A COMPARATIVE STUDY OF INTRATHECAL DEXMEDETOMIDINE AND CLONIDINE AS AN ADJUVANT TO INTRATHECAL BUPIVACAINE IN ELECTIVE LOWER LIMB SURGERIES

Dissertation submitted to

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

In partial fulfillment for the award of the degree of

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IN

ANAESTHESIOLOGY

BRANCH X

DEPARTMENT OF ANAESTHESIOLOGY
THANJAVUR MEDICAL COLLEGE
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CERTIFICATE

This is to certify that the dissertation entitled "**A COMPARATIVE STUDY OF INTRATHECAL DEXMEDETOMIDINE AND CLONIDINE AS AN ADJUVANT TO INTRATHECAL BUPIVACAINE IN ELECTIVE LOWER LIMB SURGERIES**" submitted by

DR.V.SANKARA GANAPATHYin partial fulfilment for the award of the degree of **Doctor of Medicine in Anaesthesiology** by the TamilnaduDr.M.G.R Medical University, Chennai is a bonafide record of the work done by him in the Department of Anaesthesiology, Government Thanjavur medical College, during the academic year 2014-2017.

Prof.Dr.ShanthiPaulraj M.D(Anaes),
Associate Professor,
Department of Anaesthesiology,
Thanjavur Medical College,
Thanjavur

Prof.Dr.R.Muthukumaran M.D.,D.A.,
Professor & Head of the department,
Department of Anaesthesiology,
Thanjavur Medical College,
Thanjavur

Place :
Date :

Dean
Thanjavur Medical college
Thanjavur

DECLARATION

I, **DR.V.SANKARA GANAPATHY** solemnly declare that the dissertation titled“A COMPARATIVE STUDY OF INTRATHECAL DEXMEDETOMIDINE AND CLONIDINE AS AN ADJUVANT TO INTRATHECAL BUPIVACAINE IN ELECTIVE LOWER LIMB SURGERIES”is a bonafide work done by me at Thanjavur Medical College Hospital, Thanjavur, during 2014-2017.

The dissertation is submitted to“**The TamilnaduDr. M.G.R. Medical University, Chennai”** Tamilnadu as a partial fulfilment for the requirement of **M.D** Degree examinations – Branch -X (Anaesthesiology) to be held in April 2017.

Place: Thanjavur

Date: (DR.V. SANKARA GANAPATHY)

Thanjavur Medical College

THANJAVUR, TAMILNADU, INDIA - 613001

(Affiliated to the T.N.Dr.MGR Medical University, Chennai)

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submitted by Dr. V. SANKARA GANAPATHY **of**

Dept. of ANAESTHESIOLOGY **Thanjavur Medical College, Thanjavur**

was approved by the Ethical Committee.

Thanjavur

Dated : 19/8/16

19/8/16

Secretary
Ethical Committee
TMC, Thanjavur.

THE SECRETARY
INSTITUTIONAL ETHICAL COMMITTEE
THANJAVUR MEDICAL COLLEGE,
THANJAVUR.

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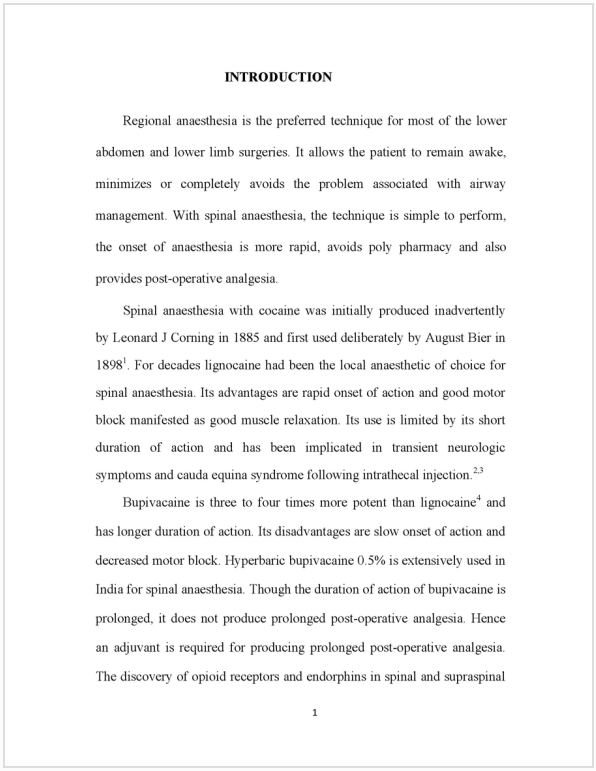

INTRODUCTION

Regional anaesthesia is the preferred technique for most of the lower abdomen and lower limb surgeries. It allows the patient to remain awake, minimizes or completely avoids the problem associated with airway management. With spinal anaesthesia, the technique is simple to perform, the onset of anaesthesia is more rapid, avoids poly pharmacy and also provides post-operative analgesia.

