A dissertation on

EFFECT OF LOW DOSE DEXMEDETOMIDINE OR CLONIDINE ON THE CHARACTERISTICS OF BUPIVACAINE SPINAL BLOCK

DISSERTATION SUBMITTED FOR THE DEGREE OF
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BRANCH – X (ANAESTHESIOLOGY)

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BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled **"EFFECT OF LOW DOSE DEXMEDETOMIDINE OR CLONIDINE ON THE CHARACTERISTICS OF BUPIVACAINE SPINAL BLOCK"** is bonafide record work done by **Dr. J.S. KARTHIK KAMAL** under my direct supervision and guidance, submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment of University regulation for MD, Branch X – Anaesthesiology.

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DECLARATION

I **Dr. J. S. KARTHIK KAMAL** solemnly declare that this dissertation titled **"EFFECT OF LOW DOSE DEXMEDEOMIDINE OR CLONIDINE ON THE CHARACTERISTICS OF BUPIVACAINE SPINAL BLOCK"** has been done by me under the guidance of **Dr. S. PONNAMBALA NAMASIVAYAM, M.D., D.A, DNB.** Additional Professor of Anaesthesiology. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any other University board either in India or abroad.

This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulation for the award of Doctor of Medicine degree Branch –X (Anaesthesiology) to be held in March 2011.

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Date :

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INTRODUCTION

Transurethral Resection Of Prostate (TURP) is the surgical procedure done for benign prostatic hypertrophy. The standard anaesthetic technique for TURP is subarachnoid block[1]. Lignocaine and Bupivacaine are the local anaesthetic drugs used to achieve the subarachnoid block. Adjuvants are a different pharmacological class of drugs, which are used to enhance and prolong analgesia, to lower the dose requirements and to reduce the dose dependent side effects. Many drugs have been tried as spinal adjuvants. They are Opioids, Sodium bicarbonate, Ketamine, Neostigmine, Midazolam, Clonidine and the latest inclusion is Dexmedetomidine.

Initially opioids have been the standard choice as spinal adjuvant. But since there were many side effects and complications like early and late depression of ventilation, pruritus, nausea, vomiting, urinary retention, central nervous system excitation, delayed gastric emptying and ocular dysfunction, there is an active search for an alternative ideal adjuvant which is devoid of these side effects and complications.

Preservative free Dexmedetomidine when administered into subarachnoid space produce analgesia. Activation of post synaptic alpha 2 receptors in the substantia gelatinosa of the spinal cord is the presumed mechanism by which it produces analgesia.

Dexmedetomidine at appropriate doses when used as an adjuvant with Bupivacaine in subarachnoid block seems to prolong the duration of surgical anaesthesia and postoperative analgesia. The side effects like dry mouth, hypotension, bradycardia, are not usual in this dose. The added advantages are sedation and prevent shivering.

Both Clonidine and Dexmedetomidine belong to the same group, α2 agonists. They cause sedation and analgesia, in that Dexmedetomidine produces more analgesia and sedation because of its high selectivity to α2A receptor compared to Clonidine.

This study has been taken to compare Dexmedetomidine as well as Clonidine as spinal adjuvants with Bupivacaine.

AIM OF THE STUDY

The aim of this study is to compare the onset and duration of sensory and motor block, hemodynamic changes and level of sedation following intrathecal Bupivacaine supplemented with either Dexmedetomidine or Clonidine.

ANATOMY OF SUBARACHNOID SPACE

Subarachnoid block[3] is the regional anesthesia obtained by blocking the spinal nerves. In this block the anesthetic agents are deposited in the subarachnoid space and act on the spinal nerve roots.

Applied anatomy of vertebral canal:

Vertebral canal[2, 3] extends from foramen magnum to the sacral hiatus and it protects the spinal cord.

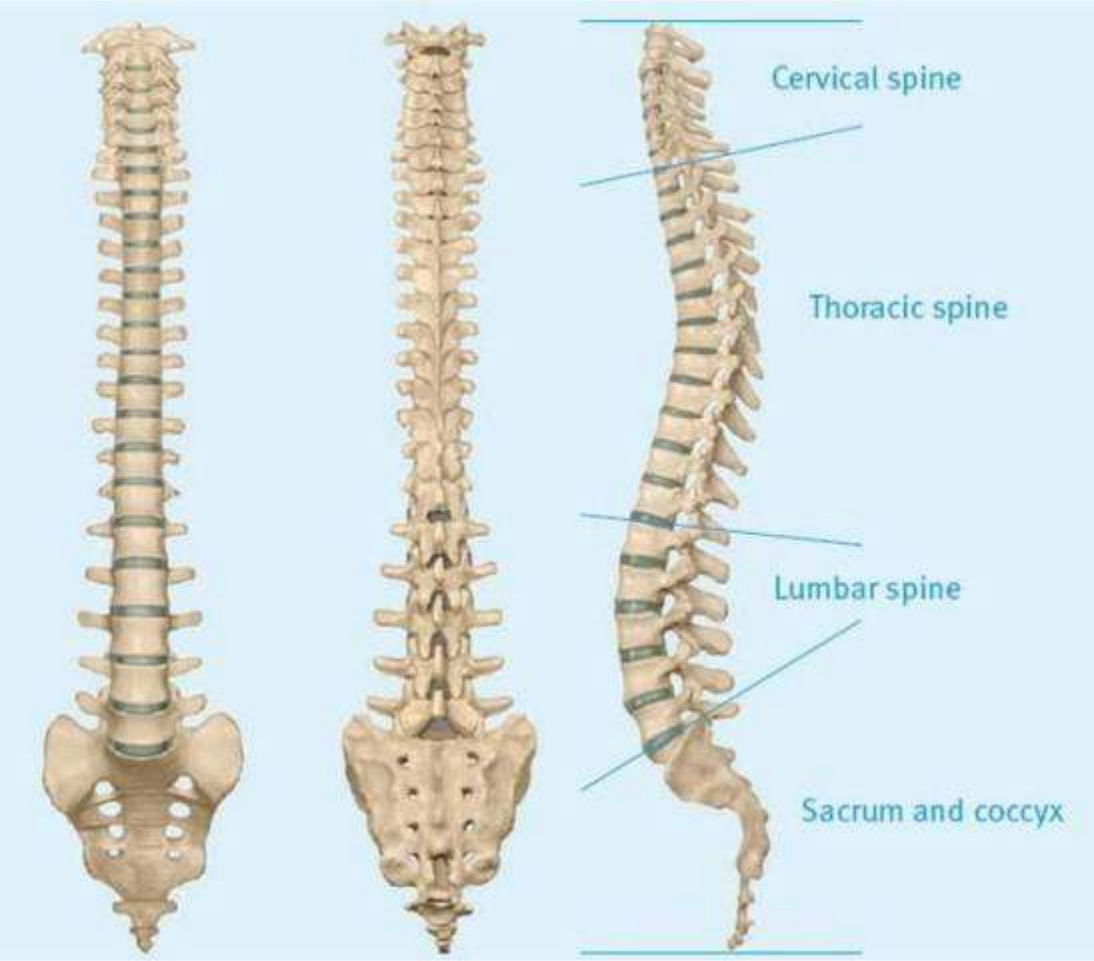
The vertebral column comprises of 33 vertebrae (7-cervical, 12-thoracic, 5-lumbar, 5-fused sacral and 4-coccygeal) and has four curves. In that, Cervical and lumbar curves are convex anteriorly and thoracic & sacral curves are convex posteriorly. The curves of the vertebral column influence the spread of the local anaesthetic in the subarachnoid space.

Each vertebra is composed of a body separated from the adjacent vertebra by intervertebral disc and formed by pedicles and lamina, which surround and protect the cord laterally and posteriorly.

The vertebral column is bound together by several ligaments. The ligaments [5, 6] are,

1. Supraspinous ligament – passes longitudinally over the tips of the spinous processes from C7 to the sacrum.
2. Interspinous ligament – connects the adjoining spinous processes together.

VERTEBRAL COLUMN



3. Ligamentum Flavum – known as yellow ligament, connects the adjacent lamina composed of yellow elastic fibers. They become progressively thicker from above downwards.
4. Posterior longitudinal ligament – It is on the posterior surface of bodies of vertebra.
5. Anterior longitudinal ligament – It runs along the front of the vertebral bodies.

There are seven projections from these vertebral (or) neural arches. They are,

a) Three muscular processes – (2-Transverse processes, 1-spinous process for the attachment of muscle and ligaments).
b) Four articular processes – Two upper & two lower which in the lumbar region prevent rotation but allow limited flexion and extension between contiguous vertebrae.

Vertebral canal is formed by these structures has deficiencies posteriorly in the midline called inter laminar foramina which enlarge during flexion making it accessible for the passage of spinal needle. The direction of spinous process determines the direction of spinal needle.

SPINAL CORD:

Spinal cord [7, 8] is the direct continuation of the medulla oblongata extending from the upper border of the atlas to the first lumber vertebra below where there is a bunch of nerve roots termed cauda equina. Spinal nerves are 31 pairs totally.

8 – Cervical

12 – Thoracic

5 – Lumbar

5 – Sacral

1 – Coccygeal

Each of the spinal nerve is composed of anterior and posterior roots which unite at the intervertebral foramina and forming a nerve trunk. Membranes covering the spinal cord from without are duramater, arachnoidmater and piamater. Dura and arachnoidmater end at S_2 level. Piamater is closely applied to the spinal cord.

An important factor that determines the spread of drug in cerebrospinal fluid is the baricity of the solution. Baricity is the density of the solution in relation to cerebrospinal fluid, the density of the solution is the mass of drug (gram) per ml of the solution.

PHYSIOLOGY OF SUBARACHNOID BLOCK

Subarachnoid block[9-17] implies the temporary interruption of nerve transmission within the subarachnoid space by injection of local anaesthetics.[9] The blockade of nerve fibers occurs in the order of Temperature, Pain, proprioceptive and then motor fibers.

FACTORS INFLUENCING BLOCK HEIGHT: [11]

a - Site of injection

b - Angulations' of needle

c - Characteristic of local anaesthetic- Baricity

d - Dose of local anaesthetic

e - Position of the patient during and after injection

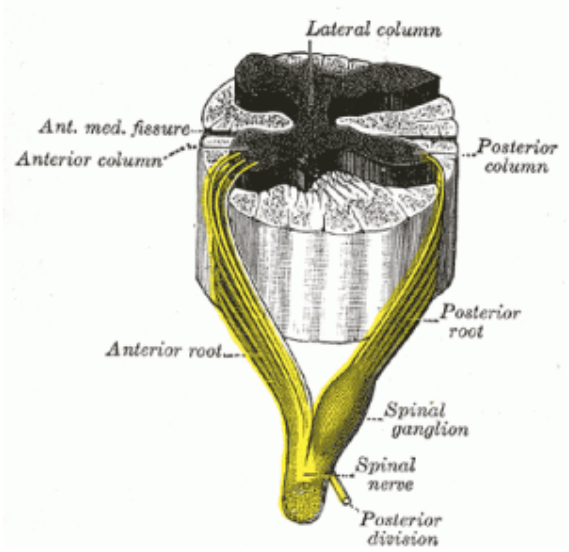
f - Anatomic configuration of spinal column.

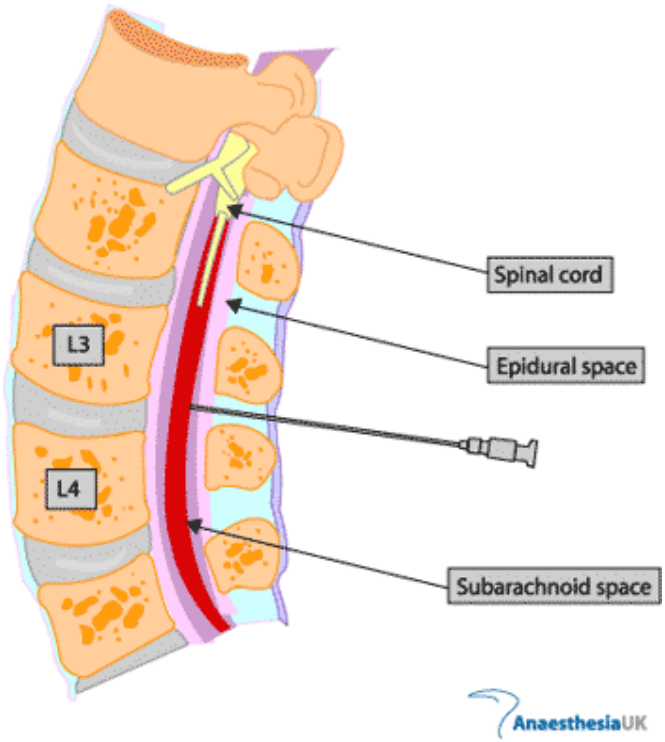
g - Patient height (at extremes)

h - Volume of cerebrospinal fluid

i - Reduced cerebrospinal fluid with increased intra abdominal pressure (e.g. Pregnancy)

SUBARACHNOID BLOCK





a) Effects on Cardio Vascular System:

Most important physiological responses[9-13] to subarachnoid block involve cardiovascular system due to combined effect of autonomic denervation, higher level of neural block, added effect of vagal innervation.

Local anaesthetics and vasoactive substances administered in small doses intrathercally leads to direct cardiovascular effect.

Level of sympathetic denervation determines the magnitude of cardiovascular system responses, but the relationship is neither predictable nor precise.

Sympathetic denervation produces venodilatation and arteriolar dilatation which produces fall in blood pressure.

Due to Bainbridge reflex, the fall in blood pressure is associated with bradycardia, blockade of cardiac sympathetic fibers from T1-T4 is an additional factor that causes bradycardia.

b) Effects on Respiratory System:

Respiration is not depressed normally. High spinal[14, 15, 16] can cause paralysis of intercostal muscles but the resting tidal volume, maximum inspiratory volume, respiratory rate, negative intrapleural pressure and also the phrenic nerve are unaffected. Hypoxia may accompany hypotension and is corrected by oxygen administration via face mask.

c) Gastro Intestinal Effect:

Preganglionic fibers from T_5-L_1 are inhibitory to gut[16, 17]. So in sympathetic blockade the small intestine contracts with relaxed sphincters and peristalsis remains normal. Handling of viscera causes discomfort and bradycardia since vagus is not blocked.

d) Hepatic and Renal Effects:

The hepatic blood flow[17] decreases and is directly proportional to the decrease in blood pressure. Renal blood flow is maintained by auto regulation and does not decrease till mean arterial pressure falls below 50mmHg.

e) Genito Urinary System:

Sphincters of bladder are not relaxed, and the ureteric tone is not greatly altered. Urinary retention occurs, Penis is often engorged. Uterine tone is unchanged in pregnancy. In the absence of hypotension spinal anaesthesia has got no effect on the progress of labour and uterine blood flow.

f) Metabolic and hormonal effect:

Spinal anaesthesia blocks the hormonal and metabolic responses[17] to nociceptive stimuli arising from the operative site. It minimizes the rise in blood sugar, coritsol, catecholamine, and renin and aldosterone release

which is associated with stress. Post operative negative nitrogen balance and secretion of antidiuretic hormone are inhibited.

g) Thermo Regulation:

Hypothermia[17] results from heat loss due to vasodilatation in the cold environment.

TRANSURETHRAL RESECTION OF PROSTATE (TURP) SURGERIES:

Among the infraumbilical surgeries transurethral resection of prostate (TURP) surgeries one of the common sugeries in elderly. TURP surgical procedure is insertion of cystoscope and resection of enlarged prostate using electrical cautary through urethra.

The usual of anaesthetic plan is subarachnoid block for TURP surgeries, because of its advantage over the general anaesthesia[18]. Advantages are following:

1. Can look for the water overload or TURP Syndrome by assessing the higher function.
2. Can assess the bladder perforation
3. Reduce the blood loss
4. Reduces the incidence of thrombosis.

PHARMACOLOGY OF DRUGS

BUPIVACAINE:

Bupivacaine[19-28] is an amide linked local anaesthetic. It is a hydrochloride salt of 1-butyl-N-(2, 6-dimethylphenyl) piperidine-2-carboxamide and is presented as a racemic mixture.

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

Properties:

Pka	-	8.1
Molecular weight	-	288
Protein binding	-	95%
Lipid solubility	-	28
Elimination half life	-	210mts
Toxic plasma concentration	-	>3μg/ml
Approximate duration of action	-	175mts

Availability:

Ampoules - 0.5% Bupivacaine hydrochloride 4cc

- 0.5% Bupivacaine hydrochloride with Dextrose (heavy) 4cc

Vials - 0.25% and 0.5% Bupivacaine hydrochloride 20cc

Dosage - Maximum dosage 3mg/kg of body weight.

Uses: [20]

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

Onset time and duration of action:

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

Pharmacokinetics:

Once injected intrathecally, it gets absorbed[21] by the nerve rootlets and produces the desired effect. It is rapidly absorbed from the site of injection, but the rate of absorption depends on the vascularity at the site.

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

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

Biotransformation:

Metabolism[22] of Bupivacaine include aromatic hydroxylation and conjugation. Only the N-dealkylated metabolite, N-desbutyl Bupivacaine has been measured in blood (or) urine after epidural (or) spinal anaesthesia. Alpha-1 acid glycoprotein is the most important plasma protein binding site of Bupivacaine and its concentration is increased by many clinical situations including post operative trauma.

Excretion:

Bupivacaine is exceted[22] through the kidney; 4-10% of the drug is excreted unchanged.

