subclavian vessels and aberrant vessels traversing the plexus before choosing the needle trajectory.

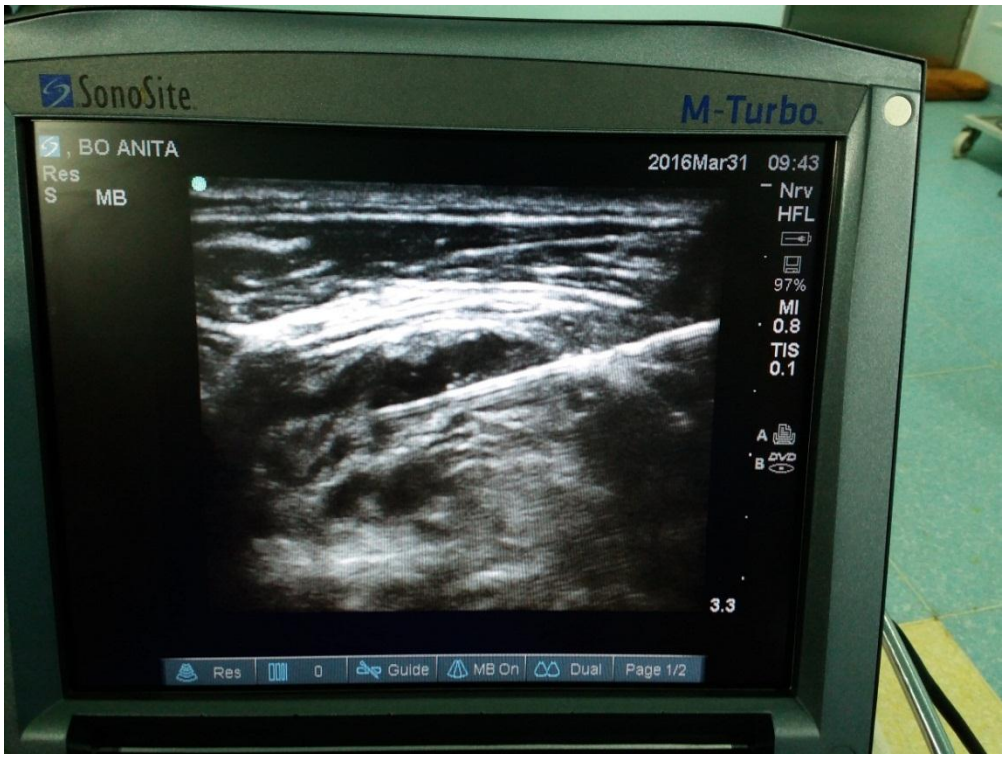


Fig 11 : Showing whole length of needle near the bracheal plexus

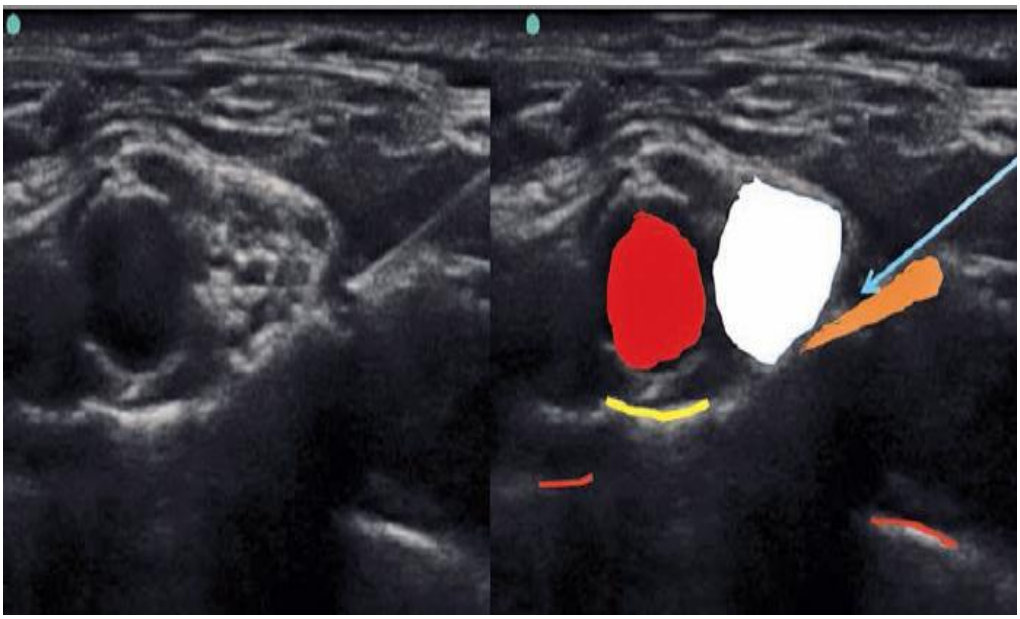


Fig.12 : Scout scan of supraclavicular fossa and needle insertion in plane. Red area: subclavian artery, white area: brachial plexus, yellow line: periostium of first rib, orange line: periostium of clavicle, red line: pleura, blue arrow: needle.

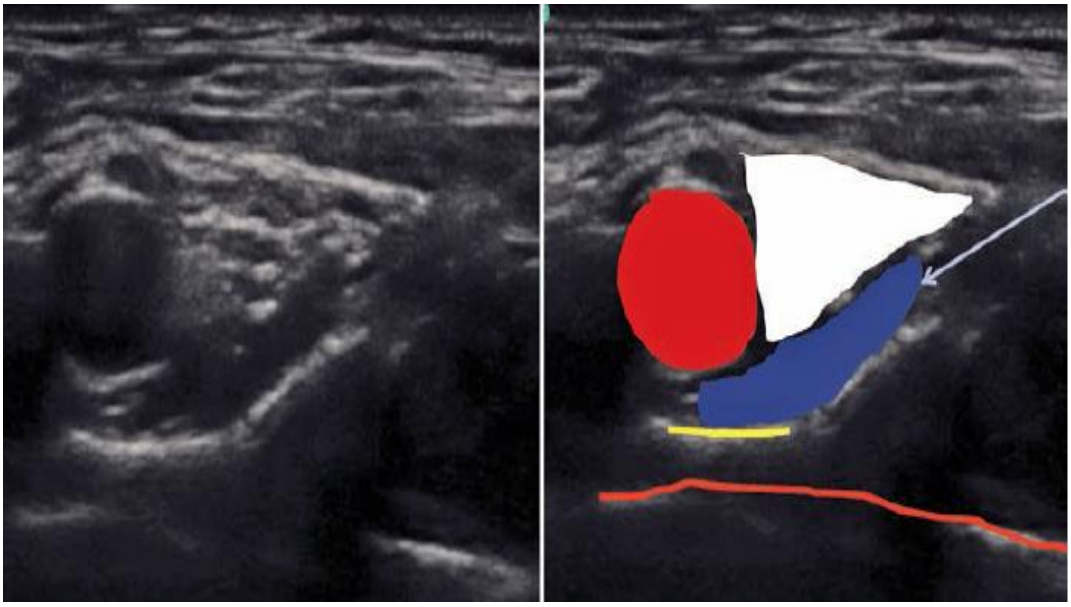


Fig.13: Spread of local anaesthetic solution deep to the plexus. Red area: subclavian artery, white area: brachial plexus, yellow line: periostium of first rib, red line: pleura, blue arrow: needle, navy area: local anaesthetic.

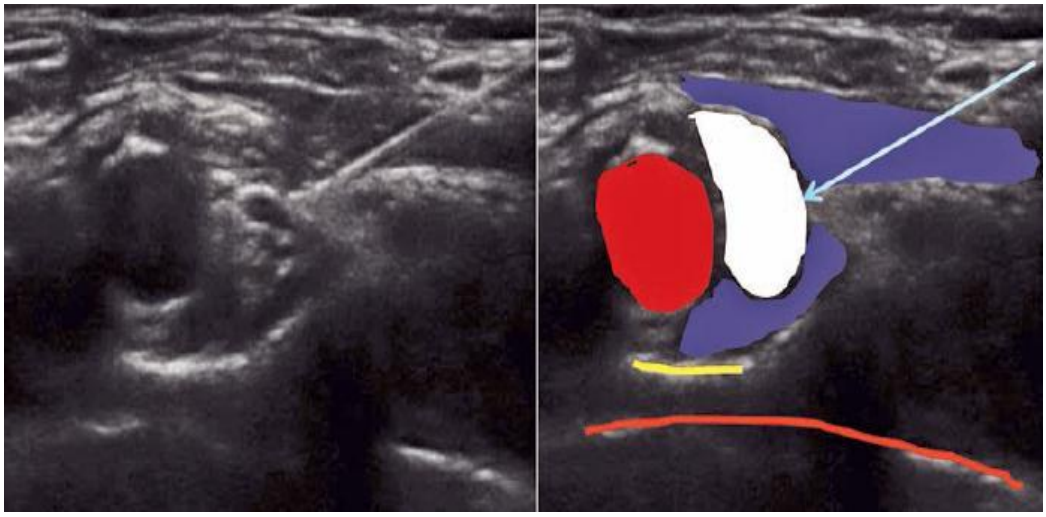


Fig.14: Spread of local anaesthetic solution superficial to the plexus. Red area: subclavian artery, white area: brachial plexus, yellow line: periostium of first rib, red line: pleura, blue arrow: needle, navy area: local anaesthetic.

