A Dissertation on

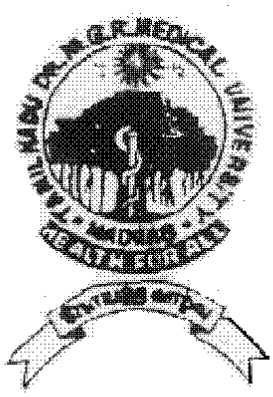
PROSPECTIVE RANDOMISED COMPARISON OF THREE DIFFERENT DOSES OF HYPERBARIC BUPIVACAINE MIXED WITH FENTANYL IN RANDOMLY SELECTED ELDERLY PATIENTS POSTED FOR TURP SURGERIES.

Dissertation Submitted in partial fulfillment of

M.D. DEGREE EXAMINATION

BRANCH X- ANAESTHESIOLOGY

MADRAS MEDICAL COLLEGE, CHENNAI



THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

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DECLARATION

I hereby declare that the dissertation entitled

" PROSPECTIVE RANDOMISED COMPARISON OF THREE DIFFERENT DOSES OF HYPERBARIC BUPIVACAINE MIXED WITH FENTANYL IN RANDOMLY SELECTED ELDERLY PATIENTS POSTED FOR TURP SURGERIES" has been prepared by me under the Guidance of **PROF. DR C.R.KANYAKUMARI M.D.,D.A.,** Professor and Director,Institute Of Anesthesiology And Critical Care, Madras Medical College, Chennai in partial fulfillment of the regulations for the award of the degree of M.D. [Anaesthesiology], examination to be held in April 2012.

This study was conducted at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.

I have not submitted this dissertation previously to any university for the award of any degree or diploma.

Date:

Place: Chennai

Dr M.SENDIL MURUKAN

CERTIFICATE

This is to certify that the dissertation **"Prospective randomized comparison of three different doses of Hyperbaric Bupivacaine combined with Fentanyl in randomly selected elderly patients posted for TURP surgery"** presented herein by **Dr. M.Sendil Murukan,** is an original work done in the Institute of Anaesthesiology and Critical Care, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai for the award of Degree of M.D. Anaesthesiology under my guidance and supervision during the academic period of 2009-2012.

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INTRODUCTION

"The relief of pain purchased is always at a price"

- R.M.Water's

"For all the happiness mankind can gain is not in pleasure but in rest from pain"

- John Dyrden

The aim of anaesthesiology as a science is the removal of pain temporarily have been started initially with pain relief for surgeries, extending now to post operative pain relief and relief from chronic pain and cancer pain.

Spinal anaesthesia plays an important role in alleviating pain intraoperatively and also in the post operative period also. The entry of Corning's needle in 1885 into subarachnoid space paved the way for the greatest leap into spinal anaesthesia. As a neurologist, Corning's objective was to relieve chronic pain in his patients, not to produce operative anaesthesia . Cocaine was the drug first used experimentally in dogs . In men the first spinal anaesthesia was conducted by August Bier on 16.08.1898 with cocaine 3cc as 0.5% solution followed by Rudolph Matas in America and Theodore Tuffier in France .

TURP and other cystoscopic urologic procedures are usually done under spinal anesthesia because it provides an adequate anaesthesia for the patient and good relaxation of the pelvic floor and perineum for the surgeon. The complication of cystoscopic procedures can be easily recognized because the patient is awake .Change in the mental status in a conscious patient can be detected early . Sympathetic blockade produced by regional anaesthesia will increase the venous capacitance thereby decreasing the effect of fluid absorption . Bladder perforation is recognized earlier . Decreased requirement of analgesics in the immediate postoperative period . The advantages of neuraxial opioids over neuraxial local anaesthetics are that it produces prolonged, intense and selective segmental analgesia without motor blockade and sympathetic dysfunction.

Opioids and local anaesthetics administered together have a potent synergistic analgesic effect . Intrathecal opioids enhance analgesia from subtherapeutic dose of local anaesthetic and make it possible to achieve successful spinal anaesthesia using otherwise inadequate doses of local anesthetic . Hence the present study has been under taken to combine "Fentanyl" a potent synthetic opioid and "Bupivacaine" a long acting local anesthetic for intrathecal administration to provide anaesthesia for endoscopic urological procedures in elderly patients.

AIM OF THE STUDY

Regional anaesthesia is the most frequently employed anaesthetic technique for TURP and other endoscopic urologic procedures. These patients are mostly elderly with low cardiac reserve . The conventional dose of Bupivacaine(12.5-15mg) may produce haemodynamic instability . The aim of my study is to find out the minimum effective dose of hyperbaric Bupivacaine with Fentanyl for spinal anaesthesia in elderly patients undergoing TURP surgery.

ANATOMY OF SUBARACHNOID SPACE

Subarachnoid block means the temporary interruption of nerve transmission within the subarachnoid space produced by injection of a local anaesthetic solution into cerebrospinal fluid.

Applied anatomy of vertebral canal(38) :

Vertebral canal extends from foramen magnum to the sacral hiatus . It protects the spinal cord . The vertebral column comprising of 33 vertebrae (7-cervical , 12-thoracic , 5-lumbar , 5-fused sacral and 4-coccygeal) has four curves . Cervical and lumbar curves are convex anteriorly and thoracic & sacral curves are convex posteriorly . The curves of the vertebral column influences the spread of the local anaesthetic in the subarachnoid space.

The vertebral column is bound together by several ligaments . They are

1. Supraspinal ligament – passess longitudinally over the tips of the spinous processes from C7 to the sacrum.
2. Interspinous ligament – connects the adjoining spinous processes together.
3. Ligamentum Flavum – known as yellow ligament , connects the adjacent laminae and is composed of yellow elastic fibres.
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.

Vertebral canal has deficiencies posteriorly in the midline called inter laminar foramina which enlarge in flexion accessible for the passage of spinal needle . The direction of spinous process determine the direction of spinal needle.

SPINAL CORD(38):

It is the direct continuation of the medulla oblongata extending from the upper border of the atlas to the first lumbar vertebra below which there is leash of nerve roots termed cauda equine .

There are 31 pairs of spinal nerves

8 – Cervical,12 – Thoracic,5 – Lumbar,5 – Sacral,1 – Coccygeal

Each of the spinal nerve is composed of anterior and posterior roots uniting at the intervertebral foramina 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.

BLOOD SUPPLY(38):

It is from the anterior spinal artery which is a branch of vertebral artery and also by a pair of posterior spinal arteries which arise

from the posterior inferior cerebellar arteries .

SPINAL VEINS:

The spinal veins are arranged into anterior and posterior plexus which drain into vertebral , azygos and lumbar veins .

CEREBROSPINAL FLUID(38):

This is an ultrafiltrate of the blood plasma formed from choroids plexus of the lateral ventricles with a pH of 7.32 (7.27 - 7.37) . It is a clear, colourless fluid found in the cranial and spinal subarachnoid spaces and in the ventricle of the brain . The total volume of CSF in an average adult ranges from 120 - 150ml of which 25 - 35 ml is in the spinal subarachnoid space.

Composition of cerebrospinal fluid:

Specific gravity - 1.006 (1.003-1.009) at 37^0C, Pressure - 60-80 mm of water

Pco_2 – 48 mm Hg, $HCo3^-$ - 23 meq/l, Na^+ - 133-145 meq/l, Ca^+ - 2-3 meq/l

Po4 - 1.6 mg/dl, Mg^+ - 2-2.5 mg/l, Cl^- - 15-20 mg/l, Protein - 23-38 mg/dl

Sugar - 45-80 mg/dl, Lymphocytes - 0-5 cells/cu.mm .

An important factor that determine the spread of drug in cerebrospinal fluid is the specific gravity of the drug in relation to that of cerebrospinal fluid (Baricity) which is 1.003 - 1.009 . Hyperbaric solution is one which is denser than CSF at 37 degree Celsius .

PHYSIOLOGY OF SUBARACHNOID BLOCK(38)

Subarachnoid block implies the temporary interruption of nerve transmission within the subarachnoid space by injections of local anaethetics . The blockade of nerve fibres occur in the order of temperature , pain , proprioception and then motor fibres .

Factors influencing block height :

a - Site of injection , b - Angulation of needle

c - Characteristic of local anaesthetic

i) Density of local anaesthetic ,ii) Specific gravity,iii) Baricity

d - Dose of local anesthetic , e - Position of the patient

f - Anatomic configuration of spinal column , g - Patient height

h - Volume of cerebrospinal fluid , i - Reduced cerebrospinal fluid with increased intra abdominal pressure (eg. Pregnancy)

Effects on Cardio Vascular System:

Most important physiological responses to subarachnoid block involves 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 intrathecally leads to direct cardiovascular effect .

Level of sympathetic denervation determines the magnitude of cardiovascular system responses . Sympathetic denervation produces arterial and more physiologically important arteriolar dilatation and vasodilatation in the venous circulation producing fall in blood pressure . Due to Bainbridge reflex , fall in blood pressure is associated with bradycardia . Blockade of cardiac sympathetic fibre from T1-T4 is an additional factor that causes bradycardia.

Effects on Respiratory System:

Respiration is not depressed normally . High spinal blockade can cause paralysis of intercostals muscles but resting tidal volume , maximum inspiratory volume , respiratory rate , ABG , negative intrapleural pressure are unaffected . The phrenic nerve is also unaffected . Hypoxia may accompany hypotension and is corrected by oxygen administration via face mask.

Gastro Intestinal Effect:

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

Hepatic and Renal Effects:

The hepatic blood flow decreases and is directly proportional to the decrease in blood pressure . Renal blood flow is maintained by autoregulation and does not decrease till mean arterial pressure goes below 50 mmHg.

Genito Urinary System:

Sphincters of bladder are not relaxed , and ureteric tone is not greatly altered . Urinary retension 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 .

Metabolic and hormonal effect:

Spinal anaesthesia blocks hormonal and metabolic responses to nociceptive stimuli arising from the operative site . It minimizes the rise in blood sugar , coritsol , catecholamines renin and aldosterone release associated with stress . Post operative negative nitrogen balance and secretion of antidiuretic hormone are inhibited .

Thermo Regulation:

Hypothermia results from heat loss to the cold environment due to vasodilatation .

ANATOMICAL AND PHYSIOLOGICAL ANAESTHETIC IMPLICATIONS IN ELDERLY PATIENTS(38)

There is no standard definition of elderly , but it is often arbitrarily taken as more than 60 years(30) . They have an increased risk of morbidity and mortality associated with anaesthesia and surgery due to physiological changes of ageing.

Cardiovascular System:

- 50 – 65 % of patients have cardiovascular disease.
- Reduction in ventricular compliance due to myocardial fibrosis and wall thickening.
- Systolic hypertension and widened pulse pressure.
- Autonomic responses decreases .
- Increased capillary permeability leading to pulmonary oedema.

Respiratory System:

- Ventilatory responses to hypoxia and hypercarbia decreases .
- Oxygen consumption and carbondioxide production fall by 10 – 15 % by the seventh decade.
- Lung compliance increases , chest wall compliance decreases . Total thoracic compliance decreases.
- Closing volume increases .

- Airway protective reflexes decreases leading to pulmonary aspiration .
- In edentulous patients face mask seal becomes difficult .

Renal System:

- Decreased Glomerular filtration rate , decreased creatinine clearance , tubular function reduces leading to reduced concentrating ability .
- Clearance of renally excreted drugs are reduced necessitating dose adjustments .

Hepatic System:

- Cellular function is relatively well preserved in healthy patients .
- Hepatic mass and hepatic blood flow decreases .

Central Nervous System:

- Brain size and mass decreases , cortical atrophy , dementia affects 10% of patients over 65 years of age .
- They require lower dose of opioids and sedatives .
- Pain threshold may be increased .
- Post operative cognitive dysfunction is common .
- The thirst response to reduced extracellular fluid volume and increased plasma osmolality is reduced in the elderly , increasing susceptibility to fluid depletion .

ANAESTHETIC IMPLICATIONS OF ENDOSCOPIC UROLOGICAL PROCEDURE(38)

Neuro anatomy of the penis prostate and urinary bladder:

Organ	Sympathetic	Parasympathetic	Spinal level of pain conduction
Bladder	T 11 – 12	S 2 – 4	T11-12(dome)S2-4(neck)
Prostate	T 11 – 12	S 2 – 4	T 11-12,S 2-4
Penis and urethra	L 1 – 2	S 2 - 4	S 2 - 4

The stretch sensation of the bladder are carried by the afferent parasympathetic fibres , whereas pain , touch and temperature sensations are carried by the sympathetic nerves . Sympathetic fibres are predominantly α – adrenergic in the bladder base and urethra and β – adrenergic in the bladder dome and lateral wall .Majority of patients undergo procedure for Benign prostatic hypertrophy . The incidence increases over 60 years of age . Spinal anaesthesia works well for rigid cystoscopic procedures , and is commonly used for Transurethral resection of prostate . Sensory supply to the bladder is from T_{11} & T_{12} and urethra , prostate and bladder neck is from S_2 - S_4 . So block upto T_{11} is necessary for TURP Surgery .

Complications of TURP Surgery(38):

Bladder distension due to large volume of irrigant fluid used in cystoscopic procedure is a potent stimulant to produce autonomic hyper reflexia.

The complications of TURP surgery are mainly due to irrigation fluid used. i) TURP syndrome , ii) Haemorrhage , iii) Perforation of Bladder iv) Hypothermia , v) Transient Bacteremia , Septicemia , vi) Transient Blindness , vii) Hyper ammonemia

TURP Syndrome(38)

Combination of fluid overload and hyponatremia due to large volume of irrigation fluid absorbed via open venous sinuses . About 20ml/mt of fluid is absorbed and an average patients absorb a total of 1-1.5 litres . Amount of absorption depends on pressure of infusion, venous pressure and duration of procedure .

Clinical Features:

Restlessness , head ache , tachypnea, respiratory distress , nausea , vomiting , visual disturbance , pulmonary oedema , heart failure , cerebral oedema hyponatremia , confusion , convulsions and coma.

Diagnosis

Serum sodium level and Arterial blood gas analysis.