Spinal anaesthesia with cocaine was initially produced inadvertently by Leonard J Corning in 1885 and first used deliberately by August Bier in 1898[1]. For decades lignocaine had been the local anaesthetic of choice for spinal anaesthesia. Its advantages are rapid onset of action and good motor block manifested as good muscle relaxation. Its use is limited by its short duration of action and has been implicated in transient neurologic symptoms and cauda equina syndrome following intrathecal injection.[2,3]

Bupivacaine is three to four times more potent than lignocaine[4] and has longer duration of action. Its disadvantages are slow onset of action and decreased motor block. Hyperbaric bupivacaine 0.5% is extensively used in India for spinal anaesthesia. Though the duration of action of bupivacaine is prolonged, it does not produce prolonged post-operative analgesia. Hence an adjuvant is required for producing prolonged post-operative analgesia. The discovery of opioid receptors and endorphins in spinal and supraspinal

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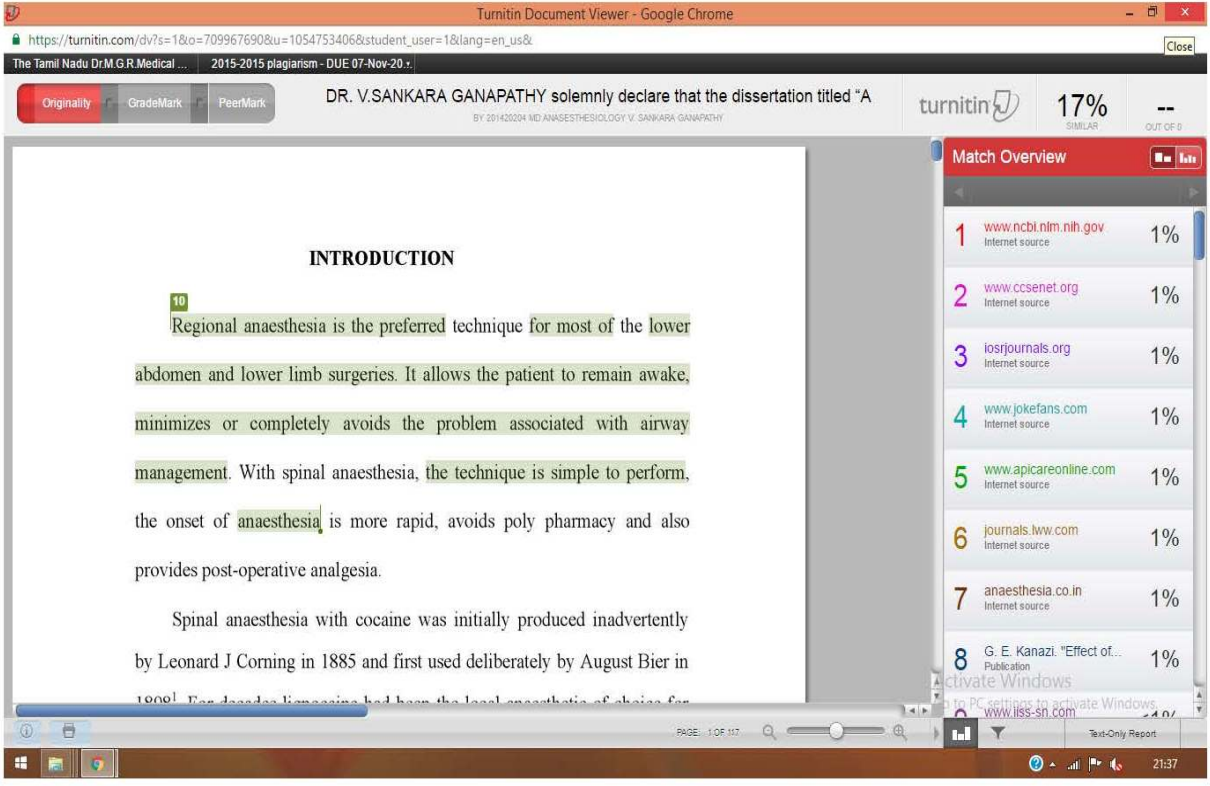

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supraspinalregions soon led to the use of spinal opiates. Morphine was the first opioid administered intrathecally to augment neuraxial blocks.[5] Opioid analgesic drugs produce intense, prolonged analgesic action without any gross autonomic changes, loss of motor power or impairment of sensation other than pain when injected into subarachnoid or epidural space.[5]

Morphine can produce serious side effects like delayed and unpredictable respiratory depression, post-operative nausea and vomiting, pruritus and urinary retention.[7,8]

Recently α-2 adrenoreceptor agonists have been used as adjuvants to local anaesthetic agents because of their sedative, analgesic and haemodynamic stabilizing effect. They have been found to prolong the duration of spinal block following intrathecal administration.[9]

Clonidine, an α-2 adrenergic agonist, has a variety of different actions. Oral clonidine was used to prolong spinal anaesthesia. Hypotension was more pronounced after oral than intrathecal clonidine.[10] Addition of intrathecal clonidine to bupivacaine prolongs analgesia and decreases morphine consumption postoperatively more than oral clonidine. Clonidine has antihypertensive properties and the ability to potentiate the effects of local anaesthetics.[11]