Mode of Action:

a) Site of action:

i) The spinal nerve rootlets [23, 24] have fine nerve filaments. And it has large surface area which are exposed to the local anaesthetics.

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

b) Sodium Channel blockade:

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

Pharmacodynamics:

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

Cardiovascular System:

It reduces cardiac output[25] by reducing the sympathetic tone, by slowing the heart rate and by reducing the venous return, it produces a fall in arterial blood pressure but it is relatively slow and is seldom very profound. It produces a fall in central venous pressure. It causes an increase in lower limb blood flow. It causes a reduction in incidence of deep vein thrombosis.

Respiratory System:

It relaxes bronchial smooth muscle [25]. Apnea can results from phrenic and intercostal nerve paralysis or depression of the medullary respiratory center following direct exposure to drug.

Gastro intestinal tract:

There is an increase in gastro intestinal motility and the emptying of the gastric contents is better[25].

Toxicity:

Toxicity[26 - 28] is related to plasma level of unbound drug and more likely due to an inadvertent intravenous injection. Systemic toxicity reactions primarily involve central nervous system and cardio vascular system. The blood level required to produce central nervous system toxicity is less than that required to produce circulatory collapse.

Central Nervous System Toxicity:

Early symptoms are circumoral numbness, tongue paresthesia, and dizziness. Sensory complaints include tinnitus and blurred vision. Excitatory signs (restlessness, agitation, nervousness, paranoia) often precede central nervous system depression (slurred speech, drowsiness, unconsciousness) [28]. Muscle twitching heralds the onset of tonic clonic seizures. Respiratory

arrest often follows. The excitatory reactions are the result of selective blockade of inhibitory pathways.

Cardiovascular System Toxicity:

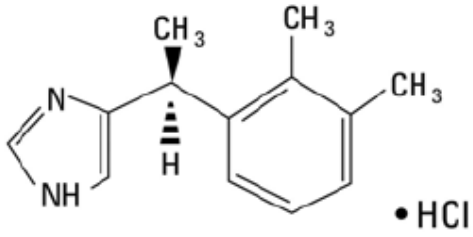
The rate of depolarization in fast conducting tissue of purkinje fibres and ventricular muscle is decreased. The rate of recovery of Bupivacaine induced block is slower than that of lignocaine. Extremely high concentration of the drug causes sinus bradycardia, hypotension, atrioventricular heart block,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

CLONIDINE HYDROCHLORIDE

Introduction:

Clonidine hydrochloride[29 - 34] is a centrally acting selective partial alpha -2 agonist introduced in early 1960s, it was during its use as a nasal decongestant that its anti- hypertensive property was found out. Subsequently more insights into the pharmacological properties have led to its use in clinical anaesthesia practice as well.

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



Clonidine Hydrochloride

The molecular weight is 266.56. Clonidine is an odourless, bitter, white, crystalline substance, soluble in alcohol and water. Clonidine improves the quality of anaesthesia, provides a more stable cardiovascular course during anaesthesia, presumably because of their sympatholytic effect reduces the dose requirement of the anaesthetic agent[31.] Clonidine may

reduce the halothane MAC by up to 50% in a dose dependent manner. Clonidine potentiates the anaesthetic action of the local anaesthetics with fewer side effects in peripheral nerve blocks and central neuraxial blockade.

Availability:

Clonidine is available as one ml ampoule, containing 150 micrograms. It should be stored below 25^{o}c.

Mechanism of action:

Clonidine is a centrally acting selective partial α2 adrenergic agonist[30] with a selectivity ratio of 220: 1 in favour of α2 receptors. The three subtypes of α2 receptors are α2a, α2b, α2c. α2a receptors mediate sedation, analgesia, and sympatholysis . α2b receptors mediate vasoconstriction and anti- shivering. The antinociception response may reflect the activation of α2c receptors. The drug is lipid soluble, penetrates the blood brain barrier to reach the hypothalamus and medulla when injected epidurally[30]. It stimulates the inhibitory α2 adrenoreceptors to reduce the central neural transmission in the spinal neurons. Inhibition of substance- P release is believed to be involved in the analgesic effect.

The α2 adrenoreceptors are located on the afferent terminals of both peripheral and spinal neurons in the superficial laminae of the spinal cord and within several brain stem nuclei implicated in analgesia[30]. The

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

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

Clonidine affects the blood pressure[30, 32] in a complex fashion after neuraxial or systemic administration because of opposing action at multiple sites. In the nucleus tractus solitarius and locus ceruleus of the brain stem, activation of post- synaptic α2 adrenoreceptors reduces sympathetic drive. It also activates nor-adrenergic imidazoline preferring binding sites in the lateral reticular nucleus producing hypotension and anti- arrythmogenic action. In the periphery it acts on pre-synaptic α2 adrenoreceptors at sympathetic terminals reduces the release of nor-epinephrine causing vasorelaxation and reduced chronotropic drive. The brainstem and the peripheral effects of α2 adrenoreceptor stimulation are counterbalanced by

the direct peripheral vasoconstriction through its action on α2 adrenoreceptors from the circulating concentrations of Clonidine.

Sedation[31] is a desired property. Clonidine produces a dose dependent sedation at the dose of 50 μg or more dose acts in less than 20 minutes regardless of the route of administration.

Clonidine doesn't induce profound respiratory depression even after massive dose. It does not potentiate respiratory depression from Opioids.

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

Pharmacokinetics:

Clonidine is well absorbed orally and is nearly 100% bio available and reaches peak plasma concentration within 60 to 90 minutes. The mean half life of the drug in plasma is about 9 to 12 hours, with approximately 50% metabolized[34] in the liver whereas is it is excreted in an unchanged form by the kidney, and its half- life can dramatically increase in the presence of impaired renal function.

A transdermal delivery system is available in which the drug will be released at constant rate for about a week. Three or four days are required to achieve steady state concentration.

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

300 micrograms intravenously over 10 min produces:

Distribution t ½	:	11 ± 9 minutes.
Elimination t½	:	9 ± 2 hour, 41 hours in severe Renal dysfunction.
Volume of distribution	:	2.1 ± 0.4 l/kg
Plasma protein binding	:	20-40 % in vitro.
Metabolism	:	minor pathways with the major metabolite – p - hydroxyClonidine.

Excretion:

70% of the dose is mainly excreted in the form of unchanged in urine. So, the elimination t1/2 of Clonidine varies as a function of Creatinine clearance. In subjects undergoing hemodialysis only 5% of the body Clonidine store is removed.

Dosage Regimen;

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

Precautions:

1. In patients with renal insufficiency, lower dose is needed.
2. Sudden withdrawal of prolonged continuous epidural infusion produces hypertensive crisis[31]. So it should be gradually discontinued over 2 to 4 days.
3. Use with caution in patients with cerebrovascular or coronary insufficiency.
4. If a patient with beta blocker is on continuous epidural therapy, beta blocker should be withdrawn several days before discontinuation of epidural Clonidine.
5. Intrathecal / epidural Clonidine often causes bradycardia. If symptomatic, it can be treated with inj. Atropine.

Contraindications:

1. Known hypersensitivity[33] to Clonidine or components of the product.
2. In patients with bradyarrhythmia or AV block.
3. Patients with severe cardiovascular disease
4. Patients with cardiovascular / hemodynamic instability.

Interactions:

1. Clonidine may potentiate the CNS- depressive effect of alcohol, barbiturates or other sedative drugs.
2. The hypotensive effects are potentiated by narcotics.
3. Tricyclic antidepressants antagonize the hypotensive effects of Clonidine.
4. Concominttent administration of Beta Blocker, Digoxin, can cause bradyarrythmias.
6. Epidural Clonidine may prolong the duration of pharmacologic effects of epidural local anaesthetics, Opioids, Neostigmine and other drugs.

USES:

1. **Preanaesthetic Medication:**

   In oral Clonidine Preanaesthetic medication (5 μg/kg), it (a) blunts reflex tachycardia associated with direct laryngoscopy for intubation of trachea, (b) decrease plasma catecholamine level, and (c) dramatically decrease anaesthetic requirements for inhaled and injected drugs. Clonidine also attenuates the rise in intraocular pressure associates with laryngoscopy and intubation.

2. **Epidural block**: Clonidine as a sole agent or in combination with Opioids or local anaesthetics provides excellent analgesia in labour analgesia. Epidural Clonidine is also indicated for the treatment intractable pain, which is unresponsive to maximum dose of oral or epidural opioid, as in patients with reflex sympathetic dystrophy, neuropathic pain.

3. **Spinal Anaesthesia:** Clonidine combined with local anaesthetics improves the quality and duration of the block, minimize the tourniquet pain during lower limb surgery, and prevents shivering.

4. **Caudal Anaesthesia:** Clonidine combined with local anaesthetics increases the duration of anaesthesia and analgesia by 2 or 3 times without hemodynamic side effects. Dose 2-3 μg/kg

5. **Peripheral Nerve Blocks:** Clonidine prolongs the duration of anaesthesia and analgesia with local anaesthetics by two times in a dose of 75 to150 micro grams.
9. Clonidine is used in the treatment of hypertensive crises
10. Diagnosis of pheochromocytoma- Clonidine, 0.3 mg will decrease the plasma concentrations of catecholamine in normal patients but not in the presence of pheochromocytoma.
11. Treatment of shivering- Administration of Clonidine, 75 μg I.V. stops shivering by inhibiting thermoregulatory control.
12. Treatment of opioid and alcohol withdrawal syndrome

Side Effects:

1. The most common side effects are sedation and xerostomia.
2. Cardiovascular complaints are bradycardia, hypotension, and ECG abnormalities like sinus node arrest, junctional bradycardia, and high degree AV block and arrhythmia are reported rarely. Occasionally require treatment of bradycardia with I.V anticholinergics. Orthostatic hypotension occurs rarely.
3. Rebound hypertension- in abrupt discontinuation of Clonidine can result in rebound hypertension as soon as 8 hours and as late as 36

hours after the last dose. Symptoms of nervousness, diaphoresis, headache, abdominal pain, and tachycardia often precede the actual increase in systemic blood pressure. Labetalol is useful in treatment of rebound hypertension.

4. Skin rashes are occurs frequently.

Over dosage and treatment:

There is no specific antidote for Clonidine over dosage. Supportive measures like atropine, ephedrine, and I.V. fluids are enough.

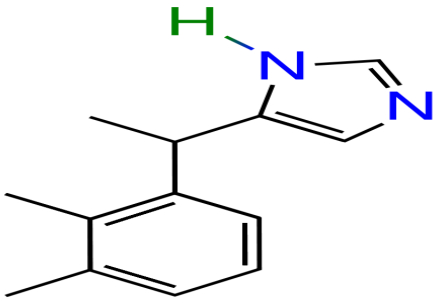
Yohimbine partially reverses the analgesia and sedation. But it will not reverse the blood pressure and heart rate changes produced by the epidural Clonidine.

DEXMEDETOMIDINE HYDROCHLORIDE:

Introduction:

Clonidine was initially introduced as antihypertensive. That is the most commonly used alpha 2 agonist by anaesthesiologists. Dexmedetomidine[33-49] is the most recent agent in this group approved by FDA in 1999 for use in humans for analgesia and sedation.

Dexmedetomidine hydrochloride[33] injection is a sterile, nonpyrogenic solution suitable for intravenous infusion following dilution. Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2, 3-dimethylphenyl) ethyl]-1H-imidazole monohydrochloride. Dexmedetomidine hydrochloride has a molecular weight of 236.7 and the empirical formula is $C_{13}H_{16}N_2$• HCl.



Dexmedetomidine Hydrochloride

Dexmedetomidine hydrochloride[34, 35] is a white or almost white powder that is freely soluble in water and has a pKa of 7.1. Its partition coefficient in-octanol: water at pH 7.4 is 2.89. Dexmedetomidine

hydrochloride is supplied as a clear, colorless, isotonic solution with a pH of 4.5 to 7.0.

Availability:

Each milliliter contains 100 μg of Dexmedetomidine and 9 mg of sodium chloride in water. The solution is preservative-free and contains no additives or chemical stabilizers.

Mechanism of action:

The mechanism of action[34] of Dexmedetomidine differs from Clonidine as it posses selective alpha 2-adrenoceptor agonism especially for the 2A subtype of this receptor, which causes it to be a much more effective sedative and analgesic agent than Clonidine. It stimulates the inhibitory α2 adrenoreceptors to reduce the central neural transmission in the spinal neurons. Inhibition of substance- P release is believed to be involved in the analgesic effect.

The majority of patients receiving Dexmedetomidine were effectively sedated yet were easily arousable, a unique feature not observed with other sedatives[34].

Dexmedetomidine[36, 37] does not appear to have any direct effects on the heart. A biphasic cardiovascular response has been described after the administration of Dexmedetomidine. The bolus of 1 mcg/kg

Dexmedetomidine initially results in a transient increase of the blood pressure and a reflex fall in heart rate, especially in younger, healthy patients. Stimulation of alpha β-2-adrenoceptor in vascular smooth muscle seems to be responsible for the initial rise in the blood pressure, which can be attenuated by a slow infusion.

The initial response lasts for 5 to 10 minutes and is followed by a slight decrease in blood pressure due to the inhibition of the central sympathetic outflow. The presynaptic[38,39] alpha 2-adrenoceptors are also stimulated decreasing the nor epinephrine release resulting in fall in blood pressure & heart rate. These effects may also be observed in the postoperative period, and can be easily managed with atropine, ephedrine and volume infusion.

Pharmacokinetics:

Dexmedetomidine undergoes almost complete hydroxylation through direct glucuronidation and cytochrome P450 metabolism in liver[40, 41].

Metabolites are excreted in the urine (about 95%) and in the feces (4%). The elimination half-life is approximately 2 hours.

It may be necessary to decrease the dose in patients with hepatic failure, since hepatic failure will lower rates of metabolism of the active drug. In cases of renal failure, the metabolites may accumulate, and the effects of metabolites have not yet been studied.

The average protein binding of Dexmedetomidine is 94%, with negligible protein binding displacement by Fentanyl, Ketorolac, Theophylline, Digoxin, and Lidocaine, drugs commonly used during anesthesia and in the ICU.

Dose:

The doses should be titrated to the desired clinical effect. For adult patients, Dexmedetomidine is generally initiated with a loading infusion of 1 mcg/kg over 10 minutes, followed by a maintenance infusion of between 0.4 to 0.7 μg/ kg/hr. [42]

Side Effects:

Dexmedetomidine crosses the placenta and its safety is not established in pregnancy and in children. The common adverse effects[43] of Dexmedetomidine include hypotension, hypertension, nausea, bradycardia, atrial fibrillation, hypoxia and various atrioventricular blocks. Most of these adverse effects occur during or briefly after bolus dose of the drug. Omitting or reducing the loading dose can reduce adverse effects.

Uses:

1. Use during anaesthesia[43,45,46,47] Dexmedetomidine possesses anxiolytic, sedative, analgesic, and sympatholytic properties, it might be a used for premedication, especially for patients in whom preoperative stress is undesirable.
2. Dexmedetomidine has also been found to be an effective drug for premedication before i.v regional anesthesia as it reduces patient anxiety, sympathoadrenal responses, and opioid analgesic requirements.
3. For the intraoperative period, it is used in the dose 0.4 to 0.7 µg/kg/hr. Dexmedetomidine, like Clonidine attenuates the stress-induced sympathoadrenal responses to laryngoscopy, intubation and surgery and provides good hemodynamic stability.
4. It potentiates the anaesthetic effects of all intraoperative anesthetics, regardless of method of administration (intravenous, volatile, or even regional block).
5. Dexmedetomidine administration during anaesthesia maintains hemodynamic stability, allows lower doses of anesthetics and opiates to be used, resulting in more rapid recovery from anesthesia and a reduced need for pain medication in the PACU, thereby reducing the length of stay.

6. Dexmedetomidine also provides intense analgesia during the postoperative period. The postoperative analgesic requirements were reduced by 50% in cardiac patients and the need for rescue Midazolam for sedation was diminished by 80%.
7. Dexmedetomidine seems to have few respiratory side effects and it can be continued safely during extubation, spontaneously breathing patient.
8. Like Clonidine, Dexmedetomidine is associated with a lower rate of shivering.
9. Dexmedetomidine produces a powerful antinociceptive[48] effect, mediated at the spinal level, while systemic redistribution of the drug leads to a hypnotic state with significant cardiorespiratory effects.
10. Patients who received Dexmedetomidine in the intensive care unit were observed to be arousable and alert when stimulated from sedation and quickly return to their sleep-like state.

REVIEW OF LITERATURE

1. **Kanzai et al**[49] , they compared the onset and duration of sensory block, as well as the hemodyanamic changes and level of sedation following intrathecal Bupivacaine supplemented with either Dexmedetomidine or Clonidine in transurethral resection of porostate surgeries.

   They monitored the time to reach the peak sensory and motor levels, and sensory and motor regression times. They recorded hemodynamic changes and the level of sedation. In the group where they supplemented with 3 μg Dexmedetomidine (group D) or 30 μg Clonidine (group C) had significantly faster the onset of motor block and long duration of sensory and motor block. The mean time of sensory regression to S1 segment and regression of motor block to bromage 0 were more in group D then in group C and group B(Group B Vs Group B and D $p<0.001$). The onset and regression time were not significant in group C and D. The mean arterial pressure, heart rate and level of sedation were similar in the three groups intra operatively and postoperatively. They came to conclusion that Dexmedetomidine (3μg) or Clonidine (30μg) when added to intrathecal Bupivacaine produces a similar prolongation in the duration of the motor and sensory block with preserved hemodynamic

stability and lack of sedation. Acta Anaesthesiology Scandinavia 2006: 50: 222-227

2. **Subhi M. Al-Ghanem et al**[50] they were conducted this study in 60 patients to evaluate the onset and duration of sensory and motor block as well as operative analgesia and adverse effects of Dexmedetomidine (DXM) or fentanyl given intrathecally with plain 0.5% Bupivacaine for spinal anesthesia.