Treatment:

- Patient is reassured
- Surgery is stopped as soon as possible .
- Switch over to normal saline for bladder irrigation .
- Injection Furosemide administered intravenously.
- 100% oxygen administered through face mask .
- If the develops pulmonary oedema , patient intubated and given positive pressure ventilation . Invasive haemodynamic monitors may be needed .
- Sample is drawn for arterial blood gas analysis and serum sodium estimation.
- Intravenous Hypertonic saline 3% or 5% may be needed if the hyponatremia is refractory or severe.
- Anticonvulsants administered if the patient develops seizures
- Packed red cells transfused if blood loss is more .

Bladder perforation.

This may occur in up to 1% of cases . Most are extraperitoneal , and cause periumbilical or suprapubic pain in the awake patient under regional anaesthesia . Intraperitoneal bladder perforation leads to generalised abdominal pain, which may be referred from the diaphragm to the chest or shoulder . It may also be associated with pallor , sweating , hypotension and nausea and vomiting .

Bleeding

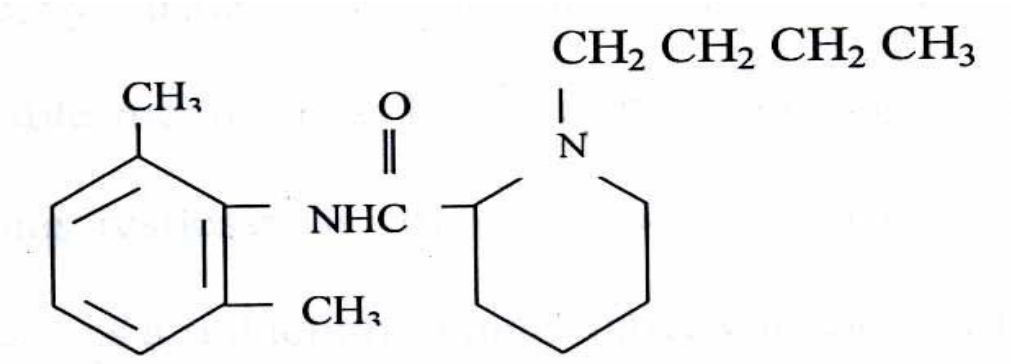
It may be substantial , and depends on the size of the prostate , length of surgery and surgical technique . It may be difficult to estimate due to dilution with irrigating fluid . Rough estimates of blood loss include 2-5 mL per minute of resection time , and 20-50 mL per gram of prostate resected . Monitoring of the patients vital signs and haematocrit level are probably the best way to assess blood loss and the need for transfusion . Abnormal bleeding may be due to the release of plasminogen activator from the prostate , which results in fibrinolysis.This occurs in less than 1% of cases and may be treated with aminocaproic acid.

Significant heat loss may occur due to use of cold irrigation fluids . Perforation of rectum can occur which may require defunctioning colostomy .

PHARMACOLOGY OF BUPIVACAINE(37)

Bupivacaine is an amide local anaeshetic , synthesized by A.F. Ekenstam in 1957 and brought into clinical use in 1963 . It is produced for clinical use as a racemic mixture , containing equal proportions of the 'S' and 'R' enantiomers .

Chemical Structure



1– Butyl – N - (2,6-dimethylphenyl) -2-piperidine Decarboxamide Hydrochloride monohydrate

Physical properties

Molecular Weight (base) 288 , pKa 8.1 ,Solubility in Alcohol 1 in 8, Water 1in 25 , Octanol/water partition coefficient 19 , Lipid solubility 28 , Plasma Protein Binding 95%

Mechanism of action

Bupivacaine exerts its effect by inhibition of sodium channels . It acts to block conduction in the nerves by decreasing or preventing the large transient increases in permeability of the cell

membrane to sodium ions that follows depolarization of the membrane . Bupivacaine also reduces the permeability of the resting nerve membrane to potassium as well as sodium ions .

Pharmacodynamics:

Bupivacaine by virtue of its pharmacological effects , has a stabilizing action on all excitable membranes . The duration of action is considerably longer . The sensory block produced by Bupivacaine tends to be more marked than the motor block .

Pharmacokinetics

Bupivacaine is rapidly absorbed from the site of injection . The rate of rise in plasma Bupivacaine concentration and the peak plasma concentrations obtained depend on the route of administration .

Pharmacokinetic Profile

Volume of distribution at steady state (Vdss) 72 litres. Clearance 0.47 l/min.

Metabolism

Possible pathways for metabolism of Bupivacaine include aromatic dealkylated metabolite , N-desmethyl bupivacaine has been measured in blood and urine after epidural and spinal administration . The degradation

of Bupivacaine takes place in the liver . Renal disease is unlikely to alter the kinetics of Bupivacaine to any great extent . Less than 10% of the drug is excrete unchanged in urine .

Clinical Applications

Infiltration anaesthesia , Peripheral nerve blocks ,

Central neuraxial blocks (intrathecal , epidural and caudal)

Contraindications

Paracervical block (in Obstetrics) , Known hypersensitivity to amide local anaesthetics , Intravenous regional anaesthesia (IVRA)

Preparations Available

0.25% , 0.5% solutions in 10 ml and 20 ml vials .

5 mg/ml (0.5%) Bupivacaine and 80 mg dextrose in 4 ml ampoules for intrathecal injection (Baricity 1.027) .

Concentration used and Maximum permitted dose

- 0.125% - 0.5% --2 mg/kg body weight
- 0.75% (not to be used in obstetric epidurals). Maximum over 4 hours – 150 mg . Maximum during 24 hours – 400 mg.
- 0.5% plain / hyperbaric solution (intrathecal use)—20 mg.

Adverse Reactions

Adverse reactions are associated mainly with excess plasma levels of the drug , which may be due to over dosage , unintentional intravascular injection or slow metabolic degradation .

CNS Reaction

Excitation characterized by restlessness , anxiety , dizziness , tinnitus , blurred vision or tremors were possible proceeding to convulsions, followed by drowsiness , unconsciousness and cardiac arrest .

Cardiovascular System Effects

Bupivacaine appears to be more cardiotoxic than Lidocaine and this relates to the action of Bupivacaine on cardiac sodium channels (fast in , slow out agent) and physic – chemical properties like high lipid solubility and high protein binding , particularly at low pH . Accidental intravenous injection of Bupivacaine causes dysrhythmias , atrioventricular block , ventricular tachycardia and ventricular fibrillation . Pregnancy increases the sensitivity to cardiotoxic effects of Bupivacaine .

Allergic Reactions

Manifests as urticaria , pruritis , angioneurotic edema etc. Cross sensitivity among members of amide type local anaesthetics is reported .

ADJUVANTS TO LOCAL ANAESTHETICS IN SPINAL ANAESTHESIA(38)

Local anesthetic agents have been widely used in spinal anaesthesia . One of the main disadvantage is the limited duration of block achieved with local anaesthetics . To overcome this , various adjuvants have been tried and used successfully . This addition of adjuvant has further expanded the advantage of regional anaesthesia over general anaesthesia .

ADJUVANTS:

These may be opioids like Morphine , Fentanyl , Sufentanil or Buprenorphine . It may be Benzodiazepines , Alpha 2 agonist Clonidine , Acetylcholine esterase inhibitors like Neostigmine , NMDA receptor antagonist Ketamine or Nonsteroidal anti inflammatory agents . These adjuvants usually confer the advantages of rapid onset time, differential blockade, inhibition of tourniquet pain, improved and prolonged duration of post operative analgesia .

Also these adjuvants decrease the amount of local anesthetic required to produce same effect thereby reducing the risk of local anesthetic toxicity , hypotension and profound motor blockade .

OPIOIDS(37)

The term opioids refer to all compounds related to opium , derived from juice of opium poppy , papaver somniferum . Morphine is the prototype opioid . Opioid compounds can be classified as naturally occurring , semisynthetic and synthetic opioids .

CLASSIFICATION:

Naturally occurring opioids are divided into two chemical classes

1. Phenanthrenes - eg. Morphine and codeine

2. Benzylisoquinolones - eg. Papaverine

Semisynthetic opioids result from relatively simple modification of morphine molecule eg. Diacetylmorphine .

Synthetic opioids contain phenanthrene nucleus . They are classified into four subdivisions .

1. Morphinan derivatives - eg.Levorphanol

2. Methadone derivatives - eg.Methadone

3. Benzomorphan derivatives - eg.Pentazocine

4. Phenylpiperidine derivatives - eg.Meperidine , Fentanyl , Sufentanil , Alfentanil.

OPIOID RECEPTORS:

The presence of opioid binding sites in the nervous system was reported in the year 1973 . Immuno histochemical studies have demonstrated opioid receptors in various areas of the central nervous system. These indude the amygdala, the mesencephalic reticular formation , the periaqueductal gray matter and the rostral ventral medulla .

Based on pharmacological experiments three types of opioid receptors were published.

(i) mu or µ for Morphine type , (ii) Kappa or K for Ketocyclazocine type

(iii) Sigma or S for SKF 10047 type

In addition two other receptors have been identified in the vas deferens of mouse namely the delta (s) and epsilon (å) receptors . All the receptors bind to a super family guanidine protein coupled receptors. The mu or morphine preferring receptors are principally responsible for supraspinal and spinal analgesia . μ_1 rceptor is speculated to produce analgesia , while μ_2 receptor is responsible for hypotension , bradycardia and respiratory depression . Delta receptors serve to modulate the activity of µ receptor . Kappa receptors are those to which most of the opioid agoinst – antagonist bind . Respiratory depression is less common with Kappa receptor activation than µ . Dysphoria and diuresis may occur .

CHARACTERISTIC OF OPIOID RECEPTORS

	Mu(μ1)	Delta(s)	Kappa(k)
Endogenous ligand	Beta endorphin,endomorphine	Leucoenkephalin, metenkephalin	Dynorphin
Agonist	Morphine,Fenanyl	Deltorphin DPDPE	Buprenorphine Pentazocine
Antagonist	Naloxone Naltrexone	Naloxone	Naloxone
Coupled G Protein	$G_{I/O}$	$G_{I/O}$	$G_{I/O}$
Aenylate cyclase	Inhibition	Inhibition	Inhibition
Effect	Analgesia-supraspinal,spinal respiratory depression euphoria,constipation, bradycardia	Analgesia,respiratory depression,constipation	Analgesia (spinal),miosis dysphoria, sedation, diuresis

MECHANISM OF ANALGESIC ACTION

Opioids act as agonists at stereospecific opioid receptors at presynaptic and postsynaptic sites in the central nervous system and also outside central nervous system in peripheral tissues .

MECHANISM OF ACTION IN CENTRAL NERVOUS SYSTEM

The analgesic effect of opioids results from their ability to directly inhibit the ascending transmission of nociceptive information from

the spinal cord dorsal horn . It has a descending inhibitory analgesic action by activation of pain control circuits that descend from the midbrain via the rostral ventromedial medulla (RVM) to the spinal cord dorsal horn . In addition , local spinal mechanisms also take part in the analgesic action of opioids . The affinity of most opiod agonists for receptors correlated with their analgesic property . The principal effect of opioid receptor activation is a decrease in neuro transmission .The neurotransmitters whose release are inhibited include Acetylcholine, Dopamine, Norepinephrine and Substance P.

MECHANISM OF ACTION IN PERIPHERAL TISSUES

Opioids are effective in inflammatory hyperalgesic conditions. The opioids bind to receptors in the primary afferent neurons and mimic the action of endogenous ligands , resulting in the activation of pain modulating (antinociceptive) systems .

EFFECT OF OPIOIDS ON VARIOUS SYSTEMS OF THE BODY

These can be classified into therapeutic drug effects and non-therapeutic drug effects .

THERAPEUTIC DRUG EFFECTS

OPIOIDS AS ANAESTHETIC

The capacity of opioids to produce anesthesia is debated .

General anaesthesia can be considered in terms of its component parts ; amnesia , analgesia , unconsciousness , immobility , muscle relaxation and control of autonomic and endocrine responses to surgery. Of these , opioids produce effects of analgesia , unconsciousness and control of autonomic and endocrine responses to surgery .

CENTRAL NERVOUS SYSTEM

Opioids generally produce modest decrease in cerebral methabolic rate (CMR) . They cause decrease in cerebral blood flow when coadministered with nitrous oxide and a cerebral vasodilating anaesthetics . Opioids affect intracranial pressure minimally , but may cause increase in intracranial pressure when compliance is compromised .

NON THERAPEUTIC DRUG EFFECTS

RESPIRATORY EFFECTS

Opioids decrease resting minute ventilation and tidal volume . Respiratory rate may be decreased or normal , whereas μ agoinsts produce a dose related depression of breathing . Ventilatory responses to hypoxia and hypercarbia are blunted . Sufficient doses may produce , apnoea , but the apnoeic conscious patient may breathe on command .

CARDIOVASCULAR EFFECTS

The action of opioids on cardiovascular system is

mostly due to histamine release . Morphine or Meperidine which cause release of histamine provide hypotension and tachycardia . Opioids also depress contractility of isolated heart muscle , but at doses greatly in excess of those used clinically . An exception to this is Meperidine which produce myocardial depression at clinically relevant concentrations . Morphine and Fentanyl analogs decrease heart rate due to vagomimetic action . Meperidine , due to its anticholinergic properties increase heart rate.

RIGIDITY

Opioid induced muscle rigidity occurs usally during induction of anaesthesia , especially with largers doses . This rigidity is central in origin , being mediated by **μ** receptors in brainstem medulla .

NEUROEXCITATORY EFFECTS

Opioids are also associated with tonic-clonic movements or myoclonus .

GASTRO INTESTINAL EFFECTS

Nausea and vomiting is a commonly observed effect of opioids due to its stimulation of receptors at chemoreceptor trigger zone .

PRURITIS

It is a common opioid-induced side effect , especially with neuraxial opioids .

INTRATHECAL OPIOIDS(37)

In the context of Augmentation strategies for spinal anaesthesia , the discovery of opioid receptors and the development of technique of intrathecal opioid administration is one of the most significant advances in pain management in the last three decades . Neuraxial opioids , in contrast to local anaesthetics , do not cause sympathetic block , skeletal muscle weakness or lack of proprioception .

