A Dissertation on

"A COMPARATIVE STUDY OF BUPIVACAINE WITH MIDAZOLAM AND BUPIVACAINE ALONE IN BRACHIAL PLEXUS BLOCKADE"

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CERTIFICATE

This is to certify that the dissertation titled **"A COMPARATIVE STUDY OF BUPIVACAINE WITH MIDAZOLAM AND BUPIVACAINE ALONE IN BRACHIAL PLEXUS BLOCKADE"** presented herein by **Dr. V.J. KARTHIK** is an original work done in the Department of Anaesthesiology, Government Stanley Medical College Hospital, Chennai for the award of the degree of M.D. (Branch X) Anaesthesiology under my guidance and supervision during the academic period of 2003 – 2006.

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DECLARATION

I, **Dr. V.J. KARTHIK** solemnly declare that the dissertation titled **"A COMPARATIVE STUDY OF BUPIVACAINE WITH MIDAZOLAM AND BUPIVACAINE ALONE IN BRACHIAL PLEXUS BLOCKADE"** is a bonafide work done by me in the Department of Anaesthesiology, Government Stanley Medical College and Hospital, Chennai under the able guidance of **PROF. J. RANGANATHAN M.D., D.A.,** Professor & HOD, Department of Anaesthesiology, Government Stanley Medical College and Hospital, Chennai – 600001.

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CONTENTS

INTRODUCTION

Regional anesthesia as the name implies is the blocking of peripheral nerve conduction in a reversible manner by using local anesthetic agents, thereby one region of the body is made insensitive to pain and is devoid of reflex response to surgical stimuli. The central nervous system is spared, so the patient is conscious during the surgical procedure.

Regional anesthesia offers many advantages over general anesthesia[1-5] for surgery on upper extremities, particularly in emergency operations.

Advantages of Regional over General anesthesia:

- Causes least disturbance to the normal physiology than any other type of anesthesia.
- Proven to be safe for high risk patients who are in greater risk due to the stress imposed by general anesthesia.
- Only method of anesthesia, which prevents all afferent impulses from the site of surgery from reaching the CNS. Hence the need for polypharmacy and its attended risks are eliminated.
- Along with complete pain relief and total muscle relaxation it produces vasodilatation, which improves blood circulation and prevents tissue hypoxia.

- Many intraoperative and postoperative complications of general anesthesia are avoided.
- Postoperative pain relief is ensured for a longer duration by using long acting local anesthetic drug and for several days if continuous block using catheter technique is employed.
- It is cost effective and safe.
- Avoids theatre pollution.
- Safest technique for patients with full stomach.
- All the adverse effects of airway manipulation can be avoided.

The frequent use of pneumatic tourniquet[33] to provide a bloodless field during surgery makes individual nerve blocks impractical. Brachial plexus block[6] is the answer in such a situation. There are different approaches but the ones frequently employed for blocking the brachial plexus[2] include

a) Supraclavicular approach
b) Infraclavicular approach
c) Axillary approach
d) Interscalene approach

Axillary approach[16] has the lowest incidence of serious complications and can be performed with ease. But there are limitations associated with axillary approach[8-10] like

- It is inadequate for operations on the arm and shoulder.
- It is difficult to block the musculocutaneous nerve predictably with resultant sparing of the radial aspect of forearm and dorsum of hand.
- Tourniquet pain is not well tolerated.
- Also abducting the arm by 90 degrees for giving the block may be painful and even dangerous in traumatic lesions of the upper extremity.

The brachial plexus is approached at the level of trunks and the compact arrangement of trunks at supraclavicular level gives a high success rate with minimum local anesthetic drug volume and a dense & fast onset block. Hence the supraclavicular approach is the method of choice for blocking the brachial plexus[2]

.

William Steward Halsted first performed brachial plexus block in 1885. In 1911, Kulenkampff and Hirshel described the first percutaneous brachial plexus block by supraclavicular and axillary routes respectively.

Since then several techniques of brachial plexus block have been described with the purpose of improving the efficacy and success rate and minimizing the risk and rate of complications. Of the various techniques[2] the most widely practiced methods are the classical technique described by Patrick (1940), Vertical plumb bob approach described by Brown, 1st rib walk over technique described by

Bonica and Moore and the Subclavian perivascular technique described by Winnie and Collins (1964).

Of the several local anaesthetic drugs used for brachial plexus block, Bupivacaine is used most frequently in our set up as it has a long duration of action varying from 3 – 8 hours[16,32,38,43].

To prolong the duration of analgesia various drugs have been studied as adjuvant to the local anaesthetic solution and techniques like the continuous catheter placement in the plexus have evolved. These adjuvant drugs ideally are expected to prolong the analgesic effect without causing any systemic side effects or prolonging motor blockade. Commonly used additives to local anesthetic solution are epinephrine, clonidine and opioids[1,2].

Midazolam, a water soluble benzodiazepine, is known to produce antinociception[71,72] and to enhance the effect of local anesthetic when given epidurally or intrathecally[73-80]. Midazolam produces this effect by its action on GABA-A receptors[71,76,80]. The presence of GABA receptors in peripheral nerves is also demonstrated[67,69,81].

This study is intended to determine the effects of adding midazolam to Bupivacaine in brachial plexus blockade by supraclavicular approach with regard to the onset, intensity and duration of blockade along with its analgesic efficacy.

AIM OF THE STUDY

The aim of the present study is to evaluate the effect of addition of 50µg/kg of preservative free Midazolam to 0.5% Bupivacaine solution in supraclavicular brachial plexus block on the

- Onset of blockade
- Duration of blockade
- Intensity of blockade
- Sedation
- Complications if any &
- Quality of analgesia

ANATOMY OF BRACHIAL PLEXUS [11-15]

Knowledge of the formation of the brachial plexus and of its distribution is absolutely essential for the precise and effective use of brachial plexus analgesia for surgeries of the upper limb. A thorough understanding of the vascular, muscular and fascial relationships of the plexus throughout its formation and distribution is equally essential in order to master the various techniques of brachial plexus analgesia.

In its course from the intervertebral foramina to the arm, the fibres that constitute the plexus are composed consecutively of roots, trunks, divisions, cords and terminal branches, which are formed through a complex process of combining, dividing, recombining and finally redividing.

The brachial plexus is formed by the union of the anterior primary rami of the fifth to eighth cervical nerves and first thoracic nerve with occasional contributions from the fourth cervical nerve (prefixed) above and second thoracic nerve (postfixed) below. These nerves unite to form trunks, which lie in the neck above the clavicle. Its roots pass through the fascia enclosed space between the scalenus anterior and the scalenus medius accompanied by the subclavian artery and invaginate the scalene fascia to form a neurovascular bundle. This fascia becomes the axillary sheath in the axilla.

Relations of brachial plexus

Anterior relations

The skin, superficial fascia, platysma, and supraclavicular branches of the superficial cervical plexus, the deep fascia and external jugular vein. The clavicle is in front of the lower part and scalenus anterior is in front of the upper part.

Posterior relations

Scalenus medius and the long thoracic nerve of Bell.

Inferior relations

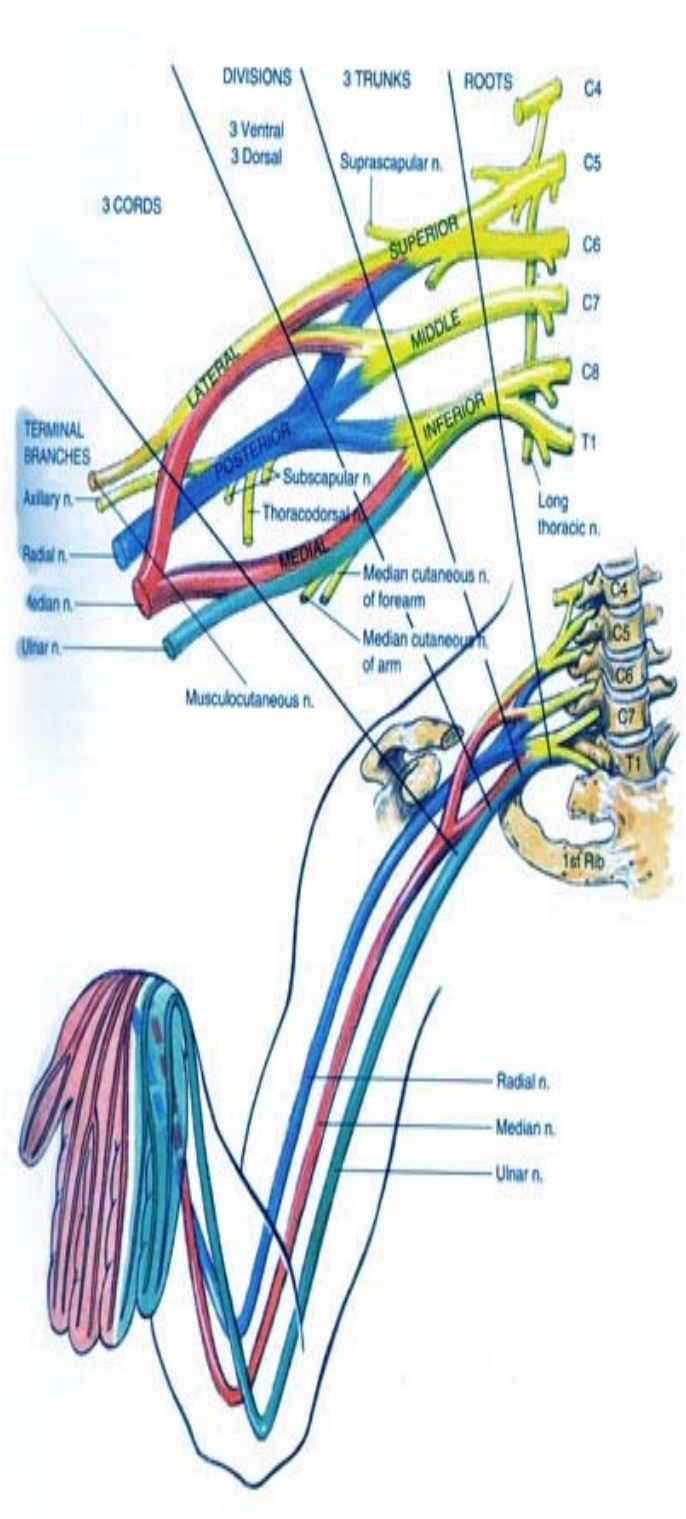
Related to the first rib.

