A STUDY TO COMPARE THE EFFECT OF MIDAZOLAM AND CLONIDINE ADDED AS AN ADJUVANT TO INTRATHECAL BUPIVACAINE IN LOWER ABDOMINAL SURGERIES

Dissertation submitted for the degree of
DOCTOR OF MEDICINE
Branch – X (ANAESTHESIOLOGY)
APRIL – 2013

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,
CHENNAI, TAMIL NADU.

CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY TO COMPARE THE EFFECT OF MIDAZOLAM AND CLONIDINE ADDED AS AN ADJUVANT TO INTRATHECAL BUPIVACAINE IN LOWER ABDOMINAL SURGERIES"** is a bonafide record of the work done by **Dr. T.CHANDRAKUMAR** under my supervision and guidance in the Department of Anaesthesiology at Thanjavur Medical College, Thanjavur during the period of his post graduate study from April 2010 to March 2013 for the partial fulfillment of M.D. (Branch X - Anaesthesiology) degree.

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I Dr.T.Chandrakumar, solemnly declare that the dissertation titled **"A STUDY TO COMPARE THE EFFECT OF MIDAZOLAM AND CLONIDINE ADDED AS AN ADJUVANT TO INTRATHECAL BUPIVACAINE IN LOWER ABDOMINAL SURGERIES"** is a bonafide work done by me at Thanjavur Medical College Hospital, Thanjavur, during 2010 – 2013.

The dissertation is submitted to **"The Tamilnadu Dr. M.G.R. Medical University, Chennai",** Tamilnadu as a partial fulfillment for the requirement of **M.D** Degree examinations– Branch -X (Anaesthesiology) to be held in April 2013.This has not been submitted previously by me for the award of any degree or diploma from any other university.

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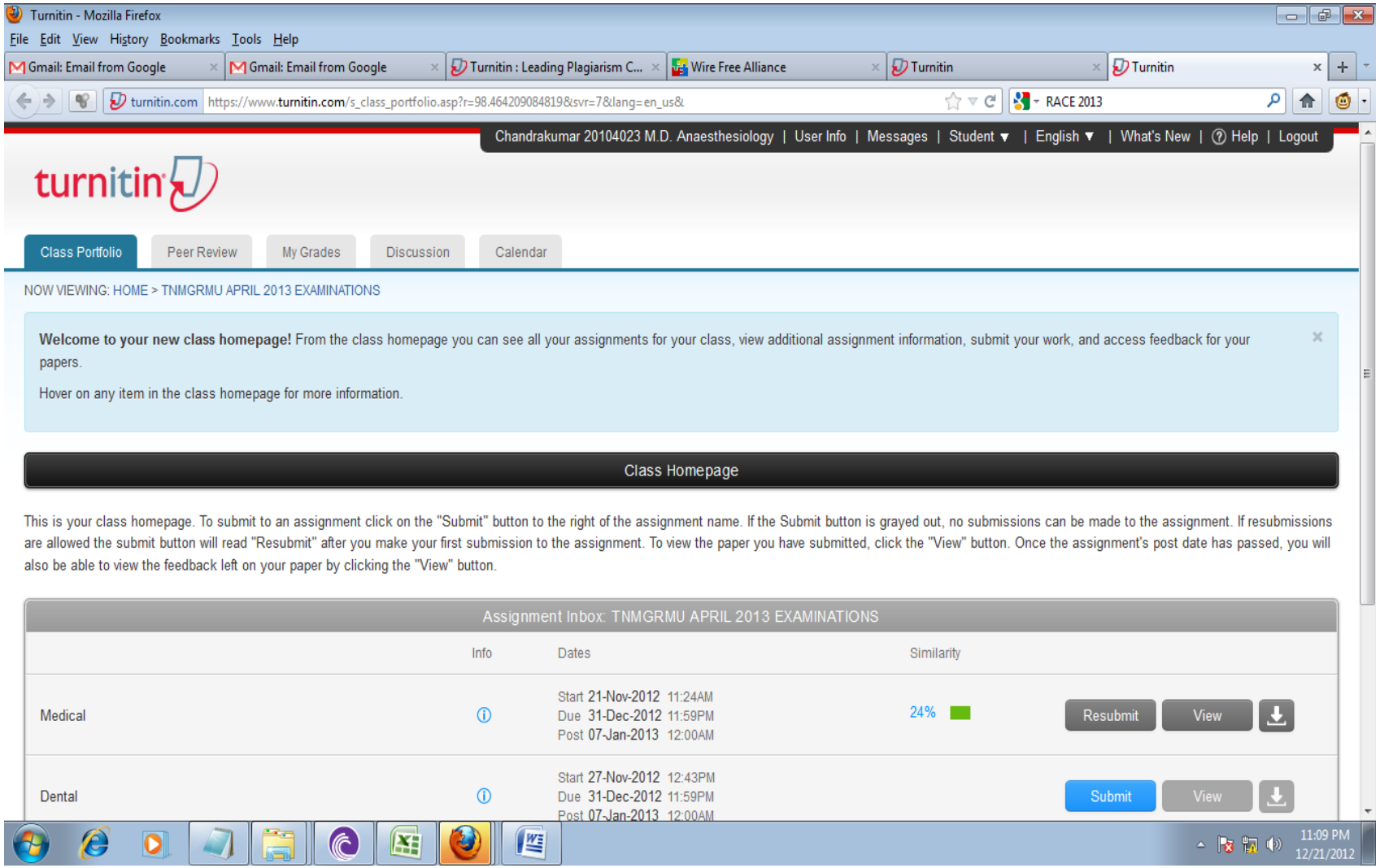
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INTRODUCTION “It is the duty of the anesthesiologist to study the well being of the patient as well as the convenience of the surgeon” - Ralph Waters The International Association for the study of pain (IASP) defined pain as “an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage”. Spinal anaesthesia was first performed by August Bier on 16 th August 1898 when he injected 3 ml of 0.5% Cocaine intrathecally. It is a simple technique which has many advantages over epidural anesthesia. In addition, correct placement of the needle in the subarachnoid space is confirmed by a clearly defined end point (appearance of...

ABSTRACT

We conducted double blinded randomized control study in 60 patients undergoing elective lower abdominal surgeries in spinal anaesthesia. Our aim was to evaluate the effects of intrathecal midazolam 2mg and clonidine 30mcg as adjuvant for hemodynamic stability and postoperative analgesia. Patients were divided into two groups BM and BC. BM Group received 3ml of 0.5% heavy bupivacaine, 0.4 ml of midazolam and 0.1ml of normal saline. BC Group received 3 ml of 0.5% heavy bupivacaine, 0.2ml clonidine and 0.3ml normal saline. The total volume of the injected solution was 3.5ml in both groups. The onset and duration of sensory and motor blockade, pulse rate, mean arterial pressure, duration of analgesia and average dose of postoperative analgesia were observed in both groups. In our study the duration of analgesia was 486.17 minutes in BM group and 306.17 minutes in BC group. The average dose of postoperative analgesia in BM group was 87.5 mg whereas in BC group it was 132.5 mg. The MAP was significantly lower in 15 minutes and 20 minutes in BC group. We concluded in BM group the duration of postoperative analgesia was longer and hemodynamic stability was better than BC group.

CONTENTS

INTRODUCTION

"It is the duty of the anesthesiologist to study the well being of the patient as well as the convenience of the surgeon"

- Ralph Waters

The International Association for the study of pain (IASP) defined pain as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage"(1).

Spinal anaesthesia was first performed by August Bier on 16th August 1898 when he injected 3 ml of 0.5% Cocaine intrathecally. It is a simple technique which has many advantages over epidural anesthesia. In addition, correct placement of the needle in the subarachnoid space is confirmed by a clearly defined end point (appearance of CSF).

Spinal anaesthesia with local anaesthetic agents is extensively used for lower abdominal surgeries. It provides the excellent pain relief as compared to intravenous or epidural route.

There are many advantages for spinal anesthesia over general anaesthesia which makes it the anesthesia of choice in current surgical practice. Many clinical studies support the fact that Postoperative morbidity and mortality may

be reduced when neuraxial blockade is used either alone or in combination with general anaesthesia. Since it decreases the stay, it is cost effective for both patient and hospital. It is suitable for patients with respiratory diseases and helps preventing intubation related problem like laryngospasm. It is also helpful in maintaining the airway patency and reduced blood loss. Early return of gastro intestinal function following surgery can be considered as an added advantage. Other advantage may be reduced hypercoagulable state associated with surgery, increased tissue blood flow due to sympathectomy, decreased splinting which improves oxygenation, enhanced peristalsis, and reduced stress response to surgery due to suppression of neuroendocrine system (2).

Apart from the theoretical risk of infection to the brain, difficulty in finding the space in old age and bony abnormalities can pose a challenge to the anesthesiologist. The serious complication associated with spinal anaesthesia includes bradycardia, hypotension, prolonged motor block and high spinal (3). It is related to the sympatholytic effect of local anaesthetic agents.

If the level of the block is higher, the sympatholytic effect will be more and leads to more serious complications. Though these effects cannot be abolished completely, they can be considerably minimized by using either low dose or low concentration of local anesthetics. One of the main disadvantages 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 anesthesia like

i) Rapid onset of action

ii) Reduces the local anesthetic requirements

iii) Reduces the risk of local anesthetic toxicity

iv) Prolongs the sensory block

v) Reduces the duration of motor block

vi) Improves the analgesic quality

vii) Improves the hemodynamic stability

viii) Inhibition of tourniquet pain

ix) Improved and prolonged duration of postoperative analgesia.

Initially opioids like morphine, fentanyl are used as spinal adjuvants. But these have got many side effects and complications like early / late respiratory depression, pruritus, nausea, vomiting, delayed gastric emptying and urinary retention. There is an active search for an alternative for an ideal adjuvant which is devoid of these side effects and complications.

In the last decades benzodiazepines, alpha 2 agonist, acetylcholine esterase inhibitors like neostigmine and NMDA receptor antagonist like ketamine are all used as adjuvants to local anaesthetics.

Ketamine and Neostigmine were used as adjuvants compared with Midazolam in **Maryam shokrpur et al** (4)**, Abdul muthalib hussain et al** (5) respectively. Both studies have shown that Midazolam group had an effective analgesia with minimal side effects compared to the other adjuvants.

Among the neuraxial adjuvants, Midazolam and Clonidine are becoming increasingly popular, because of their prolonged duration of analgesia, good intraoperative comfort like anxiolysis, sedation and sparing effect on postoperative analgesic consumption. Comparative studies with Midazolam and Clonidine as adjuvants to intrathecal bupivacaine are very few.

In order to address these existing problems we need better pain management which is helpful for early recovery of motor function and reduction in requirement of postoperative analgesics.

Suchita A.Joshi et al (6)**,** have carried out studies to compare the effect of intrathecal midazolam and clonidine added as an adjuvant to bupivacaine in lower abdominal surgeries. The results were promising with prolonged duration of analgesia with lesser amount of rescue analgesics.

This research is designed to study the efficacy of such combination in our setup and compare the results with the previous studies done at other institutions.

AIM OF THE STUDY

To evaluate the efficacy of intrathecally administered adjuvants Midazolam and Clonidine with Bupivacaine for hemodynamic stability and postoperative pain relief in lower abdominal surgeries.

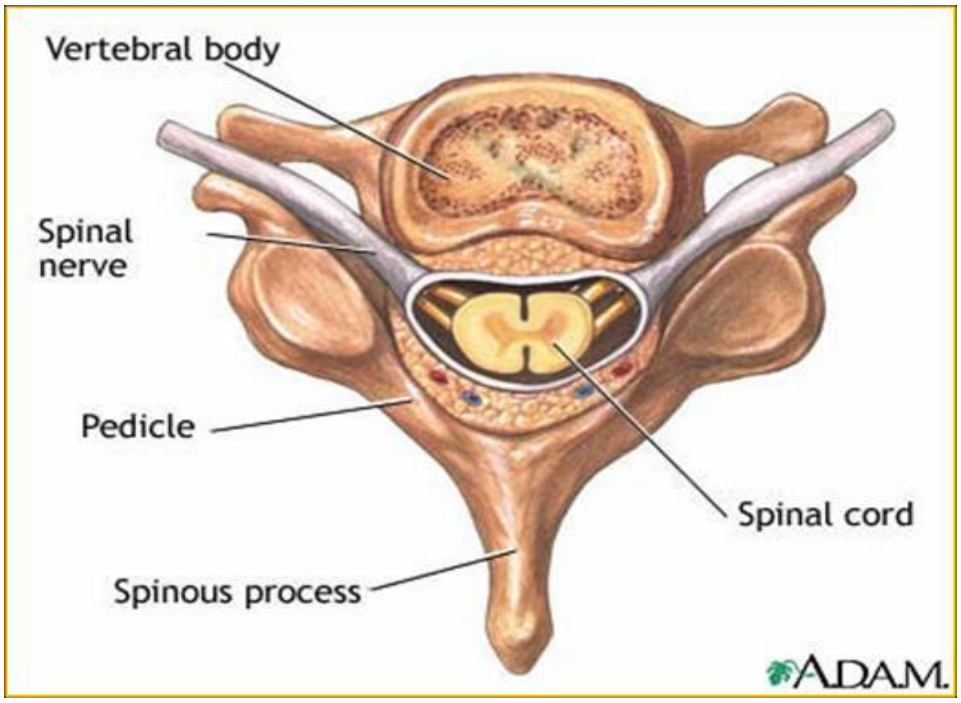
SPINAL ANAESTHESIA

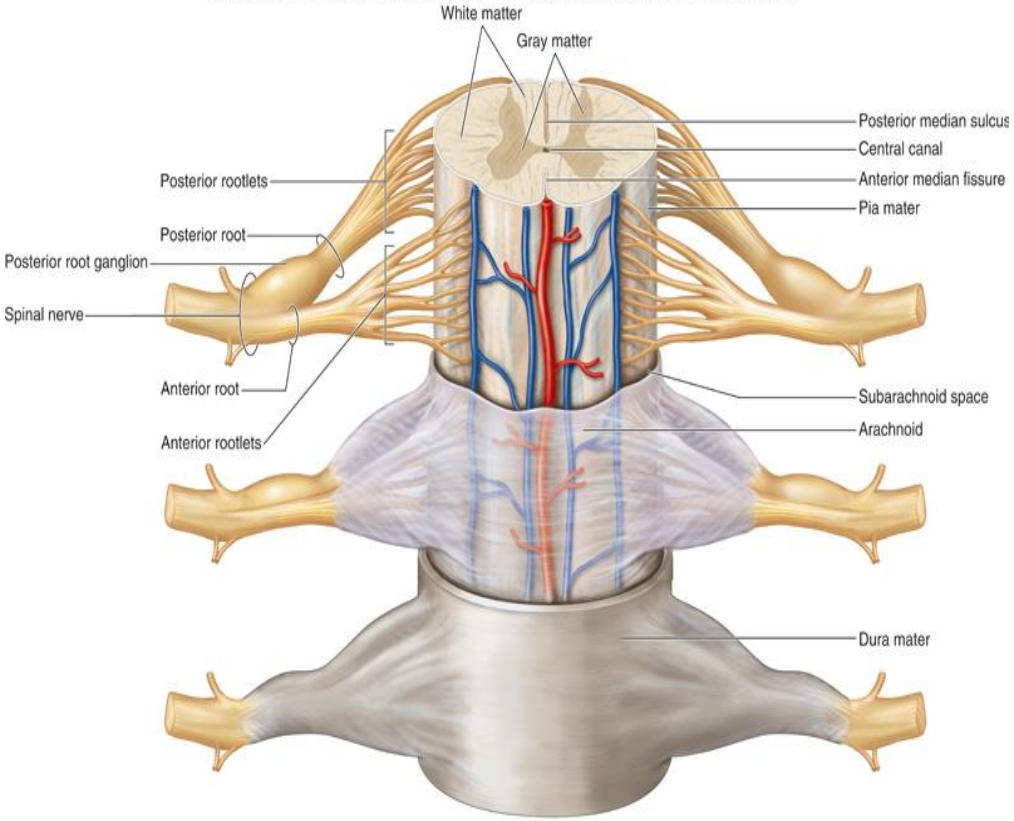
Spinal (subarachnoid / intrathecal) anaesthesia is a form of central neuraxial block in which a temporary interruption of nerve transmission is achieved following injection of local anesthetic and / or adjuvant solutions into the subarachnoid space. Spinal anaesthesia is the most frequently employed method of regional anesthesia.

ANATOMY

The vertebral canal extends from the foramen magnum to the sacral hiatus.It is formed by the dorsal spine, pedicles and lamina of successive vertebrae (7 cervical, 12 thoracic, *5* lumbar and ***5*** sacral). The vertebrae are held together by a series of overlapping ligaments namely the anterior and posterior longitudinal ligaments, ligamentum flavum, interspinous ligament, supraspinous ligament and the intervertebral discs.

The spinal cord, a direct continuation of the medulla oblongata begins at the upper border of the atlas and terminates distally in the conus medullaris. The distal termination, because of the differential growth rates between the bony vertebral canal and central nervous system varies from L3 in the infant, to the lower border of Ll or upper border of L2 in the adult.


Vertebral body
Spinal nerve
Pedicle
Spinal cord
Spinous process
A.D.A.M.



(b) Anterior view

Surrounding the spinal cord in the bony vertebral column are three membranes innermost the piamater ,middle one arachnoid and outer duramater. The piamater is a highly vascular membrane that closely invests the spinal cord. The arachnoidmater is a delicate nonvascular membrane closely attached to the outermost duramater. Between the two innermost membranes is the subarachnoid space. In this space are the cerebrospinal fluid, spinal nerves, blood vessels that supply the spinal cord and the denticulate ligaments. Although the spinal cord ends at the lower border of L1 in adults, the subarachnoid space continues to S2.