PHARMACODYNAMICS

The exact mechanism of local anaesthetic - opioid interaction remains unkown . When administered alone , spinal opioids selectively modulate C and A fibres with minimal impact on dorsal root axons . Local anaesthetics potentiate the antinociceptive effect of Morphine , without an enhancement in motor block . Transient change in temperature perception has been observed with spinal Meperidine , Fentanyl and Sufentanil The dorsal root entry zone is speculated to be the active site for conduction block for spinal opioids .

PHARMACO KINETICS

It is believed that hydrophilic opioids remain unbound in the CSF for a long time and hence move rostrally in the CSF , thereby resulting in delayed respiratory depression (eg) Morphine . In contrast

lipophilic opioids do not move rostrally in CSF , but move more rapidly than hydrophilic opioids from CSF to spinal cord .

ONSET OF ACTION

Lipophilic opioids spread more rapidly from the CSF into the spinal cord . Hence they have faster onset of action (eg.Fentanyl) than hydrophilic opioids . The delayed onset of action of Morphine , a hydrophilic opioid may in fact limits its utility as an intraoperative adjuvant.

ANALGESIC MECHANISMS

The dorsal horn of the spinal cord is richly populated with opioid receptors . Majority of these are localized within substansia gelatinosa. Upon receptor activation , a G protein mediated effects result in inhibition of adenyl cyclase and inward flux of potassium . This flux results in membrane hyperpolarization and decrease in neural excitability (anti nociceptive effect) . Opioids may act at synapses in spinal cord either presynaptically or postsynaptically . μ receptor activation results in the presynaptic inhibition of substance P release . All clinically useful intrathecal opioids are strong μ receptor agoinsts within the dorsal horn . Their supraspinal and spinal effects act synergistically to blunt somatic as well as visceral pain . But analgesic effect is more specific for visceral pain . Analgesia of neuraxial opioids is also dose related .

DURATION OF ACTION

The duration of analgesic action will depend upon the efficacy , lipophilicity , receptor affinity and the dose of the drug administered .

POTENCY

H.J.McQuay et al in 1989 published that the intrathecal potency is defined as the amount of drug required to produce a particular degree of receptor occupancy . It is inversely related to their lipid solubility and related directly to the affinity of the drug for the receptor .

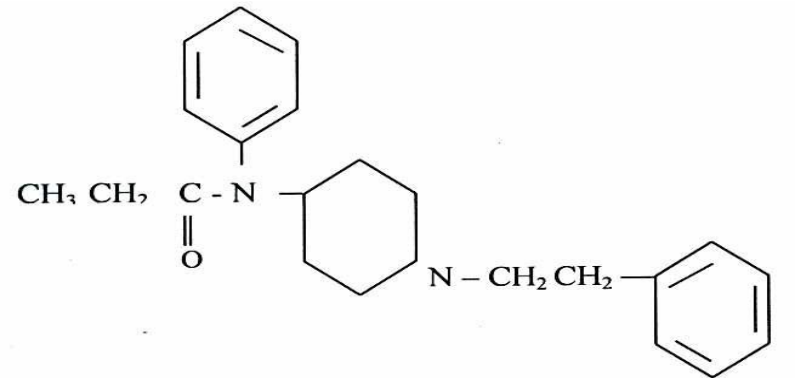
SIDE EFFECTS

Main side effects are pruritus , nausea and vomiting and urinary retention .

PHARMACOLOGY OF FENTANYL(37)

Fentanyl is a Phenylpiperidine derivative , synthetic opioid agonist that is structurally related to Meperidine . As an analgesic , Fentanyl is 75 to 125 times more potent than Morphine .

Chemical Structure



Pharmacokinetics and Physicochemical properties

Fentanyl has a more rapid onset and shorter duration of action than Morphine . Effect – Site equilibration time between blood and the brain for Fentanyl is 6.4 min . The greater potency and more rapid onset of action reflects the greater lipid solubility of Fentanyl compared with that of Morphine . Short duration of action of a single dose reflects its rapid redistribution to inactive tissues such as fat , skeletal muscle and lungs.

pKa – 8.4 , % Unionized at pH 7.4 - < 10 , Octanol / water partition coefficient – 813 , % Bound to plasma protein – 84 , Diffusible fraction (%) – 1.5 , Clearance (ml/kg/mt) 10 – 20 , Hepatic extraction ratio 0.8 – 1.0

Metabolism

Fentanyl is extensively metabolized by N – demethylation producing Norfentanyl , which is structurally similar to Normeperidine . It is excreted by the kidneys and can be detected in the urine for 72 hours after a single IV dose of Fentanyl .

Routes of Administration

Oral , parenteral (IV / IM) , transmucosal , transdermal , neuraxial (subarachnoid / epidural) .

Clinical Uses

Intravenous Fentanyl

Low doses of Fentanyl 1 to 2 μgm/kg IV , are injected to provide analgesia . Fentanyl 2 to 20 μgm/kg IV . Large doses of Fentanyl , 50 to 150 μgm/kg IV, have been used alone to produce surgical anaesthesia. It has the advantage of stable hemodynamics due to lack of direct myocardial depressant effect absence of histamine release suppression of stress responses to surgery .

Disadvantages

Failure to prevent sympathetic nervous system responses to painful surgical stimulation at any dose , possible patient awareness and postoperative depression of ventilation

HISTORY AND REVIEW OF LITERATURE

SUBARACHNOID BLOCK

In 1885 , J.Leonard Corning a NewYork neurologist first used cocaine experimentally in dogs . In men the first spinal anaesthesia was conducted by August Bier on 16.08.1898 with cocaine 3cc as 0.5% solution . It was followed by Rudolf Matas in America and Tuffier in France .

BUPIVACAINE

It was synthesized in Sweden by Ekenstam and his Colleagues in 1957 and used clinically by L . J . Telivl Jo in 1963 .

INTRATHECAL OPIOIDS

Gate control theory of pain (1965) by Melzack and Wall focused the attention on importance of dorsal horn of spinal cord in the modulation of pain .

In 1973 , Pert (and) Snyder identified the specific opiate receptors in the substantia gelatinosa of dorsal horn of spinal cord (35).

In 1976 , spinal effects of intrathecal opiates in animals were demonstrated by Yaksh and Rudy (47).

In 1977 , Wang , Nauss and Thomas studied the effect of intrathecal morphine in men with intractable pain of lowerlimb due to malignancies invading lumbosacral plexus(44) .

In 1980 , Davies et al , identified that respiratory depression with intrathecal morphine was reversed with systemic Naloxone without reversing analgesia(15).

Behar M et al [1979] reported the first effective use of epidural opioids in human(1) .

Wang JK et al [1979] reported the first controlled study of intrathecal opioids in human . They demonstrated that small doses of morphine given intrathecally or extradurally produced long lasting relief of chronic and post operative pain in man (44).

Crawford JS [1980] claimed that spinal opioids act predominantly on the brain(12).

Willer JC and Bussel B [1980] and Maruyama Y et al [1980] suggested a selective spinal analgesic effect in humans (45).

Willer JC and Bussel [1980] and Yaksh TL [1981] suggested that opioids act on presynaptic and postsynaptic receptors in the substantia gelatinosa of spinal cord dorsal horn where they inhibit neurone cell excitation (45).

Reiz and Westberg [1980] and Yaksh TL [1981] and Samii J , Chanin M and Viars P [1981] reported adverse reactions such as pruritus and urinary retention after intrathecal administration of opioids .

Bromage PR et al [1982] suggested that pruritus may be due to alterations in sensory modulations following opioid spread over the spinal cord to the brain . They also found Naloxone to be effective in the control of pruritus (5).

FENTANYL AND INTRATHECAL ANAESTHESIA

Mok et al 1984 studied the effect of intrathecal injection of Fentanyl , Sufentanil , Alfentanil and Nalbuphine for postoperative analgesia with promising results .

Wang , Chen MB et al 1993 , This study examined the effect of Bupivacaine administered intrathecally on sympathetic efferent and 'A' delta and 'C' fibre mediated afferent pathways in dogs and the interactions with intrathecal Fentanyl . The results showed that intrathecal Bupivacaine has no selectivity for the afferent and efferent pathways and intrathecal Fentanyl acts synergistically to enhance the effect of Bupivacaine on the afferent pathway without a measurable effect on sympathetic out flow (43).

Singh , Harbheo , Yang et al 1995 studied the effect of intrathecal Fentanyl on the onset and duration of hyperbaric Bupivacaine induced spinal block in adult male patients undergoing genito urinary surgery . They concluded that Fentanyl 25 mg , prolongs the duration

of Bupivacaine induced sensory block by 28% and increased the post operative analgesia(39) .

Hunt et al reported that addition of Fentanyl 6.25mg to the hyperbaric Bupivacaine reduced the intraoperative opioid requirement in patients undergoing caesarean delivery under subarachnoid block

Ben David et al explored the synergism between intrathecal opioids and local anaesthetics , it may be possible to augment the spinal anesthesia without prolonging the recovery. Based on this fact they have done the study on 50 patients undergoing ambulatory surgical arthroscopy . Implications : Small dose Bupivacaine is inadequate for this procedure but the addition of Fentanyl makes it reliable (4).

Roussel JR et al concluded a study on the effects of intrathecal Fentanyl on duration of Bupivacaine spinal blockade for outpatient knee arthroscopy and concluded that Fentanyl does not enhance the onset and duration of sensory (or) motor block produced by intrathecal Bupivacaine . Fentanyl however prolong postoperative analgesia and increases the risk of pruritus .

Ben David B , Frankel R et al studied the effect of mini dose Bupivacaine –Fentanyl spinal anaesthesia for surgical repair of hip fracture in the aged . The synergism between intrathecal opioids

and local anaesthesia may make it possible to achieve reliable spinal anaesthesia with minimal hypotension using a small dose of local anaesthetic . 20 patients of more than 70 years of age for surgical repair of hip were divided in to groups of ten each .

Group A - Received Bupivacaine 4 mg and Fentanyl 20 mg

Group B - Received 10 mg of Bupivacaine alone .

They concluded that the mini dose combination caused dramatically less hypotension than 10 mg Bupivacaine(3).

Ozgun Cuvas et al studied the effect of Levobupivacaine with or without Fentanyl in spinal anesthesia for transurethral resection operation . They found that addition of Fentanyl to Levobupivacaine shortens the duration of motor block (34).

Mohammed Al - Talhouni et al studied the advantage of combined spinal epidural anesthesia for TURP and found that it is an useful alternative technique to either spinal or epidural anesthesia (31).

Fauzia A Khan et al compared the effect of combination of Bupivacaine and Fentanyl with Bupivacaine and Buprenorphine in elderly patients coming for urological surgeries .They found that both groups were equally effective with higher incidence of nausea and vomiting in group of Bupivacaine and Buprenorphine (17).

Fontes D Chalo et al studied the effect of adding Fentanyl to Bupivacaine in spinal anesthesia with respect to hemodynamic stability . They found that there was reduction in MAP when high dose of Bupivacaine is combined with Fentanyl but not with low dose of Bupivacaine (19).

Pramod Patra , Mukul Chandra Kapoor , Trevor Gordon Michael Nair studied the effect of low dose Bupivacaine with Fentanyl for elderly patients undergoing endoscopic urological procedure . They concluded that the addition of Fentanyl to Bupivacaine provide adequate surgical anaesthesia with an ideal peak sensory block height and significantly reduces the duration of both sensory and motor blockade , with no significant adverse effects apart from pruritus , facilitating early discharge of patients (36) .

Ben David B , Levin H , Solomon E et al , studied spinal anaesthesia in ambulatory surgery . The effect of saline dilution was studied . They concluded that the most important determinant of both successful surgical anaesthesia and time until recovery is the dose of local anaesthetic drug (4).

Karamaz , kaya , Turhanoglu et al studied the effect of intrathecal low dose Bupivacaine - Fentanyl in elderly patients undergoing

transurethral prostatectomy . Patients were randomly assigned to one of two groups . Group F received plain Bupivacaine 4 mg with 25 mcg of Fentanyl and sterile water to a total of 1.5 ml , and Group B received only 0.5% plain Bupivacaine 7.5 mg for spinal anaesthesia . Sensory block was adequate for surgery in all patients . The mean level of motor block was higher and the duration of motor block was longer in Group B . Hypotension and shivering were significantly more common in Group B .They concluded that The addition of Fentanyl 25 mcg to plain Bupivacaine 4 mg provides adequate analgesia for transurethral prostatectomy with fewer side-effects in elderly patients when compared with conventional dose of Bupivacaine (25).

Iheb Labbene , Khaled Lamine , Hedi , Adel et al

compared the efficiency of low dose vs varying doses of hyperbaric Bupivacaine in spinal anesthesia for endoscopic urological procedures . Sixty consecutive patients were studied in a randomized prospective manner . They received either of 5 , 7.5 or 10 mg of hyperbaric Bupivacaine 0.5% combined with 25 μg of Fentanyl . They suggested that the use of a low dose of Bupivacaine (5 mg) added to Fentanyl (25 μg) for endoscopic urological surgery resulted in short-acting sensory block , without prolonged motor block and a lower incidence of cardiovascular side effects(24) .

MATERIALS AND METHODS

After getting the approval from the institutional ethical committee study was conducted in 75 patients aged above 60 years undergoing TURP surgery . After getting consent and explaining the procedure details the anaesthetic technique was performed .

INCLUSION CRITERIA

- Elective elderly male surgical patients posted for TURP surgery .
- ASA physical status 2 .
- Age 60 yrs and older who have given valid informed consent .

EXCLUSION CRITERIA

- Patient refusal
- Post spinal surgeries
- Coagulation abnormalities
- Cardiac or Renal failure
- Neurological illness, Mental illness
- Deformity of spinal column
- Allergy to local anesthetics.
- Not fitting into inclusion criteria.

