COMPARISON OF CLONIDINE AND ADRENALINE AS ADJUVANTS TO BUPIVACAINE IN SUPRACLAVICULAR APPROACH TO BRACHIAL PLEXUS BLOCK

A STUDY OF 80 CASES

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CHENNAI, TAMILNADU

BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled **"COMPARISON OF CLONIDINE AND ADRENALINE AS ADJUVANTS TO BUPIVACAINE IN SUPRACLAVICULAR APPROACH TO BRACHIAL PLEXUS BLOCK "** a bonafide record work done by **Dr. S. KUMARESAN** under my direct supervision and guidance, submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment of University regulation for MD, Branch X –Anaesthesiology.

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DECLARATION

I **Dr. S. KUMARESAN** solemnly declare that this dissertation titled **"COMPARISON OF CLONIDINE AND ADRENALINE AS ADJUVANTS TO BUPIVACAINE IN SUPRACLAVICULAR APPROACH TO BRACHIAL PLEXUS BLOCK"** has been done by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any other University board either in India or abroad.

This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulation for the award of M.D. degree Branch –X (Anaesthesiology) to be held in March 2010.

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CONTENTS

INTRODUCTION

“For all the happiness that mankind can gain

It is not in pleasure but in relief from pain”

- JOHN DYRDEN

“Pain, like pleasure is passion of the soul,

That is an emotion and not one of the senses”

- PLATO and ARISTOTLE (375 B.C)

Pain is a fundamental biological phenomenon. The International Association for the Study of pain has defined pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain is always underestimated and under treated. The relief of pain during surgery is the main part of anaesthesia.

In 1784 James Moore used mechanistic concepts to promote neural compression as a useful technique for the provision of surgical anaesthesia.

In 1855, neurologic pain can be treated by circum-neural injection of pain relieving drug. At the same year Gadecke (German) isolated of alkaloid from leaves of coca plant. In 1860 Albert Nieemann was successful in isolating and naming the alkaloid from the leaves of erythroxylon coca.

In 1884 idea of injecting cocaine into nerve trunk introduced by William Halsted and Alfred Hall. After that Heinrich F Braun found that adding epinephrine to cocaine prolong the effect of local anaesthetics. But later 1911 G.Hirschel performed first percutaneous axillary brachial plexus block.

In 1911 Kullenkampff introduced the classic supraclavicular approach of brachial plexus block. Winnie and Collins introduced the subclavian perivascular approach of brachial plexus block. Moorthy introduced the modified lateral paravascular approach. With introduction of barbiturate and cyclopropane, the enthusiasm for block anaesthesia waned in early 1940s. In current recent years however, the technique has had resurgence, due in large part to increased understanding of neural plasticity and the possibility of minimizing hospital stay length by effective use of regional block anaesthesia.

Several techniques have been used to prolong the duration of regional anaesthesia. Besides the continuous infusion of local anaesthetics through catheters and recently opioids as adjuvants to local anaesthetic solutions, the addition of epinephrine appears to be the most widely used. The prolongation of action is generally related

to local vasoconstriction which slows down the vascular absorption of local anaesthetics. Vasoconstriction is related to the action of epinephrine on alpha-type receptors. Nevertheless, this action remains controversial and other mechanisms have been proposed. The existence of alpha-type receptors, which take part in the transmission of nociceptive stimuli at the spinal level, emphasizes a possible direct action of alpha-adrenergic agonists on neural tissues. These receptors are of the Alpha-2 type. Several experimental and clinical studies have shown that Alpha-2 adrenergic agonists like clonidine were able to prolong sensory and motor blockade.

This study involves the addition of an alpha-2 adrenergic agonist, Clonidine to local analgesic solution in supraclavicular approach to brachial plexus block and the effects are evaluated and compared with brachial plexus block using local analgesic solution and adrenaline

AIM OF THE STUDY

To compare the effectiveness of Clonidine and adrenaline as adjuvants to bupivacaine in supraclavicular approach to Brachial plexus block for prolonging the duration of post operative analgesia and prolonging the motor blockade.

HISTORY

1. 1858- theory of pain was a separate and distinct sense was definitely formulated by Mortiz S.Schiff
2. 1884-William Halsted and Alfred Hall – idea of injecting cocaine into nerve trunk
3. 1911- G. Hirschel performed first percutaneous axillary brachial plexus block
4. 1911- D.Kulenkampff performed supraclavicular brachial plexus block
5. 1943- Lidocaine was synthesized by Lofgreen and Lundquvisit
6. 1956- Bupivacaine synthesized by Ekenstam
7. 1963- Bupivacaine introduced clinical practice by Telivuo
8. Melzock and Walts (1965) propounded the Gate Control Theory of pain.

ANATOMICAL CONSIDERATIONS

Knowledge of the formation of the brachial plexus and of its distribution is essential to the intelligent and effective use of the brachial plexus block for the surgeries in the upper limb. Close familiarity with the vascular, muscular and fascia relationship of the plexus throughout the formation and distribution is equally essential to the mastery of various techniques of Brachial plexus Blockade.

Derivation of plexus:

The brachial plexus is derived from the anterior primary rami of the fifth, sixth, seventh, eighth cervical nerves and 1st thoracic nerve, with variable contributions from the Fourth cervical (pre fixed) and second thoracic nerves (post fixed).

COURSE:

After leaving their intervertebral foramina, the roots course anterolaterally and inferiorly to lie between the anterior and middle scalene muscles, which arise from anterior and posterior tubercles of cervical vertebrae respectively. Here unite to form the trunks.

C5
C6 → Superior trunk

C7 → middle trunk

C8
T1 → Inferior trunk

The prevertebral fascia invests both the anterior and middle scalene muscles, fusing laterally to enclose the brachial plexus in a fascial sheath. Trunks emerge from the lower border of the muscle running inferiorly and anterolaterally covering towards the upper border of the 1st rib, where they lie cephaloposterior to the subclavian artery.

At the lateral edge of the 1st rib each trunk divides into anterior and posterior divisions passing inferior to mid portion of clavicle. They reunite within the axilla to form the lateral, medial and posterior cords and related to the second part of the axillary artery. The anterior divisions from upper and middle trunk unite to form the lateral cord. The posterior divisions from all three trunks unite to form the posterior cord. The anterior divisions from the lower trunk continue as the medial cord.

At the lateral border of the pectoralis minor, the three cords divide into the peripheral nerves of the upper extremity.

Lateral cord:-

i. Lateral root of median nerve

ii. Lateral pectoral nerve

iii. Musculocutaneous nerve

Medial cord:

i. Medial root of median nerve

ii. Medial cutaneous nerve of arm

iii. Medial cutaneous nerve of forearm

iv. Medical pectoral nerve

v. Ulnar nerve

Posterior cord:

i. Radial nerve

ii. Axillary nerve

iii. Upper and lower subscapular nerve

iv. Nerve to latissimus dorsi

Branches from roots

i. Dorsal scapular nerve to Rhomboid muscles(C5)

ii. Nerve to serratus anterior (C5, C6, C7)

Branches from trunk:

i. Nerve to subclavius (C5-C6)

ii. Supra scapular nerve (C5-C6)

RELATIONS:

Brachial plexus has its roots between the scalene muscles, trunks in the posterior triangle of the neck, divisions behind the clavicle and cords at the level of the Axilla and nerves beyond the axilla. In the course it lies superior and posterior to the subclavian artery. Dome of pleura is anteromedial to the lower trunk and postermedial to the subclavian artery .The trunks emerge between the fascia covering the anterior and middle scalene muscles.

TECHNIQUE OF BLOCKADE;

SUPRACLAVICULAR APPROACH TO BRACHIAL PLEXUS BLOCKADE

Classic approach:

Anatomical landmarks: The three trunks are clustered vertically over the first rib cephaloposterior to the subclavian artery. Neurovascular bundle lies inferior to the clavicle at about its midpoint.

POSITION OF THE PATIENT:

Patient is placed in a supine position with the head turned to opposite side from the side to be blocked. The arm is pushed down to depress the clavicle.

TECHNIQUE:

The midpoint of clavicle is identified and marked. The posterior border of sternocleidomastoid is felt, by asking the patient to raise the head while keeping the head turned to opposite side. The interscalene groove is palpated by rolling the fingers back from the posterior border of the lower end of the strenocleidomastoid muscle over the anterior scalene muscle.

The anterior and middle scalene muscles can be highlighted by asking the patient to inspire vigorously. A mark is made in the groove 1.5 to 2 cm above the midpoint of clavicle, palpation of subclavian artery confirms this landmark. On the right side, interscalene groove is palpated with the left index finger and the needle is inserted with the right hand and reversing the hands for the left side.

After appropriate preparation of aseptic measures and intradermal wheel, a short bevelled 22gauge 3.5 -4 cm long needle

is inserted at the marked point. Subclavian artery is guarded with thumb, the needle is directed caudally, posteriorly and slightly medially until paraesthesia is elicited or first rib is encountered. Needle enters the Fascial sheath 1-2cm deep to the skin approximately. Marked resistance will give way to pop as the fascia is pierced and paraesthesia may occur.

The needle is held firmly and then the local analgesic solution is injected after careful aspiration to exclude intravascular placement. If needle is in the subclavian artery just take the needle out and direct the needle posterolaterally to elicit paresthesia.

If the first rib is encountered without elicitation of paraesthesia, the needle is systematically walked over the rib until the plexus or subclavian artery is located. The rib is contacted at a depth of 3-4 cm. The solution should flow without resistance. High resistance or pain on injection may indicate intraneural injection and the needle must be repositioned.

Volume of local anaesthetic (either 1% lignocaine or 0.25% bupivacaine) that can be used is 25-40 ml depending on the weight of the patients. When large volumes are used the sheath may be felt to distend during injection and is easily distinguished from the

subcutaneous swelling of an extra fascial injection. To encourage the spread proximally, digital pressure distal to the needle point may be used and digital pressure proximal to needle insertion point may help to encourage distal spread.

Complications:

i. Supraclavicular approach has the highest risk of pneumothorax 0.5-6% when compared to other techniques. Majority of pneumothorax takes 24 hrs to develop and rarely develop in short duration. Tall thin patients with high apical pleura are prone to develop pneumothorax in shorter duration. Incidence of pneumothorax reduced by avoiding multiple probing and by using small needles.

ii. Unilateral Phrenic nerve block can occur but has no significance

iii. Horner syndrome – occurs when large volume is used, resolves spontaneously

iv. Unintentional intravascular injection

v. Stellate ganglion block and recurrent laryngeal nerve palsies (very rare)

Physiological considerations

International association for the study of pain has defined pain as “Unpleasant sensory and emotional experiences associated with actual or potential tissue damage are defined in terms of such damage”.