   They selected pateients who underwent vaginal hysterectomy, vaginal wall repair and tension free vaginal tape were prospectively studied. Patients were randomly allocated to receive intrathecally either 10 mg isobaric Bupivacaine plus 5 μg Dexmedetomidine (group D n = 38) or 10 mg isobaric Bupivacaine plus 25 mg Fentanyl (group F n = 38), the onset time to reach peak sensory and motor level, the regression time for sensory and motor block, hemodynamic changes, and side effects were recorded. In that study they got result as follow as, patients in group D had significant longer sensory and motor block times than patients in group F. They concluded that the women undergoing vaginal reconstructive surgery under spinal analgesia, 10 mg plain Bupivacaine supplemented with 5 μg Dexmetedomidine produces prolonged motor and sensory block compared with 25 μg fentanyl. American Journal of Applied Sciences 6 (5): 882-887, 2009

3. **Ibrahim F. A. Khalifa et al**[51] they compared the Dexmedetomidine (5μ) and sufentanil(5μ) as additive with the Bupivacaine heavy for postoperative analgesia in patients undergoing inguinal hernia repair. He took two groups with 25 patients in each group. He observed the heamodyanamic changes and time to reach the peak sensory level, time to reach the peak motor level, regression time to S1 dermatome, time to regress to bromage 0 and duration of post operative pain relieve were studied. The difference in pulse rate, mean arterial pressure is insignificant between the groups intraoperatively and postoperatively. None of the patients was experienced repiratory depression, hypoxemia or sedation score >2. But the time to regression modified bromadge, and time reach S1 segment were significantly increased in Dexmedetomidine group. Time to reach peak sensory, peak motor level and duration of pain relief is statistically insignificant between two groups. And they finally concluded that 5μg of Dexmedetomidine is an attractive adjuvant to spinal Bupivacaine in surgical procedures especially in those that need long time with minimal side effects. Benha Medical Journal 2009

4. **Mustafa et al**[52]**.** in that study 60 patients were studied for the effect of Dexmedetomidine added to spinal Bupivacaine for urological procedures. They allocated patients randomly in 3 groups, each

receiving spinal 12.5mg combined with normal saline, Dexmedetomidine 5µg or Dexmedetomidine 10µg. the onset times to reach T10, the onset time to reach bromage 3 motor block, regression time to reach sensory level S1 and regression time to reach bromage 0 were recorded. The time of sensory block to reach the T10 dermatome and time to reach bromage 3 were faster in 10µ Dexmedetomidine group compare to 5µg Dexmedetomidine group. The regression time to reach S1 dermatome and the regression time to reach bromage 0 was significantly increased. And there were no significant side effects. So they concluded that Dexmedetomidine has a dose dependent effect on the onset and regression of sensory and motor block when used as an adjuvant to Bupivacaine in spinal anaesthesia. Saudi medical Journal 2009: vol 30 (3): 365-370.

5. **Dilek Memis et al**[53] designed a study to evaluate the effect of Dexmedetomidine when added to Lidocaine in IV regional anesthesia (IVRA). They investigated in the onset and duration of sensory and motor blocks, intraoperative-postoperative hemodynamic variables, and intraoperative-postoperative pain and sedation. Sensory and motor block onset and recovery times and anesthesia quality were noted. Shortened sensory and motor block onset times, prolonged sensory and motor block recovery times, and prolonged tolerance for the tourniquet were found in Dexmedetomidine group. Intrapostoperative

analgesic requirements were significantly less in Dexmedetomidine group. The time to first analgesic requirements was significantly longer in Dexmedetomidine group in the postoperative period. So they conclude that the addition of 0.5 µg/kg of Dexmedetomidine to Lidocaine for IVRA improves perioperative analgesia without causing side effects. Anesthesia Analgesia 2004; 98:835–40

6. **Stephan Strebel et al**[54] they examined the dose-response relationship of intrathecal Clonidine at small doses (≤150µg) with respect to prolonging Bupivacaine spinal anesthesia. They studied to establish the doses of intrathecal Clonidine that would produce clinically relevant prolongation of spinal anesthesia and pain relief without significant side effects. They took eighty orthopedic patients in randomly assigned into intrathecally receive isobaric 0.5% Bupivacaine 18 mg, plus saline (Group 1), Clonidine 37.5µg (Group 2), Clonidine 75µg (Group 3), and Clonidine 150µg (Group 4). They conclude that small doses of intrathecal Clonidine (≤150µg) significantly prolong the anesthetic and analgesic effects of Bupivacaine in a dose-dependent manner and that 150µg of Clonidine seems to be the preferred dose, in terms of effect versus unwarranted side effects, when prolongation of spinal anesthesia is desired. Anesthesia Analgesia 2004; 99:1231–8

7. In **Sethi et al**[55] study they used maximum dose of Clonidine 70 μg in spinal anaesthesia with 0.5% Bupivacaine. They concluded that addition of Clonidine to Bupivacaine in the dose of 1 μg.kg-1 significantly increases the duration of spinal analgesia as compared to Bupivacaine alone with clinically insignificant influence on haemodynamic parameters and level of sedation. Indian Journal of Anaesthesia 2007; 51 (5): 415-419.
8. **D. J. In Fogarty et**[56] al they had studied the anaesthetic and analgesic properties of intrathecal Clonidine and intrathecal morphine in patients undergoing total hip replacement under spinal anaesthesia. Intrathecal Clonidine prolonged the duration of spinal analgesia, but was markedly inferior to the intrathecal morphine in providing subsequent postoperative analgesia. British Journal of Anaesthesia 1993; 71: 661–664

MATERIALS AND METHODS

After getting the ethical committee approval the study was conducted in 60 patients undergoing elective **TURP surgeries**. It was a double blinded study in which patients were randomly allocated into three groups A, B and C by using the computer based randomization. After getting informed consent and explaining the procedure details to the patients, the anaesthetic technique was performed.

INCLUSION CRITERIA:

- Grade I prostatic hypertrophy with duration of surgery less than one hour
- Age 50 – 70 years.
- ASA I and II.

EXCLUSION CRITERIA :

- Patient refusal
- ASA III & IV patients
- Known case of diabetics mellitus and hypertension.
- Spinal deformity
- H/o drug allergy

PREOPERATIVE PREPARATION:

Routine preoperative assessment was done to all the patients, as for all elective surgery patients. Investigations were done prior to surgery are Blood Haemoglobin, Total Count, Differential Count, Blood Sugar, Blood Urea, Serum Creatinine, Serum Electrolytes, Chest X-Ray, Electrocardiogram And ECHO Cardiogram.

Group A

- Received Inj. 0.5% Bupivacaine 2.0 cc+

  Normal saline 0.5cc = 2.5 cc

Group B

- Received Inj. 0.5% Bupivacaine 2.0 cc +

  Inj.Clonidine (30µg) 0.5cc = 2.5 cc

Group C

- Received Inj. Bupivacaine 2.0 cc+

  Inj. Dexmedetomidine (5µg) 0.5cc=2.5 cc

PROCEDURE DETAILS:

On the day of surgery, preoperative baseline parameters like Pulse Rate, Blood Pressure, Respiratory Rate were recorded. Intravenous line started with 18 gauge intra venous cannula in right dorsum of hand. All the patients were preloaded with 500 ml of Lactated Ringer solution.

Following emergency drugs and equipments were kept ready before anaesthesia intervention.

- Boyles machine with oxygen cylinder
- Oxygen source
- Laryngoscope with various blades
- Airway in all sizes
- Suction apparatus
- Emergency drugs like ephedrine, dopamine, atropine and adrenaline
- Inj. Clonidine diluted to 2.5cc with sterile normal saline and made into 60μ/ml
- Inj. Dexmedetomidine diluted to 10cc with sterile normal saline and made into 10μ/ml
- Drug was diluted and was loaded by another person as per randomization. And this diluted drug was given to the performer in 1ml (40units) insulin syringe.

Patients were positioned in the right lateral position. With strict aseptic precautions, after infiltration of 2ml of 2% lignocaine, lumbar puncture was done with Quincke standard 25 guage spinal needle. In all patients, in L3-L4 interspinous space.

After ensuring free flow of CSF, first 0.5 ml (20units) of testing drug was injected. Following the testing drug, 2ml of 0.5% hyperbaric Bupivacaine was injected.

After the injection, patients were placed in supine position. Level of sensory and motor block was assessed. All the patients received oxygen through face mask with 5 liter per minute. After 5 minutes patients were positioned in lithotomy. Then the surgeon was asked to proceed.

The level of sensory block was assessed by pin prick sensation using 25G needle along the mid clavicular line bilaterally.

The onset and duration of motor blockade was assessed by using modified bromage scale[57]. The scale is:

0 – patient able to move the hip, knee and ankle.

1 - Patient unable to move the hip. But able to move knee and ankle.

2 - Patient unable to move the hip and knee. But able to move ankle.

3 - Patient unable to move the hip, knee and ankle

Time to peak sensory level is defined as the time to reach T 10 dermatome (the highest dermatome).

Intra operative mean arterial blood pressure (MAP) was recorded by putting blood pressure cuff in the left arm. The pulse rate (PR) and the oxygen saturation were recorded using pulse oxymeter. The parameters were recorded every 2 minutes for 10 minutes followed by every 5 minutes for first hour, then every 15 minutes for second hour and every hourly till the first rescue analgesia after spinal block post operative intensive care unit.

Hypotension is defined as decrease in systolic blood pressure by 30% from baseline or systolic blood pressure lower than 90 mmHg. Hypotension is treated with 6mg of intravenous ephedrine

Bradycardia is defined as pulse rate <50 beats/minute and it is treated with 0.3mg intravenous atropine in increments.

Level of sedation was evaluated intraoperatively and post operatively every 15 minutes for first three hours then hourly for next 8 hours by using **Ramsay sedation score :**[58]

1 – Anxious and agitated or restless or both
2 – Co-operative, oriented and calm
3 – Responsive to commands only
4 – Exhibiting brisk response to light glabellar tap or loud auditory stimulus
5 – Exhibiting a sluggish response to light glabellar tap or loud auditory stimulus
6 – Unresponsive.

Pain was assessed by the verbal rating score every 15 minutes for 3 hours then every hourly for 8 hours.

Verbal Rating Score :[59]

0 – No pain

1 – Mild pain

2 – Moderate pain

3 – Severe pain

The rescue analgesia for pain was given with inj. Diclofenac sodium 1mg/kg intramuscularly when the patient feels verbal rating score mild pain. If patients had intraoperaive and postoperaive nausea vomiting and shivering, they were recorded.

OBSERVATION AND RESULTS

In this randomized double blinded study conducted in 60 patients, the subjects were allocated in to three groups.

Group A (Bupi+Placebo)

- Inj. 0.5% Bupivacaine 2.0 cc +

  0.5 cc normal saline

Group B (Bupi+Clo)

- Inj. 0.5% Bupivacaine 2.0 cc +

  0.5 cc Clonidine (30 µg)

Group C (Bupi+Dex)

- Inj.0.5% Bupivacaine 2.0 cc+

  0.5 cc Inj. Dexmedetomidine (5µg)

Statistical Tools :

The information collected from the study was documented in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2008).**

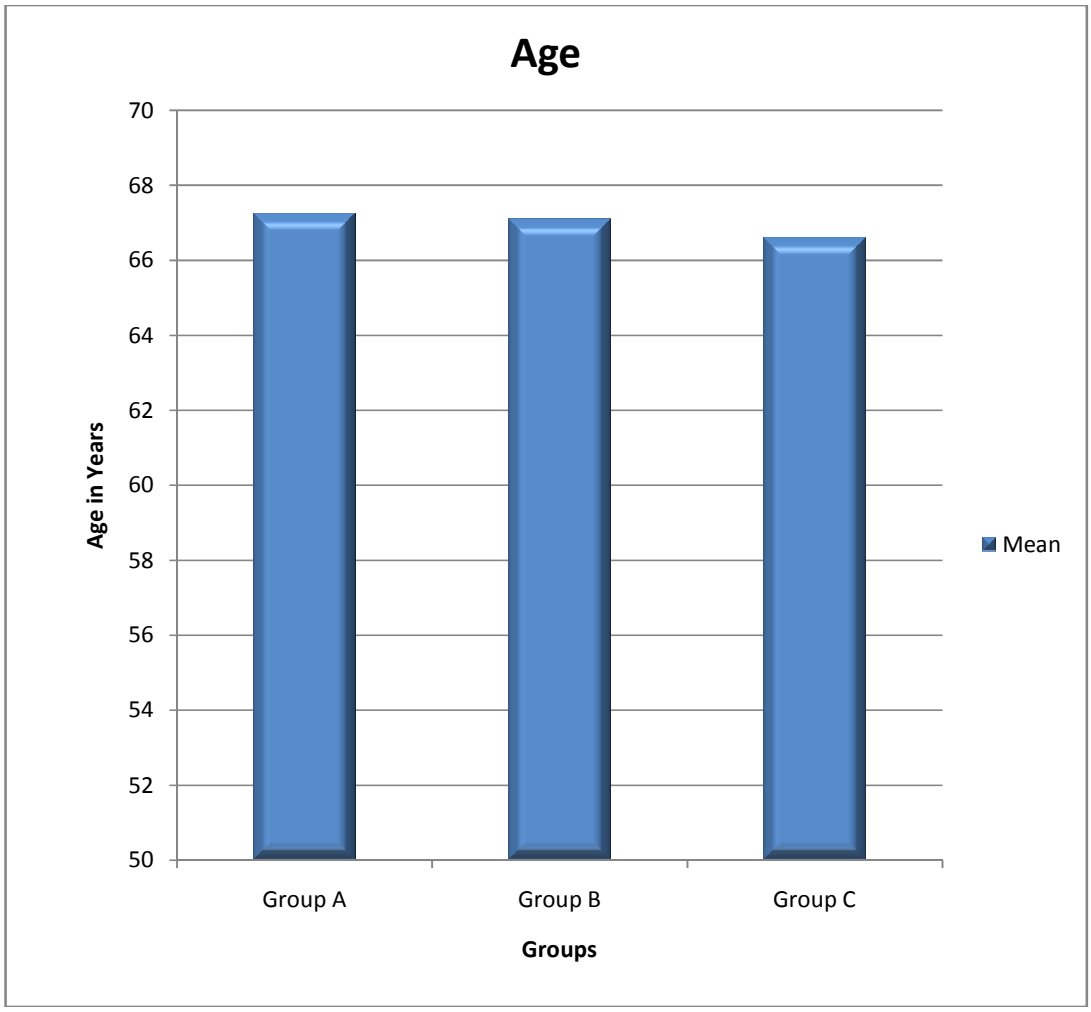
Using this software range, frequencies, percentages, means, standard deviations and ‘p’ values were calculated. ANNOVA t test was used to test the significance of difference between quantitative variables. A 'p' value of less than 0.05 is taken to denote significant relationship.