The outermost membrane in the spinal canal is the longitudinally organized fibroelastic membrane, the duramater. This layer is the direct extension of the cranial duramater and extends as the spinal duramater from the foramen magnum to S2, where the filum terminale (an extension of thç piamater beginning at the conus medullaris) blends with the periosteum of the Coccyx. There is a potential space between the duramater and arachnoid, subdural space which contains only small amounts of serous fluid to allow the duramater and arachnoidmater move over each other.

Surrounding the duramater is the epidural space which extends from the foramen magnum to the sacral hiatus. Posterior to the epidural space is the ligamentum flavum which extends from the foramen magnum to the sacral hiatus.

The ligamentum flavum connects the caudal edge of the vertebrae above to the cephalad edge of the lamina below. This ligament is composed of elastic fibres and is usually recognized by its increased resistance to the passage of the needle. Immediately posterior to the ligamentum flavum is the interspinous ligament. It connects the spinous processes on their horizontal surface. Extending from the external occipital protuberance to the coccyx, posterior to these structures is the supraspinous ligament. It connects the apices of the spinous processes. Lumbar puncture is routinely done below the L2 vertebrae down to the L5-Si interspace to avoid damaging the spinal cord which ends at the lower border of L1 in adults.

PHYSIOLOGY OF SUBARACHNOID BLOCK:

Cercbrospinal Fluid

The cerebrospinal fluid (CSF) is an ultrafiltrate of blood plasma with which it is in hydrostatic and osmotic equilibrium. It is a clear, colorless fluid found in the spinal and cranial subarachnoid space and in the ventricles of the brain. The average volume in the adult ranges from 120-150 ml of which 35 ml is in the ventricles, *25* ml is in the cerebral subarachnoid space and *75* ml is in the spinal subarachnoid space. It is secreted by the choroid plexus at a rate of 0.3-0.4 mi/minute and is absorbed into the venous sinuses through the arachnoid villi.

PHYSICAL CHARACTERISTICS OF CEREBROSPINAL FLUID (7)

pH	7.4
Specific gravity At body temperature At 4 degree centigrade	 1.007 1.0003
Density	1.0003 g/ml
Baricity	1.000
Pressure	8-12 mm Hg/70-80 mm H20
Cells	3-5/cu.mm
Proteins	20 mg/dl

The cerebrospinal fluid plays an important role in spinal anesthesia as a media for dispersion of the local anesthetic drug to the spinal nerve roots. An important factor determining the spread of drugs in the subarachnoid space is the specific gravity of the injected solution compared with that of CSF.

MECHANISM OF SPINAL ANAESTHESIA

Injection of local anesthetic solution into the spinal CSF allows access to sites of action both within the spinal cord and the peripheral nerve roots. The nerve roots leaving the spinal canal are not covered by epineurium and are readily exposed to the local anesthetic within the CSF. Therefore afferent

impulses entering the central nervous system via dorsal nerve roots and efferent impulses, leaving via the ventral nerve roots are blocked during spinal anesthesia. Local anesthetics block sodium channels and electrical conduction in spinal nerve roots. There are also multiple potential actions of local anesthetics within the spinal cord at different sites. Local anaesthetics can exert sodium channel block within the dorsal and ventral horns, inhibiting generation and propagation of electrical activity (8).

The order in which the nerve fibres are blocked are preganglionic sympathetic B fibres followed by temperature fibres. (Cold before warmth), fibres carrying pin prick sensation, touch, deep pressure, somatic motor sensation and lastly fibres conveying vibration sense and proprioceptive impulses. Sympathetic fibres are blocked two segments higher than sensory level. Sensory fibres are blocked two segments higher than motor fibres. Recovery is roughly in the reverse order.

Spread of Local Anaesthetics in subarachnoid space

Local anesthetic solution is diluted by CSF and therefore its original concentration is of less amount than the actual mass of drug injected. Spread is also determined by the baricity of the injected solution. Baricity is a ratio comparing the density of a local anesthetic solution at a specified temperature to

the density of CSF at the same temperature. A hypobaric solution has a baricity less than 1.0000 or specific gravity less than 1 .0069(the mean value of specific gravity). A hyperbaric solution has a baricity greater than 1.0000 or specific gravity more than 1.0069. Hypobaric and Hyperbaric solutions are prepared from isobaric solutions by the addition of various amounts of sterile distilled water and dextrose respectively. Isobaric solutions do not move under the influence of gravity in the CSF. Hyperbaric solutions, being heavier than CSF, settle to the most dependent aspect of the subarachnoid space, which is determined by the position of the patient. In supine patient, hyperbaric solutions gravitate to the thoracic kyphosis. Hypobaric solution floats up to the nerves innervating the surgical site. The major factors affecting height of the block are the baricity of the local anesthetic solution and the dosage of drug injected.

Fate of Local Anaesthetics in Subarachnoid Space:

Following injection of local anaesthetic solution into subarachnoid space, its concentration falls rapidly. The initial steep fall is due to mixing with CSF and subsequent absorption into nerve roots and spinal cord, The progress of local anesthetic solution following subarachnoid injection is primarily by vascular absorption with no hydrolysis or degradation taking place in the CSF. Depending on the type of the drug used, it is metabolized in plasma by

pseudocholinesterase or in the liver. As duration of anaesthesia is in the part, a result of the rate of absorption from the subarachnoid space, the addition of a vasoconstrictor to the local anaestheric solution will retard absorption of the drug and thus increase the duration of anesthesia.

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 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 (eg. Pregnancy)

INDICATIONS FOR SUBARACHNOID BLOCK:

Spinal anesthesia can be administered whenever a surgical procedure can be done with a sensory level of anesthesia that does not produce adverse patient outcome which includes

• Lower abdominal surgeries

• Lower limb surgeries

• Urological procedures

• Obstetric procedures

• Gynecological surgeries

• Perineal and rectal surgeries

Contraindications for subarachnoid block

Absolute contraindication

- Patient refusal
- Local sepsis

Relative contraindication

- Uncorrected coagulopathy
- Uncontrolled blood loss / shock
- Fixed cardiac output states
- Documented allergy to local anesthetics
- Raised intracranial pressure

- Neurological disease
- Major spine deformities / previous surgery on the spine
- Severe cardiac disease

Complications of subarachnoid block

Immediate

- Hypotension
- Bradycardia
- Toxicity due to intra vascular injection
- Allergic reaction to local anesthetic
- Hypoventilation (in patients with higher thoracic levels)
- Postdural puncture headache
- Retention of urine
- Back ache
- Meningitis
- Transient lesions of cauda equinae
- Sixth nerve palsy
- Anterior spinal artery syndrome
- Horner's syndrome

CIRCULATORY CHANGES

a) Neural Blockade

Local anaesthetic solutions injected into the subarachnoid space produce a conduction block of small diameter unmyelinated (sympathetic) fibres before interrupting conduction in larger unmyelinated (sensory and motor) fibres. As a result level of automatic blockade extends above the level of the sensory blockade by two to six segments. This phenomenon is termed differential blockade (9).

Similarly fibres conveying sensation are more easily blocked than larger motor fibres so that sensory blockade will extend above the level of the motor blockade.

b) Cardiovascular system

Hypotension is directly proportional to the degree of sympathetic blockade produced. Sympathetic blockade results in dilation of arteries and venous capacitance vessels leading to decreased systemic vascular resistance and decreased venous return.

If the block is below T4, increased baroreceptor activity produces an increase in activity to cardiac sympathetic fibres and vasoconstriction of the upper extremities. Blockade above T4 interrupts cardiac sympathetic fibres

leading to bradycardia, decreased cardiac output and a further decrease in blood pressure and fall in Right atrial filling which decreases outflow from intrinsic chronotropic stretch receptors located in the right atrium and great veins(9).

c) Respiratory system

1. Usually not clinically significant in healthy patient because the diaphragm is innervated by phrenic nerve (C3-C5)
2. Respiratory rate and tidal volumes remain unchanged, though a high thoracic level block can result in decreased expiratory reserve volume from deafferentation of the abdominal wall and intercostal muscles (10).

Caution is advised in performing neuraxial blocks in patients with limited respiratory reserve, who may be dependent on these muscles for active respiration and clearing of secretions. Respiratory arrest associated with high spinal is attributed to hypo perfusion of the medullary respiratory neurons, rather than phrenic nerve block.

e) Hepatic and Renal Effects

The hepatic blood flow decreases and is directly proportional to the decrease in blood pressure (11). There may be normal hepatic oxygen extraction.

Renal blood flow is maintained by autoregulation and does not decrease till mean arterial pressure go below 50mmHg.

f) Gastrointestinal and genito urinary system

Nausea and vomiting may be associated with neuraxial block related to gastrointestinal hyper peristalsis caused by unopposed parasympathetic activity. Handling of the viscera causes discomfort and bradycardia since vagus is not blocked.

Sacral blockade (S2 to S4) results in an atonic bladder that can retain large volumes of urine Blockade of sympathetic afferent and efferent innervation of the spincter and detrusor muscle produces urinary retention. Penis is often engorged.

g) 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, cortisol, catecholamines, renin and aldosterone release associated with stress. Vagal afferent fibres from upper abdominal viscera are not blocked and can stimulate release of hypothalamic and pituitary hormones such as antidiuretic hormone and adrenocorticotrophic hormone.

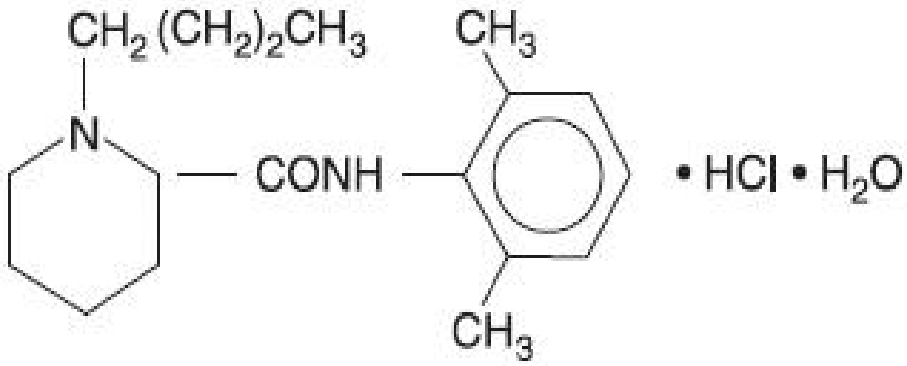
h) Thermo Regulation

Hypothermia results from redistribution of central heat to the periphery secondary to vasodilatation. Thermoregulation is impaired given the loss of vascoconstriction to preserve the heat below the level of sympathectomy.

PHARMACOLOGY OF DRUGS

a) Bupivacaine

Bupivacaine is an amide linked local anaesthetic. It is a hydrochloride salt of d(1)-1-butyl 2'6' pipecoloxylidide and is presented as a racemic mixture.



- It was synthesized in Sweden by Ekenstem and his colleagues in 1957.
- First reports of its use were published in 1963 by Telivuo.
- It is derived from Mepivacaine which has a methyl group on the piperidine nitrogen atom of the molecule. Addition of a butyl group to the piperidine nitrogen of the mepivacaine results in bupivacaine which is 35 times more

lipid soluble and has a potency and duration of action 3 to 4 times that of mepivacaine.

Pka is 8.1

MW - 288

Protein binding - 95%

Volume of Distribution – 73 Litres

Lipid solubility – 28

Clearance - 0.47 l/min

Elimination half life - 210mts

Toxic plasma concentration - > 3 μg/ml

Availability

Ampoules - 0.5% Bupivacaine hydrochloride 4cc

– 0.5% Bupivacaine hydrochloride with dextrose (heavy) 4cc

Vials - 0.25% and 0.5% Bupivacaine hydrochloride 30cc

Dosage - Maximum dosage 3mg/kg body weight.

Uses

- Spinal anaesthesia
- Epidural anaesthesia
- Caudal anaesthesia

- Continuous epidural anaesthesia
- Peripheral nerve block

Onset time and duration of action

Site of action	Onset (minutes)	Duration (minutes)
Intrathecal	5	180-240
Epidural	15-20	165-225
Brachial plexus	20-30	360-720

Pharmacokinetics

It is a weak base that has pka value above physiological pH. At pH 7.4 only 17% exists in nonionised form.

Once injected intrathecally, it gets absorbed by the nerve rootlets and results in the desired effect. It is rapidly absorbed from the site of injection, but the rate of absorption depends on the vascularity at the site and presence of vasoconstrictors.

Absorption of a local anaesthetic from its site of injection into the systemic circulation is influenced by site of injection dosage and use of epinephrine. The plasma concentration is determined by rate of tissue distribution and rate of clearance of the drug. High lipid solubility of bupivacaine makes it easy for nerve and vascular tissue penetration (12).

Lung is capable of extracting bupivacaine from circulation, which will limit

concentration of drug that reaches systemic circulation. This first pass pulmonary extraction is dose dependent suggesting that the uptake process becomes saturated rapidly.

Placental transfer

There may be clinically significant transplacental transfer between mother and fetus. Plasma protein binding influences the rate and degree of diffusion of local anaesthetics across the placenta.

Distribution

Rapid distribution phase: (α)

In this phase the drug is distributed to highly vascular region.

t ½ of α - being 2.7 minutes.

Slow disappearance phase: (β)

In this phase the drug distributes to slowly equilibrating tissues

t ½ of β – being 28mts.

Biotransformation and excretion phase: (δ)

t ½ of δ is 3.5hours, clearance is 0.47 litre/minute.

Biotransformation

Possible pathways of metabolism of bupivacaine include aromatic hydroxylation N-dealkylation, amide hydrolysis and conjugation. Only the N-dealkylated metabolite, N-desbutyl bupivacaine has been measured in blood (or) urine after epidural (or) spinal anaesthesia. Alpha1 acid glycoprotein is the most important plasma protein binding site of bupivacaine and its concentration is increased by many clinical situations including postoperative trauma.

Excretion:

The poor water solubility of local anaesthetics usually limits renal excretion of unchanged drug to <5%

Mode of Action

a) Site of action

i) The spinal nerve rootlet fine nerve filaments having a large surface area are exposed to the local anaesthetics.

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

b) Sodium Channel blockade

Local anaesthetics prevent transmission of nerve impulses by inhibiting passage of sodium ions though ion-selective sodium channels in nerve membranes. Failure of sodium ion channel permeability to increase slows the rate

of depolarization such that threshold potential is not reached and thus an action potential is not propagated. Local anaesthetics do not alter the resting transmembrane potential or threshold potential.

Pharmacodynamics

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

Cardiovascular system

It reduces cardiac output 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

Spinal blockade seldom, if ever causes respiratory problem.

Gastro intestinal tract

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

Toxicity

Toxicity 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

Initial symptom includes feeling of light headedness and dizziness, followed by visual and auditory disturbances. Objective signs are excitatory and include shivering, muscle twitching and tremor. Ultimately generalized tonic, clonic seizures occurs.

Cardiovascular System Toxicity

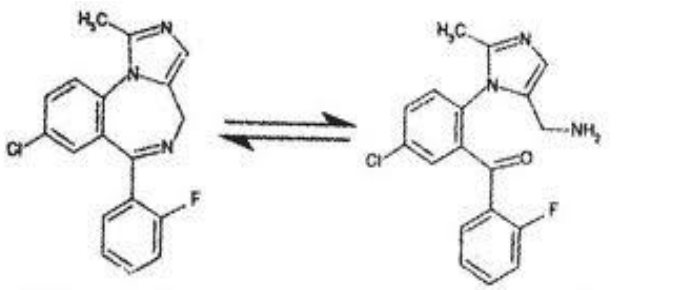
Bupivacaine is more cardiotoxic than equieffective doses of lignocaine. This is manifested by severe ventricular arrhythmias and myocardial depression. Bupivacaine blocks cardiac Na+ channels rapidly during systole and dissociates more slowly during diastole, so that a significant fraction of Na+ channels remain blocked at the end of the diastole. Thus the block by bupivacaine is cumulative and substantially greater.

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 and cardiac arrest.

PHARMACOLOGY OF MIDAZOLAM

Benzodiazepines were introduced in early 1960s. Diazepam was the most popular drug in this group for the initial 2 decades. It water insoluble, has a prolonged effect and painful during injection. Midazolam was synthesized in 1976 by Tryer and walser and is midazolam is a water soluble imidobenzodiazepine. The unique chemical structure of midazolam confers a number of physicochemical properties that distinguish it from other benzodiazepines.

CHEMISTRY



Benzodiazepines are so called because they consist of a benzene ring fused with a seven member diazepine ring. Various modifications in the structure of the ring systems have yielded compounds with similar activities.

Midazolam has a fused imidazole that is different from classic benzodiazepines. The imidazole ring accounts for the stability of an aqueous solution and rapid metabolism. **The ring exhibits a pH dependent ring opening phenomenon.** The ring opens at pH less than 4 making the drug soluble in aqueous solution. Once midazolam enters the body, the pH changes to 7.4 and drug assumes closed ring structure and becomes highly lipid soluble.

AVAILABILITY

Available as one ml ampoule containing 5mg of preservative free midazolam

- 1 vial containing 10mg of midazolam (preservative added)
- Nasal spray
- Oral preparation

PHARMACOKINETICS

After oral administration, midazolam is rapidly absorbed from the gastrointestinal tract. Peak concentrations are achieved within one hour of

ingestion. Because of extensive first pass metabolism only 40-50 percent of oral dose reaches systemic circulation. Hence Oral dose should be twice higher than intravenous dose to achieve comparable clinical effects.

Peak plasma concentrations are seen within an hour of ingestion. When given intramuscularly, the absorption is more predictable than diazepam. Being highly fat soluble it crosses blood brain barrier more easily than diazepam, to gain access to the receptors. It has a more rapid onset (within 30-60 seconds) of action. The half life of equilibrium between plasma concentration and EEG effect is 2 to 3 minutes and is not affected by age.