Pain perception requires noxious stimuli is encountered .It is transformed from its native form by the activated nociceptors into electrical signals which are then transmitted along the corresponding nociceptive fibres. These fibres in turn synapse onto second order neurons in the spinal cord. These interneurons are located in the dorsal horn. It is at these interneurons where the initial modulation of nociceptive input occurs. From the spinal cord nociceptive input is transmitted to the brain stem, thalamus and cortex.

Peripheral neuroanatomy of nociception

C and Aδ fibres are the main peripheral nociceptors. The skin joints and periosteum are richly innervated with C and Aδ nociceptors as well as the non nociecptive AB sensory fibres.

Aδ are responsible for the sensation of first pain, the initial sharp pain experienced following an injury. C fibres are

unmyelinated and are responsible for second pain, the slowly building throbbing burning pain experienced following an injury.

Classification of sensory fibres

Sensory receptors	Speed of transmission	Sensory function	Myelination
C fibres	0.5 – 2 m / sec	Noxious chemical, mechanical, thermal activation (slow burning second pain)	Unmyelinated
A-Alpha fibres	70 – 120 m / sec	Noxious chemical thermal, mechanical stimuli, (sharp fast, first pain)	Lightly myelinated
A-Beta Fibres	30 – 70 m / sec	Non painful, light touch,pressure, vibration proprioception	Heavily myelinated
A-Gamma fibres	30 – 70 m / sec	Proprioception / Motor to muscle spindle	myelinated
A-Delta Fibres	12 – 30 m / sec	Pain, cold, touch	myelinated
B fibres	3 – 15 m / sec	Pre ganglionic autonomic (sympathetic)	myelinated

Peripheral neurochemistry and neurotransmitters:

Commonly released inflammatory mediators implicated in pain and hyperalgesia include Bradykinins, potassium, substance P cytokines, histamine, serotonin, prostaglandins. These peripheral neurotransmitters either activate or sensitise the peripheral nociceptors to pain.

Peripheral neuro chemistry Algogenic Agents:

Algogenic Agent	Action on nociceptors
Bradykinin	Activates
Substance P	Sensitizes
Potassium	Activates
Hydrogen	Activates
Arachidonic acid	Sensitizes
Cytokines	Sensitizes
Serotonin	Sensitizes
Nor adrenaline	High concentration activates and sensitizes after injury.

Peripheral alpha 2 receptors:

Alpha 2 adrenoreceptors are located on primary afferent terminals, on neurons in the superficial laminae of the spinal cord, and within several brainstem nuclei implicated in analgesia, supporting the possibility of analgesic action at peripheral, spinal, and brainstem sites.

Clonidine enhances both sensory and motor blockade from peripheral nerve injection and epidural / spinal injection of local anaesthetics.

Clonidine blocks conduction of C and A gamma fibers and increases potassium conductance in isolated neurons and intensifies conduction block of local anaesthetics.

Local vasoconstriction resulting in reduced absorption from injection site was another point of discussion, but compared with adrenaline as adjuvant it failed to influence plasma levels, indicating a direct action on nerve.

Pain pathways

SPINAL CORD

The gray matter of the spinal cord is divided into ten lamina with lamina I-IV representing the dorsal horn. The dorsal horn is capped by the Lissauer's tract which consists of branches of cutaneous Aδ and C-fibres and few visceral afferents.

Nociceptive fibres terminate in the superficial layers of lamina 1 & II while the non-painful myelinated fibres terminate in the deeper layers of lamina III, IV. Lamina II has the highest concentration of opioid receptors in the spinal cord. Modulation and inhibition of nociception may occur at this level through the use of opioids (systemic and neuraxial)

ASCENDING SENSORY PATHWAYS

Peripheral sensory neurons synapse onto the secondary interneurons of the dorsal horn. The axons of the non nociceptive secondary neurons travel isobilateral in the dorsal columns of the spinal cord as fasciculus cuneatus (upper body through T6) and fasciculus gracilis (lower body below T6) and synapse in thalamus.

The axons of the nociceptive secondary neurons after synapsing, travel contra laterally in the anterolateral aspects of the spinal cord as the neospinothalamic and paleospinothalamic tract.

Neospinothalamic tract carries fine discrimination of pain eg. Location, intensity, and first pain.

Paleospinothalamic tract responds to noxious stimuli. The paleo spinothalamic tract synapses in the thalamus, hypothalamus and limbic system and plays a role in emotional aspects of pain via limbic system. The thalamus has multiple connections to limbic system and cortex.

DESCENDING INHIBITORY PATHWAYS

The descending controls of pain project specifically onto laminas I, II,V of the dorsal horn from mesencephalon, raphenuclei

and reticular tract. The mesencephalon is rich in opioid receptors. This area sends excitatory transmissions to the rostroventral medulla which sends nordrenaline and seratonin inhibitory tracts via the dorsolateral funiculus to lamina I,II,V of spinal cord.

The noradrenaline and serotonin fibres meditate transmission between the primary afferents and the secondary neurons of the dorsal horn. Increased activity of these fibres leads to increased inhibition of pain transmission.

Location of Alpha 2 receptors;

Primary afferent terminals, on neurons in the superficial laminae of spinal cord and brainstem nuclei.

Location of opioid receptors (central);

Opioid receptors are found in the various regions in CNS namely, cerebral cortex, limbic cortex (anterior and posterior amygdale, hippocampus, hypothalamus, medial thalamus, mid brain, periaqueductal gray matter, extrapyramidal areas, substantia gelatinosa and sympathetic preganglionic neurons.

Opioid receptors are also found in the cardiac sympathetic fibres, cardiac branches of vagus, adrenal medulla, and the gastro intestinal tract.

PHARMACOLOGY

BUPIVACAINE;

Bupivacaine is an amide linked local anaesthetic. It is a hydrochloride salt of 1-butyl-N-(2, 6-dimethylphenyl) piperidine-2-carboxamide and is presented as a racemic mixture.

- It was synthesized by Ekenstam in 1957.
- First report of its use was published in 1963 by Telivuo.
- It is derived from Mepivacaine and is very stable compound and may be autoclaved repeatedly.

Pka	-	8.1
Molecular weight	-	288
Protein binding	-	95%
Lipid solubility	-	28
Elimination half life	-	210 minutes
Toxic plasma concentration	-	>1.5μg/ml
Approximate duration of action	-	175minutes

Availability:

Ampoules - 0.5% Bupivacaine hydrochloride with dextrose (Heavy) 4cc

- 0.5% Bupivacaine hydrochloride (lain)

Vials - 0.25% and 0.5% Bupivacaine hydrochloride 20cc

Dosage - Maximum dosage 3mg/kg body weight.

Uses:

- Spinal anaesthesia
- Epidural anaesthesia
- Caudal anaesthesia
- Continuous epidural anaesthesia
- Peripheral nerve block

Onset time and duration of action

Site of action	**Onset (minutes)**	**Duration (minutes)**
Intrathecal	5	90-120
Epidural	15-20	165-225
Brachial plexus	10-20	600

Pharmacokinetics:

Once injected intrathecaly, it gets absorbed by the nerve rootlets and results in the desired effect. It is rapidly absorbed from the site of injection, but the rate of absorption depends on the vascularity at the site and presence of vasoconstrictors.

High lipid solubility of bupivacaine makes it easy for nerve and vascular tissue penetration.

80-95% of the absorbed bupivacaine binds to the plasma proteins.

Distribution:

Rapid distribution phase: (α)

In this phase the drug is distributed to highly vascular region t½ of α - being 2.7 minutes.

Slow disappearance phase: (β)

In this phase the drug is distributed to slowly equilibrating tissues $t1/_2$ of β – being 28minutes.

Biotransformation and excretion phase: (δ)

$T1/_2$ of δ is 3.5hours. Clearance is 0.47 litre/ minute.

Biotransformation:

Possible pathways of metabolism of bupivacaine include aromatic hydroxylation and conjugation. Only the N-dealkylated metabolite, N-desbutyl bupivacaine has been measured in blood (or) urine after epidural (or) spinal anaesthesia. Alpha-1 acid glycoprotein is the most important plasma protein binding site of

bupivacaine and its concentration is increased by many clinical situations including post operative trauma.

Excretion:

It is through the kidney, 4-10% of the drug is excreted unchanged.

Mode of Action:

a) Site of action:

i) Peripheral nerve rootlet , fine nerve filaments

ii) The spinal nerve rootlet fine nerve filaments having a large surface area are exposed to the local anaesthetics

iii) Posterior and lateral aspects of the spinal cord itself.

b) Sodium Channel blockade:

They impede sodium ion access to the axon interior by occluding the transmembrane sodium channels thus delaying the process of depolarization and axon remains polarized. It is a non-depolarization blockade.

Pharmacodynamics:

It has got a longer duration of action but a slower onset.

Cardio vascular system:

It depresses myocardial automaticity (spontaneous phase iv depolarization) and reduce the duration of the refractory period. Myocardial contractility and conduction velocity are also depressed at high concentrations. It causes some degree of arteriolar vasodilatation. The ensuing combination of bradycardia, heart block, and hypotension may culminate in cardiac arrest.

Respiratory System:

It relaxes bronchial smooth muscle. Apnea can results from phrenic and intercostal nerve paralysis or depression of the medullary respiratory center following direct exposure to drug.

Toxicity:

Toxicity is related to plasma level of unbound drug and more likely due to an inadverdant intravenous injection. Systemic toxicity reactions primarily involve central nervous system and cardio vascular system. The blood level required to produce central nervous system toxicity is less than that required to produce circulatory collapse.

Central Nervous System Toxicity:

Early symptoms are circumoral numbness, tongue paresthesia, and dizziness. Sensory complaints include tinnitus and blurred vision. Excitatory signs (eg, restlessness, agitation, nervousness,paranoia) often precede central nervous system depression (eg, slurred speech, drowsiness, unconsciousness). Muscle twitching heralds the onset of tonic clonic seizures. Respiratory arrest often follows. The excitatory reactions area result of selective blockade of inhibitory pathways.

Cardiovascular System Toxicity:

The rate of depolarization in fast conducting tissue of purkinje fibres and ventricular muscle is decreased. The rate of recovery of bupivacaine induced block is slower than that of lignocaine. Extremely high concentration of the drug causes sinus bradycardia, hypotension, atrioventricular heart block, idioventricular rhythms, and life threatening arrhythmias such as ventricular tachycardia, ventricular fibrillation and cardiac arrest.

CLONIDINE HYDROCHLORIDE

Introduction:

Clonidine hydrochloride is a centrally acting selective partial alpha -2 agonist introduced in early 1960s, it was during its use as a nasal decongestant that its anti- hypertensive property was found out. Subsequently more insights into the pharmacological properties has led to its use in clinical anaesthesia practice as well.

Clonidine hydrochloride is an imidazoline compound and exists as a mesomeric compound. The chemical name is 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride. The structural formula is C9H9C12N3HCl.