ASSESSMENT OF SENSORY BLOCK

Sensory block was assessed by pin prick with 23 guaze hypodermic needle in skin dermatomes C_4-T_2 once in every minute for initial 30 minutes and then after every 30 minutes till patient regained normal sensations and graded according to Visual analogue scale (VAS) as

0-No Pain

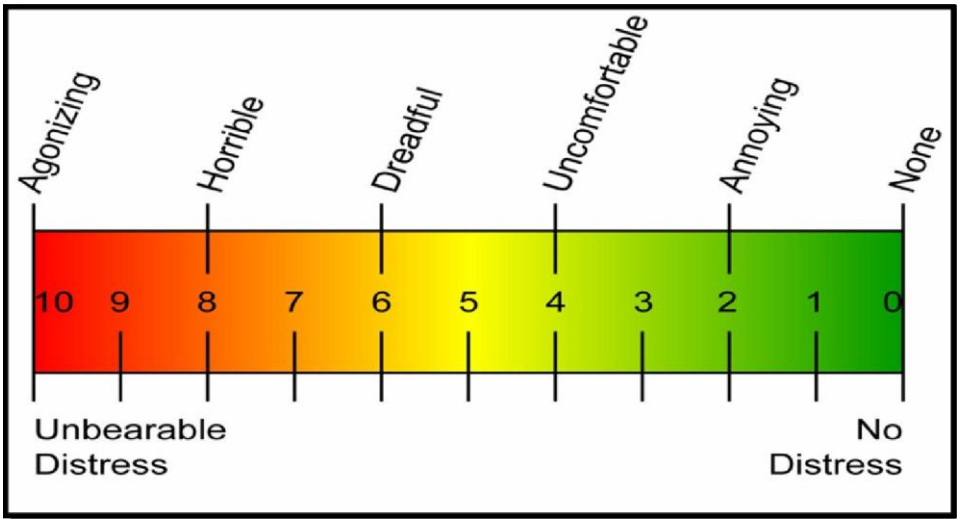
2-Annoying (Mild pain)

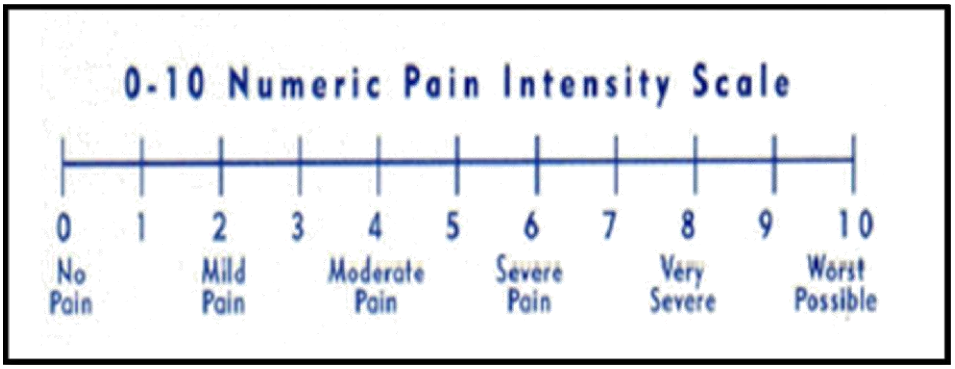
4-Uncomfortable (Moderate pain)

6-Dreadful (Severe pain)

8-Horrible (Very severe pain)

10-Agonizing (Worst possible pain)





ASSESSMENT OF MOTOR BLOCK

Quality of motor block was assessed at the same intervals and graded according to Modified Lovett's Scoring as

Grade 6- Normal

Grade 5 –slightly reduced muscular force

Grade 4 – pronounced reduction.

Grade 3 – slightly impaired mobility.

Grade 2 – pronounced mobility impairment.

Grade 1 – Almost complete paralysis

Grade 0– Complete paralysis.

The effect on the following parameters were observed :

Onset of motor blockade- time taken from the completion of injection of studydrug till the patient develops motor blockade.(Lovett"s Grade 1)

Onset of sensory blockade- time taken from the completion of injection of studydrug till the patient does not feel the pin prick.(Visual analogue scale score -0)

Duration of motor blockade- time taken from the onset of motor blockade tillcomplete recovery of motor power. (Lovett's grade 6)

Duration of sensory blockade – time taken from the onset of sensory blockade till thepatient feels pin prick. (visual analogue scale of 2)

- Patients were watched for bradycardia, convulsions, restlessness, disorientation, drowsiness, nausea, vomiting & any other complications.
- All the values were expressed as Mean ± Standard deviation, statistical comparison was performed by student's t-test & chi-square test.
- A two tailed P value of >0.05 was considered to be statistically not significant, < 0.05 as statistically significant, < 0.01 as statistically highly significant.

- IM injection of Diclofenac sodium would be given as rescue analgesic when patients complains of pain.
- Number of rescue analgesics in 24 hours of post-operative period would also be recorded.

Sedation score described by University of Michigan Sedation Scale(UMSS)[38] would be used to assess sedation.

1 – Awake & Alert.

2 – Minimally Sedated: tired/sleepy, responding to verbal stimulus.

3 – Moderatly Sedated: somnolent/sleeping, responding to mild physical stimulus.

4 – Deeply Sedated: deep sleep, responding to moderate to severe physical stimulus.

5 – Unarousable.

RESULTS

Nintey six ASA I and II of either sex aged between 20-60 years, posted for upper limb surgeries under supraclavicular brachial plexus block were selected for the study. The study was undertaken to evaluate the efficacy of Clonidine (1µg/kg) as adjuvant to Bupivacaine (0.375%) in comparison with plain Bupivacaine (0.375%) for brachial plexus block by supraclavicular approach.

Table 1 : Mean Distribution of age among study groups

AGE (Yrs)	BUPIVACAINE		BUP+CLONIDINE		t value	Mean Difference	p value	95% CI	
	Mean	SD	Mean	SD				Lower	Upper
	39.44	12.68	36.73	11.96	1.08	2.71	0.284	-2.29	7.70

The minimum age of the patient was 20 years and maximum age was 60 years. The mean age of patients in group BC was 36.73 ± 11.96 and in group B 39.44 ± 12.68 years .Age incidence between two groups were comparable.

Graph 1: Mean Distribution of age among study groups

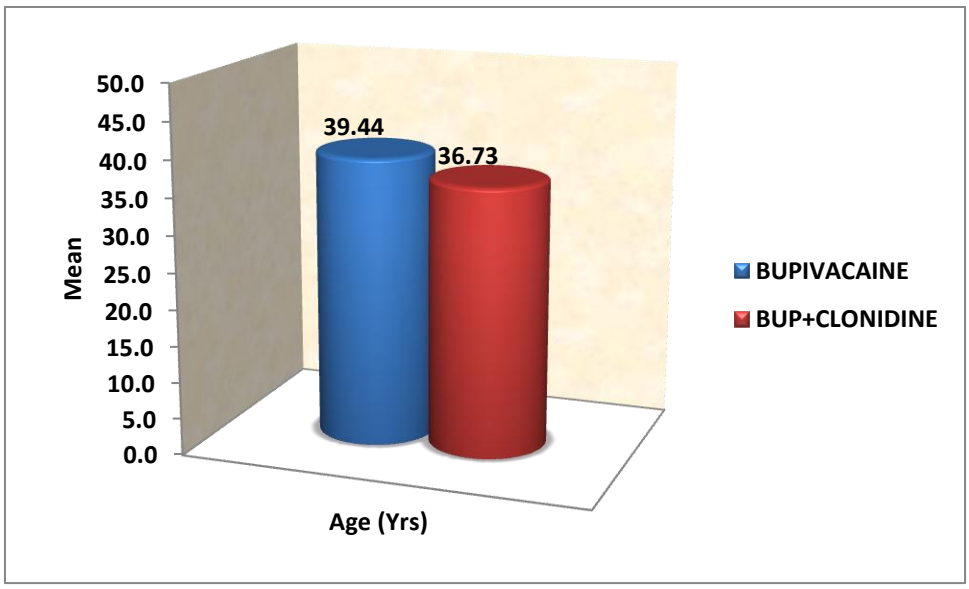


Table 2 : Percent Distribution of age among study groups

Age groups (Yrs)	BUPIVACAINE		BUP+CLONIDINE		Total		Chi square p value
	N	%	N	%	N	%	
20-30	14	29.20%	18	37.50%	32	33.30%	0.516
31-40	10	20.80%	13	27.10%	23	24.00%	
41-50	11	22.90%	9	18.80%	20	20.80%	
51-60	13	27.10%	8	16.70%	21	21.90%	
Total	48	100.00%	48	100.00%	96	100.00%	

From above table we can tell that

There are 11 pateints in Group B and 18 patients in Group BC between the age group 20-30 years.

There are 10 pateints in Group B and 13 patients in Group BC between the age group 31-40 years.

There are 11 pateints in Group B and 9 patients in Group BC between the age group 41-50 years.

There are 13 pateints in Group B and 8 patients in Group BC between the age group 51-60 years.

