COMPARISON OF THREE DIFFERENT DOSES OF DEXMEDITOMIDINE AS ADJUVANT TO BUPIVACAINE IN SUPRA CLAVICULAR BRACHIAL PLEXUS BLOCK FOR UPPER LIMB ORTHOPAEDIC SURGERIES

A STUDY OF 60 CASES

DISSERTATION

SUBMITTED IN PARTIAL FULFILMENT OF UNIVERSITY

REGULATIONS FOR THE AWARD OF

M.D. DEGREE EXAMINATION

BRANCH X – ANAESTHESIOLOGY

THE TAMIL NADU

Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMIL NADU

MARCH, 2016

CERTIFICATE

This is to certify that this dissertation **"COMPARISON OF THREE DIFFERENT DOSES OF DEXMEDITOMIDINE AS ADJUVANT TO BUPIVACAINE IN SUPRA CLAVICULAR BRACHIAL PLEXUS BLOCK FOR UPPER LIMB ORTHOPAEDIC SURGERIES"**presented herein by **Dr. B. DHANALAKSHMI** is an original work done in the Department of Anaesthesiology, Kanyakumari Govt Medical College Hospital, Asaripallam, Nagercoil for the award of Degree of M.D (Branch – X) Anaesthesiology under my direct supervision and guidance, during the academic period of **2013 – 2016**.

DEAN,

Kanyakumari Govt Medical College Hospital,

Asaripallam, Nagercoil - 629201

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Professor and HOD,

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DECLARATION

I, **Dr. B. DHANALAKSHMI** hereby declare that the dissertation titled "**COMPARISON OF THREE DIFFERENT DOSES OF DEXMEDITOMIDINE AS ADJUVANT TO BUPIVACAINE IN SUPRA CLAVICULAR BRACHIAL PLEXUS BLOCK FOR UPPER LIMB ORTHOPAEDIC SURGERIES"**has been done by me.

This is submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the requirement for the award of M.D. degree, Branch – X (ANAESTHESIOLOGY) Degree Examination to be held in **March 2016**.

Place : Asaripallam

Date :

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In accordance with the powers delegated in the Govt. orders cited, permission is granted to the following PG Anaesthesia students of this Institution.

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to do the project work regarding their dissertation on

1. Comparison of 3 different does of dexmedetomedine as adjuvant to local anaesthetics in Supraclavicular Brachial Plexus Blocks in upper limb orthopedic surgeries - By Dr. B. Dhanalskhmi
2. Comparative study of spring – loaded syringe with glass syringe using loss of Resistance Technique with saline for Identification of Epidural space in lower Thoracic Epidurals – Dr. Dinesh Kumar

in the Departments of General Surgery and Orthopaedics with effect from 01.02.2015, during their study period.

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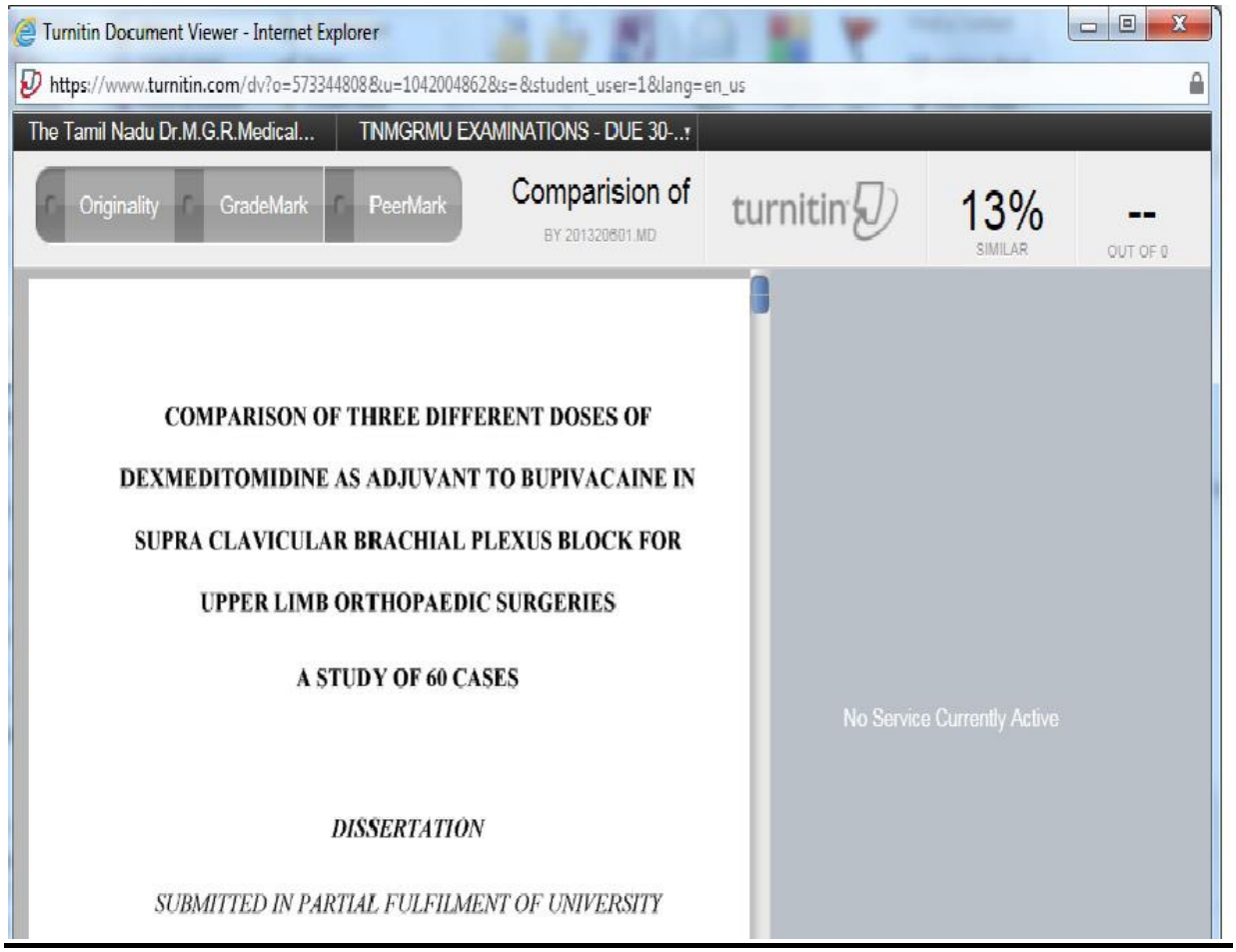
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ABSTRACT

COMPARISON OF THREE DIFFERENT DOSES OF DEXMEDITOMIDINE AS ADJUVANT TO BUPIVACAINE IN SUPRA CLAVICULAR BRACHIAL PLEXUS BLOCK FOR UPPER LIMB ORTHOPAEDIC SURGERIES

Dr.B.Dhanalakshmi, Dr.Annie geetha, Dr.Pratheepa Durairaj, Dr.J.Edward jhonson, Dr.A.Vasuginathan. Kanyakumari government medical college,Nagercoil.

Background and goals of study: The aim and objective of the study is to compare the three different doses of dexmeditomidine and to know the optimal dose of dexmeditomidine as adjuvant to bupivacaine in supra clavicular brachial plexus block for upper limb orthopedic surgeries.

Methods : We studied 60 ASA l & ll patients undergoing upper limb orthopaedic surgeries including fracture humerus and fracture radius and ulna under supra clavicular brachial plexus block done by paresthesia technique. . Patients were randomly allocated to three groups. Group A :(n-20) – 30 ml 0.33% bupivacaine + dexmeditomidine 50mcg.Group B :(n-20) – 30ml 0.33% bupivacaine + dexmeditomidine 75mcg.Group C: (n-20) – 30ml 0.33% bupivacaine + dexmeditomidine 100mcg. Patients were evaluated for sensory & motor block onset and duration, duration of analgesia, sedation score, complications, hemodynamic parameters including non-invasive blood pressure, pulse rate , saturation intra operatively and post operatively.

Results & Conclusion : Sensory block onset was longer in group A (16.3±3.31) than group B(12.4±2.5) which is longer than group C (7.35±1) and motor block onset also longer in group A (20.4±2.7) than group B (16.15±2.89) which is longer than group C(12.15±2.81). The duration of both sensory and motor block was longest with group C (sensory mean 722.5±55.1minutes, motor mean 704±41.4minutes) compared with group B (sensory mean 625.5±72.7 minutes , motor mean 604±98.6 minutes) which is longer than group A (sensory mean 432±69.8minutes, motor mean 426.5±81.8). The mean duration of analgesia was dose dependent (tableB5) with C (736±67.1) >B (642±76.5) > A(480.5±81.3)minutes. We conclude that dexmeditomidine 100µg is an optimal dose to provide prolonged post-operative analgesia without significant side effects

INTRODUCTION

In peripheral nervous system blockade, a local anesthetics injected into the tissues or in the proximity to peripheral nerves. Initially these techniques were empirical resulting in failure and complications. In the last 3-4 decades the new scientific knowledge about pain and new modalities for conducting peripheral nerve blockade helped to reduce failure rate and complications and also extended its applications.

Peripheral nerve blocks can provide ideal operating conditions, post-operative analgesia and diagnostic, therapeutic role in acute and chronic pain management. The basis for use of peripheral nerve blocks is to interrupt nociceptive impulses coursing in the peripheral nerves.

The advantages of peripheral nerve blocks when compared to the general anesthesia are it causes less interference with physiology of human body, less stress response and avoids using of many drugs and its related complications.

In 1880's American Surgeon Halstead and Hall described the injection of cocaine into the peripheral sites. In 1885 James Leonard corning recommended use of esmarch bandage to prolong cocaine induced block .In 1903 Braun used epinephrine as a chemical tourniquet.

Local anesthetics developed in first half of 20th century were amino ester compounds with unfavorable properties of short duration of action, systemic toxicity and allergic reactions. This lead to advent of long acting amino amide compounds. The drawbacks of which are delayed onset of action, varying quality of blockade and inadequate post-operative analgesia.

Adjuvants are added to local anesthetics in peripheral nerve blocks to fasten the onset of action, to prolong the duration of action and improve the quality of blockade.

Various adjuvants like morphine, fentanyl, sufentanil, clonidine, midazolam, ketamine, neostigmine are added to local anesthetics. Previously, clonidine the α2 agonist was used as adjuvant to local anaesthetic which was associated with adverse effects like hypotension and bradycardia. In our study dexmeditomidine, the other drug belongs to α2 agonist is used as an adjuvant to potentiate the action of local anaesthetics. Since dexmeditomidine has α2:α1 selectivity ratio of 1620:1 as compared to 220:1 for clonidine, it decreases unwanted side effects of α1 and much more sedative and analgesic.

This study is designed to compare the effect of three different doses of dexmeditomidine when added to bupivacaine in brachial plexus block.

AIM OF THE STUDY

The aim and objective of the study is:

To compare the three different doses of dexmeditomidine and to know the optimal dose of dexmeditomidine as adjuvant to bupivacaine in supra clavicular brachial plexus block for upper limb orthopedic surgeries.

ANATOMY OF THE BRACHIAL PLEXUS

Brachial plexus block is one of the most commonly used peripheral nerve blocks in clinical practice. It can be used as the sole anaesthetic technique or in combination with general anaesthesia for intra operative and post-operative analgesia. Continuous catheterization of the brachial plexus is one of the best methods of post-operative analgesia.

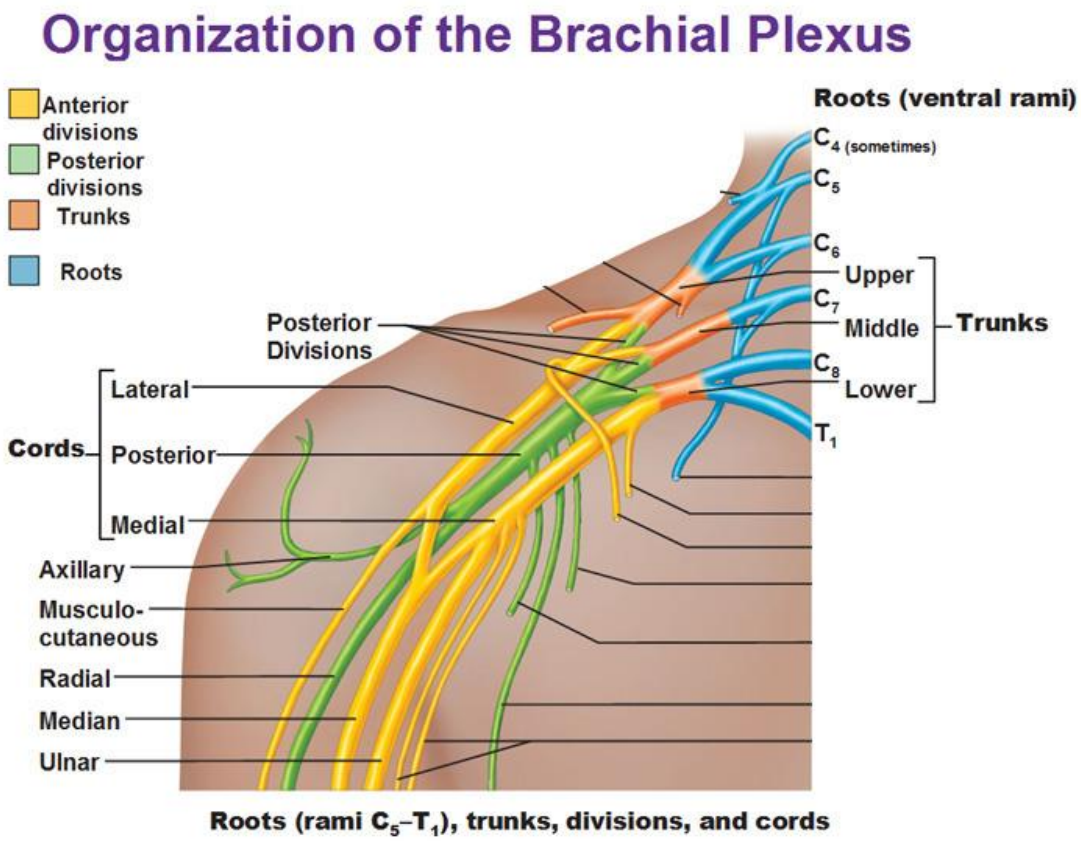
For successful brachial plexus blockade it is essential to know the anatomy of the brachial plexus in terms of vascular, muscular, fascial relationships of the nerves throughout its formation and distribution.

In its course from the intervertebral foramina to the upper arm, the plexus composed of roots, trunks, cords, divisions and terminal branches which are formed by process for combining and dividing.

FORMATION OF THE PLEXUS

ROOTS

The brachial plexus arises from the union of the spinal nerve roots of C5, C6, C7, C8 and T1 and often it also contains few fibers from the C4 above and T2 below. Occasionally, the plexus is mainly derived from C4-C8 (Pre fixed plexus) or from C6-T2 (post fixed plexus). These variations are usually associated with the presence of anamolous first rib.



TRUNKS

After they leave their intervertebral foramina, the roots of the plexus appear in the interscalene groove between the scalenus anterior and scalenus medius muscles. There the roots combine to form trunks. The C5 and C6 roots combine to form the upper trunk, C7 continues as the middle trunk and C8 and T1 combines to form the lower trunk.

After passing through the interscalene groove the plexus lies close together, move towards first rib. When crossing the first rib, the trunks of the plexus lies dorso lateral to the sub clavian artery and are enclosed along with the artery by a connective tissue sheath.

DIVISIONS

The plexus runs under the middle of the clavicle into the tip of the axilla. Behind the clavicle each trunk divides into anterior and posterior divisions.

CORDS

In the upper part of the axilla the six divisions combine to form lateral, medial and posterior cords.

- The lateral cord is formed by the union of anterior divisions of the upper and middle trunks.
- The medial cord is the continuation of the anterior division of the lower trunk.
- The posterior cord is formed by union of the posterior divisions of all the three trunks.

Terminal branches – Lower down in the axilla the cords give rise to terminal branches.

In summary, there are

1. Five roots – The anterior primary rami of C5-C8 and T1.
2. Three trunks (in the posterior triangle)
    a. Upper trunk – C5 & C6
    b. Middle trunk – C7
    c. Lower trunk – C7 & T1
3. Six divisions (behind the clavicle)

    Each trunk divides into an anterior and posterior division.

4. Three cords (within the axilla)
    a. Lateral cord – anterior divisions of upper and middle trunks C5-C7
    b. Medial cord – anterior division of lower trunk C8-T1
    c. Posterior cord – posterior division of all three trunks C5-T1

RELATIONSHIP OF THE BRACHIAL PLEXUS

Roots

These lie between the scalenus anterior and medius muscles. It lies above the second part of subclavian artery. The classical interscalene approach to the brachial plexus blocks the plexus at the root level.

Trunks

In the posterior triangle, the trunks of the plexus invested in a sheath of prevertebral fascia, are superficially placed, being covered only by skin, platysma and deep fascia.

The upper and middle trunks lie above the subclavian artery, the lower trunk lie behind the artery. The subclavian perivascular approach of plexus blocks the trunks

Divisions

At the lateral border of the first rib, the trunks bifurcate into divisions which are situated behind the clavicle, the subclavius muscle and the suprascapular vessels.

Cords

The cords are formed at the apex of the axilla and become grouped around the axillary artery, the medial cord lies behind the artery, the posterior and lateral cords lies lateral to the artery but behind the pectoralis minor muscle. The cords are arranged as signified by their names.

Terminal branches

They are formed lower down in the axilla at the lateral border of pectoralis minor muscle. The axillary approach causes blockade at this level.