PATIENTS DEMOGRAPHICS

Table 1 : AGE DISTRIBUTION

AGE GROUP	CASES					
	Group-A (Bupi+Placebo)		Group-B (Bupi+Clo)		Group-C (Bupi+Dex)	
	NO.	%	NO.	%	NO.	%
50-60 years	8	40	7	35	8	40
61-70 years	12	60	13	65	12	60
Total	20	100	20	100	20	100
Mean SD	67.25 9.6		67.1 9.1		66.6 6.8	

GROUP A & B & C	0.969	P > 0.05 not significant
GROUP A & B	1.000	P > 0.05 not significant
GROUP B & C	0.923	P > 0.05 not significant
GROUP A & C	0.897	P > 0.05 not significant


Age
70
68
66
64
62
60
58
56
54
52
50
Age in Years
Group A
Group B
Group C
Groups
Mean

Age distribution in the Group A (Bupi+Placebo) mean age is 67.27 years and standard deviation with 9.6 years. In group B the mean age is 67.1 years and standard deviation with 9.1 years. In group C the mean is 66.6 and standard deviation with 6.8 years. **The p values for three groups are not significant, so age groups in three groups are identical.**

TABLE 2

HEIGHT AND WEIGHT

Variables	Group-A (Bupi+Placebo)		Group-B (Bupi+Clo)		Group-C (Bupi+Dex)		'p'
	mean	S.D	Mean	S.D	mean	S.D	
Height(cms)	157	7.5	161	7.8	161	8.4	0.191 not significant
Weight(kgs)	60	4.9	59	4	59	5	0.736 not significant

For Height :

GROUP A & B & C	0.191	P > 0.05 not significant
GROUP A & B	0.107	P > 0.05 not significant
GROUP B & C	1.000	P > 0.05 not significant
GROUP A & C	0.120	P > 0.05 not significant

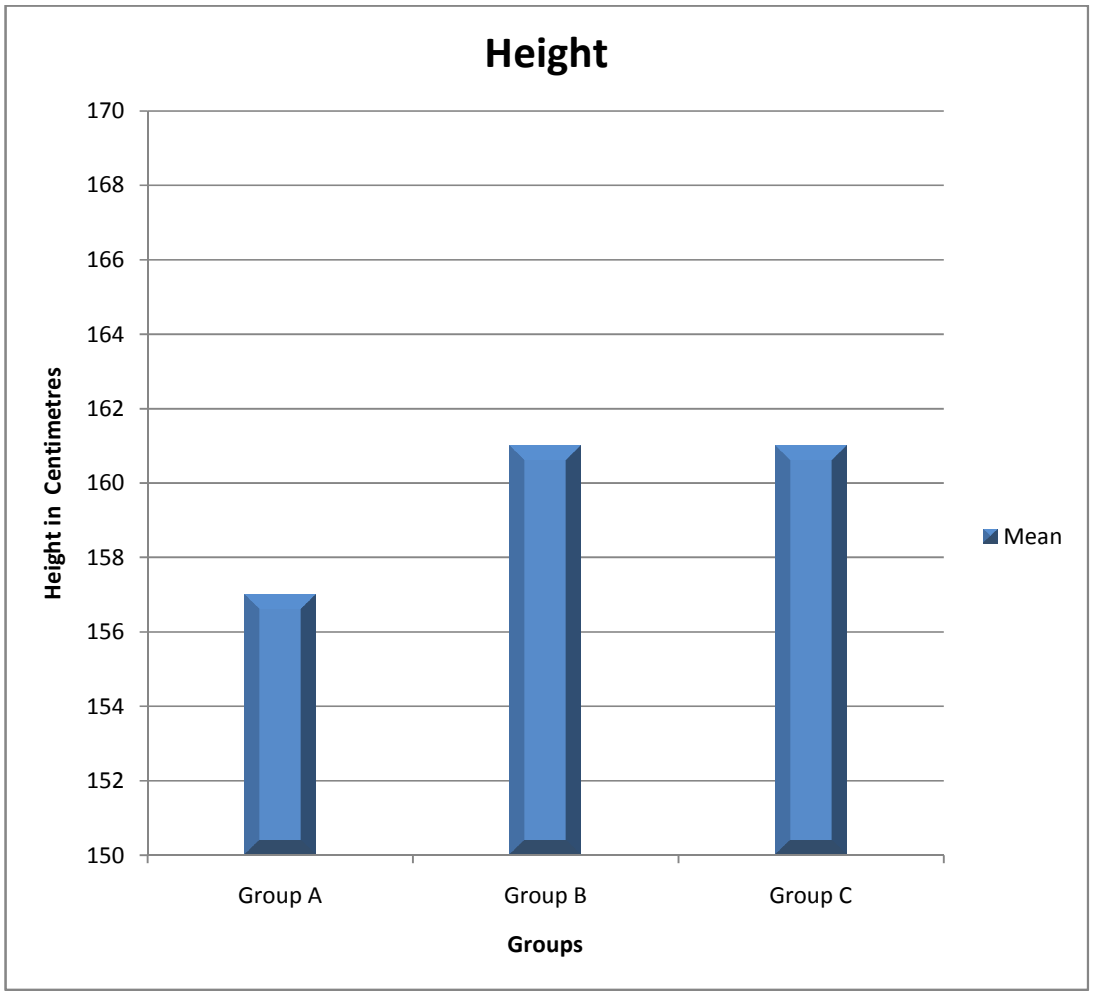
For weight:

GROUP A & B & C	**0.736**	**P > 0.05 not significant**
GROUP A & B	**0.484**	**P > 0.05 not significant**
GROUP B & C	**1.000**	**P > 0.05 not significant**
GROUP A & C	**0.527**	**P > 0.05 not significant**

In group A the mean height is 157cm with standard deviation of 7.5. In group B the mean height is 161 cm with standard deviation of 7.8. In group C the mean height is 161 cm with standard deviation of 8.4

In group A the mean weight is 60 kg with standard deviation of 4.9. In group B the mean weight is 59 kg with standard deviation of 4. In group C the mean weight is 59 kg with standard deviation of 5.

The 'p' values for the height and weight of the three groups are not significant, so the three groups are identical.


Height
170
168
166
164
162
160
158
156
154
152
150
Height in Centimetres
Group A
Group B
Group C
Groups
Mean

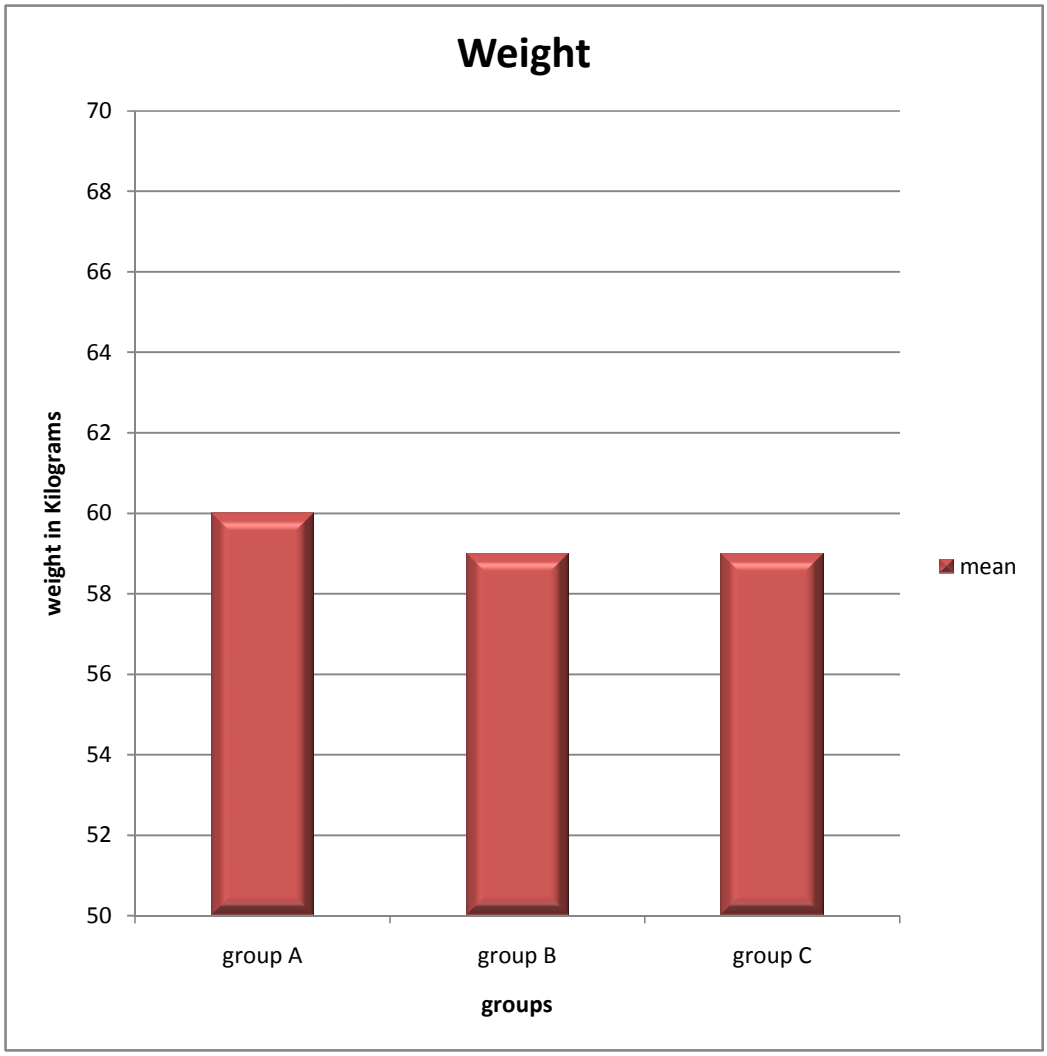

Weight
70
68
66
64
62
60
58
56
54
52
50
weight in Kilograms
group A
group B
group C
groups
mean

TABLE 3

ASA STATUS

ASA	Group-A (Bupi+Placebo)		Group-B (Bupi+Clo)		Group-C (Bupi+Dex)	
	No.	%	No.	%	No.	%
I	17	85%	16	80%	16	80%
II	3	15%	4	20%	4	20%
Total	20	100%	20	100%	20	100%

In group A 85% belongs to ASA I and 15% ASA II

In group B 80% belongs to ASA I and 20% ASA II

In group C 80% belongs to ASAI and 20% ASA I

clinically there is no significant difference in ASA distribution in all three groups.

EFFICACY OF THE THREE GROUPS
TABLE 4
TIME TO PEAK SENSORY LEVEL IN MINUTES

Group-A (Bupi+Placebo)		Group-B (Bupi+Clo)		Group-C (Bupi+Dex)	
Mean	**S.D**	**Mean**	**S.D**	**Mean**	**S.D**
4.5	**0.2**	**3.5**	**0.3**	**2.1**	**0.5**

GROUP A & B & C	**0.001**	**P < 0.05 significant**
GROUP A & B	**0.000**	**P < 0.05 significant**
GROUP B & C	**0.000**	**P < 0.05 significant**
GROUP A & C	**0.001**	**P < 0.05 significant**

(Time to teak sensory level is the time taken to reach the sensory level to T10 dermatome)

In group A mean time to reach peak sensory level is 4.5 minutes with standard deviation of 0.2 minutes. In group B mean time to reach peak sensory level is 3.5 minutes with standard deviation of 0.3 minutes. In group C mean time to reach peak sensory level is 2.1 minutes with standard deviation of 0.5 minutes. **P value shows there is significant change in the time for peak sensory level among the three groups.**

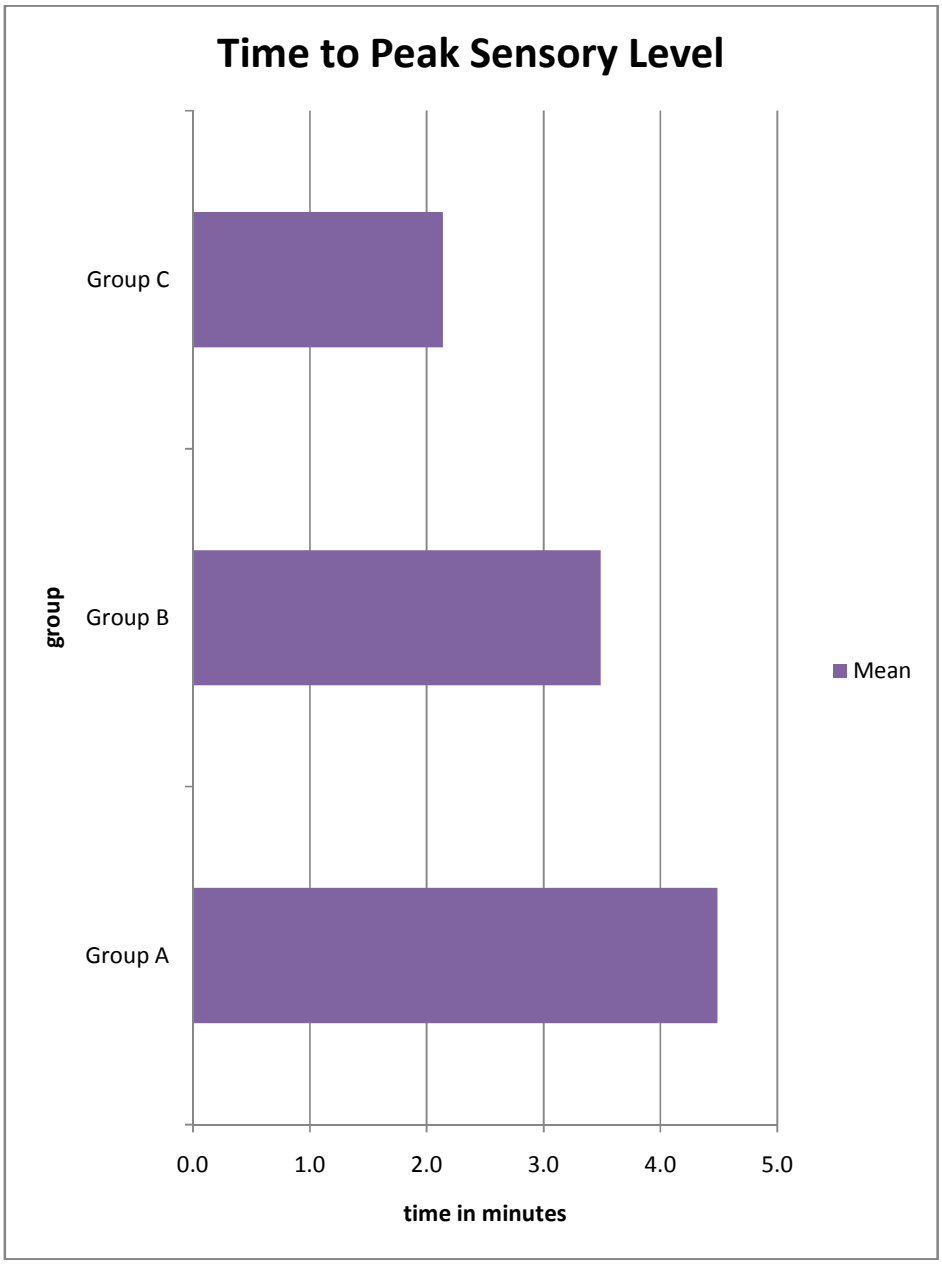

Time to Peak Sensory Level
group
Group C
Group B
Group A
0.0
1.0
2.0
3.0
4.0
5.0
time in minutes
Mean

TABLE 5 : TIME FOR MODIFIED BROMAGE 3 MOTOR BLOCK IN MINUTES

Group-A (Bupi+Placebo)		Group-B (Bupi+Clo)		Group-C (Bupi+Dex)	
Mean	**S.D**	**Mean**	**S.D**	**Mean**	**S.D**
5.3	**0.3**	**4.4**	**0.3**	**2.9**	**0.4**

GROUP A & B & C	**0.001**	**P < 0.05 significant**
GROUP A & B	**0.000**	**P < 0.05 significant**
GROUP B & C	**0.001**	**P < 0.05 significant**
GROUP A & C	**0.001**	**P < 0.05 significant**

(In modified Bromage 3 motor block, patients will be unable to move the hip, knee and ankle)

In group A mean time to reach for motor block to modified Bromage 3 is 5.3 minutes with standard deviation of 0.3 minutes. In group B mean time to reach for motor block to modified Bromage 3 is 4.4 minutes with standard deviation of 0.3 minutes. In group C mean time to reach for motor block to modified Bromage 3 is 2.9 minutes with standard deviation of 0.4 minutes.

P value shows there is significant change in the time for motor block to modified bromage 3 among the three groups.

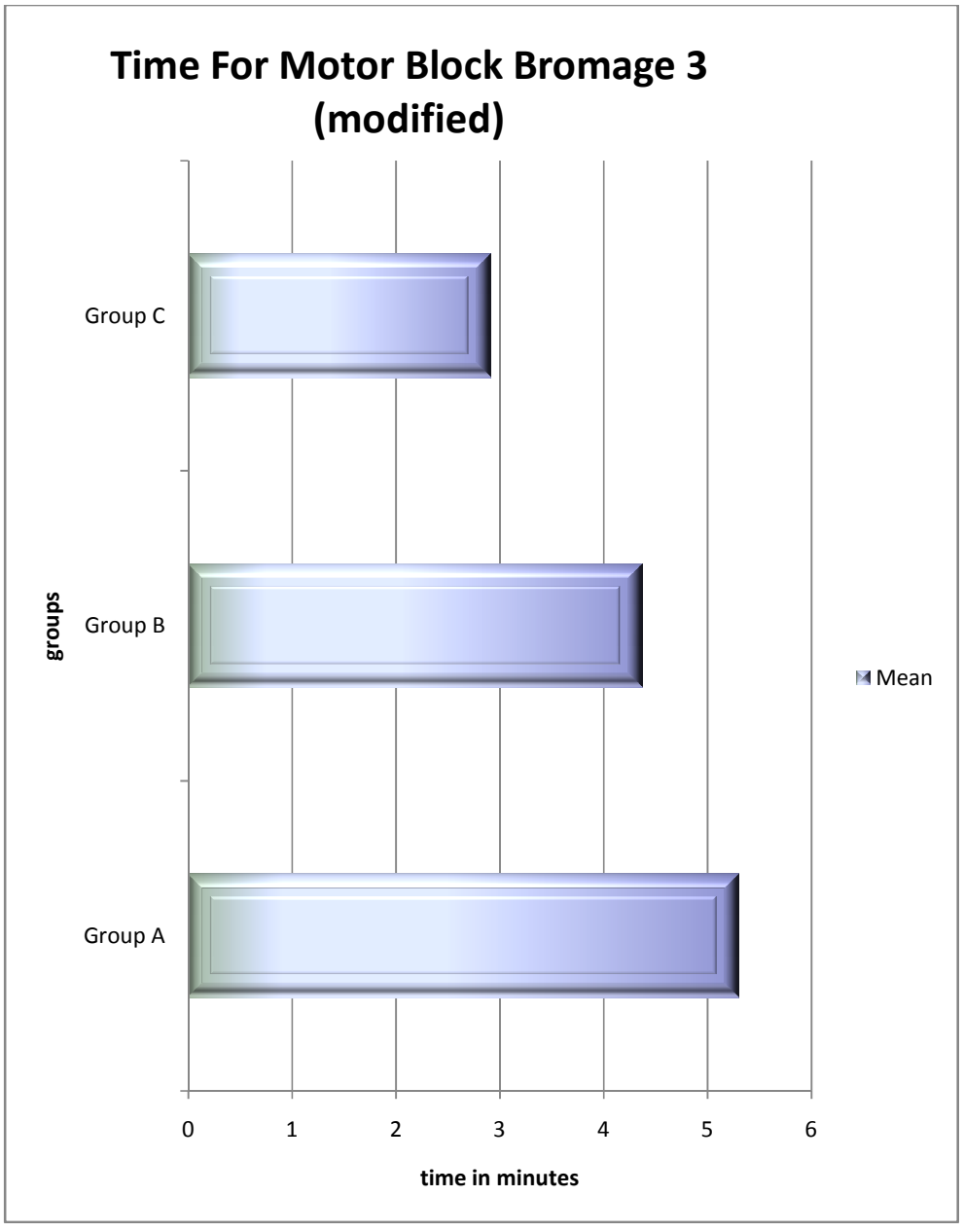

Time For Motor Block Bromage 3 (modified)
Group C
Group B
Group A
groups
0
1
2
3
4
5
6
time in minutes
Mean

TABLE 6

TIME FOR TWO SEGMENT REGRESSION IN MINUTES

Group-A (Bupi+Placebo)		Group-B (Bupi+Clo)		Group-C (Bupi+Dex)	
Mean	**S.D**	**Mean**	**S.D**	**Mean**	**S.D**
59.3	**10.3**	**91.5**	**9.6**	**105**	**9.7**

GROUP A & B & C	**0.001**	**P < 0.05 significant**
GROUP A & B	**0.001**	**P < 0.05 significant**
GROUP B & C	**0.000**	**P < 0.05 significant**
GROUP A & C	**0.001**	**P < 0.05 significant**

In group A mean time to sensory level to regress two dermatome level is 59.3 minutes with standard deviation of 10.3 minutes. In group B mean time to sensory level to regress two dermatome level is 91.5 minutes with standard deviation of 9.6 minutes. In group C mean time to sensory level to regress two dermatome level is 105 minutes with standard deviation of 9.7 minutes.