Graph 2 : Percent Distribution of age among study groups

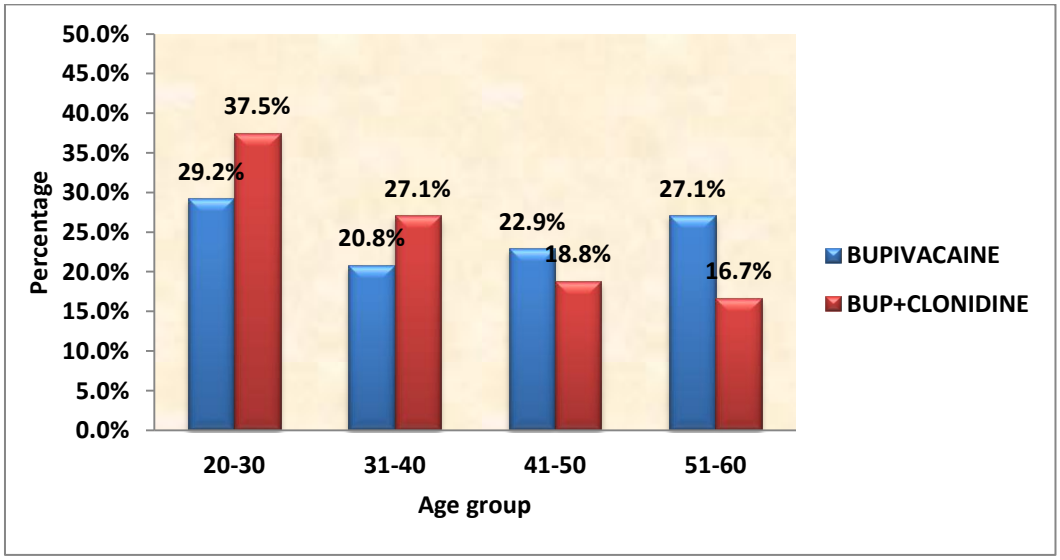


Table 3 : Percent Distribution of Sex among study groups

Sex	BUPIVACAINE		BUP+CLONIDINE		Total		Chi square p value
	N	%	N	%	N	%	
Male	26	54.20%	30	62.50%	56	58.30%	0.408
Female	22	45.80%	18	37.50%	40	41.70%	
Total	48	100.00%	48	100.00%	96	100.00%	

Percentage of male and female patients in Group B was 54.20% and 45.80%, in Group BC was 62.50% and 37.50% respectively. p value was not significant. Hence sex distribution between two groups were not comparable.

Graph 3 : Percent Distribution of Sex among study groups

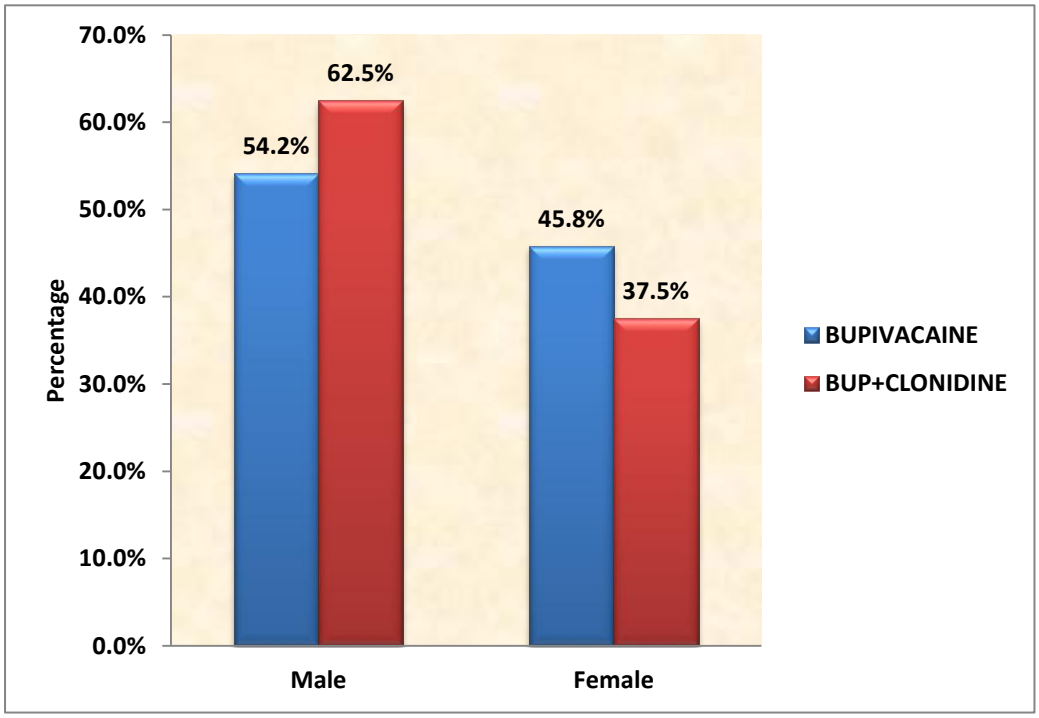


Table 4 : Mean Distribution of Onset of Block among study groups

	BUPIVACAINE		BUP+CLONIDINE		t value	Mean Difference	p value	95% CI	
	Mean	SD	Mean	SD				Lower	Upper
SENSORY (min)	19.60	1.62	11.10	1.26	28.70	8.50	<0.001*	7.91	9.09
MOTOR (min)	14.77	1.56	9.92	1.27	16.72	4.85	<0.001*	4.28	5.43

*Statistically significant at 5% level of significance

The onset of sensory block in group BC was **11.10 ± 1.26** min and in group B was **19.60 ± 1.62** min. The statistical analysis by student's unpaired 't' test showed that, the time for onset of sensory block in group BC was significantly faster when compared to group B (P< 0.001).

The onset of motor block in group BC was **9.92 ± 1.27** min and in group **14.77 ± 1.56** min. The statistical analysis by unpaired student's 't' test showed that, the time for onset of motor block was significantly faster when compared to group B (P< 0.001).

Graph 4 : Mean Distribution of Onset of Block among study groups

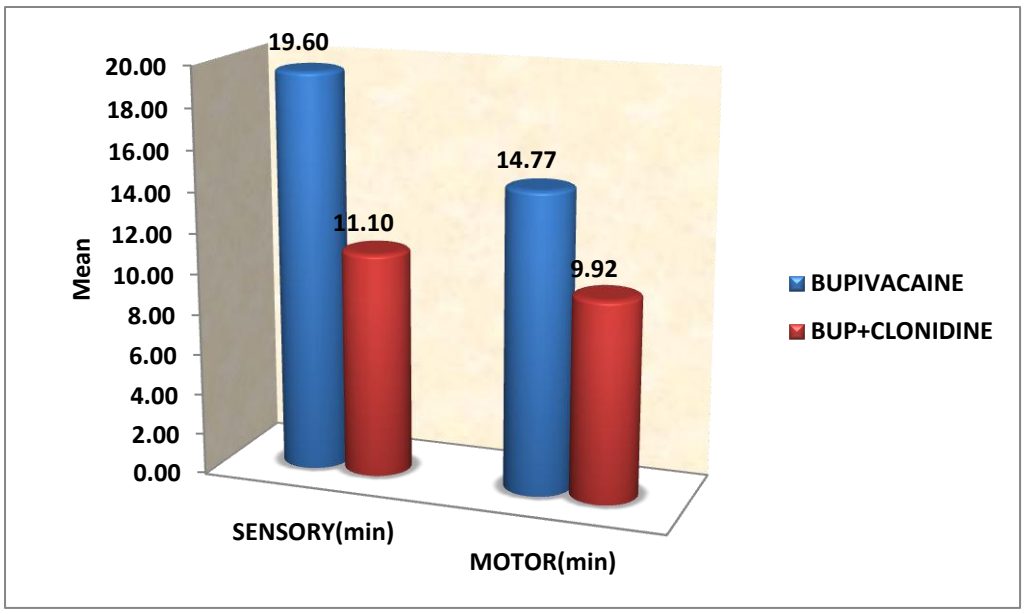


Table 5 : Mean Distribution of Duration of Block among study groups

	BUPIVACAINE		BUP+CLONIDINE		t value	Mean Difference	p value	95% CI	
	Mean	SD	Mean	SD				Lower	Upper
SENSORY(hr)	5.82	0.49	12.88	0.95	-45.76	7.06	<0.001*	-7.36	-6.75
MOTOR(hr)	5.13	0.44	7.86	0.44	-30.17	2.73	<0.001*	-2.91	-2.55

*Statistically significant at 5% level of significance

Patients of both groups were observed for 24 hours. Time was noted when the patient asked for rescue analgesics. The mean duration of sensory block in group BC was **12.88 ± 0.95** hours and in group B was **5.82 ± 0.49** hours. The statistical analysis by students unpaired 't' test showed that the duration of sensory block in group BC was significantly longer when compared to group B (P < 0.001).

The mean duration of motor block in group BC was **7.86 ± 0.44** hours and in group B was **5.13 ± 0.44** hours. The statistical analysis by students unpaired 't' test showed that the difference between duration of motor block in group BC was significantly longer when compared to group B (P < 0.001).

Graph 5 : Mean Distribution of Duration of Block among study group

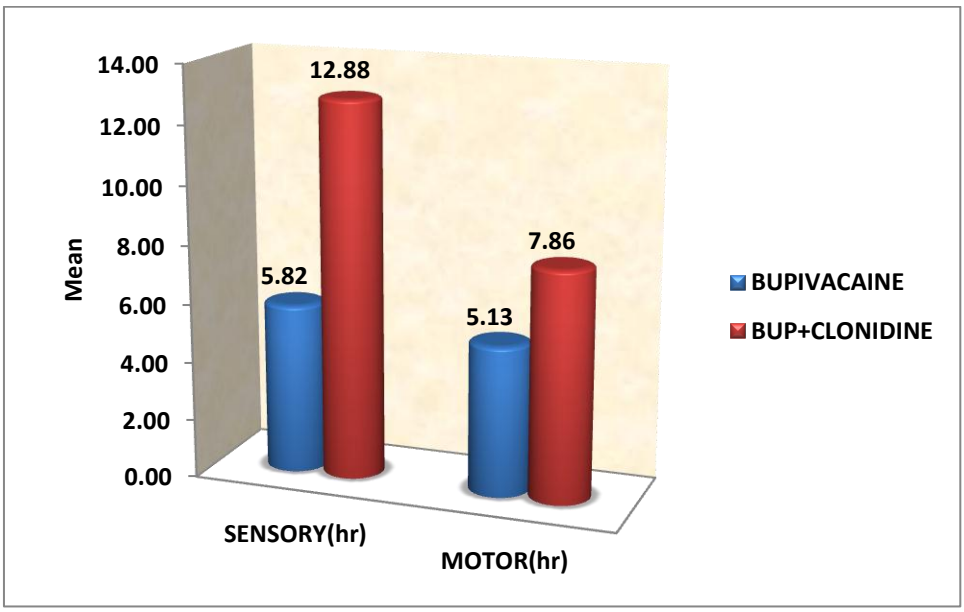


Table 6 : Mean Distribution of Number of rescue analgesic among study groups

	BUPIVACAINE		BUP+ CLONIDINE		t value	Mean Difference	p value	95% CI	
	Mean	SD	Mean	SD				Lower	Upper
NO OF RA IN 24HRS	2.33	0.48	1.27	0.45	11.24	1.06	<0.001*	0.87	1.25

*Statistically significant at 5% level of significance

The mean of number of rescue analgesic required in post –operative period for 24 hrs in group BC was 1.27 ± 0.45 and in group B was 2.33 ± 0.48. The statistical analysis by students unpaired 't' test showed that the difference between number of rescue analgesics in post-op 24hr in group BC was lesser when compared to group B (P < 0.001).