PROCEDURE DETAILS

Patients were randomly allocated to one of three groups . Group I (n = 25) received Hyperbaric Bupivacaine 5 mg with Fentanyl 25 μg Group II (n = 25) received Hyperbaric Bupivacaine 7.5 mg with Fentanyl 25 μg. Group III (n = 25) received Hyperbaric Bupivacaine 10 mg with Fentanyl 25 μg

On preoperative visit the patients were explained about the procedure details . Then preoperative baseline parameters like pulse rate , blood pressure , respiratory rate were recorded . Iv line started with 18 gauge intravenous cannula and infused with 500 ml crystalloid.

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

- Boyles machine with oxygen cylinder
- Disposable Hudsons face mask for oxygen administration
- Laryngoscope with various blades
- Airway in all sizes
- Suction apparatus
- Appropriate sizes of endotracheal tubes .
- Emergency drugs like Inj Ephedrine,Inj Dopamine,Inj Atropine and Inj Adrenaline,Inj Naloxone.

Patients were put in right lateral position and with strict aseptic precaution lumbar puncture was done with Quinke standard 25 Gauge spinal needle in L3—L4 interspace . After ensuing free flow of CSF, drug was injected as per the group assigned . After injecting the drug patients were put in supine position . After attaining T 10 level of sensory block and Modified Bromage Grade 2 or 3 motor block the patient was put up in lithotomy position. Oxygen was given through ventimask .

Following parameters were recorded

- Time to reach sensory block T 10
- Maximal sensory block height
- Motor blockade (Grade)
- Time to two segment regression
- Time to complete sensory regression
- Time to complete motor regression
- Heart Rate , BP , SPO_2 , RR every five minutes till the end of surgery
- Pruritus , nausea , vomiting , pain , bradycardia , hypotension , respiratory depression .

The level of sensory block , defined as the loss of sharp sensation by using a pinprick method with a 20 Gauge hypodermic needle , was recorded bilaterally at the midclavicular line at the dermatomal level .

Motor block was assessed using the **Modified Bromage Scale .**

0 = no motor block

1 = inability to raise extended legs

2 = inability to flex knees

3 = inability to flex ankle joints

After adequate spinal block (sensory level T10 & motor Grade 2,3) , the patient was positioned in the lithotomy position and surgery started .

Hypotension was defined as a systolic blood pressure (SBP) < 90 mm Hg or a decrease in SBP by 30% or more from baseline values(3) , and was initially treated by Normal saline solution ; when needed Inj Ephedrine 3 mg was given in increments until the correction of SBP(36) .

Bradycardia was defined as a heart rate <50 bpm or a decrease of more than 20% from the initial value and was treated by Atropine 0.5 mg in addition to the treatment of hypotension(3) in our study (36).

Respiratory depression was defined as a respiratory rate less than 8 breaths / min and / or oxygen saturation less than 85% in room air(36).

Other adverse effects , including pruritus , nausea and vomiting were recorded .

Analgesia was noted by the **Visual Analog Scale**

0-1 - Excellent

2-4 - Good

5-6 - Fair

7-8 - Poor

9-10 - No relief

With the Pain score > 6 – supplementary analgesia was given .

Duration of the procedure was recorded . Sensory level at the end of the surgery was noted . All patients were followed up in the postoperative period for any complications like postoperative nausea , vomiting , pruritus , hypotension and respiratory depression .

STATISTICAL TOOLS

The information collected regarding all the selected cases were recorded in a Master Chart . Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2002) .** Using this software , range , frequencies , percentages , means , standard deviations , chi square and 'p' values were calculated . Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables . A 'p' value less than 0.05 is taken to denote significant relationship. Statistical significance was brought out by ANOVA.

OBSERVATION

Table-1 Age Distribution of the study Sample

Age Group	Group-A		Group-B		Group-C	
	N	**%**	**N**	**%**	**N**	**%**
60 – 65	15	60.00	16	64.00	16	64.00
66 – 70	07	28.00	06	24.00	08	32.00
71 – 75	01	04.00	03	12.00	01	04.00
76 – 80	02	08.00	00	-	-	-
TOTAL	25	100	25	100	25	100
Mean	66.76		66.20		64.44	
Sd	4.88		4.12		3.39	
P-Value & Significant	**F=2.09 p=0.130 Not Significant**					

Table-2 Comorbid Illness

Comorbid Illness	**Group – A**		**Group – B**		**Group - C**	
	N	**%**	**N**	**%**	**N**	**%**
DM	4	16	4	16	5	20
HT	2	08	3	12	3	12
IHD	2	08	2	08	2	08
COPD	2	08	3	12	2	08

Table-3 Height and Weight of the study Sample

	Group-A		Group-B		Group-C		F-Value	P-Value
	Mean	Sd	Mean	Sd	Mean	Sd		
Height	163	3.10	164	2.81	164	3.38	**0.162**	**0.85 ***
Weight	60.64	5.60	60.52	5.21	59.64	5.10	**0.265**	**0.77 ***

* Not Significant

Table-4 BaseLine Heart Rate , Blood Pressure

	Group-A		Group-B		Group-C		F-Value	P-Value
	Mean	**Sd**	**Mean**	**Sd**	**Mean**	**Sd**		
SBP	121.60	27.97	118.35	27.46	124.08	9.56	**0.357**	**0.70 ***
DBP	70.96	16.01	70.61	16.36	73.17	4.64	**0.252**	**0.78 ***
MAP	88.20	19.67	86.17	19.74	89.25	5.88	**0.212**	**0.81 ***
HR	66.64	16.02	71.20	6.73	68.80	6.58	**1.130**	**0.33 ***
RR	12.96	2.98	13.52	1.39	13.40	1.26	**0.527**	**0.59 ***
SPO2	94.92	19.80	98.92	1.04	98.92	0.95	**1.015**	**0.37 ***

Table-5 Maximum Sensory Level

Maximum Sensory Level	Group – A		Group – B		Group - C	
	N	%	N	%	N	%
T5	0		0		2	08
T6	0		0		9	36
T7	0		2	08	9	36
T8	0		7	28	4	16
T9	5	25	14	56	1	04
T10	20	75	2	08	0	-
Total	25	100	25	100	25	100

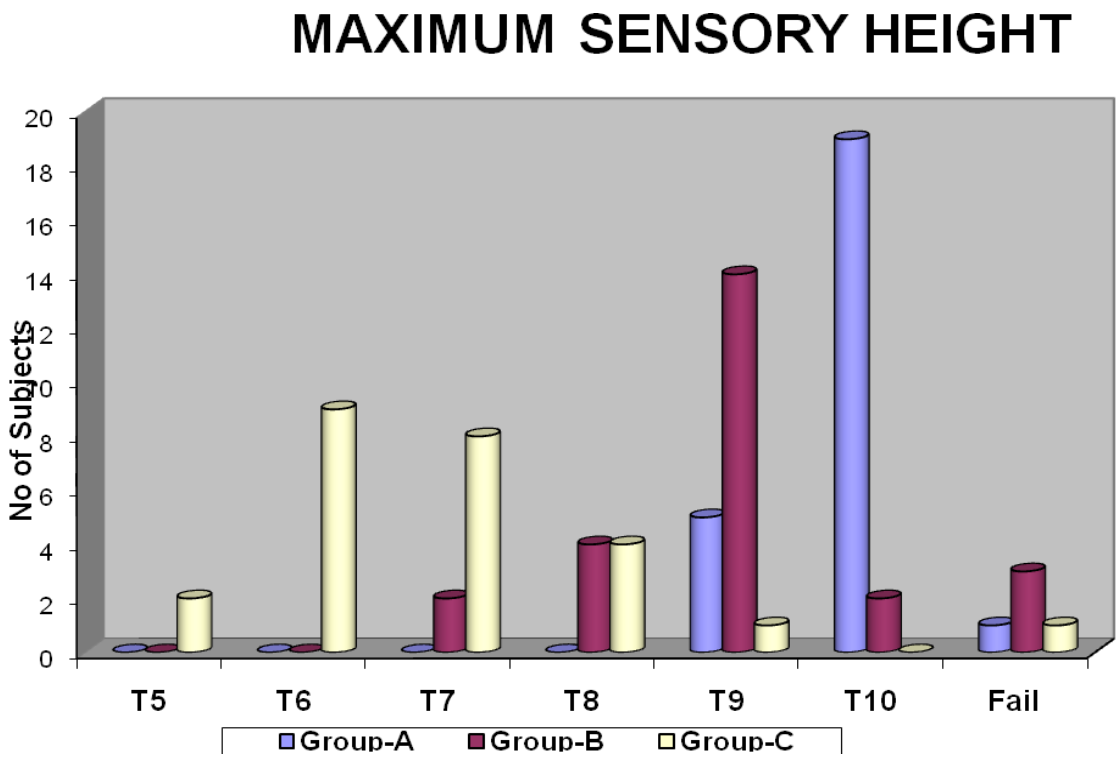


Table – 6 T10 time

Group-A		Group-B		Group-C		F-Value	P-Value
Mean	**Sd**	**Mean**	**Sd**	**Mean**	**Sd**		
7.88	0.80	5.41	0.50	3.33	0.65	**279.12**	**0.000**

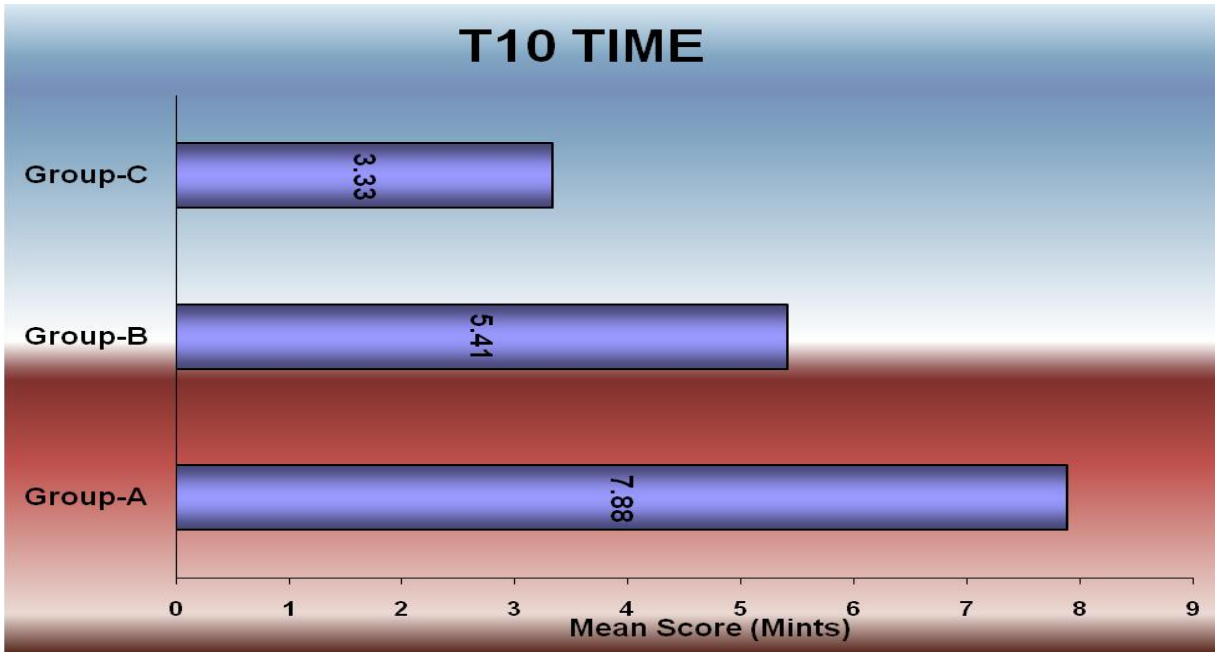


Table-7 Motor Grade

Group-A		Group-B		Group-C		F-Value	P-Value
Mean	**Sd**	**Mean**	**Sd**	**Mean**	**Sd**		
2.08	0.28	3.00	0.00	3.00	0.00	**242.16**	**0.000**

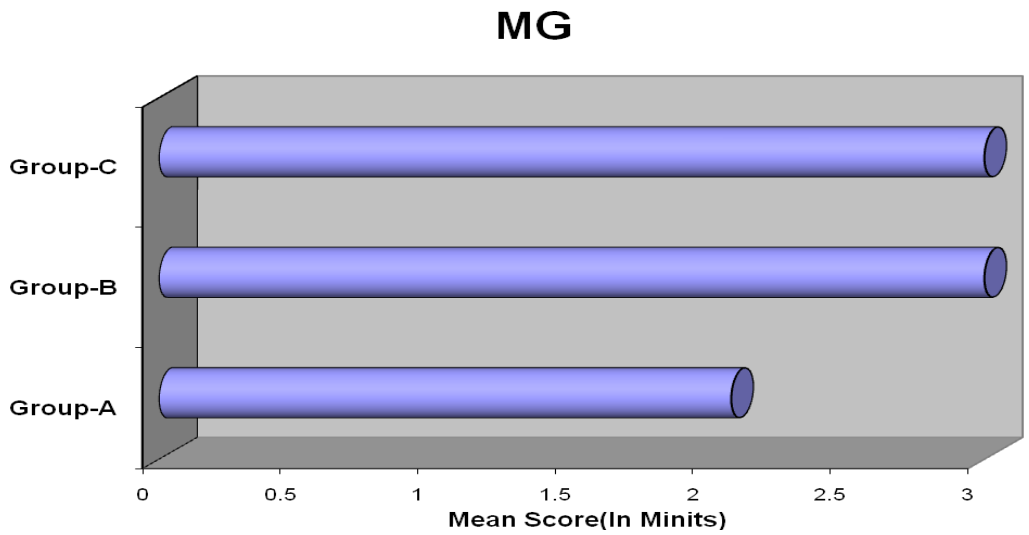
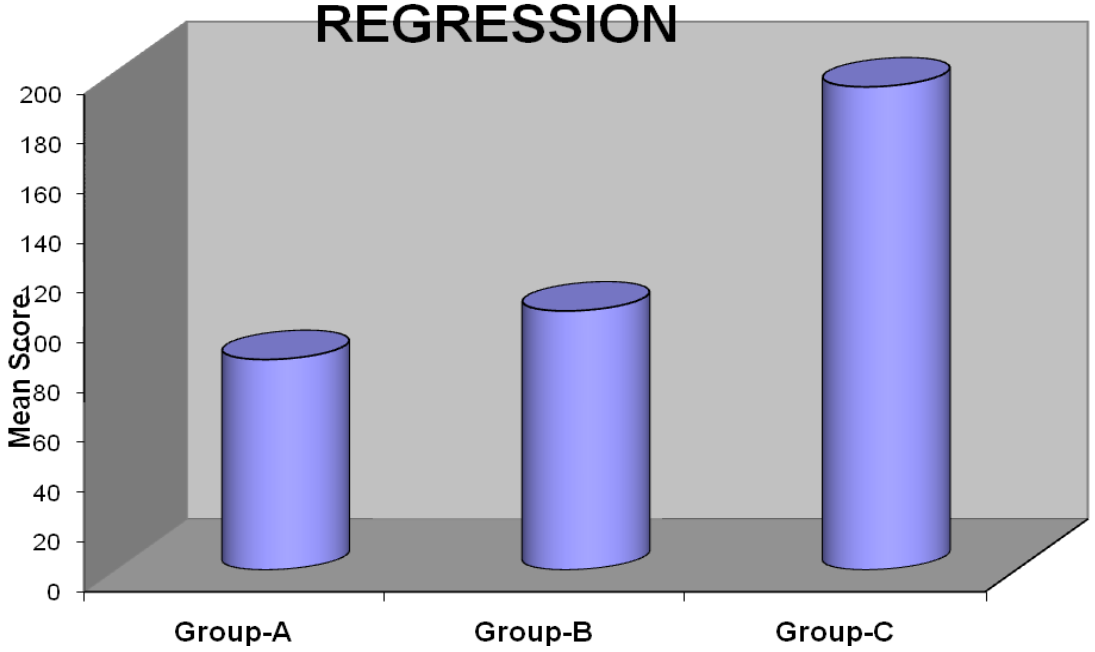