P value shows there is significant change in the time for peak sensory level among the three groups.

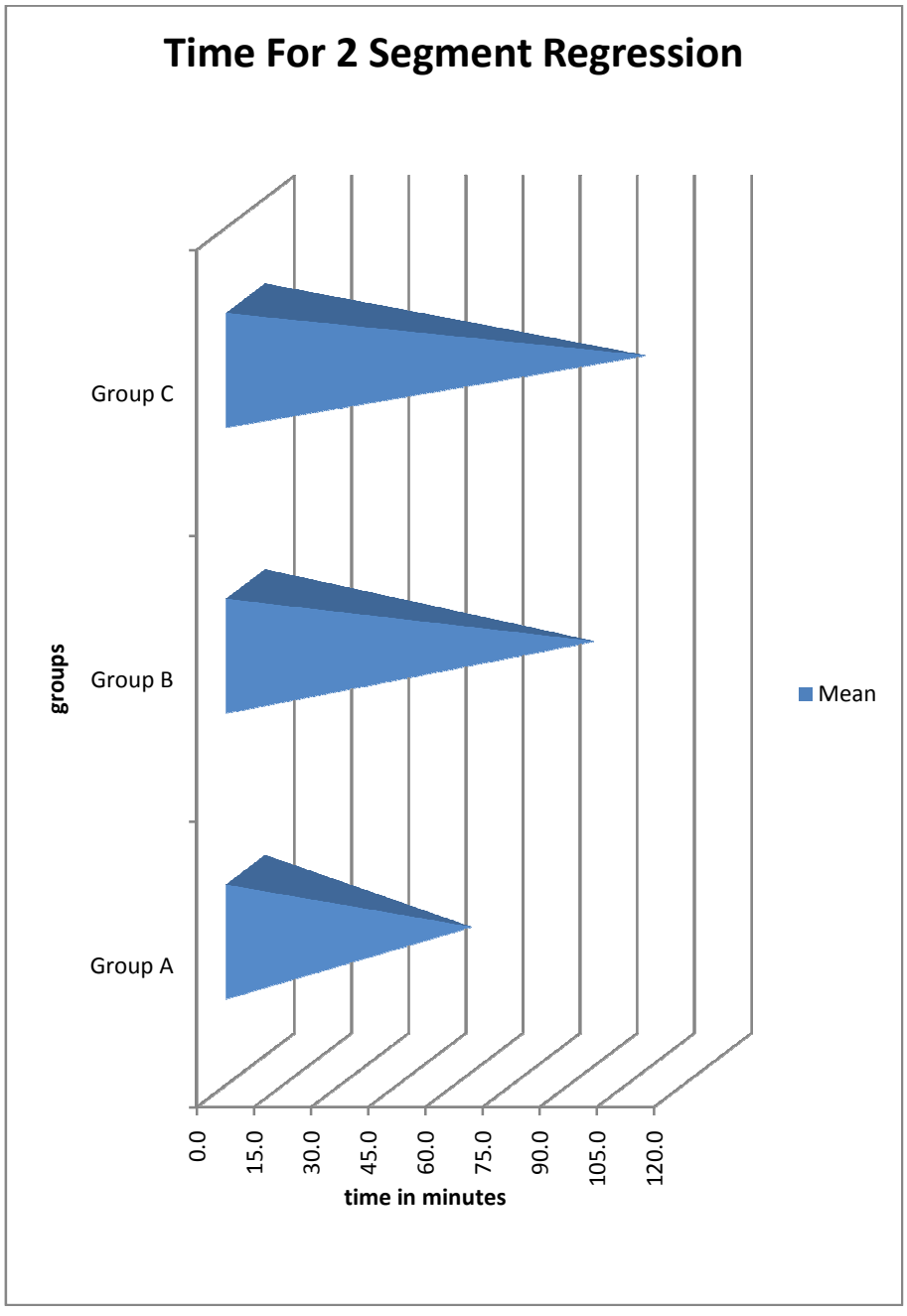

Time For 2 Segment Regression
Group C
Group B
Group A
groups
0.0
15.0
30.0
45.0
60.0
75.0
90.0
105.0
120.0
time in minutes
Mean

TABLE 7

TIME TO REGRESS MODIFIED BROMAGE 0 MOTOR BLOCK

IN MINUTES

Group-A (Bupi+Placebo)		Group-B (Bupi+Clo)		Group-C (Bupi+Dex)	
Mean	**S.D**	**Mean**	**S.D**	**Mean**	**S.D**
123	**14.3**	**150.8**	**11.4**	**175.5**	**13.0**

GROUP A & B & C	**0.001**	**P < 0.05 significant**
GROUP A & B	**0.000**	**P < 0.05 significant**
GROUP B & C	**0.001**	**P < 0.05 significant**
GROUP A & C	**0.001**	**P < 0.05 significant**

(In modified Bromage 0 patient will be able to move the hip, knee and ankle)

In group A mean time to regress motor block to modified bromage 0 level is 123 minutes with standard deviation of 14.3 minutes. In group B mean time to regress motor block to modified bromage 0 level is 150.8 minutes with standard deviation of 11.4 minutes. In group C mean time to regress motor block to modified bromage 0 level is 175.5 minutes with standard deviation of 13.0 minutes. **P value shows there is significant change in the time to motor block to regress modified bromage 0 level among the three groups.**

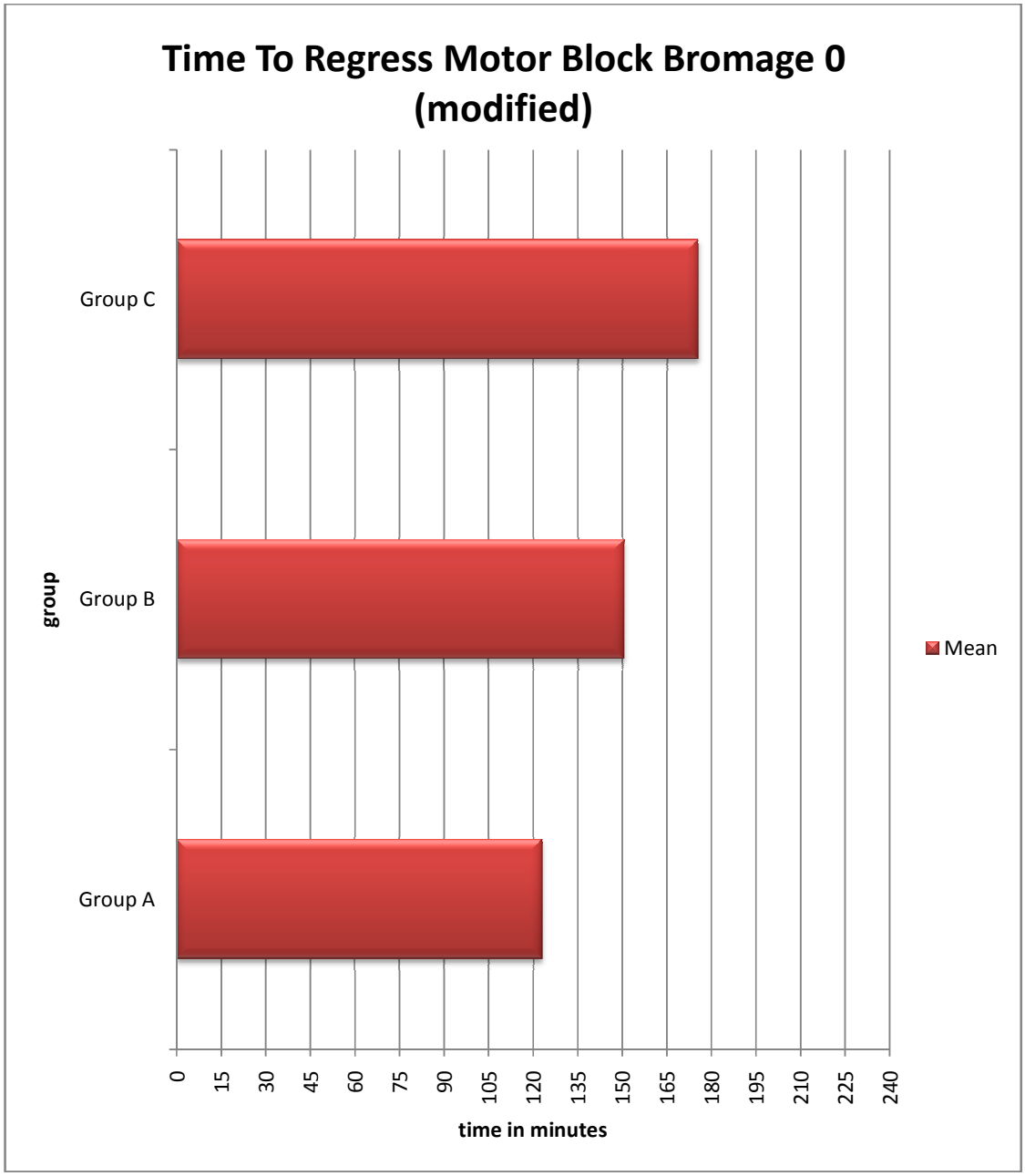

Time To Regress Motor Block Bromage 0 (modified)
group
Group C
Group B
Group A
0
15
30
45
60
75
90
105
120
135
150
165
180
195
210
225
240
time in minutes
Mean

TABLE 8

TIME TO REGRESS TO S1 LEVEL IN MINUTES

Group-A (Bupi+Placebo)		Group-B (Bupi+Clo)		Group-C (Bupi+Dex)	
Mean	**S.D**	**Mean**	**S.D**	**Mean**	**S.D**
119.3	**11.4**	**147**	**13.4**	**169.5**	**8.6**

GROUP A & B & C	**0.001**	**P < 0.05 significant**
GROUP A & B	**0.001**	**P < 0.05 significant**
GROUP B & C	**0.000**	**P < 0.05 significant**
GROUP A & C	**0.001**	**P < 0.05 significant**

In group A mean time to regress sensory level to S1 is 119.3 minutes with standard deviation of 11.4 minutes. In group B mean time to regress sensory level to S1 is 147 minutes with standard deviation of 13.4 minutes. In group C mean time to regress sensory level to S1 is 169.5 minutes with standard deviation of 8.6 minutes. **P value shows there is significant change in the time to motor block to regress bromage 0 level among the three groups.**

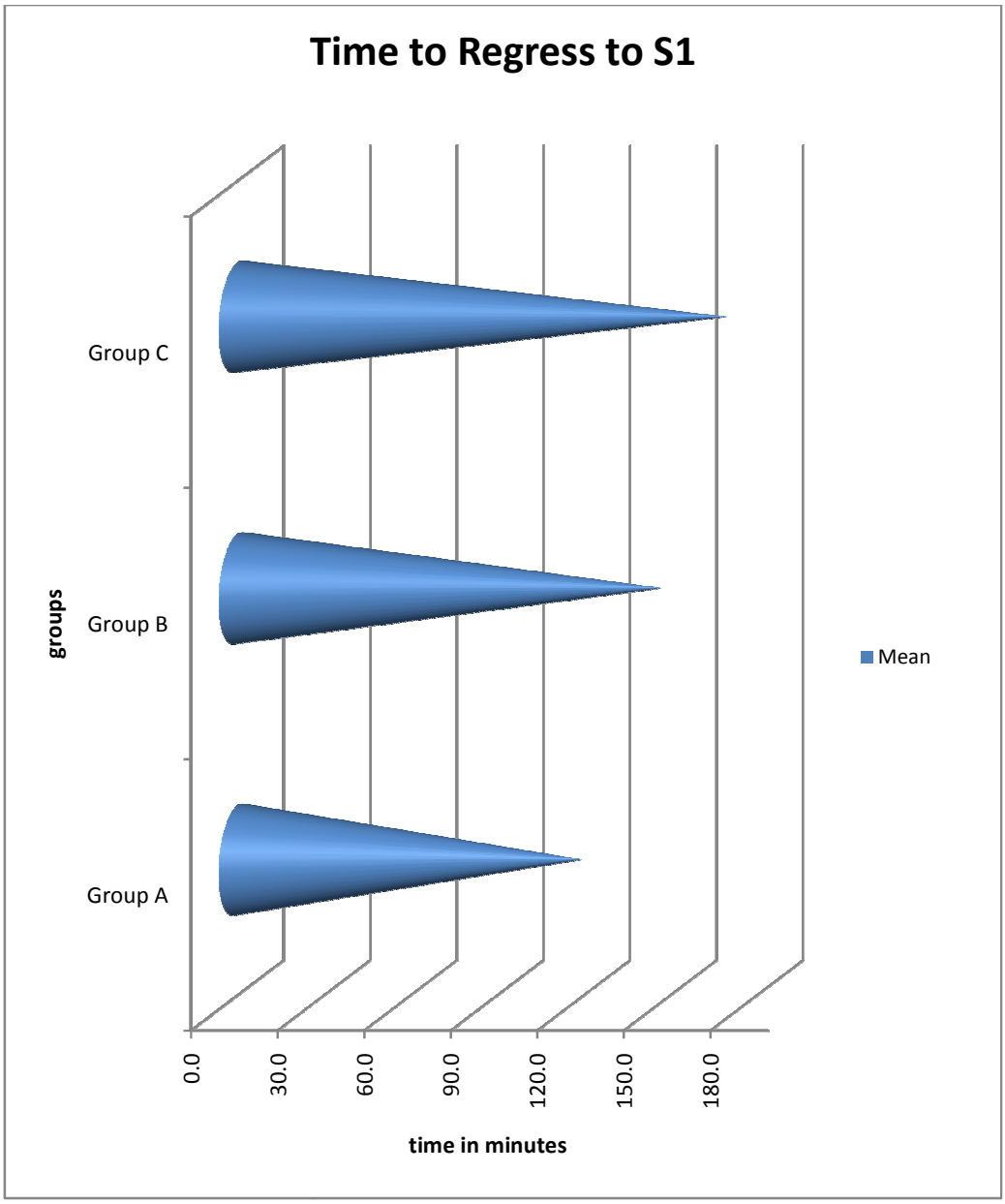

Time to Regress to S1
Group C
Group B
Group A
groups
0.0
30.0
60.0
90.0
120.0
150.0
180.0
time in minutes
Mean

TABLE 9
DURATION FOR REQUIREMENT OF RESCUE ANALGESIA

IN MINUTES

Group-A (Bupi+Placebo)		Group-B (Bupi+Clo)		Group-C (Bupi+Dex)	
Mean	**S.D**	**Mean**	**S.D**	**Mean**	**S.D**
180.5	**10.0**	**423**	**16.6**	**544.5**	**17.6**

GROUP A & B & C	**0.001**	**P < 0.05 significant**
GROUP A & B	**0.000**	**P < 0.05 significant**
GROUP B & C	**0.001**	**P < 0.05 significant**
GROUP A & C	**0.001**	**P < 0.05 significant**

In group A mean time for requirement of analgesia is 180.5 minutes with standard deviation of 10 minutes. In group B mean time for requirement of analgesia is 423 minutes with standard deviation of 16.6 minutes. In group C mean time for requirement of analgesia is 544.5 minutes with standard deviation of 17.6 minutes. **P value shows there is significant change for time for requirement of analgesia among the three groups.**