Graph 6 : Mean Distribution of Number of rescue analgesic among study groups

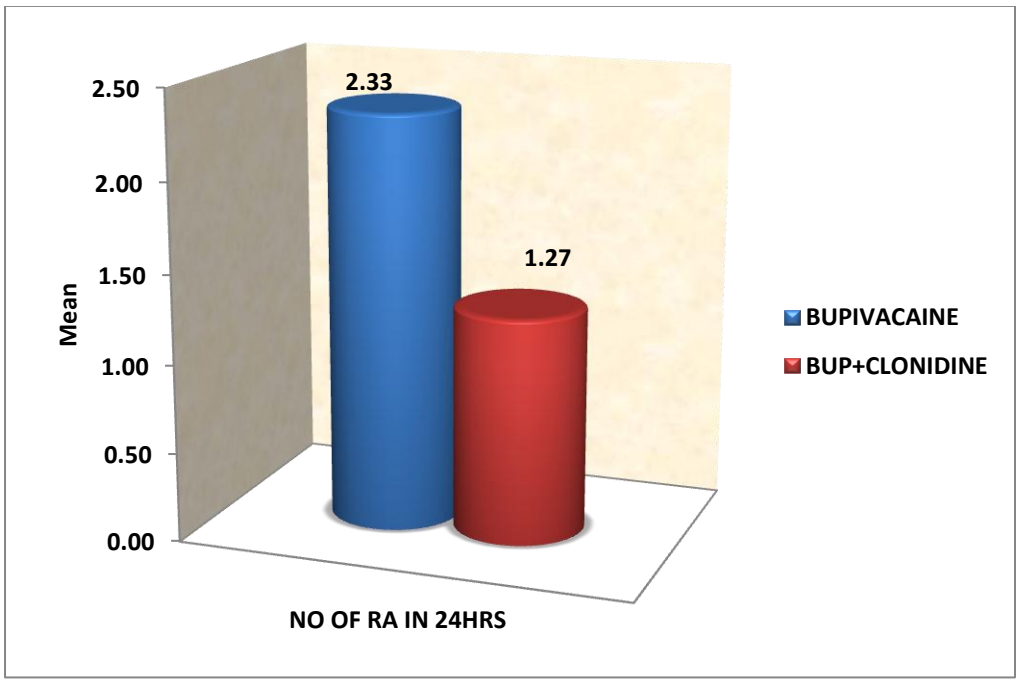


Table 7 : Percent Distribution of Number of rescue analgesic among study groups

NO OF RA IN 24HRS	BUPIVACAINE		BUP+CLONIDINE		Total		Chi square p value
	N	%	N	%	N	%	
1	0	0.00%	35	72.90%	35	36.50%	<0.001*
2	32	66.70%	13	27.10%	45	46.90%	
3	16	33.30%	0	0.00%	16	16.70%	
Total	48	100.00%	48	100.00%	96	100.00%	

*Statistically significant at 5% level of significance

In group BC, 72.90% patients required only 1 rescue analgesic dosage and 27.10% of patients required 2 rescue analgesic doses in post-op 24 hours. In group B 66.70% of patients required 2 and 33.30% of patients required 3 rescue analgesic doses in post-op 24 hours. This difference in number of rescue analgesic doses required by patient of both groups is statistically significant by chi-square test.

Graph7:Percent Distribution of Number of rescue analgesic among study groups

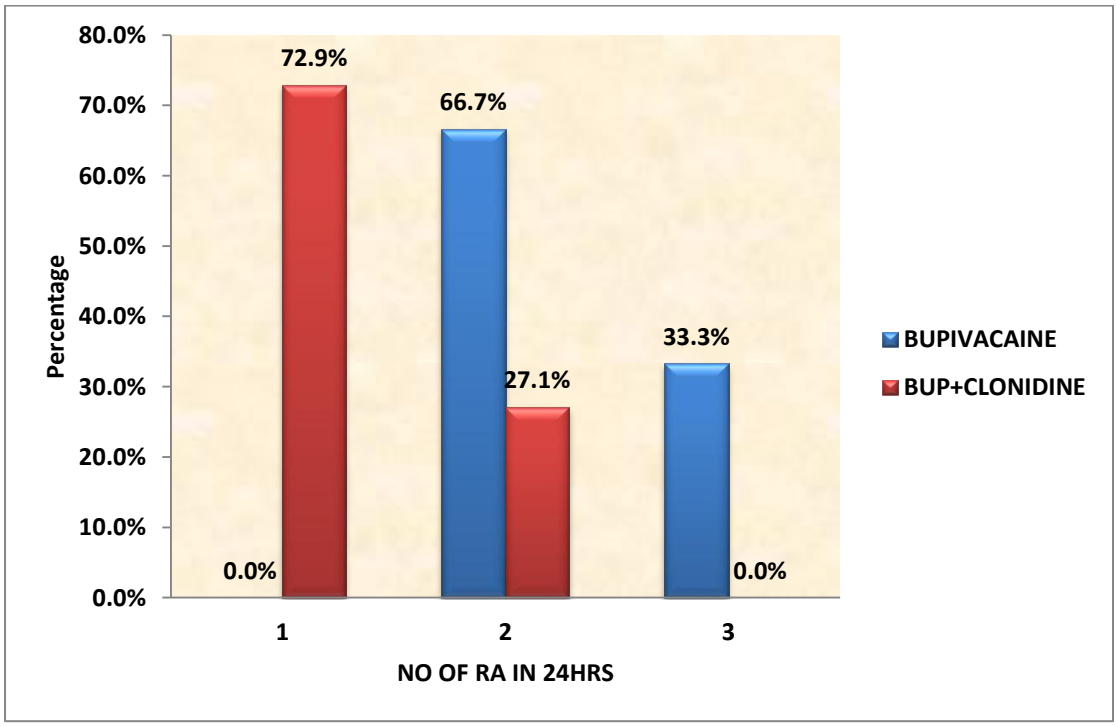


Table 8 : Percent Distribution of Sedation Score among study groups

Time	SEDATION SCORE	BUPIVACAINE		BUP+CLONIDINE		Total		Chi square p value
		N	%	N	%	N	%	
0MIN	1	48	100.00%	48	100.00%	96	100.00%	No difference
	2	0	0%	0	0%	0	0%	
5MIN	1	48	100.00%	48	100.00%	96	100.00%	No difference
	2	0	0%	0	0%	0	0%	
15MIN	1	48	100.00%	38	79.20%	86	89.60%	<0.001*
	2	0	0.00%	10	20.80%	10	10.40%	
30MIN	1	48	100.00%	32	66.70%	80	83.30%	<0.001*
	2	0	0.00%	16	33.30%	16	16.70%	
60MIN	1	48	100.00%	35	72.90%	83	86.50%	<0.001*
	2	0	0.00%	13	27.10%	13	13.50%	
2HR	1	48	100.00%	48	100.00%	96	100.00%	No difference
	2	0	0%	0	0%	0	0%	
6HR	1	48	100.00%	48	100.00%	96	100.00%	No difference
	2	0	0%	0	0%	0	0%	
12HR	1	48	100.00%	48	100.00%	96	100.00%	No difference
	2	0	0%	0	0%	0	0%	
24HR	1	48	100.00%	48	100.00%	96	100.00%	No difference
	2	0	0%	0	0%	0	0%	
Total		48	100.00%	48	100.00%	96	100.00%	

*Statistically significant at 5% level of significance

1 – Awake & Alert

2 – Minimally Sedated: tired/sleepy, responding to verbal stimulus

3 – Moderatly Sedated: somnolent/sleeping, responding to mild physical stimulus

4 – Deeply Sedated: deep sleep, responding to moderate to severe physical stimulus

5 – Unarousable.

In group B, all patients were awake and alert and had sedation score of 1. In group BC, sedation corresponding to score 2 was observed in some patients between 15 min from time of injection and 60 min. 20.80% of patients at 15 min, 33.30% of patients at 30 min and 27.10% of patients at 60 min had sedation score of 2. None of the patients had sedation score of 3 and above during the study period. Statistical analysis of sedation score by Chi-square test showed that the difference in sedation score was significant ($P < 0.05$).