The molecular weight is 266.56. Clonidine is an odourless, bitter, white, crystalline substance, soluble in alcohol and water. Clonidine improves the quality of anaesthesia, provides a more stable cardiovascular course during anaesthesia, presumably because of their Sympatholytic effect and need for lower dose of cardioactive anaesthetic and reduces the dose requirement of the anaesthetic agent. Clonidine may reduce the halothane MAC by upto 50% in a dose dependent manner. Clonidine potentiates the anaesthetic action

of the local anaesthetics with fewer side effects in peripheral nerve blocks and central neuraxial blockade.

Availability:

Available as one ml ampoule containing 150 micrograms.It should be stored below 25^{o}c.

Mechanism of action:

Clonidine is a centrally acting selective partial α2 adrenergic agonist with a selectivity ratio of 220: 1 in favour of α2 receptors. The three subtypes of α2 receptors are α2a, α2b, α2c. α2a receptors mediate sedation, analgesia, sympatholysis. α2b receptors mediate vasoconstriction and anti- shivering. The startle response may reflect the activation of α2c receptors. The drug is lipid soluble, penetrates the blood brain barrier to reach the hypothalamus and medulla when injected epidurally. It stimulates the inhibitory α2 adrenoreceptors to reduce the central neural transmission in the spinal neurons. Inhibition of substance- P release is believed to be involved in the analgesic effect.

The α2 adrenoreceptors are located on the afferent terminals of both peripheral and spinal neurons in the superficial laminae of the spinal cord and within several brain stem nuclei implicated in

analgesia. The superficial laminae contain three groups of neurons: tonic, adapting, single- spike firing, all of which receive their primary sensory input from Aδ and C fibres. Clonidine inhibits voltage gated Na+ and K+ channels and suppresses the generation of action potentials in tonic- firing spinal dorsal horn neurons, contributing to analgesic effect. The ability of clonidine to modify the function of potassium channels in the CNS (cell membrane become hyperpolarized) may be mechanism for profound decrease in anaesthetic requirements.

Another contribution to analgesic effect may be through the release of acetylcholine in the neuraxial region. The α2 adrenergic agonists also enhance analgesia from intraspinal opioids. Sedation is produced by its action on locus ceruleus.

Clonidine affects the blood pressure in a complex fashion after neuraxial or systemic administration because of opposing action at multiple sites. In the nucleus tractus solitarius and locus ceruleus of the brain stem, activation of post- synaptic α2 adrenoreceptors reduces sympathetic drive. It also activates nor-adrenergic imidazoline preferring binding sites in the lateral reticular nucleus producing hypotension and anti- arrythmogenic action. In the

periphery it acts on pre-synaptic α2 adrenoreceptors at sympathetic terminals reduces the release of nor-epinephrine causing vasorelaxation and reduced chronotropic drive. The brainstem and the peripheral effects of α2 adrenoreceptor stimulation are counterbalanced by the direct peripheral vasoconstriction through its action on α2 adrenoreceptors from the circulating concentrations of clonidine.

Sedation is a desired property. Clonidine produces a dose dependent sedation at the dose of 50 micrograms or more in less than 20

minutes regardless of the route of administration.

Clonidine doesn't induce profound respiratory depression even after massive overdose nor do they potentiate respiratory depression from opioids.

In peripheral nerves it produces a minor degree of blockade at high concentrations with some preference for C- fibres in the peripheral nerves and this effect in part enhance the peripheral nerve block when added to local anaesthetics, probably because the α2adrenoreceptors are lacking on the axons of peripheral nerves.

Pharmacokinetics;

Clonidine is well absorbed orally and is nearly 100% bio available and reaches peak plasma concentration with in 60 to 90 minutes. The mean half life of the drug in plasma is about 9 to 12 hours, with approximately 50% metabolized in the liver whereas is it is excreted in an unchanged form by the kidney, and its half- life can dramatically increase 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 concentration.

Clonidine is highly lipid soluble and readily distributes into extra- vascular sites including the central nervous system.

300 micrograms intravenously over 10 min produces:

Distribution t ½ : 11 ± 9 minutes.

Elimination t½ : 9 ± 2 hour, 41 hours in severe Renal dysfunction.

Volume of distribution : 2.1 ± 0.4 l/kg

Plasma protein binding : 20-40 % in vitro.

Metabolism : minor pathways with the major

Metabolite, p- hydroxyclonidine.

Excretion:

70% of the dose, mainly in the form of unchanged parent drug (40-60%) in urine.

So, the elimination t1/2 of clonidine varies as a function of creatinine clearance. In subjects undergoing hemodialysis only 5% of the body clonidine store was removed.

Dosage regimen;

Oral	- 3-5 μg/kg
Intramuscular	- 2 μg/kg
Intravenous	- 1-3 μg/kg
Spinal	- 50-100 μg
Epidural	-1-2 μg/kg
Transdermal	- 0.1- 0.3 mg released per day

Precautions:

1. In patients with renal insufficiency, lower dose is needed.
2. Sudden withdrawal of prolonged continuous epidural infusion produces hypertensive crisis. So it should be gradually discontinued over 2 to 4 days.

3. Use with caution in patients with cerebrovascular or coronary insufficiency.
4. If a patient with beta blocker is on continuous epidural therapy, beta blocker should be withdrawn several days before discontinuation of epidural clonidine.
5. Intrathecal / epidural clonidine often causes bradycardia that if symptomatic can be treated with inj. Atropine.

Contraindications:

1. Known hypersensitivity to clonidine or components of the product.
2. In patients with brady arrhythmia or AV block.
3. Patients with severe cardiovascular disease
4. Patients with cardiovascular / hemodynamic instability.

Interactions:

1. Clonidine may potentiate the CNS- depressive effect of alcohol, barbiturates or other sedative drugs.
2. Narcotics may potentiate the hypotensive effects of clonidine.
3. Tricyclic anti depressants may antagonize the hypotensive effects of clonidine.

4. Concomitant administration of drugs with a negative chronotropic/ dromotropic effect (beta blockers, digoxin) can cause or potentiate bradycardiac rhythm disturbances.

5. Beta blockers may potentiate the hypertensive response seen with clonidine withdrawal.

6. Epidural clonidine may prolong the duration of pharmacologic effects of epidural local anaesthetics, opioids, neostigmine and other drugs.

USES:

1. Preanaesthetic Medication;

Oral clonidine Preanaesthetic medication (5 μg/kg) (a) blunts reflex tachycardia associated with direct laryngoscopy for intubation of trachea, (b) decrease intraoperative lability of blood pressure and heart rate, (c) decrease plasma catecholamine concentrations, and (d) dramatically decrease anaesthetic requirements for inhaled and injected drugs. Clonidine also attenuates the rise in intraocular pressure associates with laryngoscopy and intubation.

2. Epidural block: Clonidine as a sole agent or in combination with opioids or local anaesthetics to provide excellent

analgesia in labour analgesia. Epidural clonidine is also indicated for the treatment intractable pain, which is unresponsive to maximum dose of oral or epidural opioid, as do patients with reflex sympathetic dystrophy, neuropathic pain.

3. Spinal anaesthesia: Clonidine combined with local anaesthetics improves the quality and duration of the block, minimize the tourniquet pain during lower limb surgery, and prevents shivering.
4. Caudal anaesthesia: clonidine combined with local anaesthetics increases the duration of anaesthesia and analgesia by 2 or 3 times without hemodynamic side effects. Dose 2-3 μg/kg
5. Peripheral nerve blocks: Clonidine prolongs the duration of anaesthesia and analgesia with local anaesthetics by two times in a dose of 75 to150 micro grams.
6. Bier's block: 150 microgram of clonidine enhances the tolerance of tourniquet
7. It is also used in intra articular analgesia.

8. Protection against perioperative myocardial ischemia; clonidine decreases myocardial ischemia, infarction and mortality following cardiovascular surgery.

9. To treat hypertensive crises

10. Diagnosis of pheochromocytoma; clonidine, 0.3 mg will decrease the plasma concentrations of catecholamine in normal patients but not in the presence of pheochromocytoma.

11. Treatment of shivering; Administration of clonidine, 75 μg IV stops shivering by inhibit thermoregulatory control.

12. Treatment of opioid and alcohol withdrawal syndrome;

Side effects;

1. The most common side effects are sedation and xerostomia.

2. Cardiovascular complaints are bradycardia, hypotension, and ECG abnormalities like sinusnode arrest, junctional bradycardia; high degree AV block and arrhythmia are reported rarely. Occasionally require treatment of bradycardia with I.V anticholinergics. Orthostatic hypotension occurs rarely.

3. Rebound hypertension; Abrupt discontinuation of clonidine can result in rebound hypertension as soon as 8 hours and as late as 36 hours after the last dose. Symptoms of nervousness, diaphoresis,

headache, abdominal pain, and tachycardia often precede the actual increase in systemic blood pressure. Labetalol is useful in treatment of rebound hypertension.

4. Skin rashes are occurs frequently.

5. Impotence occurs occasionally.

Over dosage and treatment:

There is no specific antidote for clonidine overdosage. Supportive measures like atropine, ephedrine, and i.v fluids are enough.

Yohimbine partially reverses the analgesia and sedation but not the BP and heart rate changes produced by the epidural clonidine.

ADRENALINE (EPINEPHRINE)

Adrenaline is the prototype drug among the sympathomimetics. Its natural function on release from adrenal medulla, include regulation of a) myocardial contractility b) heart rate c) vascular and bronchial smooth muscle tone d) Glandular secretion e) Metabolic processes such as glycogenolysis and lipolysis. It is the most potent activation of alpha adrenergic receptors, being two to ten times more active than isoproterenol. Adrenaline also activates beta 1 and beta 2 receptors.

Adrenaline – α1 + α2 +β1 + β2 + weak β3 action.

Pharmacokinetics:

Oral administration is not effective because adrenaline is rapidly metabolized in gastrointestinal mucosa and liver by MAO and COMT present in intestinal wall and liver. Therefore adrenaline is administered SC or IV. Absorption after SC injection is slow because of local adrenaline induced vasoconstriction. Adrenaline is poorly lipid soluble, preventing its ready entrance into the CNS and accounting for the lack of cerebral effects.

Clinical Uses:

a) Addition to local anaesthetic solution to decrease systemic absorption and prolong the duration of action of local anaesthetics. (5 µg/ml of local anaesthetics)

b) Treatment of life threatening allergic reactions.

c) Administration during cardio pulmonary resuscitation as the single most important therapeutic drug.

d) Continuous infusion to increase myocardial contractility. The administration of supraphysiologic doses (100µg/kg) of adrenaline during cardiopulmonary resuscitation has not been shown to be more effective than standard doses. (10µg/kg) of this catecholamine.