Clonidine has been shown to result in prolongation of the sensory blockade and reduction in the volume or concentration of local anesthetic required to produce post-operative analgesia.[12] Clonidine also has the

ability to prolong the motor blockade produced by bupivacaine. Large doses of intrathecal clonidine (as much as 450μg) without local anaesthetics provide sedation and intense and long lasting postoperative analgesia, are inadequate for surgical anaesthesia and for this reason, clonidine has been used as an adjuvant to local anaesthetics rather than used alone.[9]

Dexmedetomidine also an α-2 adrenergic agonist is pharmacologically related to clonidine and is the most recent agent in this group approved by FDA in 1999 for the use in humans as short term medication (<24 hrs) for analgesia and sedation in intensive care unit. Its unique properties render it suitable for sedation and analgesia during the whole of perioperative period. Various studies have also found that intravenous dexmedetomidine can decrease the haemodynamic response to laryngoscopy and intubation.[13]

Dexmedetomidine is a highly specific and selective alpha- 2 adrenoceptor agonist with8 times more affinity for alpha- 2 adrenoceptor than clonidine. The ratio of alpha- 1:alpha- 2 receptor binding selectivity for dexmedetomidine is 1:1620 compared to 1:220 for clonidine.[13]While clonidine has been used as an adjuvant to local anaesthetic agents for intrathecal purposes with successful results, there are only a few studies available for dexmedetomidine for such studies.Hence, we have undertaken this study to evaluate and compare the efficacies of clonidine and dexmedetomidine as an adjuvant tointrathecal hyperbaric 0.5% bupivacaine in patients scheduled for elective lower limb surgeries.

AIM OF THE STUDY

The present study was undertaken to evaluate and compare the efficacy of dexmedetomidine and clonidine added as an adjuvant to 0.5% hyperbaric bupivacaine intrathecallyfor elective lower limb surgeries, with respect to

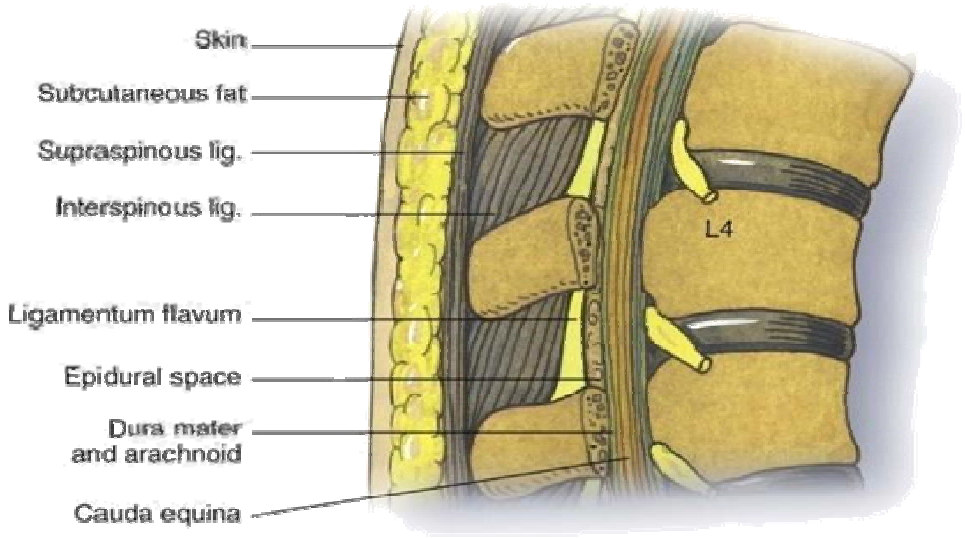
1. **Block characteristics**
2. **Haemodynamic changes**
3. **Adverse effects**

ANATOMY

Spinal anaesthesia results in sympathetic blockade, sensory analgesia, anaesthesia and motor blockade. It depends on the dose, concentration, volume of local anaesthetic injected into the subarachnoid space.

The vertebral canal extends from the foramen magnum to the sacral hiatus. There are seven cervical, twelve thoracic and five lumbar vertebrae. The sacrum comprises five and the coccyx four fused segments. The adult spine presents four curvatures: those of the cervical and lumbar zones are convex forwards (lordosis), whereas those of the thoracic and sacral regions are concave forwards (kyphosis).The former are postural, while the latter are produced by the actual configuration of the bones themselves. The vertebrae are held together by a series of overlapping ligaments[14,15] namely

- Anterior longitudinal ligament
- Posterior longitudinal ligament
- Ligamentumflavum
- Interspinous ligament
- Supraspinous ligament
- Intervertebral discs.



There are certain common palpable landmarks that may correspond to particular level, including the most prominent spinous process which usually corresponds to the seventh cervical vertebra. The inferior angle of scapula usually corresponds to the seventh thoracic vertebra. Tuffier line, the line connecting the two iliac crests almost crosses the vertebral column at the level of L4-L5 intervertebral space.