Branches

1. Branches of roots
    a. To longus cervicis (C5-8)
    b. To the scalenus muscles (C5-8)
    c. Nerve to rhomboids (C5)
    d. Nerve to serratus anterior (C5-7)
    e. Contribution to the phrenic nerve

Roots receive sympathetic fibres from

a. Grey rami from the cervical sympathetic chain
b. C5 and C6 from the middle cervical ganglion
c. C7 and C8 from the inferior cervical ganglion
d. T1 from the ganglion of T1

2. Branches of trunks

a. Nerve to subclavius (C5,6)

b. Suprascapular nerve (C5,6)

3. Branches of cords

a. Lateral cord

Lateral pectoral nerve (C5-7)

Musculo cutaneous nerve (C5-7)

Lateral head of median nerve (C6,7)

b. Medial cord

Medial pectoral nerve (C8, T1)

Medial cutaneous nerve of arm (C8, T1)

Medial cutaneous nerve of forearm (C8, T1)

Medial head of median nerve (C8, T1)

Ulnar nerve (C7-8, T1)

c. Posterior cord

Upper subscapular nerve (C5,6)

Nerve to lattismusdorsi (C6-8)

Lower subscapular nerve (C5,6)

Axillary nerve (C5,6)

Radial nerve (C5-8, T1)

ANATOMICAL CONSIDERATIONS

The anatomic factors which determine the success and complications of the blockade are,

- The perivascular sheath
- The vertical arrangement of the cervical roots
- The interconnection due to combining dividing recombining and redividing.
- Relationship of site of needle entry to vital structures.

IMPORTANCE OF PERIVASCULAR SHEATH

The perivascular sheath is a fibrous sheath covering the brachial plexus in its entirety. It extends from the origin of scalenus muscles down to middle of the upper arm. This sheath gives a classical “Pop Off” feel when pricked by the needle.

This sheath is the single most important factor in determining the success of blockade. The plexus can be blocked by introducing the needle at any point along the sheath

TECHNIQUES OF BRACHIAL PLEXUS BLOCK

History

The block was first performed by William Steward Halsted in 1889 using cocaine by directly exposing the plexus in the neck. Hirschel first described the percutaneous approach. Kulenkamf first described the classical supraclavicular approach. Winnie and Collins first described the subclavian perivascular block. The infraclavicular approach was first developed by Raj. The axillary approach was first performed by Accardo and Adriano in 1949.

Techniques

According to the proposed site of surgery on the upper limb, brachial plexus can be blocked at various levels. The common sites of approach to the plexus are,

a. Interscalene approach
b. Supraclavicular approach
    i. Classical approach
    ii. Subclavian perivascular technique
    iii. Plumb bob technique
c. Infraclavicular approach
d. Axillary approach
e. Posterior approach

SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK

a) Classical approach of Kulenkampff[6]

The patient is positioned in supine position with head turned away from the side to be blocked. The arm is adducted and extended towards ipsilateral knee. The needle insertion site is 1cm posterior to the clavicular midpoint. A 22 gauge 4cm needle is directed caudad and posterior direction until paraesthesia elicited or rib is hitched. After negative aspiration for blood calculated dose of local anaesthetic is injected.

b) Subclavian perivascular technique of Winnie and Collins[6]

The interscalene groove is palpated and tracked down at its most inferior point subclavian artery pulse palpated. The needle is inserted just above and posterior to the pulse and directed caudally. Needle is advanced until paraesthesia elicited and the local anaesthetic injected after negative aspiration for blood

c) Plumb-bob supra clavicular block[6]

The needle entry site is at the point where the lateral border of the sternocleido mastoid muscle inserts into the clavicle. The needle is inserted while mimicking a plumb bob suspended over the needle entry site until eliciting paraesthesia.

Complications

1 .Pneumothorax

This is the commonest complication after supra clavicular brachial plexus block with prevalence ranges from 0.5 to 6 %. It occurs due to apex of lung lies just medial and posterior to the brachial plexus. The symptoms may be sudden onset of chest pain and may associate with dyspnea and cough and it may take 24 hour to manifest. On examination there may be increased resonance on percussion and decreased breath sounds on auscultation and may beconfirmed wit chest xray in upright position.This condition may be managed with inter costal chesttube insertion in 5^{th} inter costal space in

2. Horner's syndrome

This consist ofmiosis, anhidrosis, ptosis due to concomitant stellate ganglion block

3. Phrenic nerve palsy

It is less likely than inter scalene brachial plexus block

4. Intra vascular injection

Local anaesthetic may be accidentaly injected into intravascularly resulting in local anaesthetic toxicity. To avoid this the drug should be aspirated every 3-5 ml while injecting

5. Haematoma formation

6. Nerve injury

APPLIED PHYSIOLOGY

The nervous tissue is made up of neurons which are the basic building blocks. Nerves consist of a cell body, dendrites and an axon which ends as a presynaptic terminal[.1]. Nerves may be myelinated or unmyelinated. In myelinated nerve fibres (all large motor and sensory) myelin is made up of Schwann cells that wrap around the axon up to 100 times. Whereas in unmyelinated nerve, fibresare simply surrounded by Schwann cell without wrapping.

Nerve fibres are classified as A, B and C according to their size&velocity of conduction. A and B fibres are myelinated whereas C fibres areunmyelinated[.1] The largest A fibres are subdivided into alpha, beta, gamma, delta. Aα fibres supply skeletal muscle; Aβ fibres transmit tactile sensation; Aγ fibres supply skeletal muscle spindle; Aδ fibres transmit acute pain; Type C fibres transmit dull, aching pain[.1]

Within the myelinatedfibres there are interruptions called nodes of Ranvier. Action potentials pass from node to node rather than continuously as in unmyelinated C fibres. Two or three adjacent nodes must be affected to prevent conduction. A typical peripheral nerve consists of several axon bundles and each axon has its own covering, the endoneurium. Each fascicle of many axons covered by perineurium and the entire nerve wrapped by epineurium. To reach nerve axon, a local anaesthetic molecule must traverse four to five layers of connective tissue or lipid membranous barrier.

PHYSIOLOGY OF NERVE CONDUCTION

Nerves allow conduction of electrical signals from central nervous system to periphery without loss of information.

Nerve membrane is made up of a bimolecular framework of phospholipid & protein channels protruding through the lipid bilayer. The globular protein is a sodium or potassium ion channel.

When the nerve is stimulated, following changes occurs in the cell membrane.

Resting membrane potential

At rest, an electrical potential of 70mV exist across the membrane with the negative potential inside of the cell relative to the outside of the cell. This is due to higher concentration of sodium ions outside than inside of the cell.

Potassium channels maintain the resting membrane potential because more K^+ channels opened at rest and permeability to K+ is greater than permeability to Na^+.

Depolarization Phase

During excitation, Na+ channels will open and allowing sodium ions flow into the cell thereby depolarising the membrame.

Repolarization phase

Because of opening of voltage gated K^+ channels, potassium ions pass out of the cell so that electrical neutrality is maintained

LOCAL ANAESTHETIC MODE OF ACTION

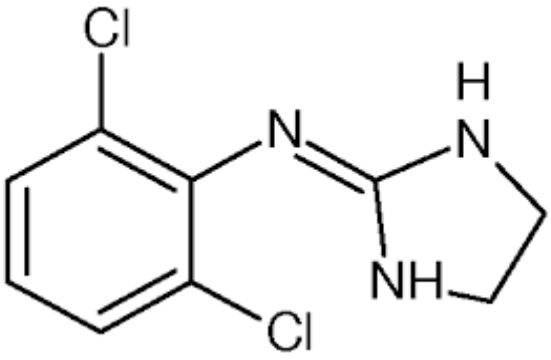
Local anaesthetics reversibly inhibit peripheral nerve conduction by blocking voltage gated sodium and potassium channels on the internal cell membrane[7]

Binding of local anaesthetics to the sodium channel prevents opening of the channel by inhibiting the conformational changes that underlie channel activation.

As the concentration of local anaesthetics increases, the height of action potential is reduced, the firing threshold elevated, the spread of impulse conduction slowed, the refractory period lengthened.

Peripheral nerves are differentially sensitive to local anaesthetics. Smaller the fibre diameter the greater its blockade. Myelinated fibres more sensitive than unmyelinated fibres. Aγ spindle efferents, Aδ nociceptive fibres and B fibres are easily blocked while C fibres are less susceptible to block.

PHARMACOLOGY OF BUPIVACAINE



Bupivacainehydrochloride is an amino-amide local anaesthetic synthesized by EKENSTAM et al in 1957 and first used by L.J. Telivuo in 1963. It is a member of the homologous series of n-alkyl substituted pipecholylxylidines.

It is available for clinical use as racemic mixtures of the R&S enantiomers (50:50). The S enantiomer of bupivacaine is less toxic than commercially available racemic mixtures.

Physicochemical Properties

Bupivacaine has butyl group on the piperidine nitrogen atom of the molecule. It is more lipid-soluble and highly protein bound. The physicochemical properties of bupivacaine are

Molecule weight	-	288
Protein binding	-	95%
Partition coefficient	-	346

Pka	-	8.1
Lipid solubility	-	28
Relative conduction blocking potency	-	8

Pharmacological properties

Bupivacaine is very stable to acids, alkalis and repeated autoclaving. Bupivacaine undergoes metabolism by aromatic hydroxylation, N-dealkylation, amide hydrolysis and conjugation. Alpha1 – acid glycoprotein is the most important plasma protein binding site for bupivacaine

Bupivacaine is 3-4 times as potent as lignocaine; hence 0.5% solution is approximately equivalent to 2% lignocaine. It causes more sensory block than motor block.

Duration of action is between 5 and 16 hours and it is one of the longest acting local anaesthetic which is related to binding to the nervous tissue.

Pharmacokinetics

After injected into subarachnoid space and peripheral nervous site, it gets absorbed by the nerve roots and rapidly absorbed from the site of injection. The rate of absorption depends on the vascularity and presence of vasoconstrictors.

Because of high lipid solubility, it easily penetrates nerve and vascular tissue. Small percentage of absorbed bupivacaine is excreted unchanged in urine and the remainder is metabolized in liver.

Volume of distribution = 72 litres

Elimination half life = 210 minutes

Clearance = 0.47 litres / minute

Pharmacodynamics

Cardiovascular system[6]

Bupivacaine has dose related effect on the heart. In purkinje fibres and ventricular muscles it depresses the rapid phase of depolarization and in bupivacaine treated papillary muscles the rate of recovery from use dependent blockade is slower which results in incomplete restoration of sodium channel availability in between action potentials. This results in arrhythmogenic potential of bupivacaine.

Respiratory System

Systemic absorption of bupivacaine stimulates the ventilator response to carbon dioxide[6]

Gastro intestinal system

Bupivacaine when administered as continuous or intermittent epidural infusion associated with increased plasma concentrations of transaminases enzyme

Central Nervous System

The CNS is vulnerable to toxicity and mechanism of toxicity may be local an aesthetics induced increased intra cellular calcium ion concentration. The risk of transient neurologic symptoms less than lignocaine.

DRUG DOSAGE

The maximal dose of bupivacaine is 2.5mg/kg and the strength used is 0.125% - 0.75% with or without epinephrine. Epinephrine does not greatly prolong its effect but reduces its toxicity.

Clinical uses

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

TOXICITY

Local an aesthetic systemic toxicity (LAST) are range from mild systemic symptoms to cardiovascular (hypertension, hypotension, tachycardia, bradycardia

, ventricular arrhythmia, cardiac arrest) and central nervous system symptoms(seizure , coma, respiratory depression)

CVS Toxicity

Accidental IV Injection of bupivacaine may result in precipitous hypotension, cardiac dysrhythmia and atrioventricular heart block. After IV injection protein binding sites quickly saturated leaving significant free drug available for diffusion into conducting tissue of heart. Cardiotoxic plasma concentration of bupivacaine is 8-10mcg/ml.

The R enantiomer of bupivacaine is more toxic than S enantiomer.

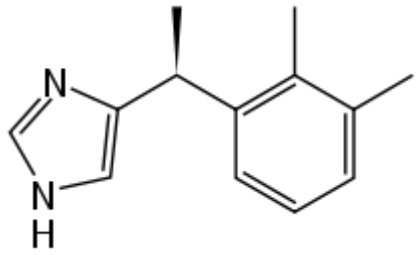
CNS Toxicity

Early symptoms of CNS toxicity are circumoral numbness, tongue paraesthesia, dizziness followed by tinnitus, blurred vision, tonic clonicseizures, respiratory arrest often develops.

Treatment

Treatment of local anaesthetic systemic toxicity includes supportive treatment with application of supplemental oxygen and injection thiopentone sodium or propofol for seizure activity . Now the treatment is emphasised on 20% lipid emulsion. Lipid emulsion consist of soya bean oil made isotonic with glycerin.It will absorb the local anaesthetics into the lipid layers

PHARMACOLOGY OF DEXMEDETOMIDINE



Dexmedetomidine is a selective α2 adrenoreceptor agonist which received FDA approval in 1999. Dexmedetomidine has 1600:1 preference for α2 receptors relative to α1 receptors. It is used as adjunct to regional, local, general anaesthetics.

Dexmedetomidine is an attractive choice in perioperative clinical setting because it has many favourable characteristics like analgesia, 'rousable' sedation, hemodynamic stability and anaesthetic sparing property.

Physiology of α2 – adrenoceptors

α2-adrenoceptors are found in peripheral and central nervous system and also in liver, kidney, vascular smooth muscles, platelets.[1]

There are three types of receptor.

α2A – found in CNS which responsible for the sedative, analgesic, sympatholytic effect.

α2B – found mainly in vasculature, which responsible for short term hypertensive responses.

α2C – found in CNS, responsible for anxiolytic effects.

All these receptors produce cellular action by signaling through G-protein.

MECHANISM OF ACTION

α2adrenoceptors are found in many site of CNS with highest density found in locus ceruleus, which is the predominant noradrenergic nuclei of brain stem. Locus ceruleus is site of origin of descending medullospinal noradrenergic pathway which is modulator of nociceptive neurotransmission.

Presynaptic activation of α2A adrenoceptor results in inhibition of norepinephrine release which results in sedative, hypnotic effects. Post synaptic activation of this receptor results in decreased sympathetic activity and leads to hypotension, bradycardia.[6]

The analgesic mechanism of dexmedetomidine is due to stimulation of α2 receptors at the substantia gelatinosa of spinal cord, inhibition of release of substance P, and preventing nor adrenaline release at the nerve endings.[6] Analgesic mechanism exist in spinal, supraspinal and peripheral sites.

α2-adrenoceptors causes contraction of vascular and other smooth muscles leading to vasoconstriction and other actions like decreased bowel motility in gastro intestinal tract. It also causes decreased salivation, inhibition of renin release, increased glomerular filtration rate, decreased insulin secretion from pancreas, decreased platelet aggregation and decreased shivering threshold by $2^{o}C$.

PHYSICOCHEMICAL CHARACTERISTICS

Dexmedetomidine is d-enantiomer of medetomidine. It belongs to imidazole subclass of α2 receptor agonist. It is freely soluble in water.

PHARMACOKINETICS

It is rapidly distributed and metabolized in liver, excreted in urine and feces.

It undergoes metabolism through pathways of conjugation, n-methylation and hydroxylation. It displays nonlinear pharmacokinetics. Its pharmacokinetic parameters are unaltered by age, weight, or renal failure.

Protein binding - 94%

Elimination half life - 2 to 3 hours

Context sensitive half time - 4 minutes after 10 minutes infusion

250 minutes after 8 hour infusion

Distribution half life - <5 minutes

PHARMACODYNAMICS OF DEXMEDETOMIDINE

Dexmedetomidine has α2: α 1 selectivity of 1600:1, so it is 8 times more potent α2-adrenoceptor agonist than clonidine.

Cardio vascular system

Effects of dexmedetomidine on cardio vascular system are decreased heart rate, decreased systemic vascular resistance, decreased myocardial contractility, and cardiac output.

The hemodynamic effects to bolus dose of dexmedetomidine show a biphasic response. Intravenous injection of dexmedetomidine initially produces

increase in blood pressure and decrease in heart rate from baseline. Then gradually blood pressure declined below baseline.

The incidence of hypotension and bradycardia associated with dexmedetomidine administration may be related to loading dose. Avoiding the loading dose or dose <4ug/kg reduces these side effects and transient hypertension can be minimized by giving the loading dose over 20 minutes.

Younger patients with high vagal tone develop severe bradycardia and sinus arrest which can be effectively treated with anticholinergic agents.

Respiratory system

Even at high doses it does not produce respiratory depression which is the unique feature of this drug. Hence it is widely used in ICU setup as infusion for the patients on mechanical ventilation. This allows daily wakeup test to assess their mental status and titrate sedation according to the need. So it shortens the duration of mechanical ventilation and reduces ICU length of stay.

Central nervous system

The CNS protective effects of dexmedetomidine not well defined. It reduces cerebral blood flow and CMRO2 in animal models. It has sedative, analgesic, anxiolytic effects due to much number of mechanisms in CNS. FDA has approved dexmedetomidine only for short term sedation less than 24 hr so the problems of tolerance, dependence, or addiction are not there.

Dexmedetomidine can be used for opioid detoxification, cocaine withdrawal, iatrogenic induced benzodiazepine and opioid tolerance. No reports of seizures are seen in human following dexmedetomidine administration. Dexmeditomidine also reduces muscle rigidity after high dose opioid. It ablates memory in dose dependent manner.

Endocrine

Dexmedetomidine reduces catecholamine release so that sympathetic response to surgery is reduced. It increases growth hormone secretion, but no effects on other pituitary hormones.

ANTAGONIST

α2 agonists have the advantage of their effects readily reversed by α2-adrenergic antagonist eg: Atipamazole. Note: Atipamazole is not approved for human use

ADVERSE EFFECTS

- Hypotension
- Hypertension
- Nausea, vomiting
- Bradycardia
- Dry mouth
- Pyrexia, chills

CLINICAL APPLICATIONS

PREMEDICATION

Since this drug has sedative, anxiolytic, analgesic, sympatholytic, hemodynamic stability it can be used as adjuvant for premedication. The dose is 0.33 to 0.67 ug/kg intravenously 15 minutes before surgery.