1-2 µg / min	-	Beta 2 Stimulation
4 µg / min	-	Beta 1stimulation
10-20 µg/min	-	Alpha & Beta

Side effects:

CVS effects:

Adrenaline stimulates beta 1 receptors to cause increased systolic BP, heart rate and cardiac output. There is modest decreased in diastolic BP reflecting vasodilatation in skeletal muscle

vasculature due to stimulation of beta 2 receptors. The net effect of these systemic blood pressure changes are an increase in pulse pressure and minimal change in MAP. Adrenaline is also increase the likehood of cardiac dysrhythmias.

Adrenaline predominantly stimulates alpha 1 receptor in skin, mucosa and hepatorenal vasculature producing intense vasoconstriction. Renal blood flow is substantially decreased by adrenaline.

Metabolic Effects:

Beta 1 - increase liver glycogenolysis and adipose tissue lipolysis.

Alpha1 - inhibit release of insulin

So, these effects produce hyperglycemia

Electrolytes:

Adrenaline induced hypokalemia by activation of Na-K pump in skeletal muscle leading to transfer K ions into cells could contribute to cardiac dysrhythmias.

Ocular Effects: Adrenaline causes contraction of the radial muscles of iris producing mydriasis. Contraction of orbital muscles produces on appearance of exophthalmus.

Gastrointestinal and Genitourinary effects:

Adrenaline produces relaxation of gastrointestinal smooth muscles. Activation of beta receptors relaxes the detrusor muscle of the bladder, whereas activation of alpha receptor contract the trigone and sphincter muscles.

Coagulation:

Blood coagulation is accelerated by adrenaline due to increased activity of factor V. Adrenaline increases the total leukocyte count but at the same time causes eosinopenia.

REVIEW OF LITERATURE

1**.** Eledjam jj, Deschodt j et al, **Canadian journal of anaesthesia 1991;** Brachial plexus block with bupivacaine: effects of added alpha-adrenergic agonists: comparison between clonidine and epinephrine. In this study, 60 patients were randomly allocated in two groups. So that 30 patients received 150 micrograms of clonidine and 30 patients received 200 micrograms of adrenaline. In clonidine group there is no difference in the onset of sensory blockade and motor blockade compare to adrenaline. Duration of motor blockade prolonged in clonidine group (580.4 ± 38.7 vs 290.6 ± 34.5minutes) compare to adrenaline group. The block produced with addition of clonidine was longer. (994.2 $\pm$ 34.2 Vs 728.3 $\pm$ 35.8 minutes) and superior to that with adrenaline. The injection of clonidine into the brachial plexus sheath is an attractive alternative to epinephrine to prolong the duration of analgesia following upper limb surgery under conduction anaesthesia.

2. Dorothee M. Gaumann, et al, **Anesthesia Analgesia** 1992; 74:719-725. Clonidine Enhances the Effects of Lignocaine on C-

Fiber Action Potential. This study concluded that the enhancing effect of a low dose of clonidine (500 μM) on lignocaine induced (500 μM) inhibition of C-fiber AP might explain the clinical observation that clonidine, at approximately 1000-fold lower concentrations than lignocaine, prolongs the action of lignocaine in peripheral nerve block.

3. Dorothee Gaumann et al, **Anaesthesia & Analgesia 1992** Comparison between clonidine (150 mics) and epinephrine (200 mics) admixture to lignocaine in brachial plexus block in this study suggests that the adding of 150 microgram clonidine prolong the duration of analgesia by > 12 hours and also useful adjuvant to those in whom the administration of epinephrine is contraindicated.

4. Singelyn et al, Regional **anaesthesia and pain medicine 1992**; Adding Clonidine to Mepivacaine Prolongs the Duration of Anesthesia and Analgesia after Axillary Brachial Plexus Block. In this study 90 patients three groups divided into group A 40 ml 1% mepivacaine + adrenaline 200 mics, group B 40 ml 1% mepivacaine + adrenaline 200 mics + S/C clonidine 150 mics, group C 40 ml 1% mepivacaine + adrenaline + clonidine 150 mics. Duration of

anaesthesia and analgesia prolonged respectively by 37 ± 6% and 103 ± 16% when compared to group A and 32 ± 7% and 89±15% when compared to group B. One hundred fifty micrograms clonidine added to mepivacaine for brachial plexus block prolongs the duration of anesthesia and analgesia. Our results suggest that this effect of clonidine is local rather than systemic.

5. FJ Singelyn et al**,** Anesthesia **& Analgesia, 1996;** A minimum dose of clonidine added to mepivacaine prolongs the duration of anesthesia and analgesia after axillary brachial plexus block. This study reported that the dose of clonidine required prolonging significantly the duration of both anesthesia and analgesia after axillary brachial plexus blockade is 0.5 microgram/kg and that, at this dose, clonidine may be used without important reported side effects even in outpatients.

6. Bernard, Jean-Marc et al, **Anaesthesiology 1997** ; Dose-Range Effects of Clonidine Added to Lidocaine for Brachial Plexus Block In this study, 3 doses of clonidine 30, 90, 300 micrograms added to lignocaine. Clonidine prolonged analgesia by the mean of 770 minutes (Range 190 to 1440 minutes) for larger doses. This study

suggests that a small dose of clonidine enhances the quality of the peripheral blocks from lignocaine and limits the classical alpha$_2$ - agonist side effects to sedation.

7. A. .El Saied, M. P. Steyn et al, **Canadian Journal of anaesthesia 2000;** Clonidine prolongs the effect of ropivacaine for axillary brachial plexus blockade**.** In this study, the clonidine patients shows that increased duration of sensory loss from 489 to 628 minutes with mean difference 138 minutes, the motor blockade from 552 to 721 minutes with mean difference 170 minutes, analgesia 587 to 828 minutes with mean difference of 241 minutes. This study concluded that the addition of 150μg of clonidine to ropivacaine, for brachial plexus blockade, prolongs motor and sensory block and analgesia, without an increased incidence of side effects**.**

8. Henri Iskandar, et al **Anesthesia Analgesia 2001;** The enhancement of Sensory Blockade by Clonidine Selectively added to Mepivacaine After Midhumeral Block. This study concluded that the addition of clonidine to local anesthetics prolongs the duration of sensory block in the nerves. Such a finding could have interesting

clinical applications in ambulatory or planned surgery in which motor function is best maintained.

9. W. Erlacher, C. Schuschnig, F. et al, **Acta anaesthesia 2001** ; The effects of clonidine on ropivacaine 0.75% in axillary perivascular brachial plexus block.

10. Wolfgang Erlacher et al, Canadian **journal of anaesthesia 2001**; Clonidine as adjuvant for mepivacaine, ropivacaine and bupivacaine in axillary, perivascular brachial plexus block**.** The present study shows that the addition of clonidine has a different impact on each of the three local anesthetics investigated in terms of onset and duration of block. Mepivacaine group rapid onset compared to ropivacaine and bupivacaine group. Duration of sensory blockade was prolonged by clonidine only in mepivacaine and bupivacaine groups. The Mepivacaine + clonidine – 468 $\pm$ 62 mins Vs mepivacaine alone - 212 $\pm$ 47 mins, ropivacaine + clonidine – 712 $\pm$ 82 mins Vs ropivacaine alone - 702 $\pm$ 52 mins, bupivacaine + clonidine – 972 $\pm$ 72 mins Vs bupivacaine alone – 728 $\pm$ 36 mins.

11. Henri Iskandar et al **Anesthesia Analgesia 2000;** The Analgesic Effect of Interscalene Block Using Clonidine as an Analgesic for

Shoulder Arthroscopy. This study reported that Clonidine administered via an interscalene catheter enhanced analgesia compared with systemic administration.

12. D. Hutschala et al, **European Journal of Anaesthesiology 2004;** Clonidine added to bupivacaine enhances and prolongs analgesia after brachial plexus block via a local mechanism in healthy volunteers. This study suggested that admixture of clonidine 2mics / kg to bupivacaine 0.25% 40 ml plus epinephrine prolongs and enhances brachial plexus blockade by 270 minutes compared without clonidine. Lower clonidine plasma concentrations for block treatment strongly suggest a local effect.

13**.** A. Duma, B. Urbanek, et al, **Br. J. anaesthesia 2005** ; Clonidine as an adjuvant to local anaesthetic axillary brachial plexus block: a randomized, controlled study.

14. Gabriella Iohom, et al, **Anesthesia Analgesia 2005 ;** The Effects of Clonidine Added to Mepivacaine for Paronychia Surgery Under Axillary Brachial Plexus Block. This study suggest that in the setting of distal infected tissue surgery under ABPB infected tissues are resistant to anesthesia compared with healthy areas within the

same nerve distribution and clonidine added to mepivacaine enhances both anesthesia and postoperative analgesia.

15. Brian M. Ilfeld et al, **Anaesthesia Analgesia 2003** ; Continuous Infraclavicular Perineural Infusion with Clonidine and Ropivacaine Compared with Ropivacaine Alone: A Randomized, Double-Blinded, Controlled Study. This study reported that clonidine is often added to long-acting local anesthetic perineural infusions in an effort to improve postoperative analgesia.

16. Cucchiaro G, Ganesh A et al, **Anaesthesia Analgesia 2007 ;** The effects of clonidine on postoperative analgesia after peripheral nerve blockade in children. This study concluded that the addition of clonidine to bupivacaine and ropivacaine can extend sensory block by a few hours, and increase the incidence of motor blocks.

17. Popping DM, Elian et al, **Anaesthesiology 2009;** clonidine as an adjuvant to local anaestheics for peripheral nerve and plexus block: Meta analysis of randomized trials. This study reported that the clonidine prolonged the duration of post operative analgesia by 122 minutes, sensory blockade by 74 minutes, and motor blockade by 41 minutes.

18. Nakamura M et al, **European Journal of Pharmcology 1988;** Peripheral analgesic action of clonidine: mediation by release of endogenous enkephalin-like substances. These studies suggest that, in addition to its central analgesic action, clonidine can induce peripheral antinociception by an alpha 2-adrenoceptor-mediated local release of enkephalin-like substances.

19. Maze & Tranquil et al. **Anaesthesiology 1991;** Alpha-2 adrenergic agonists role in clinical anaesthesia. This study concluded that clonidine has analgesic activity like a potent opioid narcotic, as anxiolytic & sedative as benzodiazepine, and sympatholytic & its action is reversible.

MATERIALS AND METHODS

This study was conducted at Government Rajaji Hospital attached to Madurai medical college. 80 patients of ASA grade I or II of either sex and age more than 20 years undergoing upper limb surgery (mostly orthopedic and plastic surgeries) were included. Patients allergic to local anaesthetics and contraindicated to clonidine were excluded from this study. It was double blinded study in which patients were randomly allocated into two groups A and B. Each group comprises of 40 patients, surgery was done under supraclavicular approach to Brachial plexus block.