After intravenous administration of midazolam to healthy adults the disappearance of midazolam from the plasma proceeds in two distinct phases. The initial phase of rapid disappearance is due to distribution of the drug while the final and slower phase of disappearance is attributable mainly to biotransformation. The more rapid redistribution accounts for the shorter duration of action.

Molecular weight	-	362
PKa	-	6.2 (20°)
Elimination half life	-	1.7-2.6 hr
Clearance	-	6.4 -11 ml/ kg/min
Volume of Distribution	-	1.1-1.7 l / kg

Protein binding - 96 – 98%

METABOLISM

Midazolam is metabolized mainly by hepatic microsomal oxidative mechanism, by a process of hydroxylation. The fused imidazole ring is oxidized very rapidly to both 1 and 4 hydroxy midazolam. Both these products are conjugated to glucuronides and are excreted in the urine. The metabolites have less than 1% activity of the parent drug.

MECHANISM AND SITE OF ACTION

1. Gamma – aminobutyric acid (GABA), the principal inhibitory neurotransmitter in CNS. Benzodiazepines do not activate the $GABA_A$ receptor but rather enhance the affinity of the receptors for GABA. As a result, there is enhanced opening of chloride gating channels, resulting in increased chloride conductance producing hyper polarization of the post synaptic cell membrane and rendering post synaptic neurons more resistant to excitation. This resistance to the excitation is presumed to be the mechanism.
2. Sedation, anterograde amnesia and anticonvulsant properties are

mediated via α1 $GABA_A$ receptors. Anxiolysis and Muscle relaxation are mediated by the α2 $GABA_A$ receptor (13).

3. Benzodiazepine receptors are found in highest densities in the olfactory bulb, cerebral cotex, cerebellum, hippocampus, substantia nigra and inferior calculus but in lower densities in the striatum, lower brainstem and spinal cord.
4. Benzodiazepine receptors in the Spinal cord can play an important role in analgesia.
5. Intrathecal midazolam reduces excitatory GABA – mediated transmission in interneurons, leading to a decrease in the excitability of spinal dorsal horn neurons (14).
6. Intrathecal midazolam added to bupivacaine spinal increases analgesia and shortens the time to return of motor function (15).

PHARMACODYNAMICS

CENTRAL NERVOUS SYSTEM

Midazolam has anxiolytic, hypnotic, anticonvulsant, muscle relaxant and anterograde amnestic properties. It decreases the cerebral metabolic oxygen requirements ($CMRO_2$) and cerebral blood flow. Midazolam induces dose dependent changes in regional cerebral perfusion in the parts of the brain that

subserve arousal, attention and memory. Cerebral vasomotor responsiveness to carbondioxide is preserved during midazolam anaesthesia. Cerebral perfusion pressure decrease as the systemic pressure falls more than the intracranial pressure. Given in doses of 0.25mg/kg it does not alter intracranial tension and therefore it can be used for neurosurgical procedures. Emergence from induction is more rapid than diazepam, but not so, when compared with thiopentone. Midazolam decreases the anaesthetic requirement of inhalational agents.

When Midazolam is compared with propofol for sedation, the two are generally similar except that emergence (or) wakeup is more rapid with propofol. Midazolam causes better amnesia and a smoother hemodynamics when compared with Thiopentone.

Arousal time after repeated bolus (or) continuous infusion is less with midazolam than diazepam and lorazepam because of the shorter contex- sensitive half time and greater clearance of midazolam. Midazolam can increase the seizure initiation threshold to local anaesthetics. Midazolam can cause dose related protective effect against cerebral hypoxia (16). The protection afforded by midazolam is superior to that of diazepam but less than that of phenobarbital.

CARDIOVASCULAR SYSTEM

Benzodiazepines maintain relatively stable hemodynamics. It involves the

preservation of homeostatic reflex mechanism (17) but there is an evidence that baroreflex is impaired by midazolam and diazepam.

Midazolam decreases the myocardial contractility and systemic vascular resistance and causes vasodilatation, thus causing fall in arterial pressure. The fall in blood pressure is similar to that caused by hypnotic doses of thiopentone, greater than that caused by equipotent doses of diazepam and less than that caused by propofol (18). It increases the heart rate. Midazolam does not abolish the stress response to intubation (19), but the combination of benzodiazepines with opiates produce greater decrease in systemic blood pressure due to reduction in the sympathetic tone (20) and decreased catecholamines.

Midazolam does not alter coronary vascular resistance and does not cause coronary steal phenomenon.

RESPIRATORY SYSTEM

Midazolam causes dose dependent depression of ventilation. Peak decrease in minute ventilation after midazolam (0.15 mg/kg) is identical to diazepam 3 mg/kg IV (22). The slopes of the ventilatory response curves to carbondioxide are flatter than normal, but not shifted to right as with opioids.
The peak onset of ventilatroy depression with midazolam (0.13 to 0.2 mg /kg) is rapid (About 3minutes) and significant depression remains for about 60-120 min

(23).

Apnoea produced by midazolam is dose related and is more common in patients premedicated with opioids, in chronic obstructive pulmonary disease patients and following faster injection of the drug. The respiratory depression is reversed by flumazenil but not by naloxone. It also depresses the swallowing reflex and decrease upper airway activity.

INTRATHECAL MIDAZOLAM

It is an agonist at the benzodiazepine binding site on a subunit of the pentameric $GABA_A$ receptor. This receptor is a chloride inophore that, when activated typically stabilizes the transmembrane potential at or near the resting potential. In neurons, this typically serves to decrease the excitability. In primary afferent terminals, a modest depolarization is observed that serves paradoxically, to reduce the transmitter release, a form of presynaptic inhibition. Consistent with these effects and benzodiazepine subunit expression in dorsal root ganglia and on spinal neurons, benzodiazepine tends to suppress afferent evoked excitation in the substantia galatinosa and motor horn.

DRUG INTERACTIONS

Erythromycin, clarithromycin and fluconazole increase the effect of midazolam due to inhibition of cytochrome P450 III A enzyme. H2 receptor antagonist also inhibit cytochrome P450 III A enzyme.

Asprin and probenecid increase the effect by competing for protein binding site. Phenytoin, rifampicin and xanthines decrease the efficacy of midazolam due to increased metabolism by inducing cytochrome P450.

Old age, liver disease and renal disease decrease and smoking and habitual alcohol consumption increase the clearance of midazolam.

USES OF MIDAZOLAM	**DOSAGE**	**ROUTE**
1. Induction of Anaesthesia	0.15.0.40mg/kg	iv
2. Maintenance Titration	0.25-1 μg/kg/min	iv
3. Premedication	0.07 - 0.10mg/kg	im
	0.25 - 0.5mg/kg	Oral
4. Intravenus sedation	0.05 -0.15 mg/kg	iv

Adverse effects:

Depending on its dose, midazolam can cause any stage of a cardiovascular and respiratory depression. High i.v. doses have caused cardiac and respiratory arrest with lethal consequences. Usual doses normally cause a minor decrease of the blood pressure and oxygen saturation. The amnesia desired can last much

longer than the intervention, sometimes for hours (semi consciousness). In addition to a multitude of central nervous symptoms (vertigo. dizziness, headaches, rarely hallucinations. etc.), midazolam can also cause visual disturbances and nausea. Repeated administration (e.g. as a sleeping aid) leads to tolerance and dependence within weeks: withdrawal syndrome often occurs if the drug is discontinued abruptly.

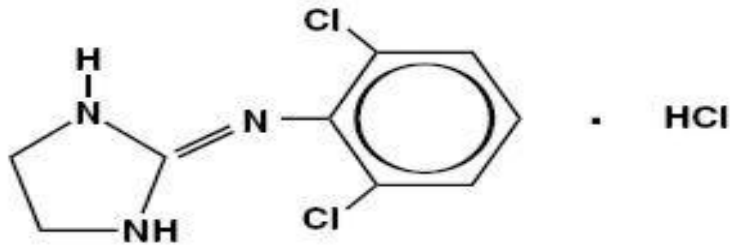
Toxicity:

Signs of overdose include sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, and deleterious effects on vital signs.

PHARMACOLOGY OF CLONIDINE

INTRODUCTION

Clonidine hydrochloride is a centrally acting selective partial α_2 agonist (220:1) that was initially introduced as a nasal decongestant in early 1960s during its use its anti- hypertensive property was found out.



$C_9H_9Cl_2N_3 \cdot HCl$
M. W. 266.56

Clonidine hydrochloride is an imidazoline compound. The chemical name is 2-(2, 6- dichlorophenylamino)-2-imidazoline hydrochloride.

The molecular weight is 266.56. Clonidine is an odourless, bitter, white crystalline substance. It is soluble in alcohol and water.

AVAILABILITY

Oral 0.1 mg, 0.2 mg, 0.3 mg tablet.

Intravenous 1 ml ampoule containing 150 mcg of clonidine as preservative free solution.

Transdermal patches 0.1 mg, 0.2 mg, 0.3 mg / 24 hrs.

MECHANISM OF ACTION

Clonidine is a centrally acting selective partial α_2 adrenergic agonist with a selectivity ratio of 220: 1 in favor of α_2 receptors. There are three subtypes of α_2 receptors α_2A, α_2B and α_2C. α_2A receptors mediate sedation, analgesia & sympatholysis. α_2B receptors mediate vasoconstriction and anti- shivering. The startle response may reflect the activation of α2C receptors. 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 α_2 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 (24). The superficial laminae contain three groups of neurons: tonic, adapting, singlespike firing, all of which receive their primary sensory input from Aδ and C fibres. Studies in rat models show that clonidine inhibits voltage gated Na+ and K+ channels and suppresses the generation of action potentials in spinal dorsal horn neurons, contributing to analgesic effect.

Another contribution to analgesic effect may be through the release of acetylcholine in the neuraxial region. This enhances sensory and motor block of C and Aα fibres by local anaesthetics and by increasing potassium conductance. Sedation is produced by its action on locus coeruleus.

Clonidine affects the blood pressure in a complex fashion after neuraxial or systemic administration because of opposing action at multiple sites. In the nucleus tractus solitarius and locus coeruleus of the brain stem, activation of post- synaptic α2 adrenoreceptors reduces sympathetic drive (25). It also activates noradrenergic imidazoline preferring binding sites in the lateral reticular nucleus producing hypotension and anti-arrythmogenic action. In the periphery it acts on presynaptic α2 adrenoreceptors at sympathetic terminals reduces the release of norepinephrine causing vasorelaxation and reduced chronotropic drive (26). The brainstem and the peripheral effects of α2 adrenoreceptor stimulation are counterbalanced by the direct peripheral vasoconstriction through its action on α21 adrenoreceptors from the circulating concentrations of clonidine.

PHARMACOKINETICS

Clonidine is rapidly absorbed after oral administration and reaches peak plasma concentration within 60 to 90 minutes. The elimination half life of clonidine is between 9 and 12 hours with approximately 50% metabolised in the liver whereas rest is excreted unchanged in urine. The transdermal route requires about 48 hrs to produce therapeutic plasma concentrations.

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

Distribution t ½ : 11+/- 9 minutes.

Elimination t1/2 : 9+/- 2 hour

Volume of distribution: 2.1+/- 0.4 L/kg

Plasma protein binding: 20-40 % in vitro.

Excretion : 70% of the dose, mainly in the form of unchanged parent drug (40-60%) in urine.

PHARMACODYNAMICS

The analgesic effect of clonidine is more potent after neuraxial administration indicating a spinal site of action, favors neuraxial administration, though it is possible to achieve analgesia from systemic administration as well.

CARDIOVASCULAR SYSTEM

The decrease in systolic blood pressure product by clonidine is more potent than decrease is diastolic blood pressure.

The ability of clonidine to decrease systemic blood pressure without paralysis of compensatory homeostatic reflexes is highly desirable.

RESPIRATION

α2 agonists have minimal depressant effects on ventilation and do not potentiate ventilatory depressant effects of opioids.

SEDATION

Clonidine produces a dose dependent sedation at the dose of 50 mcg or more in less than 20 minutes regardless of the route of administration.

PERIPHERAL NERVES

It produces a minor degree of blockade at high concentrations with some preference for C fibres in the peripheral nerves and this effect in part enhance the peripheral nerve block when added to local anaesthetics, probably because the α2 adrenoreceptors are lacking on the axons of peripheral nerves.

Clonidine prevents opioid induced skeletal muscle rigidity and produces skeletal muscle flaccidity.α2 agonists have no effect on the responses evoked by neuromuscular blocking drugs.

ADVERSE EFFECTS

1. Drowsiness, Dryness of mouth, Nasal mucosa and eyes. Weakness, fatigue, headache and withdrawal syndrome.
2. **Cardiovascular:** Bradycardia, Hypotension, syncope, congestive heart failure, ECG abnormalities like sinus node arrest, junctional bradycardia, high degree AV block and arrhythmias are reported rarely.
3. **Central nervous system:** nervousness, agitation, mental depression, insomnia, vivid dreams or nightmares, anxiety, visual and auditory hallucinations have been reported rarely.
4. **Skinrash:** angioneurotic edema, pruritus, utricaria and alopecia rarely.
5. **Gastro intestinal tract:** nausea and vomiting, anorexia.
6. **Genitourinary:** decreased sexual activity, impotence, loss of libido.
7. **Hematologic:** thrombocytopenia rarely.
8. **Metabolic:** weight gain and gynaecomastia

Precautions

1. In patients with renal insufficiency, lower dose is needed.
2. Rebound hypertension can occur after abrupt discontinuation of clonidine

therapy (1.2 mg / day) as early as 8 hours and as late as 36 hours after the last dose (27). Rebound hypertension can usually be controlled by reinstituting clonidine therapy or by administering a vasodilating drugs such as hydralazine or sodium nitroprusside.

3. Use with caution in patients with cerebrovascular or coronary insufficiency.

CONTRAINDICATIONS

1. Known hypersensitivity 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. Narcotics may potentiate the hypotensive effects of clonidine.
3. Tricyclic anti depressants may antagonize the hypotensive effects of clonidine.
4. Concomitant administration of drugs with a negative chronotropic/

dromotropic effect (beta blockers, digoxin) can cause or potentiate bradycardiac rhythm disturbances.

5. Beta blockers may potentiate the hypertensive response seen with clonidine withdrawal.

ANAESTHETIC USES

1. Premedication: Clonidine acting on locus ceruleus produces sedation. Also got an anesthesia- sparing effect.
2. Control of hemodynamics: It prevents hypertension and tachycardia during laryngoscopy and intubation as well as during surgical stimulation decreased incidence of myocardial ischemia in cardiac and vascular surgeries.
3. Epidural: It acts as a sole agent or in combination with opioids or local anaesthetics to provide excellent analgesia.
4. In labour analgesia.
5. Spinal: with local anaesthetics clonidine improve the quality and duration of the block, minimize the tourniquet pain during lower limb surgery, and prevents shivering.
6. Caudal: with local anaesthetics increases the duration of anaesthesia and

analgesia 2 or 3 times without hemodynamic side effects.

7. Peripheral nerve blocks: prolongs the duration of anaesthesia and analgesia with local anaesthetics in a dose of 75- 150 mcg.
8. Bier's block: 150 mcg enhance the tolerance of tourniquet.
9. Intra articular analgesia.

DOSAGE GUIDELINES

Intrathecal - 15 mcg to 30 mcg

Epidural - 1 mcg / kg (or) 50 mcg - 30 mcg / hr (for infusion)

Intravenous - 50-75 mcg or 1 mcg /kg 15 minutes prior to induction for intubation response attenuation.

OVERDOSAGE AND TREATMENT

There is no specific antidote for clonidine over dosage. Supportive measures like atropine, ephedrine, i.v fluids is enough. For hypertensive crisis i.v furosemide, diazoxide, phentolamine can be used. Yohimbine partially reverses the analgesia and sedation but not the BP and heart rate changes produced by the epidural clonidine.

Naloxone may be a useful adjunct for the management of clonidine induced respiratory depression, hypotension and or coma. Blood pressure should be monitored after injecting naloxone as it may produce paradoxical hypertension.

REVIEW OF LITERATURE

C.S.Goodchild and J.Nobel et al (28)**,** conducted a pilot study on effects of intrathecal midazolam on sympathetic reflexes in man. Nine patients received intrathecal midazolam, blood pressure, central venous pressure, E.C.G were monitored continuously. Sensation, motor power and valsalva manouer were also tested. It is concluded intrathecal midazolam blocks somatic nociceptive afferent pathways. Visceral nociceptive afferent pathways are not affected.

BR.J.CLIN.PHARMAC (1987) 23;279-285

C.S.Goodchild et al (29)**,** has published about intrathecal midazolam in rats. In this study antinociceptive effect of intrathecal midazolam involves release of endogenous neurotransmitters acting at the spinal cord delta opioid receptors.

These effects were demonstrated by measuring electrical current threshold for avoidance behavior in rats. The results of the study implied that, intrathecal midazolam combines with GABA 'A' receptors in the spinal cord and releases endogenous opioid that acted at Kappa or delta opioid receptor but not on μ opioid receptors.

Kim MH et al (30) in 2001, in a double-blinded study conducted the postoperative analgesic effects of intrathecal midazolam with bupivacaine undergoing haemorrhoidectomy surgeries, Forty-five patients were divided into three groups: the control group received 1ml of 0.5% heavy bupivacaine plus 0.2 ml of 0.9% saline intrathecally, group BMI received 1 ml of 0.5% bupivacaine plus 0.2ml of 0.5% preservative-free midazolam and group BM2 received 1ml of 0.5% bupivacaine plus 0.4 ml of 0.5% midazolam. In this study addition of 0.2ml (or) 0.4ml intrathecal midazolam prolong the postoperative analgesic effect by

6.03 hours and 8.37 hrs respectively. All patients required analgesic during 24 hours after surgery.

