COMPARISON OF DEXMEDETOMIDINE WITH CLONIDINE AS AN ADJUVANT TO BUPIVACAINE IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK

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CERTIFICATE

This is to certify that the dissertation entitled **"**COMPARISON OF DEXMEDETOMIDINE WITH CLONIDINE AS AN ADJUVANT IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK" is the bonafide original work of **Dr.K.HEMALATHA** in partial fulfillment of the requirements for M.D. Branch-X (anaesthesiology) Examination of the Tamil Nadu Dr. M.G.R. Medical University to be held in April 2013.

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DECLARATION

I **Dr.K.HEMALATHA**, solemnly declare that dissertation titled, "COMPARISON OF DEXMEDETOMIDINE WITH CLONIDINE AS AN ADJUVANT IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK**"** is a bonafide work done by me at K.A.P.V. Government Medical College, during 2010-2013 under the guidance and supervision of my Professor & Head of the department of Anaesthesiology **Prof. Dr. N. JOTHI, M.D.,D.A** .

The dissertation is submitted to the Tamilnadu Dr. M.G.R. Medical University, towards the partial fulfillment of requirement for the award of M.D. Degree (Branch – X) in Anaesthesiology.

Place: Trichy

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INTRODUCTION

Brachial plexus blocks provides a useful alternative to general anaesthesia for upper limb surgeries. They achieve near ideal operating conditions by producing good muscular relaxation, maintaining stable haemodynamics and associated sympathetic block. The sympathetic block reduces the postoperative pain, vasospasm and edema.

Although various anaesthetic agents have been used, bupivacaine is a better choice due to its longer duration of action of 3 to 8hrs. However it has certain disadvantages like delayed onset, patchy or incomplete analgesia etc,

Various adjuvants like neostigmine, midazolam, opioids etc,[1-4] have been tried to improve the onset of block, quality of block, prolong the duration of block and postop analgesia. But these were associated with side effects.

Clonidine an alpha-2 agonist which had been used as antihypertensive initially has sedative, sympatholytic and analgesic properties. It is also known to have anti nociceptive action and enhances the effect of local anasthetics when given intrathecally, epidurally and in peripheral nerve blocks. This effect is produced by modulating pain pathways through presynaptic alpha-2 adrenergic receptors. It also produces sedation through its action on pontine locus ceruleus where highest number of alpha-2 receptors are present.

Dexmedetomidine, the next recent highly potent alpha-2 agonist, is also a sedative, anxiolytic and analgesic similar to clonidine. The peculiar features of

dexmedetomidine is its high selectivity for alpha-2 receptors and its ability to produce sedation and analgesia while still maintaining patient arousability and respiratory function.

So the present study has been undertaken as randomized single blinded manner to compare the onset time, duration and analgesic efficacy of clonidine with dexmedetomidine when added as adjuvant to bupivacaine(0.25%) for brachial plexus block by supraclavicular approach.

OBJECTIVES

- This study of adding clonidine (1µg/kg) or dexmedetomidine (1µg/kg) to bupivacaine (0.25%) in brachial plexus block for surgeries involving the upper limb has the following objectives:
- To compare the
    - Onset of sensory and motor blockade
    - Duration of sensory and motor blockade
    - Sedation score intra and postoperatively
    - Haemodynamic variables (HR,BP,SPO2)
    - No of rescue analgesics in postoperative 24hrs

between clonidine and dexmeditomedine.

AIM OF THE STUDY

To compare the effectiveness of clonidine and dexmedetomidine as adjuvant in brachial plexus block by supraclavicular approach for prolongation of sensory and motor blockade and duration of analgesia.

REVIEW OF LITERATURE

HISTORY[5-7]

1858 – theory of pain as a separate and distinct sense was formulated by Mortiz S.Schiff.

1885 – the first brachial plexus block was performed by William Stwart Halsted and Alfred Hall – idea of injecting cocaine into nerve trunk in 1885, less than a year after Koller demonstrated the anaesthetic properties of cocaine on the eye of a patient.

1897 – Crile used a similar trchnique in which the plexus was exposed under local anaesthesia. Just behind the sternocleidomastoid, cocaine was injected into the nerve trunks under direct vision which was done as a therapeutic measure in a 12yr old boy who developed tetanic spasms following a compound fracture of the forearm, after which it was used to provide anaesthesia for surgeries in the upper limb.

EVOLUTION OF SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK:

1911 – 1912 – KULENKAMPFF performed 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.

1922 – LABAT injected at three separate points, first beneath the deep fascia towards the first rib, second towards the chassaignac's tubercle and third towards the lateral margin of the first rib behind the clavicle.

1926 – LIVINGSTON proved that the plexus and the artery are separated by a fascial investment.

1940 – PATRICK chose to deposit the anaesthetic along the plexus in its course over the first rib where 60-70ml of solution was injected during 5-6 insertions. The technique became the 'standard technique' of supraclavicular block, subsequently reffered to many as 'classical supraclavicular technique'.

1942 – KNIGHT modified Patrick's technique by using three needle insertions.

1944 – MURPHEY used a single injection technique by using the lateral border of anterior scalene muscle as the landmark.

1949 – BONICA AND MOORE followed the 'walking the rib' method using Kulenkampff and Patrick's technique which was used over the subsequent twenty years.

1958 – LOOKMAN like Livingston realized the fascial investment of the plexus and identified that it lies between the anterior and the middle scalene muscles, but passed the needle too posteriorly .

1964 – WINNIE showed that the relation of the plexus and the subclavian artery to the midpoint of the first rib is not constant, but there is a constant relationship between the scalene muscles, plexus and the first rib. The plexus between the two scalene muscles always inserted on the first rib. He inserted needle between the two muscles in the direction of the space between them. Once paresthesia is elicited he injected the drug into the space.

ANATOMY OF BRACHIAL PLEXUS[8-11]

Knowledge of the formation of brachial plexus and of its distribution is essential to the intelligent and effective use of brachial plexus anesthesia for surgeries of the upper limb. Close familiarity with the vascular, muscular and fascial relationships of the plexus throughout its formation and distribution is equally important.

While travelling from the intervertebral foramina to the upper limb, the fibres that constitute the plexus are composed of roots, trunks, divisions and terminal nerves.

FORMATION OF BRACHIAL PLEXUS:

The plexus is formed by the anterior primary rami of the 5^{th} to 8^{th} cervical nerves, together with the bulk of the 1^{st} thoracic nerve (C – 8 and T -1). In addition there might be a contribution above from 4^{th} to 5^{th} cervical root and another below from 2^{nd} to 1^{st} thoracic nerve. Occasionally the plexus is may also be derived from C_4 to C_8 (pre-fixed plexus) or from C_6 to T_2 (post-fixed plexus).

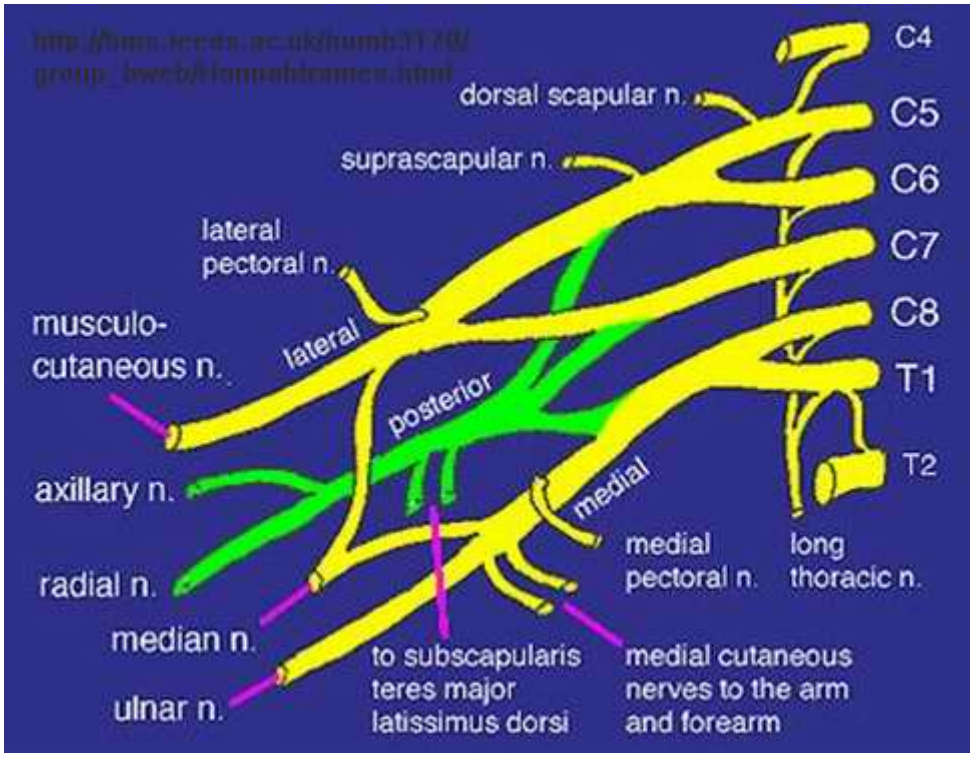


Fig. 1: Formation of brachial plexus

Fig.2: Relation of brachial plexus

Roots:

Represents the anterior primary divisions of lower four cervical and first thoracic nerves. They emerge from the intervertebral 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. C5 and C6 unite to form the upper trunk. C8 and T1 unite behind the scalenus anterior to form the lower trunk and C7 continues as a sole contributor to form the middle trunk.

Divisions:

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

Cords:

The fibres as they emerge from under the clavicle, again combine to form the three cords. The anterior divisions of the upper and the middle trunks forms the lateral cord, lateral to the axillary artery. The medial cord is formed by the anterior division of the lower trunk which descends medial to the axillary artery .The posterior cord is formed by the posterior divisions of all three trunks, behind the axillary artery.

The medial and lateral cords supply the flexor surface of the upper extremity, whereas nerves from the posterior cord supply the extensor surface.

Major terminal nerves:

Each of these cords gives rise to one of the major nerves of the upper extremity and then terminate as a major nerve. The lateral cord gives off the lateral head of the median nerve and the medial cords give off the medial head of the median nerve and continue as major terminal nerves. The lateral cord terminates as musculocutaneous nerve and the medial cord as the ulnar nerve. Posterior cord branches off as axillary nerve and continues as radial nerve.

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

Distribution of the 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. Nerve to scalene and longus colli muscle – C5,6,7,8
2. Branch to phrenic nerve – C5
3. Dorsal scapular nerve – C5
4. Long thoracic nerve of Bell – C5,6,(7)

From trunks:

1. Nerve to subclavius muscle – C5,C6
2. Suprascapular nerve – C5,C6

Infraclavicular branches:

They branch from cords but their fibres may be tracked back to spinal nerves.

Lateral cord:

1. Lateral pectoral nerve – C5,6,7
2. Musculocutaneous nerve – C5,6,7
3. Lateral root of median nerve – C5,6,7

Medial cord:

1. Medial pectoral nerve – C8,T1
2. Medial cutaneous nerve of forearm – C8,T1

3. Ulnar nerve – C7,T1
4. Medial root of median nerve – C8,T1
5. Medial cutaneous nerve of arm – C8,T1

Posterior cord:

1. Upper subscapular nerve – C5,6
2. Thoracodorsal nerve - C6,7,8
3. Lower subscapular nerve – C5,6

Sympathetic contribution to brachial plexus:

The segmental preganglionic sympathetic contributions are variable, but generally extend more caudal. The highest contribution is T2 with T1 contributing very rarely, while lowest may be as far as T8, T9 or even T10. The postganglionic contributions are from grey rami communicants from the sympathetic chain.

RELATIONS OF THE BRACHIAL PLEXUS

Roots: Lies between the scalenus anterior and medius above the second part of the subclavian artery.

Trunks: The upper and the middle trunks lie above the subclavian artery as they stream across the 1st rib, but the lower trunk lies behind the artery and may groove the rib immediately posterior to the subclavian groove.

Divisions: At the lateral border of the first rib, the trunks bifurcate into divisions, which are situated behind the clavicle.

Cords: The cords are found at the apex of the axilla and become grouped around the axillary artery.

The interscalene sheath:

As the roots $C_5 – T_1$ emerge in the groove between the transverse process and the tubercles, they lie in the fibro-fatty space between the two layers of fibrinous sheath. Posterior sheath from the posterior tubercle covers the front of the scalenus medius and anterior sheath from the anterior tubercle covers the posterior aspect of scalenus anterior. The sheath extends into the axilla around the plexus. Significance of this space is that the local anaesthetic can be injected into this sheath to produce block either by interscalene, subclavian perivascular or axillary approach.

TECHNIQUE OF BRACHIAL PLEXUS BLOCK

Surgical anesthesia for the upper extremity and shoulder can be obtained by blocking the brachial plexus at various sites. There are various approaches that can be used for this blockade as follows

1.Interscalene approach

2.Supraclavicular approach

a.Classic approach

b. Plumb – bob technique

c.Subclavian perivascular technique

3.Axillary approach

4.Infraclavicular approach

Complications:

1. Intravascular injection
2. Pneumothorax
3. Phrenic nerve block

PATHOPHYSIOLOGY OF PAIN

Definition of Pain:

The Taxonomy Committee of International Association for the study of Pain (IASP) defines pain as "An unpleasant sensory and emotional experience associated with potential tissue damage or described in terms of such damage". Postoperative pain is defined as a form of acute pain caused by surgical trauma with an inflammatory reaction and with initiation of an afferent neuronal barrage.