Superior relations

Lies first above and then lateral to the subclavian artery.

Sympathetic contribution to the plexus

Close to their emergence, the 5^{th} and 6^{th} cervical nerves, each receive a grey ramus from the middle cervical sympathetic ganglion. The 7^{th} and 8^{th} cervical nerves each receive a grey ramus from the inferior cervical ganglion.


DIVISIONS
3 TRUNKS
ROOTS
3 Ventral
3 Dorsal
3 CORDS
Suprascapular n.
SUPERIOR
MIDDLE
INFERIOR
LATERAL
POSTERIOR
MEDIAL
C4
C5
C6
C7
C8
T1
TERMINAL BRANCHES
Axillary n.
Radial n.
Median n.
Ulnar n.
Subscapular n.
Thoracodorsal n.
Long thoracic n.
Median cutaneous n. of forearm
Median cutaneous n. of arm
Musculocutaneous n.
1st Rib
Radial n.
Median n.
Ulnar n.

Roots

Anterior primary rami of C5 – C8 and T1 (occasionally C4 or T2).

Trunks

- Upper trunk – anterior rami of C5 and C6
- Middle trunk – anterior ramus of C7
- Lower trunk – anterior ramus of C8 and T1.

Divisions

Behind the clavicle each trunk divides into anterior and posterior divisions.

Cords

- Lateral cord – Anterior divisions of upper and middle trunks (C5 – C7)
- Medial cord - Anterior division of lower trunk (C8 – T1)
- Posterior cord – Posterior divisions of all the three trunks (C5 – T1)

Branches

From Roots

- Nerve to serratus anterior C5 – C7
- Muscular branches to longus cervices C5 – C8.
- Nerve to the three scalene C5 – C8.
- Nerve to Rhomboids C5
- A twig to phrenic nerve C5.

From Trunks

- Suprascapular nerve C5 & C6
- Nerve to subclavius C5 & C6

From Cords

- Lateral cord (three):

  Lateral pectoral C5 – C7

  Lateral root of the Median C5- C7

  Musculocutaneous C5 – C7

- Medial cord (five):

  Medial root of median nerve C8 – T1

  Medial pectoral C8 – T1

  Medial cutaneous N of forearm C8 – T1

  Medial cutaneous N of arm C8 – T1

  Ulnar C8 – T1

- Posterior cord

  Radial C5 – T1

  Axillary C5 – C8

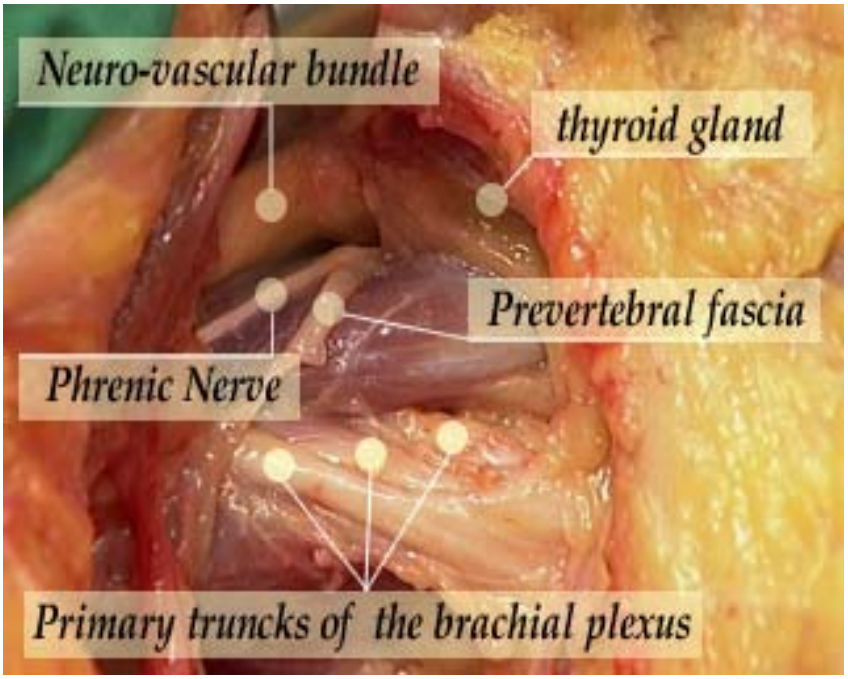
  Thorocodorsal C6 – C8

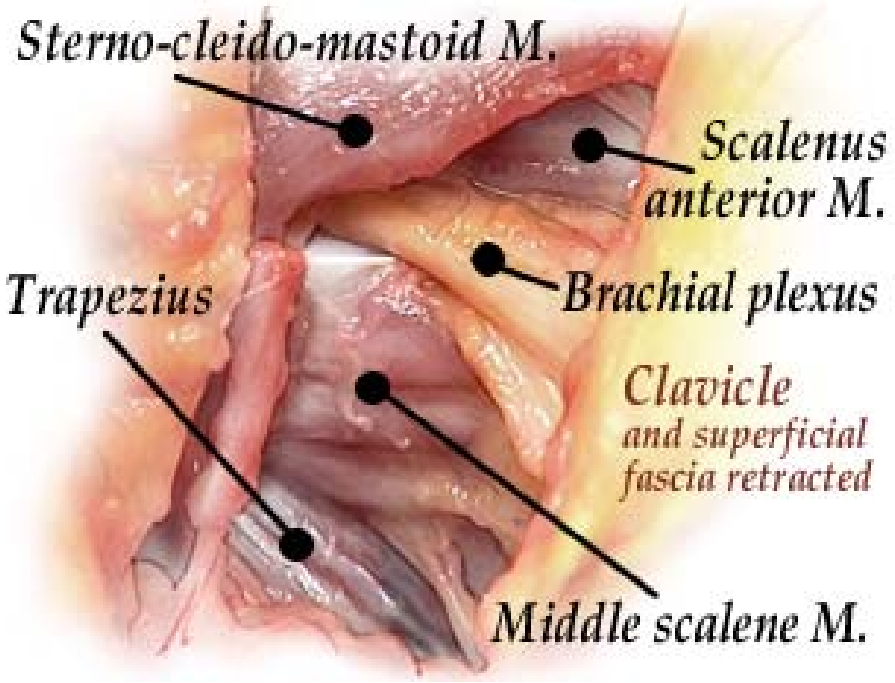
  Upper and lower subscapular C5 – C6

Familiarity with the perineural structures that surround and accompany the brachial plexus as it leaves the vertebral column on its course to the upper arm is as important as the knowledge of the formation and distribution of the neural plexus itself. Palpable muscular and vascular landmarks allow accurate location of the plexus percutaneously. An appreciation of the fascial relations is absolutely essential since this is the basis for all the perivascular techniques.

After leaving the intervertebral foramina, the anterior primary rami of the nerves destined to become the brachial plexus travel in the gutter formed by the anterior and posterior tubercles of the corresponding transverse processes of the cervical vertebrae. After leaving the transverse process, the roots of the plexus descend in front of the middle scalene muscle, which arises from the posterior tubercles of the transverse processes of the lower six cervical vertebrae. The insertion of this muscle on the first rib is separated from that of the anterior scalene muscle by the inferior trunk of the brachial plexus. The anterior scalene muscle arises from the anterior tubercles of the transverse process of the 3^{rd} – 6^{th} cervical vertebrae and inserts on the scalene tubercle of the first rib, thus separating the subclavian artery from the subclavian vein.

The fascia covering both the scalene muscles is derived from the prevertebral fascia, which splits to invest these muscles and then fuses again at their lateral margins to form an enclosed interscalene space. Therefore, as the roots leave the transverse processes, they emerge between two walls of the fascia


Neuro-vascular bundle
thyroid gland
Prevertebral fascia
Phrenic Nerve
Primary truncks of the brachial plexus


Sterno-cleido-mastoid M.
Scalenus anterior M.
Brachial plexus
Trapezius
Clavicle
and superficial fascia retracted
Middle scalene M.

covering the anterior and middle scalene muscles. In their descent toward the first rib to form the trunks of the plexus, the roots may be considered to be sandwiched between the anterior and middle scalene muscles, the fascia of which serves as a sheath of the plexus. As the trunks approach the first rib, they are arranged (as their designations – superior, middle and inferior imply) one above the other vertically, not one next to the other horizontally as depicted in so many texts.

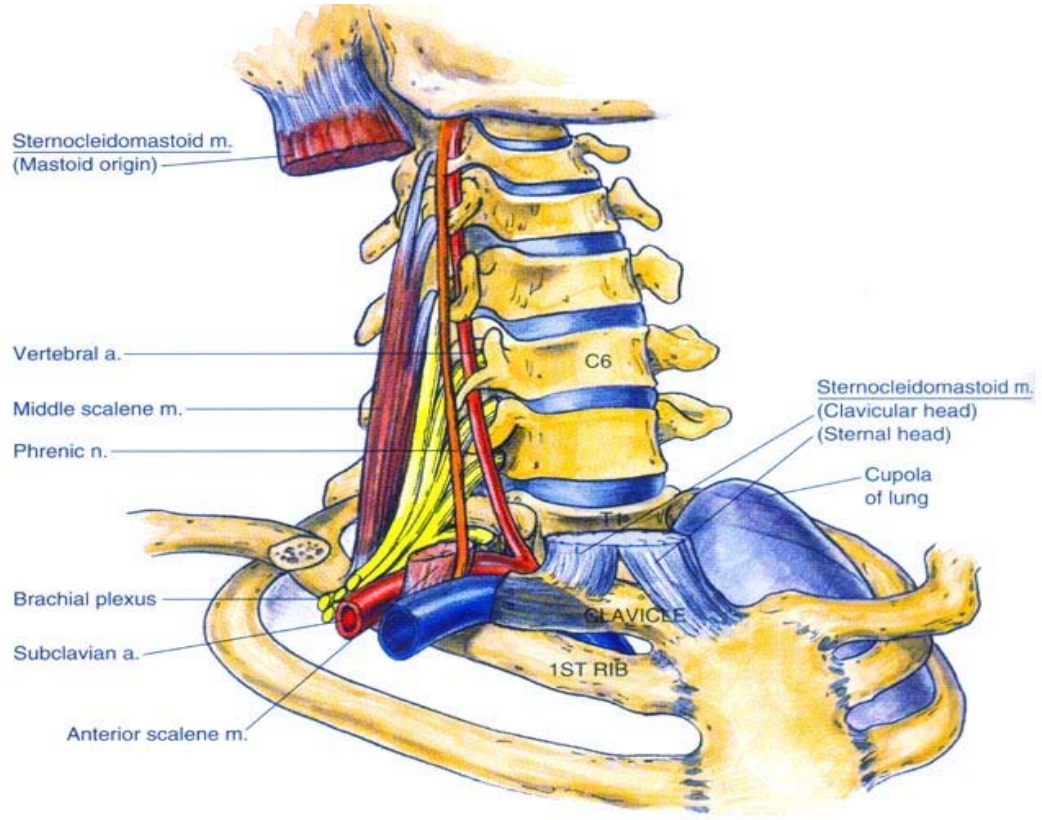
As the trunks of the plexus cross the first rib, they are joined by the subclavian artery, which lies in a plane anterior to the trunks, so that the inferior trunk lies behind the artery in the subclavian groove with the middle and superior trunks above the level of the vessel. At this level the artery and trunks are moving laterally; across the ribs and invaginate the scalene fascia to form the subclavian perivascular space, which is continuous medially and superiorly with the interscalene space and inferiorly and laterally with the axillary perivascular space.