INTRAOPERATIVE USE

It has anaesthetic sparing effect by potentiating effect of all the anaesthetic agents thereby reducing their requirements and related adverse effects. It reduces stress response of intubation, extubation and surgery and maintains hemodynamic stability profile intra operatively.

REGIONAL ANAESTHESIA

Dexmedetomidine has high lipid solubility and penetrate nerve membrane rapidly. So during spinal anaesthesia blockade and peripheral nerve blockade it prolongs the duration of local anaesthetics. It may also be used in intravenous regional anaesthesia and intra articularly.

PROCEDURAL SEDATION

Dexmedetomidine can be used for elective awake fibreoptic intubation, transoesophageal echocardiography, colonoscopy, shock wave lithotripsy, pediatric MRI. Initial loading dose 1ug/kg followed by infusion of 0.2 ug/kg/hr infusion.

ICU SEDATION

Dexmedetomidine produces ‘rousable’ sedation and doesnot interfere with respiratory drive, does not produce respiratory depression. So it helps forearly weaning from the ventilator, reducing the cost and length of ICU stay.

CARDIAC SURGERY

Dexmedetomidine reduces the extent of myocardial ischemia and used in management of pulmonary hypertension in patients undergoing mitral valve replacement.

NEUROSURGERY

Dexmedetomidine is also used in functional neuro surgery like awake craniotomy, implanatation of deep brain stimulators for parkinsons disease.

MONITORED ANAESTHESIA CARE

It is used for sedation for monitored anaesthesia care. Average infusion rate to maintain BIS value of 70-80 is 0.7 ug/kg/min intra operatively.

OPHTHALMIC SURGERY

It is used as premedication in patients undergoing cataract removal, 10 minutes before surgery.

OBESITY

Dexmedetomidine has narcotic sparing effect and used in morbidly obese patients intra operatively and post-operatively after bariatric surgery.

Dexmedetomidine originally approved for sedation in ICU setup, now a days it has many off label applications in operating room and perioperative environment.

Availability of dexmeditomidine

Dexmeditomidine available as ampoule containing 1ml and 2ml solution with the strength of each ml containing 100mcg

REVIEW OF LITERATURE

Several studies were conducted using α2 advenergic agonists as adjuvant to bupivacaine and other local anaesthetics for prolongation of post-operative analgesia. The proposed hypothesis for the mechanism of action as follows,

1. α2adrenoreceptors are located on the neurons in the superficial laminae of the spinal cord and the locations implicated are a) several brain stem nuclei implicated in producing analgesia b) afferent terminals of the peripheral neurons. α2 adrenergic agonists acts by inhibiting voltage gated Na+ and K+ channels and suppresses the generation of action potentials thus reduce neural transmission.

2. By release of acetylcholine inhibits the release of substance P in the neuraxial region.

3. Presynaptic activation of α2 receptor in CNS inhibits release of noradrenaline and terminates propagation of pain signal.

Lipid solubility and affinity toα-adrenergic receptors are factors determining the duration of action of the drug.

1.**Franco CD, Vieria ZE** (2000) did a study on success of subclavian perivascular block using a nerve stimulator. This study concluded that this technique provides an effective block for upper extremity surgeries. Also explains that the success of this block due to the fact that at injection site the plexus reduced to its smallest volume and sheath reduced to its smallest volume.

2. **Brown DL** (1993) did a study and analysed the various sites supraclavicular, interscalene, infraclavicular and axillary approaches at which brachial plexus can be blocked. The study concluded that supra clavicular approach produces most consistent anaesthesia of entire upper limb than any other technique.

3. **Winnie and Ramamoorthy**[2](1977) postulated that the brachial plexus are arranged so that central fibres are longest supplying the extremities of limb, the shorter fibres arranged more peipheraly as their area of supply is proximal.

4. **Rachana Gandhi et al**[9] conducted study (2012) on 70 patients by comparing 30ug dexmeditomidine added to 0.25%. Bupivacaine with control group who received plain 0.25% bupivacaine. Supraclavicular brachial plexus block done by subclavian perivascular technique. This prospective randomized study concluded that dexmeditomidine prolongs the duration of analgesia in supraclavicular brachial plexus block without any significant side effects.

5. **Amit R. Khade**[49] **et al** (2013) conducted a study to evaluate the effect of dexmeditomidine as an adjunct to bupivacaine in brachial plexus block. The study was conducted on 40, ASA 1 and ASA II risk patients who were randomized to two groups, Group A received 20 ml 0.5% bupivacaine + 10ml 2% Lignocaine + 50 mcg of dexmeditomidine, group B received 0.5ml normal saline instead of dexmeditomidine along with above 30ml local anaesthetic. Supra clavicular block doneby peripheral nerve stimulator technique. This prospective randomized double blinded study concluded that adding 50mcg dexmeditomidine in supra clavicular block shortens onset of sensory andmotor block, improves

block quality, increases interval to first analgesic use, provides better hemodynamic stability, and decreases intra operative sedative requirements.

6.**SandhyaAgarwal et al**[22](2014) compared the effect of dexmeditomidine 100mcg added to 30ml of 0.325% bupivacaine in supra clavicular brachial plexus block using peripheral nerve stimulator technique. This prospective randomized double blinded study done on 50 patients by dividing into two groups control groups received 30ml 0.325% bupivacaine + 1ml normal saline,Study group SD received 30ml 0.325% bupivacaine + 1ml (100 mcg) dexmeditomidine. The study concluded that dexmeditomidine as adjuvant to bupivacaine for supraclavicular brachial plexus block significantly shortens the onset time and prolongs the duration of sensory and motor blocks and duration of analgesia with adequate sedation and no adverse side effects.

7. **Amany S. Ammar et al**[37] (2012) designed study to test the efficacy of adding dexmeditomidine to bupivacaine during placement of ultrasound guided infraclavicular brachial plexus block. This prospective randomized double blinded study done on 60 patients divided two groups, Group 1 received 30ml 0.33% bupivacaine with 0.75mcg/kg of dexmeditomidine and group 2received 30ml 0.33%bupivacaine with normal saline.They concluded that adding dexmeditomidine to bupivacaine provides 1) enhancement of onset of sensory and motor blockade. 2) Prolonged duration of analgesia 3) increases duration of sensory and motor blockade. 4) Yields lower VRS pain scores. 5) Reduces supplemental opioid requirements.

8.**F.W.Abdallah et al**[13] (2013) done a systematic review and meta analysis which examined wheather perineural dexmeditomidine as local anaesthetic adjuvant for neuraxial and peripheral nerve blocks can prolong the duration of analgesia compared with LA alone. Five trials investigated dexmeditomidine as part of spinal anaesthesia and four as part of brachial plexus block. Total of 516 patients were analysed from nine RCTs. They summarized that dexmeditomidine is a potential adjuvant to LA that can exibit facilitary effect when administered intrathecaly or in periphery as a part of brachial plexus block.

9.**SaumyaBiswas et al**[50] (2014) evaluated the effect of combining dexmeditomidine with levobupivacaine with respect to duration of sensory, motor block and duration of analgesia. They concluded that dexmeditomidine added to levobupivacaine in supraclavicular brachial plexus block prolongs the duration of block and duration of post-operative analgesia.

10. **Kenankaygusuzet al**[12] (2012) evaluated the effect of dexmeditomidine added to levobupivacaine for an axillary brachial plexus block. The study concluded that dexmeditomidine to axillary plexus block shortens sensory block onset time increases the sensory and motor block duration and time to first analgesic use and decreases total analgesic use with no side effects.

11.**Sarita S Swami et al**[11] conducted randomized double blinded study to compare dexmeditomidine and clonidine as an adjuvant to local anaesthetics in supra clavicular brachial plexus block. The study concluded that

dexmeditomidine prolongs the duration of sensory and motor block and enhances the quality of block as compared with clonidine.

12.**KeshavGovindRaoet al**[32] (2014) conducted a study to compare clonidine and dexmeditomidine as an adjuvant to supraclavicular brachial plexus block. The study concluded that dexmeditomidine is better and more effective as an adjuvant to bupivacaine in supraclavicular brachial plexus block.

13.**Yogiheesatishraopatkiet al**[39] (2015) evaluated the efficacy of dexmeditomidine as an adjuvant to 0.5% ropivacaine in supra clavicular brachial plexus block for post-operative analgesia. The study concluded that dexmeditomidine prolongs the duration of post-operative analgesia, useful in early onset of sensory and motor blockade and reduced the need of analgesics in first 24hr post-operatively. The advantage of conscious sedation, hemodynamic stability and minimal side effects makes it as a potential adjuvant to peripheral nerve block.

14.**Harshavardhana H S et al** [40]conducted prospective randomized, double blinded study to compare dexmeditomidine with clonidine added to ropivacaine in supraclavicular nerve blocks. They concluded that when dexmeditomidine added to ropivacaine for brachial plexus block is a better adjuvant when compared to clonidine.

15.**Don Sebastian et al**[42] **(2015)** conducted a study to compare dexmeditomidine and clonidine as adjuvant to ropivacaine in supra clavicular brachial plexus block

and they concluded that dexmeditomidine had faster onset, greater duration of sensory and motor block and duration of analgesia than clonidine.

16.**VinodHosalli et al[45] (2015)** conducted randomized double blinded prospective study to compare dexmeditomidine and clonidine as adjuvant to levobupivacaine in ultrasound guided axillary brachial plexus block. They concluded that dexmeditomidine is more effective in prolonging the duration of sensory block, motor block and post-operative analgesia compared to clonidine.

17.**Dr.SidharthSrabanRoutrayet al[20]** studied the effects of clonidine on ropivacaine in supraclavicular brachial plexus block. They concluded that clonidine added to ropivacaine increases the onset and duration of sensory and motor block.

18.**Yu Zhang et al [46](2014)**conducted a study by adding dexmeditomidine 100mcg to ropivacaine in axillary brachial plexus block. They concluded that dexmeditomidine added to ropivacaine prolongs the duration of block. However it may also lead to side effects such as bradycardia, hypotension, and hypertension.

19.**VaniaKanvee et al (2015)** conducted a comparative study of clonidine and dexmedetomidine as an adjuvant with ropivacaine in supraclavicular brachial plexus block for upper limb surgeries. The study concluded that the duration of sensory, motor blockade and post-operative analgesia was significantly prolonged by dexmeditomidine without significant hemodynamic alterations.

MATERIALS AND METHODS

This study was carried out in the orthopaedic surgery theatre, Kanyakumari government medical college after obtaining institutional ethical committee approval.

AIM:

To compare the effect of three different dose of dexmeditomidine as adjuvant to bupivacaine in supra clavicular brachial plexus block in terms of

- Onset and duration of sensory block
- Onset and duration of motor block
- Duration of analgesia
- Peri operative hemodynamics
- Complications

Study design

This was a randomized, prospective, double blinded study.

The study has started after receiving Institutional Ethical Committee approval and informed written consent from all the patients.

Randomisation

Simple randomized sampling was done by computer generated random numbers.

Sample Size

Sixty patients were studied.

Group allocation

Patients were allocated into three groups,

- Group A(n-20) – 30 ml 0.33% bupivacaine + dexmeditomidine 50mcg
- Group B(n-20) – 30ml 0.33% bupivacaine + dexmeditomidine 75mcg
- Group C (n-20) – 30ml 0.33% bupivacaine + dexmeditomidine 100mcg

Masking

The anaesthesiologist who administered the drug and the observer were blinded to the study. Local anaesthetic, study drug mixture was prepared by another anaethesiologist not participating in the study. The intra operative monitoring and post-operative observation was done by the same anaesthesiologist who administered the drug, who was unaware of the group allocation

Inclusion Criteria

Age – 20-60 years

Weight – 50-70 kg

ASA I & II

Written informed consent

Upperlimb orthopedic surgeries

Exclusion Criteria

Consent not given

Significant neurological disease

Psychiatric disorder

Pregnancy and lactation

Patients on anticoagulation

Significant systemic disorder

Known hypersensitivity to study drugs

Patients on adrenergic drugs

Materials

Sterile tray for regional block

Drugs for the block

Equipment & drugs for resuscitation

Preparation of study drug

Bupivacaine is prepared as 30ml of 0.33% solution by adding 10ml distilled water to 20ml of 0.5% bupivacaine. Dexmeditomidine is prepared by taking the drug in insulin syringe .40 units syringe equalent to1ml - 40 units equal to 100µg, 30 units equal to 75µg, and 20 units equal to 50µg

Methods

Pre Operative Preparation

Patients were pre operatively assessed and procedure was explained to the patient regarding the technique and consent obtained.

Conduct of anaesthesia

On arrival of the patient in the operating room, monitors like pulse oximeter, non invasive blood pressure and ECG were connected and baseline values recorded. An intra venous access was obtained in the opposite arm.

Supraclavicular brachial plexus block

Patient were positioned supine with the head turned away from the side to be blocked and the ipsilateral arm adducted. The neck was prepared with povidone iodine solution and draped with sterile towels.

Supraclavicular brachial plexus block was done by subclavian perivascular technique – paraesthesia technique.

Procedure

A line was drawn laterally from the cricoids cartilage to cross the sternomastoid at its midpoint. The interscalene groove was located behind the midpoint of posterior border the muscle. Then the groove was followed distally towards the clavicle. Approximately 1-1.5cm above the midpoint of the clavicle, the pulsation of subclavian artery was made out in the interscalene groove.

Under strict aseptic precautions after local infiltration of 2% lignocaine, a 22G short beveled needle is inserted in the interscalene groove 1 to 1.5 cm above the clavicle and directed towards ipsilateral nipple posteriorly and caudally. After elicitation of paraesthesia the local anaesthetic drug mixture injected after repeated aspiration.

Evaluation of block

The following observations were made;

- Vital signs monitoring -heart rate, non-invasive blood pressure, oxygen saturation and sedation score were measured every minute for the first 5 minute and every 5 minutes for 1 hour, every 15 minutes thereafter until the end of surgery& in the post-operative period. For statistical purposes they were documented at 0,5,10,15,30,45,60,90,120,150 minutes.
- Immediately following the administration of the drug, patient was evaluated for the onset of sensory and motor blockade every minute.
- Onset time for sensory block – time from completion of injection to loss of cold and pain sensation (score 2)
    - Loss to cold sensation using alcohol swab in all dermatomes of brachial plexus.
    - Atraumatic pin prick test
        - Score 0 – normal sensation
        - Score 1 : loss of sensation to pin prick
        - Score 2 : loss of sensation to touch
- Onset time for motor block-Time from completion of injection to complete motor blockade with inability to move fingers

  Modified bromage scale
    - Score 0 – normal motor function with full flexion, extension of elbow, wrist and fingers.

- Score 1 – decrease motor strength with ability to move fingers and/or wrist only
- Score 2 – complete motor blockade with inability to move fingers.

- Sedation was assessed by modified ramsay sedation scale .The scale isas follows
    - 1 = anxious, agitated, restless;
    - 2 =cooperative, oriented, tranquil;
    - 3 = responds to commands only;
    - 4 = brisk response to light glabellar tap or loud noise;
    - 5 = sluggish response to light glabellar tap or loud noise;
    - 6 =no response.

Only patients with complete sensory & motor blockade are included in the study. Failure of block to be established even after 20 minutes was taken as block failure. Block failure patients managed with local anaesthetic supplementation or general anaesthesia as appropriate and those patients excluded from the study.

Sedation is assessed using Ramsay Sedation score and if the patient is anxious even 1 hr after blocking the plexus, 1mg midazolam was given to achieve a sedation score of 2-3.When the saturation falls below 92% supplemental o2 was given.

Patients were monitored for local anaesthesic toxic reactions including subjective and objective manifestations like circumoral numbness, tinitus, twitching, and convulsions.

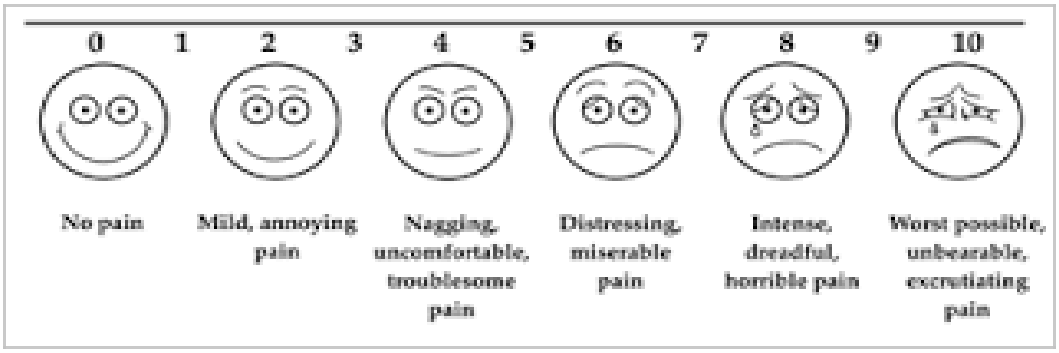
Patients were also monitored for complications associated with the technique, drug like intravascular injection, Intrathecal injection, pneumothorax, hypotension & bradycardia.

Post-operative ly heart rate, NIBP, Oxygen saturation, sedation score recorded at 0,30,60 min, 2 hr, 3 hr, 4 hr, 6 hr, 12 hr, 24 hr.

- Duration of sensory block – time from injection of localanaesthetic to complete recovery from cold and pain sensation in all dermatomes.
- Duration of motor block – time from injection of local anaesthetic to complete recovery of motor function modified bromage scale score 0.
- Duration of Analgesia – time from onset of sensory block to vas score 4.

VAS Score

- 0 – No pain
- 3 – Mild pain
- 5 – Moderate pain
- 10 – Most severe pain



Inj. Diclofenac 75mg intramuscularly is given as a rescue analgesic when the pain score is more than 4.