Adam P.Tucker et al (31), conducted cohort study on intrathecal midazolam. This study focused on neurotoxicity with Intrathecal midazolam. Eleven hundred patients were followed postoperatively up to one month for the symptoms suggestive neurotoxicity. Intrathecal midazolam up to 2 mg. did not increase the neurologic symptoms.

ANAESH ANALG 2004; 98; 1512-20

Dr.Nithi agarwal et al (32**)** conducted double blind study among 53 adult patients on efficacy of intrathecal bupivacaine with midazolam for Postoperative analgesia. Patients were randomly divided into two groups. Group B received 3 ml of heavy bupivacaine with 0.2 ml of 0.9% saline. BM group received 3 ml of heavy bupivacaine with 0.2 ml of preservative free 1 mg midazolam intrathecally. The time for regression of sensory block in group B was 164 minutes where as in group BM 158.6 minutes. Time to first rescue analgesic was 4 hrs in group B

and 17 hrs in group BM. In conclusion, the duration of Postoperative analgesia was longer in Intrathecal midazolam combination without affecting the duration of dermatomal sensory level. There were no side effects such as nausea, vomiting, urinary retention, hypotension, bradycardia and itching in their study.

INDIAN J.ANAESTH 2005; 49;1;37-39

Prakash et al (33) conducted study regarding analgesic efficacy of 1 mg and 2 mg of intrathecal midazolam with bupivacaine in 60 patients undergoing cesarean section. Patients were divided into three groups randomly. Group B received 2 ml of hyperbaric bupivacaine 0.05. % . Group BM1 received 2 ml of bupivacaine and 1 mg midazolam, and group BM2 received 2 ml of bupivacaine with 2 ml midazolam. The mean duration of Postoperative analgesia are 4.3 hrs and 6.1 hrs in 1 mg and 2 mg midazolam groups respectively. The supplementary analgesic dose of diclofenac was 93 mg in BM2 group and 148 in BM1 group. They have concluded that the 2 mg of midazolam adjuvant causes prolongation of post operative analgesia.

REG ANAESH PAIN MED 2006 MAY-JUNE 31 220-226

Hema saxena M.D. et al (34)**,** conducted study on intrathecal clonidine

regarding onset and duration of block with hemodynamic stability. Among eighty patients who underwent lower abdominal surgeries were divided randomly into 4 groups. Control group (I) received 13.5 mg of 0.5% bupivacaine. Group II , Group III, Group IV received 15 mcg , 30 mcg and 37.5 mcg of clonidine respectively along with 13.5 mg of bupivacaine. In their study, the duration of analgesia in patient who received 30 mcg of clonidine was 264 minutes, motor blockade was 220 minutes and the onset of sensory block was 0.098 minutes. With the addition of clonidine, they observed the onset time, duration of block improved in a dose dependant manner.

In group IV (who received 37.5 mcg of clonidine) 30% of the patients had fall in pulse rate and blood pressure and 90% of the patients were sedated. The hemodynamic stability was better maintained in group II and group III than group IV. There was no significant difference between group III and group IV regarding the time of onset of sensory and motor blockade. In conclusion, their study has demonstrated 30 mcg of clonidine provides maximum benefits and minimum side effects.

INTERNET JOURNAL OF ANAESTHESIOLOGY 2010.VOL.23.NO.1

Shadhangi B K et al (35), at AIIMS, in 2011 in a prospective double

blind study evaluated postoperative analgesic efficacy of Intrathecal midazolam 2 mg as an adjuvant to Bupivacaine for spinal anesthesia in 100 patients scheduled for elective lower abdominal, lower limb and gynecological procedures. Patients were allocated in two groups. Group B received 3 ml of 0.5% heavy Bupivacaine with 0.4 ml normal saline and Group BM received 3 ml of 0.5% Bupivacaine and 0.4 ml (2 mg) of midazolam. The following parameters are recorded and comparable. Onset and duration of sensory/motor block, time to first postoperative analgesia and adverse effects.

Onset of sensory block was 4.8 minutes in Group B and Group BM was 4.6 minutes, Onset of motor block was 5.9 minutes in Group B and 6 minutes in Group BM. Duration of sensory block was 90.8 minutes in Group B and 115.8 minutes in Group BM, Duration of motor block was 151.8 minutes in Group B and 151.3 minutes in Group BM. Duration of analgesia was 121.3±5.4 minutes in Group B and 221.1±15.6 in Group BM.

Respiratory rate and O2 saturation did not differ between B and BM groups. They concluded that intrathecal midazolam 2 mg provided moderate prolongation of Postoperative analgesia without increasing motor block.

Singapore Med J 2011 52(6)432-435

Nanjegowda et al (36), in 2011 in a prospective, randomized double blind study, investigated the intrathecal midazolam on postoperative analgesic efficacy and adverse effects in patients undergoing knee arthroscopy.50 ASA-I and ASA-II patients of either sex aged between 18-56 years were allocated into two groups. Group M received 2 ml of 0.5% Bupivacaine with 2 mg(0.4 ml) preservative free midazolam and Group S received 2 ml of 0.5% heavy Bupivacaine with 0.4 ml of 0.9% saline. Peak sensory level, total duration of analgesia, duration of motor blockade, Pain score, and sedation score were compared. Vital parameters like Heart rate, mean arterial blood pressure were assessed.

Pain score(i.e)VAS was lower in Group M than Group S and total duration of analgesia was significantly high in group M and significantly prolonged regression in group M. The peak sensory levels achieved in both groups were comparable without any statistical difference.

VAS score was 33.6±4.6 and 56.6±8.64 in Group M and Group S respectively. Duration of analgesia was 399.40±88.11 minutes and

301.60±110.14 minutes in Group M and Group S respectively. Two segment regression times was 120.12±7.26 minutes and 90.20±4.51 minutes in Group M and Group S respectively.

They concluded that intrathecal adjuvant preservative free midazolam 2 mg to intrathecal 0.5% bupivacaine prolongs the duration of analgesia without any adverse effects.

South Afr J Anaesth Analg 2011 17(3) 255-259

Maryam shokrpur et al (4), conducted comparative study of intrathecal midazolam and intrathecal neostigmine with lidocaine in spinal anathesia in women undergoing colporrhaphy.

In this study sixty women were divided in to three groups. I group received hyperparic lidocaine with on milligram of midazolam, II group received hyperparic lidocaine with 50 mcg of neostigmine and III group received lidocaine with normal saline. Pain score at 4 hrs, 12 hrs and 24 hrs were compared . The duration of sensory block was prolonged in midazolam group . The VAS pain score in midazolam group was lower than the other two groups.

JOURNAL OF FAMILY AND REPRODUCTIVE HEALTH VOL.6 , NO.2, JUNE 2012

Abdul muthalib hussain et al (5)**,** conducted comparative study of intrathecal ketamine and midazolam with bupivacaine for Postoperative analgesia in lower limb and perianal surergeries. Among 80 patients, two groups were divided. Group I received ketamine as adjuvant. Group II received midazolam as adjuvant. In their study midazolam group had prolonged Postoperative analgesia compared to ketamine group.

BIO MEDICAL RESEARCH 2012; 23 (2); 259-267

Suchita A. Joshi et al (6) conducted study among 50 patients to assess the comparative efficacy, safety and duration of analgesia produced by 30 mcg clonidine and 2 mg midazolam with 15 mg hyperbaric 0.5% bupivacaine in lower abdominal surgeries. In midazolam the onset of sensory block was 1.84 minutes and duration of sensory block was 210.84 minutes where as in clonidine group the onset of sensory and duration of block was 2.44 minutes and 169.28 minutes respectively. The duration of postoperative analgesia was 391.64 minutes in midazolam group but in clonidine group it was 296.60 minutes . The number of analgesic doses was significantly less in midazolam group postoperatively in 24 hours. But in clonidine group 36% of patients had bradycardia and 44% of patients had hypotension. None of the patients had bradycardia in midazolam group and only 16% of the patient had hypo tension. In their study they

administered first dose diclofenac 75 mg to all patients immediately after shifting to ward. The average amount of diclofenac requirement was 153 mg in midazolam group and 117 mg in clonidine group. They have concluded with clonidine the postoperative analgesia is short lived with adverse effects. Intrathecal midazolam provides superior analgesia without clinically relevant side effects.

MATERIALS AND METHODS

Study Design: Double blinded randomized case control study.

After obtaining approval from the institutional ethics committee, Thanjavur Medical College, Thanjavur, the study was conducted in 60 ASA grade I or II patients undergoing elective lower abdominal surgeries like Hernia repair and appendicectomy under spinal anesthesia. Before including the patients for the study, all patients were explained about the procedures and a written informed consent was obtained.

INCLUSION CRITERIA

- Adult Patients aged 20-60 years of either sex
- ASA I & II Patients
- Weight: 35- 70 kg
- Height : 150-170 cm

EXCLUSION CRITERIA

- Infection at the site of injection
- Spinal deformity
- H/o Bleeding diathesis

- H/o Chronic pain and on analgesics
- H/o Drug Allergy.
- H/o Psychiatric illness

PREOPERATIVE PREPARATION:

After routine preoperative assessment all patients were familiarized with Visual Analog Scale (VAS). The patients were shown a 10 cm long scale marked 0-10 on a blank paper and told that 0 represented “no pain” and 10 represented worst possible pain.

At the patient’s waiting room in the OT, basal line readings of the vital parameters were recorded. Intravenous line started. Each patient received inj. ranitidine 50 mg and inj. metoclopromide 10 mg before shifted to theatre. The patients were randomly allocated into two groups of 30 each by using closed cover technique.

In the operating room, appropriate equipment for airway management and emergency drugs were kept ready. The horizontal position of the operating table was checked. Patients were shifted to the operating room and positioned.

Noninvasive blood pressure monitor, pulse oximeter and ECG leads were connected to the patient. Preoperative baseline systolic and diastolic blood pressure, mean arterial pressure, pulse rate, respiratory rate and oxygen

saturation were recorded. Patients were preloaded with 10ml/ kg of ringer lactate 15min prior to the subarachnoid block. The Patient was placed in right lateral position. The skin over the back was prepared with antiseptic solution and draped with sterile towel.

BM GROUP

- Patients received 3ml 0.5% bupivacaine (15mg)
- 0.4 ml Midazolam (2 mg) preservative free
- 0.1 ml normal saline

BC GROUP

- Patients received 3 ml 0.5% bupivacaine (15mg)
- 0.2 ml clonidine (30 μg)
- 0.3 ml normal saline

The total volume of the injected solution was 3.5ml in both groups.

Lumbar puncture performed with a 25G Quincke's spinal needle at L3 – L4 inter space via midline approach. After confirming free flow of CSF, the prepared solution was injected. The patients were made to lie supine immediately after injection and the time at which the spinal anaesthesia performed was noted.

The following parameters were recorded.

- Time of injection of subarachnoid Block.
- Time of onset of sensory block at T_{10} level.
- Maximum level of sensory block achieved (by pinprick method)
- Time to achieve maximum level of sensory Block.
- Two segment regression time.
- Onset of Motor Block
- Duration of Complete motor recovery.
- Duration of Surgical procedure
- Sedation score
- Time to first dose of Postoperative analgesic
- Total dose of Postoperative analgesic
- Systolic and diastolic blood pressure, mean arterial Blood pressure pulse rate and oxygen saturation were recorded every 2 minutes for the first 10 minutes and thereafter every 5 minutes up

to one hour.

- Hypotension is said to have occurred if the MAP falls less than 70mmHg and was treated with 100% 02, increasing the infusion rate of IV fluids and inj. Ephedrine in incremental doses of 6 mg at an interval of 2 minutes.
- Bradycardia was defined as heart rate less than 60/min and was planned to be managed with intravenous atropine in incremental doses.
- Respiratory depression was said to be present if respiratory rate was less than 8 per minute and / or SpO_2 <90%. It was planned to be managed with mask ventilation or intubation and IPPV.
- Any discomfort like Nausea, Vomiting, Shivering, respiratory depression and urinary retention are noted.
- Vomiting was planned to be managed with Inj. Odansetron 4 mg intravenously.
- On completion of surgery Patients were shifted to post anesthesia care unit for observation. Patients were transferred to postoperative ward after complete resolution of motor blockade and stabilization of blood pressure. Vital signs were recorded every 15 minutes in the first hour after surgery, 30 minutes for

the next 2 hours and thereafter every hour for next 3 hours. Pain assessment was done using VAS every 30 minutes till VAS score of 4 was reached. The VAS was also noted whenever the patient complained of pain. Inj. Diclofenac sodium 75 mg was given intramuscularly when VAS of 4 or more was reached. Urinary retention was monitored postoperatively and catheterization was planned in patients with retention more than 6 hours. Patients were monitored for 24 hours to detect side effects like nausea, vomiting, dry mouth, Headache, Shivering, respiratory depression.

SENSORY BLOCK

The onset of sensory block was defined as the time between the injection of anaesthetic solution and the absence of pain at the T10 dermatome. Sensory block was assessed by loss of sensation to pinprick using 21G Sterile needles bilaterally along the midclavicular line. This assessment started immediately after turning the patient to supine position and continued every minute till loss of sensation to pinprick at T10 level was noted. This pinpricking continued till the peak block height was reached and the time was noted. The duration of sensory

block was defined as the time for regression of two segments from the maximum block height evaluated by pin prick. Sensory block was checked every 15 minutes till it reached two segment regression levels.

MOTOR BLOCK

Motor Block was assessed bilaterally using Modified bromage scale.

MODIFIED BROMAGE SCALE

O - No block. Able to raise extended legs against gravity

1 - Unable to raise extended leg, but just able to flex knees.

2 - Unable to flex knees but able to flex ankle.

3 - Total block. Inability to flex ankle/ move leg.

Assessment of motor block was started immediately after turning the patient to supine position and continued every minute till bromage score of 1 was reached. The onset of motor block was defined as the time to achieve bromage score of 1 from the time of injection. Duration for complete motor block recovery was taken as the time from subarachnoid injection to return of bromage score of 0.

RAMSAY SEDATION SCORE

Used to assess the degree of sedation.

1. Anxious and Agitated
2. Cooperative , oriented, tranquil
3. Responds only to verbal commands
4. Asleep with brisk response to light Stimulation
5. Asleep with Sluggish response to light stimulation
6. Asleep Without response to light stimulation

VISUAL ANALOG SCALE

0-1 - Excellent

2-4 - Good

5-6 - Fair

7-8 - Poor

9-10 - No relief

When Pain score ≥4 – supplementary analgesic was given.

DURATION OF ANALGESIA

The time at which the patient first complained of pain was noted. The duration of effective analgesia was defined as the period from the spinal injection to the first occasion when the patient complained of pain in the postoperative period.

OBSERVATION AND ANALYSIS

We conducted a double blinded randomized control study in Thanjavur medical college, Thanjavur to evaluate the effects of two adjuvants added to intrathecal bupivacaine.

The collected data were analyzed by chi square test and results obtained in the form of range, mean and standard deviation. The probability value 'P' of less than 0.05 considered statistically significant.

Patient's demographic data that includes age, sex and duration of surgery between two groups were comparable.

TABLE : 1

AGE DISTRIBUTION

Sl.no	Variables	Sample group					
		BM Group		BC Group		Total	
		n = 30	*100%*	*n = 30*	*100%*	*n = 60*	*100%*
	Age						
	Below 30yrs	12	40.0%	12	40.0%	24	40.0%
	31 to 40yrs	7	23.3%	7	23.3%	14	23.3%
	41 to 50yrs	5	16.7%	7	23.3%	12	20.0%
	51yrs & above	6	20.0%	4	13.3%	10	16.7%

The age distribution was in the range of 22-60 years in BM group and 22-65 years in BC group. The 'P' value for mean age was not statistically significant ('P' value = 0.866 > 0.05).

FIGURE : 1

AGE DISTRIBUTION

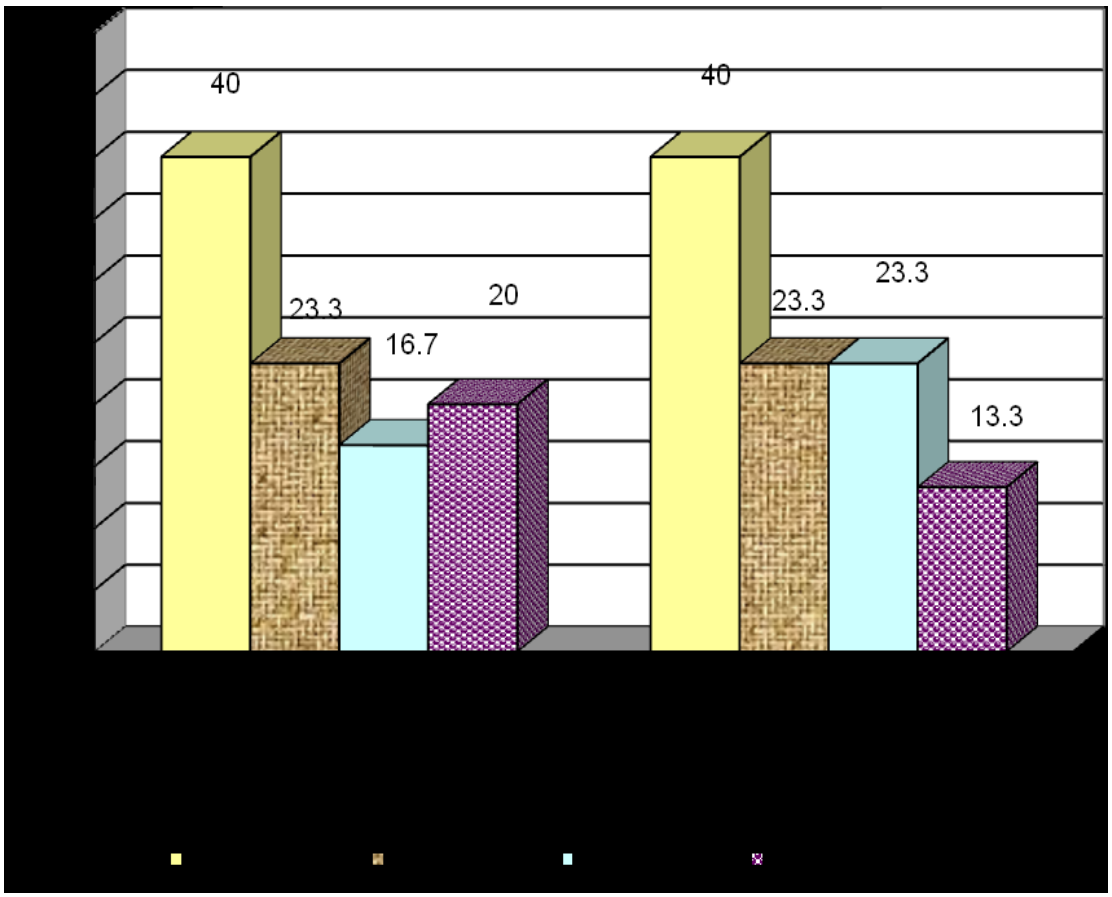


TABLE : 2

SEX DISTRIBUTION

Sl.no	Variables	Sample group					
		BM Group		BC Group		Total	
		n = 30	*100%*	*n = 30*	*100%*	*n = 60*	*100%*
	Sex						
	Male (BM)	25	83.3%	0	0%	25	41.7%
	Female (BM)	5	16.7%	0	0%	5	8.3%
	Male (BC)	0	0%	23	76.7%	23	38.3%
	Female (BC)	0	0%	7	23.3%	7	11.7%

Though male and female ratio are not equal in either group, statistics between the groups for sex distribution was not significant ('P' value 0.752 > 0.05 by chi square test).