The intervertebral canal consists of:

1. Roots of spinal nerves
2. Spinal membrane with spinal cord and cerebrospinal fluid
3. Vessels, fat and areolar tissue.

The spinal cord is the continuation of medulla oblongata and it ends below in conusmedullaris from which filumterminale descends vertically as caudaequina. The extent of the spinal cord is from the upper border of atlas

to the lower border of first lumbar vertebra in adults. The spinal cord extends till the upper border of second lumbar vertebra and still lower in infants.

The coverings of spinal cord from outside to inside areduramater, arachnoidmater, piamater. The duramater is attached to the margins of foramen magnum above and ends below at the lower border of the second sacral vertebra. The anterior and posterior nerve roots from the spinal cord pierce the investing layer of duramater and carry the prolongation (dural cuff) which blends with the perineurium of the mixed spinal nerve.

The arachnoid mater is a thin transparent sheath closely applied to duramater. The subdural space is a potential space which contains only small amount of serous fluid to allow the dura and arachnoid to move over each other.

The piamater closely invests the cord and sends delicate septa into its substances. From each lateral surface of the piamater, a fibrous band, the denticulate ligament projects into the subarachnoid space. Inferiorly the piamater ends as a prolongation termed as filumterminale which penetrates the distal end of dural sac and is attached to the periostium of coccyx.

The subarachnoid space is filled with the cerebrospinal fluid and it contains the spinal nerve roots and the denticulate ligament. Lumbar puncture is routinely done below the second lumbar vertebra to L5-S1

interspace to avoid damaging the spinal cord which ends at the lower border of first lumbar vertebra.

Blood supply of spinal cord[16]

Blood supply of spinal cord is mainly from three longitudinal arterial channels, one anterior spinal artery and two posterior spinal arteries. The main source of blood supply to the spinal arteries is from the vertebral arteries. However it reaches only up to the cervical segment of the cord. The spinal arteries also receive blood through radicular arteries that reaches the cord along the roots of spinal nerves. These radicular arteries are branches from vertebral, ascending cervical, deep cervical, intercostal, lumbar and sacral arteries.

Only few of these radicular arteries are larger in size. The arteriaradicularis magna, or artery of Adamkiewicz, the largest of the radicular arteries and it may be responsible for supplying blood to as the lower two-thirds of the spinal cord. Its position is variable.There is no anastamosis between the anterior spinal artery and the posterior spinal artery. So the occurrence of thrombosis in any of these arteries will cause spinal cord infarction.

Venous drainage of the spinal cord is mainly through six longitudinal venous channels. They are anteromedian and posteromedian venous channels which lie in the midline and two paired anterolateral and

posterolateral channels. These channels join together and form a venous plexus, from here the venous blood drains through the radicular vein into segmental veins; the vertebral veins in the neck, the azygos veins in the thorax, lumbar veins in the abdomen and lateral sacral veins in the pelvis.

CEREBROSPINAL FLUID[16]

The cerebrospinal fluid is an ultrafiltrate of plasma secreted by choroid plexus of third, fourth and lateral ventricles at a rate of 0.3 to 0.5ml/min. The average volume ranges from 120 to 150 ml, of which 25 ml is in the cerebral subarachnoid space, 35 ml in the ventricles and about 75 ml is in the spinal subarachnoid space . It is a colourless liquid with slight opalescence due to globulin.

Circulation of cerebrospinal fluid

From the lateral ventricles it enters the 3rd ventricles through the interventricular foramina. Then it flows through the cerebral aqueduct and it reaches the 4th ventricle. Through the foramen of magendie and luschka in the roof of the 4th ventricle it enters the subarachnoid space and circulates over the cerebral hemispheres and around the spinal cord.

Absorption

The main site of cerebrospinal fluid absorption is into the venous system through the arachnoid villi and arachnoid granulations. These are most numerous in superior saggital sinus and its lateral lacunae.

Approximately 300-380 ml of cerebrospinal fluid enters venous circulation each day.It plays an important role in spinal anaesthesia as a media fordispersionof the local anaesthetic drug to the spinal nerve. Specificgravity of the injected solution is an important factor in determining the spread of the local anaesthetic drug in the subarachnoid space.

SITE OF ACTION OF LOCAL ANAESTHETIC DRUGS[17]

Local anaesthetic solution injected into the subarachnoid space mixes with the cerebrospinal fluid and comes into contact with the spinal cord and the peripheral nerve roots. The nerve roots leaving the spinal canal are readily exposed to the local anaesthetic solution as they are not covered with epithelium.

Zone of Differential Blockade

In subarachnoid block, sympathetic fibres are blocked two to six segments higher than the sensory fibres. Sympathetic block will be greater when more concentrated solutions are used or when adrenaline is added. Motor block will be two segments below the sensory block.

Spread of local anaesthetics in subarachnoid space

The local anaesthetic solution is diluted by CSF and therefore its original concentration is less 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 anaesthetic solution at a specific

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 against the gravity to the nerves innervating the surgical site.