- Patients were followed for upto 24 hrs for any adverse effects
    - Bradycardia – heart rate <60 beats / minute and treated with inj.atropine 10-20 µg/kg
    - Hypotension – 20% decrease from baseline value and treated with IV fluid bolus and inj.ephedrine 6mg IV in incremental boluses.
    - Sedation
    - De-Saturation
    - Nausea and vomiting
    - Dizziness, Pruritis
    - Arrhythmia

OBSERVATION & RESULTS

Statistical Tools

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2010) developed by Centre for Disease Control, Atlanta.

Using this software range, frequencies, percentages, means, standard deviations, chi square , 'F' value and 'p' values were calculated. ANOVA test was used to test the significance of difference between quantitative variables and Yate's and Fisher's chi square tests for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

RESULTS

Group A ; Dexmed 50 mcg

Group B ; Dexmed 75 mcg

Group C ; Dexmed 100 mcg

A:PROFILE OF CASES STUDIED

Table A1 : Age distribution

Age group	Group A		Group B		Group C	
	No.	**%**	**No.**	**%**	**No.**	**%**
Up to 30 yrs	9	45	8	40	9	45
31 – 40 yrs	5	25	4	20	3	15
41 – 50 yrs	1	5	2	10	2	10
51 – 60 yrs	5	25	6	30	6	30
Total	20	100	20	100	20	100
Range Mean S.D.	20 – 60 yrs 36.1 yrs 13.8 yrs		22 – 60 yrs 39.5 yrs 13.8 yrs		22 – 60 yrs 39.2 yrs 13.9 yrs	
'p'	0.6898 Not significant					

The three groups were matched according to their age for randomization and found that there was no statistical difference between the mean ages between them (36.1±13.8 ≈ 39.5±13.8 ≈ 39.2±13.9 and P >0.05)

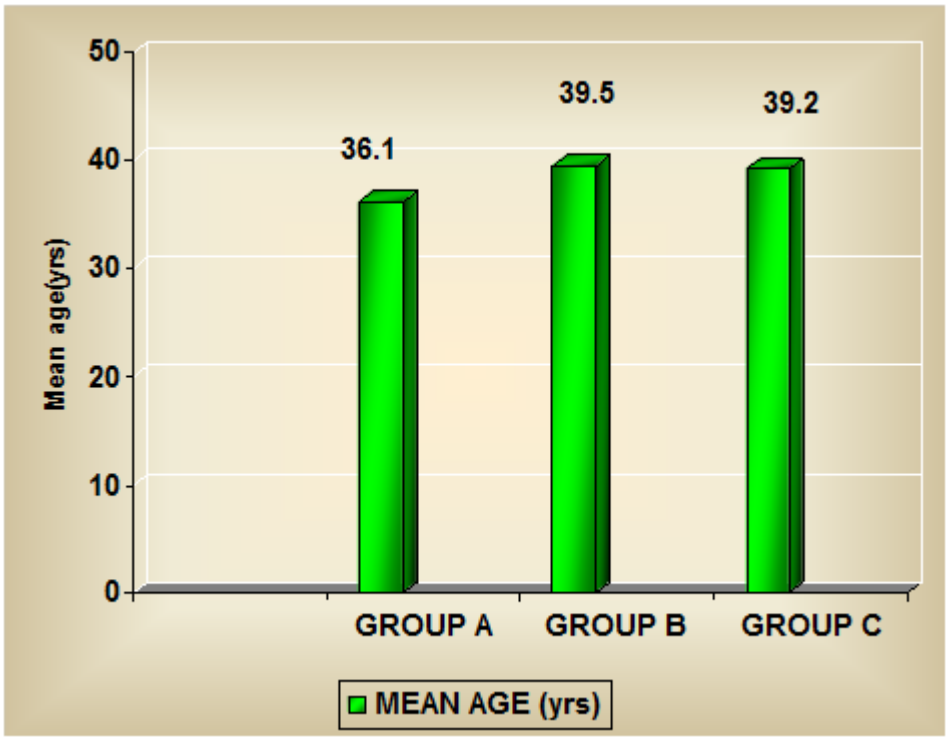


Table A 2 : Sex distribution

Matching of three groups according to their sex

Sex	Group A		Group B		Group C	
	No.	**%**	**No.**	**%**	**No.**	**%**
Male	13	65	10	50	11	55
Female	7	35	10	50	9	45
Total	20	100	20	100	20	100
'p' value between Group A &B Group A & C Group B & C	0.5224 Not significant 0.7469 Not significant 1.0 Not significant					

The three groups were matched according to their sex and found that there was no significant statistical difference between them

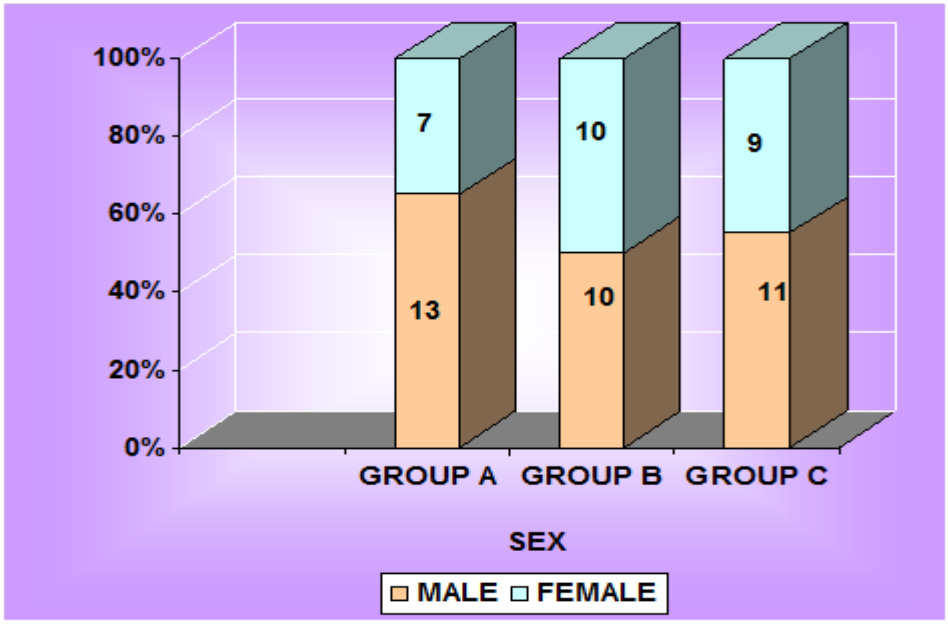

100%
80%
60%
40%
20%
0%
7
10
9
13
10
11
GROUP A
GROUP B
GROUP C
SEX
MALE
FEMALE

Table A3 : Weight

Matching of three groups according to their weight

Parameter	Weight (kgs)		
	Group A	**Group B**	**Group C**
Range	48 – 65	45 - 65	45 – 65
Mean	55.8	56.2	56.2
S.D.	5.3	5.7	6.5
'p'	0.9726 Not significant		

The three groups were matched according to their weight and found that there was no difference between them (55.8±5.3 ≈ 56.2±5.7 ≈ 56.2±6.5 and P >0.05)

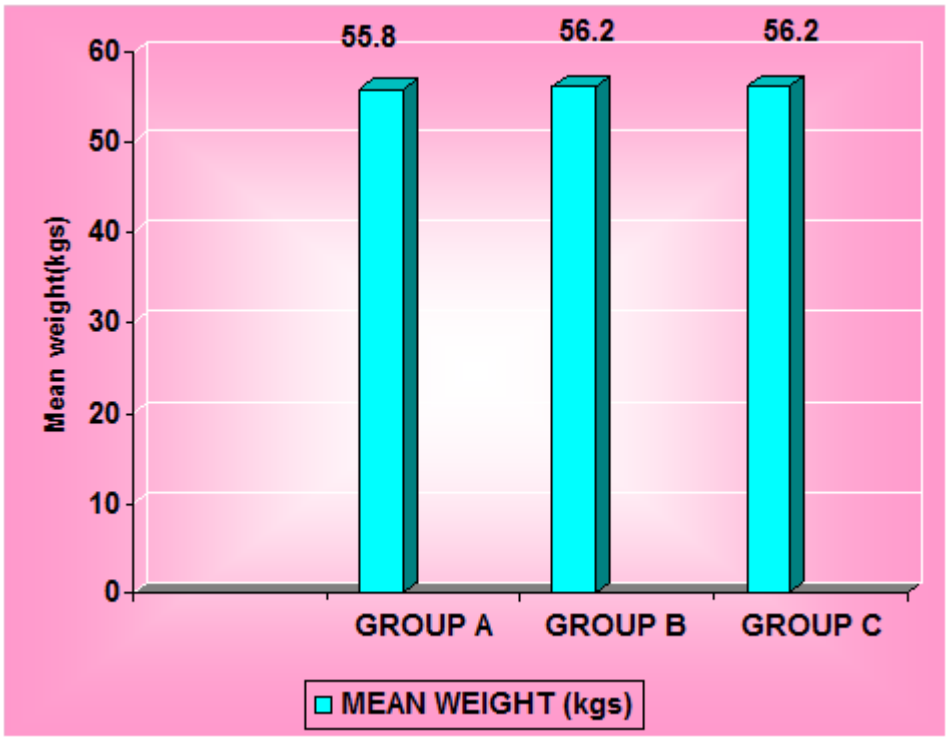
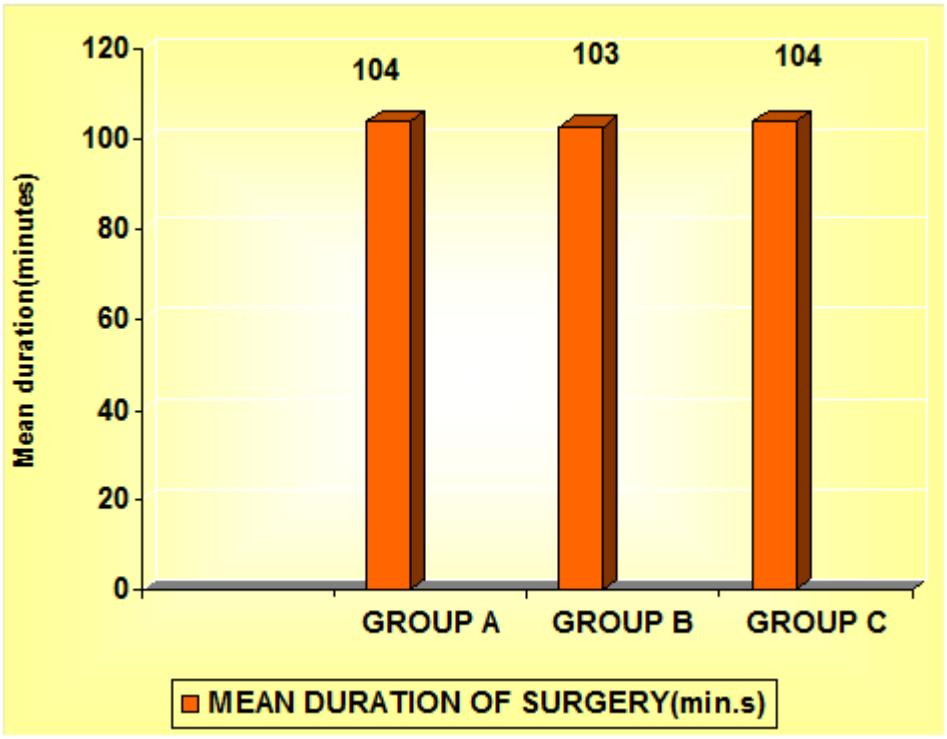


Table A4 : Duration of Surgery

Parameter	Duration of Surgery (minutes)		
	Group A	**Group B**	**Group C**
Range	70 – 150	60 – 150	70 – 150
Mean	104.0	103.0	104.0
S.D.	22.5	25.5	22.5
'p'	0.9881 Not significant		

The three groups were matched according to the duration of surgery & found that there is no statisticaly significant difference between them (104±22.5≈ 103±25.5≈104±22.5andP>0.05)



B : COMPARATIVE EFFICACY OF THE THREE DOSES

Table B1 : Sensory Block onset

Parameter	Sensory Block onset (minutes)		
	Group A	**Group B**	**Group C**
Range	10 - 22	10 - 18	5 – 10
>Mean	16.3	12.4	7.35
S.D.	3.31	2.5	1.5
'p' value between Group A & Group B Group A & Group C Group B & Group C	 **< 0.0001 Significant** **< 0.0001 Significant** **< 0.0001 Significant**		

Table B1 shows the comparison of onset of sensory blockade between the three groups .The mean onset time of group A was significantly longer than group B which was significantly longer than group C. A (16.3±3.31) >B(12.4±2.5) >C(7.35±1);

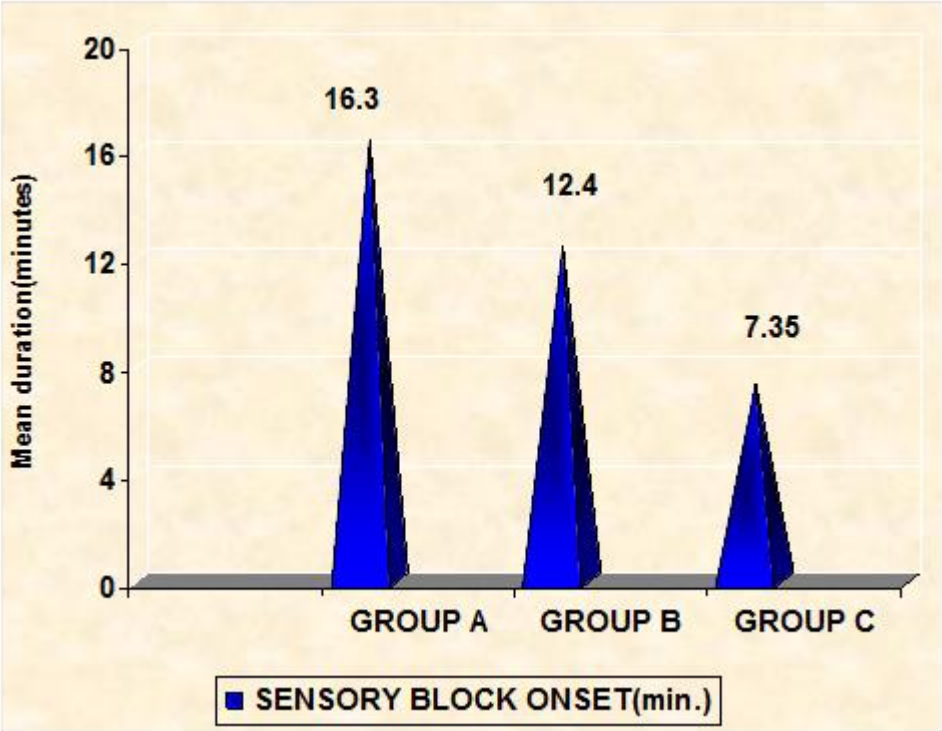

20
16
12
8
4
0
Mean duration(minutes)
16.3
12.4
7.35
GROUP A
GROUP B
GROUP C
SENSORY BLOCK ONSET(min.)

Table B2: Motor Block onset

Parameter	Motor Block onset (minutes)		
	Group A	**Group B**	**Group C**
Range	15 - 24	12 - 22	8 – 18
Mean	20.4	16.15	12.15
S.D.	2.7	2.89	2.81
'p' value between Group A & Group B Group A & Group C Group B & Group C	 **< 0.0001 Significant** **< 0.0001 Significant** **< 0.0001 Significant**		

Table B2 shows the comparison of onset of motor blockade between the three groups. The mean onset time of group A was significantly longer than group B which was significantly longer than group C. A(20.4±2.7) >B(16.15±2.89) >C(12.15±2.81)

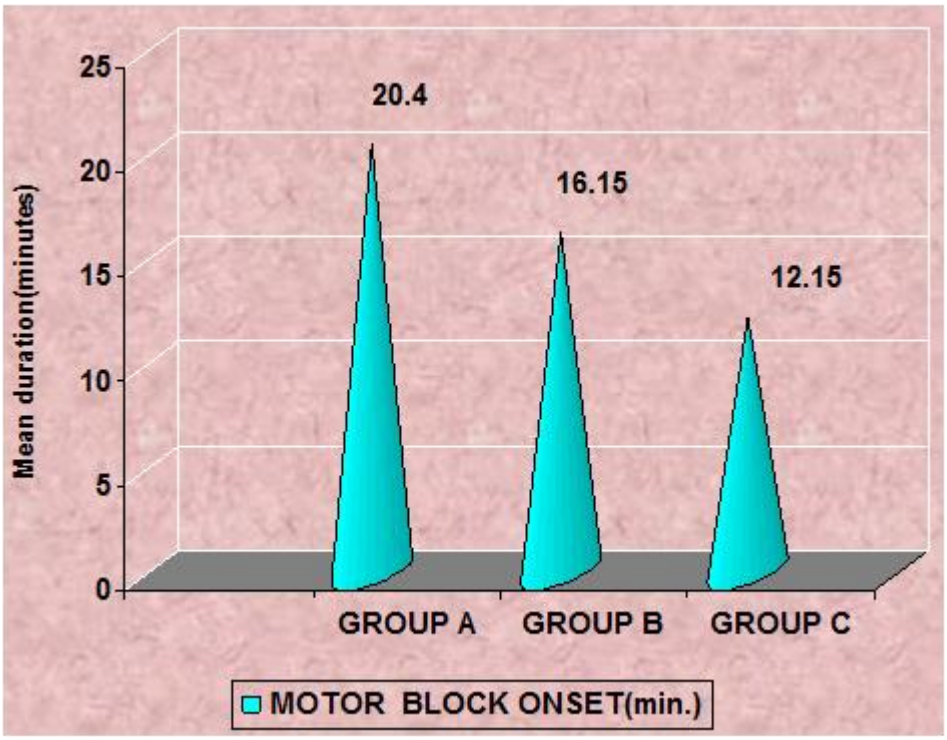

25
20
15
10
5
0
Mean duration(minutes)
20.4
16.15
12.15
GROUP A
GROUP B
GROUP C
MOTOR BLOCK ONSET(min.)