Table-8

	Group-A		Group-B		Group-C		F-Value	P-Value
	Mean	**Sd**	**Mean**	**Sd**	**Mean**	**Sd**		
Two Seg Sensory regression	56.80	13.61	79.58	25.32	116.25	9.35	**72.51**	**0.000**
Complete Sensory Regression	84.60	20.41	104.12	45.89	194.20	41.53	**60.36**	**0.000**
Complete Motor Regression	63.20	15.87	85.32	32.96	136.88	29.20	**48.93**	**0.000**

COMPLETE SENSORY REGRESSION



COMPLETE MOTOR REGRESSION

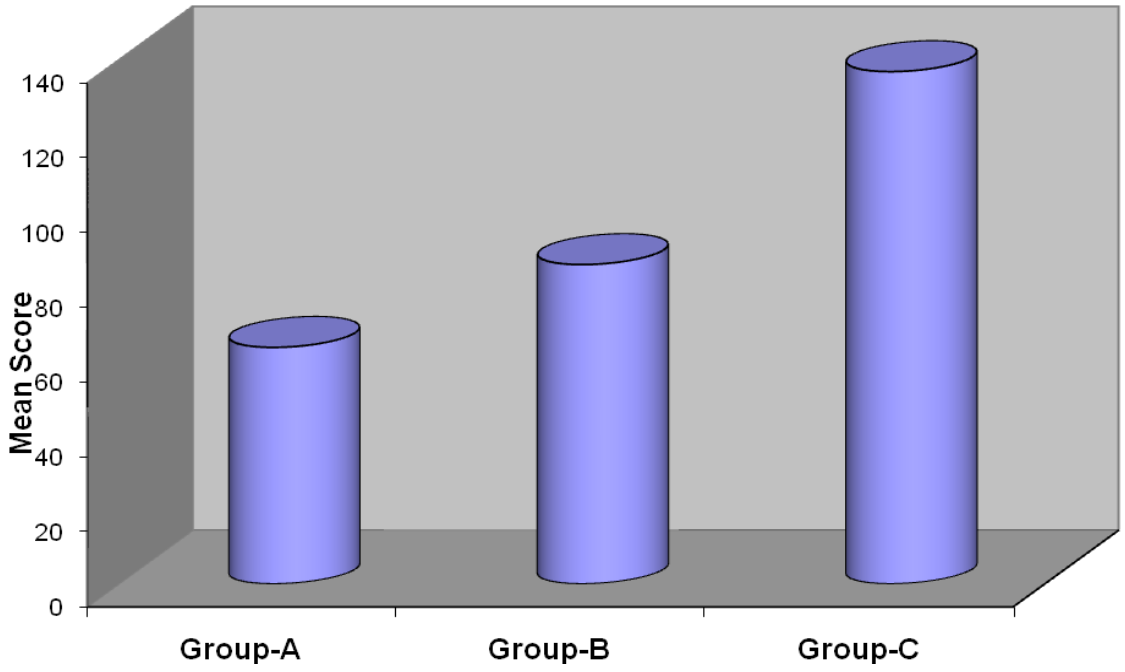


Table-9 Changes in Heart Rate

Heart Rate	Group-A	Group-B	Group-C	F-Value	P-Value
	Mean (sd)	Mean (sd)	Mean(sd)		
At Base Mints	66.64 (16.02)	71.20 (6.73)	68.80 (6.58)	**0.33**	**NS**
At 05 Mints	65.04 (15.35)	66.56 (6.62)	64.56 (5.58)	**0.77**	**NS**
At 10 Mints	64.56 (15.36)	63.76 (5.73)	60.96 (5.17)	**0.41**	**NS**
At 15 Mints	64.16 (15.22)	62.64 (5.99)	57.92 (5.73)	**0.08**	**NS**
At 20 Mints	63.76 (15.00)	61.55 (5.66)	57.17 (6.57)	**0.08**	**NS**
At 25 Mints	63.84 (15.24)	61.64 (5.88)	57.75 (8.86)	**0.13**	**NS**

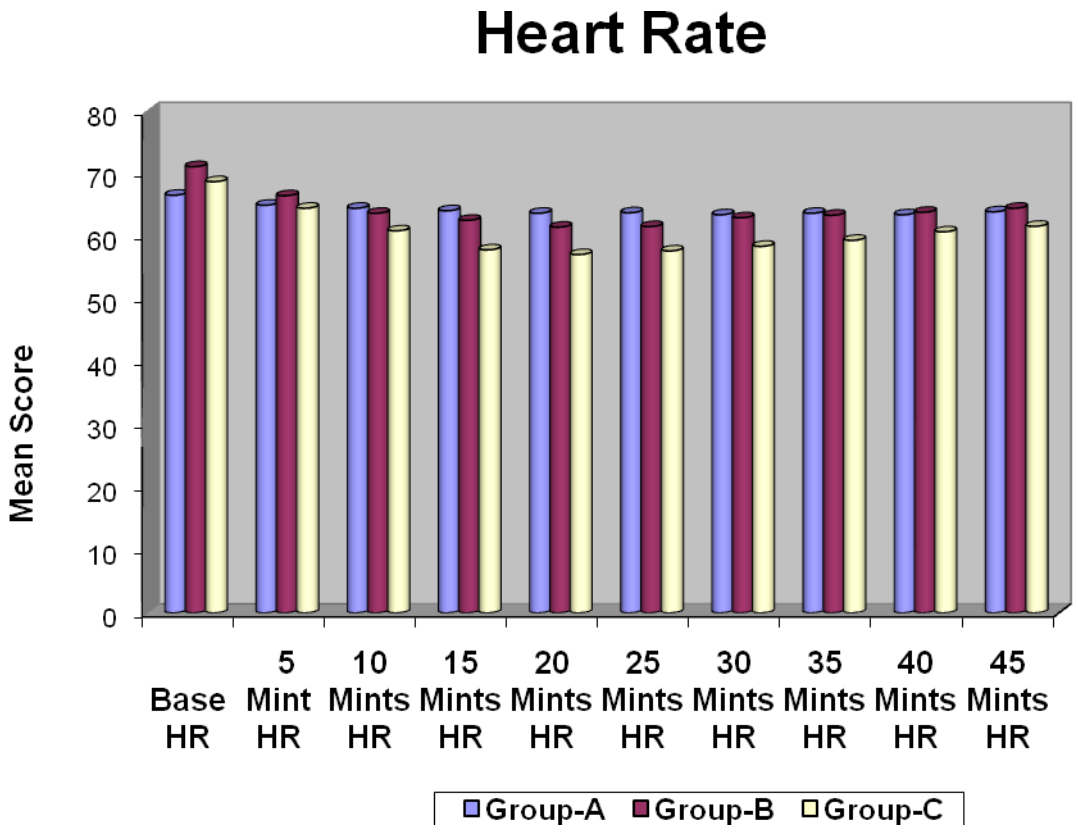


Table-10 Changes in RR

RR	Group-A	Group-B	Group-C	F-Value	P-Value
	Mean (sd)	Mean (sd)	Mean(sd)		
At Base Mints	12.96 (2.98)	13.52 (1.39)	13.40 (1.26)	**0.527**	**NS**
At 5 Mints	12.88 (2.98)	13.44 (1.42)	13.32 (1.28)	**0.521**	**NS**
At 10 Mints	12.60 (2.94)	13.12 (1.51)	13.16 (1.34)	**0.574**	**NS**
At 15 Mints	12.20 (2.78)	12.72 (1.34)	12.76 (1.17)	**0.672**	**NS**
At 20 Mints	12.20 (02.71)	12.76 (0.97)	12.76 (0.97)	**0.851**	**NS**

Table-13 Changes in SPO2

SPO2	Group-A	Group-B	Group-C	F-Value	P-Value
	Mean (sd)	Mean (sd)	Mean(sd)		
At Base Mints	94.92 (19.80)	98.92 (1.04)	98.92 (0.95)	**1.02**	**NS**
At 5 Mints	94.92 (19.80)	98.92 (1.04)	98.92 (0.95)	**1.02**	**NS**
At 10 Mints	95.20 (19.84)	99.28 (0.54)	99.20 (0.58)	**1.04**	**NS**
At 15 Mints	95.20 (19.84)	99.24 (0.60)	99.20 (0.58)	**1.03**	**NS**

Table-12 Changes in SBP

SBP	Group-A	Group-B	Group-C	F-Value	P-Value
	Mean (sd)	Mean (sd)	Mean(sd)		
At Base Mints	121.60 (27.97)	118.35 (27.46)	124.08 (09.56)	**0.357**	**NS**
At 5 Mints	123.33 (10.90)	110.64 (11.72)	90.88 (18.32)	**32.23**	**0.000**
At 10 Mints	120.00 (9.64)	105.28 (11.41)	89.83 (3.06)	**71.97**	**0.000**
At 15 Mints	118.92 (9.87)	103.73 (10.52)	93.33 (3.42)	**55.16**	**0.000**
At 20 Mints	112.88 (25.25)	100.26 (24.23)	97.58 (06.21)	**3.86**	**0.03**
At 25 Mints	113.36 (26.71)	102.52 (24.34)	102.33 (07.48)	**2.14**	**NS**
At 30 Mints	110.88 (25.11)	104.78 (24.29)	104.50 (08.26)	**0.740**	**NS**
At 35 Mints	110.56 (24.85)	106.43 (24.73)	108.00 (09.18)	**0.239**	**NS**
At 40 Mints	110.80 (24.94)	107.74 (24.79)	110.00 (07.95)	**0.158**	**NS**

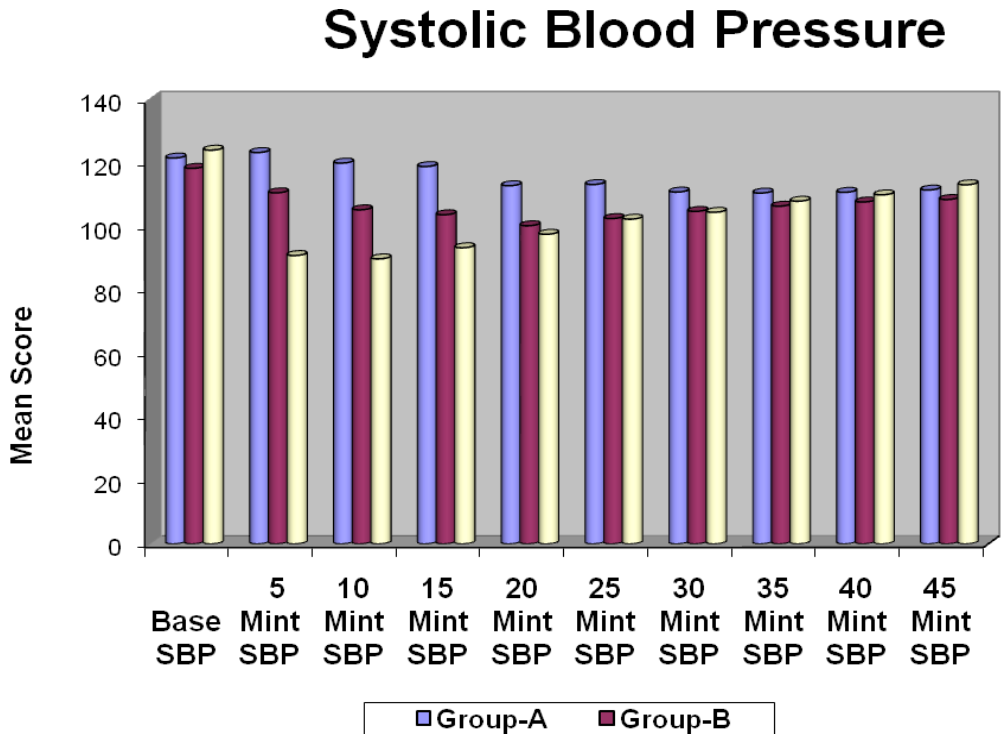


Table-13 Changes in DBP

DBP	Group-A	Group-B	Group-C	F-Value	P-Value
	Mean (sd)	Mean (sd)	Mean(sd)		
At Base Mints	70.96 (16.01)	70.61 (16.36)	73.17 (04.64)	**0.252**	**NS**
At 5 Mints	71.25 (6.21)	65.18 (6.64)	60.83 (04.60)	**19.135**	**0.000**
At 10 Mints	71.75 (8.03)	63.55 (5.91)	59.25 (03.22)	**26.356**	**0.000**
At 15 Mints	68.08 (6.17)	63.55 (6.62)	63.33(4.40)	**5.103**	**0.01**
At 20 Mints	65.44 (14.86)	62.52 (14.86)	66.25 (04.18)	**0.588**	**NS**
At 25 Mints	65.76 (14.81)	65.39 (15.44)	68.42 (03.68)	**0.415**	**NS**
At 30 Mints	65.92 (14.95)	65.39(14.98)	69.67 (04.71)	**0.828**	**NS**
At 35 Mints	66.80 (14.80)	66.52(15.14)	70.58 (04.06)	**0.80**	**NS**