Fate of local anaesthetics in subarachnoid space

After 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 removal of local anaesthetic solution following subarachnoid injection is primarily by vascular absorption.Depending on the type of the drug used, it is metabolized in plasma by pseudo cholinesterase or in the liver. The addition of a vasoconstrictor to the local anaesthetic solution will decrease

the absorption of the drug and thus increase the duration of anaesthesia.

PHYSIOLOGICAL EFFECTS OF SUBARACHNOID BLOCK

Cardiovascular effects

Vasomotor tone is determined by sympathetic fibers arising from T5 to L1 and innervating arterial and venous smooth muscle. Hence sympathetic block will cause a decrease in blood pressure that may be accompanied by a decrease in heart rate. With high sympathetic block, sympathetic cardiac accelerator fibers arising at T1-T4 are blocked, leading to decreased cardiac contractility. Bezold-Jarisch reflex has been implicated as a cause of bradycardia, hypotension and cardiovascular collapse after central neuraxial anaesthesia, in particular spinal anaesthesia.

Respiratory effects

Even with high thoracic levels, the tidal volume remains unchanged. A small decrease in vital capacity is due to paralysis of abdominal muscles necessary for forced exhalation and not due to phrenic nerve involvement or impaired diaphragmatic function. Effective coughing and clearing of secretions may get affected with higher levels of block. Respiratory arrest associated with spinal anaesthesia is rare and is due to hypo perfusion of respiratory centers in brain stem

Gastrointestinal function

Nausea and vomiting is seen in upto 20% of patients. It is due to gastrointestinal hyperperistalsis caused by unopposed parasympathetic activity. Vagal tone dominance results in a small contracted gut with active peristalsis and can provide excellent operative conditions. Hepatic blood flow will decrease with reductions in mean arterial pressure.

Renal function

Renal function has a wide physiological reserve. Decrease in renal blood flow is of little physiological importance. Neuraxial blocks are a frequent cause of urinary retention which delays discharge of outpatients and necessitates bladder catheterization of inpatients.

Complications of subarachnoid block

The Immediate complications include

- Hypotension
- Bradycardia
- Toxicity due to intravascular injection
- Allergic reaction to local Anaesthetic
- Hypoventilation (brain stem hypoxia)

The late complications include

- Postdural puncture headache
- Retention of urine

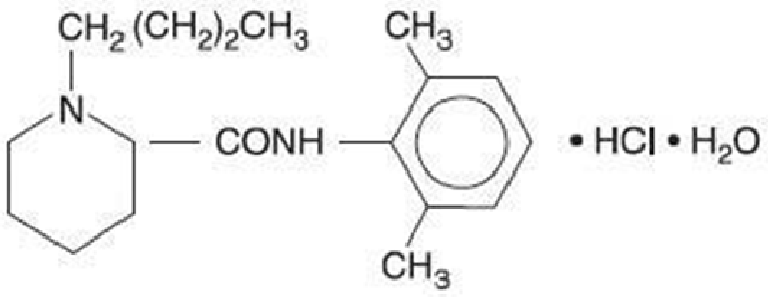
- Backache
- Meningitis
- Transient neurological symptoms
- Cauda equine syndrome
- Anterior spinal artery syndrome
- Horner’s syndrome

PHARMACOLOGY OF BUPIVACAINE[18,19,20]

Bupivacaine, an amino amide local anaesthetic was first synthesized in Sweden by A.F Ekenstam and his colleagues in 1957. First report of its use was in 1963 by L.J Teluvio. It is one of the long acting local anaesthetic agents available, which is extensively used for intrathecal, extradural and peripheral nerve blocks. It is a white crystalline powder soluble in water

CHEMICAL STRUCTURE OF BUPIVACAINE

Bupivacaine has an IUPAC nomenclature of 1-butyl-n-(2,6-dimethylphenyl) piperidine-2-carboxamide



Physiochemical properties[21]

Molecular formula	: C_{18} H_{28} N_{2O}HCl
Molecular weight	: 288.43 g/mol
Protein binding	: 95%
pH of saturated solution	: 5.2
pKa	: 8.1
Specific gravity	: 1.021 at 37 °C

Mechanism of action[22,23]

Mechanism of action of bupivacaine is similar to that of any other local anaesthetic. The primary action of local anaesthetics is on the cell membrane axon, on which it produces electrical stabilization. Bupivacaine prevents transmission of nerve impulses (conduction blockade) by inhibiting passage of sodium ions through ion-selective sodium channels in nerve membranes.

The sodium channel is a specific receptor for local anaesthetic molecules. 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.

The mechanism by which local anaesthetics block sodium conductance is as follows

1. Local anaesthetics in the cationic form act on the receptors within the sodium channels on cell membrane and block it. The local anaesthetics can reach the sodium channel either via the lipophilic pathway directly across the lipid membrane, or via the axoplasmic opening. This mechanism accounts for 90% of the nerve blocking effects of amide local anaesthetics.
2. The second mechanism of action is by membrane expansion. This is a nonspecific drug receptor interaction.