Table B3 : Sensory Block Duration

Parameter	Sensory Block Duration (minutes)		
	Group A	**Group B**	**Group C**
Range	300 - 560	450 - 740	620 – 800
Mean	432.5	625.5	722.5
S.D.	69.8	72.7	55.1
'p' value between Group A & Group B Group A & Group C Group B & Group C	 **< 0.0001 Significant** **< 0.0001 Significant** **< 0.0001 Significant**		

Table- B3 shows the comparison of duration of sensory blockade between the three groups. The mean duration of sensory block of group C was significantly longer than group B and group B was significantly longer than group A. C(722.5±55.1) >B(625.5±72.7) >A(432.5±69.8)

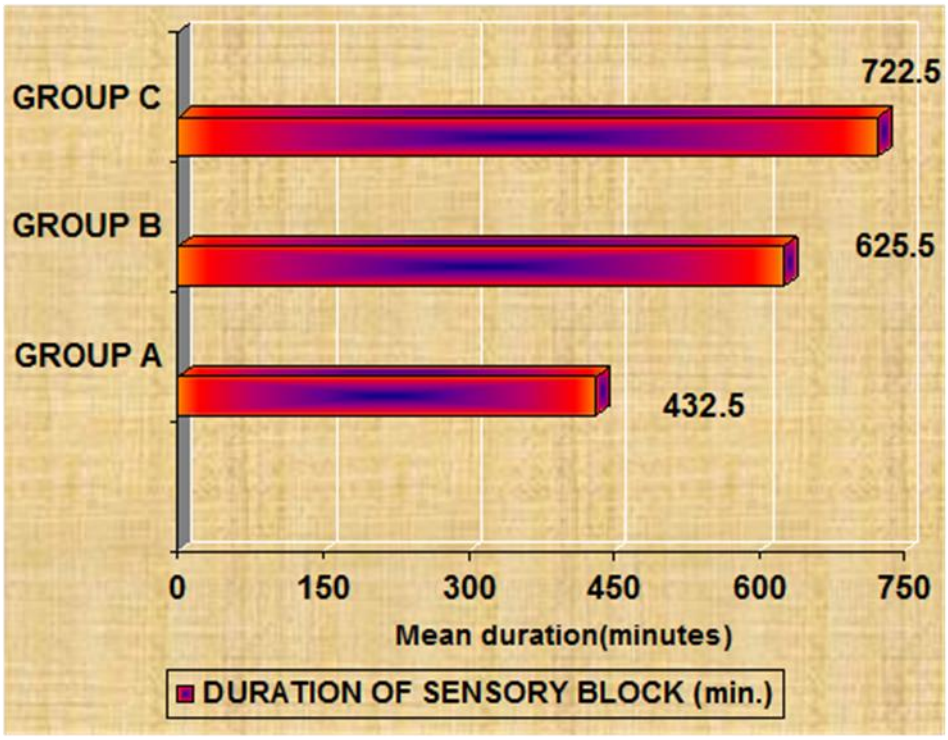

GROUP C
722.5
GROUP B
625.5
GROUP A
432.5
0
150
300
450
600
750
Mean duration(minutes)
DURATION OF SENSORY BLOCK (min.)

Table B 4: Motor Block Duration

Parameter	Motor Block Duration (minutes)		
	Group A	**Group B**	**Group C**
Range	270 - 580	360 - 720	620 – 800
Mean	426.5	604.5	704.5
S.D.	81.8	98.6	41.4
'p' value between Group A & Group B Group A & Group C Group B & Group C	 **< 0.0001 Significant** **< 0.0001 Significant** **< 0.0001 Significant**		

The duration of motor block shown in the above table B 4 . The duration of motor block of group C was significantly higher than group B and group B was significantly higher than group A. C(704.5±41.4) > B (604.5±98.6) > A (426.5±81.8)

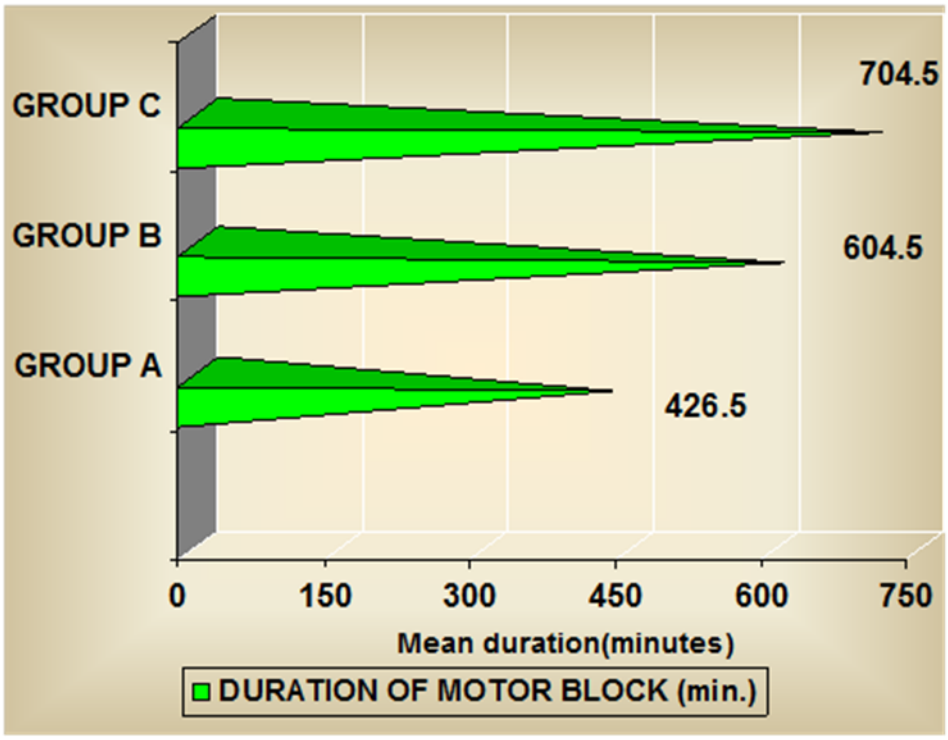

GROUP C
GROUP B
GROUP A
704.5
604.5
426.5
0
150
300
450
600
750
Mean duration(minutes)
DURATION OF MOTOR BLOCK (min.)

Table B 5: Duration of Analgesia

Parameter	Duration of Analgesia (minutes)		
	Group A	**Group B**	**Group C**
Range	330 - 610	460 - 780	620 – 820
Mean	480.5	642.0	736.5
S.D.	81.3	76.5	67.1
'p' value between Group A & Group B Group A & Group C Group B & Group C	 **< 0.0001 Significant** **< 0.0001 Significant** **< 0.0001 Significant**		

The duration of analgesia between the three groups were 480±81.3,642±76.5 and 736±67.1 minutes respectively. The mean duration of analgesia of C group was significantly longer than the B group and B group was significantly longer than the A group .C (736±67.1)>B(642±76.5)>A(480±81.3)

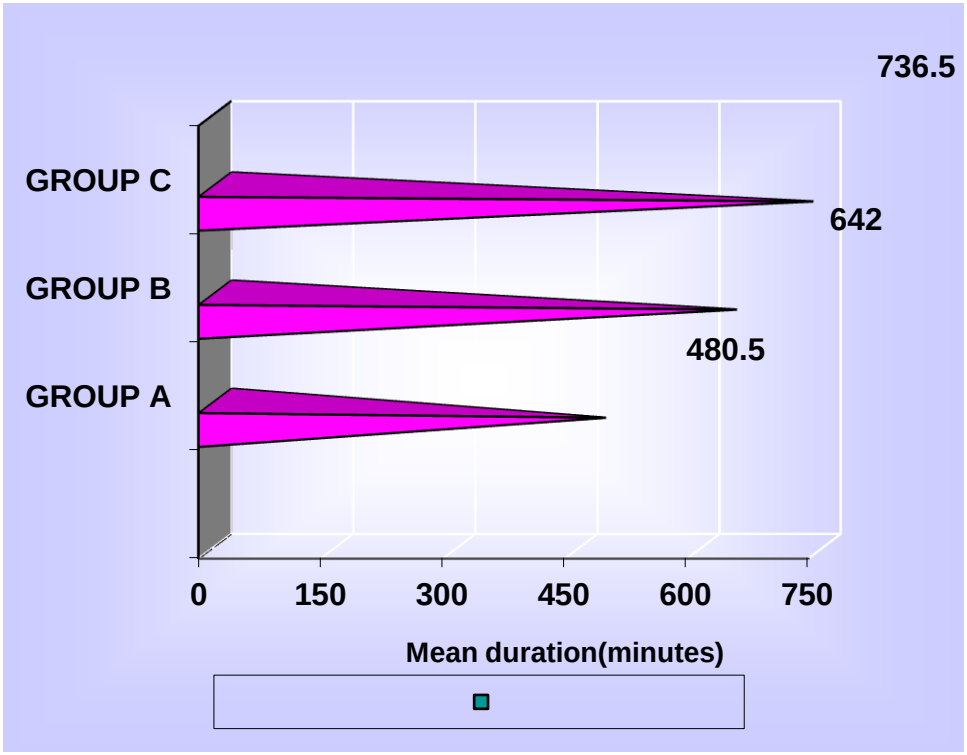

736.5
GROUP C
642
GROUP B
480.5
GROUP A
0
150
300
450
600
750
Mean duration(minutes)

Table B6: Sedation Score

Parameter	Sedation Score		
	Group A	**Group B**	**Group C**
Range	1 - 5	2 - 6	3 – 6
Mean	2.95	3.8	4.65
S.D.	1.05	1.15	10.4
'p' value between Groups A,B and C Group A & Group B Group A & Group C Group B & Group C	 **< 0.0001 Significant** **0.0195 Significant** **< 0.0001 Significant** **0.019 Significant**		

The sedation score of three groups are compared in table B6.The C group achieved more sedation level than group B and group B achieved more sedation level than group A. C(4.65±10.4)>B(3.8±1.15)> A (2.95±1.05)

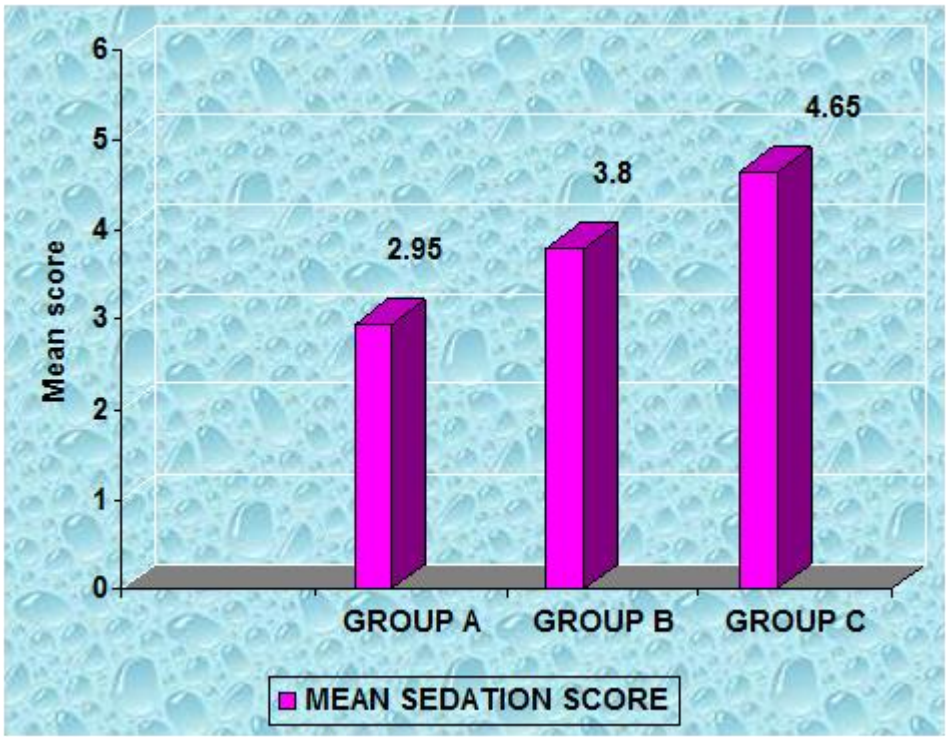
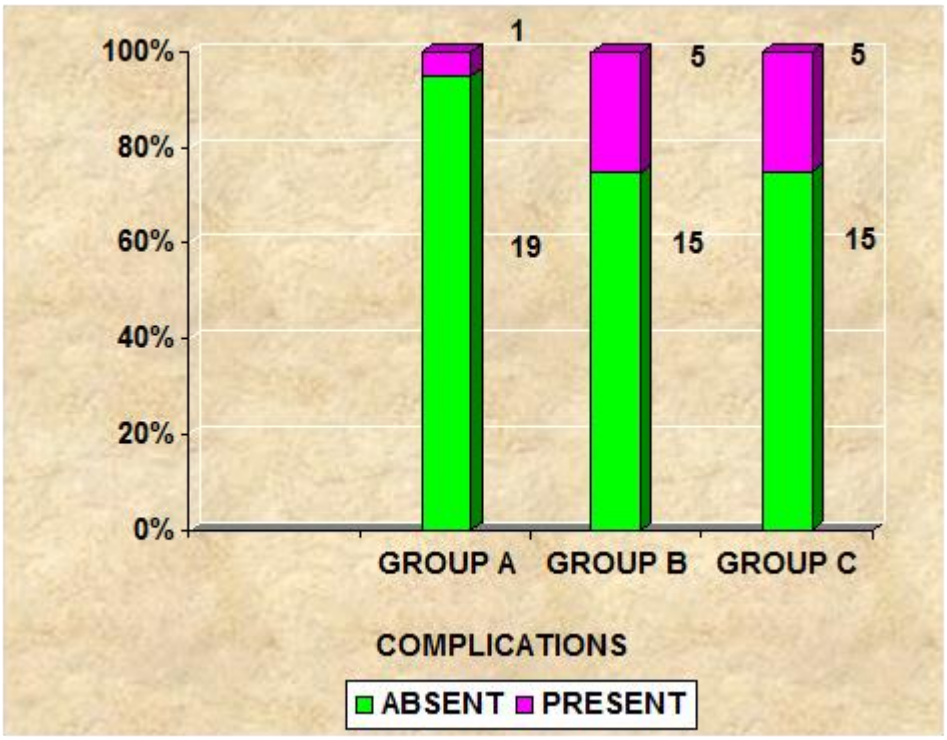

6
5
4
3
2
1
0
Mean score
2.95
3.8
4.65
GROUP A
GROUP B
GROUP C
MEAN SEDATION SCORE

Table B 7: Complications

Complications	Group A		Group B		Group C	
	No.	**%**	**No.**	**%**	**No.**	**%**
Hypotension	-	-	2	10	1	5
Bradycardia	1	5	3	15	4	20
Cases with complications	**1**	**5**	**5**	**25**	**5**	**25**
Cases without complications	**19**	**95**	**15**	**75**	**15**	**75**
'p' value between Group A & Group B Group A & Group C Group B & Group C	0.1818 Not significant 0.1818 Not significant 1.0 Not significant					

The above table compares the adverse effects between three groups .Bradycardia and Hypotension were the only adverse effects noted and was much associated with the group C.But the association within the groups did not have any statistical significance(P>0.05)


100%
80%
60%
40%
20%
0%
1
19
5
15
5
15
GROUP A
GROUP B
GROUP C
COMPLICATIONS
ABSENT
PRESENT

C : HEMODYNAMIC STABILITY

Table C1 : Changes in Pulse Rate

Pulse rate at	Group A		Group B		Group C		'p'	Significance
	Mean	S.D.	Mean	S.D.	Mean	S.D.		
INTRA OPERATIVE								
0 min.	85.9	7.3	86.0	6.2	86.6	11.5	0.9564	Not significant
5 min.	87.5	7.2	87.1	7.5	88.1	11.7	0.9342	Not significant
10 min.	89.1	7.5	87.1	8.7	86.6	13.1	0.701	Not significant
15 min.	87.9	7.3	85.0	8.2	87.8	17.3	0.6807	Not significant
30 min.	85.3	7.7	83.1	11.5	86.7	18.5	0.6982	Not significant
45 min.	83.2	9.4	81.9	13.9	87.2	19.5	0.5046	Not significant
60 min.	82.2	9.8	81.5	13.3	84.6	15.9	0.7395	Not significant
90 min.	81.8	8.4	81.6	11.2	84.9	12.6	0.5721	Not significant
120 min.	81.2	8.4	83.5	9.7	83.6	11.7	0.6833	Not significant
150 min.	81.0	8.5	84.4	8.7	85.5	11.3	0.3091	Not significant
POST-OPERATIVE								
0 min.	84.1	6.3	84.5	10.9	83.2	5.8	0.8782	Not significant
15 min.	85.9	6.6	86.0	10.9	84.3	5.4	0.7663	Not significant
30 min.	86.9	7.0	86.5	10.9	85.0	5.4	0.7516	Not significant

1 hour	86.7	5.6	86.4	11.7	84.9	5.0	0.7494	Not significant
2 hrs.	86.8	5.3	86.4	11.9	84.3	5.2	0.5869	Not significant
3 hrs.	85.4	6.4	87.0	12.6	83.0	5.6	0.3645	Not significant
4 hrs.	83.9	8.0	85.3	11.6	81.8	6.7	0.479	Not significant
6 hrs.	85.0	6.8	84.4	8.5	83.6	6.2	0.8282	Not significant
12 hrs.	85.3	5.1	84.2	8.4	84.0	4.6	0.7799	Not significant
24 hrs.	85.7	4.8	85.4	8.0	84.5	4.9	0.8097	Not significant

The pulse rate at different intervals in intra operative and post-operative periods are shown in table C1 .The mean pulse rate at the above different times between the three groups are not statistically significant(P>0.05)