The important concept is that there is a continuous fascial enclosed perineural and perivascular space extending from the cervical transverse processes to several centimeters beyond the axilla; this space has been divided into an axillary perivascular space and an interscalene space. The existence of such a continuous perineural space renders brachial plexus block simple. The space described may be entered at any level, and the volume of the anesthetic injected at that level would determine the extent of anesthesia. Thus, the technique to be used

in any case should be determined on the basis of the surgical site, the required level of anesthesia, the physical status and habitus of the patient.

The upper medial aspect of the arm is not anesthetized by any brachial plexus block technique, since this area is innervated by the intercostobrachial nerve T2. This nerve can be blocked by subcutaneous infiltration across the upper medial aspect of arm using 3-5ml of local anaesthetic solution for surgical anesthesia or tourniquet.

The brachial plexus can be blocked at the level of the roots, trunks, cords or peripheral branches. The block at each level has a distinct distribution of anaesthesia, advantages, disadvantages, and complications.



CLINICAL PHARMACOLOGY[35-47]

BUPIVACAINE

Synthesized by Bo Af Evenstam in 1957 in Sweden.

First came into clinical use in 1963.

Bupivacaine is an anilide compound.

It is an amide local anesthetic (1-butyl-N-(2, 6-dimethylphenyl)-piperidine-2-carboxamide).

Presentation

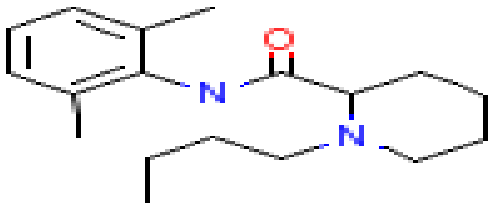
As a clear 0.25 / 0.5 / 0.75 % solution of bupivacaine hydrochloride. The hyperbaric solution used for subarachnoid block contains 80 mg/ml of glucose.

Physiochemical properties

pKa = 8.1

protein binding : 96%

lipid solubility : 28



$C_{18}H_{28}N_2O$

Mechanism of Action

Local anesthetics such as bupivacaine block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone. The analgesic effects of Bupivacaine are thought to be due to its binding to the prostaglandin E2 receptors, subtype EP1 (PGE2EP1), which inhibits the production of prostaglandins, thereby reducing fever, inflammation, and hyperalgesia.

Routes of administration / doses

Bupivacaine may be administered topically by infiltration, intrathecally or epidurally. The therapeutic dose of bupivacaine is 2 – 3 mg/kg (with or without adrenaline).

The drug acts within 10 to 20 minutes and has duration of action of 5 - 6 hours.

Pharmacokinetics

The absorption of local anesthetics is related to

- The site of injection (intercostals > epidural > brachial plexus > subcutaneous)
- The dose - a linear relationship exists between the total dose and the peak blood concentration achieved.
- The presence of vasoconstrictors which delay absorption.

The addition of adrenaline to bupivacaine does not influence the rate of systemic absorption as,

- The drug is highly lipid soluble and therefore uptake into fat is rapid.
- The drug has a direct vasoconstrictory effect.

The possible pathways for metabolism of bupivacaine include aromatic hydroxylation, N-dealkylation, amide hydrolysis and conjugation. Only the N-dealkylated metabolite N-desbutyl bupivacaine has been measured in the blood or urine.

Alpha 1 acid glycoprotein is the most important protein binding site of bupivacaine. 5% of the dose is excreted in the urine as pipcolloxylidine. 16% is excreted unchanged. Clearance is 0.47 l/min and the elimination half life is about 210 minutes.

Systemic toxicity

Cardiovascular system

Bupivacaine is markedly cardiotoxic. It binds specifically to the myocardial proteins. In toxic concentrations the drug decreases the peripheral vascular resistance and myocardial contractility producing hypotension and possible cardiovascular collapse. Cardiotoxic plasma concentration of bupivacaine is 8-10 ug /ml.

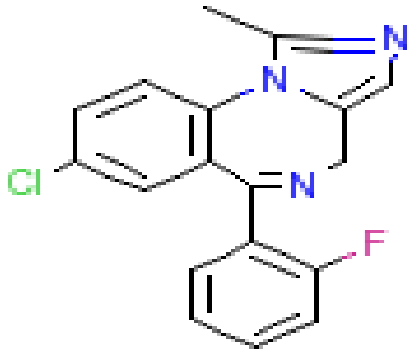
Central nervous system

The principal effect of bupivacaine is reversible neural blockade. This leads to a characteristically biphasic effect in the central nervous system. During accidental overdosage or direct vascular injections the clinical signs are numbness of tongue, lightheadedness, visual and auditory disturbances, muscular twitching and tremors. The signs may progress to generalized convulsions of the tonic – clonic nature. When plasma levels continue to rise, CNS excitation is rapidly superseded by depression. (drowsiness, disorientation and coma)

The typical plasma concentration of bupivacaine associated with seizures is 4.5 to 5.5 µg/ml.

MIDAZOLAM

Midazolam is a water soluble imidazobenzodiazepine (8-chloro-6-(2-fluorophenyl) -1-methyl-4H-imidazo[1,5-a] [1,4]benzodiazepine) and its unique feature being its pH dependent imidazole ring which open at pH < 4 and accounts for its stability in aqueous solution and rapid metabolism. At pH > 4, the ring closes leading to increase in lipid solubility.



$C_{18}H_{13}ClFN_3$

Pharmacokinetics

- It has a pH of 3.5 with pKa of 6.15
- Protein binding : 96 – 98%
- Volume of distribution : 1 – 1.5 l/kg

- Clearance : 6 – 8 ml/kg/min
- Elimination half time: 1.4 hours. Increased in elderly/obese.
- Metabolised by hepatic microsomal enzyme cytochrome p – 450 by hydroxylation to 1 OH and 4 OH midazolam.

Excreted in urine as glucuronide conjugates. Erythromycin decreases its hepatic clearance leading to increased duration of action. Less than 0.02% is excreted unchanged. Therefore it is not affected by renal failure.

Mechanism of Action

It is thought that the actions of benzodiazepines such as midazolam are mediated through the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), which is one of the major inhibitory neurotransmitters in the brain. Benzodiazepines increase the activity of GABA, thereby producing a calming effect, relaxing skeletal muscles, and inducing sleep. Benzodiazepines act as agonists at the benzodiazepine receptors, which form a component of the benzodiazepine-GABA receptor-chloride ionophore complex. Most anxiolytics appear to act through at least one component of this complex to enhance the inhibitory action of GABA.

Dosage and Routes of Administration :

Routes

Oral, nasal, intramuscular, intravenous, intrathecal and epidural.

Dosage

Sedation : 0.05 – 0.1 mg/kg

Premedication : 0.07 – 0.08 mg/kg

Induction : 0.1 – 0.3 mg/kg

Infusion : 2 – 5 mcg/kg/min

Intrathecal : 0.3 – 2 mg

Epidural : 0.1 – 0.2 mg/kg

Actions

Central nervous system

Decreases cerebral blood flow, cerebral oxygen requirement and intracranial pressure.

Sedation, hypnosis, anxiolysis

Anterograde amnesia

Anticonvulsant

Respiratory system

Transient apnoea occurs when administered in doses greater than 0.15 mg/kg and in opiod premedicated subjects.

Potent respiratory depressant especially in chronic obstructive pulmonary disease patients.

Cardiovascular system

Decrease in peripheral vascular resistance and transient attenuation of baroreceptor reflexes leading to hypotension and tachycardia. In hypovolemic and elderly patients there is increased risk of significant hypotension.

Local effects

No venous irritation and thrombophlebitis.

Mechanism of pain relief in central neuraxial blockade

It acts on spinal GABA receptors. There are 2 types of GABA receptors: GABA-A and GABA-B. Midazolam binds to the alpha subunit of the pentamer GABA-A receptor leading to its conformational change causing increased chloride ion conductance and hyperpolarisation and thereby acts by potentiating the inhibitory neurotransmitter, GABA. This is mainly a postsynaptic action while GABA-B receptors mainly have presynaptic antinociceptive effect by decreasing the excitatory neurotransmitter release.

Intrathecal midazolam positively modulates GABA-A / benzodiazepine receptor complex causing the release of an endogenous opioid acting at opioid receptors and also intrathecal midazolam causes antinociception by combining with three different receptor subtypes of GABA-A in the spinal cord.

PHARMACOKINETICS OF LOCAL ANESTHETICS IN BRACHIAL PLEXUS BLOCKADE[34]

When a local anesthetic is injected around a nerve trunk, it will soak the trunk in an advancing front. Transmission in fibers situated in the periphery of the trunk (mantle fibres) will be first blocked and those in the centre of the trunk (core fibres) last. Further, transmission in peripherally placed fibres will be blocked over a longer length of time compared to central fibres. Thus analgesia will appear first and last longest in the territory supplied by the peripheral fibres. If the pool of local anesthetics is small or if the injection was not accurate or too dilute, the fibres in the centre of the trunk will escape blockade.

Theory of Winnie

The trunks are arranged so that the central fibres are the longest supplying the extremities of the limb while shorter fibres are arranged more peripherally as their area of supply is more proximal. Winnie groups the fibres into two: the peripheral mantle fibres which contain the motor fibres and core fibres which are

mainly inner sensory. Peripheral motor fibres supply the muscles of the forearm and the central fibres carry sensation from the hand.