Other site of action targets

- Voltage dependent potassium ion channels
- Calcium ion currents (L-type most sensitive)
- G protein coupled receptors

Dosage depends on

Area to be anaesthetized

Number of nerve segments to be blocked

Individual tolerance

Technique of local anaesthesia

Vascularity of area

Anaesthetic potency

Hydrophobicity appears to be a primary determinant of intrinsic anaesthetic potency and Bupivacaine is highly hydrophobic, hence is very potent.

Onset of action

The onset of conduction blockade is dependent on the dose or concentration of the local anaesthetic. The onset of action of Bupivacaine is between 4 – 6 mins and maximum anaesthesia is obtained between 15 – 20 minutes.

Duration of block

The duration of anaesthesia varies according to the type of block. The average duration of peridural block is about 3.5 – 5 hours, for nerve block 5-6 hours and for intrathecal block, it is about 1.5 to 2 hours.

PHARMACOKINETICS

The concentration of Bupivacaine in blood is determined by the amount injected, the rate of absorption from the site of injection, the rate of tissue distribution and the rate of biotransformation and excretion of Bupivacaine.Bupivacaine can be detected in the blood within 5 minutes of infiltration or following epidural or intercostal nerve blocks. Plasma levels are related tothe total dose administered. Peak levels of 0.14 to 1.18 µg/ml were found within 5 mins to 2 hrs, and they gradually declined to 0.1 to 0.34 µg/ml by 4 hrs.

Plasma binding

In plasma, drug binds avidly with protein to the extent of 70 -90%. The rank order of protein binding for this and its homologues is bupivacaine, mepivacaine, lidocaine. Conversely, the unbound active fraction is one seventh of lidocaine and one fifth of mepivacaine

Absorption

The site of injection, dose and addition of a vasoconstrictor determine the systemic absorption of Bupivacaine .The maximum blood level of Bupivacaine is related to the total dose of drug administered from any particular site. Absorption is faster in areas of high Vascularity.

Toxicity

The toxic plasma concentration is set at 4 - 5 μg/ml. Maximum plasma concentration rarely approach toxic levels.

Distribution

Rapid distribution phase: (α)

In this phase the drug is distributed to highly vascular region. Half-life of α- being 2.7 minutes.

Slow disappearance phase: (β)

In this phase the drug distributes to slowly equilibrating tissues. Half-life of (β)- being 28 minutes.

Biotransformation and excretion phase: (δ)

Half-life of δ is 3.5 hours, clearance is 0.47litre/minute.

More highly perfused organs show higher concentrations of the drug. Bupivacaine is rapidly excreted by lung tissue. Though skeletal muscle does not show any particular affinity for bupivacaine it is the largest reservoir of the drug.

Biotransformation and Excretion

Bupivacaine undergoes enzymatic degradation primarily in the liver. The excretion occurs primarily via the kidney. Renal perfusion and factors affecting urinary pH affect urinary excretion. Less than 5% of Bupivacaine is excreted via the kidney unchanged through urine

The major portion of injected agent appears in urine in the form of 2,6pipecolyoxylidine(ppx) which is a n-dealkylated metabolite of bupivacaine. Renal clearance of the drug is related inversely to its protein binding capacity and pH of urine.

PHARMACODYNAMICS

Central Nervous System

Bupivacaine readily crosses the blood brain barrier causing CNS depression following higher doses. The initial symptoms involve feeling of light-headedness and dizziness followed by visual and auditory disturbances. Disorientation and drowsiness may occur. Objective signs are

usuallyexcitatory in nature, which includes shivering, muscular twitches and tremors, initially involving muscles of the face (perioral numbness) and part of extremities.

At still higher doses cardiovascular or respiratory arrest may occur. Acidosis increases the risk of CNS toxicity from Bupivacaine, since an elevation of PaCO2 enhances cerebral blood flow, so that more anaesthetic is delivered rapidly to the brain

Autonomic nervous system

Bupivacaine does not inhibit the Noradrenaline uptake and hence has no sympathetic potentiating effect. Myelinated preganglionic B fibers have a faster conduction time and are more sensitive to action of Bupivacaine. When used for conduction blockade, all local anaesthetics, particularly Bupivacaine produces higher incidence of sensory than motor fibers.

Cardiovascular System

The primary cardiac electrophysiological effect of a local anaesthetic is a decrease in the maximum rate of depolarization in Purkinje fibers andventricular muscle. This action by Bupivacaine is far greater compared to Lignocaine. Also, the rate of recovery of block is slower with Bupivacaine.Therefore there is complete restoration of Vmax between action potential particularly at higher rates. Therefore Bupivacaine is highly arrythmogenic. Bupivacaine reduces the cardiac contractility by blocking

the calcium transport. Low concentration of Bupivacaine produces vasoconstriction whereas high doses cause vasodilatation.

Respiratory System

Respiratory depression may be caused if excessive plasma level is reached which in turn results in depression of medullary receptor center. Respiratory depression may be also caused by paralysis of respiratory muscles of diaphragm as may occur in high spinal or total spinal anaesthesia.

Adverse Effects

Adverse effects are encountered in clinical practice mostly due to overdose, inadvertent intravascular injection or slow metabolic degradation.