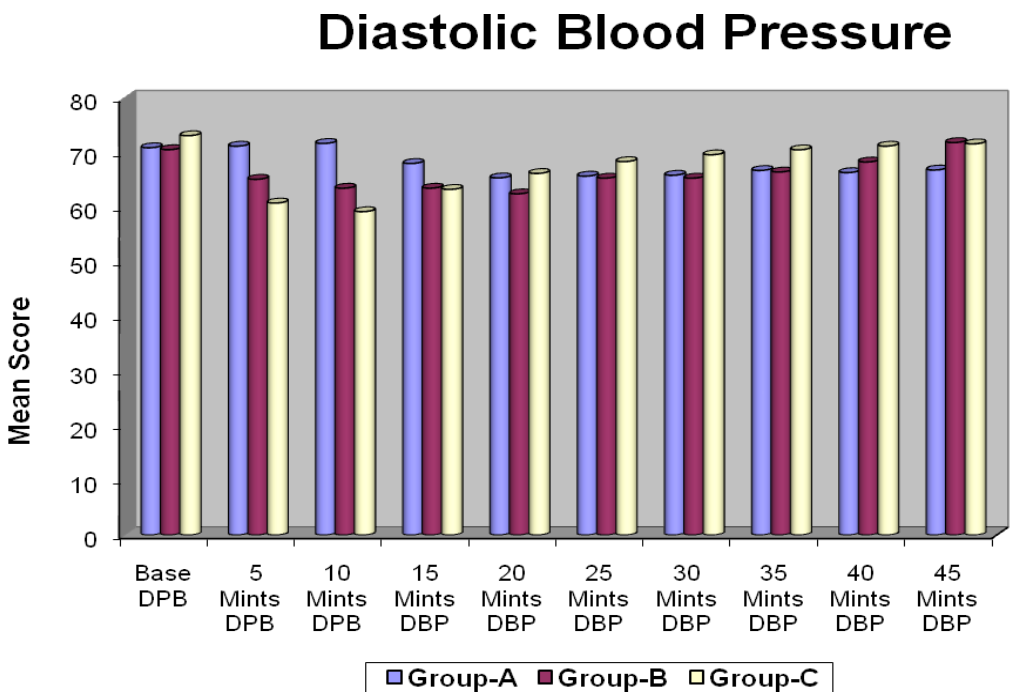


Table-14 Changes in MAP

MAP	Group-A	Group-B	Group-C	F-Value	P-Value
	Mean (sd)	Mean (sd)	Mean(sd)		
At Base Mints	88.20 (19.67)	86.17 (19.74)	89.25 (5.88)	**0.212**	**NS**
At 5 Mints	89.21 (6.95)	80.09 (7.63)	72.25 (4.74)	**40.633**	**0.000**
At 10 Mints	87.42 (7.31)	77.14(6.84)	69.67 (2.99)	**52.842**	**0.000**
At 15 Mints	85.08 (6.12)	76.64 (7.11)	73.63 (4.22)	**24.228**	**0.000**
At 20 Mints	81.20 (18.12)	75.22 (17.83)	76.95 (4.97)	**1.026**	**NS**
At 25 Mints	81.20 (17.83)	77.52 (17.99)	80.04 (4.56)	**0.381**	**NS**
At 30 Mints	81.08 (17.94)	78.39 (17.78)	81.00(05.57)	**0.246**	**NS**
At 35 Mints	81.56 (17.89)	79.70 (18.03)	82.96 (5.39)	**0.280**	**NS**
At 40 Mints	81.36 (18.23)	81.35 (18.05)	84.67 (4.59)	**0.388**	**NS**
At 45 Mints	81.88 (18.20)	85.64 (03.75)	85.67 (4.20)	**0.906**	**NS**

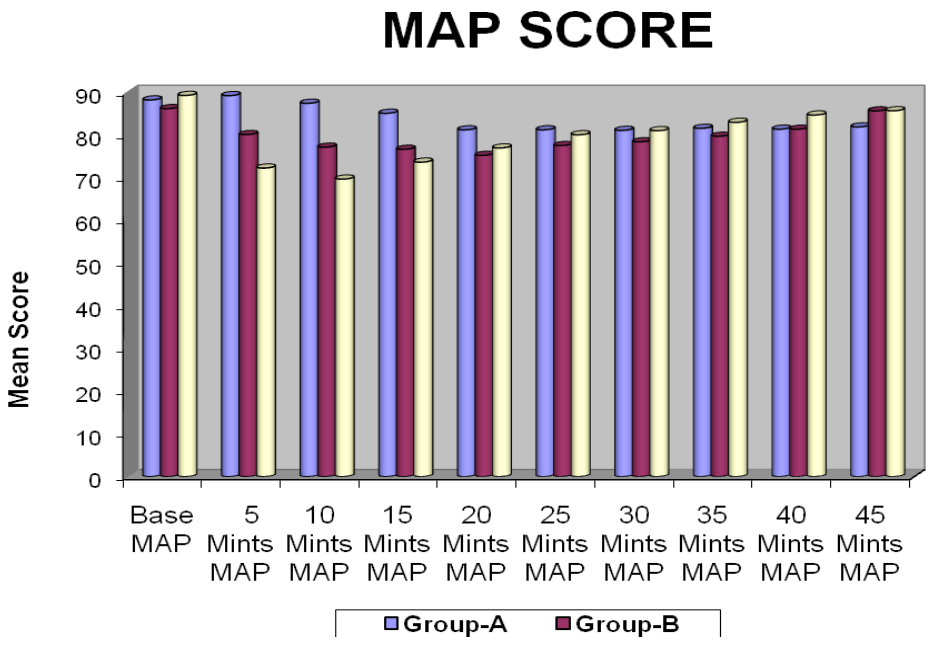


Table-15 Pain

Pain	Group – A		Group – B		Group - C	
	N	%	N	%	N	%
Vas 30	2.33	1.13	0.00	0.00	0.00	00
Vas at End	4.08	0.41	2.00	0.00	0.00	00
Difference	1.75	-0.72	2.00	0.00	00.00	00
Total	**25**	**100**	**25**	**100**	**25**	**100**

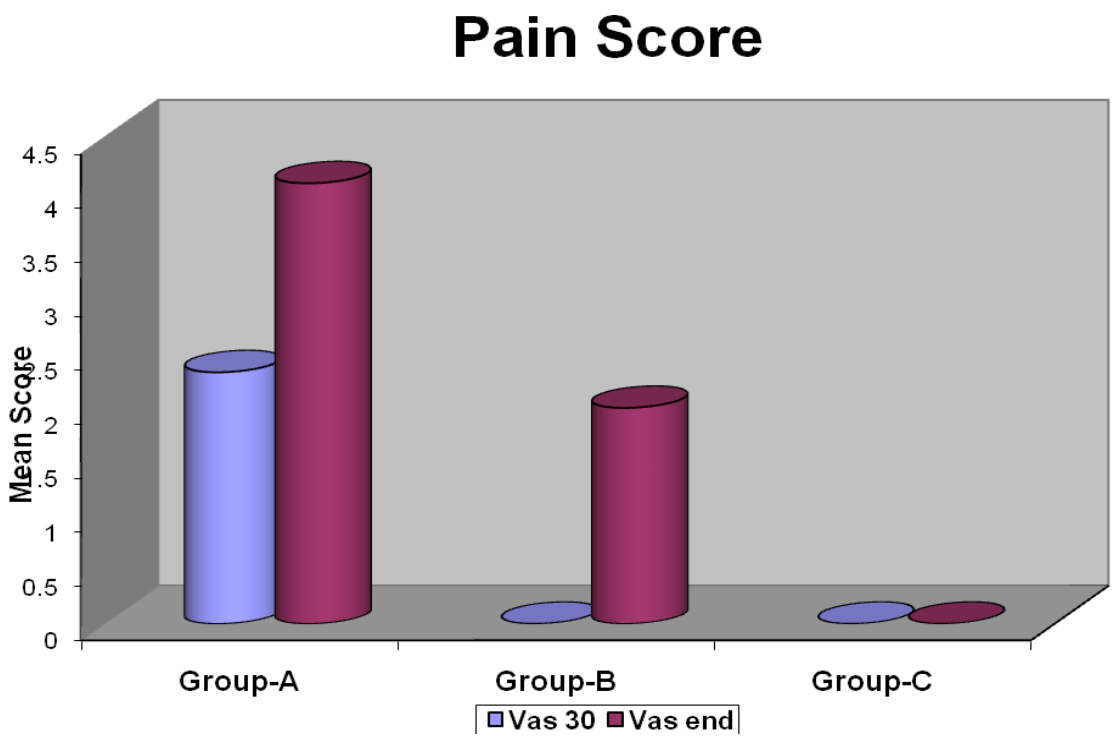


Table-16 Pruritus

Pruritus	Group – A		Group – B		Group - C	
	N	%	N	%	N	%
Yes	02	08	03	12	04	16
No	23	92	22	88	21	84
Total	**25**	**100**	**25**	**100**	**25**	**100**

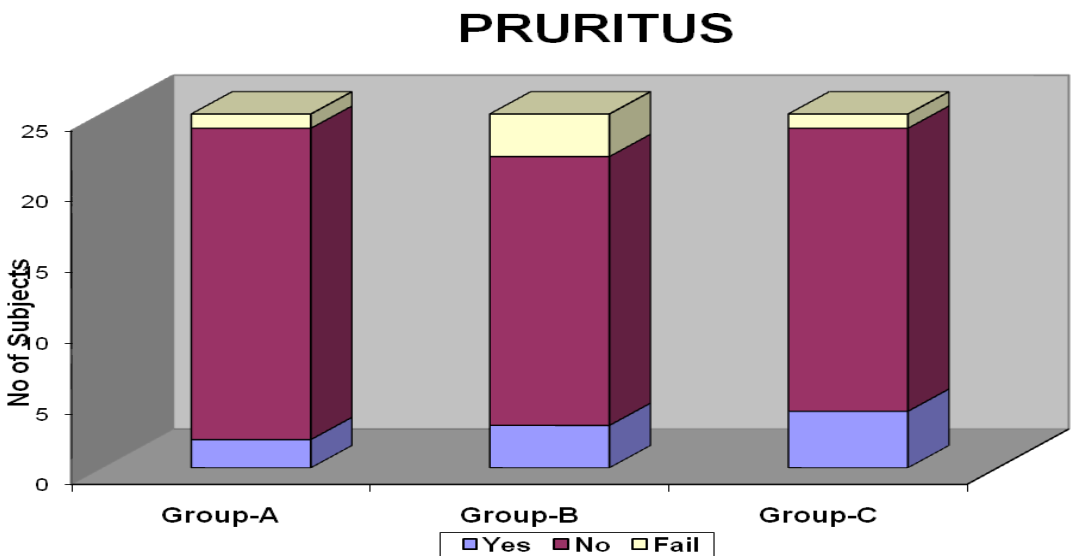
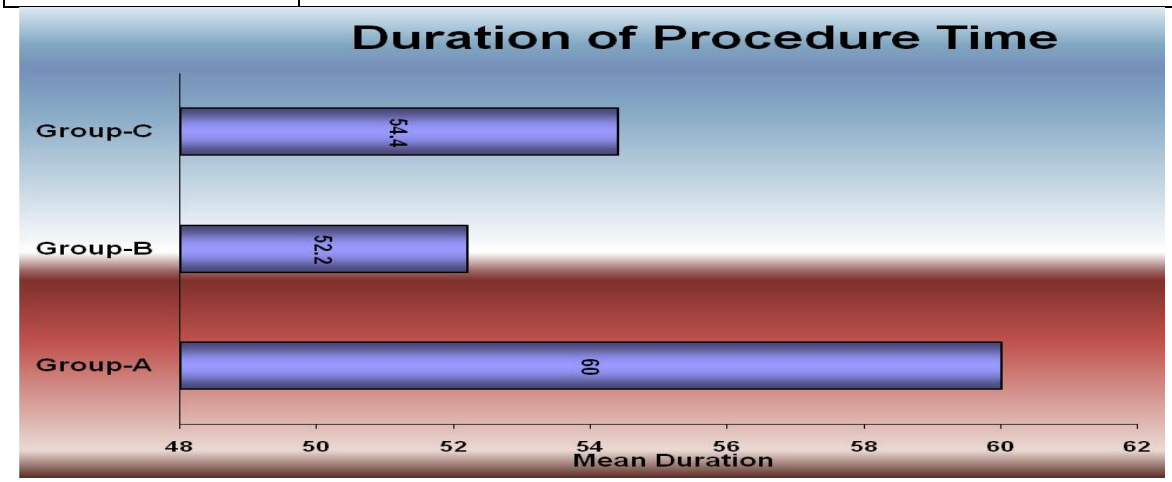


Table -17 Duration of Procedure

Duration	Group-A	Group –B	Group -C
Mean	60.00	52.20	54.40
Sd	08.66	21.46	13.49
Range (Min – Max)	45.00 – 90.00	43.06 – 61.06	48.83 – 59.97
P-Value	**1.691**		
Significant	**Not Significant**		



RESULTS

In this randomized single blinded study conducted in 75 patients , the subjects were allocated in to three groups .

Group A - Received Inj. 0.5% Bupivacaine 1.0 cc

Group B - Received Inj. 0.5% Bupivacaine 1.5 cc

Group C - Received Inj.0.5% Bupivacaine 2.0 cc

All the three groups received 25 mcg of Inj Fentanyl.

DEMOGRAPHIC DATA

All 3 groups were comparable in age , sex , height , weight , comorbid illness and nature of surgery .