Thus the onset of block in the limb is as follows:

- Loss of motor power to the shoulder and upper arm
- Loss of sensation on the upper arm
- Loss of motor power of the forearm
- Loss of sensation to the hand.

So the spread of block is from proximal to distal.

REVIEW OF LITERATURE

Technique and drug:

Winnie & Collins[16] described the subclavian perivascular technique.

McGlade et al.[43], ***Hickey et al***.[44] compared the effectiveness of 0.5% ropivacaine and 0.5% bupivacaine for brachial plexus block. They appeared equally effective in providing brachial plexus anesthesia.

Peripheral GABA receptors:

The presence of peripheral GABA receptors is suggested by the following studies:

Brown et al.[67,68] observed that extrasynaptic GABA-receptors occur on both neurone somata and unmyelinated axons in the mammalian peripheral nervous system. Activation of these receptors leads to depolarization, reduced spike amplitude and slowed conduction, probably mediated through increased 1. Cl- conductance. 2. GABA also depolarizeds preganglionic nerve terminals in the rat superior cervical ganglion and reduces the release of acetylcholine by preganglionic nerve impulses. 3. The Schwann and satellite neuroglial cells surrounding peripheral unmyelinated axons and neurones possess a GABA-carrier

promoting net uptake of GABA at external concentrations greater than or equal to 1 microM. 4. The possible significance of extrasynaptic receptors and carriers for GABA is discussed.

Bhisitkul et al[69] used a sucrose gap chamber to study the effect of gamma-aminobutyric acid (GABA) on normal and regenerating rat peripheral nerve fibers. The results indicate that GABA receptors are selectively present on normal mammalian sensory axons, and are reestablished on regenerated sensory axons.

Cairns et al.[70] suggest that $GABA_A$ receptors are located within the TMJ region and that their activation appears to attenuate the nociceptive reflex response that can be evoked from this region.

Intrathecal midazolam:

Batra et al.[83] observed that addition of midazolam to bupivacaine intrathecally provided better post-operative analgesia without any adverse effects.

Bharti et al.[75] found out that addition of intrathecal midazolam to bupivacaine significantly improves the duration and quality of spinal anaesthesia and provides prolonged perioperative analgesia without significant side-effects.

Yegin et al.[74] demonstrated the use of intrathecal midazolam combined with intrathecal bupivacaine producing a more effective and longer analgesia with a mild sedative effect in perianal surgery.

Kim et al.[80] observed that intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy.

Epidural midazolam:

Nishiyama et al.[76,79] observed that adding midazolam increased not only analgesic but also sedative effect with increasing dose of bupivacaine in a postoperative continuous epidural administration.

Nishiyama et al.[78] observed that adding midazolam (10 to 20 mg per 12 h) to continuous epidural infusion of bupivacaine for postoperative pain can provide a better analgesia, amnesia and sedation than bupivacaine alone.

Caudal Midazolam:

Gulec et al.[82] found that a Bupivacaine and midazolam combination prolonged postoperative analgesia compared to a bupivacaine-morphine combination when administered caudally.

Midazolam in brachial plexus:

Koj Jarbo et al.[90] observed that midazolam in combination with Bupivacaine hastened onset of sensory and motor block, and improved postoperative analgesia when used in brachial plexus block, without producing any adverse events.

MATERIALS AND METHODOLOGY

Forty adult patients of both sexes in the age group of 20 – 60 years belonging to ASA I / II category and their weight ranging between 50 – 70 kgs, posted for various types of upper limb surgeries at the Department of Plastic Surgery, Institute of Research and Rehabilitation of Hand, Government Stanley Hospital, formed the study group.

This study was designed as a prospective, randomized comparative study. After receiving the institutional ethical committee approval and informed consent, the patients were randomly allocated into two groups. Supraclavicular brachial plexus was performed via subclavian perivascular technique.

GROUPS

1. BM - 20 patients received 30 ml of 0.5% Bupivacaine with preservative free Midazolam 50 µg/kg.
2. B - 20 patients received 30 ml of 0.5% Bupivacaine alone.

Inclusion criteria

- ASA I & II

- Age group 20 – 60 years.
- Weight 50 – 70 kilograms.
- Surgeries of forearm and hand

Exclusion criteria

- Patient refusal
- Coagulopathy
- Infection at injection site
- Pneumothorax or previous pneumonectomy on the opposite side.

Patients were all preoperatively evaluated, clinically examined and investigations done prior to assessment. Procedures were explained in detail and written consent obtained.

The procedure was carried out in the preparation room or in the theatre were facilities for resuscitation were available.

Equipment

- Sterile tray
- Sterile towel
- 2 nos. sterile cups
- 2 nos. 20 ml glass syringes

- 1 no 2 ml syringe
- sterile gloves
- sterile swabs
- sponge holding forceps
- Betadine solution

Appropriate needles

1 no. 24G, 3.75 cms long needle.

1 no. 22G, 4cm long, short beveled blunt needle

Drugs

0.5% Bupivacaine vial

Preservative free Midazolam ampoule 5mg/ml.

Intraoperative and postoperative monitors

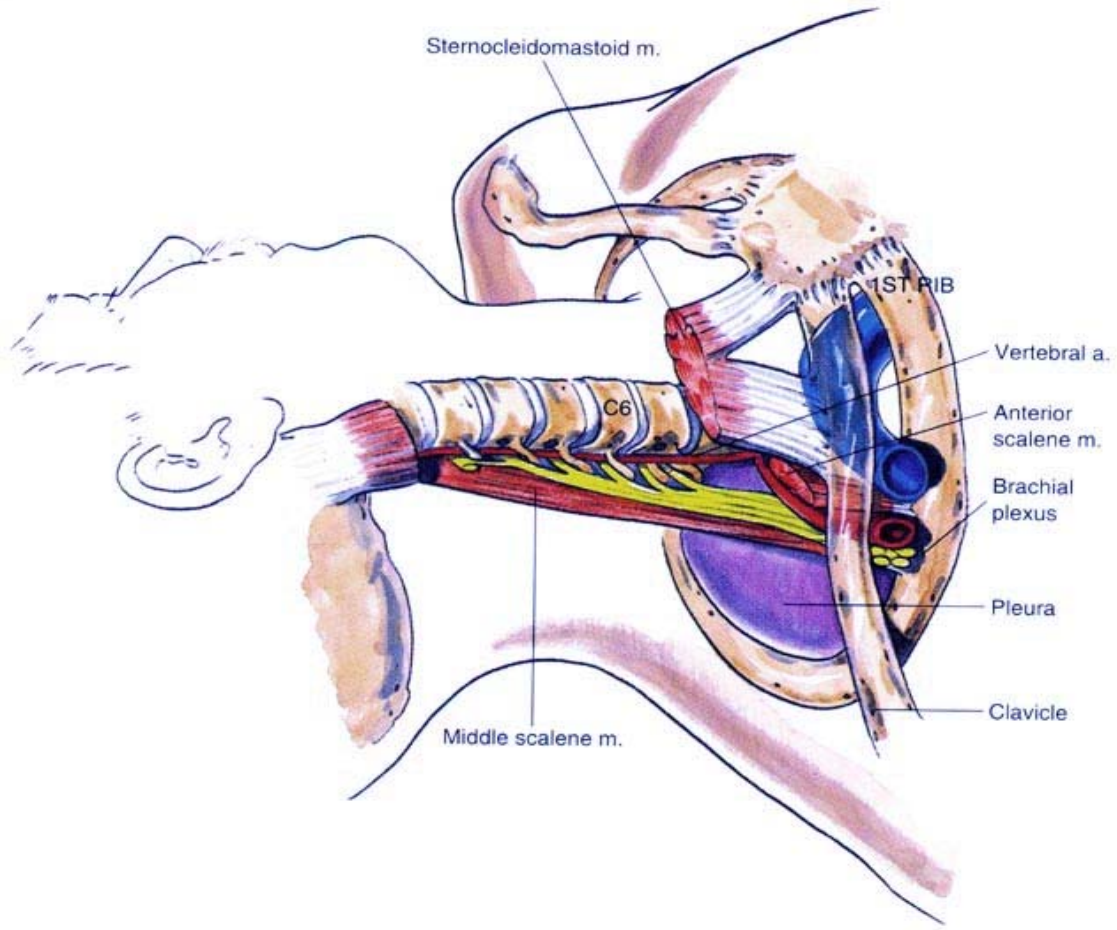
- Pulseoximeter
- NIBP
- ECG

Initially the pre procedure parameters were recorded i.e. pulse rate, BP, SpO2 and Ecg. Then the block was administered. All through the study these

parameters were monitored continuously except the NIBP which was recorded intermittently. Postoperatively they were monitored for 24 hours.

Patients were observed vigilantly for development of various complications and necessary instructions given.

Subclavian Perivascular Technique



Position

- Patient placed in supine position with head turned to the side opposite to the side that is to be injected.
- The arms are at the patient's side with the hands pointing towards the knee.
- The arm on the side to be injected may be pulled to depress the clavicle and the shoulder.
- A rolled towel is placed lengthwise between the shoulders along the spine to give the best exposure to the area.

Landmarks

- The anaesthesiologist stands at the head end of the table.
- The patient is asked to lift the head slightly to bring the clavicular head of the sternomastoid muscle into prominence.
- The index finger is placed lateral to the muscle and the patient is told to relax. Roll the index finger laterally across the belly of the muscle until the interscalene groove is palpated.
- The finger is then moved inferiorly down the groove until the pulse of the subclavian artery is palpated between the scalene muscles.
- After aseptic preparation, a skin wheal is raised at this point with 2ml of lignocaine with a 24G needle about 2 - 3 cms above the midpoint of and perpendicular to the clavicle.

- The pulsation of the subclavian artery against the palpating finger or needle is the surest guide to supraclavicular block.
- The needle enters at the level of C7 in the interscalene groove.
- The needle is directed caudally and the hub is in line with the ear.

Procedure

- After a sterile preparation of the region, the 22G, 4cm needle is inserted through the skin wheal and above the palpating finger immediately lateral to the subclavian artery.
- It is directed dorsolaterally and parallel to the scalene muscles and towards the patient's feet. There will be a click once the sheath is entered and there will be a give way.
- The needle advancement is stopped at this level and conducted subclavian pulsation is observed. If the needle is pulsating then the anaesthetic solution is injected.
- If the needle pulsation is not satisfactory then the needle is advanced further till it hits one of the three trunks of the plexus.
- A paraesthesia to any part of the upper extremity as long as it is below the shoulder indicates that the needle is in the perivascular space.