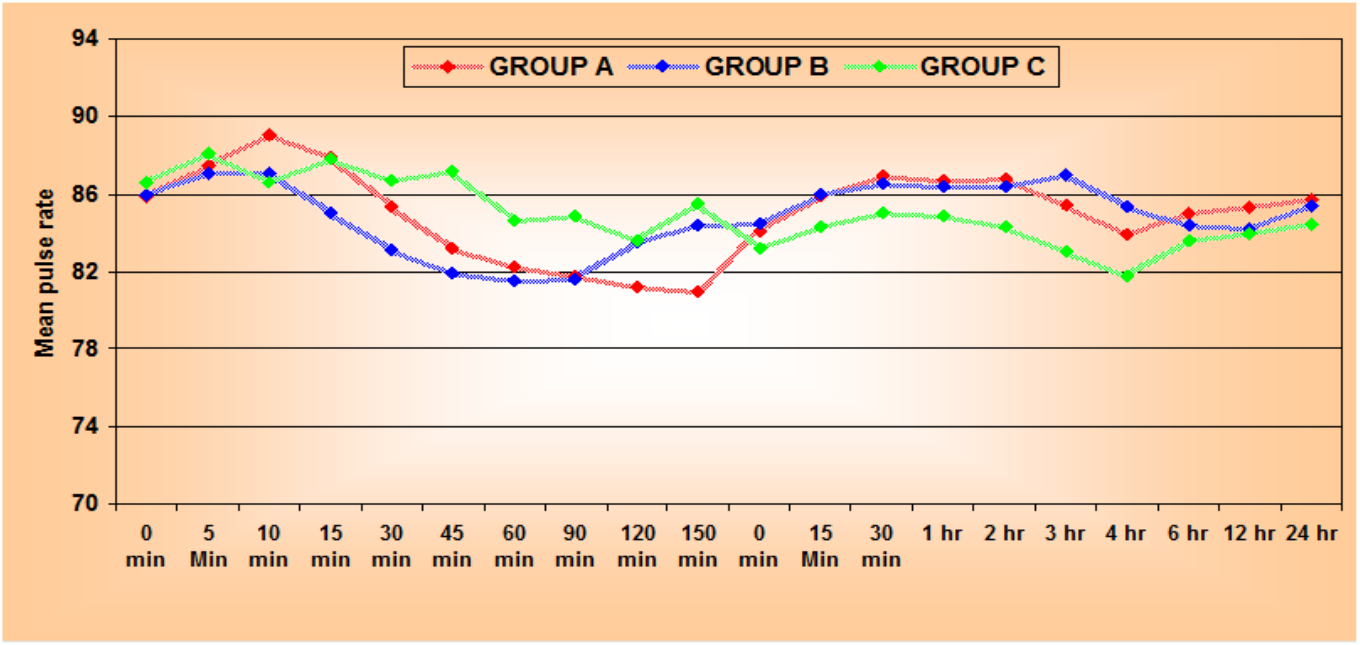


Table C2 : Changes in Systolic Blood Pressure

Sys. B.P. at	Group A		Group B		Group C		'p'	Significance
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**		
INTRA OPERATIVE								
0 min.	124.0	9.7	123.4	9.1	121.5	10.9	0.7091	Not significant
5 min.	122.8	9.2	122.5	10.5	121.0	10.2	0.8393	Not significant
10 min.	121.5	9.2	117.1	11.4	118.5	9.3	0.3723	Not significant
15 min.	119.1	10.0	114.4	11.0	115.0	9.5	0.2937	Not significant
30 min.	118.4	9.1	113.6	10.7	113.5	11.0	0.2189	Not significant
45 min.	114.9	9.4	113.1	10.0	112.5	10.7	0.7424	Not significant
60 min.	112.0	7.4	110.9	9.9	110.0	10.8	0.8086	Not significant
90 min.	115.7	7.5	112.9	9.7	112.0	12.8	0.5027	Not significant
120 min.	112.8	6.4	111.4	8.6	108.0	15.1	0.3524	Not significant
150 min.	112.7	6.8	111.1	8.1	109.5	16.4	0.6782	Not significant
POST-OPERATIVE								
0 min.	107.6	15.4	109.5	11.9	110.0	11.7	0.8299	Not significant

15 min.	111.0	11.7	109.5	9.8	109.3	10.0	0.871	Not significant
30 min.	111.3	14.8	110.7	12.1	110.2	12.4	0.9656	Not significant
1 hour	111.3	14.8	111.0	12.5	110.5	12.8	0.982	Not significant
2 hrs.	108.4	5.0	109.0	9.7	109.5	9.4	0.9376	Not significant
3 hrs.	107.5	7.9	108.5	9.3	109.0	9.1	0.8604	Not significant
4 hrs.	109.1	9.5	109.3	10.0	109.8	9.8	0.9731	Not significant
6 hrs.	109.1	9.5	109.3	10.5	109.8	10.3	0.9749	Not significant
12 hrs.	108.4	9.7	109.1	10.4	108.9	9.5	0.974	Not significant
24 hrs.	108.8	9.7	109.8	9.8	109.3	9.5	0.9527	Not significant

The systolic blood pressure at different intervals in intra operative and post-operative periods are shown in table C2 .The mean systolic blood pressure at the above different times between the three groups are not statistically significant.

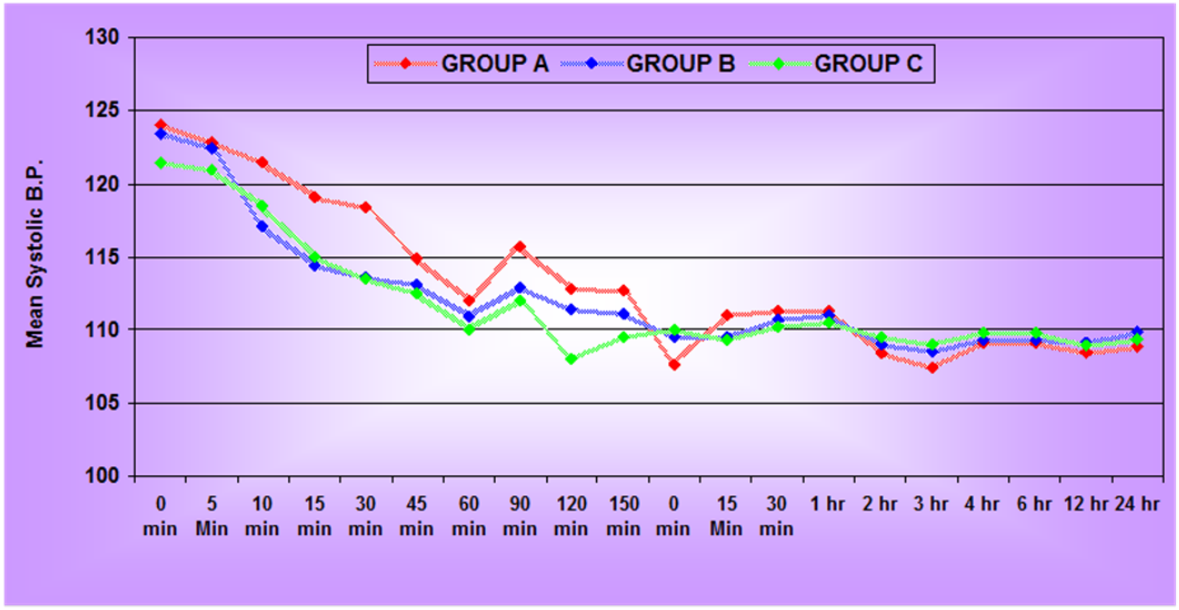


Table C3 : Changes in Diastolic Blood Pressure

Dias. B.P. at	Group A		Group B		Group C		'p'	Significance
	Mean	S.D.	Mean	S.D.	Mean	S.D.		
INTRA OPERATIVE								
0 min.	78.6	7.8	78.1	8.6	78.2	8.0	0.9753	Not significant
5 min.	74.9	5.4	74.3	6.4	74.8	5.5	0.9403	Not significant
10 min.	73.0	6.8	73.0	6.8	72.6	7.7	0.9791	Not significant
15 min.	69.2	6.1	69.4	5.9	68.9	6.9	0.9687	Not significant
30 min.	68.4	5.8	68.9	6.5	68.5	6.5	0.9721	Not significant
45 min.	68.5	6.1	69.0	5.7	68.8	6.9	0.9584	Not significant
60 min.	67.9	6.1	68.4	5.8	67.9	6.9	0.9562	Not significant
90 min.	70.2	8.2	74.5	9.8	74.9	9.6	0.2124	Not significant
120 min.	71.9	7.0	73.4	9.0	73.5	8.9	0.8066	Not significant
150 min.	73.1	6.0	72.1	8.6	71.9	8.8	0.8759	Not significant
POST-OPERATIVE								
0 min.	66.4	6.3	68.7	8.5	69.7	9.5	0.4336	Not significant
15 min.	67.7	7.1	67.0	10.5	69.3	9.7	0.7222	Not significant
30 min.	71.6	7.9	71.9	9.9	72.4	8.5	0.9533	Not significant
1 hour	71.4	6.8	71.9	4.8	70.9	7.8	0.8914	Not significant

2 hrs.	71.8	6.0	71.5	5.6	70.8	9.2	0.8906	Not significant
3 hrs.	73.5	6.3	71.9	6.2	70.7	13.9	0.6485	Not significant
4 hrs.	72.7	6.7	72.8	6.7	69.1	8.9	0.2166	Not significant
6 hrs.	72.7	5.9	71.6	6.5	72.8	8.1	0.8236	Not significant
12 hrs.	73.1	5.7	73.1	5.4	72.9	8.2	0.995	Not significant
24 hrs.	73.5	5.8	73.8	4.8	72.4	8.3	0.7563	Not significant

The diastolic blood pressure at different intervals in intra operative and post-operative periods are shown in table C3 .The mean diastolic blood pressure at the above different times between the three groups are not statisticaly significant (P>0.05)

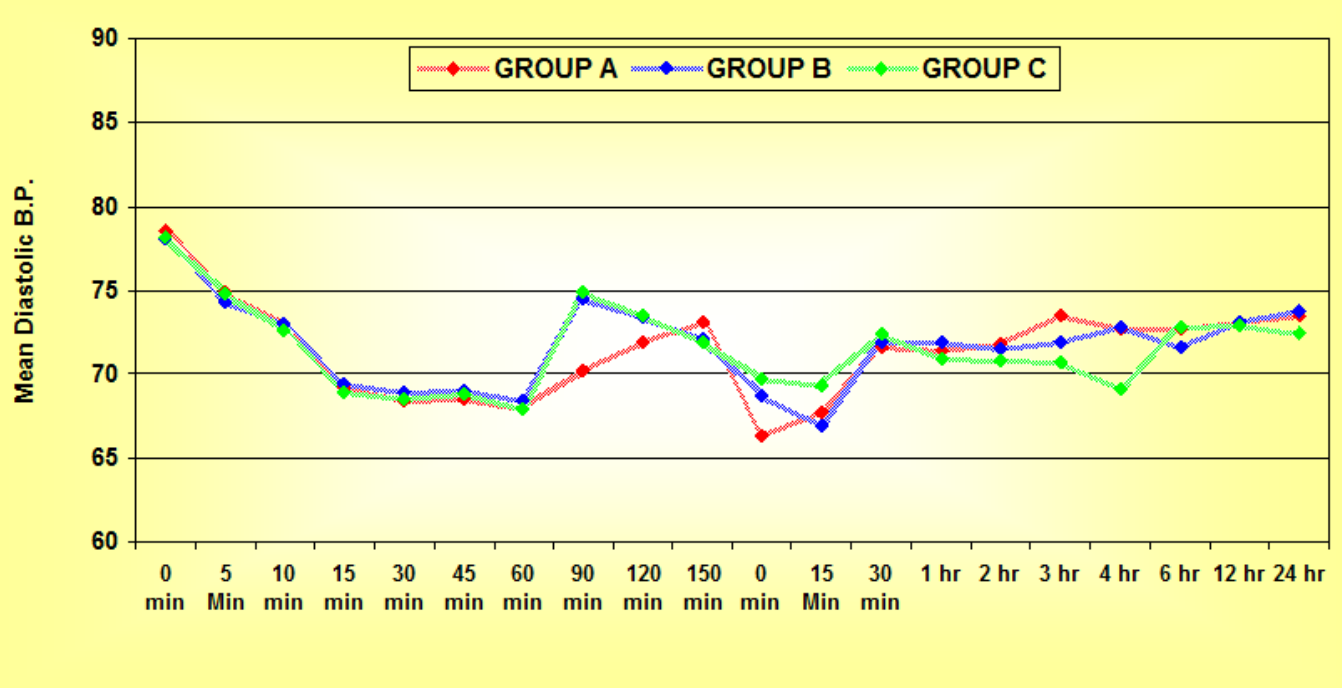
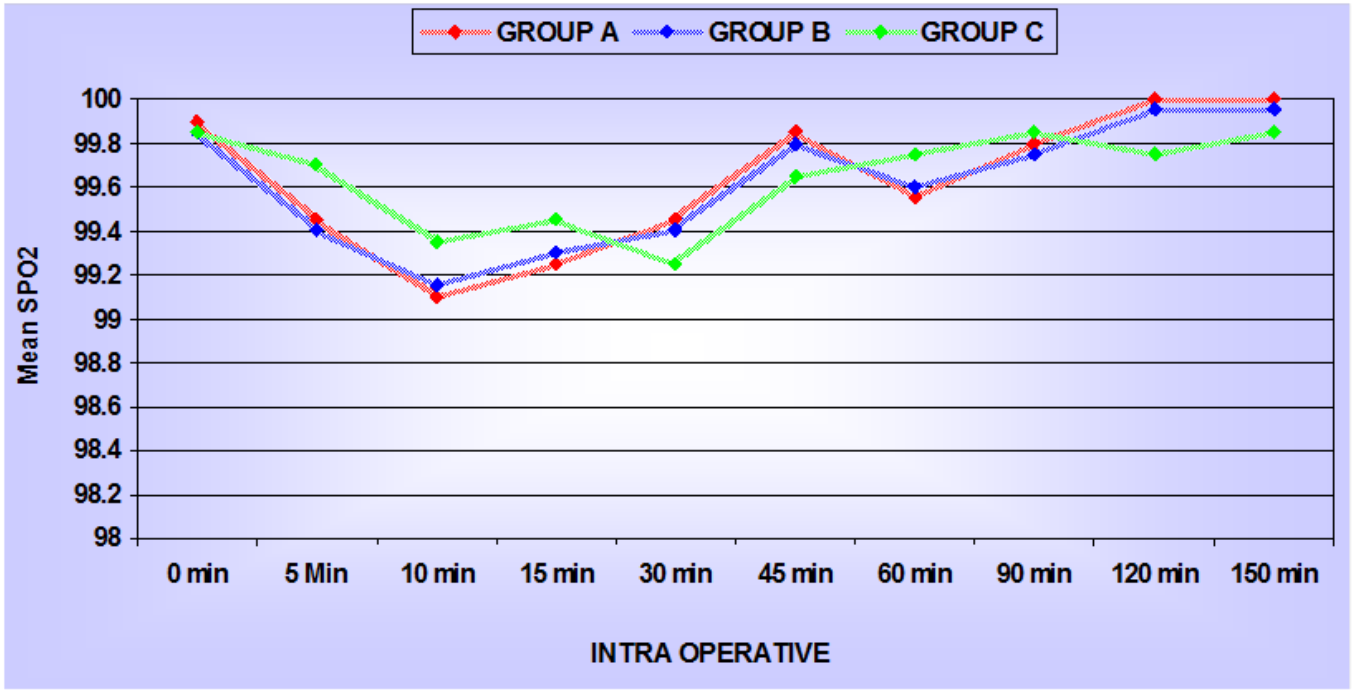


Table C4 : Changes in SPO2

SPO2 at	Group A		Group B		Group C		'p'	Significance
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**		
INTRA OPERATIVE								
0 min.	99.9	0.31	99.85	0.37	99.85	0.37	0.8717	Not significant
5 min.	99.45	0.69	99.4	0.68	99.7	0.57	0.3	Not significant
10 min.	99.1	0.79	99.15	0.81	99.35	0.75	0.5678	Not significant
15 min.	99.25	0.79	99.3	0.73	99.45	0.76	0.6887	Not significant
30 min.	99.45	0.69	99.4	0.68	99.25	0.97	0.7077	Not significant
45 min.	99.85	0.37	99.8	0.41	99.65	0.49	0.309	Not significant
60 min.	99.55	0.69	99.6	0.68	99.75	0.44	0.5663	Not significant
90 min.	99.8	0.41	99.75	0.55	99.85	0.37	0.7813	Not significant
120 min.	100.0	0.0	99.95	0.22	99.75	0.51	0.1003	Not significant
150 min.	100.0	0.0	99.95	0.22	99.85	0.37	0.1589	Not significant

The SPO2 at different intervals in intra operative and post-operative periods are shown in table C4 .The mean SPO2 at the above different times between the three groups are not statistically significant(P>0.05)


GROUP A
GROUP B
GROUP C
100
99.8
99.6
99.4
99.2
99
98.8
98.6
98.4
98.2
98
Mean SPO2
0 min
5 Min
10 min
15 min
30 min
45 min
60 min
90 min
120 min
150 min
INTRA OPERATIVE

DISCUSSION

Several researches have revealed that the administration of an α2 adrenergic agonist in the peripheral nerve blockade produces prolonged post-operative analgesia without much complications. Several mechanism have been hypothesized to explain the analgesic effect of α2 adrenergic agonist including complex interaction with axonal ion channels which result in direct suppression of impulse propagation ,vasoconstriction around injection site and local release of encephalin like substances.