Central nervous system

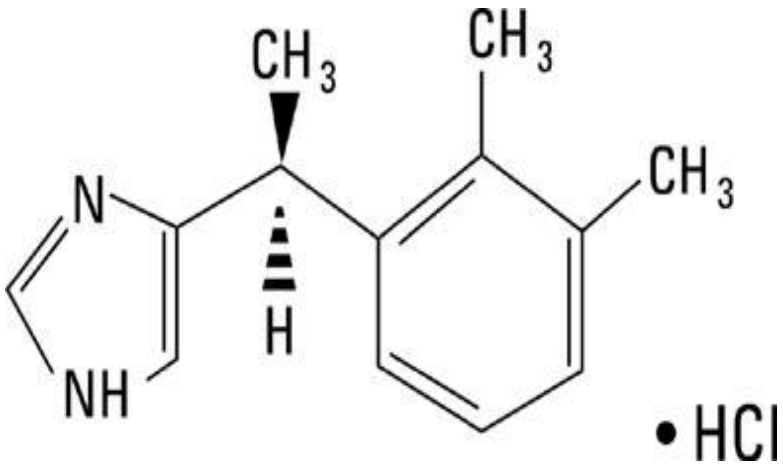
It is characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurring of vision or tremors, followed by drowsiness, convulsions, unconsciousness and respiratory arrest.

Cardiovascular system

Myocardial depression, hypotension, arrhythmia, ventricular type conduction defect, SA node depression and cardiac arrest

PHARMACOLOGY OF DEXMEDETOMIDINE[24,25]

Dexmedetomidine is the d-enantiomer of medetomidine, belongs to the imidazole subclass of α_2 receptor agonists. It is a more selective α_2 agonist with a 1600 greater selectivity for the α_2 receptor compared with the α_1 receptor. It was introduced in clinical practice in 1999 and the only FDA approved use of dexmedetomidine is for sedation in mechanically ventilated patients in intensive care unit. It is now being used off-label outside of the ICU in various settings, including sedation and adjunct analgesia in the operating room, sedation in diagnostic and procedure units, and for other applications.



MECHANISM OF ACTION

Alpha$_2$adrenoreceptors are membrane-spanning G proteins. There are three subtypes of α_2 adrenergic receptors in humans: α_{2A}, α_{2B}, and $\alpha_{2C.}$ The α_{2A} receptors are distributed mainly in the periphery, likewise α_{2B} and α_{2C} receptors are primarily distributed in spinal cord and brain.

Postsynaptic α_2 receptors in the peripheral blood vessels produce vasoconstriction, whereas α_2 receptors located in the presynaptic region inhibit the release of norepinephrine, potentially attenuating the vasoconstriction. These receptors are involved in the sympatholysis, sedation, and antinociceptive effects of α_2 receptors.

PHARMACOKINETICS

Dexmedetomidine when injected intravenously, it is rapidly distributed in the body and it is metabolized mainly in the liver and excreted in urine and faeces. Dexmedetomidine is 94% protein bound. The elimination half-life of dexmedetomidine is around 2 hours and with a context-sensitive half-time of 4 minutes to 250 minutes after an 8-hour infusion. Volume of distribution is 118 litres. Clearance is estimated to be approximately 39litres/ hour.

Central nervous system

Sedation

Dexmedetomidine acts on the alpha 2 receptors in locus ceruleus and causes sedation as well as hypnosis. It exerts sedative effect by acting through the endogenous sleep-promoting pathways.

Analgesia

Analgesia produced by dexmedetomidine is complex and not clearly known. The spinal cord is thought to be the primary site of action. It causes analgesia when injected either in intrathecal or epidural space.

Respiratory System

When dexmedetomidine is given at doses required to produce significant sedation it reduces minute ventilation, but the response to increase in carbon dioxide concentration is preserved. Ventilatory changes caused by dexmedetomidine is identical to the changes that appear during normal sleep.

Cardiovascular System

Dexmedetomidine causes a decrease in heart rate, myocardial contractility, cardiac output, systemic vascular resistance and blood pressure myocardial contractility and cardiac output. Dexmedetomidine when given in bolus dose has shown a biphasic response. Rapid injection of dexmedetomidine in a dose of 2 μg/kg causes a brief rise in the blood pressure (22%) and a decrease in the heart rate (27%) from the base line valve.This brief rise in blood pressure is due to the stimulation of peripheral alpha 2 receptors which causes vasoconstriction. After 15 minutes the heart rate came back to the baseline level, and blood pressure gradually declined to approximately 15% below baseline by 1 hour.

USES

Dexmedetomidine is used for sedation in mechanically ventilated patients and for procedural sedation prior to or during surgery.In operating room, it is used for premedication and a sole anaesthetic in monitored anaesthesia care. It is also used as an adjunct with localanaesthetic drugs in peripheral nerve block, intravenous regional anaesthesia, epidural and spinal anaesthesia.