Graph 8 : Percent Distribution of Sedation Score among study groups

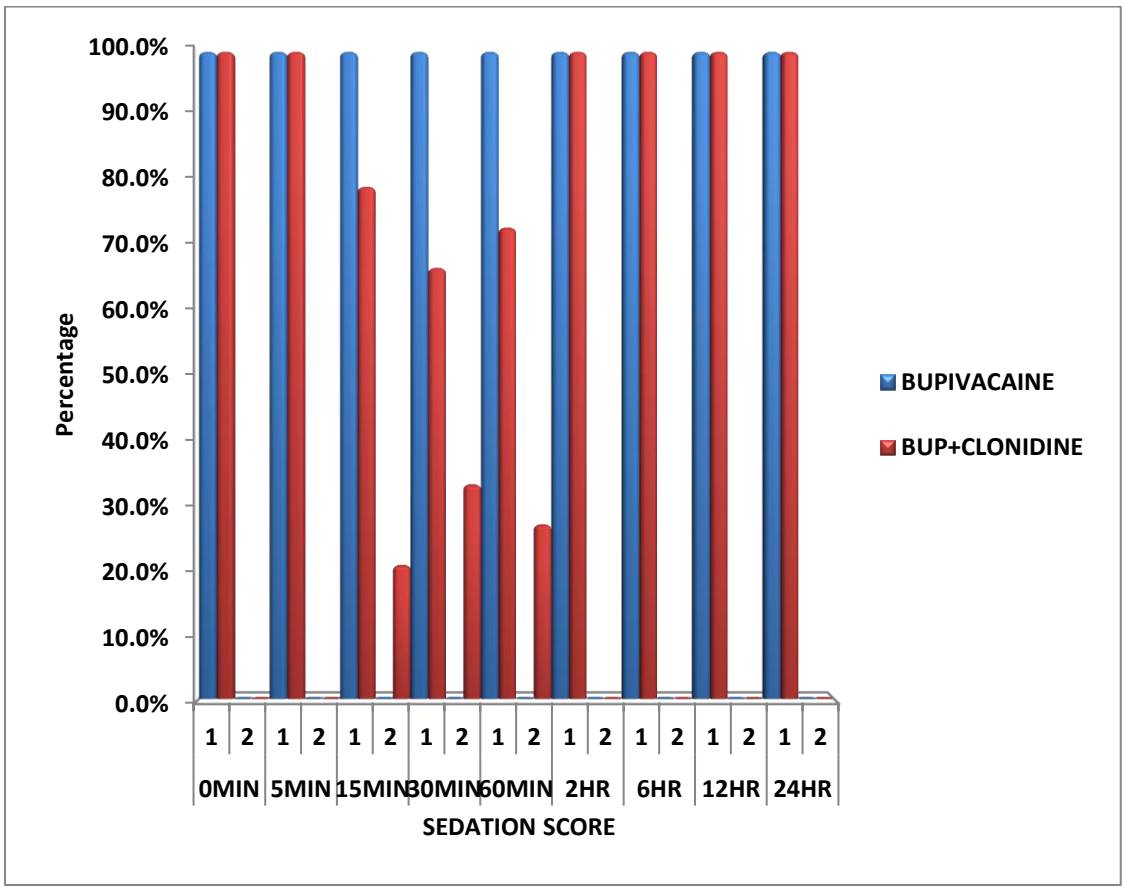


Table 9 : Mean Distribution of Pulse Rate among study groups

Time	BUPIVACAINE		BUP+CLONIDINE		t value	Mean Difference	p value	95% CI	
	Mean	SD	Mean	SD				Lower	Upper
0MIN	77.27	8.06	75.73	8.38	0.92	1.54	0.361	-1.79	4.87
5MIN	76.98	7.80	76.25	8.19	0.45	0.73	0.656	-2.51	3.97
15MIN	77.33	7.41	77.38	8.73	-0.03	-0.04	0.980	-3.32	3.24
30MIN	77.25	7.59	77.33	8.36	-0.05	-0.08	0.959	-3.32	3.15
60MIN	77.54	7.50	78.02	8.24	-0.30	-0.48	0.766	-3.67	2.71
2HR	77.15	7.70	78.29	8.71	-0.68	-1.15	0.496	-4.48	2.19
6HR	77.31	7.89	77.65	8.10	-0.20	-0.33	0.839	-3.57	2.91
12HR	77.52	7.27	78.29	7.76	-0.50	-0.77	0.617	-3.82	2.28
24HR	78.04	7.63	79.04	7.82	-0.63	-1.00	0.528	-4.13	2.13

In group B, the mean pulse rate ranged from 76.98± 7.80 to 78.04 ± 7.63 beats / min. In group BC, the mean pulse rate ranged from 75.73 ± 8.38 to 79.04 ± 7.82 beats / min. The statistical analysis by student's unpaired 't' test showed that there was no significant difference in pulse rate between the two groups (P > 0.05).

Graph 9 : Mean Distribution of Pulse Rate among study groups

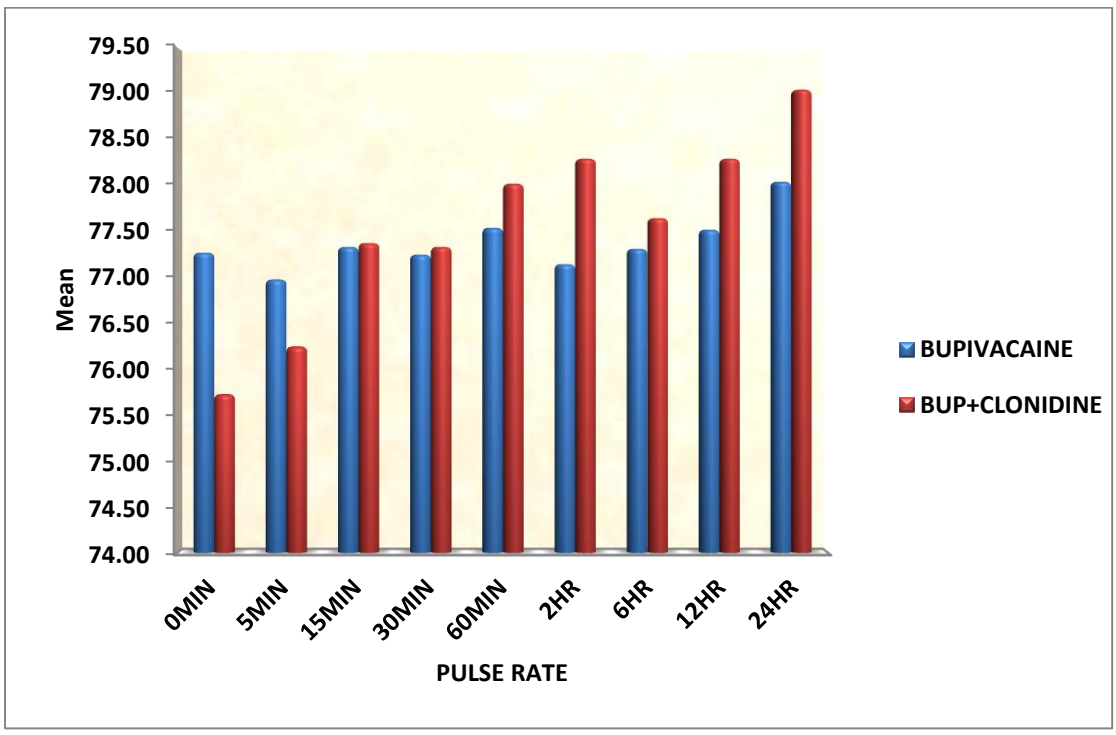


Table 10 : Mean Distribution of Systolic BP among study groups

Time	BUPIVACAINE		BUP+CLONIDINE		t value	Mean Difference	p value	95% CI	
	Mean	SD	Mean	SD				Lower	Upper
0MIN	116.71	8.83	118.00	9.27	-0.70	-1.29	0.486	-4.96	2.38
5MIN	116.77	9.18	118.17	9.61	-0.73	-1.40	0.469	-5.21	2.41
15MIN	117.58	9.18	118.21	10.11	-0.32	-0.63	0.752	-4.54	3.29
30MIN	117.77	8.67	118.79	9.71	-0.54	-1.02	0.588	-4.75	2.71
60MIN	118.06	9.36	119.63	9.40	-0.82	-1.56	0.417	-5.36	2.24
2HR	118.23	9.57	119.44	9.82	-0.61	-1.21	0.543	-5.14	2.72
6HR	118.44	9.04	119.42	8.89	-0.54	-0.98	0.594	-4.61	2.65
12HR	118.69	8.97	119.85	8.91	-0.64	-1.17	0.524	-4.79	2.46
24HR	118.54	8.81	120.23	8.76	-0.94	-1.69	0.349	-5.25	1.87

In group B the mean systolic blood pressure ranged from 116.71 ± 8.83 to 118.69 ± 8.97mm of Hg and in group BC the mean systolic blood pressure ranged from 118 ± 9.27 to 120.23 ±8.76mm of Hg. The statistical analysis by unpaired student's t test showed that there was no significant difference in systolic blood pressure between the two groups.