Studies have shown that clonidine when added to bupivacaine in brachial plexus block prolongs the duration of analgesia but was associated with side effects such as hypotension, bradyardia and respiratory depression. Several animal studies have been investigated the effect of dexmeditomidine as adjunct to local anaesthetics. Brummet &colleagues reported that dexmeditomidine added to ropivacaine in sciatic nerve block provided prolonged analgesia than systemic administration. Another study conducted by Brummett and colleagues discovered that dexmeditomidine added to bupivacaine prolong sensory & motor block duration however it alone failed to show significant sensory & motor blockade.

Recently there are several study available using dexmeditomidine as adjunct to various local anaesthetics in central neuraxial blockade and peripheralnerve blockade. There are many studies available with various dose of dexmeditomidine as adjuvant to local anaesthetics in supra clavicular brachial plexus block . In our study we designed to compare the three doses

50µg,75µg,100µg of dexmeditomidine to know the optimal dose in supra clavicular brachial plexus block for upper limb orthopedic surgeries.

Demographic characters like age, sex, weight, duration of surgery comparable in all three groups.In our study we observed that sensory block onset was longer in group A (16.3±3.31)than group B(12.4±2.5) which is longer than group C (7.35±1)(table B1) and motor block onset also longer in group A (20.4±2.7) than group B (16.15±2.89) which is longer than group C(12.15±2.81) (table B2) .So we conclude that onset of sensory &motor blockade was earlier as the dose increases.These observations were comparable with Agarwal S etal[22] ,in their study earlier onset of blockade with 100µg dexmeditomidine but different from Yu zhang et al[46], in their study there is no significant difference in sensory and motor block onset between dexmeditomidine 50µg and 100µg group.

The duration of both sensory and motor block was longest with group C (sensory mean 722.5±55.1minutes, motor mean 704±41.4minutes) compared with group B (sensory mean 625.5±72.7 minutes , motor mean 604±98.6 minutes) which is longer than group A (sensory mean 432±69.8minutes, motor mean 426.5±81.8).So we conclude that sensory & motor block duration is longer as the dose increases .This observation is comparable with previous studies Yu zhang et al [46] who observed the duration of sensory and motor block significantly differ between groups and Agarwal S et al[22]. The mean duration of analgesia was dose dependent (tableB5) with C (736±67.1) >B(642±76.5) > A(480.5±81.3)minutes. This is also comparable with the other studies Yu zhang

et al[46],Agarwal S et al [22]and Amany S Ammar[37].The sedation was also (table B6) dose dependent with group C achieved more sedation than group B who achieved more sedation than group A. C(4.65±10.4) > B(3.8±1.15) > A(2.95±1.05) In respect of complications bradycardia and hypotension were the only adverse effects noted and was much associated with the group C.But the association within the groups did not have any statistical significance(P>0.05). This observation is coinciding with SawmyaBiswas et al[50] and SandhyaAgarwal et al[22] but differ from yu Zhang et al[46]. The statistical analysis of intra operative and post-operative hemodynamic variables such as PR,SBP,DBP,SPO2 between the three groups showed no statistical significant hemodynamic fluctuation.

SUMMARY

To summarise, dexmeditomidine added to bupivacaine in supraclavicular brachial plexus block had a dose dependent effect on the sensory and motor block charecteristics showing

1. Earlier onset of sensory and motor blockade
2. Increased duration of sensory and motor blockade
3. Increased duration of post-operative analgesia
4. Increased level of sedation

Three different doses 50,75,100µg did not vary in their effect on the hemodynamic stability and adverse effects.

CONCLUSION

Dexmeditomidine ,added to bupivacaine in supra clavicular brachial plexus block for upper limb orthopedic surgeries , has a dose dependent effect on the sensory and motor blockade , with earlier onset and increased duration of blockade and prolonged post-operative analgesia , gives better level of sedation and provides stable hemodynamic control during the intra operative period.

Dexmeditomidine 100µg is an optimal dose to provide prolonged post-operative analgesia without significant side effects

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PROFORMA

COMPARISON OF THREE DIFFERENT DOSES OF DEXMEDITOMIDINE AS ADJUVANT TO BUPIVACAINE IN SUPRA CLAVICULAR BRACHIAL PLEXUS BLOCK FOR UPPER LIMB ORTHOPAEDIC SURGERIES

Date :

Name : Age/sex : IP no:

Height : Weight : ASA risk:

Diagnosis : Plan of surgery:

Duration of surgery:

Plan of anaesthesia :

Pre anaesthetic status:

PR: BP: RR:

CVS: RS:

Procedure:-Supraclavicular block

30ml 0.33% bupivacaine with dexmeditomidine 50µg		30ml 0.33% bupivacaine with dexmeditomidine 75µg		30ml 0.33% bupivacaine with dexmeditomidine 100µg	

Monitoring

Time of performance of block	Sensory block onset	Motor block onset

Monitors	PR(bpm)	BP(mm hg)	RR	SpO2(%)	Sensory block grade	Motor block grade	Sedation score
0min							
5min							
10min							
15min							
30 min							
45min							
60min							
90min							
120min							
150min							

Post-operative monitoring

Time	PR	BP	RR	Spo2	Sensory block grade	Motor block grade	Sedation score
0min							
15min							
30min							
1hr							
2hr							
3hr							
4hr							
5hr							
6hr							
7hr							
8hr							
9hr							
10hr							
11hr							
12hr							

18hr							
24hr							

Time of reversal of sensory block --

Time of reversal of motor block --

Time of C/o moderate pain (VAS4) & Rescue analgesia --

Duration of sensory block --

Duration of motor block –

Duration of analgesia –

Master Chart

S.No	GROUP	Age	Weight (kg)	Sex	Duration of surgery (min)
1	A	60	50	M	140
2	A	32	55	F	70
3	A	23	58	F	100
4	A	38	62	M	80
5	A	40	55	M	90
6	A	45	65	M	100
7	A	38	48	F	95
8	A	56	52	F	120
9	A	20	56	F	90
10	A	55	62	M	90
11	A	22	60	M	140
12	A	26	52	M	110
13	A	23	50	M	100
14	A	31	51	M	130
15	A	25	54	F	95
16	A	27	65	M	150
17	A	28	62	M	80
18	A	21	54	F	80
19	A	55	50	M	120
20	A	56	55	M	100
21	B	35	62	F	80
22	B	60	60	M	100
23	B	30	55	M	70
24	B	23	58	F	90
25	B	28	50	F	90
26	B	55	65	M	95
27	B	60	45	F	120
28	B	22	65	M	60
29	B	28	48	M	90
30	B	26	56	M	140
31	B	38	60	F	100
32	B	45	50	F	150
33	B	40	55	F	120
34	B	32	52	M	95
35	B	55	57	M	150
36	B	58	52	F	80
37	B	46	60	F	90
38	B	26	65	M	120
39	B	25	54	M	90

40	B	57	55	F	130
41	C	30	52	M	70
42	C	46	50	F	100
43	C	30	65	F	80
44	C	23	58	M	90
45	C	60	50	M	100
46	C	25	65	F	95
47	C	60	45	F	120
48	C	22	56	M	90
49	C	28	57	M	90
50	C	57	65	F	140
51	C	38	58	M	110
52	C	45	60	F	100
53	C	58	55	F	130
54	C	32	52	M	95
55	C	55	48	M	150
56	C	40	62	F	80
57	C	28	60	M	80
58	C	26	46	F	120
59	C	55	54	M	100
60	C	26	65	m	140

S.No	GROUP	INTRA OPERATIVE PULSE RATE(BEATS PER MINUTE)									
		0 min	5 Min	10 min	15 min	30 min	45 min	60 min	90 min	120 min	150 min
1	A	88	88	89	86	89	91	86	88	94	90
2	A	88	90	90	88	86	82	88	76	76	77
3	A	80	88	90	86	87	90	92	84	76	84
4	A	88	80	84	89	85	84	76	87	84	85
5	A	82	78	72	71	68	62	58	55	56	62
6	A	84	86	88	96	91	93	94	85	86	89
7	A	82	84	87	78	73	73	70	74	73	73
8	A	86	91	82	78	73	68	68	86	80	84
9	A	82	86	96	90	90	88	86	80	88	76
10	A	86	89	91	91	87	86	78	76	78	76
11	A	98	91	97	90	88	86	86	90	88	86
12	A	92	97	99	96	92	89	85	84	91	97
13	A	84	99	89	87	78	76	75	82	80	70
14	A	90	78	80	88	86	78	82	84	82	78
15	A	80	78	80	85	89	80	90	81	81	87
16	A	106	102	106	100	98	97	97	96	90	92
17	A	78	76	89	78	76	72	74	76	76	74
18	A	73	93	90	89	86	82	80	78	74	72
19	A	89	89	90	94	92	90	88	86	84	82
20	A	81	87	93	97	92	96	90	88	86	85
21	B	88	88	89	86	89	91	86	88	94	90
22	B	88	90	90	88	86	82	88	77	77	76
23	B	88	88	90	90	80	87	90	96	84	89
24	B	80	80	84	89	85	84	76	84	85	87
25	B	84	86	87	80	82	76	72	80	86	89
26	B	82	80	72	70	56	54	55	64	66	67
27	B	86	86	88	78	73	73	70	74	70	74
28	B	82	84	82	78	73	68	68	80	86	85
29	B	86	91	96	90	88	90	92	66	70	77
30	B	82	96	91	87	91	93	92	85	84	88
31	B	92	90	89	88	94	90	85	87	94	98
32	B	98	98	99	99	96	92	89	98	91	97
33	B	90	94	97	87	85	89	98	87	92	90
34	B	84	80	83	87	89	93	88	94	94	85
35	B	80	78	80	85	89	84	90	80	87	87
36	B	100	104	106	98	95	99	102	98	96	94
37	B	73	74	75	70	62	54	67	65	76	81
38	B	86	89	87	90	94	88	83	88	89	81
39	B	81	87	85	88	90	94	84	79	84	85
40	B	89	78	72	71	65	56	54	62	65	67
41	C	85	89	91	87	92	95	86	88	87	89

42	C	90	94	98	99	96	98	104	88	89	94
43	C	108	110	104	114	116	122	113	102	101	104
44	C	86	86	88	86	84	80	86	85	71	79
45	C	96	98	99	110	104	99	92	96	96	92
46	C	84	87	80	91	85	94	86	82	88	93
47	C	70	68	60	52	48	63	62	73	71	75
48	C	76	78	65	58	56	56	62	64	65	67
49	C	82	94	84	82	94	96	86	94	86	85
50	C	92	92	94	93	95	98	102	87	85	87
51	C	106	106	107	106	101	104	93	96	98	96
52	C	80	85	88	89	85	83	93	91	89	89
53	C	97	94	96	105	106	102	94	95	93	90
54	C	86	80	74	65	57	51	56	62	67	68
55	C	78	84	86	85	88	83	87	86	84	87
56	C	75	77	78	85	88	94	87	80	85	91
57	C	106	109	104	107	104	101	90	94	93	99
58	C	74	72	70	65	58	47	52	54	57	59
59	C	89	82	86	95	92	97	83	91	82	85
60	C	72	77	79	81	84	80	77	89	85	80

S.No	GROUP	INTRA OPERATIVE SYSTOLIC B.P.(MM HG)									
		0 min	5 Min	10 min	15 min	30 min	45 min	60 min	90 min	120 min	150 min
1	A	130	130	130	132	126	120	114	115	110	110
2	A	126	126	126	130	126	122	114	115	114	110
3	A	140	140	140	130	130	128	96	128	124	130
4	A	120	120	120	130	126	122	116	124	118	120
5	A	140	140	138	130	130	136	126	120	116	112
6	A	120	114	118	114	108	104	120	116	112	110
7	A	130	124	124	120	120	117	120	98	96	98
8	A	124	126	120	120	112	108	106	116	114	118
9	A	136	137	132	139	138	130	117	124	119	106
10	A	110	112	108	106	114	108	106	116	109	109
11	A	120	124	118	114	118	110	108	108	110	110
12	A	120	114	110	102	114	108	106	110	116	122
13	A	116	118	116	112	116	110	114	118	114	112
14	A	128	124	128	120	110	108	102	106	110	110
15	A	116	118	118	118	120	116	114	118	114	116
16	A	120	118	110	110	112	112	108	119	108	108
17	A	110	110	120	108	106	100	108	106	110	112
18	A	108	110	108	120	126	120	118	110	108	110
19	A	136	130	128	110	106	110	120	126	108	110
20	A	130	120	118	116	110	108	106	120	126	120
21	B	110	106	108	110	120	128	120	115	110	110
22	B	130	126	126	130	126	120	114	115	110	110
23	B	140	136	140	120	126	128	130	128	126	130
24	B	110	120	108	120	106	108	116	120	118	120
25	B	130	140	136	126	126	120	126	120	128	112
26	B	126	116	106	100	99	98	95	95	100	98
27	B	130	126	120	108	108	106	120	98	96	98
28	B	124	126	120	120	112	108	106	116	114	118
29	B	136	137	132	139	138	130	117	124	119	106
30	B	126	128	108	106	110	108	116	116	109	109
31	B	120	124	118	114	118	110	108	108	110	110
32	B	108	108	110	102	110	108	106	106	116	120
33	B	120	118	116	120	116	116	114	120	114	110
34	B	130	138	120	116	110	109	100	106	108	110
35	B	116	120	120	108	110	116	106	118	110	116
36	B	130	120	106	110	110	120	110	120	108	108
37	B	118	110	96	92	90	90	88	92	95	97
38	B	110	110	106	120	120	120	108	110	108	110
39	B	126	130	128	120	106	110	108	110	108	110
40	B	128	110	118	106	110	108	110	120	120	120
41	C	120	110	110	110	100	100	100	100	100	100

42	C	120	120	120	120	120	110	120	120	130	120
43	C	120	120	120	120	120	120	120	120	110	110
44	C	120	120	110	100	100	100	100	100	110	110
45	C	130	120	120	110	110	110	110	110	100	100
46	C	140	140	140	130	130	130	130	140	140	150
47	C	110	110	110	110	110	110	110	110	90	110
48	C	130	130	130	130	130	130	120	120	110	110
49	C	120	120	120	110	110	110	110	110	100	100
50	C	120	120	120	110	110	100	100	100	100	100
51	C	140	140	130	120	120	130	130	140	140	150
52	C	130	130	120	120	120	120	120	130	120	120
53	C	110	110	100	100	100	100	110	110	110	110
54	C	140	140	130	130	130	120	110	100	110	110
55	C	110	110	110	100	100	100	100	100	110	110
56	C	120	120	120	120	120	120	110	110	90	90
57	C	120	120	120	120	120	120	110	110	90	90
58	C	120	120	120	120	110	110	100	110	110	110
59	C	100	110	110	110	110	110	100	100	90	90
60	C	110	110	110	110	100	100	90	100	100	100

S.No	GROUP	INTRA OPERATIVE DIOSTOLIC B.P.(MM HG)									
		0 min	5 Min	10 min	15 min	30 min	45 min	60 min	90 min	120 min	150 min
1	A	80	70	70	70	70	68	72	74	76	78
2	A	66	66	66	68	68	68	68	68	70	70
3	A	70	72	72	68	70	74	70	72	70	72
4	A	80	72	72	70	72	70	70	70	72	80
5	A	90	80	80	70	64	70	64	70	70	70
6	A	80	80	80	70	80	80	80	90	90	80
7	A	80	80	70	80	70	70	60	60	70	80
8	A	90	80	80	70	60	60	70	70	70	70
9	A	70	70	60	60	60	60	60	66	66	66
10	A	80	70	70	60	70	68	72	74	76	78
11	A	66	66	66	70	68	68	68	68	70	70
12	A	70	72	72	68	70	74	70	72	70	72
13	A	80	70	72	70	72	70	70	70	72	80
14	A	90	80	80	70	64	70	64	70	70	70
15	A	80	80	80	70	80	80	80	90	90	80
16	A	80	80	70	80	70	70	60	60	70	80
17	A	90	80	80	70	60	60	70	70	70	70
18	A	70	70	60	60	60	60	60	60	66	66
19	A	80	80	80	60	70	70	70	70	70	70
20	A	80	80	80	80	70	60	60	60	60	60
21	B	80	80	80	70	60	60	60	60	60	60
22	B	80	80	80	80	80	70	70	66	64	64
23	B	60	60	60	62	65	70	70	70	70	70
24	B	80	70	70	70	70	68	72	70	76	78
25	B	66	66	66	68	68	68	68	60	70	70
26	B	70	72	72	70	74	74	70	72	72	72
27	B	80	70	72	70	72	70	70	70	72	80
28	B	90	80	80	70	64	70	64	70	70	70
29	B	80	80	80	80	80	80	80	80	90	80
30	B	80	80	70	70	70	70	60	60	70	80
31	B	90	80	80	60	60	60	70	90	80	80
32	B	70	70	60	60	60	60	60	70	70	60
33	B	80	70	70	70	70	68	72	88	72	58
34	B	66	66	66	68	68	68	68	80	80	80
35	B	70	72	72	70	70	74	70	90	89	74
36	B	80	70	72	70	72	70	70	67	55	64
37	B	90	80	80	70	64	70	64	87	87	92
38	B	80	80	80	80	80	80	80	80	70	70
39	B	80	80	70	70	70	70	60	80	70	70
40	B	90	80	80	60	60	60	70	80	80	70
41	C	70	70	72	70	72	70	70	70	72	80

42	C	90	80	80	70	64	70	64	70	70	70
43	C	80	80	70	70	70	70	60	60	70	80
44	C	90	80	80	60	60	60	70	90	80	80
45	C	70	70	60	60	60	60	60	70	70	60
46	C	80	80	70	70	70	70	60	80	70	70
47	C	68	66	66	68	68	68	68	80	80	80
48	C	70	72	72	70	70	74	70	90	89	74
49	C	80	70	72	70	72	70	70	67	55	64
50	C	90	80	80	70	64	70	64	87	87	92
51	C	80	80	80	80	80	80	80	80	70	70
52	C	80	70	70	70	70	68	72	88	72	58
53	C	90	80	80	60	60	60	70	80	80	70
54	C	80	80	80	80	80	80	80	80	90	80
55	C	80	80	80	70	60	50	50	60	60	60
56	C	80	80	80	80	80	70	70	70	66	60
57	C	70	70	52	52	62	70	70	70	70	70
58	C	80	70	70	70	70	68	72	74	76	78
59	C	66	66	66	68	68	68	68	60	70	70
60	C	70	72	72	70	70	74	70	72	72	72