- In this technique paraesthesia is obtained before the first rib is contacted. If paraesthesia is not elicited then the needle is withdrawn and tried once again.
- A cough by the patient is a warning that the pleuron is being irritated by the needle.

When the desired endpoint is reached, (i.e. paraesthesia elicited in the arm and fingers or loss of resistance with " click " sensation and transmitted pulsations is observed as needle movement) the needle is halted. Success now depends on holding the needle tip near the nerve during the injection. Potential pitfalls include patient movement and failure to hold the needle firmly in place.

The local anaesthetic solution is injected once the position of needle within the sheath is confirmed.

If there is shooting pain when injecting or if blood is aspirated when injecting, the needle is removed and tried once again. This prevents the complications of accidental trauma to the nerve or accidental intravascular injection respectively. Repeated aspiration after injecting 3-5 ml of anaesthetic solution ensures that the tip is not in the vessel. After injecting the local anaesthetic, the block is tested for both sensory (using pin prick) and motor (using muscle power) and is compared with the same stimulation or power in the

contralateral arm. Motor block was evaluated by thumb abduction (Radial nerve), thumb adduction (Ulnar nerve), thumb opposition (Median nerve) and flexion of the elbow in supination and pronation of the forearm (musculocutaneous).

The Hollmens scale is used in the study for assessing both sensory and motor blockade.

Hollmen's scale

Sensory blockade(Grade)

1. 0 – Normal sensation of pin prick.
2. + - Pin prick felt as sharp pointed but weaker compared with the same area in other extremity.
3. ++ - Pin prick felt as touch with blunt object.
4. +++ - No perception of pin prick.

Onset of blockade means minimum grade 2 and complete blockade means minimum grade 3.

Motor blockade(Grade)

1. 0 – Normal muscle function
2. + - Slight depression in muscle function as compared with pre anaesthetic power.

3. ++ - Very weak muscular action persisting in muscle.
4. +++ - Complete block with absent muscular function.

Onset of blockade means minimum grade 2 and complete blockade means minimum grade 3.

Nerves studied in the block

Sensory

Lateral cutaneous nerve of arm

Medial cutaneous nerve of arm

Medial cutaneous nerve of forearm

Posterior cutaneous nerve of forearm

Lateral cutaneous nerve of forearm

Median nerve

Ulnar nerve

Radial nerve

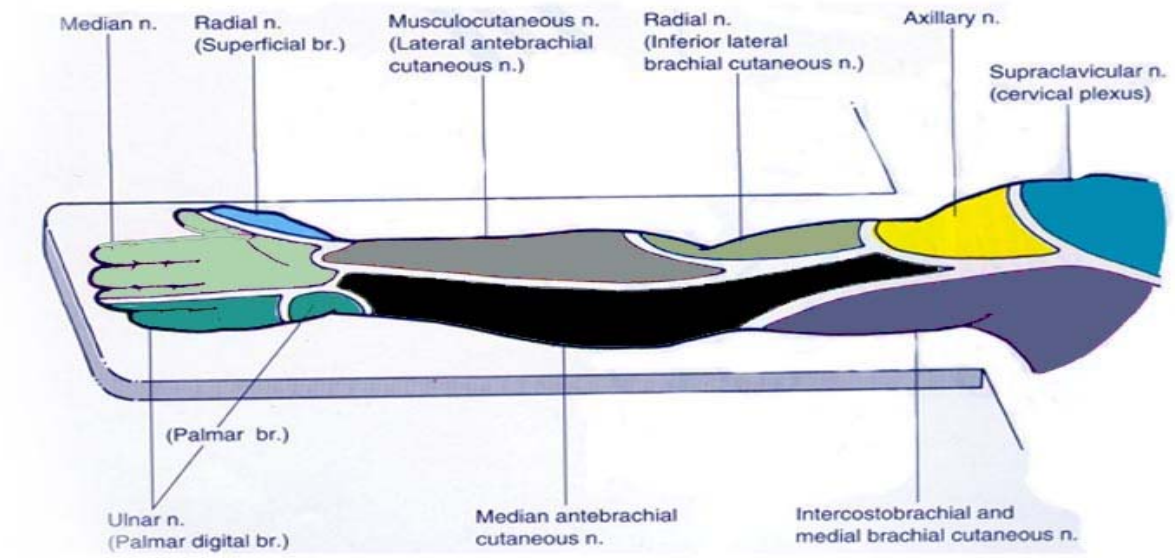
Motor

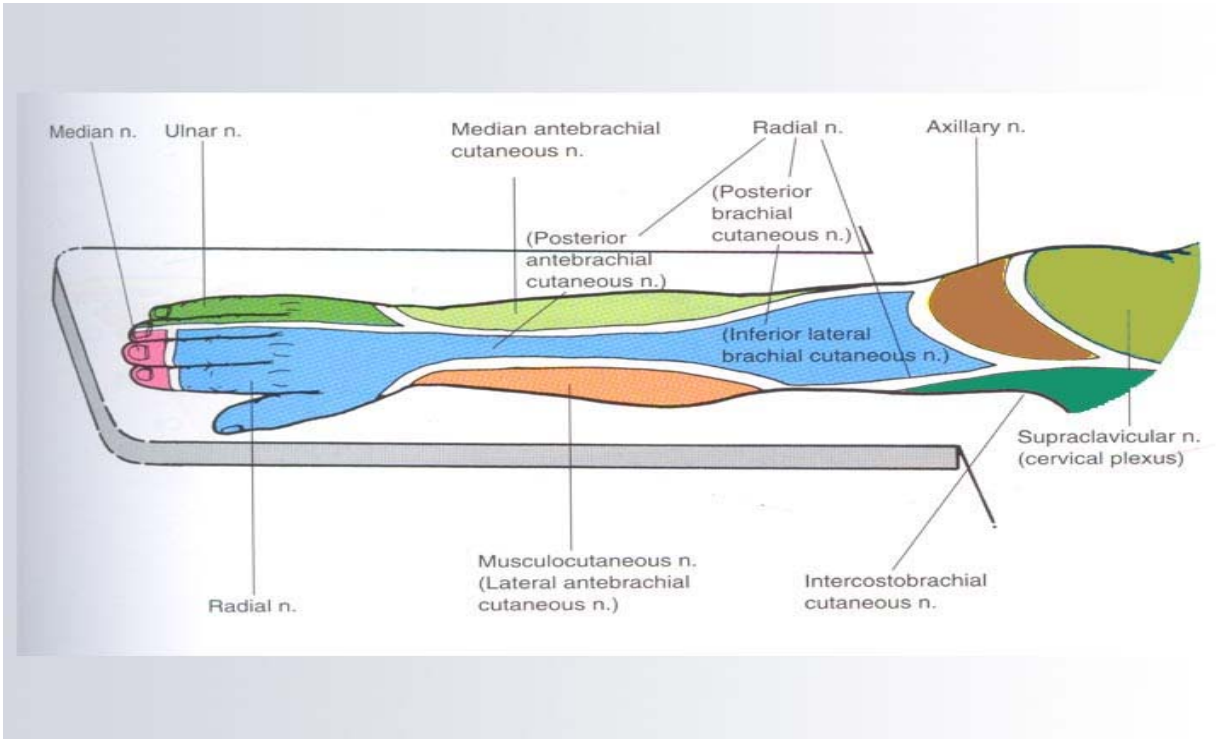
Median nerve

Ulnar nerve

Radial nerve

Musculocutaneous nerve


Median n.
Radial n.
(Superficial br.)
Musculocutaneous n.
(Lateral antebrachial
cutaneous n.)
Radial n.
(Inferior lateral
brachial cutaneous n.)
Axillary n.
Supraclavicular n.
(cervical plexus)
(Palmar br.)
Ulnar n.
(Palmar digital br.)
Median antebrachial
cutaneous n.
Intercostobrachial and
medial brachial cutaneous n.


Median n.
Ulnar n.
Median antebrachial
cutaneous n.
Radial n.
Axillary n.
(Posterior
brachial
cutaneous n.)
(Posterior
antebrachial
cutaneous n.)
(Inferior lateral
brachial cutaneous n.)
Supraclavicular n.
(cervical plexus)
Radial n.
Musculocutaneous n.
(Lateral antebrachial
cutaneous n.)
Intercostobrachial
cutaneous n.

Evaluation was carried for every minute after completion of the injection and the time of onset was noted for both sensory and motor blockade.

Onset of blockade, both sensory and motor is defined as a minimum of grade 2 in Hollmen's scale.

Blockade was considered **complete** when sensory and motor scores were at least grade 3 in Hollmen's scale. Only patients with complete motor block were included in the study.

Once block was complete, the patient was wheeled into the theatre and surgery was allowed to proceed.

Duration of sensory blockade was considered as the time interval between the local anaesthetic administration and the onset of paraesthesia (during recovery) while duration of motor block was defined as the time interval between the local anaesthetic administration and the recovery of motor block.

Sedation was assessed using the **sedation score** described by **Culebras et al.**[62] where sedation was graded on a scale of 1 to 5 as follows:

1. awake and alert
2. sedated, responding to verbal stimulus
3. sedated, responding to mild physical stimulus
4. sedated, responding to moderate or severe physical stimulus
5. not arousable.

Monitoring

Monitoring during regional anaesthesia focuses on delayed local anaesthetic toxicity from excessive tissue absorption (usually 40 – 60 min), ventilation and oxygenation and the consequences of surgical stress such as tourniquet pain or blood loss.

Baseline vital signs PR/RR/BP/SpO2 were recorded and monitored every 5 min till the procedure was over and thereafter every hour for 24 hours postoperatively.

Onset, completion of blockade, duration of blockade was assessed as described earlier.