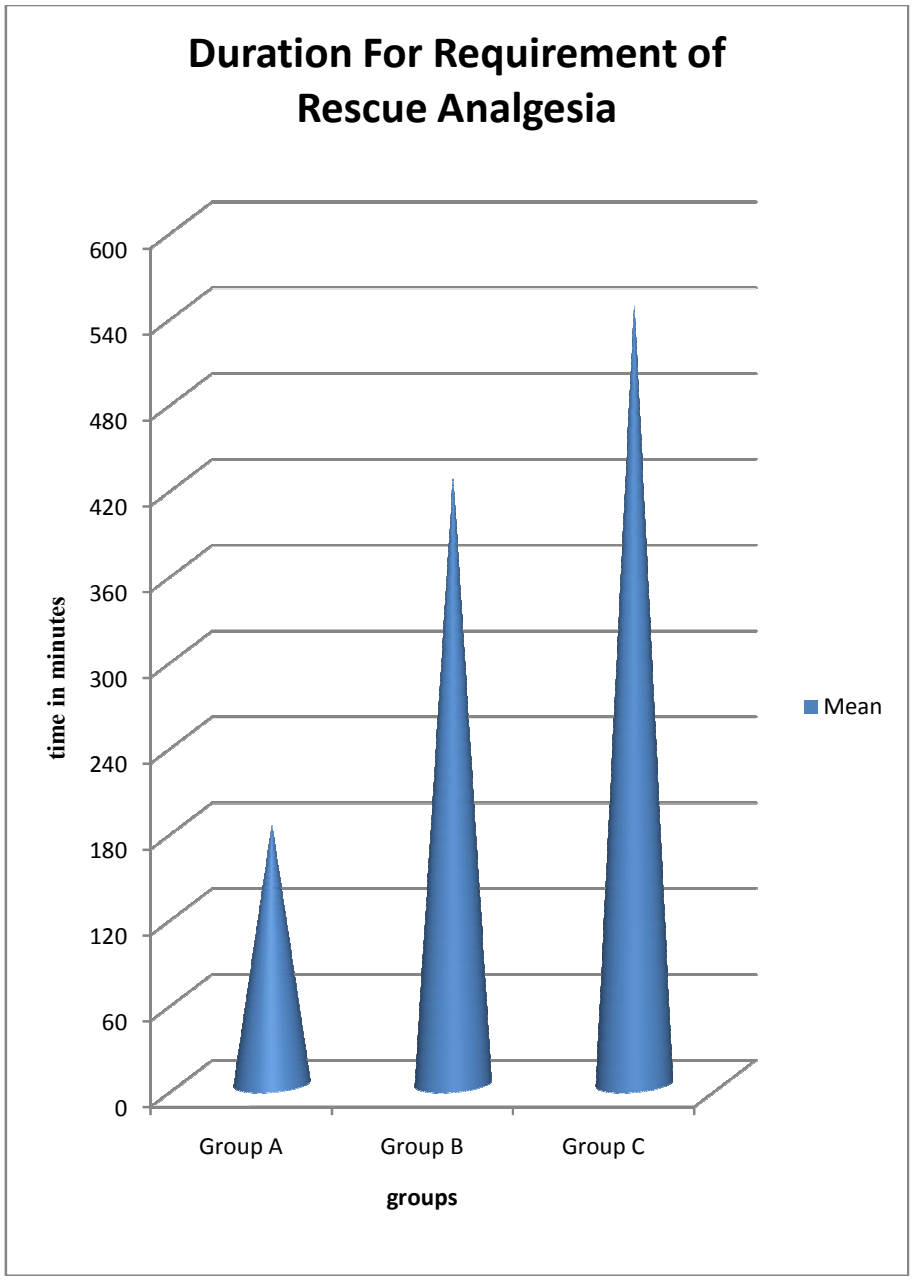

Duration For Requirement of Rescue Analgesia
600
540
480
420
360
300
240
180
120
60
0
time in minutes
Group A
Group B
Group C
groups
Mean

TABLE 10

PULSE RATE PER MINUTE

Time	Group-A (Bupi+Placebo)		Group-B (Bupi+Clo)		Group-C (Bupi+Dex)		'p' Value
	Mean	S.D.	Mean	S.D.	mean	S.D.	
Pre operative	79	19.1	80	5.1	88	4.7	0.036
2min	80	19.3	81	5.4	85	4.2	0.374
4 min	80	18.5	80	4.0	84	5.0	0.439
6 min	79	17.8	81	6.4	84	5.2	0.379
8 min	80	17.2	80	8.4	83	5.9	0.646
10 min	80	17.0	81	5.9	84	4.8	0.477
15 min	82	16.6	81	6.3	83	6.1	0.844
30 min	80	13.5	83	5.1	83	7.6	0.512
45 min	81	10.5	84	6.8	81	5.7	0.392
60 min	85	8.5	84	7.4	82	8.3	0.494
90 min	86	7.4	85	5.5	86	4.8	0.832
120 min	89	9.3	86	7.2	85	4.1	0.197
150 min	87	16.5	90	5.7	86	4.6	0.457
180 min	89	22.1	91	5.1	86	4.8	0.030
4 hours	86	7.5	85	7.1	84	4.4	0.600
5 hours	84	5.9	84	4.8	84	3.1	1.000
6 hours	85	4.9	85	7.6	85	3.7	1.000
7 hours	83	5.4	88	5.1	85	3.3	0.006
8 hours	85	4.4	84	5.8	85	3.7	0.742

In the Group A initial pulse rate was 79 beats/ minute. In the Group B initial pulse rate was 80 beats/ minute. In the Group C initial pulse rate was 88 beats/ minute.

Clinically and statistically there is no decrease in Pulse Rate in all three groups.

TABLE 11
MEAN ARTERIAL PRESSURE IN mmHg

Time	Group-A (Bupi+Placebo)		Group-B (Bupi+Clo)		Group-C (Bupi+Dex)		'p' value
	Mean	S.D.	Mean	S.D.	mean	S.D.	
Pre operative	122	27.7	115	7.1	123	7.1	0.277
2min	116	26.1	108	8	116	7.6	0.212
4 min	106	25.3	107	9.8	114	8.4	0.252
6 min	108	26.4	104	11.4	113	12.0	0.292
8 min	109	25.8	109	13.2	118	7.2	0.165
10 min	111	24.5	111	9.9	118	5.3	0.301
15 min	113	24	110	8.3	117	6.9	0.231
30 min	113	19.8	112	6.8	118	7.8	0.486
45 min	114	16.3	114	6.1	120	5.6	0.032
60 min	118	14.2	113	7.5	119	7.6	0.392
90 min	116	7.9	115	4.7	118	5.0	0.436
120 min	115	5.2	118	8.8	118	4.0	0.612
150 min	122	8.9	123	7.3	118	4.3	0.348
180 min	126	15.9	121	4.2	116	4.8	0.321
4 hours	122	10.6	119	4.7	117	4.6	0.686

5 hours	121	6.6	119	4.7	117	5.3	0.834
6 hours	122	7.9	116	3.6	117	4.6	0.808
7 hours	125	8.5	118	5.5	118	4.7	0.325
8 hours	125	8.3	122	5.5	118	4.1	0.841

In the Group A initial mean systolic blood pressure was 122mmHg. And it is reached minimum of 108mmHg at 6^{th} minute.

In the Group B initial mean systolic blood pressure was 115mmHg. And it is reached minimum of 104mmHg at 6^{th} minute.

In the Group C initial mean systolic blood pressure was 123mmHg. And it is reached minimum of 113mmHg at 6^{th} minute.

In Mean Systolic Blood Pressure, there is fall in group B in 2 to 8 th minute. But that was statistically and clinically not significant fall.

TABLE 12
RESPIRATORY RATE

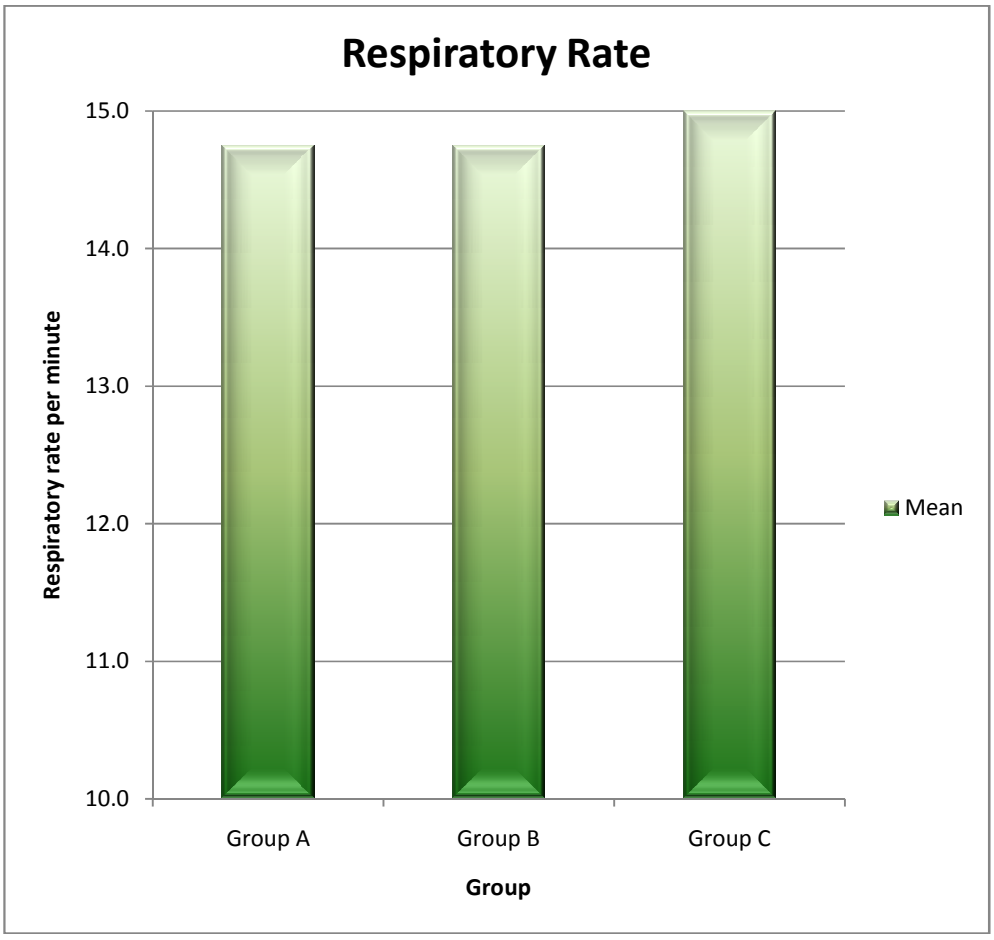
Group-A (Bupi+Placebo)		Group-B (Bupi+Clo)		Group-C (Bupi+Dex)	
Mean	**S.D**	**Mean**	**S.D**	**Mean**	**S.D**
14.8	**1.3**	**14.8**	**1.2**	**15**	**0.9**

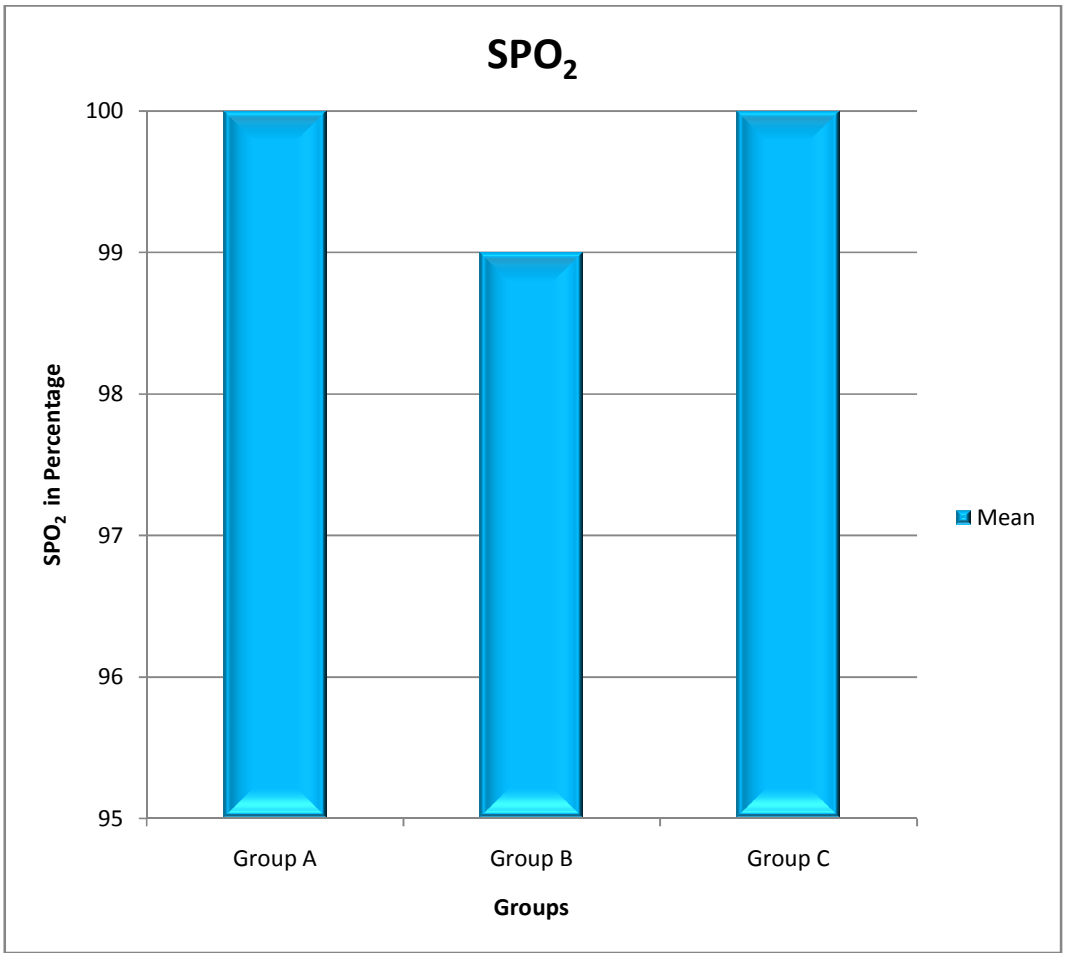
GROUP A & B & C	**0.817**	**P > 0.05 not significant**
GROUP A & B	**1.000**	**P > 0.05 not significant**
GROUP B & C	**0.627**	**P > 0.05 not significant**
GROUP A & C	**0.587**	**P > 0.05 not significant**

P values of three groups are not significant so changes in respiratory rate in the three groups are statistically insignificant.

TABLE 13
SPO_2

Group-A (Bupi+Placebo)		Group-B (Bupi+Clo)		Group-C (Bupi+Dex)	
Mean	**S.D**	**Mean**	**S.D**	**Mean**	**S.D**
100	**0.5**	**99**	**0.7**	**100**	**0.7**


Respiratory Rate
15.0
14.0
13.0
12.0
11.0
10.0
Respiratory rate per minute
Group A
Group B
Group C
Group
Mean


SPO2
100
99
98
97
96
95
SPO2 in Percentage
Group A
Group B
Group C
Groups
Mean

GROUP A & B & C	**0.625**	**P > 0.05 not significant**
GROUP A & B	**0.305**	**P > 0.05 not significant**
GROUP B & C	**0.829**	**P > 0.05 not significant**
GROUP A & C	**0.934**	**P > 0.05 not significant**

P values of three groups are not significant so changes in SPO_2 in the three groups are statistically insignificant.

TABLE 14
RAMSAY SEDATION SCORE

Ramsay Sedation Score	Group-A (Bupi+Placebo)		Group-B (Bupi+Clo)		Group-C (Bupi+Dex)	
	No.	%	No.	%	No.	%
1	-	-	-	-	-	-
2	20	100	20	100	20	100
3	-	-	-	-	-	-
4	-	-	-	-	-	-
5	-	-	-	-	-	-

In all the three groups all the patients had Ramsay sedation score of 2(Co-operative, oriented and calm). **So there is no clinically difference in all three groups.**

DISCUSSION

The newer Dexmedetomidine and Clonidine belong to the same family of α2 adrenoceptor agonists, but Dexmedetomidine has more α2A selective agonist property when compared to Clonidine.[60] So the study was performed to compare the effects of Dexmedetomidine and Clonidine with spinal Bupivacaine.

In our study, dose of Dexmedetomidine chosen was 5µg and dose of Clonidine was 30µg as additive to spinal Bupivacaine. There were very few studies done using Dexmedetomidine as an additive in spinal anaesthesia. [61-] Eisenach et al[68] had done animal studies with spinal Dexmedetomidine in the dose of 100µg. Kanzai et al[49] did an early human study with 3 µg of Dexmedetomidine and he found it is equipotent to 30µg of Clonidine (1:10 ratio) [68,69]. Subhi et al[50] chose 5µg of Dexmedetomidine as spinal additive in his studies. In both the above studies low dose of 3µg and 5µg of Dexmedetomidine were effective as an additive to spinal anaesthesia with least complication. This is the reason why we chose 5µg (low dose) Dexmedetomidine as a spinal additive.

Subhi et al[50] they had sample size of 38 people and they derived significant statistical results. Khalifa et al[51] had sample size of 25 in each group and in Mustafa et al[52] each group was allocated with 22, 21, 21 persons. They also derived significant statistic results. Kanzai et al[49] they

studied 60 subjects in three groups (n=20) and they arrived reliable statistics with that n value. So we also decided to conduct the study with sample size of 20 subjects in each group.