FIGURE :2
SEX DISTRIBUTION

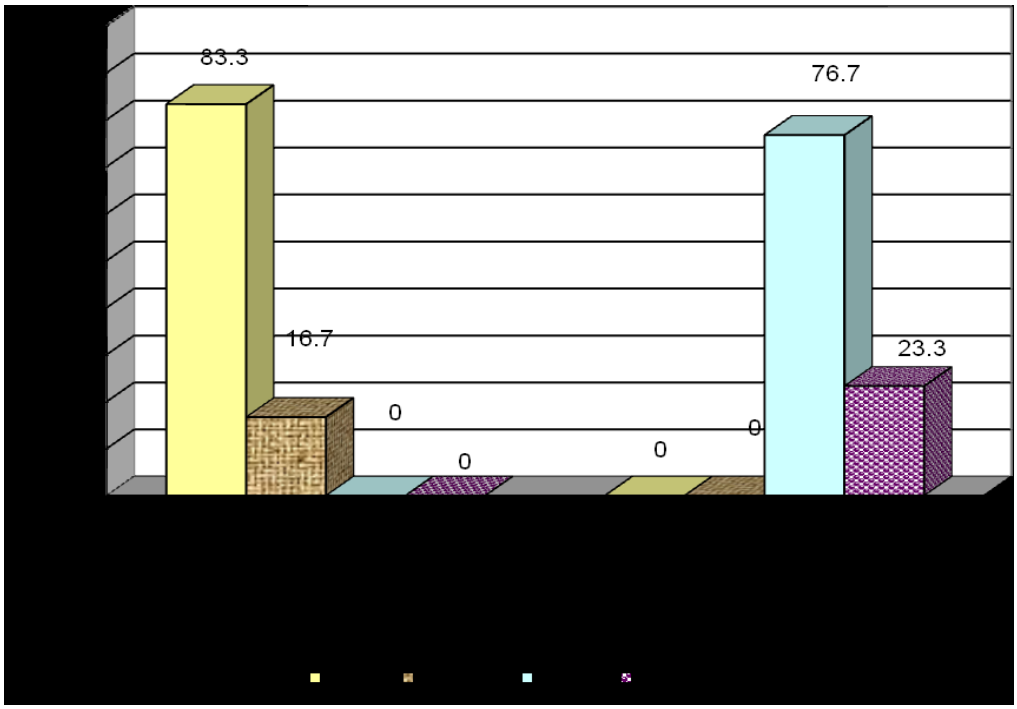


TABLE : 3

ONSET OF SENSORY AND MOTOR BLOCK

Onset of Sensory block at T10	Mean ± S.D	Statistical inference
BM Group (n=30)	2.17 ± 0.379	T=-14.253 0.000 < 0.05 Significant
BC Group (n=30)	3.90 ± 0.548	

The average time taken for onset of sensory block was 2.17 minutes in BM group and 3.9 minutes in BC group. It was statistically significant ('P' value 0.000 < 0.05).

TABLE : 4

Onset of Motor Block	Mean ± S.D	Statistical inference
BM Group (n=30)	3.20 ± 0.407	T=-13.350 0.000 < 0.05 Significant
BC Group (n=30)	4.93 ± 0.583	

The onset of motor block was significantly faster in BM group compared to BC group (3.2 minutes Vs 4.93 minutes) which was statistically significant ('P' value 0.000 < 0.05).

FIGURE : 3

ONSET OF SENSORY AND MOTOR BLOCK

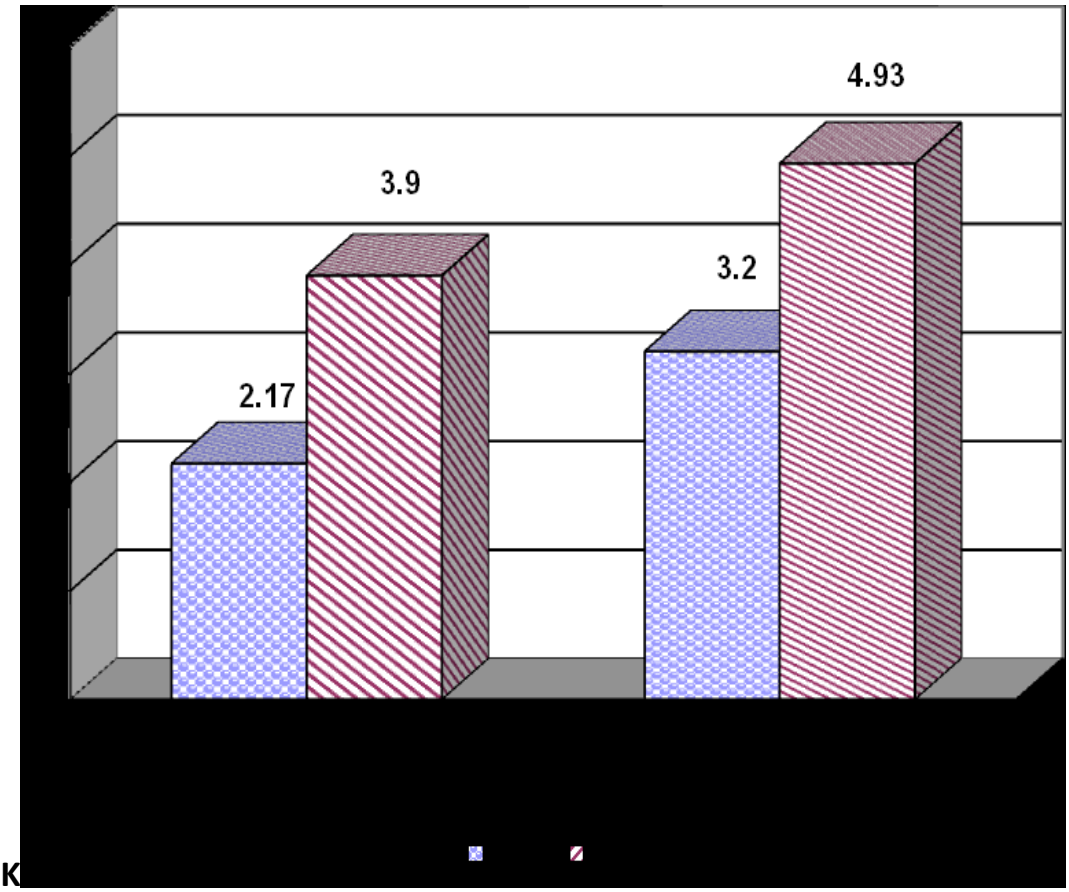


TABLE : 5

PEAK SENSORY LEVEL

Sl.no	Peak sensory Level	Group sample		Statistical inference
		BM Group (n=30)	BC Group (n=30)	
1	T4	2 (6.7%)	3 (10%)	$X^2 = 0.398$
2	T6	24 (80%)	22 (73.3%)	Df = 2
3	T8	4 (13.3%)	5 (167%)	0.820 > 0.05
				Not Significant

Level of the sensory block varied from T4 to T8 level among all patients, 46 patients attained maximum level of sensory blockade at T6. Nine patients attained up to T8 level. Five patients attained T4 level. It was statistically not significant ('P' value 0.820 > 0.05).

TABLE : 6

TIME TO ACHIEVE MAXIMUM SENSORY LEVEL

Time to achieve maximum sensory level	Mean ± S.D	Statistical inference
BM Group (n=30)	7.37 ± 0.490	T=-17.171 0.000 < 0.05 Significant
BC Group (n=30)	10.17 ± 0.747	

The mean time to achieve maximum sensory level was 7.37 minutes in BM group. But in BC group it was 10.17 minutes. The probability value as detected by students‘t’ test is 0.000 < 0.05.

FIGURE : 4

TIME TO ACHIEVE MAXIMUM SENSORY LEVEL

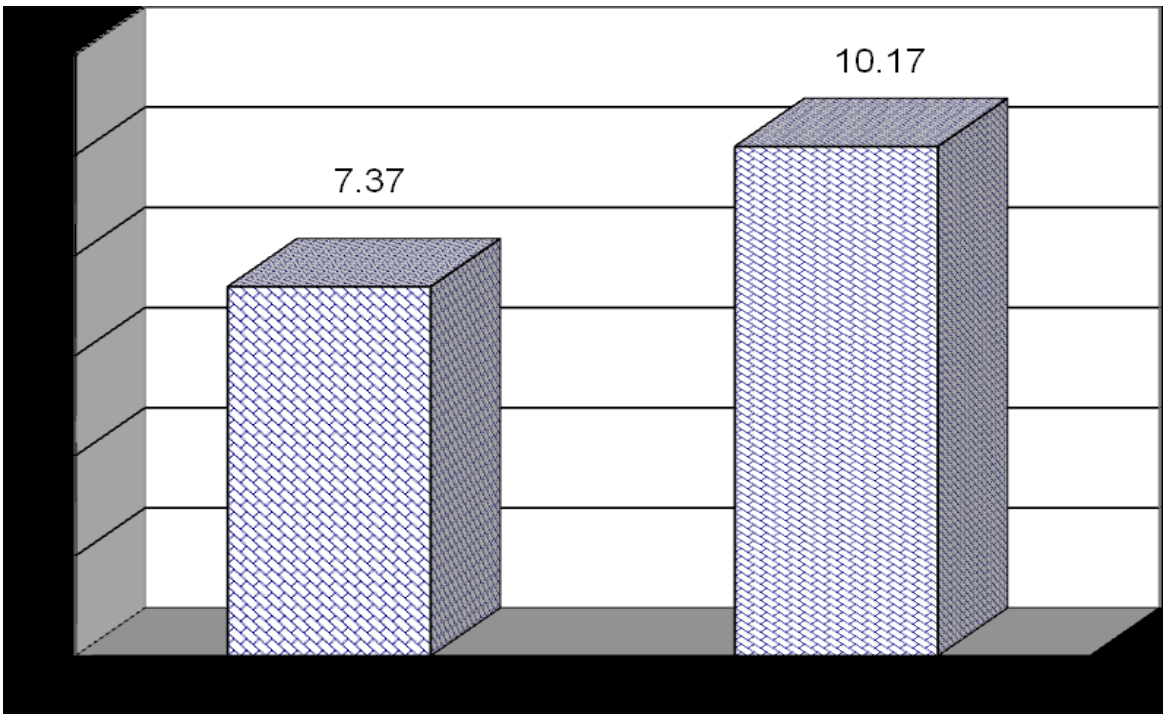


TABLE : 7

TWO SEGMENT REGRESSION TIME AND DURATION OF COMPLETE MOTOR RECOVERY

Two segment regression time	Mean ± S.D	Statistical inference
BM Group (n=30)	211.67 ± 15.444	T=15.482 0.000 < 0.05 Significant
BC Group (n=30)	156.33 ± 12.030	

Table : 7 / Figure : 5 show duration of two segment regression time in minutes in BM group comparing to BC group (211.67 Vs 156.39 minutes) with significant 'P' value (0.000 < 0.05).

TABLE : 8

Duration of complete Motor Recovery	Mean ± S.D	Statistical inference
BM Group (n=30)	292.00 ± 13.104	T=-8.904 0.000 < 0.05 Significant
BC Group (n=30)	319.00 ± 10.205	

The table : 8 / figure : 5 shows prolonged duration of complete motor recovery in BC group of 390 minutes with significant 'P' value (0.000 < 0.05).

FIGURE : 5

COMPARISON OF TWO SEGMENT REGRESSION TIME AND DURATION OF COMPLETE MOTOR RECOVERY

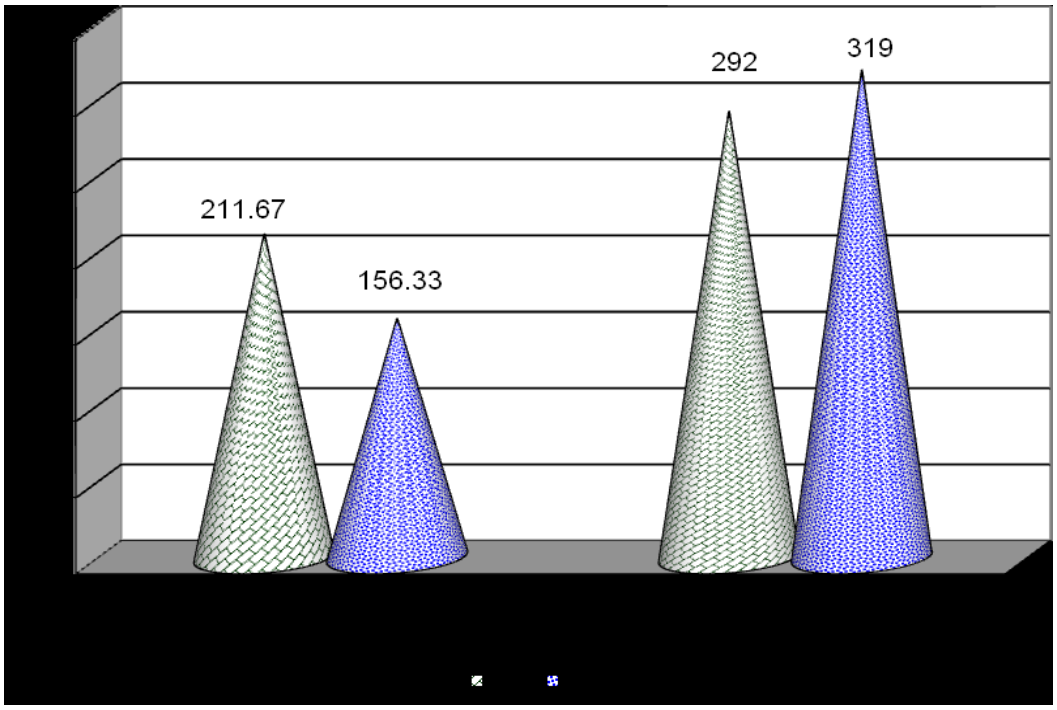


TABLE : 9

TIME TO FIRST POSTOPERATIVE ANALGSIA AND TOTAL DOSE OF POSTOPERATIVE ANALGESIA

Time to first Postoperative analgesia	Mean ± S.D	Statistical inference
BM Group (n=30)	486.17 ± 42.012	T=15.570 0.000 < 0.05 Significant
BC Group (n=30)	306.17 ± 47.374	

The mean duration of analgesia (time to first Postoperative analgesia) was 486.17 minutes with a range of 400 to 540 minutes in BM group. But in the BC group it was 306.17 minutes with a range of 255-470 minutes. The probability value, as detected by students‘t’ test was 0.000 < 0.05.