Physiology of pain:

The spinal cord conveys signal from the brain to the nerves located throughout the body. Nerves coming from the spinal cord and leading to all parts of the body enter and leave the spinal cord along its entire length. There are 31 pairs of spinal nerves that leave the spinal cord through the intervertebral foraminae. The peripheral nerves includes motor and sensory nerves. Sensory nerves are that which receive and transmit sensory stimuli to Substantia gelatinosa. Motor nerves are those which lead to the muscles and stimulate movement of muscles.

Various mechanisms are:

Nociception refers to the perception of a noxious stimulus by the brain.[13] The components include transduction, modulation, transmission and perception (fig.4).

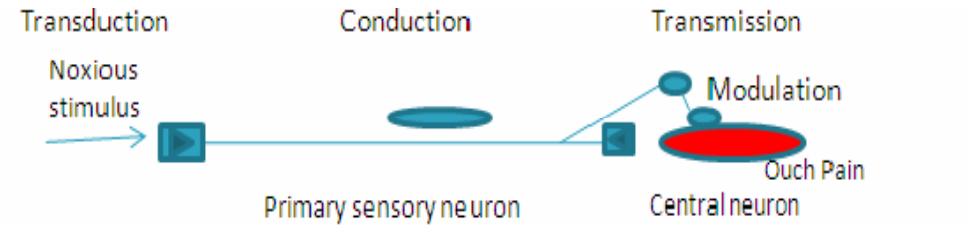


Fig. 3: Process of Nociception

Peripheral sensitization.

Central sensitization

Pathways of pain:

Pain is conducted along neuron pathways that transmits the noxious stimuli from periphery to cerebral cortex.

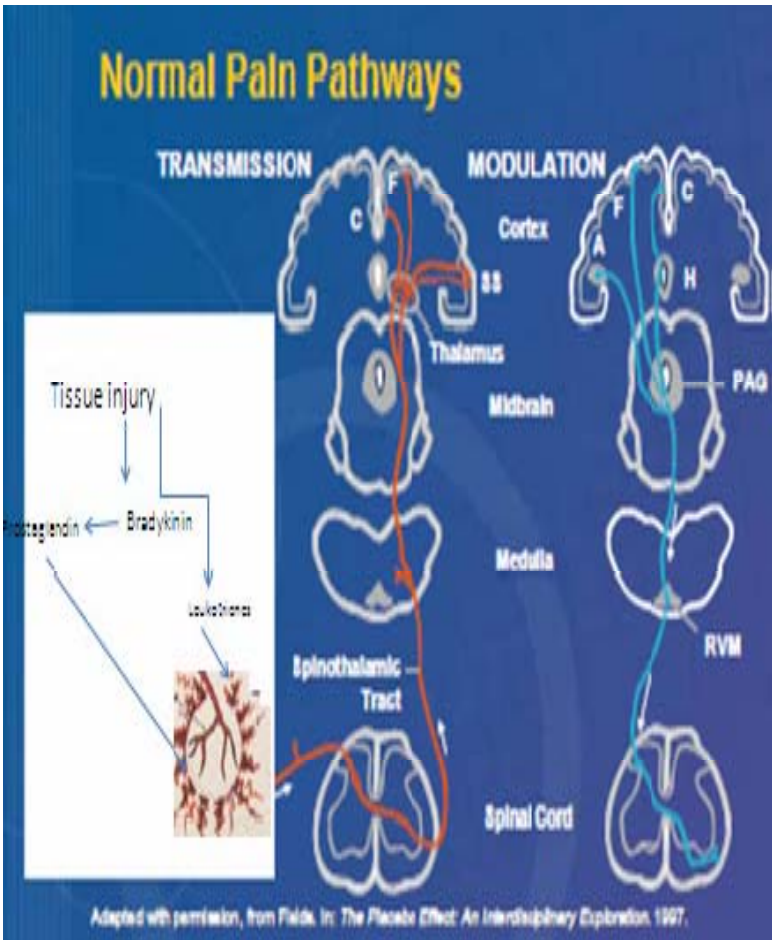


Fig. 4: Normal pathways of pain

- A first order neuron, arising in the cell body in dorsal root ganglion of the spinal cord transmits pain from a peripheral receptor to the dorsal horn of the spinal cord.
- A second-order neuron is located in the dorsal horn of the spinal cord and sends axons that crosses the midline to ascend as the spinothalamic tract to the thalamus.

- A third-order neuron in the thalamus projects its fibers to the post central gyrus through the internal capsule.

Physiological responses to pain:

It has been found that uncontrolled pain in post operative period produce physiological effects like altered stress response to surgery, increased catecholamines, deep vein thrombosis, higher incidence of pulmonary complications, and ultimately increasing the morbidity.[15-17]

Peripheral α_2 receptors:

α_2 adrenoceptors 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. It also blocks the conduction of C and A gamma fibres and increases the potassium conductance in isolated neurons and intensifies conduction block of local anaesthetics.

ASSESSMENT OF PAIN

It is important in an effective postoperative pain management. Numerous pain assessment scales are there to quantify pain.[21,22] The intensity of pain should be assessed as far as possible by the patient himself as long as he is able to

communicate and expressed what he feels like. A number of self-assessment scales are available.

Visual analogue scale (VAS) :

VAS is the most commonly used method to assess pain which was first described in 1966. It is a very simple and used in pain research. It consists of a 10 cm line with two anchor points starting from 'no pain' to 'worst pain imaginable' which is self assessed by patient (fig.5). It is the position of the mark on the line that measures how much pain the subject experiences.

Fig. 5: Wc **e**

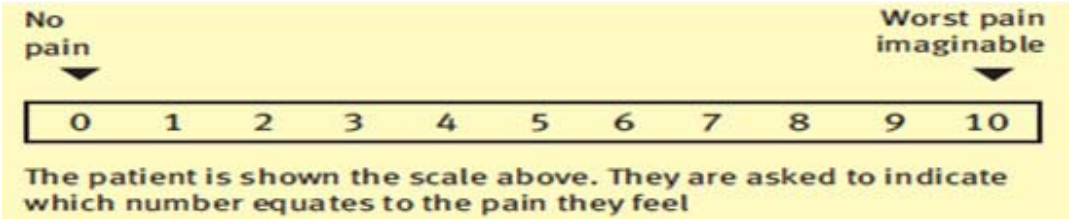


Fig.6 : Numerical Rating Scale

Others are:

- **Facial expressions**:

  This is a pictogram of six faces with different expressions from smiling or happy to tearful which can also be used(fig.5).

- **Numerical rating scale (NRS):**

  This is similar to the visual analogue scale with the two anchors starting from ‘no pain’ to ‘worst pain as from 0 to 10, assessed by patient (Fig. 6).

- **Verbal rating scale (VRS)**

The preoperative personality assessment is also helpful in assessing the patient’s psychological background and his psycho reactions to surgery and the pain that follows it. The VRS and NRS are the other mostly used assessment tools in the clinical setting while the VAS scale is primarily used as a research too.

METHODS OF ACHIEVING PAIN RELIEF:

“Pain relief has always been bought at a Price” – Bromage

Number of factors are there that contribute to effective postoperative pain management like a structured acute management team, regular staff training,

patient education, regular pain assessment tools and use of balanced analgesia to meet the needs of special patient groups.

Following any surgery, the pain after the tissue damage is usually self limiting. It persists at the most for the first 24 hrs and mostly subsides in 4 days time.[44] The post operative pain is dull in nature, aggravated by mobility and relieved by rest to that part. The acute pain of surgery is strongly accompanied by emotional elements of fear, anxiety, and depression of previous experience of pain. The goals of effective and appropriate pain management are to:

- Facilitate rapid recovery and return of full function.
- Reduce morbidity.
- Improve the quality of life for the patient.
- Allow early discharge from the hospital.

Methods adopted for providing post operative pain relief include: [45-50]

Pharmacological methods: -

i. Balanced (multimodal) analgesia
ii. Opioids
iii. Non-opioids (NSAIDS)
iv. Adjuvants
v. Patient controlled analgesia
vi. Regional analgesia

Continuous Central Neuraxial Blockade (CCNB)

Continuous Peripheral Nerve Blockade (CPNB)

Infiltration blocks

II. Non pharmacological methods: - This includes

A. Transcutaneous Electrical Nerve Stimulation (TENS)

B. Acupuncture

C. Cryotherapy

D. Heat Therapy

Regional analgesia:

Central neuraxial block involves either intermittent or continuous administration of local anaesthetics in order to interrupt sensory transmission.[49] The important draw back of this technique is the accompanying motor and sympathetic blockade which can increase the incidence of post operative complications. Extradural block offers complete pain relief, permits effective coughing & better ventilation. But the total spinal, accidental dural punctures are more with inexperience hands.

Peripheral nerve blocks are being increasingly used since they may provide more selective but still excellent postoperative analgesia with reduced need for opioids over an extended period. Peripheral nerve blocks (PNBs) avoid the side effects associated with central neuraxial blockade, such as hypotension and wide motor blockade with reduced mobility and proprioception, and complications such as epidural haematoma, epidural abscess and paraparesis.

PHARMACOLOGY

Local Anaesthetic Drugs:

Local anesthetics are drugs that produce reversible conduction blockade of nerve impulses along the central and peripheral pathways after regional anaesthesia. They produce autonomic, sensory and motor blockade of the area innervated by the affected nerve. Removal of the local anaesthetic results in complete return of nerve conductions with no structural domage to the nerve fibres.

They have similar configurations with 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 HYDROCHLORIDE

Bupivacaine hydrochloride is a aminoamide local anaesthetic, prepared by A.F.Ekenstam in 1957.

Chemistry: It is 1-n-butyl-DL-piperidine-2 carboxylic acid-2,6 dimethylamilide hydrochloride, a chiral drug possessing an asymmetrical carbon atom. Clinically it is available as racemic mixture of R & S enantiomers. The S enantiomer of bupivacaine appears to be less toxic than the commercially available racemic mixture.

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

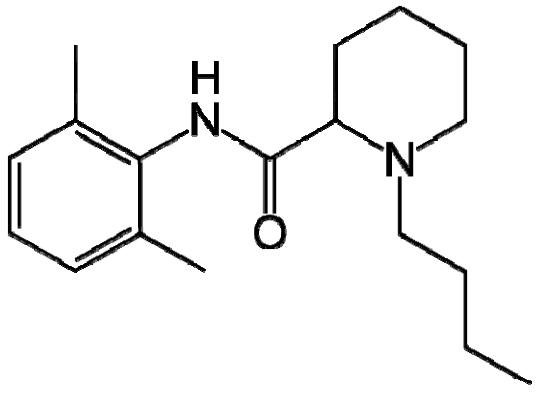


Fig. 7: Bupivacaine Hydrochloride

Physiochemical properties:

1. Molecular weight: of chloride salt is 325 and of its base form is 288.
2. pKa: 8.1
3. Protein binding: 95%
4. Solubility: The base is sparingly soluble and the hydrochloride salt is readily soluble in water.
5. Partition coefficient: 28
6. T1/2: 210min
7. Clearance: 0.47L/min
8. Moderate onset and long action.

Mechanism of action: It acts on the cell membrane of the axon producing electrical stabilization. The permeability to sodium ions necessary for impulse propagation is prevented. Thus resting membrane potential is maintained and depolarization is inhibited.

The local anaesthetics block the sodium conductance by the following mechanisms:

1. Local anaesthetics in the cationic form act on the receptors within the sodium channels, on the cell membrane and block it. They reach the sodium channels via the lipophilic pathway directly across the lipid membrane or via the axoplasmic opening. This mechanism is responsible for 90% of nerve blocking effect of amide local anaesthetic.
2. The second mechanism is by membrane expansion, which is a non specific action in contrast to more specific drug receptor interaction.

Available concentrations:

- 0.25% and 0.5%
- 0.25% and 0.5% soluble in isotonic saline – isobaric
- 0.5% soluble in 8% dextrose – hyperbaric

These doses may be repeated in three to four hours but the maximum dose is 400mgs. Addition of a vasoconstrictor produces very little increase in duration of action, but significantly reducing the peak blood levels decreasing the systemic toxicity.

Actions:

CNS effects are characterized by excitation or depression. The intial manifestation may be nervousness, dizziness, blurring of vision or tremors followed by drowsiness, convulsions and unconsciousness. In CVS, it produces reduction in the maximum rate of depolarization in the purkinji fibres and ventricular muscles. Action potential duration and effective refractory period is also decreased. The rate of recovery is also slower with bupivacaine. Therefore there is incomplete restoration of V-max between action potential particularly at higher heart rates. Hence,it is highly arrythmogenic. If excessive plasma level is reached, it produces respiratory depression.

Pharmacodynamics:

Onset – 4-6min

Peak effect – 15-20min

Average duration – 3.5-5hrs, for nerve blocks – 5-6hrs

Toxicity: The toxic plasma concentration is 4-5μ/ml. But it rarely approaches

the toxic levels. Local irritant effects on the nerve tissue has been noted but permanent nerve damage has not been found in clinical dosage.