PROCEDURE

After ethical committee approval, informed consent was obtained from the patients. No premedication was given to the patients. Intravenous access was obtained, Anaesthesia machine checked, resuscitative equipments and drugs were kept ready. Supraclavicular block was performed by classic approach after eliciting paresthesia. If paresthesia is not elicited, only first rib is encountered excluded from this study.

In GROUP A: Patients received supraclavicular block with 40ml of 0.25% Bupivacaine + 200 microgram of adrenaline.

In GROUP B: Patients received supraclavicular block with 40ml of 0.25%Bupivacaine + 150 microgram of clonidine.

Care was taken so that the toxic doses of the local anaesthetics were not exceeded according to the weight of the patients.

PARAMETERS OBSERVED

1. Onset of Analgesia

Onset of analgesia was taken as abolishment of pins prick pain over the distribution of ulnar and median and was assessed every minute after the performance of the block.

2. Onset of motor blockade:

Onset of motor blockade was assessed every 2 minute after the block using four point scales

0- Normal power

1- Weakness but able to move arm

2- Not able to move arm but the fingers

3- Complete motor Blockade

Attaining a score of 2 was considered as the onset of motor Block

3. Duration of surgery;

4. Duration of motor Blockade:

When (3) in the four point scale changes to (2) the motor blockade is said to reverse. The duration of motor block is noted from the time from scale (3) to scale (3).

5. Duration of analgesia;

The pain was assessed using visual Analogue scale having 10cm length numbered from 0 to 10. Patient was explained about the visual Analogue scale as 0 - No pain and 10 the worst possible pain and was asked the score in visual analogue scale.

The patient was observed every 30 minutes after the surgery is over till the motor block reverses and thereafter hourly for 6 hrs; 2 hourly for next 6 hrs and than of 24 hours.

a. Duration of absolute pain free period ; the post operative period during which the patient did not have pain (VAS– 0)
b. Time of which VAS score is greater than 5 is noted and patient was given intramuscular NSAID (Injection – Diclofenec)
c. Duration of post operative analgesia; the period of time after the surgery till the patient needs analgesic (VAS score more than 5)

6. Vital parameters;

Pulse rate,

Blood pressure,

Respiratory rate are monitored periodically.

7. Sedation score;

Brain & Ready score was employed

0 – Fully awake

1- Drowsy

2- Drowsy but arousable on touch or call

3- Drowsy but arousable on deep stimuli

4- somnolent

8. Side effects noted are

hypotension,

bradycardia.

9. Patients in whom the block was unsuccessful due to total failure of missed dermatomes which needed intravenous supplementation or general anaesthesia were excluded from the study.

Statistical Tools;

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2008).**

Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-square test was usd to test the significance of difference between quantitative variables and Yate's test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant result.

OBSERVATIONS AND RESULTS

This study comprised of two groups. The patients in group A received 0.25% Bupivacaine 40ml + 200 microgram of adrenaline. In group B received 0.25% Bupivacaine 40ml + 150 microgram of clonidine.

AGE & WEIGHT:

Age distribution in the Adrenaline group A varied from 20 years to 72 years with mean age of 34.6 years and standard deviation of (15.5).

In clonidine group (group B) Age varied from 20 years to 65 years with mean value of 34.9 years and standard deviation of (12.7) as shown in table 1 and figure 1.

Weight of the patients in the adrenaline group A had a mean value of 60.3 kg with standard deviation of 5.0. In clonidine group mean value of 61.7 and standard deviation of 5.0 as shown in Table 2 and figure 2.

In group A 31 patients were male and rests were female. In group B 28 patients were male and rests were female.

Table - 1

AGE DISTRIBUTION

Age (yrs)	Group A (No.of patients)	Group B (No.of patients)
20 – 30	22	17
31 – 40	8	13
41 – 50	3	5
> 50	7	5
Range (years)	20-72	20-65
Mean(years)	34.6	34.9
S.D	15.5	12.7
p value	0.5502	

Table - 2

Weight Distribution

Weight (kgs)	Group A (No.of patients)	Group B (No.of patients)
51 – 60	27	19
>60	13	21
Range (kgs)	55-68	52-68
Mean (kgs)	60.3	61.7
S.D	5.0	5.0
P value	0.2847	

Onset of Sensory Block:

Time taken for the onset of sensory blockade in group A (Adrenaline) varied from six minutes to a maximum of 12 minutes with mean values of 9.18 minutes with standard deviation of 1.55. In group B (clonidine) it varied from seven minutes to 12 minutes with mean value of 8.78 with standard deviation of 1.12 as shown Table 3, fig 3.

Table – 3

Onset of sensory Block

Onset (min)	Group A (No.of patients)	Group B (No.of patients)
5-7	3	4
8-10	31	34
11-13	6	2
>14	0	0
Range(minutes)	6-12	7-12
Mean (minutes)	9.18	8.78
S.D	1.55	1.12
p value	0.2208	

Onset of motor block:

Onset of motor block varied from 10 minutes to 18 minutes in the (adrenaline) group A with mean 14.13 minutes and standard deviation of 1.67.

In (clonidine) group B it varied from 10 minutes to 16 minutes with a mean of 13.78 minutes and standard deviation of 1.27 as shown in Table 4, fig 4.

Table – 4

Onset of Motor Blockade

On set (min)	Group A (No.of patients)	Group B (No.of patients)
8-10	3	1
11-13	9	14
14-16	27	25
> 17	1	0
Range(minutes)	10-18	10-16
Mean (minutes)	14.13	13.78
S.D	1.67	1.27
p value	0.2362	

Duration of Surgery:

The duration of surgery in group A varied from 90 minutes to 240 min with mean of 107.0 minutes standard deviation 24.4. In group B, it varied from 90 minutes to 150 minutes with mean of 113.8 minutes and standard deviation of 14.3 as shown in Table 5, fig 5.

Table – 5

Duration of Surgery

Duration (min)	Group A (No.of patients)	Group B (No.of patients)
60-90	12	3
91-120	27	31
121-150	-	6
> 150	1	-
Range(minutes)	90-240	90-150
Mean (minutes)	107.0	113.8
S.D	24.4	14.3
p value	0.0755	

Duration of Motor Blockade:

The duration of motor blockade in group A varied from 250 minutes to a maximum of 330 minutes with a mean value of 280.75 minutes and a standard deviation of (18.7)

In group B, varied from 480 minutes to 620 minutes with mean value of 550.8 minutes and standard deviation of (28.7) as shown in Table 6, fig.6.

Table – 6

Duration of Motor Block

Duration (mins)	Group A (No.of patients)	Group B (No.of patients)
250-300	30	-
301-400	10	2
401-500	-	36
>500	-	2
Range(minutes)	250-330	480-620
Mean (minutes)	280.75	550.8
S.D	18.7	28.7
p value	0.0001	

Duration of absolute pain free period;

The post operative period during which the patient did not have pain (i.e VAS – 0) in group A varied from 330 minutes to a maximum 480 minutes with mean of 371.4 minutes and a standard deviation 27.5.

In group B it varied from 500 minutes to a maximum of 720 minutes with mean of 643.8 minutes and standard deviation 36.6 as shown as table 7 and figure 7.

Table -7

Duration of absolute pain free period

Duration (mins)	Group A (No.of patients)	Group B (No.of patients)
300-400	37	-
401-500	3	1
501-600	-	4
>600	-	35
Range(minutes)	330-480	500-720
Mean(minutes)	371.4	643.8
S.D	27. 5	36.6
p value	0.0001	

Duration of post operative analgesia:

The post operative period till the patient demands systemic analgesic (ie. VAS score > 5) varied from 480 minutes to a maximum of 670 minutes in group A with a mean of 564.75 minutes and a standard deviation of (24.2).

In the group B clonidine group, it varied from 840 minutes to a maximum of 1080 minutes with mean of 959.3 minutes and standard deviation of (38.3) as shown in Table 8, fig 8.

Table – 8

Duration of Post operative Analgesia

Duration (mins)	Group A (No.of patients)	Group B (No.of patients)
400-500	4	-
501-600	30	-
601-900	6	4
>900	-	36
Range(minutes)	480-670	840-1080
Mean(minutes)	564.75	959.3
S.D	24.2	38.3
p value	0.0001	

Sedation Score:

In group A, it was mean 0.2 $\pm$ 0.1, in group B it was mean 1.7 $\pm$ 0.51 as shown in the table 9 and figure 9.

Table – 9

Sedation Score

Sedation Score	Group A (No.of patients)	Group B (No.of patients)
0	32	0
1	8	12
2	0	27
3	0	1
4	0	0
Mean	0.2	1.7
SD	0.1	0.51
p value	0.0001	

DISCUSSION

Alpha-2 agonist like clonidine was introduced in the early 1960s as a nasal decongestant. During its use a nasal decongestant, the antihypertensive property of drug was found out. Subsequently more insights into the pharmacological properties have led to its use in clinical anaesthetic practice as well.

Clonidine assumes greater importance as anaesthetic adjuvant and analgesic. Its primary effect is sympatholytic. It reduces peripheral norepinephrine release by stimulation of prejunctional inhibitory alpha-2 adrenoreceptors. It inhibits central neural transmission in the dorsal horn by presynaptic and postsynaptic mechanism and directly in spinal preganglionic sympathetic neurons. Traditionally it was used as antihypertensive drug, but uses based on sedative, anxiolytic, and analgesic properties are being developed. In 1988 Nakamura M et al reported that Peripheral analgesic action of clonidine mediated by release of endogenous enkephalin-like substances.

In 1991 Maze & Tranquil et al reported that Alpha-2 adrenergic agonists has an analgesic activity like a potent opioid, is anxiolytic & sedative as benzodiazepine, and sympatholytic and its action is reversible.

Adjuncts to local anaesthetics for peripheral plexus blockade may enhance the quality and duration of anaesthesia and postoperative analgesia. Clonidine has central analgesic action in addition to its peripheral antinociception by an alpha-2 adrenoreceptor mediated local release of encephalin like substances.

Clonidine enhances both sensory and motor blockade of local anesthetics in peripheral nerve blockade and central neuroxial blockade. Clonidine blocks conduction of C and A gamma fibers and increases potassium conductance in isolated neurons and intensifies the conduction of local anesthetics.

Clonidine may modify the action of local anaesthetics in the sodium channel either directly or indirectly.

By statistical analysis of two groups the age distribution in both groups was statistically not significant with a p value of 0.5502 ($p > 0.05$).

When comparing the weight of the patients in two groups it was statistically not significant with a p value of 0.7508 (p >0.05). Both the groups were comparable in relation to Age and Weight.

Duration of surgery was also comparable in both groups with a p value of 0.0755 (p> 0.05).

Onset of sensory Blockade:

Mean onset of sensory block in group A was 9.18 ± 1.55 minutes and in group B, it was 8.78 ± 1.12 minutes. The difference between the two groups was statistically insignificant with a p value of 0.2208 (p>0.05).