The results in our study showed that the supplementation of spinal Bupivacaine with either 5µg of Dexmedetomidine or 30µg of Clonidine significantly hastens the onset of sensory and motor block and also prolongs the both sensory and motor blockade when compared with spinal Bupivacaine alone in TURP surgeries. But the time to reach peak sensory and peak motor level is much shorter in Dexmedetomidine (5µg) group when compare to Clonidine (30µg) group. Kanzai et al[49] used equipotent dose of Dexmedetomidine (3 µg) and Clonidine (30 µg) as an additive to spinal Bupivacaine and he found the onset of sensory and motor blockade is faster with Clonidine when compared to Dexmedetomidine group.

Subhi et al[50] they used Dexmedetomidine and Fentanyl as an additive to spinal anaesthesia in different groups and found Fentanyl group to have more faster onset of peak sensory and motor level.

In Mustafa et al[52] they had three groups, Bupivacaine + placebo, Bupivacaine +5µg Dexmedetomidine and Bupivacaine + 10 µg Dexmedetomidine. In this study they found that 10 µg Dexmedetomidine group had the fastest onset of peak sensory and peak motor block compare with lower dose of Dexmedetomidine.

We infer from the above studies that higher the dose of Dexmedetomidine as spinal, faster the onset of peak sensory and motor blockade.

In our study when 10 mg of 0.5% Bupivacaine is added with 5µg of Dexmedetomidine it significantly prolongs the duration of sensory blockade, motor blockade and duration of post operative analgesia when compared to 30µg of Clonidine when added with 10mg of 0.5% Bupivacaine.

Similarly when 10 mg of 0.5% Bupivacaine added with 30µg of Clonidine, significantly prolongs the duration of sensory blockade, motor blockade and duration of post operative analgesia when compared to 10 mg 0.5% of Bupivacaine with placebo group.

In Kanzai et al[49], Khalifa et al[51] and Subhi et al[50s] studies, they all have used Dexmedetomidine as spinal additive. The above three studies have compared Dexmedetomidine as spinal additive to Clonidine 30µg or sufentanil 5µg or Fentanyl 25µg, and they found in common, that Dexmedetomidine prolongs the spinal anaesthesia more when compared to all other three additives mentioned above.

In Mustafa et al[52] they compared two doses of spinal Dexmedetomidine as spinal additive (5µg and 10µg). In that 10µg Dexmedetomidine group had prolonged sensory blockade, motor blockade and post operative analgesia compared to 5 µg Dexmedetomidine group.

The mechanism by which intrathecal α2 adrenoceptor agonists prolong the motor sensory block of local anaesthetics is not well understood. It may be an additive or synergistic effect secondary to a different mechanism of action of the local anaesthetic. The local anaesthetic acts by blocking the sodium channels, whereas the 2adrenoceptor agonist acts by binding to pre-synaptic C- fibers and post-synaptic dorsal horn neurons[70-74]. These antinocieptive effects explain the prolongation of the sensory block when added to spinal anaesthsia. The prolongation of the motor block of spinal anaesthetics may result from the binding of α2 adrenoceptor agonists to motor neuron in the dorsal horn[75] in the spinal cord.

Most of the clinical experience in the use of intrathecal α2 adrenoceptor agonists has been described with Clonidine[76-78]. Intrathecal Clonidine has a well established synergestic effect with local anesthectics. Studies using a combination of intrathecal Dexmedetomidine and local anaesthetics are few. In our study intrathecal Dexmedetomidine was selected based on Kanzai et al where he used 30μg and 3μg of Dexmedetomidine in intrathecal space. In Subhi et al, they used 5μg of Dexmedetomidine and 25μg of Fentanyl as spinal additive with spinal Bupivacaine. Our results showed that the sensory and motor were blocks prolonged significantly Dexmedetomidine group when compared to Clonidine group. This result is against Kanzai et al because they used 3μg of Dexmedetomidine and 30μg of Clonidine. They hypothesized that 3μg of intrathecal Dexmedetomidine

might be equipotent to 30μg of intrathecal Clonidine. Our study further supported by Subhi et al, where they had 10 mg plain Bupivacaine supplemented with 5 μg dexmetedomidine produces prolonged motor and sensory block compared with 25 μg Fentanyl. In al- Mustafa et al they had similar results in their study. In Khalifa et al they had similar results when they compared 5 μg of Dexmedetomidine and 5 μg of sufentanyl with spinal Bupivacaine.

In our patients the addition of Dexmedetomidine or Clonidine to Bupivacaine causes initial fall in the blood pressure especially in Clonidine group. But fall is not clinically significant and they did not require vasopressor intra operatively or post operatively. An Intrathecal local anaesthetic blocks the sympathetic outflow and reduces the blood pressure. The sympathetic block is usually near maximal with the doses used for spinal anaesthesia. The addition of low dose of α2 agonist to a high dose of local anaesthetics does not further affect the near maximal sympatholysis[70]. Clonidine in the dose range 37.5 to 150 μg did not cause significant decrease in blood pressure when added to 18 mg of Bupivacaine compared with Bupivacaine alone[73]. In contrast more than 150 μg of Clonidine added to a low dose of Bupivacaine (5mg) yielded a greater decrease in blood pressure than Bupivacaine alone[78-80].

In our study we did not encounter bradycardia in any of the group. But in Kanzai et al one patient in Clonidine group and three patients in

Dexmedetomidine group had bradycardia. Subhi et al encountered bradycardia in two patients in Dexmedetomidine group and 3 patients in Fentanyl group. Similarly in Khalifa et al two patients in each group (in Dexmedetomidine group and in Sufentanil group) had bradycardia.

In Mustafa et al two patients in Bupivacaine alone group had bradycardia, one patient group added 5µg as spinal additive had bradycardia. But no one had bradycardia in the third group where 10µg Dexmedetomidine added as a spinal additive. In all the above studies what we have commonly seen is the clinically insignificant incidence of bradycardia of lower doses of Dexmedetomidine.

In our study none of our patients were drowsy. All the patients were co-operative, oriented and calm. This is supported by Kanzai et al, Subhi et al, Khalifa et al and Mustafa et al. In Mustafa et al even with 10µg of Dexmedetomidine as spinal additive did not produce any sedation in patients. Intrathecally administered α2 agonists have a dose dependent sedative effect[81]. The doses of Clonidine and Dexmedetomidine selected in our study were at the lower end of dosing spectrum. This explains the lack of sedative effect in the study groups.

SUMMARY

This is a randomized double blinded study conducted in 60 patients of ASA I and II undergoing elective transurethral resection of prostate (TURP) surgeries. Patients were allocated in three groups.

Group A (Bupivacaine + sterile normal saline as placibo)

Group B (Bupivacaine + Clonindine 30μg)

Group C (Bupivacaine + Dexmedetomidine 5μg)

Parameters observed were time of onset of sensory block, time of onset of motor block, two segment regression time, duration of motor blockade, duration of sensory blockade, sedation score, duration of post operative analgesia, haemodynamic changes and side effects.

1. The post operative analgesia was significantly prolonged in group C and was 364 minutes more than the group A and 121.5 minutes more than group B.
2. The systolic blood pressure dropped during the early anaesthetic period but the fall was within the 30 percentage of basal systolic blood pressure.

3. There was no significant fall in pulse rate in all group A, group B, and group c.

4. No Sedation were observed in all three groups, but patient was comfortable, co-operative, oriented and calm.

5. Neither respiratory depression nor decrease in saturation was observed in any of the group.

CONCLUSION

(i) Adding 30µg Clonidine or 5µg Dexmedetomidine to 10mg of Bupivacaine significantly prolongs the duration of post operative analgesia when compare to Bupivacaine alone in elective transurethral resection of prostate (TURP) surgeries.

(ii) Bupivacaine with Dexmedetomidine prolongs significantly the duration of post operative analgesia when compared to Bupivacaine with Clonidine in spinal anaesthesia.

(iii) Bupivacaine when used alone or with adjuants like Clonidine (30µg) or Dexmedetomidine (5µg) does not produce any appreciable side effects.

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PROFORMA

Name : Height : Date :
Age : Sex : Weight :
I.P.No : Diagnosis :
ASA Status : Time of injection of drugs :
Group : Duration of surgery :
Time of incision: Time of finishing :

	INTRA– OPERATIVE VITALS MONITORING																
	Time interval (minutes)																
Sl. No	Parameter	Pre-op	2	4	6	8	10	15	20	25	30	35	40	45	50	55	60
1.	HR																
2.	SBP																
3.	DBP																
4.	MAP																
5.	RR																
6.	Shivering																
7.	Ramsay sedation socring																

Time of peak sensory block : Time to regression two dermatome : Time to regress S1 :

Time of peak motor block(bromage3) : Time to regress bromage 0 :

Intra–operative events :

IV fluids :

Ing. Ephedrine(6mg iv bolus) :

Ing. Atrpin(0.6mg iv bolus) :

POST–OPERATIVE MONINTORING					
Parameter	Time interval (every 15 minutes for next hour, every hour till rescue analgesia)				
1. HR 2. SBP 3. DBP 4. **Pain Score :** (Verbal Rating Scale) 0 – No Pain 1 – Mild Pain 3 – Severe Pain **5.Ramsay sedation scoring** 1 - anxious and agitated or restless, or both 2 - co-operative, oriented, and calm 3 - responsive to commands only 4 - exhibiting brisk response to light glabellar tap or loud auditory stimulus 5 - exhibiting a sluggish response to light glabellar tap or loud auditory stimulus 6 – unresponsive **6. Nausea/Vomiting** 8. **Adverse Effects:**					

POST–OPERATIVE ANALGESICS CONSUMPTION

Time of first rescue analgesic Inj. Diclofenac Sodium 1mg/kg I.M.	

S.No	IP.no	Group	Age	Sex	Height	Weight	ASA	Respiratory Rate	SPO2	Ramsay Sedaration score	Peak Sensory Level in Minutes	Peak Motor Block in Minutes	Motor Block Bromage 0 in Mintues	Time for two segmental regression in Minutes	Time to Regress S-1 in Minutes	Time for requirement of Rescue Analgesia in Minutes
1	14821	A	69	M	148	69	I	16	99	2	4.5	5	135	60	135	180
2	14949	A	62	M	156	53	I	14	100	2	4.75	5.25	120	45	105	195
3	15397	A	62	M	163	59	I	16	99	2	4.25	5	120	60	120	195
4	17762	A	68	M	148	59	I	15	100	2	4.25	5.75	135	75	120	180
5	18402	A	56	M	162	68	I	15	100	2	4.5	5	120	75	105	180
6	21057	A	62	M	168	58	II	16	100	2	4.75	5.25	120	60	105	195
7	19001	A	55	M	162	62	I	13	100	2	4.5	5	135	45	105	180
8	20521	A	58	M	158	68	I	12	99	2	4.25	5.25	105	60	120	165
9	21061	A	68	M	155	56	I	14	100	2	4.5	5.75	135	45	120	180
10	23520	A	65	M	164	58	I	15	99	2	4.75	5	120	60	135	180
11	24986	A	63	M	162	64	II	16	99	2	4.75	5	120	75	120	165
12	25593	A	58	M	168	63	I	13	100	2	4.5	5	105	60	120	180
13	26736	A	55	M	156	58	I	14	100	2	4.25	5.25	90	45	105	180
14	26566	A	69	M	149	53	II	14	100	2	4.5	5.25	135	60	120	165
15	30441	A	61	M	145	55	I	15	100	2	4.5	5.75	150	60	135	195
16	29510	A	67	M	166	61	I	15	100	2	4.5	5.75	135	60	120	180
17	32542	A	60	M	150	66	I	14	100	2	4.25	5.75	135	75	135	180
18	33885	A	65	M	148	63	I	15	99	2	4.25	5.25	120	60	135	165
19	36226	A	60	M	159	59	I	16	100	2	4.75	5.5	120	45	105	190
20	39734	A	50	M	149	56	I	17	100	2	4.5	5.25	105	60	120	180
21	15406	B	66	M	167	64	I	15	100	2	3.5	4.25	135	90	150	420
22	17773	B	70	M	148	60	II	16	100	2	3.25	4	150	75	135	420
23	18993	B	55	M	156	58	I	15	100	2	3.5	4.5	135	90	150	390
24	19879	B	61	M	167	57	I	14	98	2	3.25	4.5	150	90	150	420
25	18659	B	67	M	168	55	II	15	100	2	4	5	150	90	165	420
26	20442	B	54	M	166	54	I	16	100	2	3.75	4	150	105	165	420
27	21226	B	63	M	163	57	I	13	100	2	3.75	4.5	165	105	150	390
28	22150	B	66	M	169	52	I	15	100	2	2.5	3.5	165	75	135	420
29	23040	B	60	M	158	66	II	16	100	2	3.75	4.5	135	90	150	420
30	26234	B	55	M	166	57	I	16	100	2	3.25	4.25	150	90	135	450
31	26202	B	70	M	168	64	I	14	100	2	3.25	4	165	90	150	420
32	26556	B	68	M	146	63	II	15	99	2	3.5	4.75	150	105	150	420
33	28140	B	54	M	154	55	I	16	100	2	3.5	4.25	150	90	135	420
34	31504	B	57	M	156	61	I	14	100	2	3.75	4.5	135	90	150	450
35	32184	B	62	M	152	64	I	15	100	2	3.75	4.25	165	105	165	420
36	33558	B	65	M	163	59	I	16	100	2	3.25	4.5	165	90	150	450

37	33553	B	59	M	166	62	I	14	99	2	3.5	4.75	135	90	150	420
38	35102	B	69	M	163	54	I	15	100	2	4	4.75	165	75	105	420
39	35201	B	60	M	169	59	I	13	100	2	3.5	4.5	150	105	150	420
40	40019	B	65	M	147	56	I	12	100	2	3.25	4.25	150	90	150	450
41	15403	C	60	M	142	63	I	15	100	2	2.5	3.5	165	90	165	540
42	17521	C	61	M	147	60	I	16	100	2	1.5	2.5	180	105	165	540
43	19643	C	57	M	155	58	I	17	100	2	2.25	3	180	105	165	510
44	18968	C	65	M	166	50	I	15	100	2	2.75	3.5	165	105	165	510
45	20194	C	65	M	168	55	I	16	100	2	2.5	3.5	195	120	180	540
46	21044	C	59	M	159	56	I	14	99	2	2.75	3	180	105	180	540
47	21365	C	60	M	148	58	I	14	99	2	1.5	2.5	165	90	165	570
48	22184	C	58	M	155	52	I	15	99	2	1.75	2.75	195	90	165	540
49	23172	C	61	M	167	59	I	14	100	2	3	3.5	195	105	180	540
50	25729	C	62	M	163	54	I	14	100	2	1.5	2	165	120	165	570
51	26727	C	58	M	168	60	I	14	100	2	2	3	180	120	165	540
52	27790	C	68	M	169	56	I	15	100	2	2.5	3	180	105	180	540
53	32533	C	65	M	168	57	II	15	100	2	1.25	2.5	165	105	165	570
54	34621	C	63	M	157	53	I	16	100	2	2.5	3	195	105	165	540
55	33552	C	58	M	168	66	I	14	100	2	2	2.5	165	105	180	540
56	33534	C	65	M	164	69	II	15	100	2	2.5	3	180	120	165	540
57	35084	C	59	M	169	62	I	16	99	2	2.25	3	165	90	150	570
58	36849	C	55	M	166	64	II	14	100	2	2	3.25	150	105	165	570
59	41241	C	65	M	156	65	I	15	100	2	1.75	2.5	165	105	180	540
60	39672	C	64	M	169	55	II	16	100	2	2	2.75	180	105	180	540