Pharmacokinetics:

It reaches the blood within 5 min, but the plasma are related to the dosage administered. In plasma, it binds avidly to alpha 1 acid glycoprotein to the extent of 70-95%. Conversely its unbound active form is one third that of lidocaine.

Metabolism and elimination:

As it is an amide it is primarily metabolised in the liver by n-dealkylation to pipecolyloxylidine. It crosses the placental barrier, but the lowest level of placental diffusion has been reported (umbilical vein to maternal ratio – 0.31 to 0.44). No effect on fetus has been reported so far.

10% of the drug is excreted unchanged in urine within 24hrs and 5% as pipecolyloxylidine.

Adverse reactions:

Might be due to inadvertent iv injection or slow metabolic degradation, producing its effects on CNS & CVS. CNS effects include nervousness, dizziness, tremors or blurring of vision followed by convulsion and unconsciousness. CVS manifestations include myocardial depression, hypotension and cardiac arrest. Allergic reactions such as utricaria, bronchospasm and hypotension can also occur.

Treatment is symptomatic maintaining ventilation and circulation with oxygen, controlled ventilation and iv fluids and vasopressors for circulation. Diazepam (0.1 – 0.2mg/kg) or thiopentone (2-3mg/kg) can be used for convulsions and corticosteroids for allergic reactions. For ventricular fibrillation or tachycardia, amiodarone (5mg/kg) or defibrillation (2-5joule/kg) can be used.

Cardiovascular collapse/CNS ratio:

The CC/CNS ratio for bupivacaine is 3.5± 0.5or findings indicating that three times the drug was required to induce irreversible cardiovascular collapse as was needed to produce convulsions. It has also been suggested that some of the cardiac toxicity is due to myocardial depression.

CLONIDINE HYDROCHLORIDE

Clonidine hydrochloride is an imidazoline derivative which was initially used for its hypotensive properties was first introduced in Europe in 1966. It is a centrally acting alpha adrenergic agonist that lowers the BP by decreasing the sympathetic nervous system activity. It also causes sedation and analgesia in addition to sympatholysis.

Chemistry:

It is an imidazoline derivative existing as a mesomeric compound. It is (2,6-dichlorophenylamino)-2-imidazoline hydrochloride.

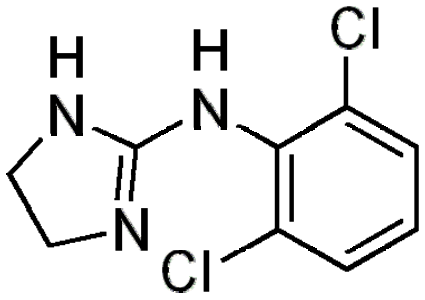


Fig. 8:Clonidine Hydrochloride

Physiochemical properties:

Molecular weight is 266.56

It is odourless, bitter, white and crystalline substance soluble in water.

Available as 1ml ampoule containing 150µgs.

It should be stored below 25°C.

Clonidine is a centrally acting partial α2 adrenergic agonist having a selectivity ratio of 220:1 in favor of α2 receptors. There are three subtypes of α2 receptors α2a, α2b, α2c. Of these sedation, analgesia and sympatholysis are mediated via α2a receptors, vasoconstriction and anti-shivering via α2b receptors and a startle response may reflect activation via α2c receptors. This startle response includes a physical movement away from the stimulus and breathing changes. It acts on the α2 receptors which are found densely in the locus ceruleus in pons and also stimulates the α adrenergic inhibitory neurons in the medullary vasomotor centre and inhibits sympathetic outflow from the CNS to the peripheral tissues.

It modifies the potassium channels in the CNS and hyperpolarises the cell membranes producing a profound decrease in anesthetic requirement.

Neuraxially it inhibits spinal substance P release and thereby inhibiting the nociceptive neuronal firing. Its acts on α2 afferent terminals situated in the superficial lamina of the spinal cord and brain stem nuclei and produces analgesic effects after neuraxial administration. It also acts on the central thermoregulatory system and decreases the threshold to cold stimuli.

Pharmacological effects:

IV clonidine causes a transient rise in BP by α2 agonistic action on the vascular smooth muscle of the skin and mucosa, followed by a decrease in BP due to its central α2 action.

Pharmacokinetics:

Well absorbed orally and 100% bioavailable.

Peak plasma concentration is achieved within 60 – 90min.

Plasma half life 9 – 12hrs.

Plasma protein binding – 20 – 40%.

Metabolism – minor pathways with major metabolite, P-hydroxyclonidine

Excreated in an unchanged form by the kidney.

A transdermal delivery system is available in which the drug is released constantly for about a week.

Dosage regimen:

Oral : 3-5µg/kg

Intranasal : 2-4µg/kg

Intramuscular: 2µg/kg

Intravenous : 1-3µg/kg

Spinal : 50-100g

Epidural : 1-2µg/kg

Transdermal : 3mg/day

Precautions:

- In patients with renal insufficiency, lower dose is needed.
- Sudden withdrawal produces hypertensive crisis, hence discontinued gradually over 2-4 days.
- Use with caution in patients with cerebrovascular or coronary disease.
- If a patient with β blocker is on continuous epidural, those drugs should be withdrawn several days before discontinuation of epidural.

Contraindications:

- Known hypersensitivity to clonidine.
- Bradyarrythmias or AV block.
- Cardiovascular disease/hemodynamic instability.

Interactions:

- Clonidine potentiates the CNS depressive effect of alcohol , barbiturates or other sedatives.
- Narcotics also potentiate the hypotensive effects of clonidine.
- Tricyclic anti-depressants antagonizes the hypotensive effects of clonidine.
- Drugs with negative chronotropic effect can potentiate bradycardia.
- Epidural clonidine prolongs the duration of epidural local anaesthetics, opoids, neostigmine, etc,.

Uses:

- Premedication:
    - Oral clonodone is used in a dose of 5µg/kg.

- This blunts stress response during laryngoscopy or intubation. Intra-operative hemodynamic stability, intravenous and inhaled anaesthetic drug requirement is reduced.
- Epidural block:

  Solely or in combination provides excellent analgesia in labor. Indicated for treatment of intractable pain which is unresponsive to opoids or reflux sympathetic dystrophy or neuropathic pain.
- Spinal anaesthesia:

  Combined with local anaesthetics, it improves the quality and duration of block, minimizes tourniquet pain and prevents shivering.
- Caudal anaesthesia:

  Clonidine with LAs ,increases the duration of anaesthesia and analgesia.
- Perpheral nerve block:

  Clonidine prolongs the duration of anesthesia and analgesia with LAs by 2 times in a dose of 75 - 150μgs.

- Bier's block:

  Enhances the tolerance of tourniquet.

- Decreasing MAC of sevoflurane:

  Oral clonidine in a dose of 4µg/kg given 2hrs before induction decreases the MAC values of sevoflurane for LMA insertion.

- Post-Op Nausea and Vomiting (PONV):

  Oral clonidine of 4µg/kg before surgery enhances the anti-emetic effect of propofol when compared with midazolam.

- Other uses:

  Protection against myocardial ischemia. Used to diagnose pheochromocytoma by administering 0.3mg of clonidine which will decrease concentration of catecholamines in normal patients but not in pheochromocytoma. At a dose of 75µg IV, it stops shivering by thermoregulatory control. Used to treat opoid and alcohol withdrawal syndrome.

Side effects:

- CVS: Orthostatic symptoms, palpitation & tachycardia/bradycardia.

  Syncope, congestive heart failure, Raynaud's phenomenon, and electrocardiographic changes (sinus node arrest, AV block, junctional bradycardia, and arrhythmias) have been reported but rarely.

  CNS: Nervousness, agitation, mental depression, insomnia occur commonly and behavioral changes, visual and auditory hallucinations, restlessness, anxiety and delirium have also been reported but rarely.

- Others include rash, pruritis, utricaria, alopecia, nausea and vomiting, anorexia and malaise and mild abnormalities in liver function tests.

- Decreased sexual activity, loss of libido, impotence, nocturia and urinary retention, thrombocytopenia, weight gain, gyenacomastia, transient elevation of blood glucose and serum creatine phosphokinase have also been reported.

Over dosage:

No specific antidote. Supportive treatment with atropine, ephedrine and IV fluids are enough. Yohimbine partially reverses the analgesia and sedation, but not the BP and heart changes.

DEXMEDETOMIDINE

It is a highly selective α_2 agonist with a selectivity ratio of α_2 receptors over α_1 of 1620:1. It decreases the sympathetic tone and attenuates the stress response to anaesthesia and surgery, and also causes analgesia, sedation and anxiolysis.

Chemistry:

Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride.

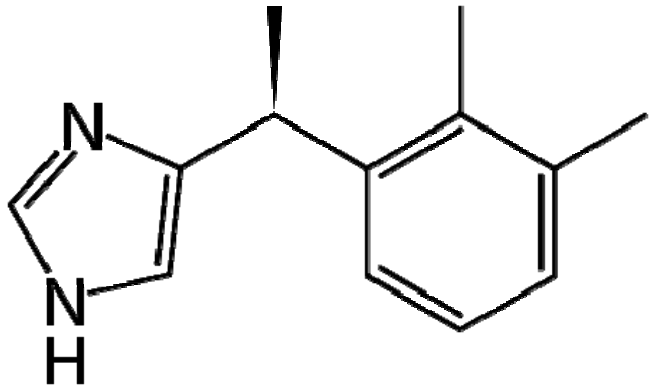


Fig. 9: Dexmedetomidine

Physiochemical properties:

- Molecular weight:236
- White powder which is freely soluble in water.
- Pka:7.1
- available as a clear, isotonic solution with pH of 4.5 – 7
- Supplied in one or two ml ampoules containing 100µ of dexmedetomidine in water.
- Solution is preservative free.

Mechanism of action:

α2 receptors are found in the central and peripheral nervous systems. They are also found in the platelets and many other organs including the liver, kidney, pancreas, and eye. Stimulation of these receptors in the spinal cord and brain inhibits neuronal firing causing hypotension, bradycardia, sedation and analgesia . The response in other organs include decreased secretions, decreased bowel motility, glomerular filtration is increased, inhibition of rennin release with increased secretion of sodium and water in the kidney. There is also

decrease in the intraocular pressure and decreased insulin release from the pancreas. It differs from clonidine in its selectivity for α2a subtype receptor causing more effective sedation and analgesia.

Majority of patients who received dexmedetomidine were sedated, but easily arousable, which is a unique feature not found in other sedative.

Pharmacodynamics:

Does not have any direct effect on the heart. It produces a biphasic response in CVS , where a bolus of 1μ/kg results in a transient rise in BP with a reflux fall in heart rate, especially in younger patients which is found to be due to stimulation of β2 receptors in the vascular smooth muscles and can be reduced by a slow infusion. This was due to inhibition of central sympathetic outflow. The norepinephrine release is decreased due to stimulation of alpha 2 receptors resulting in fall in BP and HR. These effects may be observed in the post-operative period and can easily be managed with ephedrine, atropine and volume infusion.

The respiratory depression caused by dexmedetomidine has been reported to be much lower than other sedatives.

Pharmocokinetics:

It undergoes almost complete hydroxylation via direct glucuronidation and cytochrome P450 metabolism in the liver.

Metabolites are excreted in the urine (95%) and in the feces (4%). Its elimination half life is 2hrs, hence making it necessary to decrease the dose in patients with renal failure and hepatic failure.

Uses:

It produces anxiolytic, sedative, analgesic and sympatholytic effects, hence used for premedication in patients in whom pre-operative stress is undesirable.

Found as an effective premedication before iv regional anaesthesia, as it reduces sympathoadrenal responses, patient anxiety, and opioid requirement.

For intra-operative period, it is used in the dose of 0.2 – 0.7μ/kg/hr like clonidine, it attenuates the stress induced sympathoadrenal responses to laryngoscopy, intubation and surgery as well as provides increased hemodynamic stability.

Potentiates the effects of all intra-operative anaesthetics, whatever the method of administration may be.

Dexmedetomidine should not be used in intracranial pathologies till its safety is proved by further studies.

Also provides analgesia during the post-operative period. Also reduces the post-operative analgesic requirements by 50% in cardiac patients and the need for rescue midalozam for sedation was reduced by 80%. However it may lack amnestic properties since a small no of patients were able to recall their ICU stay. It seems to have very few respiratory side effects, it can be used safely in the extubated patients, spontaneously breathing patients. Like clonidine, it is also associated with lower rate of shivering.

Clonidine on epidural/subarchnoid administration produces analgesia partly by causing spinal acetylcholine and nitric oxide release similar to which dexmedetomidine also produces dose-dependent analgesia with similar potency, but it is less dependent on acetylcholine-NO mechanism than clonidine.

In ICU it is used as sedative, analgesic and anxiolytic as it does not produce respiratory depression due to its non-opioid mechanism of analgesia. It is generally initiated in a loading infusion dose of 1μ/kg over 10min, and can be maintained by an infusion of between 0.2 – 0.7μ/kg/hr must be administered, diluted in 0.9% saline for infusion. Patients who receive dexmedetomidine in ICU were observed to be alert and arousable when stimulatd from sedation and rapidly return to their sleep like state.

Caution:

In patients with pre-existent bradycardia and conduction problems, in those with reduced ejection fraction (<30%) and in those who are hypovolemic.