Pain was assessed using a numerical rating pain score scale where 0 represents no pain and 10 means the worst possible pain. (VAS scale)

Statistics

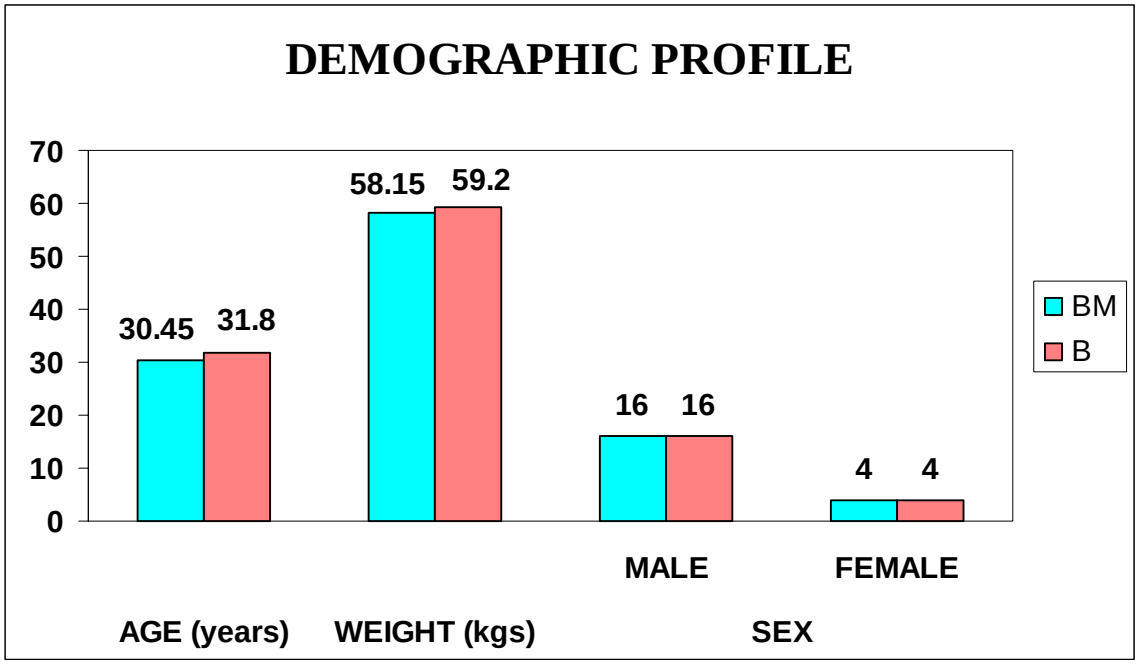
Sample size of 20 per group was adequate for the present study.

Demographic variables in qualitative form were analysed using the Pearson Chi – Squared test and quantitative form data (weight, age) were analysed using the Student independent t-test.

Clinical data like onset, completion, duration & intensity of blockade were analysed using the Student independent t-test.

Statistical significance with regard to sedation was analysed with Pearson Chi-Squared test. P value < 0.05 was taken as statistically significant.

OBSERVATIONS



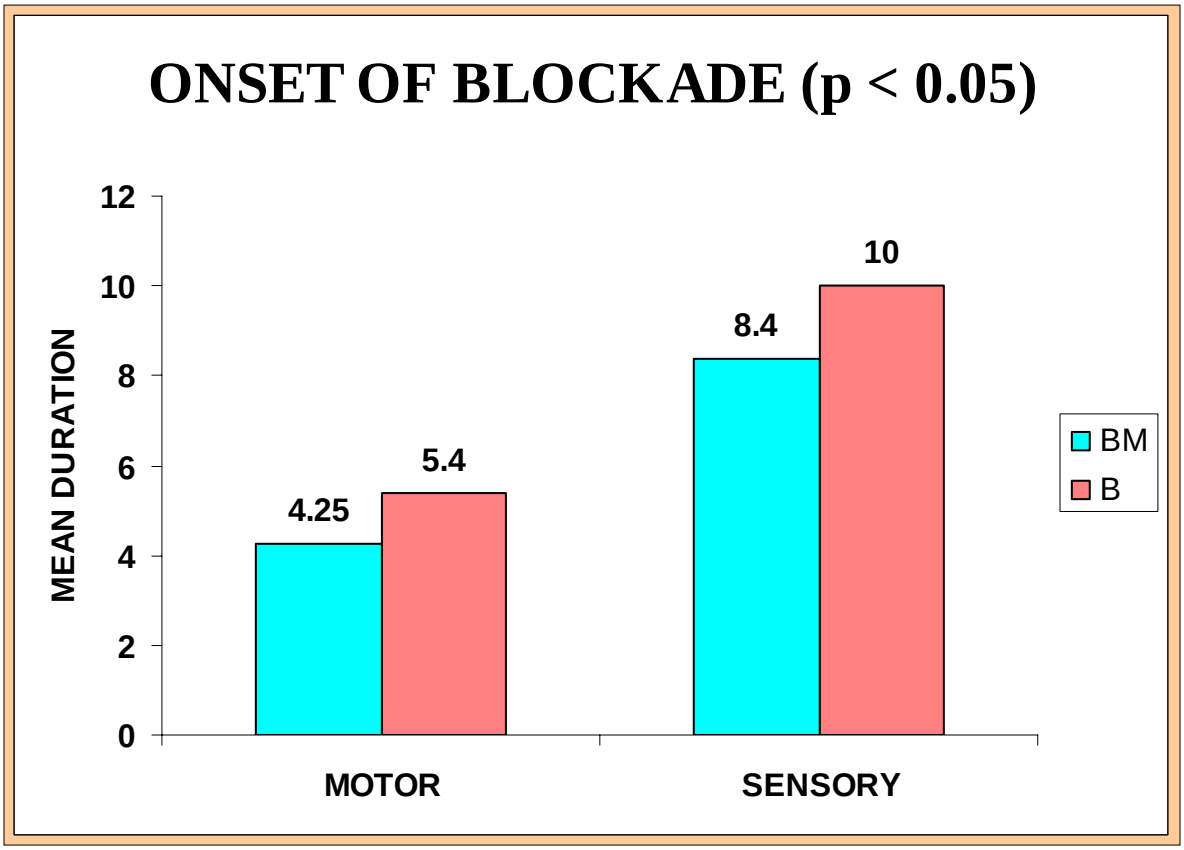
The mean **age** in BM group was 30.45 years ± 10.9 SD and in the B group it was 31.8 years ± 10.48 SD.

The mean **weight** in BM group was 58.15 kgs ±7.95 SD and in the B group it was 59.2 kgs ± 5.26 SD.

Sex distribution in each group: 16 males and 4 females.

The mean **duration of surgery** was comparable between the two groups: 94 ± 17.52 mins in Group BM and 91 ± 16.2 mins in Group B.

Thus the demographic profile was comparable between the two groups. (p value = NS).



The mean time of onset of **moto**r block in

Group BM : 4.25 $\pm$ 1.25 mins

Group B : 5.4 $\pm$ 1.27 mins

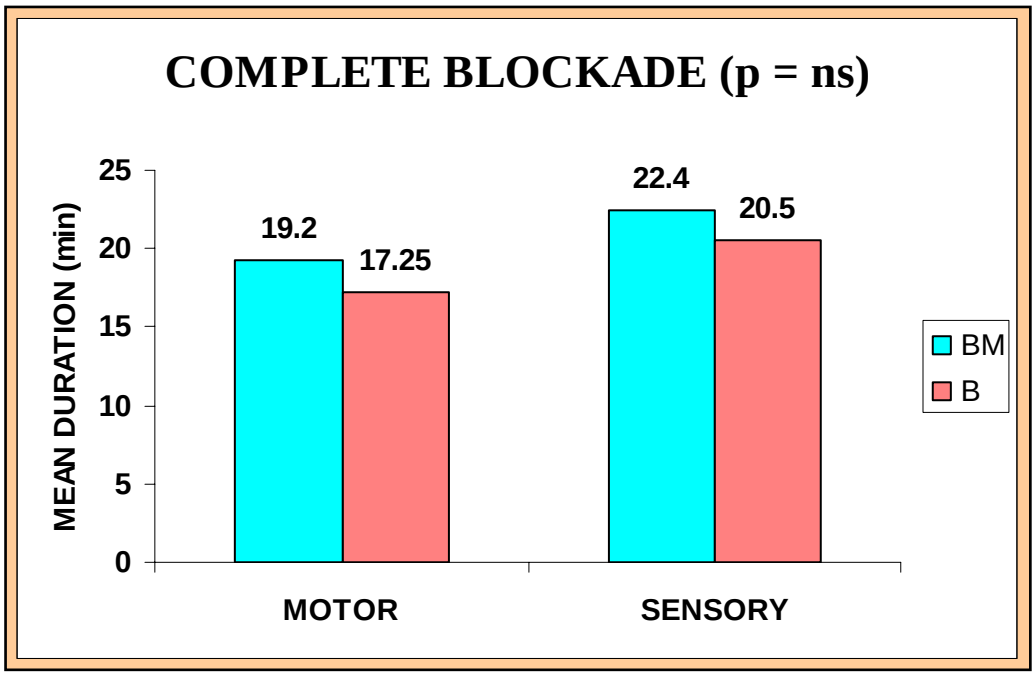
The onset of motor blockade was statistically **significant** in BM group. (t = 2.88, p = 0.001).

The **onset** time of **sensory** block in

Group BM : 8.4 $\pm$ 1.5 mins

Group B : 10 $\pm$ 1.37 mins

The onset of sensory blockade was statistically **significant** in BM group. (t = 3.51, p = 0.001). **Motor** blockade occurred **earlier than sensory** blockade in both the groups (p < 0.05).