								Systolic Blood Pressure																	
S.No.	IP.no	group	age	sex	ht	wt	ASA	0 Min	2 Min	4 Min	6 Min	8 Min	10 Min	15 Min	30 Min	45 Min	60 Min	90 Min	120 Min	150 Min	180 Min	4 hour	5 hour	6 hour	7 hour	8 hour
1	14821	A	69	M	148	69	I	134	125	126	120	126	128	122	120	124	128	115	122	114	120	127	125	130	136	120
2	14949	A	62	M	156	53	I	125	125	114	116	114	118	120	124	116	118	114	123	118	124	125	111	123	119	122
3	15397	A	62	M	163	59	I	130	125	128	130	122	126	124	120	118	126	123	112	110	111	124	121	125	121	110
4	17762	A	68	M	148	59	I	125	125	118	114	116	120	114	118	120	126	111	105	122	119	111	127	111	115	122
5	18402	A	56	M	162	68	I	112	110	104	96	92	114	120	112	114	122	126	111	115	122	109	119	116	126	120
6	21057	A	62	M	168	58	II	107	100	96	92	94	94	96	105	110	116	114	119	117	121	130	119	113	123	115
7	19001	A	55	M	162	62	I	120	118	110	122	124	118	112	116	118	112	114	115	115	121	119	113	109	124	118
8	20521	A	58	M	158	68	I	123	117	110	118	116	119	123	120	119	122	120	112	122	110	106	124	118	120	126
9	21061	A	68	M	155	56	I	129	124	122	120	123	120	126	116	118	120	114	113	124	119	116	109	117	125	123
10	23520	A	65	M	164	58	I	110	100	96	92	94	98	110	118	119	116	124	113	115	116	114	119	124	121	116
11	24986	A	63	M	162	64	II	114	110	105	110	114	106	110	112	119	109	121	117	120	110	124	113	119	125	119
12	25593	A	58	M	168	63	I	121	110	104	118	120	116	110	116	117	116	110	111	125	114	124	116	125	119	126
13	26736	A	55	M	156	58	I	134	120	122	128	128	123	128	119	118	124	118	111	130	134	126	119	120	114	128
14	26566	A	69	M	149	53	II	112	110	104	96	98	113	109	103	118	120	123	127	120	121	119	126	117	121	124
15	30441	A	61	M	145	55	I	128	120	119	123	119	118	120	119	115	120	110	112	126	134	126	128	118	120	129
16	29510	A	67	M	166	61	I	124	118	114	119	120	116	120	122	126	128	120	121	124	142	100	128	130	128	140
17	32542	A	60	M	150	66	I	127	120	111	122	120	116	128	114	120	118	110	112	135	140	136	122	143	139	144
18	33885	A	65	M	148	63	I	114	110	96	92	98	112	127	113	112	128	112	116	121	129	141	136	124	145	135
19	36226	A	60	M	159	59	I	122	120	116	125	120	120	120	124	116	116	125	111	112	142	139	120	131	140	129
20	39734	A	50	M	149	56	I	125	120	115	112	120	122	128	125	120	125	119	116	118	117	122	119	124	120	127
21	15406	B	66	M	167	64	I	128	124	120	118	120	129	122	126	129	120	117	119	120	121	123	117	114	121	129
22	17773	B	70	M	148	60	II	115	110	96	90	92	95	96	100	118	110	107	118	120	121	119	123	117	122	119
23	18993	B	55	M	156	58	I	127	120	114	100	94	100	110	118	126	114	115	121	122	123	119	122	120	126	129
24	19879	B	61	M	167	57	I	119	110	102	106	112	114	119	120	115	120	110	119	118	125	120	115	119	113	125
25	18659	B	67	M	168	55	II	110	102	96	94	98	110	116	114	112	118	115	117	118	124	117	121	116	112	117
26	20442	B	54	M	166	54	I	124	110	102	100	112	116	115	112	123	110	114	116	125	118	124	116	110	119	126
27	21226	B	63	M	163	57	I	115	110	102	94	100	112	102	110	127	120	115	116	121	118	123	117	113	109	117
28	22150	B	66	M	169	52	I	126	120	110	100	102	108	104	112	118	126	110	119	118	117	120	125	120	115	128
29	23040	B	60	M	158	66	II	129	120	113	112	134	120	118	124	112	124	119	118	120	110	117	121	124	126	130
30	26234	B	55	M	166	57	I	107	100	98	92	94	98	104	109	120	118	114	123	112	114	120	124	119	115	112
31	26202	B	70	M	168	64	I	123	122	120	116	128	114	120	118	110	96	114	118	119	117	114	120	115	117	125
32	26556	B	68	M	146	63	II	108	108	116	112	127	113	112	128	120	114	119	111	114	121	125	120	115	110	119
33	28140	B	54	M	154	55	I	122	125	120	120	120	124	116	116	110	102	121	120	110	119	122	118	114	120	125
34	31504	B	57	M	156	61	I	124	112	120	122	128	125	120	125	118	126	110	119	118	117	113	119	121	124	127
35	32184	B	62	M	152	64	I	126	118	120	129	122	126	129	120	110	115	111	121	118	115	125	127	114	121	125
36	33558	B	65	M	163	59	I	124	124	110	120	108	124	118	110	110	119	120	121	130	119	116	120	115	121	117
37	33553	B	59	M	166	62	I	119	100	110	119	129	124	126	114	120	110	119	124	143	119	122	118	114	110	116
38	35102	B	69	M	163	54	I	110	106	112	114	119	120	115	120	120	113	123	124	124	110	116	120	115	111	116
39	35201	B	60	M	169	59	I	124	116	128	114	120	118	110	114	110	118	125	115	131	113	109	105	110	115	119
40	40019	B	65	M	147	56	I	127	112	127	113	112	128	120	113	119	120	117	109	124	115	110	114	119	123	118

41	15403	C	60	M	142	63	I	130	120	120	124	116	116	110	124	120	118	123	124	114	120	113	109	114	119	123
42	17521	C	61	M	147	60	I	108	122	128	125	120	125	102	125	112	128	109	118	117	110	116	120	114	121	118
43	19643	C	57	M	155	58	I	119	129	122	126	129	120	110	126	116	116	116	114	120	116	120	123	119	115	111
44	18968	C	65	M	166	50	I	124	120	112	100	118	110	110	100	120	125	114	121	119	109	113	118	121	124	120
45	20194	C	65	M	168	55	I	127	100	110	118	126	114	120	118	129	120	121	117	116	112	109	105	110	115	119
46	21044	C	59	M	159	56	I	124	114	119	120	115	120	120	120	118	110	121	124	110	114	122	120	110	116	120
47	21365	C	60	M	148	58	I	125	110	118	126	114	120	112	114	119	110	124	123	113	121	115	119	115	109	113
48	22184	C	58	M	155	52	I	132	119	120	115	120	120	128	114	120	110	112	114	124	115	122	118	114	118	121
49	23172	C	61	M	167	59	I	110	102	98	94	110	110	127	113	112	120	119	117	120	117	111	118	121	124	117
50	25729	C	62	M	163	54	I	118	112	110	96	113	119	120	124	116	120	114	121	120	110	120	125	121	118	124
51	26727	C	58	M	168	60	I	121	116	116	110	124	120	128	125	120	112	110	119	118	120	119	121	124	118	123
52	27790	C	68	M	169	56	I	134	120	125	102	125	112	122	126	129	128	118	117	119	124	123	117	112	109	114
53	32533	C	65	M	168	57	II	112	106	100	94	110	116	120	100	118	127	118	115	127	121	118	123	119	124	117
54	34621	C	63	M	157	53	I	120	118	110	110	100	120	110	118	126	120	130	119	120	121	111	109	114	118	121
55	33552	C	58	M	168	66	I	129	126	114	120	118	129	119	120	115	128	122	119	118	110	120	116	110	114	119
56	33534	C	65	M	164	69	II	119	115	120	120	120	118	118	126	114	122	116	109	119	124	119	114	118	121	117
57	35084	C	59	M	169	62	I	130	125	102	125	118	126	114	120	112	125	121	116	114	115	117	111	118	121	124
58	36849	C	55	M	166	64	II	127	120	110	126	120	115	120	120	128	126	116	110	125	115	110	120	125	121	118
59	41241	C	65	M	156	65	I	120	110	103	96	108	110	114	110	127	100	117	118	122	114	120	119	121	124	118
60	39672	C	64	M	169	55	II	125	114	120	118	128	120	113	119	120	118	120	119	113	121	124	123	117	112	109

								Pulse Rate																		
S.No.	IP.no	group	age	sex	ht	wt	ASA	0 Min	2 Min	4 Min	6 Min	8 Min	10 Min	15 Min	30 Min	45 Min	60 Min	90 Min	120 Min	150 Min	180 Min	4 hour	5 hour	6 hour	7 hour	8 hour
1	14821	A	69	M	148	69	I	89	87	78	74	87	79	90	77	75	88	90	76	72	80	90	87	78	80	86
2	14949	A	62	M	156	53	I	78	79	89	82	84	86	83	73	74	76	83	99	79	103	94	84	84	86	86
3	15397	A	62	M	163	59	I	83	89	90	76	89	79	87	89	71	87	87	94	90	78	87	88	96	83	84
4	17762	A	68	M	148	59	I	78	88	87	70	90	86	84	82	86	87	84	91	80	84	86	76	88	86	82
5	18402	A	56	M	162	68	I	81	86	83	89	84	78	89	75	90	97	89	86	83	78	89	99	83	73	88
6	21057	A	62	M	168	58	II	85	92	89	88	82	80	86	97	93	82	86	88	86	81	79	89	82	86	83
7	19001	A	55	M	162	62	I	73	68	63	74	90	85	83	84	83	88	83	83	87	93	82	84	86	86	89
8	20521	A	58	M	158	68	I	69	78	83	85	75	79	72	74	72	73	72	79	83	86	78	82	80	86	79
9	21061	A	68	M	155	56	I	86	83	80	84	82	92	94	72	86	80	94	83	92	85	86	82	92	83	72
10	23520	A	65	M	164	58	I	93	86	93	85	75	84	82	85	84	86	82	89	83	75	74	83	86	73	82
11	24986	A	63	M	162	64	II	86	84	82	86	87	80	92	89	88	82	92	86	80	97	93	78	84	80	92
12	25593	A	58	M	168	63	I	88	90	85	83	84	83	88	87	83	93	88	86	100	88	78	75	88	85	88
13	26736	A	55	M	156	58	I	77	89	88	82	80	86	97	93	82	86	90	98	87	85	83	75	78	79	84
14	26566	A	69	M	149	53	II	89	63	74	90	85	83	84	83	88	87	89	78	71	79	84	86	82	83	87
15	30441	A	61	M	145	55	I	88	83	85	75	79	72	74	72	73	83	82	89	79	82	100	86	88	82	89
16	29510	A	67	M	166	61	I	74	80	84	82	92	94	72	86	80	92	69	86	83	83	78	89	83	72	84
17	32542	A	60	M	150	66	I	89	93	85	75	84	82	85	84	86	83	85	86	93	82	85	89	90	92	84
18	33885	A	65	M	148	63	I	85	82	86	87	80	92	89	88	82	80	80	88	83	88	98	88	88	90	88
19	36226	A	60	M	159	59	I	79	85	83	84	83	88	87	83	93	100	103	94	92	72	86	80	92	83	85
20	39734	A	50	M	149	56	I	87	89	83	95	86	90	83	86	87	87	78	86	67	90	99	89	80	87	90
21	15406	B	66	M	167	64	I	86	83	81	86	83	89	94	73	76	71	84	83	90	86	87	87	98	85	83
22	17773	B	70	M	148	60	II	89	80	86	97	93	82	86	88	81	79	78	80	89	87	90	78	83	88	88
23	18993	B	55	M	156	58	I	79	88	84	83	88	87	83	93	95	86	81	83	84	88	87	83	93	82	84
24	19879	B	61	M	167	57	I	82	83	80	86	97	93	82	86	86	83	93	84	83	83	88	87	83	93	100
25	18659	B	67	M	168	55	II	78	79	85	83	84	83	88	87	97	93	86	82	86	84	86	78	84	88	84
26	20442	B	54	M	166	54	I	86	83	79	72	74	72	73	83	83	88	85	87	89	90	67	86	90	99	89
27	21226	B	63	M	163	57	I	74	89	92	94	72	86	80	92	86	97	75	72	94	86	80	92	83	85	86
28	22150	B	66	M	169	52	I	93	86	84	82	85	95	86	90	83	86	97	88	83	87	83	93	100	86	88
29	23040	B	60	M	158	66	II	78	86	80	92	89	86	83	89	94	73	88	90	86	83	86	87	87	98	85
30	26234	B	55	M	166	57	I	83	98	83	88	87	97	93	82	86	88	85	89	83	94	73	76	71	78	79
31	26202	B	70	M	168	64	I	84	78	79	85	83	83	88	87	83	93	79	82	93	86	88	81	79	89	82
32	26556	B	68	M	146	63	II	93	89	83	79	72	86	97	93	82	86	82	69	74	76	74	85	83	86	83
33	28140	B	54	M	154	55	I	78	80	89	92	94	83	84	83	88	87	83	85	93	89	88	82	93	86	82
34	31504	B	57	M	156	61	I	85	93	85	75	63	74	90	85	83	84	82	80	89	87	90	78	83	88	88
35	32184	B	62	M	152	64	I	86	82	86	87	83	85	75	79	72	74	90	103	98	79	83	82	92	94	85
36	33558	B	65	M	163	59	I	83	85	83	84	80	84	82	92	94	72	84	93	83	82	84	87	72	90	77
37	33553	B	59	M	166	62	I	79	88	82	80	93	85	75	84	82	85	83	83	87	93	100	84	86	83	73
38	35102	B	69	M	163	54	I	83	74	90	85	82	86	87	80	92	89	86	84	78	88	84	89	79	87	89
39	35201	B	60	M	169	59	I	89	85	75	79	85	83	84	83	88	87	89	90	86	99	89	90	86	84	82
40	40019	B	65	M	147	56	I	86	84	82	92	88	82	80	86	97	93	94	83	92	85	86	84	78	89	75

41	15403	C	60	M	142	63	I	86	85	75	84	74	90	85	83	84	83	83	80	93	86	88	82	80	86	84
42	17521	C	61	M	147	60	I	80	86	87	80	85	75	79	72	74	72	86	87	87	80	85	84	85	83	84
43	19643	C	57	M	155	58	I	90	83	84	83	84	82	92	94	72	86	83	87	88	83	78	82	84	83	90
44	18968	C	65	M	166	50	I	88	83	95	86	90	83	88	87	83	93	86	79	81	89	82	82	80	82	84
45	20194	C	65	M	168	55	I	86	80	84	82	92	79	85	83	84	83	85	83	88	86	83	83	84	82	85
46	21044	C	59	M	159	56	I	86	93	85	75	84	83	79	72	74	72	93	93	82	86	82	87	80	92	89
47	21365	C	60	M	148	58	I	88	82	86	87	80	89	92	94	72	86	89	83	78	88	88	84	83	88	87
48	22184	C	58	M	155	52	I	80	85	83	84	83	85	75	63	74	90	98	92	82	94	85	79	86	82	83
49	23172	C	61	M	167	59	I	89	88	82	80	86	86	87	83	85	75	81	80	82	93	85	89	88	82	85
50	25729	C	62	M	163	54	I	88	74	90	85	83	83	84	80	84	82	87	85	90	94	98	81	79	83	82
51	26727	C	58	M	168	60	I	100	85	75	79	72	82	80	93	85	75	88	84	82	82	84	85	89	88	79
52	27790	C	68	M	169	56	I	89	84	82	92	94	90	85	82	86	87	81	92	82	78	83	86	89	83	86
53	32533	C	65	M	168	57	II	88	85	75	79	85	75	84	83	79	72	88	84	83	88	84	82	88	86	89
54	34621	C	63	M	157	53	I	88	84	82	92	86	87	80	89	92	94	82	80	87	89	86	86	83	89	78
55	33552	C	58	M	168	66	I	85	90	83	88	83	84	83	85	75	63	78	83	84	88	86	83	86	83	87
56	33534	C	65	M	164	69	II	83	92	79	85	82	80	86	86	87	83	82	86	95	80	79	78	86	89	81
57	35084	C	59	M	169	62	I	88	84	83	79	90	85	83	83	84	80	92	83	87	80	79	86	88	82	80
58	36849	C	55	M	166	64	II	98	80	89	92	75	79	72	82	80	93	88	86	83	87	87	89	85	90	85
59	41241	C	65	M	156	65	I	89	83	85	75	82	92	94	90	85	82	90	83	94	88	87	83	93	82	84
60	39672	C	64	M	169	55	II	80	88	89	88	86	81	79	89	82	82	92	90	88	86	87	87	90	92	86

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-3

Title of the Work :	Effect of Low-Dose Dexmedetomindine or Clonidine on the Characteristics of Bupivacaine Spinal Block
Principal Investigator	: Dr.J.S. Karthick Kamal
Designation	: PG In Anaesthesia
Department	: Anaesthesia

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 15.04.2010 at the Modernised Seminar Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate form the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

SECRETARY
IEC, SMC, CHENNAI

MEMBER SECRETARY
ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE
CHENNAI-600 001.

மயக்க மருத்துவத்தில் புபிவேகேன் (Bupivacaine) மருந்துடன் குனோனிடின் (Clonidine) அல்லது டெக்ஸ்மெடிட்டோமிடின் (Dexmedetomidine) மருந்தை செலுத்த இருப்பதாகவும் கூறினார்.

அதனால் முதுகில் ஊசி இட்டுகொள்ளுதலில் பக்கவிளைவுகளான நாடிதுடிப்பு குறைதல், இரத்த அழுத்தம் குறைதல், புபிவேகேன் மருந்திற்கு ஒவ்வாமை மற்றும் தலைவலி போன்ற வற்றுடன், சாதாரணமாக ஏற்படும் நாடித்துடிப்பு குறைவை விட இதில் சிறிது அதிகமாக குறையும் (Delayed Bradycardia) என்பதையும், இரத்தஅழுத்தமும் சாதாரணமாக குறைவதைவிட அதிகமாக குறையும் என்பதையும், இதய துடிப்பு தடைபடுதல் (Heart Block) போன்ற பிரச்சனைகள் ஏற்படும் என்பதையும் தெரிந்து கொண்டேன். அதற்காக மருத்துவர் மேற்கொண்டுள்ள தடுப்பு நடவடிக்கைகளையும் (Preventive Measures) அறிந்து கொண்டேன்.

மேலும் மருத்துவரின் இந்த சோதனைக்கு முழு மனதுடன் சம்மதம் தெரிவிக்கிறேன். இதனால் ஏற்படும் பிரச்சனைகளுக்கு மருத்துவரோ, மருத்துவனையோ பெறுப்பல்ல என்பதனை முழு மனதுடன், மற்றும் சுயநினைவுடன் உறுதி கூறுகிறேன்.

இங்ஙனம்

தங்கள் உண்மையுள்ள,

மருத்துவரின் கையொப்பம்

அனுமதிக்கப்பட்டவரின் கையொப்பம்
(அ) இடது பெருவிரல் ரேகை

மருத்துவரின் பெயர்

அனுமதிக்கப்பட்டவர் பெயர்