Onset of motor blockade:

Mean onset of motor blockade in group A was 14.1 ± 1.67 minutes and in group B it was 13.25 ± 1.37 minutes. The difference between the two groups was statistically insignificant with a p value of 0.0744(p>0.05).

On addition of clonidine to the local anaesthetic solution there is no difference in the onset of sensory and motor blockade compared to the adrenaline group. Eledjam JJ, Deschodt J et al study also reported that no difference in the onset of sensory blockade and motor blockade.

Duration of Motor Blockade:

Mean duration of motor block from score 3-3 in group A was 280.75 ± 18.7 minutes and in group B 550.8 ± 28.7 minutes. The difference between the two groups was statistically significant with a p value of 0.0001($p<0.05$).

Addition of clonidine to local anaesthetic solution has significantly prolonged duration of motor blockade. These results correlates with studies conducted by Eledjam JJ, Deschodt J et al, in clonidine group it was 580.4 ± 38.7 minutes, compared to adrenaline group it was 290.6 ± 34.5 minutes.

Duration of Absolute pain free period:

The mean duration of absolute pain free period is till the VAS score 0 in Group A was 371.4 $\pm$ 27.5 minutes and in group B it was 643.8 $\pm$ 36.6 minutes.

The difference between the two groups was statistically significant with a p value of 0.0001 ($p<0.05$).

Addition of clonidine to local anaesthetic solution prolonged the absolute pain free period significantly when compared to adrenaline group. These results also correlate with studies conducted by Eledjam JJ, Deschodt J et al.

Duration of post operative analgesia:

The mean duration of post operative analgesia is till the VAS score > 5 and in group A it was 564.75 ± 24.2 minutes and in group B it was 959.3 +38.3 minutes.

The difference between the two groups was statistically significant with a p value of 0.0001 ($p<0.05$).

Addition of clonidine to local anaesthetic solution prolonged the post operative analgesia significantly when compared to adrenaline group. These results correlate favorably with studies conducted by Eledjam JJ, Deschodt J et al, in clonidine group it was 994.2 ±34.2 minutes, compared to adrenaline group it was 728.3 ± 35.8 minutes.

Sedation score:

The sedation score in both groups are noted. The sedation score in group B it was mean 1.72 ± 0.51, in group A it was mean 0.2±0.1. In clonidine group since the sedation score was not more than 2, the respiratory function was not compromised. So intra operative sedation is well observed in clonidine group.

Side Effects:

Patients were observed for the side effects such as hypotension and bradycardia. In both groups there is no incidence of hypotension and bradycardia. No complications related to brachial plexus block were observed.

In this study, the addition of Clonidine to the local anaesthetic solution produces no difference in the onset of sensory and motor blockade when compared to adrenaline group. The duration of post operative analgesia is significantly higher in clonidine group when compared to adrenaline group. The duration of motor blockade is also increased in clonidine group. These inferences provide clonidine produces a prolonged sensory and motor blockade.

SUMMARY

80 patients of ASA grade I or II undergoing upper limb surgeries were randomly assigned into two groups, Group A and B

Surgery was done under supraclavicular approach to brachial plexus block.

The Patients in group A received 40 ml 0.25% bupivacaine and 200 microgram of adrenaline. In group B received 40 ml of 0.25% of bupivacaine and 150 micrograms clonidine.

Parameters observed were time of onset of sensory block and motor block, duration of motor blockade, duration of post operative analgesic, duration of absolute pain free period, sedation score and side effects.

Study shows that

1. Addition of clonidine to local anaesthetic solution shows no difference in the onset of sensory blockade and motor blockade compared to adrenaline.
2. Addition of clonidine to local anaesthetic solution significantly prolongs the duration of post operative analgesia by 395 minutes compared to adrenaline.

3. Addition of clonidine to local anaesthetic solution increases the duration of motor blockade by 170 minutes compared to adrenaline.
4. Addition of Clonidine to local anaesthetic solution increases the duration of absolute pain free period by 272 minutes compared to adrenaline.
5. In clonidine group intraoperative sedation is well observed without compromising respiratory function.
6. There are no side effects like hypotension and bradycardia in clonidine group.

CONCLUSION

The addition of clonidine to local anaesthetic solution in supraclavicular approach to brachial plexus block prolongs the duration of postoperative analgesia and motor blockade, when compared to the adrenaline.

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PROFORMA

Comparison of CLONIDINE and ADRENALINE as adjuvants to bupivacaine in supraclavicular approach to Brachial plexus block

Name: Age: Sex: ASA Grade :

Address : Weight: IP No :

Diagnosis :

Surgery :

Investigations:

Hb% : Urine → Albumin, Sugar

Blood urea - mg%

Sugar - mg%

creatinine - mg%

ECG : X ray chest:

Group A : Supraclavicular block with Bupivacaine 0.25% 40 ml +200 micrograms of adrenaline

Group B : Supraclavicular block with bupivacaine 0.25% 40 ml + 150 micrograms of clonidine

OBSERVATION :

Onset of sensory blockade :

Onset of motor blockade :

Duration of surgery :

Duration of Motor blockade :

Duration absolute pain free period :

Duration of post operative analgesia :

Side Effects :

Hypotension : Yes / No

Bradycardia : Yes / No

Motor Block :

0 - Normal power

1 - Paresis but able to move arm

2 - Not able to move arm but able to move fingers

3 - Complete motor blockade

VAS (Visual Analogue score):

Sedation score:

Brain & Ready score was employed

0 - Fully awake

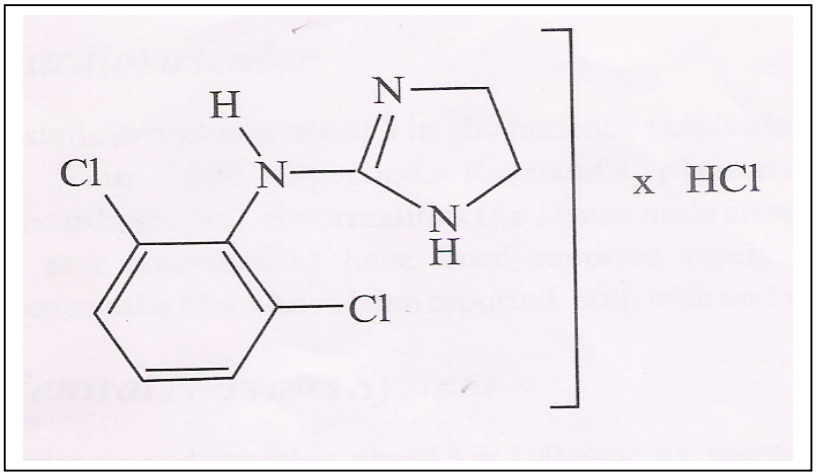
1- Drowsy

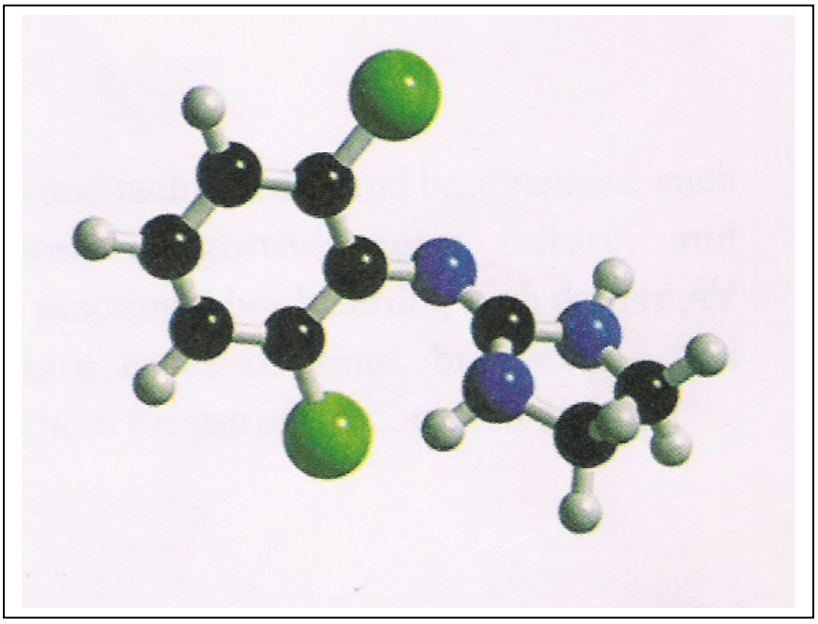
2- Drowsy but arousable on touch or call