The mean time for **complete motor block** was

Group BM : 19.2 ± 4.54 mins

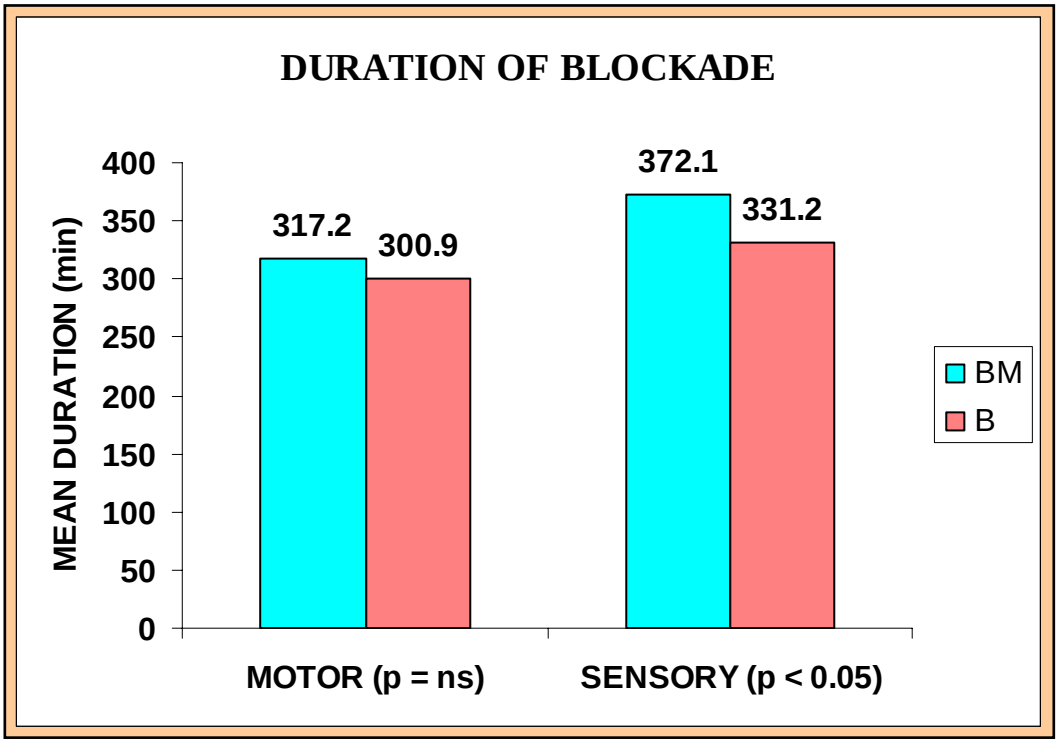
Group B : 17.25 ± 2.63 mins

The mean time for **complete sensory block** was

Group BM : 22.4 ±5.80 mins

Group B : 20.5 ± 2.50 mins

There was **no statistically significant** difference in the time taken for complete motor (t = 1.66, p = 0.1) and sensory blockade (t = 1.34, p = 0.18) between the two groups.



The mean total **duration of motor** blockade was

Group BM : 317.2 ± 31.08 mins

Group B : 300.9 ±26.01 mins

The mean total duration of motor blockade was **not** statistically **significan**t. (t = 1.8, p = 0.08)

The mean total **duration of sensory** blockade was

Group BM : 372.1 ±35.96 mins

Group B : 331.2 ± 33.54 mins

The mean total duration of sensory blockade was statistically **significan**t (t = 3.72, p = 0.001).

INTENSITY OF BLOCKADE

	Grading	Group BM	Group B
MOTOR	4	14 (70 %)	17 (85 %)
	3	5 (25 %)	3 (15 %)
	2	1 (5 %)	0
	1	0	0
SENSORY	4	15 (75 %)	13 (65 %)
	3	5 (25 %)	7 (35 %)
	2	0	0
	1	0	0

Intensity of Motor blockade

Group BM - 70% patients had grade 4 motor block while 25% had grade 3 and 5 % patients had grade 2 motor block.

Group B - 85% patients had grade 4 motor block and 15% patients had grade 3 block

This was **not** statistically **significant**. ($\chi^2 = 1.79$, $p = 0.41$)

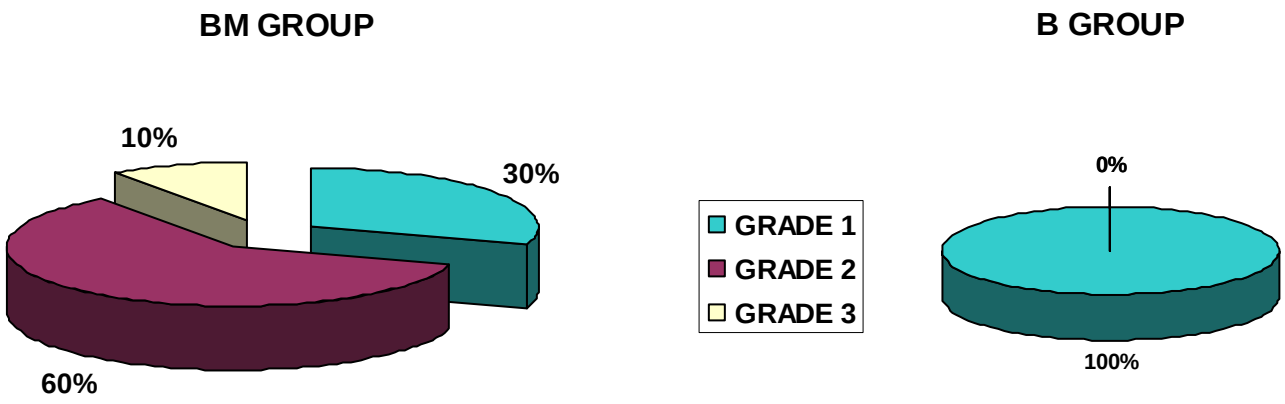
Intensity of Sensory blockade

Group BM - 75% patients had grade 4 sensory block and 25% patients had grade 3 sensory block.

Group B - 65% patients had grade 4 sensory block and 35% patients had grade 3 sensory block.

This was **not** statistically **significant**. ($\chi^2 = 0.48$, $p = 0.49$)

SEDATION



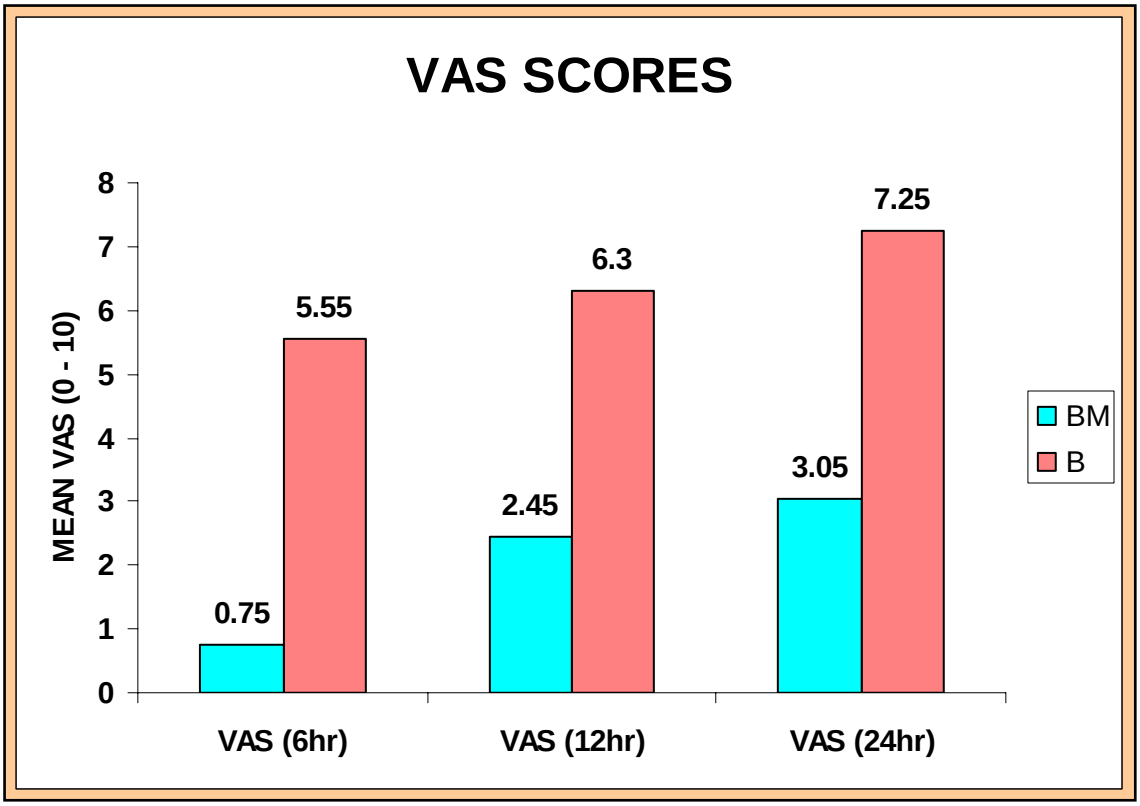
Sedation scores differed between the two groups during the intraoperative period (at 30 min).

Group BM : 10% patients were sedated and required mild physical stimulus to awaken, 30% patients sedated and required verbal stimulus to awaken and 60% not sedated.

Group B : None of the patients was sedated i.e. all were awake and alert.

No patient in BM group required assistance for airway maintenance due to sedation.

Sedation score achieved during the intraoperative period was statistically significant ($\chi 2=21.53$, P=0.001). Sedation scores did not differ between the groups during the postoperative period.



Postoperative pain scores were recorded according to Visual Analog Scale (VAS 0 -10) at 6, 12 and 24 hours. Group BM patients recorded a lower mean VAS score than their counterparts. Likewise the rescue analgesic requirement (Inj. Diclofenac sodium 3ml IM) was lower in BM group (4 patients) compared to group B (15 patients). Both were statistically significant ($p < 0.05$).

COMPLICATIONS

There was one incidence of arterial puncture without formation of hematoma. Needle was again repositioned and drug administered. Block was successful. There was no other incidence of

- Pneumothorax
- Neurological deficit
- Phrenic nerve palsy
- Horner's syndrome
- Oversedation
- LA toxicity

Heart rate, blood pressure, oxygen saturation and respiration were monitored and were stable. No differences were noted among the groups both during the intraoperative and postoperative period.

DISCUSSION

Brachial plexus blockade offers an excellent alternative technique to general anaesthesia in anaesthetising the upper limb for surgical procedures. Various approaches for successful performance of these blocks and for reducing the complications have been described.

The ***technique*** chosen in this study was the subclavian perivascular technique. In 1964 this technique was described by Winnie[17] and it allowed accurate percutaneous localisation of the plexus. He used the concept that there is a constant relationship between the anterior and middle scalene muscles, the plexus and the first rib and that there is an advantage of the continuity of the neurovascular sheath of the brachial plexus. Winnie's concept that the roots of the plexus were sandwiched between the two scalene muscles and the muscles are always found to be inserted in the 1st rib. Hence he introduced the needle between the two muscles and in the direction of the space between them. Thus by using a single needle technique eliciting paraesthesia or vascular pulsation as a guide to confirm the needle placement in the space he injected the anaesthetic solution, which will be confined to the perineural and perivascular area. Hence he was almost certain of a complete and safe block. This technique by Winnie was anatomically precise and conceptually logical.

The role of paraesthesia[20-27] is controversial. Various studies have concluded that paraesthesia during needle insertion improves the success rate of the blocks. Elicitation of paraesthesia may also pose problems in the form of direct neural damage by the advancing needle. While demonstration of paraesthesia may aid in positioning the needle for blockage, it is not absolutely essential for the success of the block. The aid of a nerve locator is definitely logical but considering the economy and large number of cases being performed under expert guidance our technique seems to be practical.