MAXIMUM SENSORY LEVEL

Maximum sensory level achieved in Group A was T 9 , Group B was T 7 and in Group C it was T 5 .

The level was T9 in 76 % and T10 in 20% of patients in Group A . The level in Group B was T9 in 56% , T8 in 16% , T7 in 8% and T10 in 8% of patients . The level in Group C was T5 in 8% , T6 in 36% , T7 in 32% and T4 in 16% of patients .

TIME TO T10 SENSORY LEVEL

Group A - 7.88 mts with SD of 0.80

Group B - 5.41 mts with SD of 0.50

Group C - 3.33 mts with SD of 0.65

The difference in the time to achieve sensory level of T 10 was statistically significant (P ‹ 0.001) among the three groups .

GRADING OF MOTOR BLOCK

All the patients in Group B and C had a motor block of Grade 3 . Two patients in group A had a motor block of Grade 3 . All others in group A had a motor block of Grade 2.

HAEMODYNAMIC VARIABLES

Baseline values of all the three groups were comparable with respect to heart rate ,systolic blood pressure ,mean arterial pressure, respiratory rate and SpO2 .

BLOOD PRESSURE

Systolic blood pressure more than 30% from the base line value or less than 90 mm hg was considered hypotension (24) .

As far as observed values are concerned , systolic blood pressure (SBP) in Group A at 5 mins was 123.33±10.90 , at 10 mins was 120±9.64 , at 15 mins was 118.92±9.87 , at 20 mins was 112.88±25.25 . In Group B at 5 mins SBP was 110.64±11.72 , at 10 mins 105.28±11.41 , at 15 mins 103.73±10.52 , at 20 mins 100.26±24.23 . In Group C , SBP was at 5 mins 90.88±18.32 , at 10 mins 89.83±3.06 , at 15 mins 93.33±3.42 , at

20 mins 97.58±6.21 . Changes observed at 5 ,10 ,15 ,20 mins were statistically significant among the three groups (P ‹ 0.001) . There was no hypotension in Group A . Five in Group B had hypotension . All the patients in Group C had hypotension .

HEART RATE

Bradycardia is defined as heart rate less than 50 or less than 20% from the baseline value (24).

There was no bradycardia observed in Groups A and B . Six patients had bradycardia in Group C which can be directly attributed to the high sensory level in this group . Mean heart rate in Group A at 5 mins was 65.42±15.35 , at 10 mins 64.56±15.36 , at 15 mins 64.16±15.22 and at 20 min 63.76±15.00 . In Group B heart rate at 5 mins was 66.56±6.62 , at 10 mins 63.76±5.73 , at 15 mins 62.64±5.99 and at 20 mins 61.55±5.66 . In Group C heart rate at 5 mins was 64.56±5.58 , at 10 mins 60.96±5.17 , at 15 mins 57.92±5.73 and at 20 mins 57.17±6.57 . The difference in heart rate between the three groups was statistically significant (P ‹ 0.001) .

TWO SEGMENT REGRESSION TIME

Duration of analgesia as measured by two segment regression time in Group A was 56.8±13.61 mins ,

Group B was 79.58±25.32 mins ,

Group C was 116.25±9.35 mins.

There was delay in the two segment regression in sensory level in Group B and C when compared to Group A , but the mean duration of analgesia before the onset of two segment regression was sufficient for the surgery to be over . There was significant statistical difference observed between the three groups ($P < 0.001$).

TOTAL DURATION OF ANALGESIA

Total duration of pain free interval in

Group A was 84.6 ± 20.41 mins

Group B was 104.12 ± 45.89 mins

Group C was 194.20 ± 41.53 mins

The postoperative analgesia was significantly prolonged in Groups B and C . The difference was statistically significant ($P < 0.001$) .

TOTAL DURATION OF MOTOR BLOCKADE

Total duration of motor blockade measured as time for complete motor regression , in

Group A was 63.2 ± 15.87 mins

Group B was 85.32 ± 32.96 mins

Group C was 136.88 ± 29.20 mins

Motor block was prolonged in Group C when compared to Groups A and B . The difference was statistically significant ($P < 0.001$) .

COMPLICATIONS

Nausea and vomiting was not found in any of the groups . Pruritus developed in 88% of patients in Group A , 76% in Group B and 80% of the patients in Group C . Pain was measured using VAS . There was mild pain in Group A at the end of surgery almost in all the patients. There was excellent pain relief in Group C and good pain relief in Group B

DISCUSSION

The pain we perceive after a burn , bite (or) pinch is readily identifiable but difficult to define because it is differently perceived at different threshold . Pain is defined as psychical adjunct of protective reflex – by Sherington in 1906 .

The International Association of Society for Pain (IASP) defined it as " An unpleasant sensory and emotional experience associated with actual (or) potential tissue damage (or) described in terms of such damage " . The use of opioids to control pain exists even in ancient history and opioids are still the primary analgesic chosen for severe pain .

Advantage of intrathecal administration of narcotics are

- Easier administration
- Very small dose and therefore reduced blood concentration of Opioid and reduced risk of complications .
- Prolongation of sensory blockade without significantly affecting motor blockade.

Because most of the cystoscopic urological procedures are performed under subarachnoid block the utility and safety of intrathecal opioids for pain relief is of important clinical concern .

This study combined Fentanyl with low dose of local anaesthetic aimed to delineate the safe limit of local anesthetic that could be added to Fentanyl for elderly patients undergoing endoscopic urological procedures without much untoward effect . Addition of Opioid aids in relieving the discomfort that could be caused by visceral handling .

Our study suggests that intrathecal injection of the low dose (Group A) 5 mg of Bupivacaine with 25 μg of Fentanyl induced less profound short-acting motor block but provides the same adequate level of analgesia for endoscopic urologic surgery than the combination of Bupivacaine 7.5 mg and Fentanyl 25 μg (Group B) or Bupivacaine 10 mg and Fentanyl 25 μg (Group C) . The low dose of local anesthetics prompted anesthesiologists to use combinations with other adjuvants . Opioids are the most commonly used drugs in combination with local anesthetics to improve quality and duration of the block and to minimize complications of sympathetic block. The addition of Fentanyl with the local anesthetic , intensifies and increases the duration of the sensory blockade without increasing the intensity of motor block or prolonging recovery to micturition or street fitness . The synergistic interaction between spinal opioids and local anesthetics is characterized by enhanced somatic analgesia without effect on the degree or level of the local anesthetic - induced sympathetic or

motor blockade .

The lumbar interspace chosen for injection of hyperbaric Bupivacaine may influence the level of the block . All patients in our study, had the anesthetic solution injected in the L3 - L4 interspace with the same velocity and the orifice of the spinal needle turned cephalad .

If the motor block was less intense , the recovery and mobilisation of the patient could be faster . These findings were demonstrated by the studies of Vaghadia when comparing a small dose hypobaric Lidocaine – Fentanyl spinal anesthesia and conventional dose hyperbaric Lidocaine .

The problem of the shortness of the sensory block with the low dose of Bupivacaine is resolved by adding Fentanyl . Kuusniemi showed that adding 25 μg of Fentanyl to 10 mg of Bupivacaine compared to 10 mg of Bupivacaine only , will prolong the sensory block . This observation is in accordance with earlier studies in which duration of the block is found to be dose-related when using either Lidocaine or Bupivacaine .

Hypotension is common during subarachnoid block and episodes of severe hypotension can be detrimental to the patient , especially for endoscopic urological surgery in the elderly . Hypotension is the most dangerous side effect and may induce many cardiovascular complications especially when coronary heart disease is present .

Pruritus is the most frequent side effect observed with the use of intrathecal opioids . It may be generalized but is more likely to be localized to the face , neck , or upper thorax . In our study it was well tolerated and none of the patients needed treatment .

Intrathecal opioids may provide benefits in increasing depth of spinal anesthesia , but carry a risk of respiratory depression . The use of 25 μg of Fentanyl during spinal anesthesia in nonpremedicated elderly men did not alter the respiratory rate , minute ventilation or oxygen saturation .

Nausea and vomiting are disagreeable side effects for the patient . No patient in this study had any nausea or vomiting .

SUMMARY

From this randomised comparison of three different doses of Bupivacaine with Fentanyl it was found that

- All three groups were comparable with respect to age , sex , height , weight , comorbid illness and nature of surgery .
- Adequate sensory level was achieved in all the three groups .
- Difference in the time to achieve sensory level of T 10 was statistically significant among the three groups ,
- Adequate motor block to the level of putting the patient in lithotomy was achieved in all the three groups .
- Hypotension was observed invariably in the group receiving high dose of Bupivacaine whereas it was less evident in groups using lower dose Bradycardia was observed in patients who had high sensory level
- Adequate analgesia was present throughout the procedure in all the three groups . Postoperative analgesia was significantly prolonged in groups receiving higher dose of Bupivacaine .
- Motor block was prolonged significantly in groups receiving higher dose of Bupivacaine .
- Nausea and vomiting was not found in any of the groups . Pruritus was found in all the groups but was not statistically significant.

CONCLUSION

This study is conducted in patients aged above 60 years. Spinal Bupivacaine was used in variable doses with Fentanyl 25mcg to find out the minimum effective dose of Bupivacaine with Fentanyl 25mcg in elderly patients undergoing endoscopic urological procedures .

From this study it can be concluded that addition of Fentanyl 25μg to 5 mg of 0.5% Bupivacaine provides reliable and satisfactory surgical anaesthesia with an ideal peak sensory block height , stable haemodynamic status and without any significant adverse effects when compared to the combination of 10 mg Bupivacaine and 25 μg Fentanyl , in elderly patients undergoing endoscopic urologic procedures .

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PROFORMA

"Prospective,randomized comparison of three different doses of Hyperbaric Bupivacaine 10mg,7.5mg,5mg combined with Fentanyl 25mcg in randomly selected elderly patients posted for TURP surgery".

NAME : AGE: SEX: I.P.No:

Group A/B/C : DOSE OF BUPIVACAINE: DOSE OF FENTANYL :

STARTING TIME :

PREOPERATIVE ASSESSMENT:

HISTORY OF CO-MORBID ILLNESS & TREATMENT DETAILS:

EFFORT TOLERANCE- _____ METS

H/O PREVIOUS SURGERY(ANY DOCUMENTED ALLERGY TO LOCAL

ANESTHETICS)

H/O TRAUMA LEADING TO SPINAL DEFORMITY

GENERAL EXAMINATION:

HEIGHT: WEIGHT:

ANAEMIA- JAUNDICE- LUMBAR SPINE&BACK-

AIRWAY-

PULSE- BP- CVS- RS-

CNS-

INVESTIGATIONS

Hb- BT CT

PRELOADING-

SUBARACHNOID BLOCK-

POSITION SPACE NEEDLE SIZE

PARAMETERS TO BE OBSERVED

TIME TO REACH SENSORY BLOCK T10

MAXIMAL SENSORY BLOCK HEIGHT

MOTOR BLOCKADE LEVEL

TIME TO TWO SEGMENT REGRESSION

TIME TO COMPLETE SENSORY REGRESSION

TIME TO COMPLETE MOTOR REGRESSION

INTRA OP EVENTS

INJ ATROPINE DOSE TIME

INJ EPHEDRINE DOSE TIME

SIDE EFFECTS

NAUSEA/VOMITING

PRURITUS

HYPOTENSION

BRADYCARDIA

PAIN(NEED FOR INTRAOP ANALGESIA)

TIME	HR	SBP	DBP	MAP	SPO2	RR

ENDING TIME : DURATION OF SURGERY:

Modified Bromage Scale

0 = no motor block

1 = inability to raise extended legs

2 = inability to flex knees

3 = inability to flex ankle joints

Visual Analog Scale

0-1 - Excellent

2-4 – Good

5-6 – Fair

7-8 – Poor

9-10 - No relief

GROUP	AGE	SEX	IP NO	DM	HT	IHD	COPD	HT	WT	T10-MIN	MSH	MG	2SEG SENREG	COM SEN REG	COM MOT REG	VAS30	VAS END	DUR
A	82	M	202					168	52	8	T9	2	60	80	55	2	4	60
A	80	M	208		Y			162	56	7	T10	2	60	95	60	2	4	60
A	65	M	312					164	53	8	T10	2	70	90	70	2	4	60
A	65	M	322			Y	Y	164	57	8	T10	2	60	90	60	2	4	75
A	65	M	412					165	66	7	T10	2	40	65	45	6	6	90
A	62	M	384					168	62	9	T10	2	60	95	65	2	4	60
A	63	M	368					165	64	7	T9	2	60	75	65	2	4	60
A	65	M	402	Y				170	54	8	T10	2	65	95	70	2	4	60
A	65	M	624					165	60	7	T10	3	60	100	65	2	4	60
A	70	M	922					164	59	8	T10	2	60	95	75	2	4	60
A	65	M	848					162	55	7	T10	2	60	95	65	2	4	45
A	70	M	1124					162	69	8	T10	2	60	85	70	2	4	60
A	60	M	1024	Y				164	53	7	T10	2	60	90	70	2	4	60
A	69	M	1242					162	58	7	T10	2	60	90	70	2	4	60
A	65	M	1418					165	71	8	T9	2	60	85	75	2	4	60
A	65	M	1624					166	59	7	T10	3	60	90	75	2	4	60
A	68	M	1899				Y	162	70	8	T10	2	60	95	70	2	4	60
A	68	M	2012		Y			170	65	8	T10	2	60	100	75	2	4	60
A	70	M	2124	Y				164	65	7	T10	2	40	60	45	6	4	60
A	63	M	2412					165	66	8	T10	2	60	90	70	2	4	60
A	63	M	2108					162	63	9	T9	2	65	100	70	2	4	45
A	71	M	2000	Y	Y	Y		161	64	10	T10	2	50	75	50	2	4	60
A	63	M	1984					164	62	8	T10	2	60	85	70	2	4	60
A	66	M	1762					157	54	9	T9	2	65	90	70	2	4	60
A	63	M	2188					158	59	8	T10	2	65	95	75	2	4	45