3- Drowsy but arousable on deep stimuli

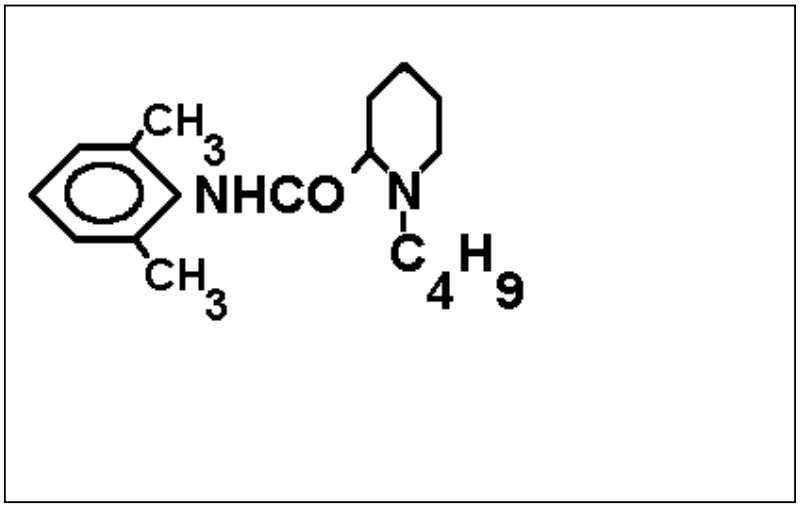
4- somnolent

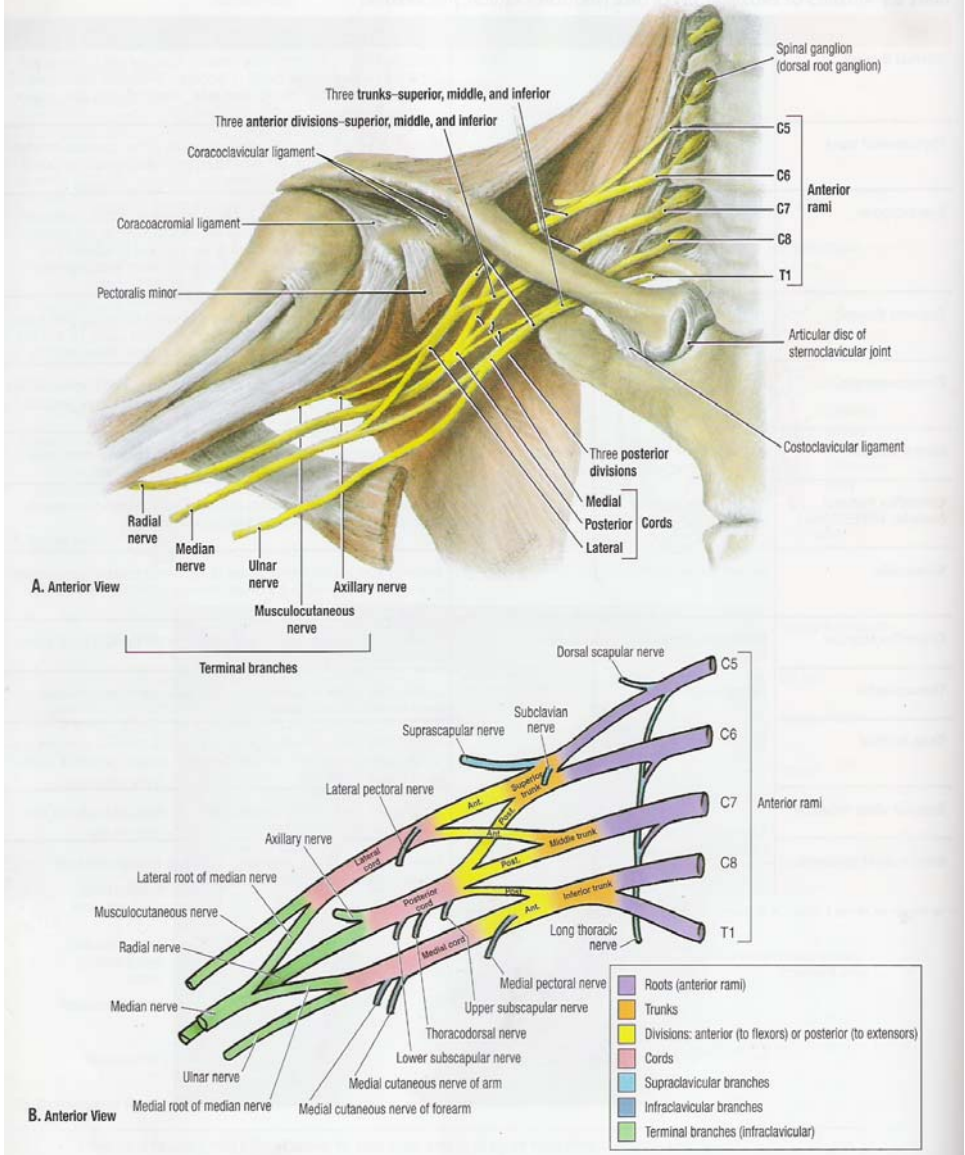
CLONIDINE HYDROCHLORIDE





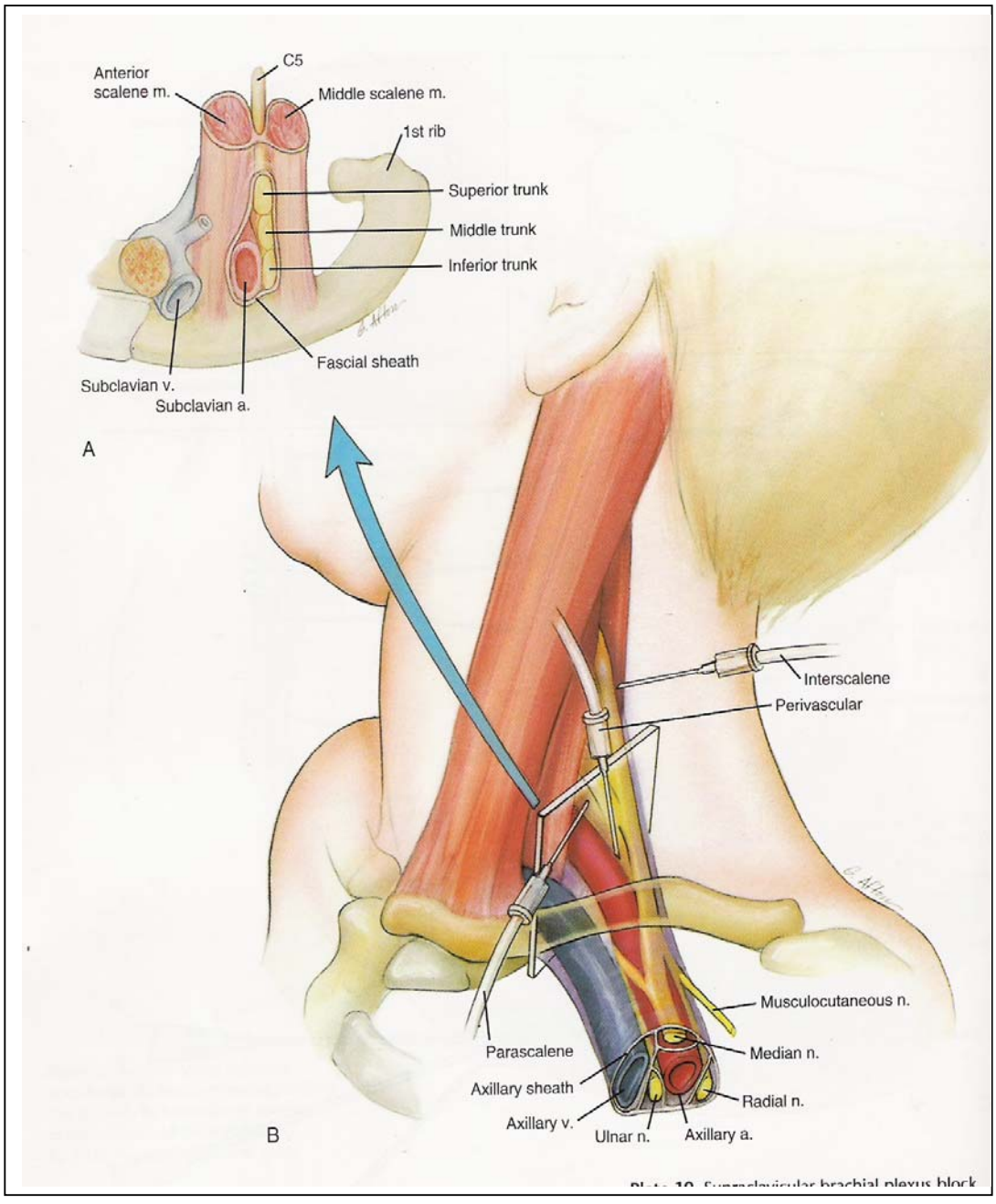
BUPIVACAINE





6.23 **Brachial plexus**

A. Dissection. B. Schematic illustration.


C5
Anterior scalene m.
Middle scalene m.
1st rib
Superior trunk
Middle trunk
Inferior trunk
Fascial sheath
Subclavian v.
Subclavian a.
A
Interscalene
Perivascular
Musculocutaneous n.
Parascalene
Median n.
Axillary sheath
Radial n.
Axillary v.
Ulnar n.
Axillary a.
B

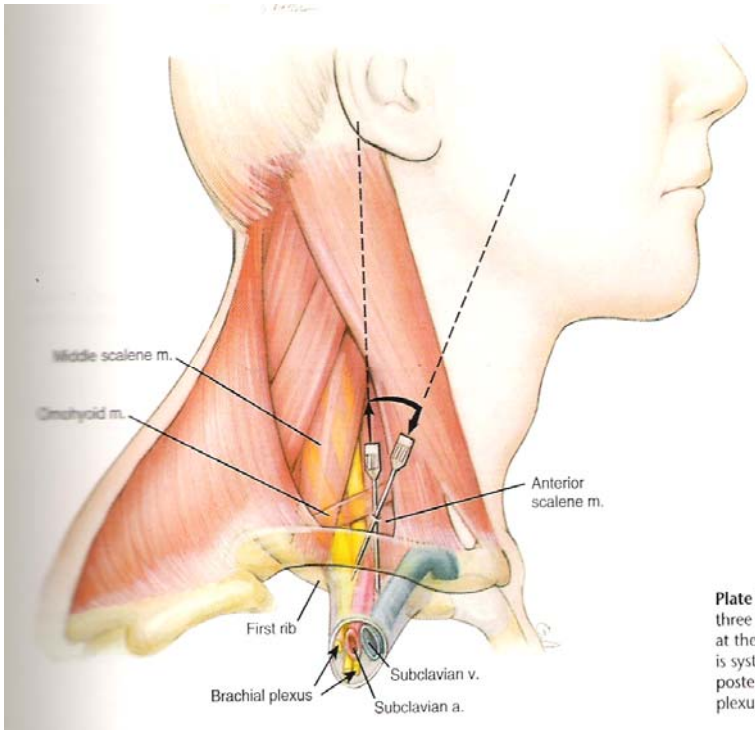


Plate 3 Supraclavicular block. The three trunks are compactly arranged at the level of the first rib. The needle is systematically walked anteriorly and posteriorly along the rib until the plexus is located.

MASTER CHART GROUP A - ADRENALINE

s.No	Group	Name	Age/sex	ASA	I.P NO	Surgery	Weight	Onset sensory block	Onset motor block	Duration surgery	Duration motor block	Duration absolute pain free period	Duration post op analgesia	First VAS score	Sedation	Hypotension	Brady cardia
1	A	Mookaye	50/F	II	29635	Debridment & Tendon repair	63	8	14	90	320	405	580	2	0	nil	nil
2	A	Thangaraj	28/M	I	39395	Debridment& k wire	63	9	14	90	260	380	560	1	0	nil	nil
3	A	Raja	34/M	I	36771	Cutinjury & Tendon repair	56	7	13	110	280	370	550	2	0	nil	nil
4	A	Anthoni	40/M	I	42330	Rt olecranon# ORIF	68	10	14	120	270	370	480	3	1	nil	nil
5	A	Karthikayan	22/M	I	46056	Debridment& k wire	60	9	14	100	280	360	560	2	0	nil	nil
6	A	Poovaye	60/F	II	40322	#BB FA & ORIF	57	8	13	110	310	360	580	2	0	nil	nil
7	A	Selvasivam	27/M	I	56317	Crush injury & Debridment	56	11	16	90	290	380	500	2	1	nil	nil
8	A	Sakthivel	31/M	I	56314	Crush injury & Debridment	67	9	14	90	280	400	590	3	0	nil	nil
9	A	krishnan	55/M	I	55285	# Montagia & ORIF	56	8	12	120	250	340	660	2	0	nil	nil
10	A	Sivakumar	23/M	I	21423	Crush injury & Debridment	58	6	10	100	280	480	580	2	0	nil	nil
11	A	Murugan	39/M	I	53977	Rt SOH # & ORIF	60	8	14	120	310	390	480	1	0	nil	nil
12	A	Balamurugan	29/M	I	57360	Rt olecranon# ORIF	56	12	16	110	290	370	670	2	0	nil	nil
13	A	Pandiyan	29/M	I	60853	Lt crush injury & debridment	68	10	14	90	280	380	560	2	1	nil	nil
14	A	Subramani	65/M	II	60747	Rt crush injury & debridment	60	8	14	90	260	380	580	3	0	nil	nil
15	A	Swaminathan	22/M	I	61916	Cutinjury & Tendon repair	55	8	14	90	280	400	660	2	0	nil	nil
16	A	Raju	21/M	I	61145	Degloving injury &Debridmrnt	58	8	12	100	280	400	580	2	0	nil	nil
17	A	Palaniammal	39/F	I	59338	# Rt BB FA & ORIF	66	10	14	110	260	350	520	2	0	nil	nil
18	A	Akilandan	20/F	I	56324	Contracture Rt hand & release SSG	59	10	16	100	280	400	530	1	1	nil	nil
19	A	Raju	26/M	I	65995	Cutinjury Rt & Tendon repair	56	12	18	90	300	410	510	1	0	nil	nil
20	A	Raju	30/M	I	59421	Rt raw area & SSG	58	10	16	100	260	390	490	2	0	nil	nil
21	A	Muthukaruppan	47/M	II	66054	Lt crush injury & debridment	58	8	12	100	250	380	590	2	1	nil	nil