All the effects of dexmedetomidine can be antagonized by α2 antagonist, atipamezole which is a drug that reverses sedation and sympatholysis of dexmedetomidine and has a half life of 1.5 – 2hrs.

Side effects:

It crosses the placenta and hence it is not safe to be administered in pregnancy and in children. Common adverse effects include nausea, hypertension, hypotension , hypoxia, bradycardia, atrial fibrillation, and AV blocks. These adverse effects can be reduced by omitting or reducing the loading dose.

Review of literature

1. A study was conducted on seven healthy volunteers,where three brachial plexus procedures were administered using bupivacaine 0.25% and epinephrine 1µg/kg a randomized double blinded cross over fashion. (a) control treatment: this group received a local analgesic with 0.9% sodium chloride and saline. (b)intramuscular treatment: this group received local injection with 0.9% NaCl and im clonidine 2µg/kg and (c) block treatment: this group received local analgesic with clonidine 2µg/kg for block and an im injection of saline. The onset and duration of complete sensory and motor blockade was evaluated in the four nerve regions of forearm and hand. Additionally, sedation score, BP, HR and plasma clonidine concentration were determined. The median duration of sensory block was 270min (range 0 – 600) for the block treatment compared to 0min (range 0 – 400) for im treatment ($P<0.05$) and 0min (range0 – 100) for control treatment ($P<0.05\%$). Similar results were obtained in motor blockade. Administration of clonidine resulted in sedation and decrease in HR and BP whatever be the route of administration. Plasma clonidine concentration was lower

for the block compared to the im treatment and it was concluded that adding clonidine to bupivacaine and epinephrine prolongs and enhances the blockade.

2. Eledjam jj , Deschodt et al, Canadian journal of anaesthesia 1991:

   This study compares the effect of adding alpha 2 agonist, clonidine and epinephrine to bupivacaine. In this study, 60 patients were randomly allocated into two groups, 30 patients receiving 150mics of clonidine and 30 patients receiving 200mics of epinephrine. No difference was found in the clonidine group in the onset of sensory and motor blockade compared to adrenaline. The duration of motor block was prolonged in clonidine group (580.4± 38.7 vs 290.6± 34.5) compared to adrenaline group. Block produced by adding clonidine was longer (994.2±34.2 vs 728 .3±5.8min) and superior to adrenaline.

3. Dorothee M,Gaumann et al,Anaesthesia and Analgesia 1992:

   This study concluded that the enhancing effect of low dose clonidine (500M) on lignocaine (500M) induced inhibition of C-fibre action potential might explain the clinical observation that clonidine, at

approximately thousand fold lower concentration prolongs the action of lignocaine in peripheral nerve block.

4. Maze and Tranquil et al anaesthesiology 1999:

   Alpha 2 adrenergic agonistic role in clinical anesthesia. This study concluded that clonidine has analgesic activity like a potent opoid, as anxiolytic and sedative as benzodiazepines, and sympatholysis.

5. Henri Iskandar et al Anaesthesia analgeais 2000: The analgesic effect of clonidine as an analgesic for shoulder arthroscopy. This study reported that clonidine administered via an interscalene catheter enhanced analgesia compared with systemic administration.

6. Wolfgang Erlacher et al, Canadian journal of anaesthesia 2001:

   This study compared the effect of clonidine as adjuvant for mepivacaine, bupivacaine and ropivacaine in axillary & perivascular brachial plexus block. This study shows that the addition of clonidine has different impact on each of the three local anaesthetics investigated in terms of onset and duration of block. Mepivacaine group shows rapid onset compared to ropivacaine and bupivacaine group. The mepivacaine + clonidine (468± 62min vs mepivacaine alone group(212± 82min),

ropivacaine + clonidine (712 ± 82min) vs ropivacaine alone (702± 52min), bupivacaine + clonidine (972± 72min) vs bupivacaine alone (728 v36min).

7. a.Duma,B.Urbanek et al, Br.J.anaesthesia 2005:

   A randomized control study with clonidine as an adjuvant to local anaesthetic in axillary approach of brachial plexus block,.

8. Cucchiaro G, Ganesh A et al, Anasthesia analgesia 2007:

   The effects of clonidine on post-operative analgesia after peripheral nerve blockade in children. This study concluded that adding clonidine to ropivacaine and bupivacaine can extend the sensory block and increase the duration of motor blocks.

9. A study by Brunett et al. showed that dexmedetomidine enhancs the duration of bupivacaine anaesthesia and analgesia of sciatic nerve block without any damage to the nerve.

10. Esmaoglu et al. added dexmedetomidine to levobupivacaine for axillary block and showed that the onset time of both sensory and motor block, prolongs the duration of the block and post-operative analgesia.

11. Memis et al. in their study showed that addition of dexmedetomidine to lignocaine for IVRA improves both the quality of anesthesia as well as the intraoperative and postoperative analgesia.

METHODOLOGY

This study was conducted on 50 patients undergoing upper limb surgeries aged between 15 & 55 yrs under supraclavicular block in Annal Gandhi Memorial Government Hospital attached to K.A.P.Viswanatham Government Medical college, Trichy. Informed written consent was obtained from each patient. Values were recorded using a preset proforma. It was a bouble blinded study in which patients were divided into two groups BD & BC comprising 25 each. Surgery was done under supraclavicular approach of brachial plexus block.

Inclusion criteria:

1.ASA grade – I & II

2.Age between 15 & 55yrs

Exclusion criteria:

1.ASA grade – III & IV

2.Patients with complications like severe anaemia, hypovolemia, septicemia, shock.

3.Known case of hypersensitivity reaction to clonidine or dexmedetomidine.

4.Bleeding disorders or on anticoagulant therapy

5.Local infection at the site of puncture.

Investigations required:

- Hb%, TC,DC,BT,CT
- Urine routine
- Serum urea,sugar, creatinine
- Chest x-ray, ECG
- HIV,HBsAg

Equipments for the procedure:

For the procedure:

A portable tray covered with sterile towel containing

Sterile syringes containing one 20ml and one 10ml.

Hypodermic needles of 5cms length, 22G.

Bowels containing povidone iodine and spirit.

Sponge holding forceps.

Towel and towel clips.

Sterile gauze pieces.

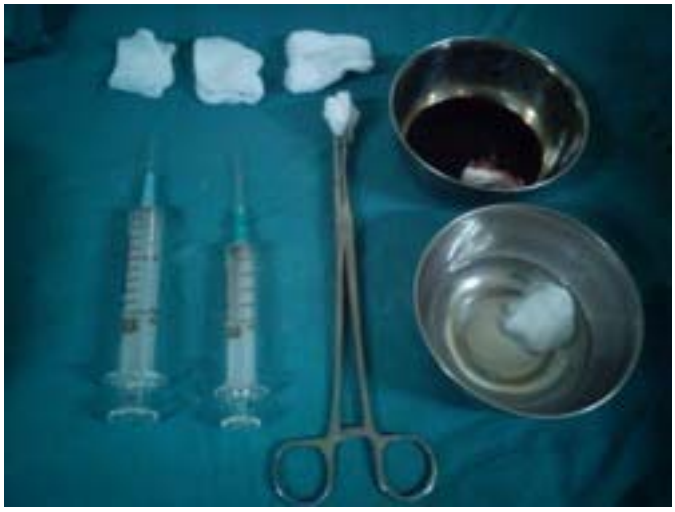


Fig. 10: Sterile tray containing drugs and equipments

Fig.11: Drugs used for study

For emergency resuscitation:

The anaesthesia machine, emergency oxygen source (E type cylinder), pipeline oxygen supply, working laryngoscopes, appropriate size endotracheal tubes and connectors.

Working suction apparatus with suction catheter.

Oropharyngeal airways.

Intravenous fluids.

Drugs: Thiopentone sodium, propofol, midazolam, succinylcholine, glucopyllorate, atropine sulphate, adrenaline, deriphylline, dexamethasone, hydrocortisone, calcium gluconate and sodium bicarbonate.

Monitors:

Pulse oxymeter.

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

Procedure:

- After obtaining ethical committee approval, informed consent was obtained from the patients. Intravenous access was obtained, anaesthesia machine checked, resuscitative equipments and drugs were kept ready. Patients were allocated into the following two groups.
- Group BD – received 35cc of 0.25% bupivacaine with dexmedetomidine 1μg/kg.
- Group BC – received 35cc of 0.25% bupivacaine with clonidine 1μg/kg.
- Patient was made to lie in supine position, with the arms by the side and the head is turned slightly to the opposite side.
- The interscalene groove and the midpoint of the clavicle were identified.
- After strict aseptic precautions of the area, just above the midpoint of the clavicle, the subclavian artery pulsation was felt and 1.5 to 2cms posterosuperior to it a skin wheel was raised with local anaesthetic.

- A 22G, 5cms needle mounted on a 20ml syringe loaded with the drug was inserted at the same point in a backward, inward and downward direction. Either paresthesia was elicited or the first rib was encountered while injection.
- If the first rib was encountered the needle was gently walked over the first rib until paresthesia was elicited in the arm or hand, after which the drug was injected following a negative aspiration of blood.
- All the patients were monitored for anaesthesia and analgesia for 24hrs post-operatively.
- Sensory block was evaluated by eliciting temperature sensation using spirit soaked cotton over the distribution of the ulnar and median nerve, whereas a motor block was assessed by asking the patient to flex the forearm against gravity.

Parameters observed:

- Onset of sensory block:
    - This was taken as abolishment of temperature sensation over the distribution of the ulnar and median nerve and was assessed every minute after performance of the block.
- Onset of motor blockade:

This was assessed every minute after the block using modified Bromage scale. Onset of motor block was considered when there was grade 1 motor blockade.

    - Grade 0: Full flexion and extension of elbow,wrist and fingers.
    - Grade 1: Weakness but able to move the arm.
    - Grade 2: Unable to move the arm but able to move the fingers.
    - Grade 3: Complete motor blockade
- Duration of sensory block:
    - The pain was assessed using Visual Analogue Scale having 10cms length. Patients were explained about the visual analogue scale as 0 as no pain and 10 as the worst possible pain and was asked about the score in the scale. Patients were

observed every 30 minutes till the surgery is over and hourly thereafter till 6 hrs, 2nd hrly for next 6 hrs and thereafter every 3rd hrly till 24 hrs. Time at which VAS score was 5 was noted and patient was given im NSAID.

- Duration of motor blockade:
  - The time interval between the administration of local anaesthetic and the return of complete motor function of the forearm and hand.
- Vital parameters:
  - The pulse rate, blood pressure, O2 saturation were monitored every 15min till 1hr, 2nd hrly till 6 hrs and 6th hrly till 24hrs.
- Sedation score:

  This was evaluated using Ramsay sedation score:
- IM injection of diclofenac sodium would be given as rescue analgesic when patient complains of pain.
- Number of rescue analgesics in 24hrs of postoperative period would also be noted.
- Quantitative data will be analysed using student's unpaired 't' test.

- Qualitative data will be analysed by Fisher's chi square test.
- P value of <0.05 would be considered statistically significant.

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

RESULTS

50 ASA I & II of either sex aged 15-55yrs, posted for upper limb surgeries under supraclavicular brachial plexus block were selected for the study. The study was undertaken to evaluate the efficacy of dexmedetomidine (1μ/kg) over clonidine(1μ/kg) as an adjuvant to bupivacaine (0.25%) for brachial plexus block.

Table.1:Age Distribution

Group	MeancSD	T value	P value	significance
BC	36.8±12.26	0.52	0.12	NS
BD	34.88±9.03			

The minimum age of the patient was 15yrs and the max age was 55yrs. The mean age of the patient in group BC was 36.8±12.26Bwas34.88±9.