FIGURE : 6

COMPARISON OF TIME TO FIRST POSTOPERATIVE ANALGSIA AND TOTAL DOSE OF POSTOPERATIVE ANALGESIA

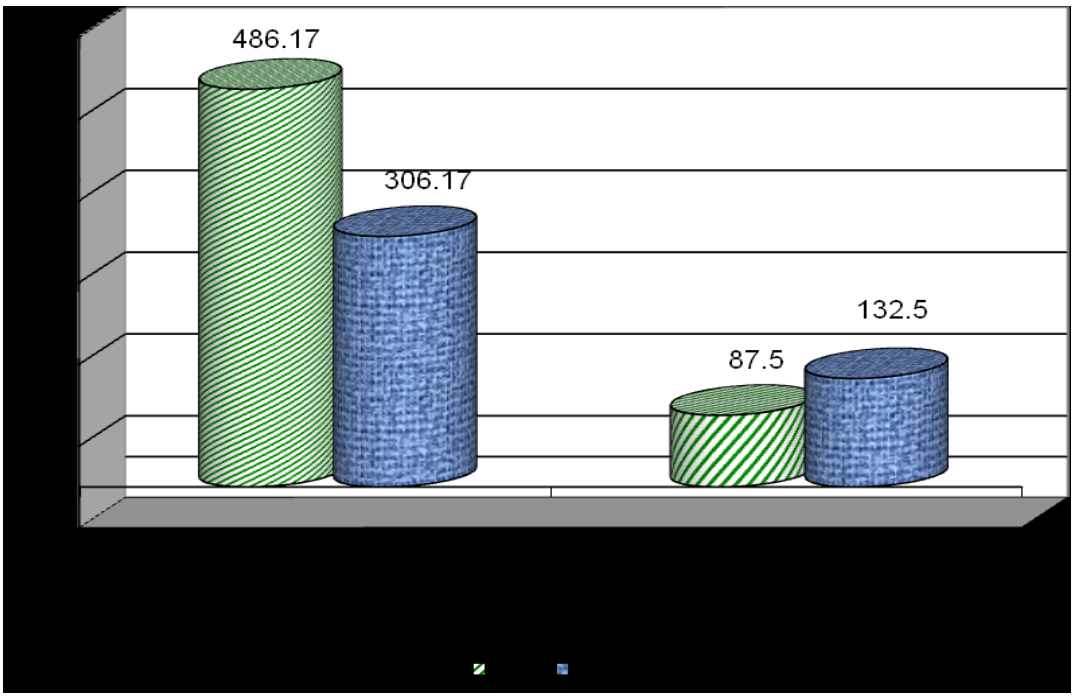


TABLE : 10

Total dose of postoperative analgesia	Mean ± S.D	Statistical inference
BM Group (n=30)	87.50 ± 28.429	T=-5.732 0.000 < 0.05 Significant
BC Group (n=30)	132.50 ± 32.264	

The mean value of total dose of Postoperative analgesia was very less in BM group comparing to BC group (87.5 Vs 132.5 mg) which was statistically significant 'P' value 0.000 < 0.05.

TABLE : 11

PULSE RATE

Time Interval	BM Group (Mean ± SD)	BC Group (Mean ± SD)	Statistical Inference
Base Line	86.40 ± 3.729	87.53 ± 2.726	0.184 > 0.05
2 minutes	81.87 ± 3.235	83.27 ± 3.600	0.119 > 0.05
4 minutes	79.63 ± 2.988	81.40 ± 3.359	0.036 < 0.05*
6 minutes	78.47 ± 3.148	79.67 ± 3.122	0.144 > 0.05
8 minutes	77.73 ± 2.59	78.37 ± 2.327	0.318 > 0.05
10 minutes	76.53 ± 2.270	77.33 ± 3.407	0.289 > 0.05
15 minutes	75.43 ± 2.788	75.63 ± 3.837	0.818 > 0.05
20 minutes	74.77 ± 2.775	73.50 ± 4.092	0.166 > 0.05
25 minutes	74.40 ± 3.147	71.57 ± 5.500	0.017 < 0.05*
30 minutes	74.63 ± 3.378	71.30 ± 5.408	0.006 < 0.05*
35 minutes	74.90 ± 3.241	71.73 ± 4.354	0.002 < 0.05*
40 minutes	74.30 ± 2.830	72.03 ± 4.214	0.018 < 0.05*
45 minutes	74.03 ± 3.368	72.5 ± 4.65	0.150 > 0.05
50 minutes	74.07 ± 3.084	72.77 ± 4.216	0.178 > 0.05
55 minutes	74.37 ± 3.479	73.87 ± 4.408	0.628 > 0.05
60 minutes	74.53 ± 3.550	74.00 ± 4.235	0.599 > 0.05
75 minutes	75.03 ± 3.168	74.97 ± 4.081	0.944 > 0.05
90 minutes	75.60 ± 3.480	75.60 ± 3.874	1.000 > 0.05
105 minutes	75.83 ± 3.733	75.53 ± 3.693	0.755 > 0.05
120 minutes	76.60 ± 3.747	76.67 ± 3.565	0.944 > 0.05
150 minutes	77.43 ± 3.607	77.00 ± 3.648	0.645 > 0.05
180 minutes	78.23 ± 3.664	77.37 ± 4.131	0.394 > 0.05
210 minutes	78.97 ± 3.882	77.77 ± 3.892	0.237 > 0.05
240 minutes	78.67 ± 3.845	78.53 ± 3.461	0.888 > 0.05
300 minutes	79.77 ± 3.181	78.50 ± 3.785	0.166 > 0.05
360 minutes	80.37 ± 3.232	79.00 ± 3.610	0.128 > 0.05
420 minutes	80.90 ± 3.209	79.53 ± 3.048	0.096 > 0.05

FIGURE : 7

COMPARISON OF PULSE RATE

We had monitored pulse rate from pre operative basal to 420th minute. But only intra operative period has shown statistical significant importance. Though there were reductions in pulse rate between 2nd and 10th intervals in BM group only at 4th minute it was statistically significant comparing to BC group (BM 79.63 ± 2.9 Vs BC 81.40 ± 3.3).

Again there were reductions in pulse rate at 25th, 30th, 35th and 40th minute intervals in BC group comparing to BM group.

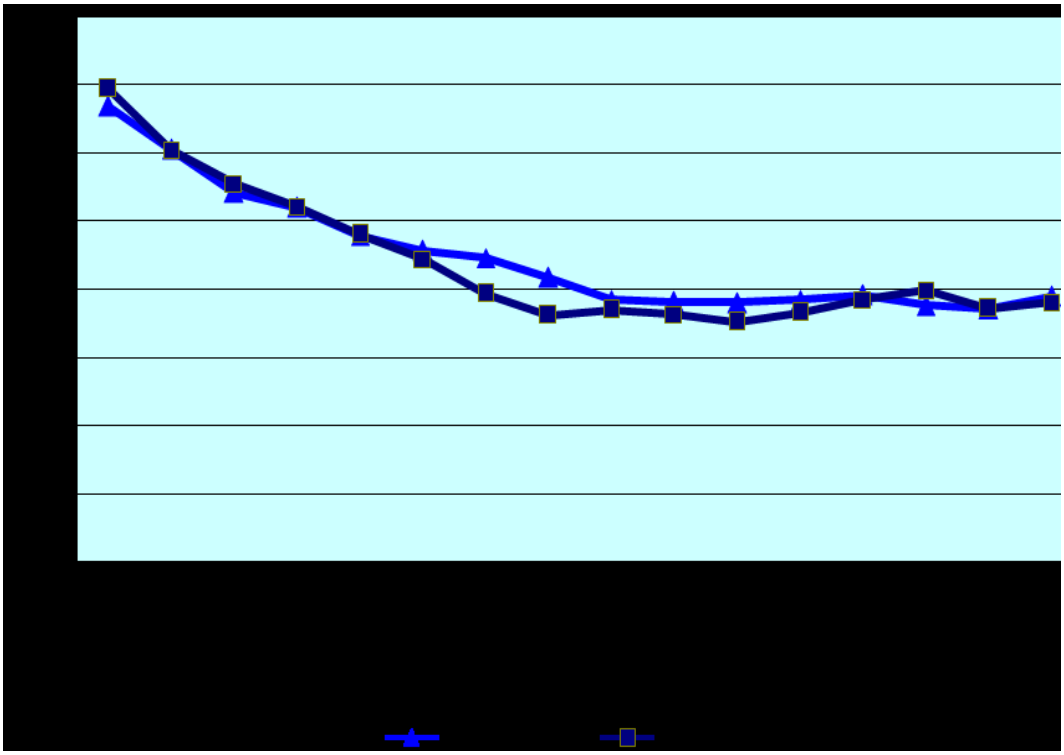
TABLE : 12

MEAN ARTERIAL PRESSURE

Time Interval	BM Group (Mean ± SD)	BC Group (Mean ± SD)	Statistical Inference
Base Line	93.43 ± 5.230	94.73 ± 5.112	0.334 > 0.05
2 minutes	90.27 ± 4.370	90.23 ± 3.980	0.975 > 0.05
4 minutes	87.13 ± 4.191	87.77 ± 4.158	0.559 > 0.05
6 minutes	86.03 ± 5.750	86.10 ± 4.358	0.960 > 0.05
8 minutes	83.93 ± 5.271	84.03 ± 4.552	0.938 > 0.05
10 minutes	82.87 ± 4.455	82.20 ± 4.021	0.545 > 0.05
15 minutes	82.33 ± 5.248	79.67 ± 4.978	0.048 <0 .05*
20 minutes	80.87 ± 5.770	78.10 ± 5.307	0.058 < 0.05*
25 minutes	79.2 7± 5.078	78.53 ± 5.438	0.591 > 0.05
30 minutes	79.10 ± 5.585	78.17 ± 4.292	0.471 > 0.05
35 minutes	79.03 ± 4.382	77.60 ± 4.651	0.224 > 0.05
40 minutes	79.27 ± 4.110	78.33 ± 3.73	0.361 > 0.05
45 minutes	79.60 ± 4.454	79.23 ± 4.150	0.743 > 0.05
50 minutes	78.83 ± 3.495	79.97 ± 4.214	0.262 > 0.05
55 minutes	78.57 ± 3.945	78.60 ± 4.005	0.974 > 0.05
60 minutes	79.50 ± 4.058	79.03 ± 3.952	0.653 > 0.05
75 minutes	80.10 ± 3.468	79.30 ± 4.380	0.436 > 0.05
90 minutes	80.47 ± 4.041	80.27 ± 4.127	0.850 > 0.05
105 minutes	80.80 ± 3.547	80.80 ± 3.881	1.000 > 0.05
120 minutes	81.37 ± 2.748	81.50 ± 4.855	0.896 > 0.05
150 minutes	82.03 ± 3.399	81.97 ± 4.279	0.947 > 0.05
180 minutes	82.83 ± 3.425	83.03 ± 4.367	0.844 > 0.05
210 minutes	82.90 ± 3.199	80.47 ± 14.788	0.382 > 0.05
240 minutes	84.40 ± 3.430	84.20 ± 4.131	0.839 > 0.05
300 minutes	85.07 ± 3.151	85.03 ± 3.378	0.969 > 0.05
360 minutes	86.83 ± 3.733	85.83 ± 3.797	0.308 > 0.05
420 minutes	87.10 ± 3.604	86.87 ± 3.461	0.799 > 0.05

FIGURE : 8

COMPARISON OF MEAN ARTERIAL PRESSURE



We had monitored mean arterial pressure from pre operative basal to 420th minute. But only intra operative period has shown statistically significant. There were reductions in mean arterial BP in 15th and 20th minute in BC group comparing to BM group and the corresponding 'P' value is 0.048 < 0.05 and 0.058 < 0.05 respectively.

TABLE : 13

RESPIRATORY RATE

RR (/ minute)	Mean ± S.D	Statistical inference
BM Group (n=30)	13.97 ± 0.414	T=0.331 0.742 > 0.05 Not Significant
BC Group (n=30)	13.93 ± 0..365	

Respiratory rate was in the range of 13-15 per minute analyzed in both groups and was not significant ('P' value 0.742 > 0.05).

TABLE : 14

O2 SATURATION

SPO2	Mean ± S.D	Statistical inference
BM Group (n=30)	98.27 ± 0.691	T=0.367 0.715 > 0.05 Not Significant
BC Group (n=30)	98.20 ± 0.714	

Oxygen saturation was in the range of 97% -100%, analyzed in both groups and was not significant ('P' value 0.715 > 0.05).

TABLE : 15

SEDATION SCORE

SedationScore	Mean ± S.D	Statistical inference
BM Group (n=30)	2.83 ± 0.379	T=-0.750 0.456 > 0.05 Not Significant
BC Group (n=30)	2.90 ± 0.305	

Most of the patients had sedation score of 3 (the patients response only to verbal comments) sedation score was not significant 'P' value 0.456 > 0.05.

TABLE :16

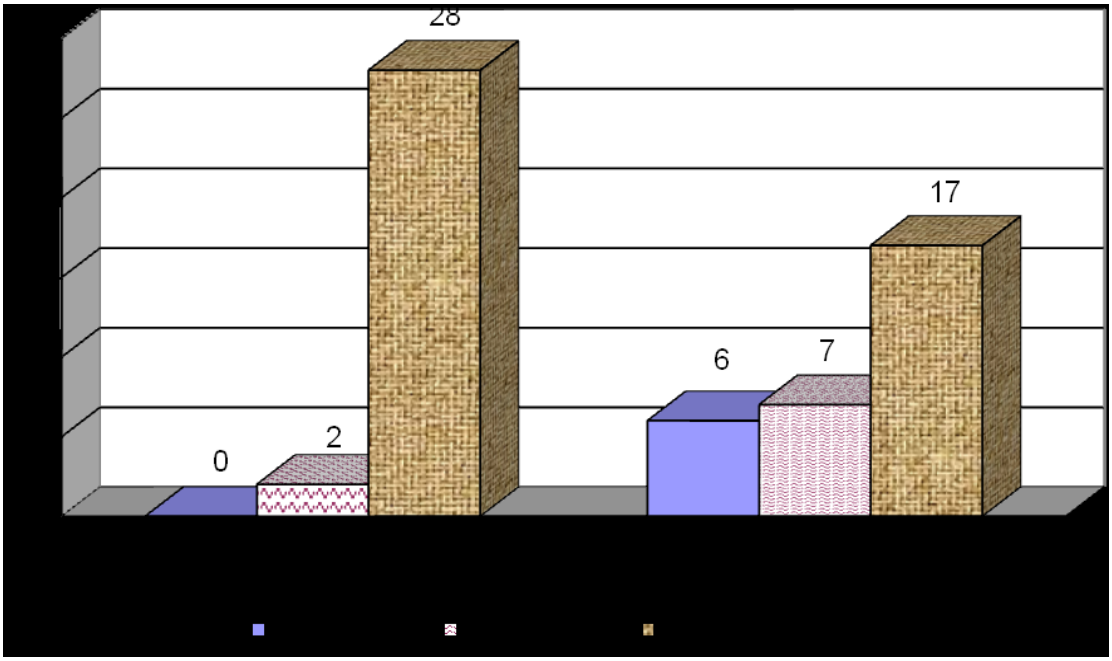
ADVERSE EFFECTS

Sl.no	Adverse effects	Group sample		Statistical inference
		BM Group (n=30)	BC Group (n=30)	
1	Bradycardia	0	6 (20%)	X^2=11.467
2	Hypotension	2 (6.7%)	7 (23.3%)	Df=2
3	No Adverse effects	28 (93.3%)	17 (56.7%)	0.003 < 0.05
				Significant

The incidents of bradycardia and hypotension in group BM was Significantly lower than that of group BC. Analysis was done using chi Square test. The 'P' value obtained was significant (0.003 < 0.05).

FIGURE : 9

COMPARISON OF ADVERSE EFFECTS



DISCUSSION

The study was conducted to evaluate the effects of intrathecal midazolam and clonidine as adjuvant to bupivacaine to assess hemodynamic stability and postoperative analgesia in spinal anaesthesia.

Sixty patients were randomly selected and equally divided into two groups. BM group received 3ml of 0.5% heavy bupivacaine, 0.4ml (2mg) of midazolam (preservative free) and 0.1ml of normal saline. BC group received 3ml of 0.5% heavy bupivacaine, 0.2 ml (30 mcg) of Clonidine and 0.3ml of normal saline.

Prakash et al (33)**,** conducted a placebo controlled study to evaluate the two different doses of intrathecal midazolam (1 mg and 2 mg) with 0.5% bupivacaine (10 mg) and concluded that intrathecal midazolam 2 mg with bupivacaine provided a moderate prolongation of postoperative analgesia and reduced requirement of Postoperative analgesic supplements.

M.H Kim and **Y.M Lee** (30) evaluated 2 mg of intrathecal midazolam with 5 mg of bupivacaine and proved prolonged Postoperative analgesia than 1 mg of intrathecal midazolam.

Adam. P Tucker et al (31), has proved that the 2 mg of intrathecal midazolam will not increase the incidence of neurological side effects. Hence in our study we have chosen 2 mg intrathecal midazolam as adjuvant with bupivacaine.

Hema Suxena et al (34), evaluated 3 different doses of clonidine (15, 30, 37.5 mcg) as adjuvant with bupivacaine (13.5 mg) in spinal anaesthesia. Even with small doses of clonidine, there was significant improvement in onset and duration of sensory and motor block with relative hemodynamic stability. They have concluded 30 mcg dose provides maximum benefit and minimum side effects. Hence we have selected 30 mcg of clonidine as adjuvant with bupivacaine for comparative study. **Suchita A. Joshi et al** (6), conducted a study to compare intrathecal midazolam and clonidine with 15 mg of 0.5% heavy bupivacaine in lower abdomen surgeries.

In our study the onset of sensory blockade was 2.17 minutes in BM group and 3.9 minutes in BC group. But **Suchita A. Joshi et al** (6) in their study had shorter onset of sensory blockade for the same volume of drug in both groups comparing to our study. This is because they had L1 as the end point for onset of sensory blockade instead of T10 in our study. This shows that intrathecal

midazolam has significantly rapid onset of sensory blockade. Because midazolam becomes highly fat soluble in body pH, it crosses the blood brain barrier more easily to gain access to the receptors. This is consistent with the study conducted by **Shadangi B et al** (35), AIIMS, New Delhi which concluded that intrathecal midazolam has rapid onset of action than control group.

The onset of motor blockade was 3.2 minutes in BM group and 4.93 minutes in BC group. This shows that intrathecal midazolam has significantly faster onset of motor block. But, In a study by **Shadangi B et al** (35)**,** BM group has shown a longer onset of motor blockade in BM group (6 minutes) which is nearly twice that of BM group in our study (3.2 minutes) . This is due to the difference in using modified bromage scale, we have taken 1 (unable to raise the extended leg, but able to flex the knees) as the onset of motor blockade where as **Shadangi B et al** (35)**,** had taken 3 (Total block, inability to flex ankle / move legs) as onset of motor blockade.

In our study the level of sensory block varied from T4 to T8 level. Among all patients, 46 patients attained maximum level of sensory blockade at T6 level. Nine patients attained up to T8 level and five patients attained T4 level. Any patient in either group does not complain of discomfort related to the sensory levels. The results of **Nanji Gowda et al** (36) study, has shown that 2 mg midazolam to intrathecal bupivacaine did not have any effect on peak level.