Graph 10 : Mean Distribution of Systolic BP among study groups

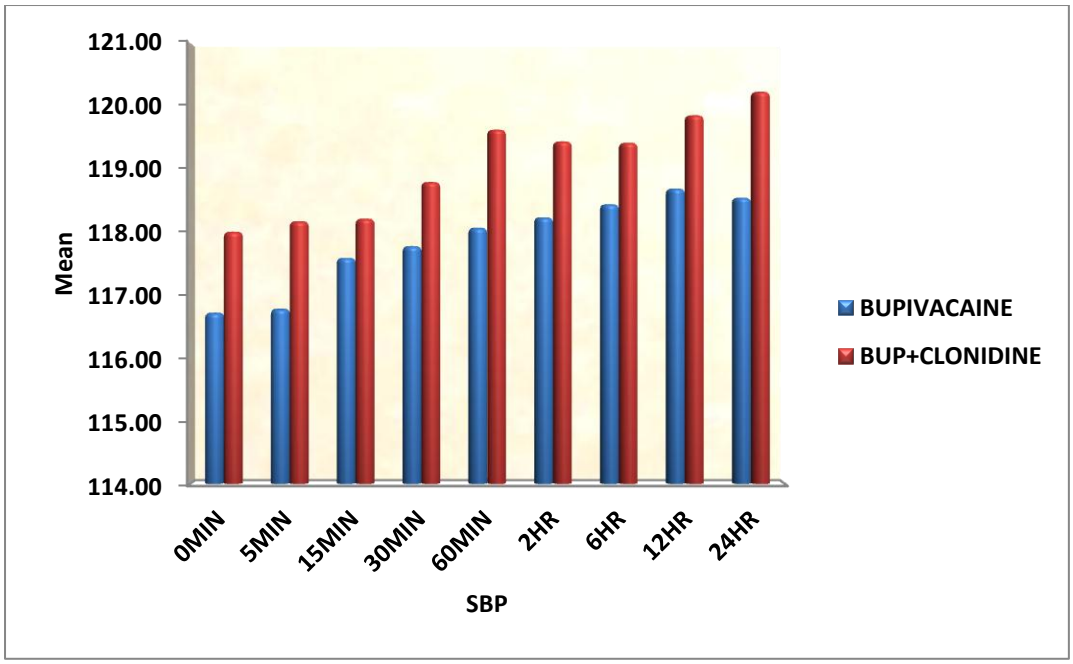


Table 11 : Mean Distribution of Diastolic BP among study groups

Time	BUPIVACAINE		BUP+CLONIDINE		t value	Mean Difference	p value	95% CI	
	Mean	SD	Mean	SD				Lower	Upper
0MIN	92.54	7.17	77.83	7.98	0.87	14.71	0.388	-18.95	48.36
5MIN	76.81	7.79	77.88	7.70	-0.67	-1.06	0.503	-4.20	2.08
15MIN	77.27	7.53	78.17	7.49	-0.58	-0.90	0.560	-3.94	2.15
30MIN	78.06	7.41	78.71	6.90	-0.44	-0.65	0.660	-3.55	2.26
60MIN	77.98	7.46	78.29	7.16	-0.21	-0.31	0.835	-3.28	2.65
2HR	78.60	8.09	78.25	6.97	0.23	0.35	0.819	-2.71	3.41
6HR	78.73	7.43	78.50	6.86	0.16	0.23	0.876	-2.67	3.13
12HR	78.81	6.77	78.75	6.76	0.05	0.06	0.964	-2.68	2.81
24HR	79.81	6.76	78.88	6.89	0.67	0.94	0.503	-1.83	3.70

In group B, the mean distolic blood pressure ranged from 76.81 ± 7.79 to 92.54 ± 7.17mm of Hg. In group BC, the mean diastolic blood pressure ranged from 77.83 ± 7.98 to 78.88 ± 6.89 mm of Hg. The statistical analysis by student's unpaired 't' test showed that there was no significant difference in diastolic blood pressure between the two groups (P > 0.05).

Graph 11: Mean Distribution of Diastolic BP among study groups

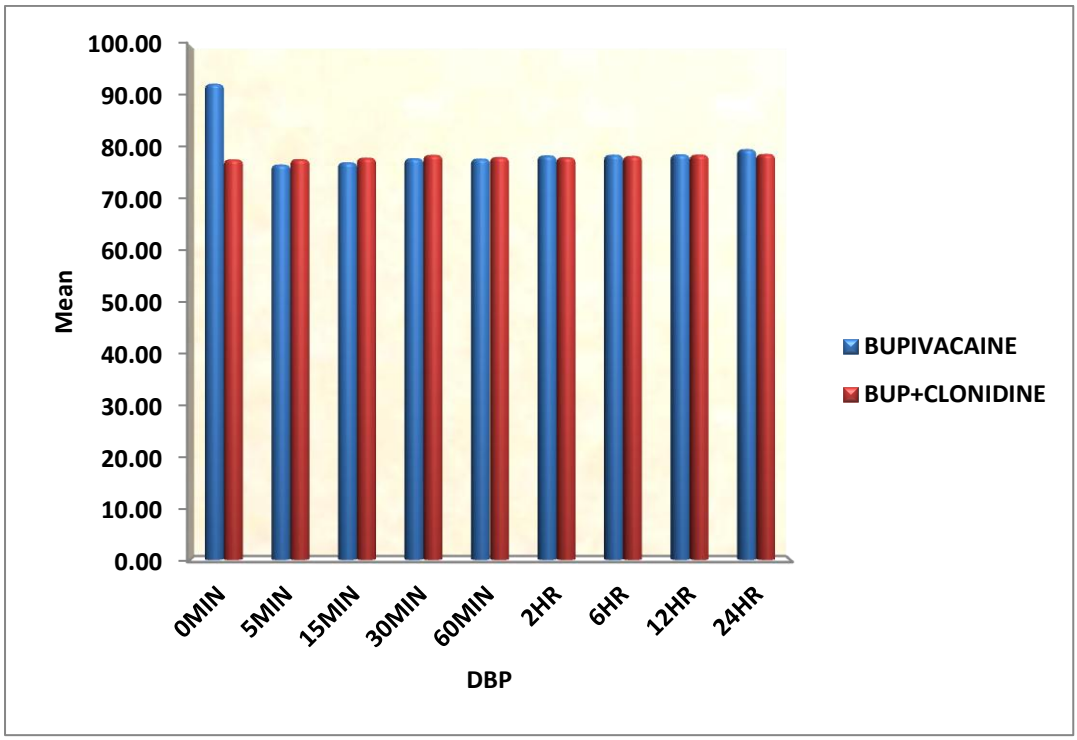
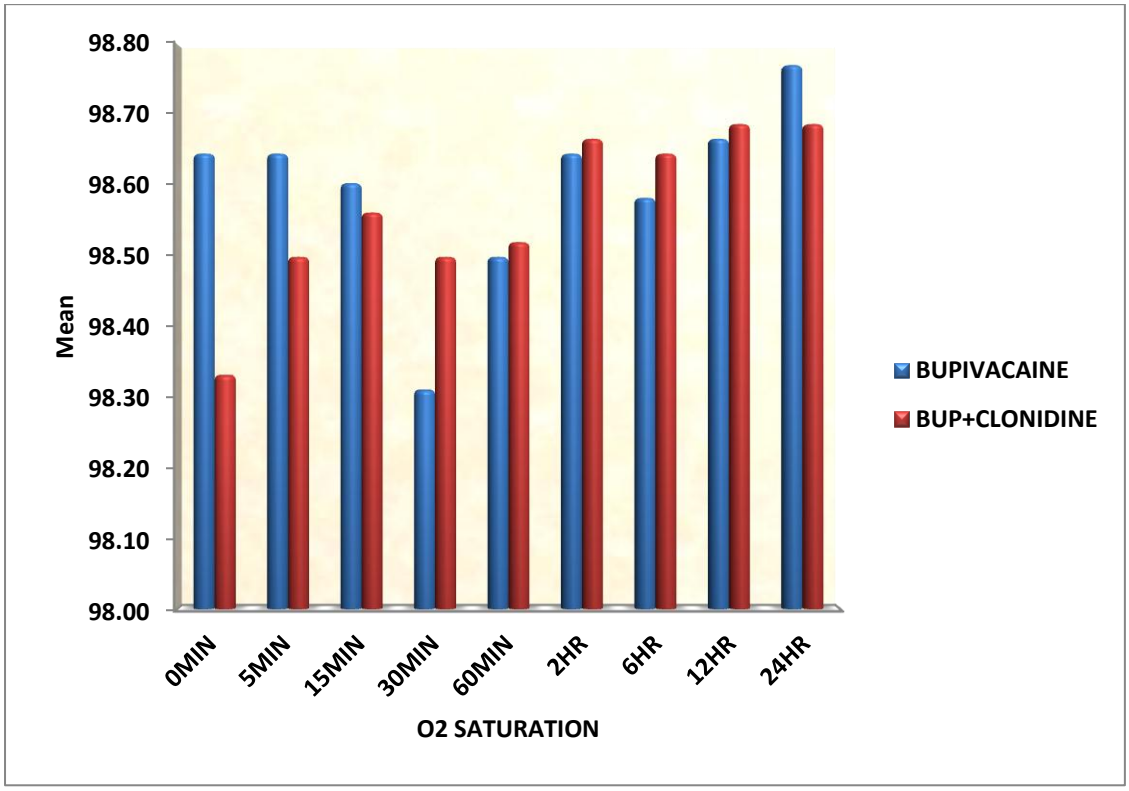


Table 12 : Mean Distribution of Oxygen Saturation among study groups

Time	BUPIVACAINE		BUP+CLONIDINE		t value	Mean Difference	p value	95% CI	
	Mean	SD	Mean	SD				Lower	Upper
0MIN	98.65	0.56	98.33	2.17	0.97	0.31	0.336	-0.33	0.95
5MIN	98.65	0.48	98.50	0.51	1.45	0.15	0.152	-0.05	0.35
15MIN	98.60	0.49	98.56	0.50	0.41	0.04	0.683	-0.16	0.24
30MIN	98.31	0.55	98.50	0.51	-1.74	-0.19	0.086	-0.40	0.03
60MIN	98.50	0.51	98.52	0.50	-0.20	-0.02	0.840	-0.23	0.18
2HR	98.65	0.48	98.67	0.48	-0.21	-0.02	0.832	-0.22	0.17
6HR	98.58	0.50	98.65	0.48	-0.62	-0.06	0.534	-0.26	0.14
12HR	98.67	0.48	98.69	0.47	-0.22	-0.02	0.829	-0.21	0.17
24HR	98.77	0.42	98.69	0.47	0.91	0.08	0.364	-0.10	0.26

In group B,the mean O2 saturation ranged from 98.31 ± 0.55 to 98.77 ± 0.42 and in group BC, the mean O2 saturation ranged from 98.33 ± 2.17 to 98.69 ± 0.47.The statistical analysis by students unpaired t test showed that there was no significant difference in saturation between two groups.(P>0.05).