S.No	GROUP	INTRA OPERATIVE SPO2.(%)									
		0 min	5 Min	10 min	15 min	30 min	45 min	60 min	90 min	120 min	150 min
1	A	100	99	100	100	100	99	100	100	100	100
2	A	99	99	100	100	99	100	100	100	100	100
3	A	100	100	99	99	100	100	100	100	100	100
4	A	100	100	99	98	99	100	99	100	100	100
5	A	100	100	99	99	100	100	99	99	100	100
6	A	100	99	99	100	99	100	100	100	100	100
7	A	100	100	98	100	98	100	100	99	100	100
8	A	100	100	99	100	98	100	100	100	100	100
9	A	100	100	98	100	100	100	100	100	100	100
10	A	100	100	99	99	99	100	100	100	100	100
11	A	100	99	98	100	100	100	100	100	100	100
12	A	100	98	100	99	100	100	100	100	100	100
13	A	100	99	100	98	99	99	100	100	100	100
14	A	100	99	100	99	99	100	100	99	100	100
15	A	100	100	100	100	99	100	100	100	100	100
16	A	100	99	99	98	100	100	98	100	100	100
17	A	99	100	98	98	100	100	99	100	100	100
18	A	100	100	100	99	100	100	99	100	100	100
19	A	100	98	98	100	100	100	98	99	100	100
20	A	100	100	99	99	100	99	99	100	100	100
21	B	99	99	99	99	99	100	100	100	100	100
22	B	100	100	100	99	99	99	99	99	100	100
23	B	100	100	100	99	100	100	99	100	100	100
24	B	100	98	98	100	100	100	98	98	99	99
25	B	100	99	99	100	99	100	100	100	100	100
26	B	100	100	98	100	98	100	100	99	100	100
27	B	100	100	99	100	98	100	100	100	100	100
28	B	100	99	100	99	99	100	100	99	100	100
29	B	100	100	100	100	99	100	100	100	100	100
30	B	100	99	99	98	100	100	98	100	100	100
31	B	99	100	98	98	100	100	99	100	100	100
32	B	100	100	99	99	100	99	99	100	100	100
33	B	100	99	100	100	100	99	100	100	100	100
34	B	99	99	100	100	99	100	100	100	100	100
35	B	100	100	99	99	100	100	100	100	100	100
36	B	100	100	98	100	100	100	100	100	100	100
37	B	100	100	99	99	99	100	100	100	100	100
38	B	100	99	98	100	100	100	100	100	100	100
39	B	100	98	100	99	100	100	100	100	100	100
40	B	100	99	100	98	99	99	100	100	100	100
41	C	100	100	100	100	99	100	99	99	99	100

42	C	100	99	99	99	100	100	100	100	99	100
43	C	99	98	98	98	100	100	100	100	99	100
44	C	100	99	99	99	100	100	100	100	100	100
45	C	100	100	99	99	100	100	100	100	100	99
46	C	100	100	98	98	100	100	100	100	100	100
47	C	99	100	99	99	100	100	99	100	100	100
48	C	99	100	98	98	99	100	100	100	99	99
49	C	100	100	100	100	98	99	100	99	99	100
50	C	100	100	100	100	98	99	99	100	99	100
51	C	100	100	100	100	99	99	99	100	99	99
52	C	100	100	100	100	100	100	100	100	100	100
53	C	100	100	100	100	100	99	100	99	100	100
54	C	100	100	100	100	100	100	100	100	100	100
55	C	100	100	100	100	100	99	100	100	100	100
56	C	100	100	99	100	98	100	99	100	99	100
57	C	100	99	99	100	97	99	100	100	99	100
58	C	100	100	99	99	98	100	100	100	100	100
59	C	100	99	100	100	99	99	100	100	100	100
60	C	100	100	100	100	100	100	100	100	100	100

S.No	GROUP	POST OPERATIVE PULSE RATE(BEATS PER MINUTE)									
		0 min	15 Min	30 min	1 hr	2 hr	3 hr	4 hr	6 hr	12 hr	24 hr
1	A	88	88	89	86	89	91	86	88	94	90
2	A	88	90	90	88	86	82	88	77	77	76
3	A	88	88	90	90	88	87	90	96	84	89
4	A	80	80	84	89	85	84	76	84	85	87
5	A	84	86	87	80	82	76	72	80	86	89
6	A	80	78	80	85	89	84	90	88	87	87
7	A	100	104	106	98	95	99	102	98	96	94
8	A	73	76	75	79	82	87	84	75	76	81
9	A	86	89	87	90	94	88	83	88	89	81
10	A	81	87	85	88	90	94	84	79	84	85
11	A	89	93	97	92	94	88	93	89	88	87
12	A	88	88	90	90	88	87	90	96	84	89
13	A	80	80	84	89	85	84	76	84	85	87
14	A	84	86	87	80	82	76	72	80	86	89
15	A	82	86	88	96	91	93	84	88	86	89
16	A	86	86	88	78	73	73	70	74	76	74
17	A	89	90	90	88	90	86	87	86	88	86
18	A	86	86	86	82	82	87	87	87	88	86
19	A	78	82	80	86	88	84	86	84	84	86
20	A	72	74	74	80	82	78	78	78	82	82
21	B	102	100	100	99	100	98	96	92	94	92
22	B	72	68	66	67	67	70	71	70	72	72
23	B	80	78	80	85	89	84	90	88	87	87
24	B	100	104	106	98	95	99	102	98	96	94
25	B	73	76	75	79	82	87	84	75	76	81
26	B	74	82	80	79	79	80	85	86	85	85
27	B	75	75	73	70	72	71	76	75	75	75
28	B	67	75	74	74	75	77	75	75	76	76
29	B	85	89	91	87	92	95	86	88	87	89
30	B	90	94	98	99	96	98	104	88	89	94
31	B	108	110	104	114	116	122	113	102	101	104
32	B	86	86	88	86	84	88	86	85	71	79
33	B	96	98	99	100	104	99	92	96	96	92
34	B	84	86	87	80	82	76	72	80	86	89
35	B	82	86	88	96	91	93	84	88	86	89
36	B	74	74	76	78	78	76	76	78	78	82
37	B	90	90	86	84	84	84	82	82	84	84
38	B	85	82	86	86	84	85	85	84	83	83
39	B	80	80	84	89	85	84	76	84	85	87
40	B	86	86	88	78	73	73	70	74	76	74
41	C	86	86	88	78	73	73	70	74	76	74
42	C	89	90	90	88	90	86	87	86	88	86

43	C	86	86	86	82	82	87	87	87	88	86
44	C	78	82	80	86	88	84	86	84	84	86
45	C	72	74	74	80	82	78	78	78	82	82
46	C	88	88	89	86	89	91	86	88	94	90
47	C	88	90	90	88	86	82	88	77	77	76
48	C	88	88	90	90	88	87	90	96	84	89
49	C	80	80	84	89	85	84	76	84	85	87
50	C	86	86	88	78	73	73	70	74	76	74
51	C	89	90	90	88	90	86	87	86	88	86
52	C	86	86	86	82	82	87	87	87	88	86
53	C	78	82	80	86	88	84	86	84	84	86
54	C	72	74	74	80	82	78	78	78	82	82
55	C	88	88	90	90	88	87	90	96	84	89
56	C	80	80	84	89	85	84	76	84	85	87
57	C	84	86	87	80	82	76	72	80	86	89
58	C	82	86	88	96	91	93	84	88	86	89
59	C	74	74	76	78	78	76	76	78	78	82
60	C	90	90	86	84	84	84	82	82	84	84

S.No	GROUP	POST OPERATIVE SYSTOLIC B.P.(MM HG)									
		0 min	15 Min	30 min	1 hr	2 hr	3 hr	4 hr	6 hr	12 hr	24 hr
1	A	100	100	100	100	100	100	100	100	100	100
2	A	130	120	120	120	120	110	110	110	100	100
3	A	100	110	110	110	110	110	110	110	110	110
4	A	100	110	110	110	110	110	110	110	110	110
5	A	100	100	100	100	100	100	100	100	100	100
6	A	140	140	150	150	120	120	130	130	130	130
7	A	90	110	110	110	100	100	100	100	100	100
8	A	110	110	110	110	120	120	120	120	120	120
9	A	96	100	100	100	100	100	106	106	106	110
10	A	100	100	100	100	120	100	100	100	100	100
11	A	130	120	120	120	100	110	110	110	100	100
12	A	100	110	110	110	100	110	110	110	110	110
13	A	100	110	110	110	120	110	110	110	110	110
14	A	140	100	100	100	110	100	100	100	100	100
15	A	90	140	150	150	110	120	130	130	130	130
16	A	110	110	110	110	100	100	100	100	100	100
17	A	96	110	110	110	120	120	120	120	120	120
18	A	110	110	100	100	100	100	106	106	106	110
19	A	100	100	110	110	`120	110	110	110	110	110
20	A	110	110	96	96	100	100	100	100	106	106
21	B	110	110	110	120	120	110	110	110	100	109
22	B	110	108	108	100	110	110	110	110	110	110
23	B	110	108	108	110	110	110	110	110	110	110
24	B	100	100	100	100	100	100	100	100	100	100
25	B	130	120	120	120	120	120	130	130	130	130
26	B	100	110	110	110	100	100	100	100	100	100
27	B	100	110	110	110	120	120	120	120	120	120
28	B	100	100	100	100	100	100	106	106	106	110
29	B	140	140	150	150	110	110	110	110	110	110
30	B	90	110	110	110	100	100	100	100	106	106
31	B	120	120	100	120	120	120	120	110	120	120
32	B	110	100	120	100	100	100	100	100	100	100
33	B	110	110	100	110	120	120	120	120	120	120
34	B	100	100	108	100	100	100	100	110	100	100
35	B	120	110	100	110	100	100	100	90	100	100
36	B	110	110	110	110	110	110	110	100	110	110
37	B	110	110	110	110	110	110	110	120	110	110
38	B	100	100	110	100	100	100	100	100	100	100
39	B	120	120	130	130	130	130	130	130	130	130
40	B	100	100	100	100	100	100	100	110	100	100
41	C	110	110	110	120	120	110	110	110	105	109
42	C	110	108	108	100	110	110	110	110	110	110

43	C	110	108	108	110	110	110	110	110	110	110
44	C	100	100	100	100	100	100	100	100	100	100
45	C	130	120	120	120	120	120	130	130	130	130
46	C	110	110	110	110	110	110	110	110	100	100
47	C	100	110	110	110	120	120	120	120	120	120
48	C	100	100	100	100	100	100	106	106	106	110
49	C	140	140	150	150	110	110	110	110	110	110
50	C	90	100	100	100	100	100	100	100	106	106
51	C	120	120	100	120	120	120	120	110	110	110
52	C	110	100	120	100	100	100	100	100	100	100
53	C	110	110	100	110	120	120	120	120	120	120
54	C	100	100	108	100	100	100	100	110	100	100
55	C	120	110	100	110	100	100	100	90	100	100
56	C	110	110	110	110	110	110	110	100	110	110
57	C	110	110	110	110	110	110	110	120	110	110
58	C	100	100	110	100	100	100	100	100	100	100
59	C	120	120	130	130	130	130	130	130	130	130
60	C	100	100	100	100	100	100	100	110	100	100

S.No	GROUP	POST OPERATIVE DIASTOLIC B.P.(MM HG)									
		0 min	15 Min	30 min	1 hr	2 hr	3 hr	4 hr	6 hr	12 hr	24 hr
1	A	70	70	70	70	80	80	80	80	80	80
2	A	60	66	66	70	70	70	66	66	68	68
3	A	80	76	78	78	80	80	82	82	82	82
4	A	70	70	70	70	74	74	74	74	74	74
5	A	72	70	72	74	74	74	74	74	74	74
6	A	70	72	80	80	80	80	80	80	80	80
7	A	70	70	70	70	70	70	70	70	70	70
8	A	60	60	60	60	60	80	80	80	80	80
9	A	60	70	80	80	70	70	70	70	70	70
10	A	70	70	70	70	80	80	80	80	80	80
11	A	70	70	70	70	60	80	80	80	80	80
12	A	60	60	60	60	70	60	60	60	70	70
13	A	60	63	53	70	70	70	70	70	70	70
14	A	60	80	80	80	80	70	80	70	70	70
15	A	75	75	71	70	72	70	60	70	75	80
16	A	70	70	71	85	70	70	70	67	67	70
17	A	60	49	86	70	70	86	70	70	70	70
18	A	60	60	72	72	70	70	72	72	72	72
19	A	60	60	60	60	68	68	68	68	60	60
20	A	70	72	72	68	68	68	68	70	70	70
21	B	72	72	80	80	80	80	80	80	82	80
22	B	70	70	70	72	76	80	80	80	82	80
23	B	70	70	71	72	70	80	80	80	80	80
24	B	70	72	71	70	72	68	68	65	67	72
25	B	55	52	65	75	70	70	70	67	70	70
26	B	70	49	86	70	70	70	70	70	70	70
27	B	80	80	80	70	70	70	70	72	74	74
28	B	60	60	60	70	60	60	60	60	70	70
29	B	57	63	53	65	70	70	70	70	70	70
30	B	80	80	80	70	80	70	80	70	70	70
31	B	72	72	80	80	80	80	80	80	82	80
32	B	70	70	70	72	70	80	80	80	82	80
33	B	70	70	71	72	70	80	80	80	75	80
34	B	75	75	71	70	72	70	68	70	67	80
35	B	55	52	70	85	70	70	70	67	70	70
36	B	70	49	86	70	70	70	70	70	70	70
37	B	80	80	80	70	70	70	70	70	70	70
38	B	60	60	60	70	60	60	60	60	70	70
39	B	57	63	53	65	70	70	70	70	70	70
40	B	80	80	80	70	80	70	80	70	70	70
41	C	80	80	80	70	70	60	70	80	80	80
42	C	70	60	60	60	60	60	60	60	60	60

43	C	70	70	70	70	70	68	72	70	70	70
44	C	66	66	66	68	68	68	68	68	66	60
45	C	70	72	72	70	70	74	70	70	72	70
46	C	70	70	72	70	72	70	70	70	72	70
47	C	70	70	80	80	80	70	64	70	70	70
48	C	80	80	80	80	80	80	80	80	80	80
49	C	70	70	70	70	70	70	60	70	70	70
50	C	80	80	80	80	80	60	70	80	80	80
51	C	80	80	80	80	80	60	70	70	70	70
52	C	60	60	60	60	60	60	60	70	70	70
53	C	60	60	58	58	51	76	63	63	63	65
54	C	80	80	80	80	90	90	90	90	90	90
55	C	70	70	74	75	70	70	75	75	75	75
56	C	50	50	64	64	64	59	54	57	57	57
57	C	87	87	92	83	80	119	86	83	83	80
58	C	60	60	70	70	60	70	70	80	80	80
59	C	60	60	70	70	70	60	60	70	70	70
60	C	60	60	70	60	70	70	70	80	80	80

S.No	GROUP	sensory block onset	motor block onset	sensory blockduration	motor block duration	duration of analgesia	Sedationscore
1	A	10	20	420	500	540	2
2	A	16	18	560	510	560	2
3	A	20	22	390	350	420	3
4	A	16	20	390	420	440	2
5	A	18	22	540	580	600	3
6	A	16	18	460	540	610	4
7	A	18	22	420	360	400	4
8	A	10	15	300	270	330	3
9	A	20	22	360	390	410	5
10	A	22	24	390	370	390	2
11	A	12	15	450	420	460	3
12	A	18	20	450	440	480	1
13	A	16	24	510	360	390	2
14	A	18	22	420	410	440	3
15	A	16	22	460	520	540	4
16	A	15	18	360	400	420	5
17	A	12	20	510	540	580	3
18	A	15	18	510	440	560	2
19	A	20	22	420	380	530	3
20	A	18	24	330	330	510	3
21	B	10	15	450	360	460	4
22	B	12	14	540	510	630	5
23	B	11	16	540	540	610	6
24	B	10	15	720	510	560	3
25	B	15	20	740	710	740	3
26	B	10	15	700	710	580	2
27	B	11	13	600	620	590	5
28	B	12	15	640	700	720	4
29	B	15	18	620	640	700	6
30	B	16	20	700	710	650	3
31	B	10	12	660	690	710	4
32	B	10	12	620	610	600	2
33	B	11	16	680	600	640	4
34	B	10	16	580	420	560	3
35	B	15	20	560	590	640	3
36	B	12	15	600	630	720	4
37	B	12	14	570	560	600	3
38	B	12	15	700	720	780	5
39	B	18	22	630	620	640	4
40	B	16	20	660	640	710	3
41	C	10	14	760	680	800	4

42	C	9	18	760	700	800	4
43	C	7	10	780	720	800	4
44	C	8	10	760	740	800	3
45	C	6	12	680	700	640	6
46	C	6	15	640	620	620	6
47	C	9	10	700	700	720	4
48	C	10	12	690	640	700	5
49	C	5	10	710	680	720	5
50	C	8	15	740	760	700	5
51	C	8	18	740	740	720	4
52	C	7	10	780	720	820	3
53	C	5	15	780	700	800	5
54	C	6	8	800	800	820	5
55	C	8	12	660	640	680	6
56	C	8	10	680	710	710	6
57	C	6	10	770	720	800	3
58	C	7	12	760	700	780	6
59	C	8	12	620	700	640	4
60	C	6	10	640	720	660	5