In BM group the time to achieve maximum sensory level was 7.37 minutes and in BC group was 10.17 minutes. This was statistically significant with the study conducted by **Suchita A. Joshi et al** (6).

In our study the duration of sensory block was 211.67 minutes in BM group and 156.33 minutes in BC group. This is very similar to the findings of BM groups (211.67±15.44 Vs 210.84±68.44) and BC groups (156.33±12.03 Vs 169.28±63.69) by **Suchita A. Joshi et al** (6)**.** But comparing to BM group in our study **Shadangi B et al** (35), had a lower duration of two segment regression time (211.67 Vs 115.8 minutes). The reason for the difference it could be made out was the volume of the drug. We have used 3.5 ml as the total volume similar to **Suchita A. Joshi et al** (6), where as **Shadangi B et al** (35) used 3.4 ml in BM group.

In our study, in BM group the duration of complete motor recovery was 292 minutes whereas in BC group it was 319 minutes. This shows that the duration of motor block was longer in clonidine group similar to **Suchita A. Joshi et al** (6) study. **Hema saxena et al** (34) studied the efficacy of three different doses of intrathecal clonidine with bupivacaine. In their study, group III patients who received 30 mcg of clonidine had duration of motor blockade 220 ±47 minutes Vs 319±10.20 minutes in our study. The prolongation of motor blockade in our study could be explained by the difference in drug concentration

(13.5 mg Vs 15 mg) and also duration of motor blockade was longer in all clonidine groups in dose dependant manner.

DURATION OF ANALGESIA

In our study, the duration of analgesia (from the time of intrathecal injection to the first dose of postoperative analgesia) was 486.17 minutes in BM group and 306.17 minutes in BC group. This has shown that intrathecal midazolam resulted in prolongation of duration of analgesia than intrathecal clonidine.

The average dose of Postoperative analgesia in BM group was 87.5mg whereas in BC group it was 132.5mg. This shows that intrathecal midazolam significantly lowers the need for supplementary Postoperative analgesia than intrathecal clonidine. So prolongation of duration of analgesia with significant reduction in postoperative analgesic requirement confirms the antinociceptive action of midazolam by its various mechanisms as shown by the **C.S.Goodchild et al.** Study **(**29). First one is through GABA 'A' receptor mediated action, second one through the endogenous release of opioids and third one is inhibition of adenosine uptake. These finding were similar with **Suchita A. Joshi et al**

study (6).

Duration of Analgesia (minutes)	BM Group		BC Group	
	Sujitha et al study	**Our Study**	**Sujitha et al**	**Our Study**
	391.64	486.17	296.60	306.17

M.H Kim and Y.M Lee et al (30) have shown that intrathecal midazolam 2mg with bupivacaine 5mg had prolonged duration of analgesia comparing to midazolam 1mg with bupivacaine (8.37 hrs Vs 6.03 hrs).

In our study also BM group (2mg midazolam + Bupivacaine 0.5% 15mg has the similar duration of analgesia (486.17 or 8.1 hrs).

Nidhi Agarwal et al (32) conducted study in lower abdominal surgeries including endoscopic procedures with control and BM groups. BM group received 15 mg of bupivacaine with 1mg midazolam. Their result shows that duration of analgesia in BM group was 17.6 ± 8.87 hrs.

The prolongation of duration of analgesia with intrathecal midazolam is definitely longer than either control group (**Kim Lee et al, and Nidhi Agarwal et al**) or clonidine group (**Hema suxena et al and Suchita A. Joshi et al**).

Variation in the duration of analgesia in midazolam group of different studies may be due to varied concentrations of bupivacaine, different doses of midazolam and types of surgery.

Eisenach JC, Dekock M et al (24) found that analgesic effect of clonidine was due to presynaptic alpha 2 agonist activities in substantia gelatinosa in spinal cord.

Hema Saxena et al (34) have shown that the duration of analgesia in patients who received 30mcg of clonidine with bupivacaine was 264 ± 43 minutes where as BC group in our study has 306.17 ± 47 minutes.

Postoperative analgesic requirements higher in both groups in **Suchita A. Joshi et al** (6) study. It is due to administration of first dose of diclofenac 75 mg to all patients immediately after shifting to the ward whereas we have administrated the first dose of analgesic either at request or VAS score more than 4.

We observed the duration of analgesia was prolonged in BM group than BC group because of multimodal analgesic action of midazolam, mild sedation mediated by alpha 1 $GABA_A$ receptor and anxiolysis mediated by alpha 2 $GABA_A$ receptor.

HEMODYNAMIC STABILITY

Various studies have demonstrated the hemodynamic stability when midazolam and clonidine are added as adjuvants to intrathecal bupivacaine. **C.S.Goodchild and J Nobel et al** (28) observed heart rate and blood pressure remains unchanged till 30 minutes after intrathecal injection of midazolam. **Nanji Gowda et al** (36) also observed similar results.

In our study there was a statistically significant reduction of pulse rate at 4^{th} minute interval in BM group comparing to BC group which could be explained by the earlier action of midazolam on α_1 and α_2 $GABA_A$ receptors producing sedation and anxiolysis. There were statistically significant reductions of pulse rate at 25^{th}, 30^{th}, 35^{th} and 40^{th} minutes in BC group comparing to BM group. This could be explained by the presynaptic inhibition of norepinephrine release and direct depression of AV node conduction after systemic absorption of clonidine ().

The mean arterial pressure was significantly lower in 15 minutes and

20 minutes in BC group when compared with BM group. The reduction in mean arterial pressure was due to inhibition of preganglionic sympathetic neurons in spinal cord. **Suchita A. Joshi et al** (6) showed no statistical significant fall in intraoperative blood pressure.

In our study in BC group, six (20%) patients developed bradycardia while none of the patients in BM group developed the same. Seven patients in BC group (23.3%) developed hypotension whereas in BM group only two (6.7%) patients. This shows that intrathecal clonidine had statistically significant adverse effects comparing to BM group. **Suchita et al** (6) had similar result which showed that the degree of bradycardia in BM Vs BC was11% Vs 33% and the degree of hypotension in BM Vs BC was 21% Vs 28%.

After administration of intrathecal midazolam, sympathetic nervous system function remains intact (**Goodchild et al** (28)). Hence incidence of bradycardia and hypotension were low in intrathecal midazolam. In our study also, intrathecal midazolam has better hemodynamic stability when compared to intrathecal clonidine.

In our study in both groups no statistically significant changes was observed in sedation score, respiratory rate and O2 saturation. This is consistent with study conducted by **Suchita A. Joshi et al** (6).

Adam P Tuker et al (31), evaluated 574 patients and observed for one month and concluded administration of 2 mg of intrathecal midazolam did not increase the neurological side effects. **Shadangi et al** (35), and **Nanje Gowda et al** (36) found no significant adverse effects in patients who received intrathecal midazolam.

SUMMARY

We conducted a double blinded randomized control study in 60 patients belonging to ASA I and II undergoing elective lower abdominal surgeries in Thanjavur Medical College. Patients of both sexes ranging between 22 to 65 years of age were included. Our aim was to evaluate the effects of intrathecal midazolam 2mg and clonidine 30 mcg as adjuvant to bupivacaine for hemodynamic stability and postoperative analgesia. Patients were divided randomly using closed cover technique into two groups of 25 each.

Group BM received 3ml of 0.5% heavy bupivacaine, 0.4ml midazolam (preservative free) and 0.1ml of normal saline. Group BC received 3ml of 0.5% heavy bupivacaine, 0.2ml clonidine and 0.3 ml of normal saline. The total volume of the injected solution was 3.5ml in both groups.

The onset of sensory and motor blockade, the duration of sensory and

motor blockade, peak sensory level, time to achieve maximum sensory level, changes in pulse rate, changes in mean arterial pressure, duration of analgesia, postoperative analgesic requirements, respiratory rate, o_2 saturation, sedation score and adverse effects were noted in both groups.

The data collected were analyzed by Chi square test and students't' tests. The results were obtained in the form of range, mean and standard deviation. The probability value 'P' of less than 0.05 considered statistically significant.

We found that onset of sensory and motor blockade, time to achieve maximum sensory level, and duration of complete motor recovery was earlier in BM group than BC group. Duration of Sensory block and duration of analgesia were prolonged in BM group than BC group.

In our study there was a statistical significant reduction of pulse rate at 4^{th} minute interval of BM group and 25^{th}, 30^{th}, 35^{th} and 40^{th} minutes in BC group. The MAP was significantly lower in 15 minutes and 20 minutes in BC group when compared with BM group.

In both groups, no significant changes were observed in respiratory rate, O_2 saturation and sedation in our study. Postoperative analgesic requirements and adverse effects were lower in BM group than BC group.

CONCLUSION

Intrathecal Midazolam as an adjuvant to bupivacaine comparing to Clonidine resulted

1. Rapid onset of sensory and motor blockade,
2. Achieves maximum sensory level at a shorter interval
3. Increased duration of sensory blockade and decreased duration of Motor blockade
4. Prolonged duration of analgesia and reduced requirement of post operative analgesics.
5. It gives stable mean arterial pressure and pulse rate.

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PROFORMA

A STUDY TO COMPARE THE EFFECT OF MIDAZOLAM AND CLONIDINE ADDED AS AN ADJUVANT TO INTRATHECAL BUPIVACAINE IN LOWER ABDOMINAL SURGERIES

NAME	HT	DIAGNOSIS
AGE / SEX	WT	SURGERY
ASA GRADE I /II		

PREANAESTHETIC EVALUATION :

HISTORY :

PR	CVS
BP	RS
AIRWAY / SPINE	OTHER SYSTEMS

INVESTIGATION :

Hb	URINE - ALBUMIN
BLOOD - SUGAR	- SUGAR
– UREA	CXR
SERUM CREATININE	ECG

PREMEDICATION : / TIME

PRE LOADING :

INTRATHECAL INJECTION

POSITION

INTERSPACE

NEEDLE

TIME OF INJECTION OF ANAESTHETIC SOLUTION

ONSET OF SENSORY BLOCK AT T10

ONSET OF MOTOR BLOCK

PEAK SENSORY LEVEL

TIME TO ACHIEVE MAXIMUM SENSORY LEVEL

TWO SEGMENT REGRESSION TIME

DURATION FOR COMPLETE MOTOR RECOVERY

TOTAL DURATION OF SURGERY

VAS PAIN SCORE										Time to first Post Operative Analgesia	Total dose of Post operative Analgesia
Interval	**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**		
Time											
Score											

SEDATION SCORE (Ramsay Sedation Score) (Time of intrathecal injection to first 6 hrs)

Interval	**0 min**	**15 min**	**30 min**	**45 min**	**1 hr**	**2 hr**	**3 hr**	**4 hr**	**5 hr**	**6 hr**
Time										
Score										

MONITORING

TIME	PR	BP (SBP/DBP/MAP)	RR	SPO_2	ADVERSE EFFCTS

LIST OF ABBREVIATIONS

1. CSF	**:**	**CEREBRO SPINAL FLUID**
2. NMDA	**:**	**N-METHYL D-ASPARTATE**
3. MW	**:**	**MOLECULAR WEIGHT**
4. GABA	**:**	**GAMMA AMINO BUTYRIC ACID**
5. ECG	**:**	**ELECTRO CARDIO GRAM**
6. EEG	**:**	**ELECTRO ENCEPHALO GRAM**
7. ASA	**:**	**AMERICAN SOCIETY OF ANAESTHESIOLOGIST**
8.VAS	**:**	**VISUAL ANALOG SCALE**
9.MAP	**:**	**MEAN ARTERIAL PRESSURE**
10.IPPV	**:**	**INTERMITENTPOSITIVEPRESSUREVENTILATION**

BC GROUP HR

S.no	HRBL	2 mins	4 Mins	6 mins	8 mins	10 mins	15 mins	20 mins	25 mins	30 mins	35 mins	40 mins	45 mins	50 mins	55 mins	60 mins	75 mins	90 mins	105 mins	120 mins	150 mins	180 mins	210 mins	240 mins	300 mins	360 mins	420 mins
1	90	82	80	78	76	73	75	72	70	73	74	75	77	75	76	74	73	75	74	77	79	77	76	80	78	82	80
2	88	84	84	80	76	74	75	77	76	75	73	70	72	73	75	74	75	76	74	77	79	77	80	82	84	85	82
3	92	86	84	80	78	76	72	73	68	68	70	71	73	75	74	73	77	76	74	75	77	79	80	82	80	81	80
4	90	91	90	88	84	85	80	78	76	77	75	74	76	77	76	75	76	75	79	80	79	82	80	81	83	80	82
5	84	82	80	80	79	80	78	79	76	73	75	74	77	74	75	76	77	79	78	80	79	80	78	80	82	81	80
6	86	80	79	76	74	73	71	70	68	70	67	69	70	71	74	75	77	78	79	75	76	75	77	75	76	77	79
7	89	84	80	80	78	79	74	73	72	71	73	71	73	72	70	72	76	75	75	74	73	72	76	77	74	78	79
8	92	86	80	78	79	80	78	72	70	64	67	66	68	69	70	71	69	70	71	73	71	72	71	74	75	74	76
9	86	80	80	76	76	78	78	76	77	74	74	77	75	72	72	74	77	78	74	77	78	80	81	78	78	82	80
10	86	80	80	79	76	72	71	71	68	69	64	65	67	68	68	69	67	69	70	73	75	74	76	77	77	75	77
11	88	86	82	80	80	78	76	70	71	68	68	67	66	68	70	72	71	72	74	75	76	79	77	80	80	79	80
12	82	78	78	78	76	74	74	70	70	68	68	68	70	70	68	70	70	68	66	68	68	66	66	68	68	68	68
13	94	92	90	86	82	80	78	72	71	73	72	75	72	75	77	76	79	80	80	82	81	80	81	83	82	80	82
14	84	79	79	80	78	77	78	70	68	60	69	74	74	72	73	75	77	79	78	80	80	78	79	80	81	81	82
15	86	80	82	80	81	79	79	76	72	74	75	72	77	74	77	74	79	77	78	79	78	79	78	79	80	80	81
16	88	82	80	71	78	77	74	75	72	73	74	71	70	68	69	70	70	76	77	76	75	77	79	80	81	80	80
17	87	82	80	80	82	84	84	82	84	82	80	80	79	82	82	82	78	80	80	81	83	85	82	80	78	78	78
18	84	80	76	76	74	76	70	70	72	70	68	64	60	76	80	78	78	78	76	78	76	78	80	82	82	80	80
19	84	80	80	81	79	79	78	79	76	75	73	72	68	64	64	63	69	70	71	72	74	73	77	76	75	77	79
20	90	90	86	84	82	78	77	76	77	75	77	78	74	75	72	74	75	76	77	75	76	77	75	77	79	80	80
21	86	82	80	82	80	78	79	77	75	74	73	75	76	74	75	77	78	76	74	73	77	79	78	80	81	80	81
22	86	82	80	79	79	77	75	70	60	74	73	75	77	78	78	79	77	76	77	79	78	77	80	79	82	81	80
23	90	87	88	82	79	79	77	75	64	60	65	72	74	77	79	77	80	80	78	79	77	78	80	80	79	80	81
24	90	84	84	81	78	79	79	77	77	78	79	79	80	81	82	82	80	78	82	80	80	82	81	79	80	82	84
25	86	80	78	79	77	77	77	75	74	71	70	69	68	66	69	68	69	70	71	73	71	73	72	74	73	77	74
26	88	87	82	80	79	79	72	64	60	70	74	73	75	72	76	77	77	79	80	79	80	79	81	80	79	80	80
27	86	82	80	80	78	78	78	76	76	76	74	72	70	70	72	68	68	69	70	72	72	74	72	72	70	70	76
28	88	82	80	80	78	74	72	70	68	66	62	64	65	67	69	70	75	73	74	75	77	74	75	77	76	77	80
29	88	82	80	80	78	79	76	75	77	78	77	75	74	73	77	76	73	77	77	79	80	78	79	79	80	81	82
30	88	86	80	76	77	68	64	65	62	60	69	74	78	75	77	79	82	83	78	84	85	87	86	85	82	84	83