SNO	GROUP	AGE	SEX	IP NO	DM	HT	IHD	COPD	HT	WT	T10-MIN	MSH	MG	2SEG SENREG	COM SEN REG	COM MOT REG	VAS30	VAS END
1	B	60	M	198					168	58	5	T9	3	90	130	92	0	2
2	B	75	M	242				Y	164	54	6	T9	3	85	120	98	0	2
3	B	70	M	362	Y				168	65	5	T9	3	90	115	95	0	2
4	B	62	M	484					165	52	5	T8	3	90	130	100	0	2
5	B	65	M	500					164	61	5	T8	3	90	130	100	0	2
6	B	73	M	942					163	55	5	T9	3	90	120	100	0	2
7	B	75	M	810		Y			168	61	5	T8	3	85	110	95	0	2
8	B	65	M	1212					171	68	5	T8	3	85	110	95	0	2
9	B	65	M	1444					165	56	5	T9	3	90	120	102	0	2
10	B	65	M	1590					162	63	6	T9	3	85	120	96	0	2
11	B	65	M	1701			Y	Y	164	63	5	T9	3	80	125	95	0	2
12	B	69	M	1910					162	51	5	T10	3	90	130	100	0	2
13	B	60	M	2111					168	68	5	T9	3	80	125	95	0	2
14	B	70	M	1611	Y				164	56	5	T7	3	100	120	100	0	2
15	B	65	M	1392					165	55	6	T9	3	90	135	110	0	2
16	B	65	M	1400					162	62	5	T9	3	90	130	95	0	2
17	B	64	M	2004					164	58	6	T9	3	65	90	70	0	2
18	B	66	M	1962					168	69	6	T9	3	65	90	70	0	2
19	B	69	M	1814		Y		Y	162	63	5	T10	3	85	13	100	0	2
20	B	65	M	1709					162	59	5	T9	3	90	130	110	0	2
21	B	64	M	1624					164	62	6	T8	3	90	130	95	0	2
22	B	63	M	1711					166	65	6	T9	3	85	130	90	0	2
23	B	65	M	1844	Y	Y			161	64	6	T8	3	90	130	100	0	2
24	B	61	M	2412					162	68	6	T7	3	80	120	95	0	2
25	B	69	M	2604					159	57	6	T9	3	90	130	100	0	2

SNO	GROUP	AGE	SEX	IP NO	DM	HT	IHD	COPD	HT	WT	T10-MIN	MSH	MG	2SEG SENREG	COM SEN REG	COM MOT REG	VAS30	VAS END	DUR
1	C	68	M	142					165	62	4	T8	3	100	210	140	0	0	60
2	C	65	M	182		Y			168	64	3	T7	3	120	205	135	0	0	50
3	C	62	M	218					164	60	3	T6	3	110	190	150	0	0	60
4	C	60	M	414	Y				172	58	3	T7	3	100	190	140	0	0	60
5	C	65	M	629					168	63	3	T6	3	130	210	150	0	0	45
6	C	62	M	717					164	52	3	T6	3	130	210	150	0	0	60
7	C	66	M	828			Y	Y	162	56	2.5	T7	3	110	185	135	0	0	60
8	C	62	M	1004					169	63	3	T6	3	120	190	140	0	0	50
9	C	61	M	989					168	62	3	T5	3	120	200	142	0	0	60
10	C	67	M	1111					162	62	3.5	T6	3	110	210	140	0	0	45
11	C	65	M	1312					164	58	3	T7	3	120	200	145	0	0	60
12	C	65	M	1800		Y			164	50	3	T9	3	125	200	145	0	0	45
13	C	60	M	1712				Y	162	52	3	T8	3	100	210	135	0	0	60
14	C	66	M	1641	Y				164	69	3	T6	3	130	200	140	0	0	60
15	C	70	M	1581					168	69	3	T6	3	120	210	160	0	0	75
16	C	70	M	1902			Y		162	56	5	T5	3	110	205	145	0	0	45
17	C	60	M	1812					164	53	4	T8	3	120	195	135	0	0	60
18	C	62	M	2121	Y	Y			165	58	3	T6	3	110	190	140	0	0	60
19	C	65	M	2141				Y	163	56	3	T7	3	120	210	150	0	0	60
20	C	62	M	2212					168	61	3	T6	3	110	220	150	0	0	60
21	C	62	M	2812					158	64	3	T7	3	135	220	145	0	0	60
22	C	68	M	3111	Y				159	58	4	T8	3	110	200	140	0	0	60
23	C	71	M	3012		Y			163	66	5	T6	3	120	195	150	0	0	60
24	C	67	M	3214				Y	159	56	4	T7	3	120	200	135	0	0	60
25	C	60	M	3414					163	63	3	T7	3	120	210	140	0	0	45

S.NO	GROUP	HR5	HR10	HR15	HR20	HR25	SBP/DBP/MAP5	SBP/DBP/MAP10	SBP/DBP/MAP15	SBP/DBP/MAP20	SBP/DBP/MAP25	RR	SPO2
1	A	62	60	60	58	58	130/82/98	128/80/96	128/76/93	126/76/89	128/78/94	14	100
2	A	70	66	66	66	64	140/82/100	138/80/99	130/82/98	130/80/97	130/82/98	16	99
3	A	58	58	58	56	56	110/72/85	108/70/86	106/72/86	104/72/83	106/70/82	14	98
4	A	80	78	78	78	76	118/68/85	116/64/82	114/62/80	114/64/81	114/62/80	14	99
5	A	66	64	62	62	62	122/76/92	120/72/88	120/70/87	120/68/85	120/70/87	15	98
6	A	68	68	66	66	66	120/80/93	120/76/95	120/70/87	120/68/85	122/70/87	12	99
7	A	76	76	74	74	74	108/78/88	106/72/83	106/70/82	104/62/79	104/66/79	14	100
8	A	56	56	56	56	56	132/72/92	130/66/88	126/72/90	124/64/84	124/68/87	16	99
9	A	82	80	80	80	78	126/68/88	124/68/87	120/68/85	118/68/85	118/66/84	12	99
10	A	72	70	70	68	68	140/80/100	138/80/99	128/86/100	130/82/98	124/66/86	13	100
11	A	64	64	62	62	62	118/70/86	118/68/85	114/62/80	114/64/81	108/60/76	12	97
12	A	68	68	68	66	66	136/68/91	130/66/88	126/82/90	124/66/86	124/64/84	14	98
13	A	78	78	78	76	76	106/68/81	104/66/79	102/68/79	102/64/77	104/64/77	14	99
14	A	78	78	78	76	76	106/68	106/68/81	102/68/79	102/64/77	104/64/77	12	99
15	A	80	74	74	74	74	130/76/94	126/68/88	124/68/87	124/64/84	118/70/86	15	100
16	A	86	80	80	78	78	138/68/101	130/76/94	128/80/96	128/78/94	126/76/89	12	99
17	A	66	64	64	64	64	124/70/86	120/68/85	118/66/84	114/62/80	108/60/76	14	97
18	A	70	70	72	72	72	118/68/85	114/64/81	104/64/77	102/64/77	102/64/77	13	99
19	A	58	58	54	54	54	146/84/104	138/80/99	128/86/100	124/66/86	132/72/92	14	99
20	A	62	62	62	62	64	130/78/95	126/68/87	124/64/84	126/76/89	122/70/87	12	100
21	A	74	68	68	68	68	124/74/91	122/70/87	120/68/85	120/66/85	118/68/85	14	99
22	A	60	60	60	62	62	140/82/101	138/80/99	130/82/98	124/66/88	122/70/87	12	100
23	A	70	72	68	68	68	150/80/104	140/80/100	136/80/92	138/66/90	128/78/94	14	99
24	A	66	60	62	62	60	110/70/83	106/68/80	104/60/74	104/58/72	102/58/70	12	97
25	A	74	72	72	72	68	124/60/82	120/60/80	124/64/84	120/70/87	118/64/88	14	99

S.NO	GROUP	HR5	HR10	HR15	HR20	HR25	SBP/DBP/MAP5	SBP/DBP/MAP10	SBP/DBP/MAP15	SBP/DBP/MAP20	SBP/DBP/MAP25	SPO2	RR
1	B	70	66	60	58	58	132/70/90	128/68/88	120/60/80	120/62/81	118/60/79	100	14
2	B	66	60	58	58	56	118/64/83	110/60/76	108/60/76	106/58/74	106/54/71	99	14
3	B	68	60	60	60	62	140/76/97	130/68/88	126/70/88	120/70/83	118/68/81	98	16
4	B	84	78	72	68	68	130/80/93	100/52/68	90/54/66	88/50/63	94/62/73	99	14
5	B	82	78	72	68	68	130/80/93	100/52/68	90/54/66	88/50/63	94/62/73	99	14
6	B	64	60	58	58	58	124/68/87	120/64/83	110/70/83	108/60/76	108/70/83	99	15
7	B	74	66	62	62	62	130/70/90	100/60/73	92/54/67	88/52/64	90/60/70	100	15
8	B	74	66	62	62	62	130/70/90	100/60/73	92/54/67	88/52/64	90/60/70	100	14
9	B	60	58	58	56	56	124/72/90	110/72/84	110/68/79	108/64/78	106/70/82	99	16
10	B	64	62	62	60	60	110/70/83	102/60/74	100/60/73	94/58/70	92/60/71	100	12
11	B	80	78	74	74	72	132/76/94	118/68/85	110/70/83	114/70/84	116/72/87	97	13
12	B	76	76	74	74	74	108/64/76	104/60/74	102/58/73	104/60/74	104/60/74	98	12
13	B	68	62	60	60	60	130/80/97	120/70/87	118/66/84	110/70/83	108/66/76	99	14
14	B	62	58	56	52	52	128/70/89	100/60/73	90/60/70	88/58/68	88/62/71	99	12
15	B	74	68	66	66	66	110/70/83	100/60/73	98/62/74	108/64/79	110/70/83	100	12
16	B	66	62	62	62	62	122/80/94	118/64/82	110/70/83	112/74/87	114/80/91	99	15
17	B	72	70	66	62	62	130/80/97	124/70/88	118/70/86	110/70/83	116/82/92	97	14
18	B	72	70	66	62	62	130/80/97	124/70/88	118/70/86	110/70/83	116/82/92	97	14
19	B	78	70	66	66	66	120/80/93	110/74/86	108/70/83	106/68/80	106/68/80	99	13
20	B	62	64	64	64	64	124/72/90	110/74/84	108/64/78	106/70/82	110/72/84	100	14
21	B	68	60	58	58	58	110/70/83	90/60/70	86/52/64	88/58/68	90/60/70	99	12
22	B	80	74	70	68	68	130/80/97	124/70/88	118/64/79	110/70/83	110/70/83	100	14
23	B	70	66	60	58	58	140/82/100	110/70/83	94/66/75	96/64/75	90/60/70	99	12
24	B	74	66	60	56	54	120/80/93	118/76/90	110/70/83	110/70/83	120/70/87	97	14
25	B	66	60	58	58	58	110/70/83	88/54/65	90/60/70	88/58/68	92/62/72	99	12

S.NO	GROUP	HR5	HR10	HR15	HR20	HR25	SBP/DBP/MAP5	SBP/DBP/MAP10	SBP/DBP/MAP15	SBP/DBP/MAP20	SBP/DBP/MAP25	SPO2	RR
1	C	72	68	66	62	62	140/80/100	100/60/70	88/58/68	90/60/70	90/60/70	100	14
2	C	66	64	58	58	58	120/74/89	92/62/72	88/60/72	90/60/70	92/62/72	99	14
3	C	70	66	62	56	54	110/74/86	88/60/72	90/60/70	90/60/70	90/60/70	98	16
4	C	80	74	70	70	70	130/76/94	110/64/79	90/60/70	92/62/72	92/62/72	99	14
5	C	66	60	56	52	48	140/78/98	100/70/80	90/60/70	94/64/74	92/62/72	98	14
6	C	66	60	56	52	48	140/78/98	100/70/80	90/60/70	94/64/74	92/62/72	98	14
7	C	68	66	60	60	60	120/76/91	100/54/69	90/48/62	88/50/63	90/60/70	100	12
8	C	60	58	58	52	50	130/76/94	90/60/70	90/60/70	94/64/74	100/70/80	99	14
9	C	80	74	66	62	62	118/74/88	88/54/65	92/62/72	100/70/80	100/70/80	99	16
10	C	64	62	58	52	48	126/68/87	100/54/69	88/60/69	94/64/74	100/70/80	100	12
11	C	74	70	66	62	62	130/80/97	92/62/72	90/60/70	96/66/76	100/70/80	97	13
12	C	58	56	56	56	52	110/70/83	100/60/73	90/60/70	92/62/72	90/60/70	98	12
13	C	68	62	60	58	58	132/72/89	100/60/73	90/60/70	94/64/74	100/68/79	99	14
14	C	72	68	66	58	56	120/70/87	88/62/70	90/62/75	96/70/82	100/72/85	99	14
15	C	68	62	58	50	48	130/68/88	92/62/72	94/64/74	100/70/80	110/70/83	100	12
16	C	60	56	50	48	48	118/74/88	84/52/64	88/58/68	90/64/76	96/66/76	99	15
17	C	76	70	66	66	68	120/76/80	90/64/76	88/58/68	94/64/74	100/70/83	97	12
18	C	76	68	62	58	58	110/70/83	88/60/69	86/54/64	90/60/70	94/64/74	99	14
19	C	60	58	56	56	56	124/68/86	100/60/73	90/60/70	92/62/72	96/66/76	99	13
20	C	80	74	72	66	60	130/70/90	90/60/70	94/64/74	96/66/76	110/70/83	100	14
21	C	70	66	62	62	62	140/80/100	110/70/83	100/60/73	98/68/78	100/70/80	99	12
22	C	62	60	58	58	58	122/74/90	84/58/67	88/58/68	90/60/70	100/68/79	100	14
23	C	64	58	56	50	48	108/60/76	90/60/70	84/56/66	92/62/72	98/68/78	99	12
24	C	74	70	66	66	66	132/74/90	104/68/80	90/60/70	98/68/78	110/70/83	97	14
25	C	68	62	58	58	60	118/74/88	100/64/76	88/60/69	90/60/70	92/62/72	99	12