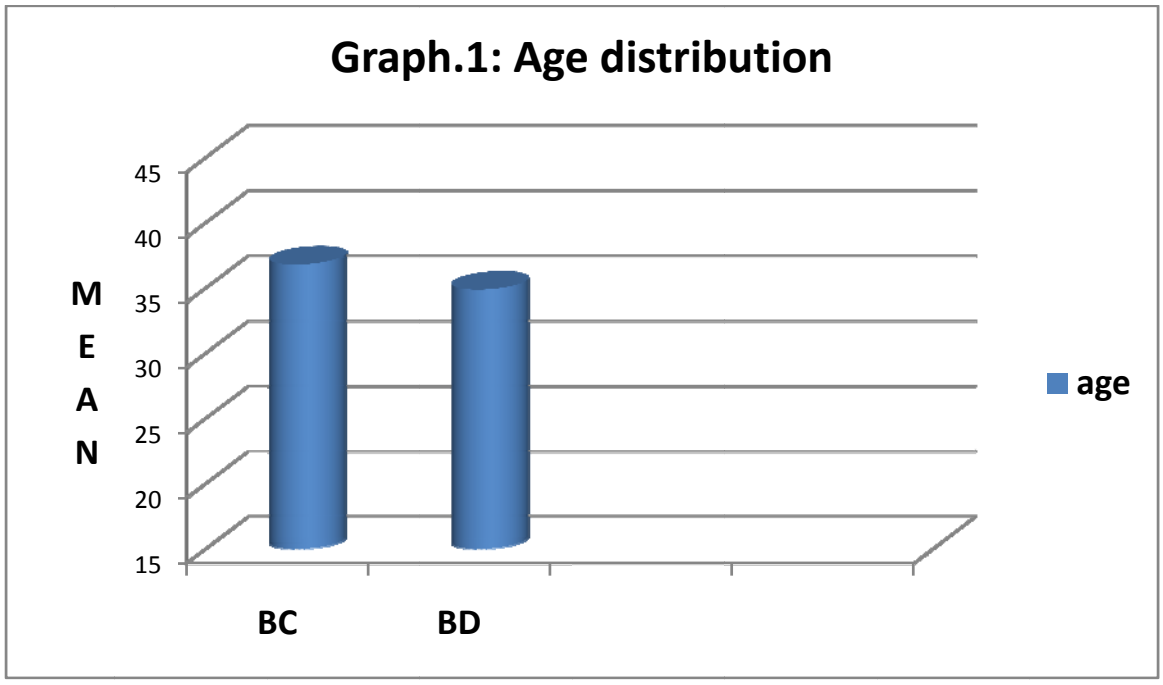


Table.2:Onset of Sensory block(in min)

Group	Mean±SD	T value	P value	significance
BC	11.14±1.13	8.05	<0.001	HS
BD	8.8±0.91			

The mean time for onset of sensory block was in group BC was 11.14±1.13 and in group BD was 8.8±0.91min. The statistical analysis by student's unpaired "t" test showed that the time of onset of sensory block in group BD was significantly faster than group BC ($p < 0.001$)

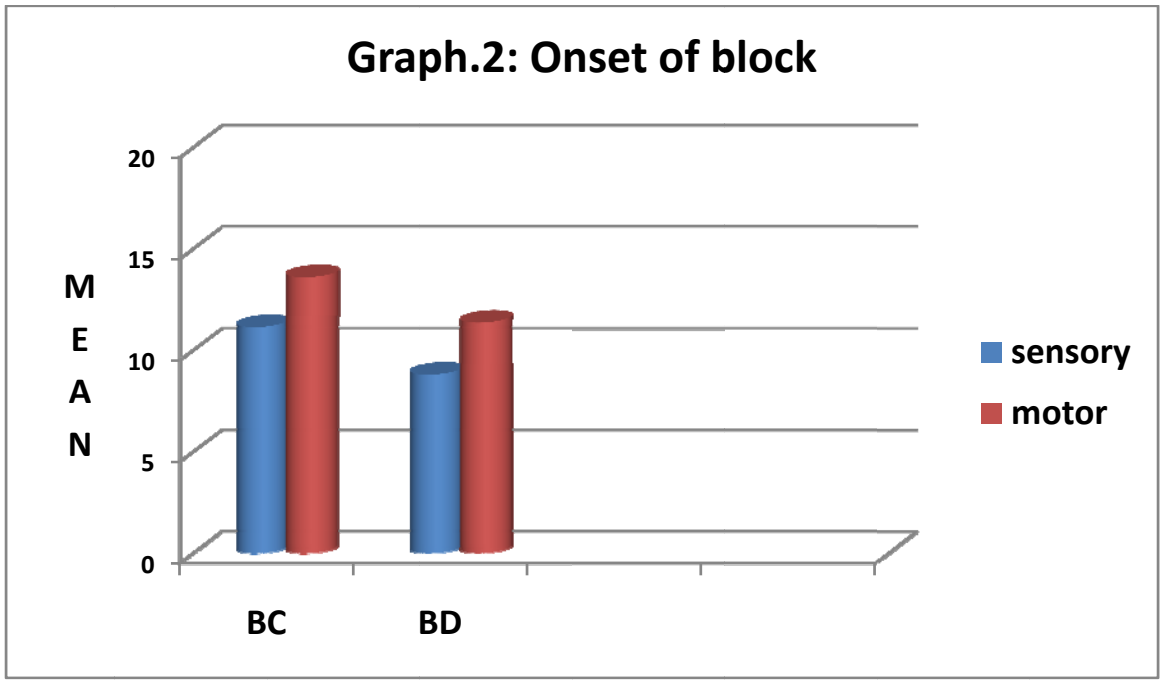


Table.3: Onset of Motor block (in min)

Group	Mean±SD	T value	P value	significance
BC	13.6±1.11	7.65	<0.001	HS
BD	11.36±0.952			

The mean time for onset of motor block in group BC was 13.6±1.11 and in group BD was 11.36±0.952. The statistical analysis by student's unpaired "t"

test showed that the time of onset of motor block in group BD was

significantly faster than group BC ($p < 0.001$).

Table.4: Duration of Sensory block (in hours)

Group	Mean±SD	T value	P value	significance
BC	7.06±0.664	11.9	<0.001	HS
BD	9.3±0.667			

Patients of both groups were observed for 24hrs. The time was noted when the patient asked for rescue analgesics. The mean duration of sensory block in group BC was 7.06±0.664 and in group BD was 9.3±0.667hrs. The statistical analysis by student's unpaired "t" test showed that the time of duration of sensory block in group BD was significantly faster than group BC ($p < 0.001$).

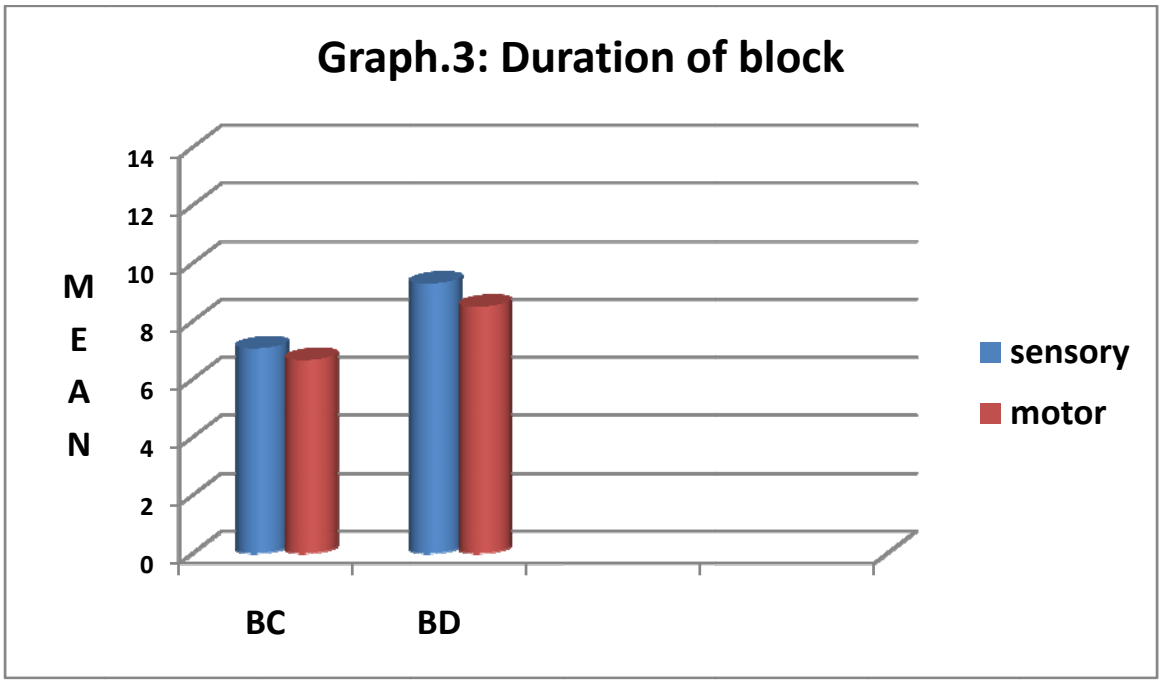


Table.5: Duration of Motor block (in hours)

Group	Mean±SD	T value	P value	significance
BC	6.66±0.657	9.64	<0.001	HS
BD	8.5±0.692			

The mean duration of motor block in group BC was 6.66±0.657and in group BD was 8.5±0.692hrs. The statistical analysis by student's unpaired "t" test showed that the duration of motor block in group BD was significantly longer than group BC ($p < 0.001$).

Table.6:No of rescue analgesics in post-op 24hrs:

No of RA in 24hrs post-op	BC	BD	P
1st dose	5(20%)	14(56%)	0.018
2nd dose	20(80%)	11()	

In group BC 20% of patients required one rescue analgesic dose and 80% required 2 analgesic doses, whereas in group BD, 56% required one analgesic dose and only 44% required 2 analgesic doses. The difference in no of rescue analgesics required by both the groups were statistically significant by Chi-square test ($p<0.018$).

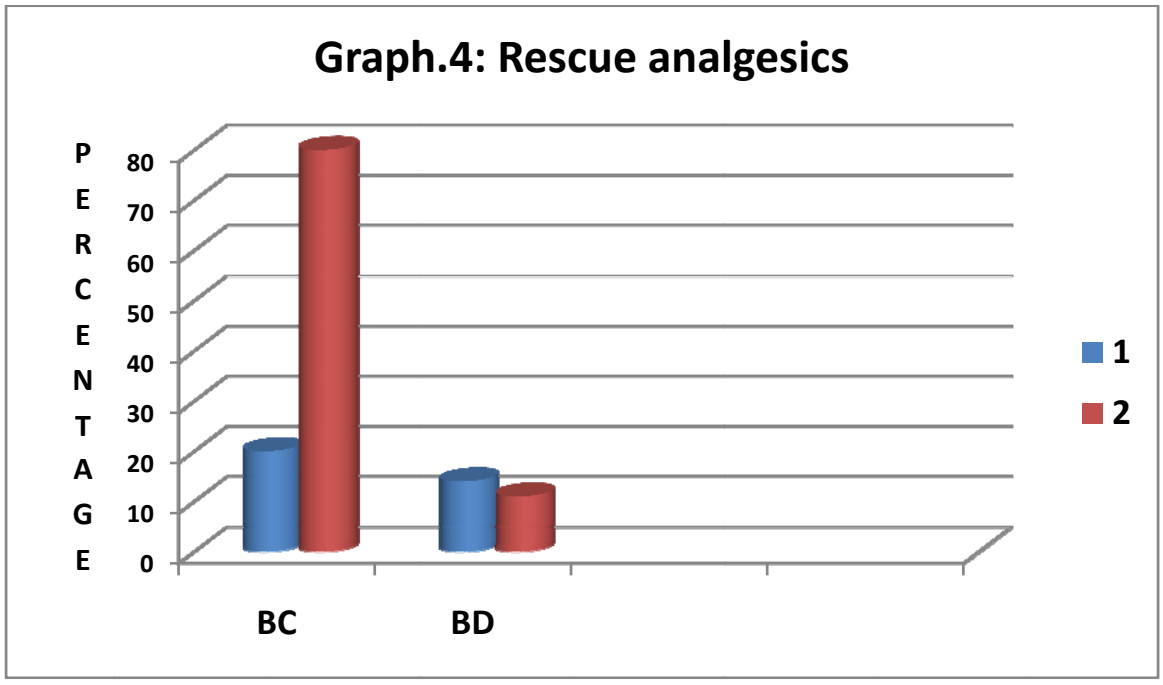
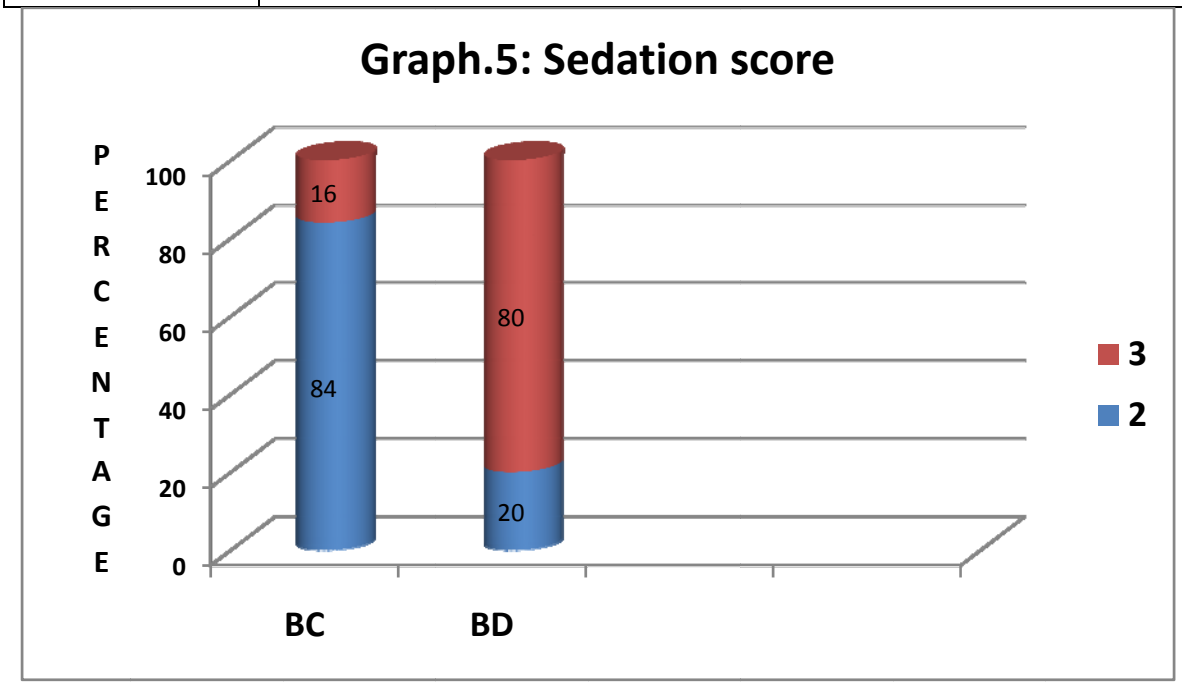


Table 7:Sedation score:

Sedation score	Group BC		Group BD	
	No of patients	%	No of patients	%
2	21	84	5	20
3	4	16	20	80
Total	25	100	25	100
Mean	2		3	
SD	0.374		0.408	
'p'	<0.001 (significant)			



This was evaluated using Ramsay sedation score:

1. Anxious and alert.
2. Conscious and oriented.
3. Sedated, responding to verbal commands.
4. Responding only to mild physical stimulus.
5. Responding to moderate & severe physical stimulus.
6. Not arousable.