Graph 12 : Mean Distribution of Oxygen Saturation among study groups



DISCUSSION

Brachial plexus block provides postoperative analgesia of short duration, even when a long-acting local anaesthetic like Bupivacaine is used alone. Various adjuvant drugs like Opioids, Midazolam, Neostigmine and Hyaluronidase have been evaluated in conjunction with local anaesthetics to prolong the period of analgesia, but they were found to be either ineffective or to produce an unacceptably high incidence of adverse effects. Clonidine is known to produce antinociception and to enhance the effect of local anaesthetic when administered intrathecally and epidurally. Clonidine produces this effect by its action on Alpha 2 adrenergic receptors found in peripheral nerves.

Hence an attempt has been made to assess the efficacy of Clonidine as an adjuvant to Bupivacaine (0.375%) in brachial plexus block (supraclavicular approach) in terms of onset time, duration of analgesia and sedation. Haemodynamic variables and rescue analgesic requirements in first 24 hours was also studied.

A total of 96 patients within the age group of 20-60 were included in the study, 48 in each group. Out of which the mean age of group B (receiving only Bupivacaine) was 39.44 ± 12.68 years and the mean age of group BC (receiving Clonidine with Bupivacaine) was 36.73 ± 11.96 years. Hence both groups were comparable in regard to age. Male to female ratio was almost same.

In our study we found that the onset of sensory and motor block was significantly faster in patients who received a combination of Clonidine and Bupivacaine. Onset of sensory block (group BC, 11.10 ± 1.26 min; group B, 19.60 ± 1.62 min). Onset of motor block (group BC, 9.92 ± 1.27 min; group B, 14.77 ± 1.56 min).

This could be due to a local direct action of Clonidine and its synergistic action with that of local anaesthetics. The onset of motor block was found to be faster than the onset of sensory block in both groups. Winnie et al.[9], presented similar observation, and attributed this to the somatotrophic arrangement of fibres in a nerve bundle at the level of the trunks in which motor fibres are located more peripherally than sensory fibres. Hence, a local anaesthetic injected perineurally will begin to block motor fibres before it arrives at the centrally located sensory fibres.

Our results showed that sensory block tended to last longer as compared to motor block which agrees with the observation by de Jong et al.[10] These authors explained that large fibres require a higher concentration of local anaesthetic than small fibres. The minimal effective concentration of local anaesthetic for large (motor) fibres is greater than that for small (sensory) fibres. Thus, motor function return before pain perception and duration of motor block is shorter than the sensory block. In our study duration of motor block was prolonged when Clonidine was added to Bupivacaine. (group BC, 7.86 ± 0.44hrs; group B, 5.13 ± 0.44 hrs).

In our study, the mean duration of sensory block (i.e. time elapsed from time of injection to appearance of pain requiring analgesia) was significantly higher ($P < 0.05$) in group BC than in group B. (group BC, 12.88 ± 0.95hrs ; group B, 5.82 ± 0.49hrs).

K Sri Hyndavi, *et al* (2016) [11] conducted prospective, randomized double-blind placebo controlled study to evaluate the effect of Bupivacaine and Clonidine combination of drugs with respect to the onset, duration of sensory and motor blockade and duration of analgesia in infra-clavicular brachial plexus block for elective upper limb orthopedic surgeries.

40 patients of American Society of Anaesthesiologists Grade I or II undergoing elective upper limb orthopedic procedures through Infra clavicular approach for brachial plexus block were randomly divided into two groups.

Group C received 30ml of 0.375%Bupivacaine and 0.4ml normal saline (n=20)
Group S received 30ml of 0.375% Bupivacaine and (60μg) Clonidine (n=20)

Analgesia duration was 753.2 ±109.6 min in group S (Clonidine) compared to 210.2 ± 32.min in group C (control). Onset time was shorter while duration of sensory and motor blockade were longer in group S(Clonidine) than group C(control) and the difference was statistically significant.

The mean onset of sensory block (group S, 14.7 ± 1.6 min, group C, 21.3 ± 2.7min) and motor block (group S, 17.4 ± 1.5 min; group C, 24.60 ± 3.0 min) was significantly faster in group S than in group C ($P < 0.001$).The duration of analgesia (group S, 11.5 ± 1.52 hrs; group C, 3.81 ± 0.83 hrs) was also longer in group S than in group C. The duration of motor block (group S 9.96 ± 1.72 hrs, group C, 3.37 ± 0.50 hrs) was also longer in group S than in group C. These results are comparable with our study.

Various studies in which Clonidine was used in peripheral nerve block found that Clonidine with Bupivacaine improves analgesic characteristics compared to Bupivacaine alone.

Sirohiya P. *et al* (2016)[12] conducted study which evaluated the effect of Bupivacaine Clonidine combination in supraclavicular brachial plexus block for upper limb surgeries and they found that duration of post operative analgesia was prolonged when Clonidine is added to Bupivacaine.

Audichya PC, Goyal S. (2016)[13] conducted study to compare the effect of Clonidine v/s placebo as adjuvant to lignocaine for brachial plexus block, by

supraclavicular approach, for different upper limb surgeries. They concluded that when Clonidine is added to local anesthetic solution in supraclavicular brachial plexus block, it provides rapid onset of block, better analgesia, good hemodynamic stability and profound & longer analgesia without any adverse effects.

Dr. Jyoti Vishnu Kale, Dr. Dhanashree Dongare, Dr. R. W. Naphade (2013)[14] conducted study on effect of Clonidine as an adjuvant to Bupivacaine for supraclavicular brachial plexus block and they concluded that addition of a small dose of Clonidine to local anaesthetic solution significantly prolonged the duration of analgesia without producing any clinically important adverse reaction.

Sumanta Ghoshmaulik, *et al.* (2012) [15] conducted study on Clonidine as an adjuvant in axillary brachial plexus block for below elbow orthopedic surgeries and they concluded that Clonidine as an adjuvant in axillary block resulted in significant prolongation of duration of sensory and motor blockade, and analgesia without any hemodynamic alteration, probably by locally mediated mechanism of action.

Shivinder Singh, Amitabh Aggarwal (2010)[16] conducted A randomized controlled double-blinded prospective study of the efficacy of Clonidine added to Bupivacaine as compared with Bupivacaine alone used in supraclavicular brachial plexus block for upper limb surgeries and they found that Clonidine added to Bupivacaine is an attractive option for improving the quality and duration of supraclavicular brachial plexus block in upper limb surgeries.

Sumitha Chakraborty, *et al.(*2010)[17] conducted study on the effect of Bupivacaine-Clonidine combination in supraclavicular brachial plexus block for upper limb orthopedic procedures and it was concluded that addition of a small dose of Clonidine to 0.5% Bupivacaine significantly prolonged the duration of analgesia without producing any clinically important adverse reactions other than sedation.

In our study, the number of patients who required rescue analgesia and the mean number of supplemental analgesic boluses required were also significantly lower in patients of Group BC. Similar observation was made in the above mentioned study by Chakraborty *et al.*[17], The prolonged analgesia in Group BC could be due to the action of Clonidine by inhibiting action potential of A & C fibers in peripheral nerves as demonstrated by Gaumann *et al.*[14]

Many authors favor the hypothesis that Clonidine exerts its local anesthetic-prolonging effect directly on nerve fiber, as a result of complex interaction between Clonidine and axonal ion channels or receptors.

Masuki *et al.*[39], suggested Clonidine may produce local vasoconstriction resulting in a delayed absorption of local anesthetic and block prolongation.

We studied Clonidine at a dose of 1 µg/kg, as others have used the same dosage in peripheral nerve block without any significant adverse effects.

Rashmi madan *et al.*[25], showed addition of 1 mcg/kg of Clonidine to local anesthetic significantly prolonged duration of anesthesia after peribulbar block without side effects.

A similar observations were made by Singelyn *et al.*[30], who suggested 0.5-1 mcg/kg of Clonidine satisfactorily prolongs the analgesia of local anesthetic in peripheral nerve blocks without undue hemodynamic side effects of alpha-2 agonism.

In our study, sedation scores were higher in patients in Group BC compared to Group B, 15 min after injecting the drug until 60 min after injection.

Similar observation was made in the above mentioned study by Chakraborty *et al.*[17]. This may have been due to partial vascular uptake of Clonidine, and its transport to the central nervous system where it acts and produces sedation. The limited duration of sedation could be explained by the fact that Clonidine is highly

lipophilic and diffuses faster into the blood vessels. Though mean sedation score in group BC was higher as compared to group B ($P < 0.05$), we did not observe clinically significant sedation in patients in group BC.

No patient experienced airway compromise or required airway assistance. This mild sedation was actually desirable during that period.

In conclusion, Clonidine 1 µg/kg when added to 30mL of Bupivacaine 0.375% for supraclavicular brachial plexus block, speeds the onset of sensory and motor blocks ($P < 0.05$). The combination produces improved analgesia, resulting in a prolonged effect and reduced requirements for rescue analgesics.

CONCLUSION

From our study, we conclude that, the addition of Clonidine (1µg / kg) as an adjuvant to Bupivacaine (0.375%) has following effects :

i) Faster onset of sensory block.

ii) Faster onset of motor block.

iii) Longer duration of sensory block.

iv) Longer duration of motor block.

v) Less number of rescue analgesics in post-op 24 hours.

vi) Comfortable sedation intraoperatively without any need for airway assistance.