BM GROUP HR

		HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR
S. no	HR BL	2 mins	4 Mins	6 mins	8 mins	10 mins	15 mins	20 mins	25 mins	30 mins	35 mins	40 mins	45 mins	50 mins	55 mins	60 mins	75 mins	90 mins	105 mins	120 mins	150 mins	180 mins	210 mins	240 mins	300 mins	360 mins	420 mins
1	86	80	78	76	74	76	78	76	74	78	76	72	70	74	76	72	76	78	80	78	82	80	82	80	82	82	80
2	82	84	80	82	76	76	74	76	72	74	70	70	69	70	68	64	67	68	70	70	72	70	74	76	74	80	82
3	80	78	76	76	77	79	79	78	76	76	77	78	78	77	79	77	78	80	79	79	79	77	75	75	80	82	80
4	76	76	72	70	72	73	71	70	68	70	68	70	72	74	70	74	72	70	68	66	70	72	70	72	76	72	70
5	92	86	80	80	82	80	78	78	78	78	76	76	72	74	74	72	78	76	76	74	76	74	72	72	80	80	82
6	84	80	80	82	80	76	76	77	77	79	76	77	75	75	77	79	77	79	78	75	75	77	78	75	78	79	80
7	86	80	79	79	80	76	76	76	78	79	80	76	76	77	78	80	81	81	80	79	80	80	81	80	80	80	80
8	86	80	76	77	79	78	77	72	74	74	77	78	79	79	69	73	73	77	78	79	78	79	80	82	81	80	84
9	86	80	80	78	78	76	78	78	76	76	72	72	72	70	70	72	72	72	70	70	72	72	74	74	80	80	82
10	88	80	78	78	76	78	74	72	76	74	78	72	68	70	70	68	70	68	70	76	78	82	84	86	84	86	80
11	86	82	80	80	78	78	80	78	78	76	76	79	79	79	80	80	78	78	80	82	84	82	82	80	80	80	82
12	80	76	74	72	73	73	72	72	70	68	68	70	68	69	70	72	70	70	73	72	72	79	80	80	80	76	80
13	88	82	80	79	79	80	79	76	70	64	67	69	67	68	70	71	73	75	71	76	77	76	79	79	80	82	80
14	92	90	86	84	84	80	78	76	72	71	73	75	77	74	75	77	78	79	77	80	82	84	83	83	85	83	86
15	90	86	82	78	78	72	71	74	75	77	76	75	78	79	76	75	73	74	75	77	76	77	76	73	72	75	78
16	90	86	82	80	80	79	77	75	76	77	79	75	74	78	79	73	75	77	79	80	79	83	85	83	81	80	84
17	88	82	83	81	77	75	73	72	71	73	75	74	72	71	76	75	77	79	79	79	80	79	77	79	80	82	81
18	84	80	81	78	77	76	74	72	73	74	77	77	79	74	74	75	76	77	79	79	79	77	80	82	84	86	86
19	86	86	80	78	77	76	72	73	74	71	76	75	73	73	75	75	74	75	71	74	75	76	77	74	75	77	74
20	86	80	80	76	77	76	72	71	74	73	72	70	73	72	68	72	73	76	79	80	84	85	87	82	82	84	84
21	88	82	80	76	76	76	72	72	77	75	75	72	75	75	76	72	74	77	76	77	78	78	80	80	82	82	82
22	86	80	80	82	78	76	77	78	77	76	78	72	72	70	74	75	76	77	79	80	80	81	82	84	82	83	83
23	86	82	78	76	77	74	73	70	68	78	76	72	74	75	77	79	78	77	79	78	77	78	79	79	80	82	84
24	92	86	86	84	80	78	78	78	80	78	78	76	76	76	77	79	80	77	79	80	77	82	80	82	82	80	80
25	82	80	78	79	77	78	79	75	74	73	75	77	76	76	78	77	72	74	76	75	77	79	82	78	81	82	80
26	90	82	80	76	75	73	72	72	75	74	73	75	74	76	73	77	74	75	76	74	77	79	80	81	82	84	80
27	88	80	78	76	75	76	74	73	74	76	75	77	76	77	75	76	77	79	76	80	80	81	80	80	81	80	83
28	86	80	78	79	80	74	75	77	73	74	75	76	75	74	77	75	75	76	74	78	74	77	76	74	73	75	80
29	88	84	80	80	80	78	78	79	80	78	76	76	77	74	76	77	78	70	70	72	72	72	74	74	76	76	78
30	90	86	84	82	80	80	76	77	72	75	77	76	75	72	74	73	76	77	78	79	81	79	80	81	80	81	82

BC GROUP MAP																												
		MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP
S. no	MAP BL	2 mins	4 Mins	6 mins	8 mins	10 mins	15 mins	20 mins	25 mins	30 mins	35 mins	40 mins	45 mins	50 mins	55 mins	60 mins	75 mins	90 mins	105 mins	120 mins	150 mins	180 mins	210 mins	240 mins	300 mins	360 mins	420 mins
1	100	92	93	89	86	83	83	80	77	75	73	78	77	77	77	77	77	76	79	80	83	80	83	82	83	83	84
2	102	95	88	90	89	87	83	83	83	85	83	82	78	80	78	80	78	80	79	79	79	81	83	84	88	86	87
3	99	93	90	93	90	87	88	88	83	81	80	79	82	84	80	79	82	84	81	82	81	83	81	83	84	88	86
4	92	91	89	89	87	88	84	80	77	75	76	77	76	77	76	75	77	75	75	77	77	77	79	79	81	84	84
5	93	90	91	88	84	81	77	76	75	75	72	75	77	77	78	81	80	83	84	82	84	82	84	86	85	87	87
6	93	84	77	76	73	73	71	69	79	80	82	83	80	82	83	84	84	84	85	84	86	88	87	84	86	88	87
7	94	86	83	80	75	75	72	69	75	78	79	80	80	83	85	82	83	85	84	88	83	84	86	88	90	90	90
8	89	95	91	88	87	85	84	84	88	84	83	85	88	87	84	82	83	81	83	86	85	87	89	87	86	86	86
9	104	89	87	88	84	83	83	81	83	80	83	79	76	77	77	74	75	76	77	74	78	76	5	83	83	83	88
10	93	90	89	88	87	86	83	83	84	81	79	77	75	77	75	77	73	71	73	73	73	79	80	78	80	79	78
11	94	90	89	85	86	81	75	74	73	71	69	75	77	79	80	81	81	82	80	81	81	82	83	84	85	87	88
12	89	84	83	77	79	83	81	79	79	77	73	75	78	80	79	77	73	75	78	80	83	83	82	88	88	88	84
13	98	92	90	89	86	83	80	78	77	75	73	74	72	75	78	77	80	81	83	82	81	83	84	85	84	84	87
14	92	89	89	87	84	83	82	75	73	80	82	81	83	85	81	83	85	84	82	84	86	87	85	93	91	90	89
15	102	98	91	93	86	82	81	72	75	79	79	75	75	72	75	79	76	77	78	81	83	83	80	81	84	87	87
16	93	89	84	87	83	81	78	75	72	74	69	78	77	78	77	78	79	79	80	81	83	84	84	88	84	85	90
17	100	95	92	94	93	89	90	92	93	86	81	82	77	89	82	77	89	80	83	78	83	83	80	84	85	93	94
18	83	83	82	81	85	83	80	80	77	73	71	71	83	83	73	71	71	83	83	81	77	78	78	85	85	83	84
19	89	87	84	83	81	80	79	80	79	80	79	75	77	75	73	73	76	77	75	75	76	77	77	77	79	78	81
20	92	89	87	85	83	81	79	75	70	75	76	78	82	83	82	83	83	85	84	88	84	86	87	84	88	83	87
21	94	86	84	82	80	83	81	81	82	79	77	72	73	72	73	72	73	74	73	74	74	75	75	76	79	79	84
22	93	87	84	81	78	75	71	75	77	79	80	79	81	81	79	81	81	83	83	84	83	86	84	80	83	86	87
23	92	89	89	86	81	81	77	75	78	69	77	79	81	79	81	81	81	83	85	88	90	89	89	88	89	91	91
24	100	95	93	90	93	90	89	84	87	83	83	83	81	79	81	79	80	83	85	83	87	88	86	88	90	90	93
25	93	88	88	86	84	84	80	75	73	72	74	73	75	74	72	75	72	72	75	73	75	76	75	77	80	81	82
26	95	90	93	87	84	81	76	73	79	80	82	83	84	83	84	83	81	84	83	84	85	87	84	86	89	88	89
27	87	87	83	84	83	79	75	77	75	75	70	77	77	82	70	77	77	82	84	84	83	85	82	87	83	83	88
28	93	91	84	83	79	76	73	74	69	78	77	78	80	81	78	80	81	80	81	83	84	85	87	86	85	87	89
29	102	98	91	86	84	82	81	83	82	85	83	84	86	84	84	86	84	83	81	82	82	84	84	84	84	86	84
30	102	95	95	88	87	81	74	73	82	81	83	83	89	84	83	87	84	86	88	94	90	93	91	91	90	92	91

BM GROUP MAP

		MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP
S.no	MAPBL	2 mins	4 Mins	6 mins	8 mins	10 mins	15 mins	20 mins	25 mins	30 mins	35 mins	40 mins	45 mins	50 mins	55 mins	60 mins	75 mins	90 mins	105 mins	120 mins	150 mins	180 mins	210 mins	240 mins	300 mins	360 mins	420 mins
1	94	89	87	91	85	83	83	81	82	84	81	81	83	81	83	81	77	83	80	77	75	80	76	77	83	82	83
2	90	95	91	95	95	92	91	89	85	85	83	83	82	80	78	80	81	79	82	84	84	88	88	90	88	92	94
3	89	92	86	84	81	83	85	80	81	80	80	78	77	79	78	77	79	77	80	81	83	85	81	80	82	84	84
4	102	95	92	89	93	93	89	95	89	90	88	88	88	80	78	83	83	88	87	84	81	84	81	85	89	93	89
5	93	89	91	93	86	84	88	87	84	83	82	83	84	82	83	80	80	80	84	82	83	83	82	85	82	83	83
6	94	91	89	93	88	84	85	83	83	83	82	79	79	75	72	73	80	78	77	79	78	77	79	81	82	85	84
7	95	92	87	88	88	88	84	82	79	81	80	82	83	80	81	80	82	83	80	83	82	80	81	85	84	88	87
8	100	95	85	82	81	79	77	75	73	69	76	80	80	79	76	76	80	80	79	78	79	87	82	81	83	88	84
9	101	97	91	95	88	88	90	88	87	83	83	83	87	81	82	83	79	86	86	82	83	84	87	90	90	95	98
10	92	94	95	95	92	89	93	93	86	88	91	89	87	83	88	91	89	87	83	81	85	82	87	90	88	94	91
11	104	102	100	98	94	88	91	90	87	89	82	84	89	88	82	78	84	85	85	82	81	84	85	83	84	89	91
12	89	87	84	83	82	85	83	80	80	80	78	79	77	80	79	83	82	83	83	84	85	85	83	87	84	84	86
13	99	90	89	89	84	81	80	78	79	77	75	75	77	79	80	80	83	82	83	84	84	87	85	85	88	89	90
14	92	90	86	82	81	79	77	76	75	73	72	74	76	75	77	79	81	83	84	84	85	87	88	88	89	85	87
15	98	94	88	83	82	81	83	85	83	80	81	83	80	80	81	83	83	83	81	82	83	84	83	81	82	84	87
16	89	89	86	80	80	78	76	75	72	71	74	77	76	75	76	77	77	79	83	85	85	81	83	86	85	88	85
17	98	91	87	88	86	83	82	81	71	77	76	77	75	75	73	72	75	77	78	80	83	83	80	83	85	84	87
18	84	85	88	82	75	75	77	70	76	79	79	82	84	85	85	83	82	86	87	82	85	83	81	88	89	87	85
19	87	82	80	79	78	79	76	78	77	77	76	75	75	74	76	75	75	74	77	78	80	80	81	83	84	86	84
20	98	89	86	87	82	81	80	77	79	77	79	78	78	79	78	79	79	79	79	80	79	80	80	84	84	88	88
21	87	88	85	89	84	87	84	82	80	87	83	81	82	81	82	87	87	83	82	88	89	90	87	90	93	94	93
22	95	91	84	83	88	84	87	81	85	80	83	81	80	79	83	80	80	79	81	83	88	84	89	87	88	89	88
23	95	88	84	77	76	78	75	76	72	78	76	74	73	75	72	76	76	74	73	75	75	76	79	80	82	83	83
24	84	88	85	83	80	81	82	79	75	69	76	78	79	79	80	84	84	85	83	83	83	82	83	85	83	84	83
25	89	89	86	83	81	80	75	75	73	74	73	72	74	77	74	77	77	79	81	82	84	84	86	85	88	87	87
26	98	93	84	83	83	80	81	80	80	79	78	77	79	80	78	78	78	78	79	80	80	80	83	86	84	86	87
27	93	80	78	75	76	77	75	76	75	77	75	77	78	79	77	77	77	79	79	81	80	82	83	81	82	83	85
28	93	89	88	86	88	85	82	78	75	73	75	79	73	72	73	74	74	73	74	77	76	75	78	80	80	82	84
29	88	88	84	84	81	83	80	79	80	77	80	75	77	80	77	79	79	77	75	80	83	85	83	83	82	85	88
30	93	86	88	82	80	78	79	77	75	73	74	74	76	73	75	80	80	75	79	80	80	83	83	83	85	84	88

		BC GROUP													
S.NO.	AGE	SEX	RR (/ minute)	SPO2	Onset of Sensory block at T10	Onset of Motor Block	Peak sensory Level	Time to achieve maximum sensory level	Two segment regression time	Duration of complete Motor Recovery	Total Duration of Surgery	Time to first Postoperative analgesia	Total dose of postoperative analgesia	Sedation Score	Adverse effects
1	48	M	13	99	4	5	T6	10	155	315	75	300	150	3	Nil
2	41	M	14	98	5	6	T6	10	145	310	90	285	150	3	Nil
3	30	M	14	99	4	5	T6	9	150	335	75	255	150	3	Nil
4	32	M	14	98	4	5	T8	11	160	300	75	285	150	3	Nil
5	50	M	14	97	3	4	T6	11	160	310	75	270	150	3	Nil
6	22	M	14	99	3	4	T6	11	160	310	75	300	75	3	Hypotension
7	29	F	14	98	4	5	T4	11	205	325	90	420	75	3	Hypotension
8	31	M	15	99	4	5	T6	11	155	300	75	300	150	3	Nil
9	33	M	14	98	4	5	T6	11	145	325	90	270	150	3	Nil
10	45	M	14	97	5	6	T6	10	165	315	75	315	150	3	Nil
11	28	M	14	98	3	4	T6	10	165	320	75	470	75	3	Hypotension
12	30	M	14	100	4	5	T6	11	160	300	90	300	150	3	Nil
13	31	F	14	98	4	5	T6	10	160	325	75	270	150	3	Nil
14	58	M	14	98	3	4	T4	11	160	320	75	290	150	3	Bradycardia
15	60	M	13	98	4	5	T8	10	150	300	75	300	150	3	Nil
16	27	M	14	98	3	4	T4	10	150	310	75	300	75	3	Hypotension
17	34	M	14	99	4	5	T6	9	165	315	80	300	150	2	Nil
18	28	M	14	99	4	6	T6	10	165	330	75	300	150	3	Bradycardia
19	18	F	13	98	4	5	T6	10	145	330	75	300	150	3	Nil
20	20	M	14	98	4	5	T6	9	145	330	75	360	75	3	Hypotension
21	45	F	14	98	4	5	T8	10	140	325	90	270	150	3	Nil
22	29	M	14	97	4	5	T6	10	150	325	75	285	150	2	Bradycardia
23	34	F	14	98	3	4	T8	10	165	325	75	285	150	3	Bradycardia
24	54	M	14	98	4	5	T6	10	150	315	75	310	150	3	Nil
25	25	F	14	99	4	5	T6	9	150	330	75	285	150	3	Nil
26	65	M	14	98	4	5	T8	11	160	325	90	285	150	2	Bradycardia
27	45	M	14	98	4	5	T6	9	160	325	75	270	75	3	Hypotension
28	36	M	14	97	4	5	T6	11	160	325	75	405	75	3	Hypotension
29	42	F	14	98	4	5	T6	9	140	330	80	300	150	3	Nil
30	28	M	14	99	5	6	T6	11	150	320	75	300	150	3	Bradycardia

BM GROUP															
S.NO.	AGE	SEX	RR (/ minute)	SPO2	Onset of Sensory block at T10	Onset of Motor Block	Peak sensory Level	Time to achieve maximum sensory level	Two segment regression time	Duration of complete Motor Recovery	Total Duration of Surgery	Time to first Postoperative analgesia	Total dose of postoperative analgesia	SedationScore	Adverse effects
1	49	M	14	98	2	3	T6	7	200	300	70	400	75	3	Nil
2	35	M	13	99	2	3	T6	7	190	290	75	450	75	2	Nil
3	50	M	13	97	2	3	T6	8	210	290	90	480	75	3	Nil
4	58	M	14	99	2	3	T6	8	195	285	75	480	75	2	Nil
5	44	M	14	99	3	4	T8	8	200	315	80	420	75	3	Nil
6	38	M	14	99	2	3	T6	7	200	305	75	420	150	3	Nil
7	34	M	14	98	3	4	T6	8	210	315	75	465	75	3	Nil
8	55	M	15	98	2	3	T4	7	225	285	80	420	75	3	Hypotension
9	32	M	14	99	3	4	T6	7	210	325	80	435	75	3	Nil
10	30	M	14	98	3	4	T6	8	180	300	80	450	75	2	Nil
11	55	M	15	99	2	4	T6	7	200	300	75	520	75	2	Nil
12	26	M	14	99	2	3	T6	7	205	310	75	480	150	3	Nil
13	60	M	13	97	2	3	T6	7	215	285	75	540	75	3	Nil
14	52	M	14	98	2	3	T8	8	225	285	75	510	150	3	Nil
15	40	M	14	98	2	3	T6	7	200	285	90	525	75	3	Nil
16	60	M	14	98	2	3	T6	7	215	285	75	525	75	3	Nil
17	41	M	14	99	2	3	T8	7	230	285	90	525	150	3	Nil
18	22	M	14	98	2	3	T4	7	240	270	75	465	75	3	Hypotension
19	22	F	14	98	2	3	T6	8	210	290	75	525	75	3	Nil
20	30	F	14	98	2	3	T6	7	250	280	80	510	75	3	Nil
21	25	F	14	99	2	3	T6	8	210	300	75	480	75	2	Nil
22	28	M	14	97	2	3	T6	8	240	300	75	480	75	3	Nil
23	22	F	14	98	2	3	T6	7	210	285	75	450	75	3	Nil
24	22	F	14	99	3	4	T6	7	220	270	75	480	75	3	Nil
25	25	M	14	98	2	3	T6	8	220	290	75	540	75	3	Nil
26	40	M	14	98	2	3	T6	8	210	290	75	540	75	3	Nil
27	28	M	14	97	2	3	T6	7	195	280	90	540	75	3	Nil
28	45	M	14	99	2	3	T8	7	215	280	75	540	150	3	Nil
29	20	M	14	99	2	3	T6	7	200	300	80	495	75	3	Nil
30	38	M	14	98	2	3	T6	7	220	280	75	495	75	3	Nil