In group, sedation score corresponding to score 2 was observed in 84% of patients and sedation score of 3 in 16% of patients, whereas in group BD, sedation score corresponding to 2 was observed in 20% of patients and sedation score of 3 in 80% of patients. The difference in sedation score between the two groups was found to be statistically significant by student's unpaired 't' test. ($p<0.001$).

Hemodynamic variables:

Pulse rate, systolic BP, diastolic BP and oxygen saturation was recorded at 0, 5, 15, 30 & 60min and 2, 6, 12 & 24hrs.

Table 8: Pulse rate (beats/min)

Time of assessment	BC		BD		T value	P value	significance
	Mean	SD	Mean	SD			
0min	79.240	7.008	78.880	6.760	0.854	0.020	NS
5min	78.920	7.427	78.800	6.782	0.953	0.028	NS
15min	78.320	7.284	78.480	7.148	0.938	0.014	NS
30min	78.080	7.729	78.080	6.964	1.000	0.051	NS
60min	77.840	7.888	78.240	6.888	0.849	0.033	NS
2hrs	77.920	7.926	78.000	6.633	0.969	0.000	NS
6hrs	78.480	7.880	78.280	7.481	0.927	0.092	NS
12hrs	78.360	7.566	78.040	7.586	0.882	0.051	NS
24hrs	78.480	7.600	78.040	7.552	0.838	0.013	NS

In group BC the mean pulse rate ranged from 73.920±9.9 to 82.760±13.18beats/min and in group BD it ranged from 76.880±0.247 to 81.92±8.11beats/min. The statistical analysis by student's unpaired "t"

test showed that there was no significant difference in pulse rate between the 2 groups($p>0.05$).

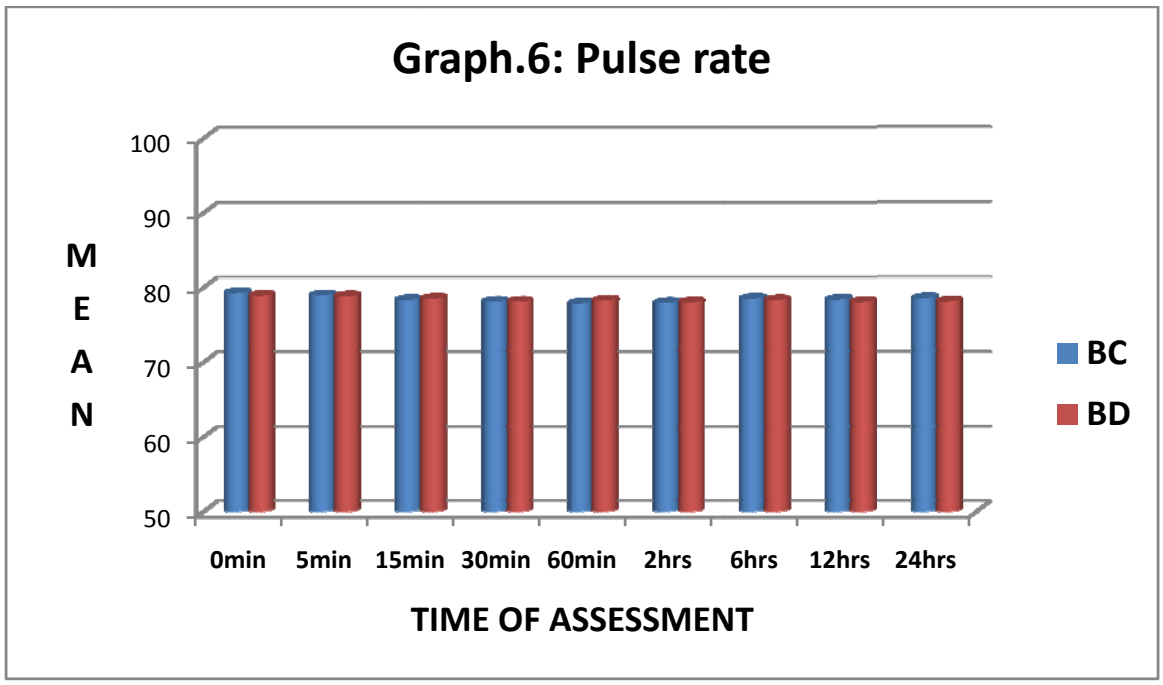


Table 9: Systolic BP(mmHg)

Time of assessment	BC		BD		T value	P value	significance
	Mean	SD	Mean	SD			
0min	123.44	8.515	120.480	7.922	0.209	0.067	NS
5min	123.28	8.244	120.320	7.993	0.204	0.042	NS
15min	123.28	8.163	119.920	7.884	0.145	0.016	NS
30min	123.04	8.023	118.880	8.167	0.075	0.073	NS
60min	122.72	7.547	119.040	7.961	0.100	0.002	NS
2hrs	122.16	6.479	119.120	7.748	0.139	0.067	NS
6hrs	121.2	7.141	119.760	7.557	0.492	0.013	NS
12hrs	121.92	7.604	120.000	7.483	0.373	0.003	NS
24hrs	122.48	7.644	120.080	7.449	0.266	0.033	NS

In group BC the mean systolic BP ranged from 122.56±9.05 to 124.08±7.77mmHg and in group BD it ranged from 116.24±7.53 to 121.36±9.12mmHg. The statistical analysis by student's unpaired "t"

test showed that there was no significant difference in systolic BP between the 2 groups($p>0.05$).

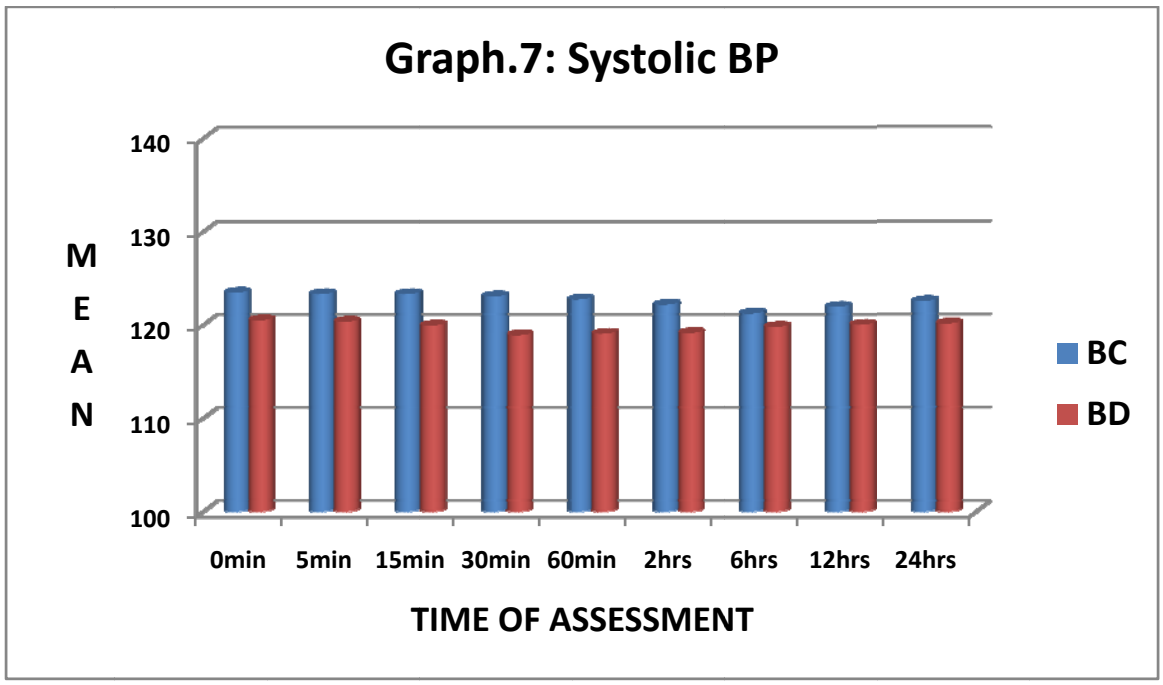


Table 10:Diastolic BP(mmHg)

Time of assessment	BC		BD		T value	P value	significance
	Mean	SD	Mean	SD			
0min	75.92	4.949	76	7.348	0.964	0.064	NS
5min	75.84	5.064	75.76	7.242	0.964	0.099	NS
15min	75.52	5.009	75.52	6.514	1.000	0.013	NS
30min	74.56	5.116	75.28	6.680	0.671	0.012	NS
60min	74.16	4.652	74.88	6.809	0.664	0.059	NS
2hrs	74.4	4.796	74.96	6.761	0.737	0.106	NS
6hrs	74.48	5.009	75.44	6.795	0.572	0.180	NS
12hrs	75.08	5.212	75.68	7.134	0.736	0.122	NS
24hrs	75.6	5.196	75.68	7.134	0.964	0.158	NS

In group BC the mean diastolic BP ranged from 71.36±5.73 to75.92±4.94mmHg and in group BD it ranged from 71.04±6.19 to76.48±7.6mmHg. The statistical analysis by student's unpaired "t" test showed that there was no significant difference in diastolic BP between the 2 groups($p>0.05$).

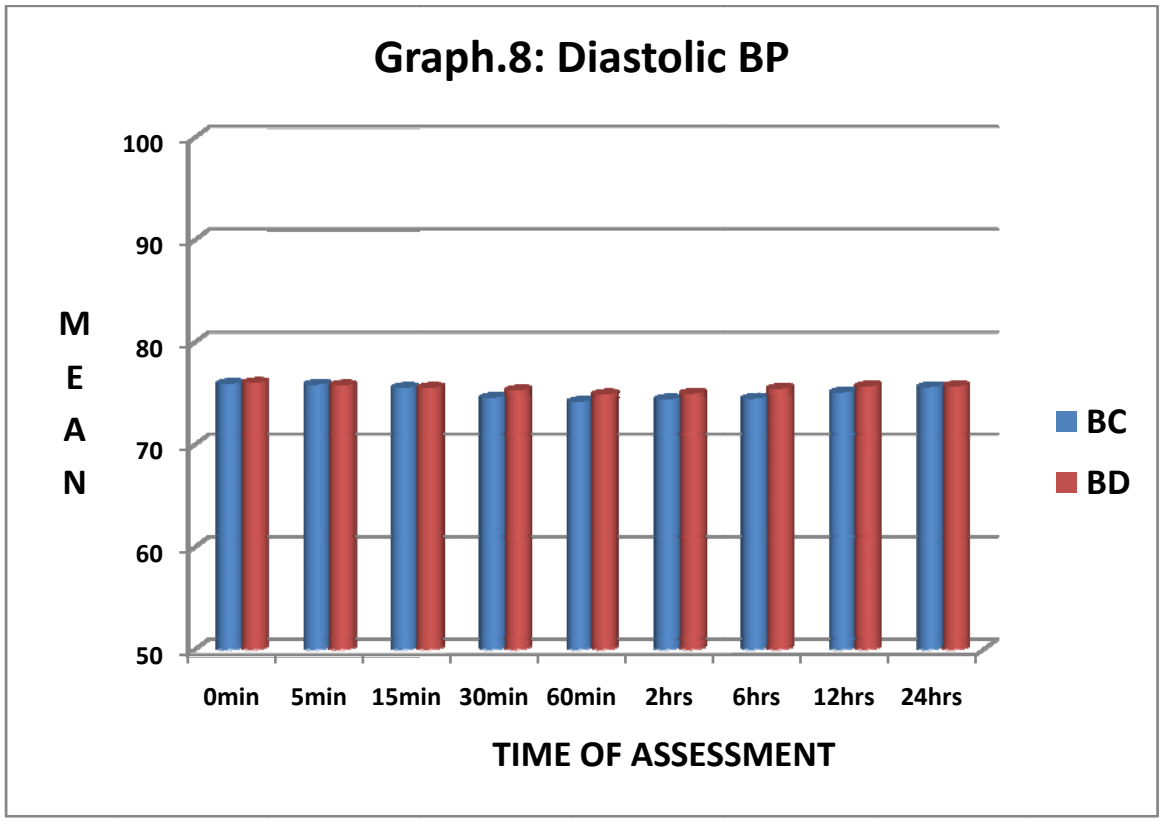
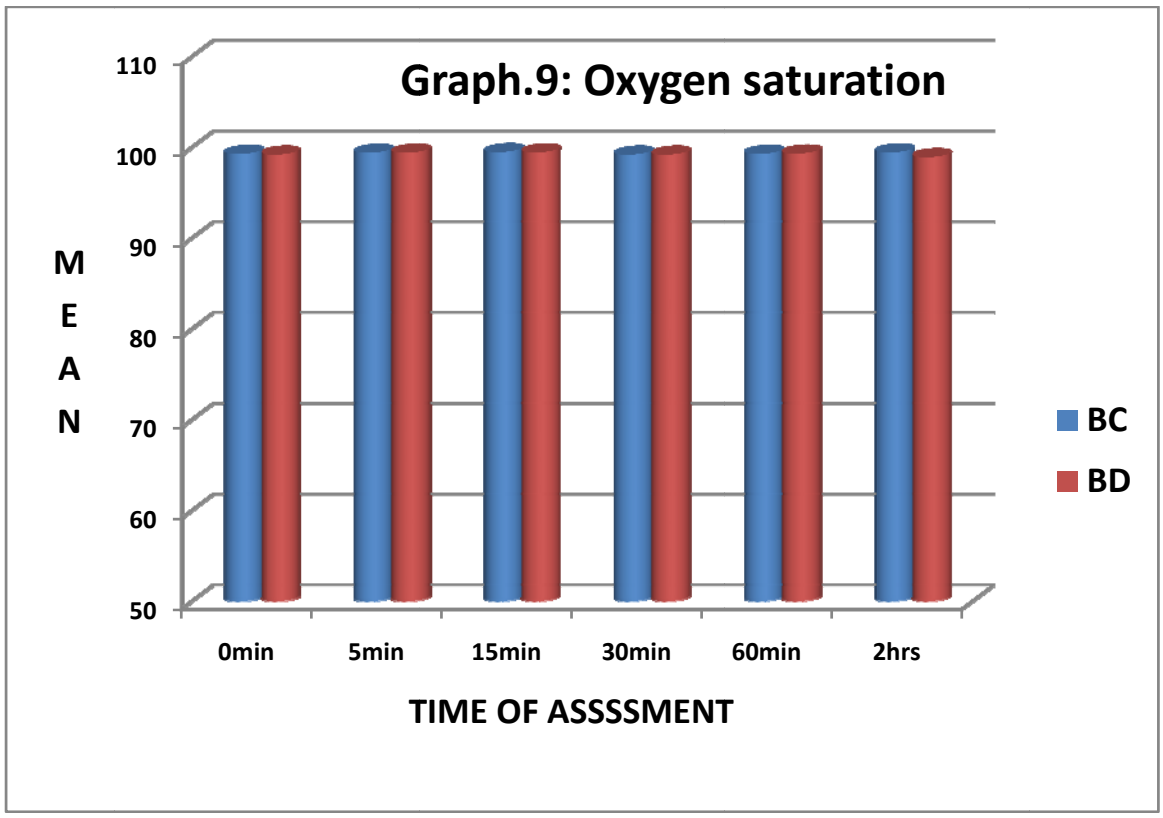