No significant difference in haemodynamic variables i.e., pulse rate, systolic BP, diastolic BP and O_2 saturation.

SUMMERY

This study "A RANDOMISED CLINICAL TRIAL TO COMPARE THE EFFECTIVENESS BETWEEN BUPIVACAINE AND BUPIVACAINE-CLONIDINE COMBINATION IN BRACHIAL PLEXUS BLOCK BY SUPRACLAVICULAR APPROACH" was conducted in 98 patients of either sex, belonging to 20-60 years of age, ASA grade I and II in the Department of Anaesthesiology, B.LD.E.U'S Shri B M Patil Medical College, Hospital and Research Centre, Vijayapur from Dec 2014 to June 2016.

They were randomly divided into 2 groups :

- Group BC – Received 30 ml of 0.375% Bupivacaine + 1µg / kg of Clonidine
- Group B – Received 30 ml of 0.375% Bupivacaine only.

The following parameters were recorded and compared.

1) Onset of sensory and motor block
2) Duration of sensory and motor block
3) Number of rescue analgesics in post-op 24 hours.
4) Sedation score
5) Haemodynamic variables like pulse rate, systolic and diastolic blood pressure and O_2 saturation.

Onset of sensory and motor block :

The mean time for onset of sensory block in group B was 19.60 ± 1.62min and in group BC was 11.10 ± 1.26 min.

The mean time for onset of motor block in group B was 14.77 ± 1.56min and in group BC was9.92 ± 1.27 min.

Both differences were statistically significant ($P < 0.05$)

Duration of sensory and motor block :

The mean duration of sensory block in group B was 5.82 ± 0.49hours and in group BC was 12.88 ± 0.95hours.

This difference was statistically significant ($P < 0.05$)

The mean duration of motor block in group B was 5.13 ± 0.44hours and in group BC was 7.86 ± 0.44 hours. This difference was statistically significant ($P < 0.05$).

Rescue analgesic requirements : In post op 24 hours

In group BC 72.90% of patients required only 1 and 27.10% of patients required 2 rescue analgesic doses in post op 24 hours.

In group B, 66.70% of patients required 2 and 33.30% of patients required 3 rescue analgesic doses in post op 24 hours.

Rescue analgesia requirement in group B was significantly higher ($P < 0.05$).

Sedation score :

In group BC 20.80%of patients at 15 min, 33.30% of patients at 30 min and 27.10% of patients at 60 min has sedation score of 2 is sedated, but responding to verbal stimulus. In group B, all patients had sedation score of 1 i.e. awake and alert. The sedation in group BC patients was mild and desirable, without any need for airway assistance.

This difference was statistically significant ($P < 0.05$)

Haemodynamic variables :

Both groups were comparable with regard to pulse rate, systolic blood pressure, diastolic blood pressure and O_2 saturation. There was no statistically significant difference ($P > 0.05$).

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ANNEXURES

ETHICAL CLEARANCE CERTIFICATE

Institutional Ethical Committee
BIJAPUR-586 103.
OUTWARD
No. 571/14
Date 24/11/14
B.L.D.E.U's Shri B.M. Patil Medical College

B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 22-11-2014 *at* 3-30pm *to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.*

Title "A randomised clinical trail to compare the effectiveness between Bupivacaine & Bupivacaine - Colonidine combination in brachial plexus block by Supraclavicular approach"

Name of P.G. student Dr Maajunath Shivapujimath.
Dept of Anaesthesiology.

Name of Guide/Co-investigator Dr S.G Talikoti, Prof & HOD.
Dept of Anaesthesiology.

for
DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

CONSENT FORM

B.L.D.E.U.'s SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR – 586103, KARNATAKA

TITLE OF THE PROJECT **:** "A RANDOMISED CLINICAL TRIAL TO COMPARE THE EFFECTIVENESS BETWEEN BUPIVACAINE AND BUPIVACAINE-CLONIDINE COMBINATION IN BRACHIAL PLEXUS BLOCK BY SUPRACLAVICULAR APPROACH"

PRINCIPAL INVESTIGATOR **:** **Dr. MANJUNATH SHIVAPUJIMATH**

Department of Anaesthesiology

Email: manjushivapujimath@gmail.com

PG GUIDE **:** **DR. D.G.TALIKOTI**

PROFESSOR AND HEAD

DEPARTMENT OF ANESTHESIOLOGY

B.L.D.E.U.'s SHRI B.M. PATIL MEDICAL COLLEGE, VIJAYAPUR

PURPOSE OF RESEARCH:

I have been informed that this study is **"A RANDOMISED CLINICAL TRIAL TO COMPARE THE EFFECTIVENESS BETWEEN BUPIVACAINE AND BUPIVACAINE-CLONIDINE COMBINATION IN BRACHIAL PLEXUS BLOCK BY SUPRACLAVICULAR APPROACH"** I have been explained about the reason for doing this study and selecting me/my ward as a subject for this study. I have also been given free choice for either being included or not in the study.

PROCEDURE:

I understand that I will be doing **"A RANDOMISED CLINICAL TRIAL TO COMPARE THE EFFECTIVENESS BETWEEN BUPIVACAINE AND BUPIVACAINE-CLONIDINE COMBINATION IN BRACHIAL PLEXUS BLOCK BY SUPRACLAVICULAR APPROACH"**

RISKS AND DISCOMFORTS:

I understand that I/my ward may experience some pain while giving spinal anesthesia and I understand that necessary measures will be taken to reduce these complications as and when they arise

BENEFITS:

I understand that my/my wards participation in this study will help in finding out **"A RANDOMISED CLINICAL TRIAL TO COMPARE THE EFFECTIVENESS BETWEEN BUPIVACAINE AND BUPIVACAINE-CLONIDINE COMBINATION IN BRACHIAL PLEXUS BLOCK BY SUPRACLAVICULAR APPROACH".**

CONFIDENTIALITY:

I understand that medical information produced by this study will become a part of this Hospital records and will be subjected to the confidentiality and privacy regulation of this hospital. Information of a sensitive, personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code key connecting name to numbers will be kept in a separate secure location.

If the data are used for publication in the medical literature or for teaching purpose, no names will be used and other identifiers such as photographs and audio or video tapes will be used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time**.**

Dr. MANJUNATH SHIVAPUJIMATH is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me.

And that a copy of this consent form will be given to me for keep for careful reading.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I also understand that **Dr. MANJUNATH SHIVAPUJIMATH** will terminate my participation in this study at any time after he has explained the reasons for doing so and has helped arrange for my continued care by my own physician or therapist, if this is appropriate

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/my ward, resulting directly to my participation in this study, if such injury were reported promptly, then medical treatment would be available to me, but no further compensation will be provided.

I understand that by my agreement to participate in this study, I am not waiving any of my legal rights.

I have explained to _____ the purpose of this research, the procedures required and the possible risks and benefits, to the best of my ability in patient's own language.

Dr. D.G.TALIKOTI
(Guide)

Dr. MANJUNATH SHIVAPUJIMATH
(Investigator)

Date:

STUDY SUBJECT CONSENT STATEMENT:

I confirm that **Dr. MANJUNATH SHIVAPUJIMATH** has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project.

_____ _____

(Participant) Date

_____ _____

(Witness to above signature) Date

ANNEXURE

PROFORMA

STUDY: "A RANDOMISED CLINICAL TRIAL TO COMPARE THE EFFECTIVENESS BETWEEN BUPIVACAINE AND BUPIVACAINE-CLONIDINE COMBINATION IN BRACHIAL PLEXUS BLOCK BY SUPRACLAVICULAR APPROACH"

Name: I.P. No. :

Age: Date:

Sex:

Preoperative Observations:

General Physical Examination:

Pulse rate: Blood Pressure:

Respiratory rate: Weight:

Systemic Examination:

C.V.S: CNS:

R.S : Others :

Investigations:

Hb% : R.B.S: ECG:

Blood Urea: S.Creatinine: Urine routine:

Preoperative Diagnosis:

Proposed surgery:

Premedication:

ASA Grade :

Anesthetic Technique: Ultra-sound guided Supraclavicular Approach to Brachial plexus block.

STUDY PROTOCOL:

Drug and Dosage: 30ml of 0.375% BUPIVACAINE with

CLONIDINE(1µg/Kg) (OR) 30mlof0.375%BUPIVACAINE alone.

Objectives:

1. Time of Injection:0min
2. Time of onset of sensory blockade :min
3. Time of onset of motor blockade :min

MONITORING:

Time	**Pulse Rate Per min**	**Systolic B.P (mmHg)**	**Diastolic B.P (mmHg)**	**SpO_2 %**	**Sedation Score**
0min					
5min					
15min					
30min					
60min					
2Hrs					
6Hrs					
12Hrs					
24Hrs					

4)Duration of sensory blockade :min

5)Duration of motor blockade :min

6)No.of rescue analgesics in post-op 24Hrs :_____

KEY TO MASTER CHART

Sl. No. -	Serial Number
IP No. -	In-patient number
RA -	Rescue analgesics
Yrs -	Years
Min -	Minutes
Hrs -	Hours
Post-Op	Post-operative
PR -	Pulse rate
SBP -	Systolic blood pressure
DBP -	Diastolic blood pressure
SpO2 -	Oxygen saturation

Sedation Scores (UMSS)

1. Awake & Alert
2. Minimally Sedated: tired/sleepy, responding to verbal stimulus
3. Moderatly Sedated: somnolent/sleeping, responding to mild physical stimulus
4. Deeply Sedated: deep sleep, responding to moderate to severe physical stimulus
5. Unarousable.