22	A	Kesavan	27/M	I	63831	Rt ext tendon injury & Repair	67	9	15	100	320	370	580	1	0	nil	nil
s.No	Group	Name	Age/sex	ASA	I.P NO	Surgery	Weight	Onset sensory block	Onset motor block	Duration surgery	Duration motor block	Duration absolute pain free period	Duration post op analgesia	First VAS score	Sedation	Hypotension	Brady cardia
23	A	Beer mohamood	23/M	I	68406	Rt cut injury & Tendon repair	59	8	13	100	260	380	590	1	1	nil	nil
24	A	Muthusamy	25/M	I	74782	Lt galazi # & ORIF	57	10	15	120	250	360	570	2	0	nil	nil
25	A	Duraipandi	72/M	II	87188	Rt Galazei # & ORIF	57	9	14	110	310	350	560	2	0	nil	nil
26	A	Sophy	30/F	I	87268	Rt # BB FA & ORIF	59	8	13	110	330	360	490	2	1	nil	nil
27	A	Mani	65/M	II	76015	Lt # SOH & ORIF	67	12	16	120	260	340	550	3	0	nil	nil
28	A	Valarmathi	33/F	I	72284	Rt # BB FA & ORIF	58	10	14	120	270	350	560	3	0	nil	nil
29	A	Mariappan	40/M	I	79332	Lt # BB FA & ORIF	58	10	16	110	290	360	570	2	1	nil	nil
30	A	Saravanan	20/M	I	79814	Rt # SOH & ORIF	59	9	15	120	280	350	560	2	0	nil	nil
31	A	Palpandi	20/M	I	89536	Rt # SOH & ORIF	57	12	16	120	270	340	550	2	0	nil	nil
32	A	Latha	26/F	I	93025	Rt montagaia # ORIF	66	8	12	120	250	350	570	2	0	nil	nil
33	A	Kasakatha perun	31/M	I	43751	Rt # SOH& vascular inj & ext fix	68	8	13	240	320	390	610	2	0	nil	nil
34	A	Ramesh	25/M	I	62516	Lt crush injury & debridment	58	8	14	100	260	380	560	2	0	nil	nil
35	A	Malliga	55/F	I	63528	Rt crush injury & debridment	56	10	16	90	320	360	620	3	0	nil	nil
36	A	krishnan	25/M	I	22331	Raw area Rt hand & debrid& SSG	67	6	10	90	300	350	580	2	0	nil	nil
37	A	Parkani	30/F	I	28451	Rt tendon injury & repair	56	10	14	100	270	360	560	3	0	nil	nil
38	A	Ramasamy	60/M	II	25378	Lt crush injury & debridment	58	12	16	90	260	340	540	2	0	nil	nil
39	A	Vanniraj	50/M	I	29286	Lt # BB FA & ORIF	69	10	14	90	260	330	610	2	0	nil	nil
40	A	Anantharaj	24/M	I	28334	PBC Lt elbow & release SSG	59	9	15	110	280	340	550	2	0	nil	nil

						MASTER CHART GROUP B - CLONIDINE											
s.No	Group	Name	Age/sex	ASA	I.P NO	Surgery	Weight	Onset sensory block	Onset motor block	Duration surgery	Duration motor block	Duration absolute pain free period	Duration post op analgesia	First VAS score	Sedation	Hypotension	Brady cardia
1	B	Vadukan	38/M	I	37052	Lt #BB FA & ORIF	56	7	13	120	560	660	900	2	2	Nil	Nil
2	B	Krishnamoorthy	30/M	I	37760	Rt # SOH & ORIF	67	10	15	140	550	650	920	1	2	nil	nil
3	B	Regina devi	21/M	I	38904	Rt # olecranon & ORIF	66	9	14	110	550	670	960	2	2	nil	nil
4	B	Booma	38/F	I	41794	Rt# lat condyle & ORIF	59	12	16	110	570	670	980	2	2	nil	nil
5	B	Prasath	38/M	I	39553	wrist injury & Debridment	67	10	14	90	570	660	960	1	2	nil	nil
6	B	Ramar	54/M	II	43264	Rt # lat condyle & ORIF	58	9	14	110	560	650	920	3	1	nil	nil
7	B	Suriyaammal	40/F	I	51923	Lt # BB FA & ORIF	67	8	12	120	540	640	900	2	1	nil	nil
8	B	Jeyaselan	35/M	I	52850	Rt # montagia & ORIF	66	10	14	110	480	500	840	2	2	nil	nil
9	B	Balakrishnan	45/M	I	54244	Rt # SOH & ORIF	58	9	14	110	560	640	960	2	2	nil	nil
10	B	Prakash	36/M	I	39553	Lt raw area FA & ORIF	68	8	13	100	540	600	940	1	2	nil	nil
11	B	vedanayam	40/M	I	55672	# BB FA ORIF	58	8	15	110	550	600	950	2	1	nil	nil
12	B	Suseela	49/F	I	57934	Lt galazi # & ORIF	67	9	13	110	550	610	960	1	1	nil	nil
13	B	pandi	34/M	I	34233	Rt # ulna ORIF	58	10	14	120	540	610	980	2	2	nil	nil
14	B	Sonai muthu	31/M	I	55545	Rt ulnar nerve injury repair	68	9	15	150	550	620	1020	2	3	nil	nil
15	B	Ramar	50/M	I	43726	Rt # SOH ext fixator	56	8	14	140	520	660	970	3	2	nil	nil
16	B	Abudal hasan	60/M	II	42726	Rt SOH # & ORIF	60	7	13	120	500	580	970	2	1	nil	nil
17	B	Sivakumar	22/M	I	61004	#BB FA & ORIF	65	8	14	110	480	650	950	1	2	nil	nil
18	B	Ramakrishanan	30/M	I	522145	Rt # lat condyle & ORIF	58	10	14	110	520	660	960	2	1	nil	nil
19	B	Alexpandiyan	35/M	I	533162	Rt # BB FA & ORIF	64	8	14	110	520	640	950	2	1	nil	nil
20	B	Karthick raja	22/M	I	68903	Rt ulnar nerve injury repair	59	9	13	130	620	700	1010	2	2	nil	nil

21	B	Palaniammal	65/F	II	73521	Rt crush injury hand & debridment	67	8	15	120	570	680	970	2	1	nil	nil
22	B	Ganesan	33/M	I	73621	Rt ulna# middle 1/3& k wire	58	7	12	120	560	680	960	2	2	nil	nil
s.No	Group	Name	Age/sex	ASA	I.P NO	Surgery	Weight	Onset sensory block	Onset motor block	Duration surgery	Duration motor block	Duration absolute pain free period	Duration post op analgesia	First VAS score	Sedation	Hypotension	Brady cardia
23	B	Rakkammal	55/F	II	74466	Lt # BB FA & ORIF	67	8	14	110	580	660	980	3	1	nil	nil
24	B	Durgadevi	22/F	I	76802	Lt # BB FA & ORIF	52	9	13	130	560	650	970	2	2	nil	nil
25	B	Raja	30/M	I	73960	Rt flexor tendon injury& repair	66	8	14	90	620	720	1080	1	2	nil	nil
26	B	palanisamy	30/M	I	76114	Dislocation MCP 5thRt &ORIF	58	9	13	90	540	660	980	2	1	nil	nil
27	B	Karthikayan	22/M	I	80268	Rt # olecranon & ORIF	66	8	14	110	550	640	960	2	2	nil	nil
28	B	Rangasamy	35/M	I	90365	Lt extenso rtendon injury&repair	57	8	12	100	560	650	950	2	2	nil	nil
29	B	Natchi	35/F	I	80406	Rt # BB FA & ORIF	65	9	13	110	580	660	970	3	2	nil	nil
30	B	Petchi	35/F	I	80226	Raw area Rt hand & debrid& SSG	59	8	12	100	580	670	980	1	2	nil	nil
31	B	Ramu	41/F	I	62986	Rt # olecranon & ORIF	65	7	10	100	550	640	950	2	2	nil	nil
32	B	Silambarasan	23/M	I	21743	t PTS hand& nerve& tendon repai	58	10	16	120	560	650	960	3	1	nil	nil
33	B	Subbulakshmi	39/F	I	27678	Rt # SOH& EXT fixator	67	10	15	150	550	660	980	2	2	nil	nil
34	B	Ramasamy	60/M	II	20672	Raw area Rt hand & debrid& SSG	57	9	14	110	580	670	1010	2	2	nil	nil
35	B	Alagumani	23/M	I	27704	LT Raw area FA & SSG	63	8	14	100	560	660	980	1	2	nil	nil
36	B	Mercy gracy	30/F	I	35178	Rt FA crush injury & k wire	54	9	15	100	560	650	970	1	2	nil	nil
37	B	Ajiskhan	24/M	I	35740	Rt crush injury FA& debridment	66	10	16	110	540	650	950	1	2	nil	nil
38	B	Muthupandi	29/M	I	34947	Rt # BB FA & ORIF	55	11	16	120	520	610	900	1	2	nil	nil
39	B	Sasikumar	25/M	I	40341	Delay union ulna #& ORIF	64	9	13	110	540	600	940	2	1	nil	nil
40	B	Panjavarnam	48/F	I	35168	Lt # SOH & ORIF	65	8	12	120	540	620	930	3	2	nil	nil