Graph.8: Diastolic BP
100
90
80
70
60
50
MEAN
0min
5min
15min
30min
60min
2hrs
6hrs
12hrs
24hrs
TIME OF ASSESSMENT
BC
BD

Table 11:Oxygen saturation(%)

Time of assessment	BC		BD		T value	P value	significance
	Mean	SD	Mean	SD			
0min	99.28	0.541	99.2	0.707	0.655	0.478	NS
5min	99.4	0.577	99.4	0.707	1	0.204	NS
15min	99.48	0.509	99.44	0.506	0.782	0.367	NS
30min	99.2	0.577	99.2	0.633	1	4.654	NS
60min	99.28	0.458	99.32	0.485	0.782	0.236	NS
2hrs	99.44	0.583	98.92	0.483	0.002	0.127	NS
6hrs	99.08	0.493	99.28	0.452	0.151	0.265	NS
12hrs	99.04	0.538	99.04	0.196	0.196	0.371	NS
24hrs	99.12	0.6	99.12	0.543	0.257	0.612	NS

In group BC the mean O2 saturation ranged from 99.04±0.53 to 99.04±0.19% and in group BD it ranged from 99.04±0.19 to 99.92±0.48% . The statistical analysis by student's unpaired "t" test

showed that there was no significant difference in O2 saturation between the 2 groups(p>0.05).



Side effects:

Patients were observed for side effects such as hypotension and bradycardia. In both the groups, there was no incidence of hypotension and bradycardia. Only one patient had a minimal pneumothorax, but the patient when followed by taking chest X-Ray the pneumothorax had gradually resolved.

4 patients had an inadequate block and were excluded from the study.

DISCUSSION

Brachial plexus provides post-op analgesia only for a short duration even when we use longer acting LA agents like bupivacaine. Hence, various adjuvants like opioids, midazolam, neostigmine,etc, have been evaluated to prolong the duration of analgesia. The newer drugs clonidine and dexmedetomidine were found to produce anti-nociception when used intrathecally and epidurally.

Hence these drugs were used as an attempt to assess the efficacy of dexmedetomidine over clonidine as an adjuvant to bupivacaine in brachial plexus block. They were compared in terms of onset time, duration of analgesia and sedation. Hemodynamic variables and no of rescue analgesics in first 24hrs were also studied.

A total of 50 patients in the age group of 15-55yrs were included in the study, 25 in each group. Out of which the mean age of group BC (receiving bupivacaine with clonidine) was 36.8±12.26yrs and the mean age of group BD (receiving bupivacaine with

dexmedetomidine) was 34.88±9.03yrs. hence both the groups were comparable in regard to age.

In our study, it was found that the onset of sensory block and motor block were significantly faster in patients who received a combination of bupivacaine and dexmedetomidine than the combination of bupivacaine and clonidine. Onset of sensory block (group BC-11.14±1.13min : group BD-8.8±0.192min). Onset of motor block (group BC-13.6 ±1.22min:group BD – 11.36±0.9min).

Clonidine was used previously for its antihypertensive properties. The central actions are mediated through $\alpha_2$adrenoceptors, which are situated at locus coeruleus and the dorsal horn of spinal cord. But, specific peripheral effects of clonidine appear to be less obvious because these adrenoceptors are not present on the axon of the normal peripheral nerve[19]. Four mechanisms have been proposed for the action of clonidine in peripheral nerve blocks. They include centrally mediated analgesia, vasoconstrictive effects via α_2 β adrenoceptor receptors , direct action on peripheral nerve and attenuation of inflammatory response[22]. The direct action of clonidine on the nerve can be

explained on the basis of a study conducted by Dalle *et al*. They proposed that clonidine, by enhancing activity-dependent hyperpolarisation generated by the Na/K pump, increases the threshold for initiating the action potential causing slowing or blockage of conduction.

Popping et al. in their metaanalysis of randomized controlled study showed that the beneficial effect of clonidine on the duration of analgesia was observed with all tested local anaesthetics[19].

A study by Brumett et al. showed that dexmedetomidine increases the duration of bupivacaine anaesthesia and analgesia without any damage to the nerve. The histopathological evaluation of these nerve axons were normal in both the control and combination groups.

In another study, the analgesic effect of peripheral perineural dexmedetomidine added to ropivacaine prolonged the duration of analgesia by enhancement of the hyperpolarisation-activated cation current, which prevents the nerve from returning from a hyperpolarized state to resting membrane potential for subsequent firing[30]. Clonidine

also inhibits compound action potential(CAPs) but the maximum effect of clonidine was only 20%.

Esmaoglu et al. added dexmedetomidine to levobupivacaine for axillary block and showed that it shortens the onset of both sensory and motor block and prolongs the duration of the block and post-operative analgesia[28]. This may be due to reduced release of norepinephrine, leading to α_2 receptor - independent inhibitory effects on nerve fibre action potential. Similarly, in our study also, we found that the onset of sensory and motor block was faster in group BD compared to group BC, which was statistically significant. The duration of analgesia was also found to be prolonged in group BD than group BC.

In our study, we compared the addition of clonidine (Group BC 1 μg/kg) and dexmedetomidine (Group BD 1 μg/kg) to bupivacaine in brachial plexus block. The result of our study shows that all patients in both groups were comparable with respect to demographic profile. With these doses, we had stable haemodynamics in patients in both the groups.

None of the patients in Group BD required sedation intraoperatively and they were comfortable throughout the surgery with arousable sedative effects. This can be explained on the basis that some amount of systemic absorption of drug could be present. As α_2 agonists produce sedation by central action, they produce inhibition of substance P release at the level of the dorsal root neuron and by activation of α_2 adrenoreceptor in locus coeruleus.

From this study, we would like to suggest that dexmedetomidine can be safely used with local anaesthetic in peripheral nerve blocks, however, further trials to determine the exact dose and effect of neurotoxicity on the human nerve are required.

CONCLUSION

To conclude, we would like to state that dexmedetomidine prolongs the duration of sensory and motor block as compared with clonidine when it is used as an adjuvant to Bupivacaine in peripheral nerve block.

Hence it is seen that dexmedetomidine when added to bupivacaine compared to clonidine has

1. Faster onset of sensory block
2. Faster onset of motor block
3. Prolonged duration of sensory block
4. Prolonged duration of motor block
5. Less no of rescue analgesics in post-op 24hrs
6. Comfortable sedation where the patient can be arousable at any time
7. No significant difference in hemodynamic variables.

SUMMARY

This study, "A clinical comparison between dexmedetomidine and clonidine with bupivacaine in brachial plexus block by supraclavicular approach" was conducted in 50 patients of either sex, in the range of 15 – 55yrs. ASA grade I & II, admitted in K.A.P.Viswanatham Government Hospital, Trichy for upper limb surgeries from 2010 – 2013. They were randomly divided into two groups;

Group BC : received 35ml of 0.25% bupivacaine with clonidine 1µg/kg

Group BD : received 35ml of o.25% bupivacaine with dexmedetomidine 1µg/kg

The following parameters were recorded and compared:

- Onset of sensory block and motor block
- Duration of sensory block and motor block
- No of rescue analgesic doses in post-op 24hrs
- Sedation score

- Hemodynamic variables like pulse rate, systolic BP, diastolic BP and oxygen saturation.
- **Onset of sensory and motor block:**

The mean time for onset of sensory block was in group BC was 11.14±1.13min and in group BD was 8.8min. The mean time for onset of motor block in group BC was 13.6±1.11 and in group BD was 11.36±0.952min.

Both differences were statistically significant ($p<0.05$).

Duration of sensory and motor block:

The mean duration of sensory block in group BC was 7.06±0.664 and in group BD was 9.3±0.667hrs.

The mean duration of motor block in group BC was 6.66±0.657and in group BD was 8.5±0.692hrs.

Both the differences were statistically significant ($p<0.05$).

Rescue analgesic requirement in post-op 24hrs:

In group BC 20% required one rescue analgesic dose and 80% required 2 analgesic doses, whereas in group BD, 56% required one analgesic dose and only 44% required 2 analgesic doses. The rescue analgesic doses required by group BD was significantly higher ($p<0.05$).

Sedation score:

In group BC, 20% of patients at 15min, 32% at 30min & 26% at 60min had sedation score of 2. In group BD, 66% at 15min, 100% at 30min, 80% at 60min and 16% at 2hrs had a sedation score of 2, both responding to verbal stimulus. Statistical analysis by Chi-square test showed that the difference in sedation score was significant ($p<0.05$).

Hemodynamic variables:

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

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GROUP BC - BUPIVACAINE WITH CLONIDINE