The longer acting ***local anaesthetics*** (Bupivacaine, Ropivacaine) have been associated with longer latencies and higher failure rates[2]. Latency can be decreased through the appropriate choice of injection site, higher concentration of drug used and appropriate volume. The efficacy and safety of 0.5% Bupivacaine is already proved[43-45]. Hence 30 ml Bupivacaine 0.5% used.

Various agents like epinephrine, opioids, clonidine, neostigmine, hyaluronidase and bicarbonate have been used as ***adjuvants***[51-64] to local anaesthetics in brachial plexus block to quicken the onset, increase the duration and enhance the quality of block and also reduce the post operative analgesic requirements. The results have been mixed and at times associated with side effects.

Midazolam as an additive to local anaesthetics has been studied in the intrathecal, epidural & caudal routes[74-80,82,83]. It has been proved in these studies that midazolam is as useful additive by way of improved analgesia and with sedation.

50ug/kg midazolam in central neuraxial blocks did not produce any significant adverse effects. Studies in animals have showed no neurotoxic effects of intrathecally administered midazolam[85,86,87.] Potentiation of analgesic effects of intrathecal fentanyl with midazolam in labouring patients has been demonstrated[88]. Intrathecal midazolam 2 mg did not increase the occurrence of neurologic or urologic symptoms[89]. Hence this dose (50µg/kg) was chosen in this study.

In this prospective randomised comparative study, 40 patients satisfying the selection criteria underwent brachial plexus block with or without addition of preservative free midazolam. Comparison of onset, completion, duration & intensity of blockade, sedation and quality of analgesia between the two groups were observed and statistically analysed.

The ***onset*** of sensory and motor blockade was quicker in the BM group. This could be due to the synergistic action of midazolam with that of local anaesthetics[71,76,80].

The onset of motor block was found to be faster than the sensory block onset. This may be attributed to the arrangement of nerve fibers in the trunks as described by Winnie[34]. Motor fibers are located more peripherally than sensory fibers hence a local anaesthetic drug will begin to block motor fibers before it arrives at the centrally located sensory fibers.

Duration of sensory block tended to last longer than motor block in the present study. This is in line with the observations made by de Jong et al[32] who explained that large fibers require a higher concentration of local anaesthetic than small fibers. The minimal effective concentration of local anaesthetic for large (motor) fibers is greater than for small (sensory) fibers. Thus, motor function return before pain perception and duration of motor block is shorter than the sensory block.

In this study, ***pain scores*** were significantly lower in patients who received Midazolam in addition to Bupivacaine. The number of patients who required rescue analgesia was also lower in this group. The prolonged analgesia in Group BM could be due to the action of midazolam on GABA-A receptors present in the brachial plexus and thus producing antinociception. Various authors have demonstrated the presence of GABA receptors in peripheral nerves. Brown and Marsh[67] demonstrated GABA receptors in mammalian peripheral nerve trunk. Bhisitkul et al.[69] showed that axonal GABA receptors are present on both normal

and regenerated sensory fibers in rat peripheral nerve. Cairns et al.[70] observed the presence of GABA receptors within the temporomandibular joint and that its activation could decrease the transmission of nociceptive signals. The action of midazolam on GABA receptors is well established.

Sedation scores were higher in patients in BM group compared to B group during the intraoperative period. This may be due to partial vascular uptake of the drug and its transport to the central nervous system where it acts and produces sedation. The limited duration of sedation could be explained by the fact that midazolam is highly lipophilic and diffuses faster into the blood vessels, by its rapid clearance (6 – 11 ml/kg/min) and short half life (1.7 – 2.6 hr). The highest sedation score achieved was 3 i.e. the patient was asleep and arousable by mild physical stimulus. No patient experienced airway compromise or required airway assistance due to this sedation.

No complications with regard to the technique or drug was observed.

SUMMARY

1. Onset time for both motor and sensory block was quicker in the Bupivacaine with midazolam group.
2. There was no significant difference between the groups in the time taken for completion of both motor and sensory blockade.
3. There was no difference between the groups in the intensity of blockade.
4. There was no difference between the groups in the mean duration of motor blockade.
5. The mean duration of sensory blockade was significantly prolonged in the Bupivacaine midazolam group.
6. Sedation was statistically significant with Bupivacaine midazolam group in the intraoperative period.
7. There was no complication due to the addition of 50µg/kg Midazolam to Bupivacaine.

CONCLUSION

In conclusion, midazolam 50µg/kg when used as an additive to 0.5% Bupivacaine solution for supraclavicular brachial plexus block, quickens the onset of sensory and motor blockade, prolongs the duration of sensory blockade and improves the quality of post operative analgesia with mild intraoperative sedation. Hence, midazolam can be considered as a safe additive to local anaestetic solution for brachial plexus block.

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PROFORMA

Name: Age/Sex: Wt: ASA Status:

IP No: Surgery: Duration of Surgery:

Group BM/B:

Onset of block - Motor : Sensory :

Completion of block - Motor : Sensory :

Intensity of block - Motor : Sensory :

Duration of block - Motor : Sensory :

Sedation Score: Complication :

		0 min	5 min	10 min	15 min	20 min	30 min	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	12 hr	24 hr
Vitals	PR														
	BP														
	RR														
	SpO2														
Sens&Motor Score															
Radial Nerve	S														
	M														
Median Nerve	S														
	M														
Ulnar Nerve	S														
	M														
Musculocut. Nerve	S														
	M														
Sensory Score															
Lat Cut N of arm															
Medial Cut N of arm															
Lat Cut N of forearm															
Med Cut N of forearm															

GROUP BM – BUPIVACAINE + MIDAZOLAM

S.No	Name	Surg Time mins	Age years	Sex	Wt (kg)	Onset		Complete		Duration		Intensity		Sedation grade	VAS (6hr)	VAS (12 hr)	VAS (24 hr)	Rescue analgesic
						motor	sensory	motor	sensory	Motor	sensory	motor	sensory					
1	Sundari	105	18	F	50	2	5	17	20	332	402	4	4	2	1	3	4	No
2	vinayagam	90	39	M	65	4	8	18	22	335	425	4	4	2	0	1	1	No
3	Prema	95	25	F	45	3	6	22	26	334	379	4	4	3	0	2	2	Yes
4	sridharan	130	38	M	60	5	9	23	25	335	420	4	4	2	0	1	2	No
5	manivannan	115	29	M	60	8	12	35	42	309	389	4	4	2	1	3	3	No
6	anbu ezhil	90	25	M	45	5	9	23	27	275	320	4	4	1	2	4	4	yes
7	govindaraj	70	23	M	57	5	8	18	22	380	440	3	3	2	1	3	3	No
8	kalanidhi	60	20	M	62	4	9	22	25	320	380	4	3	1	1	2	2	No
9	dayalan	80	35	M	68	5	9	19	22	280	345	3	4	2	0	1	2	No
10	Raja	70	28	M	50	4	8	16	17	304	364	4	3	2	1	3	4	No
11	senthil kumar	90	23	M	50	4	8	17	20	320	345	4	3	1	0	2	3	No
12	devanathan	105	58	M	54	6	10	16	19	275	305	4	4	2	1	3	4	Yes
13	dayalan	95	35	M	70	4	9	16	17	360	387	3	3	1	1	1	2	No
14	kirankumar	85	20	M	55	3	8	15	16	327	373	4	4	3	1	3	4	No
15	Gowri	75	25	F	58	4	9	14	16	333	390	4	4	2	0	2	3	No
16	vincent	95	30	M	66	4	9	20	22	300	353	4	4	2	1	3	4	No
17	Balaiah	105	57	M	68	4	9	20	28	288	348	4	4	2	1	3	4	No
18	Anand	110	25	M	66	4	8	18	21	270	320	4	3	1	0	2	3	Yes
19	anbu ezhil	115	28	M	50	3	6	18	22	302	362	4	4	2	2	4	4	No
20	Shahin	100	28	F	64	4	9	17	19	365	395	4	3	1	1	3	3	No

GROUP B – BUPIVACAINE ALONE

S.No	Name	Surg Time mins	Age year	Sex	Wt (kg)	Onset		Complete		Duration		Intensity		Sedation grade	VAS (6hr)	VAS (12 hr)	VAS (24 hr)	Rescue analgesic
						motor	sensory	motor	sensory	Motor	sensory	motor	sensory					
1	datchay	11	22	F	5	7	10	24	28	22	270	4	4	1	6	7	8	Yes

	ani	0			7					5								
2	amal raj	70	26	M	55	8	14	17	20	325	370	4	4	1	4	7	8	No
3	ramesh	75	28	M	50	5	12	17	19	316	356	4	4	1	5	6	7	Yes
4	balasubramani	95	28	M	58	7	11	15	19	275	310	3	4	1	4	5	6	Yes
5	prema	100	25	F	55	5	10	22	25	320	380	4	4	1	6	7	7	No
6	murugan	90	25	M	57	4	9	19	21	300	345	4	4	1	5	6	8	Yes
7	anilkumar	95	24	M	60	5	9	22	23	340	420	3	4	1	6	6	7	No
8	egambaram	65	50	M	64	4	9	15	19	304	319	3	3	1	6	6	8	Yes
9	raj	70	22	M	56	6	10	16	22	329	349	4	4	1	5	6	6	No
10	dayalan	80	35	M	68	7	11	15	20	290	310	4	4	1	6	7	7	Yes
11	arumugam	105	20	M	56	6	11	16	21	290	320	4	4	1	6	6	6	Yes
12	ramalingam	110	49	M	65	4	9	18	20	320	340	3	4	1	6	7	8	No
13	riyaz	95	20	M	54	5	10	15	18	290	310	2	3	1	5	6	8	Yes
14	rizwan basha	90	39	M	62	5	9	17	19	294	320	4	3	1	6	6	7	Yes
15	ramesh	85	24	M	60	4	9	18	21	335	345	4	4	1	5	5	6	Yes
16	malleswari	105	30	F	50	4	8	17	21	290	310	4	4	1	6	6	7	Yes
17	sundaramoorthy	120	45	M	66	5	9	16	19	300	320	4	4	1	6	7	8	Yes
18	somu	110	52	M	64	4	9	15	18	310	330	4	3	1	6	7	8	Yes
19	annalakshmi	80	40	F	66	6	10	16	19	275	290	3	3	1	7	7	8	Yes
20	siva	70	32	M	61	7	11	15	18	290	310	4	4	1	5	6	7	yes