S.No	Name	Age	sex	IP.No	Wt in Kg	ASA Status	Onset of block in min		Duration of block in min			Sedation score	Pulse rate									Sysolic BP									Diastolic BP									O2 Saturation								
							Sensory	Motor	sensory	Motor	no of RA in PO 24hrs		0min	5min	15min	30min	60min	2hrs	6hrs	12hrs	24hrs	0min	5min	15min	30min	60min	2hrs	6hrs	12hrs	24hrs	0min	5min	15min	30min	60min	2hrs	6 hrs	12hrs	24hrs	0min	5min	15min	30min	60min	2hrs	6hrs	12hrs	24hrs
1	Settu pillai	49	M	51068	72	II	10	12	6	6	2	0	86	86	85	82	86	86	86	80	86	120	120	120	120	120	120	120	120	122	80	80	80	78	78	80	80	80	80	98	99	100	100	100	99	100	100	100
2	Sakthivel	50	M	57298	69	II	10	12	7	6	2	2	94	94	94	96	96	96	96	95	94	120	122	122	122	122	122	120	120	122	80	80	78	78	76	76	76	76	76	100	99	100	100	100	99	100	100	100
3	Surshkumar	28	M	2423	42	I	12	14	7	7	2	2	78	76	75	74	74	74	74	76	76	120	120	120	118	118	118	118	120	120	70	70	70	70	70	70	70	70	70	100	99	100	100	100	99	100	100	100
4	Elangovan	32	M	5655	55	I	11	15	8	8	2	2	84	84	82	82	80	80	84	84	84	126	126	126	124	124	124	124	126	126	78	78	78	76	76	76	78	78	78	99	99	100	100	100	100	100	100	100
5	Ganesan	38	M	59309	52	I	12	13	9	8	1	2	98	98	96	96	96	96	98	98	98	130	130	128	128	128	128	130	130	130	80	80	80	78	78	80	80	80	80	99	99	99	100	100	100	99	99	99
6	Palanavel	42	M	9057	70	II	13	14	7	7	2	3	80	80	80	80	82	82	80	80	80	130	130	138	138	138	130	130	130	130	80	80	80	80	78	78	78	78	78	99	99	99	100	100	100	99	99	99
7	Simon	40	M	11610	67	I	11	14	8	7	2	2	82	82	80	80	82	82	82	82	80	110	110	110	110	110	110	110	110	110	70	70	70	70	70	68	68	69	68	99	98	99	99	99	100	99	99	99
8	Shanthi	38	F	16328	66	I	12	13	7	6	1	2	70	66	66	66	68	68	66	66	66	120	120	120	118	118	118	120	120	120	70	70	70	68	68	70	70	70	80	99	100	99	99	99	100	99	99	99
9	Natarajan	55	M	16564	78	I	11	15	7	6	2	2	84	84	80	80	80	80	84	84	84	110	110	110	120	122	122	110	110	110	80	80	80	78	78	80	80	80	80	100	100	99	99	99	98	99	99	99
10	Tamilarasan	21	M	23524	54	I	12	14	7	7	2	2	76	76	74	74	74	78	78	78	78	120	120	120	118	118	118	116	120	120	80	80	80	78	76	76	76	80	80	100	100	99	99	99	99	99	99	99
11	Ayyappan	37	M	25278	80	I	10	12	8	8	2	2	73	72	70	73	73	72	72	72	72	130	130	130	130	130	128	120	120	120	70	70	70	68	70	70	70	70	70	100	99	99	99	99	99	99	99	99
12	Marikannu	41	M	34735	79	I	10	14	8	7	1	2	82	82	84	84	84	84	82	82	82	130	130	130	128	122	128	130	128	128	80	80	80	80	80	80	80	80	82	100	99	99	99	99	99	99	99	99
13	Sarathkumar	16	M	36304	35	I	10	13	7	7	1	2	78	78	78	78	70	70	78	78	78	120	120	122	122	120	120	120	120	120	80	80	80	80	80	80	80	82	82	100	99	99	99	99	99	99	99	99
14	Malathi	39	F	42587	72	I	11	13	8	7	2	3	79	78	76	76	76	78	78	78	78	130	130	130	132	130	130	130	130	130	70	70	68	68	68	68	66	66	68	100	99	99	99	99	99	99	99	99
15	Balasubramanian	22	M	43730	36	I	12	15	7	6	2	2	77	76	75	77	77	76	76	76	76	120	120	120	118	116	116	120	120	120	70	70	70	68	68	68	68	68	68	99	99	99	98	99	99	99	99	100
16	Saravanan	32	M	48820	64	I	12	14	6	6	1	2	81	80	82	82	82	82	80	80	80	110	110	110	110	114	114	112	112	112	70	70	70	68	70	70	70	70	70	99	99	99	98	99	99	99	99	100
17	Mariammal	43	F	54783	77	II	10	12	7	6	2	2	86	88	88	88	86	86	86	86	86	140	140	140	140	138	130	130	138	138	80	80	80	80	78	78	78	80	80	99	99	99	99	99	99	99	98	98
18	Velankanni	33	M	54631	65	I	13	14	8	7	1	3	78	78	78	78	76	76	76	76	76	130	130	130	128	128	128	128	128	128	80	80	80	80	78	78	78	78	78	99	100	100	99	99	99	98	98	98
19	Rangasamy	19	M	9049	34	I	12	15	7	7	2	2	72	72	72	68	68	68	70	70	70	120	120	120	120	122	120	120	120	120	80	80	80	76	76	76	76	76	76	99	100	100	99	99	100	98	98	98
20	Panneerselvi	32	F	20197	56	I	11	14	9	7	2	2	74	74	74	74	74	70	70	70	70	130	130	130	128	128	128	128	130	130	80	80	78	78	78	80	80	80	80	99	100	100	99	99	100	99	99	99
21	Shanmugam	70	M	21716	82	I	10	13	8	8	2	2	76	76	76	76	74	74	74	76	76	140	138	130	130	130	130	130	130	130	80	80	78	78	78	76	76	80	80	99	100	100	99	99	100	99	99	99
22	Pitchai	45	M	34530	77	I	10	12	8	7	1	2	77	77	77	78	78	78	76	76	76	120	120	120	120	118	118	118	120	120	70	68	68	68	66	66	66	68	68	99	100	100	99	99	100	99	99	99
23	Banumathy	37	F	42844	68	I	11	13	7	6	1	3	70	70	70	70	70	72	72	72	72	120	120	120	118	118	118	116	116	120	70	70	70	68	68	70	70	70	70	99	100	100	99	99	100	99	99	99
24	Baskar	40	M	41308	78	I	12	14	7	7	2	2	78	78	78	76	76	76	78	78	78	110	110	110	108	108	108	106	106	106	80	80	80	80	78	76	78	78	78	99	100	100	99	99	100	99	99	99
25	Suresh	21	M	45106	43	I	14	16	8	7	2	2	68	68	68	64	64	64	66	66	66	130	126	126	128	128	128	124	124	130	70	70	70	70	70	70	70	70	70	99	100	100	100	100	100	99	99	99

GROUP BD - BUPIVACAINE WITH DEXMEDITOMEDINE

S.No	Name	Age	Sex	IP.No	Wt in Kg	ASA status	Onset of block in min		Duration of block in hrs			Sedation score	Pulse rate									Systolic BP									Diastolic BP									O2 Saturation								
							Sensory	Motor	sensory	Motor	no of RA in mg		0min	5min	15min	30min	60min	2hrs	6hrs	12hrs	24hrs	0min	5min	15min	30min	60min	2hrs	6hrs	12hrs	24hrs	0min	5min	15min	30min	60min	2hrs	6hrs	12hrs	24hrs	0min	5min	15min	30min	60min	2hrs	6hrs	12hrs	24hrs
1	Balaji	27	M	51068	58	I	8	11	10	9.5	2	2	78	78	76	74	76	74	78	78	78	118	118	118	116	116	116	118	118	118	70	70	70	68	70	70	70	70	70	100	100	100	99	99	99	99	99	99
2	Sikkan	50	M	56840	67	III/E	9	12	10	9	2	3	80	80	78	78	78	76	80	70	70	134	134	134	132	132	134	134	134	134	74	74	74	76	76	74	74	76	76	100	99	99	99	99	100	100	100	100
3	Kumar	30	M	37569	55	I	8	12	10	9	1	3	84	84	86	86	86	86	84	84	84	120	120	120	118	118	118	120	120	120	80	80	80	76	76	80	80	80	80	100	100	100	100	100	100	99	99	99
4	Logeswari	35	F	442	56	II	8	12	9	8.5	1	3	88	88	88	88	86	84	88	88	88	122	122	122	120	120	122	122	122	122	78	78	78	78	76	76	78	78	78	100	100	100	99	99	99	100	99	99
5	Saleem	32	M	5595	55	I	9	11	9	8.5	2	3	80	80	80	80	82	82	80	80	80	134	134	134	134	134	130	130	130	130	88	88	86	86	88	88	88	88	88	100	100	100	99	99	99	100	99	99
6	Panneer selvam	40	M	8213	60	I	9	10	10	8.5	2	2	86	86	86	86	84	84	89	89	87	120	120	118	118	118	120	120	120	120	70	70	70	70	68	68	70	68	68	100	100	100	99	99	99	100	99	99
7	Karthik	24	M	11376	45	I	10	10	10	9.5	1	3	72	72	70	70	70	70	68	68	70	118	118	116	116	120	120	120	120	120	68	68	70	70	68	68	68	68	68	99	100	100	99	99	99	100	99	99
8	Saroja	37	F	14152	50	I	9	13	10	9	1	3	78	76	76	76	74	74	74	76	76	124	124	124	124	120	120	124	124	124	80	78	78	76	80	80	80	80	80	99	100	100	99	99	99	100	99	99
9	Suresh	35	M	18048	63	I	8	12	9	8	1	3	68	68	64	64	64	68	68	68	68	112	112	112	110	110	112	112	112	112	78	78	78	76	76	76	78	78	78	99	100	100	100	100	99	100	99	99
10	Palaniammal	30	F	22229	50	I	8	11	8	7.5	2	3	74	74	74	74	78	78	78	76	76	118	116	116	116	114	114	114	116	116	70	70	70	70	70	70	70	70	70	99	100	100	100	100	99	99	99	99
11	Rajesh	16	M	24612	40	I	9	12	8	7.5	2	3	90	90	90	86	88	88	90	90	90	120	120	120	118	118	118	118	118	118	76	76	76	78	78	78	78	78	78	98	98	100	100	100	99	99	99	99
12	Ramasamy	40	M	27608	70	II	9	11	10	9	1	3	86	86	86	84	84	84	86	86	86	110	110	110	108	108	108	110	110	110	66	66	66	64	64	64	66	66	66	98	98	100	100	100	99	99	99	99
13	Gracy gnanamary	40	F	33396	60	II	9	10	10	9.5	2	2	86	86	86	84	84	84	84	84	84	112	112	110	110	112	112	112	112	112	78	78	78	74	74	78	78	78	78	98	98	99	100	100	99	99	99	100
14	Chandrasekar	35	M	33599	55	I	10	10	11	9.5	2	3	80	80	80	80	82	82	80	80	82	118	118	118	116	116	116	116	116	118	76	76	76	76	76	76	76	76	76	98	99	99	100	100	98	99	99	100
15	Karolin	46	F	37874	48	I	8	13	10	9	1	3	72	72	72	72	70	70	70	70	70	110	110	110	106	106	106	108	110	110	70	70	70	68	70	70	70	70	70	99	99	99	100	100	98	99	99	100
16	Rajalakshmi	50	F	44791	60	I	8	12	9	8	1	3	76	76	76	76	76	74	76	76	76	130	130	130	130	130	130	128	130	130	90	88	88	86	86	88	88	88	88	99	99	99	98	99	98	99	99	100
17	Gopi	37	M	52365	56	I	8	11	9	7.5	1	3	76	76	76	76	76	76	74	74	74	120	120	120	122	122	120	120	120	120	78	78	78	78	76	76	78	78	78	99	99	99	98	99	98	99	99	98
18	Sivakumar	41	M	6732	54	I	9	13	9	8.5	2	2	78	78	78	76	76	76	78	78	78	118	118	118	116	118	118	118	118	118	70	70	70	70	68	68	68	68	68	99	99	99	98	99	99	99	99	98
19	Sathishkumar	30	M	18020	45	I	9	12	10	9.5	2	3	70	70	74	74	74	74	70	70	70	120	120	120	118	120	120	120	120	120	80	80	80	86	86	80	80	80	80	99	99	99	99	99	99	99	99	99
20	Mohd.Saffiullah	18	M	24765	50	I	10	11	11	10	1	3	86	86	86	86	84	84	86	86	86	138	138	138	136	136	136	138	138	138	90	90	90	90	88	88	90	90	90	99	99	99	99	99	99	99	99	99
21	Mohanavalli	39	F	31817	55	II	11	11	10	8.5	2	3	68	68	68	70	70	70	68	68	68	118	116	116	116	116	118	118	118	118	68	68	68	70	70	70	70	70	70	99	99	99	99	99	99	99	99	99
22	Mohammed Ali	49	M	46601	76	I	7	11	9	8.5	1	3	78	78	76	76	78	78	78	78	78	120	120	120	120	118	116	120	120	120	78	78	78	78	70	70	70	70	70	99	100	99	99	99	99	99	99	99
23	Balu	35	M	45130	50	I	8	12	9	8	1	2	90	90	90	92	92	92	90	90	90	112	112	112	112	114	114	112	112	112	66	66	68	68	68	68	68	68	68	100	100	99	99	99	99	99	99	99
24	Ganesan	24	M	46913	52	I	9	11	9	8.5	2	3	78	78	76	76	76	74	74	78	78	134	134	130	130	130	130	130	130	130	88	88	80	80	80	80	80	86	86	100	100	99	99	99	99	99	99	99
25	Manjula	31	F	47491	42	I	10	10	10	9	1	3	70	70	70	68	68	68	66	66	64	112	112	112	110	110	110	112	112	112	70	68	68	70	70	70	70	70	70	100	100	99	99	99	99	99	99	99

ANNEXURE-1

PROFORMA

COMPARISON OF DEXMEDITOMEDINE WITH CLONIDINE AS AN ADJUVANT TO BUPIVACAINE IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK

NAME: AGE/SEX: IP.No:

ADDRESS: WEIGHT: ASA Gr:

GROUP:

DIAGNOSIS/SURGERY:

General physical examination:

PR: BP: RR:

Objectives:

Time of injection: min.

Onset of sensory block: min.

Onset of motor block: min.

Monitoring:

Time in Hrs	PR	BP	SPO2	Sedation score	VAS score

Duration of surgery in hrs:

Duration of sensory analgesia:

Duration of post-op analgesia:

No of rescue analgesics in postop 24hrs:

K.A.P.VISWANATHAM GOVT.MEDICAL COLLEGE

TIRUCHY-1

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DR J.KALIAMURTHY

CERTIFICATE OF CLEARANCE

This is to certify that the project work titled **"COMPARISON OF CLONIDINE AND DEXMEDITOMEDINE AS AN ADJUVANT TO BUPIVACAINE IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK "** proposed by Dr.K.Hemalatha of K.A.P.V. Govt.medical college, Tiruchy as part of fulfillment of M.D course in the subject of Anaesthesiology for the year 2012-13 by The Tamilnadu Dr.MGR medical university has been cleared by the ethical committee.

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