Intensive care unit

Dexmedetomidine has several advantages over propofol while sedating postoperative patients in intensive care units. It reduces opioids consumption, Pa_{O_2}/F_{IO_2} ratio was significantly higher and heart rate was slower in dexmedetomidine group. Due to its unique character of providing good sedation with less respiratory depression it can be used while weaning patients from the ventilator.

Anaesthesia

Dexmedetomidine when used as a premedicant it reduces the requirements of induction agents, volatile anaesthetics and opioids. It suppresses the hemodynamic response to intubation. When used in ophthalmic cases it reduces the intraocular pressure and catecholamine secretion is reduced. Perioperative analgesic requirements are less, and recovery is more rapid. In a morbidly obese patient, the narcotic-sparingeffect of dexmedetomidine was evident in the intraoperative and

postoperative period after bariatric surgery.Dexmedetomidine has been successfully used in the treatment of withdrawal of narcotics, benzodiazepines, alcohol, and recreational drugs. It is also used for procedural sedation in paediatric patients.

Dosage and administration:

For adults, dexmedetomidine is administered intravenously at a loading dose of 0.5 to 1 μg/kg as a slow infusion over a period of ten minutes, followed by a maintenance infusion of 0.2 to 0.7 μg/kg/hr.Dexmedetomidine should be diluted in 0.9 % normal saline for infusion. Dexmedetomidine is recommended for infusion lasting up to 24 hrs. It is freely soluble in water.

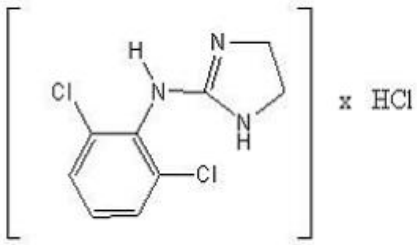
Adverse effects:

Major adverse effects include transient hypertension, hypotension haemorrhage, bradycardia, atrial fibrillation, sinus tachycardia, sinus arrest, ventricular tachycardia, myocardial infarction, agitation, confusion, delirium, hallucination, illusion and dry mouth

PHARMACOLOGY OF CLONIDINE

Clonidine is a centrally acting selective partial $alpha_2$ -adrenergic agonist (220:1 $alpha_2$ to $alpha_1$) that acts as an antihypertensive drug by virtue of its ability to decrease sympathetic nervous system output from central nervous system.[26]

Structural Formula



Pharmacokinetics[26]

Clonidine is rapidly and almost completely absorbed from gastrointestinal tract. The bioavailability is nearly hundred percent. After oral intake, peak plasma concentration reaches within 60 to 90 minutes. The elimination half life of clonidine is between 9 and 12 hours, with approximately 50% metabolized in the liver whereas the rest is excreted unchanged in urine. The transdermal route requires about 48 hours to produce therapeutic plasma concentrations. Clonidine can be administered via nasal, oral, intravenous, intramuscular, transdermal, epidural and intrathecal route. Clonidine is metabolized mainly by the liver to produce P-

hydroxy clonidine which subsequently undergoes glucuronidation and is excreted in urine.

Pharmacodynamics

Analgesic effects

Activation of post synaptic alpha$_2$ receptors in the substantiagelatinosa of the spinal cord is the presumed mechanism by which clonidine produces analgesia.

Alpha$_2$-Adrenoceptors are located on primary afferent terminals (both at peripheral and spinal endings), on neurons in the superficial laminae of the spinal cord, and within several brainstem nuclei implicated in analgesia, supporting the possibility of analgesic action at peripheral, spinal, and brainstem sites.[9]

The cardiovascular effects

Action of clonidine on cardiovascular system classified as peripheral and central. Clonidine affects blood pressure in a complex fashion after neuraxial or systemic administration because of opposing actions at multiple sites. In the nucleus tractussolitarius and locus ceruleus of the brainstem, activation of postsynaptic alpha$_2$-adrenoceptors reduces sympathetic drive. In addition, clonidine is not a pure alpha$_2$/alpha$_1$ adrenergic agonist; it also activates nonadrenergicimidazoline-preferring binding sites in the lateral reticular nucleus, thereby producing hypotension and an antiarrythmogenic action. In the periphery, activation of presynaptic

alpha sub2-adrenoceptors at sympathetic terminals reduces their release of norepinephrine by the sympathetic nerve terminals, which could cause vasorelaxation and reduced chronotropic drive. These brainstem and peripheral effects of $alpha_2$ -adrenoceptor stimulation are counter-balanced by direct peripheral vasoconstriction from circulating concentrations of the $alpha_2$/$alpha_1$ adrenergic agonist, clonidine. As a result, the dose response for clonidine by neuraxial or systemic administration is U-shaped, with peripheral vasoconstriction from circulating drug concentrations at high doses opposing central sympatholysis.[9]

Clonidine reduces heart rate partly by a presynaptically mediated inhibition of norepinephrine release at the neuroreceptor junction and partly by a vagomimetic effect. Clonidine depresses atrioventricular nodal conduction.[9]

Clonidine and haemodynamic response to intubation

Various studies have shown that, IV clonidine administration before laryngoscopy and intubation, in the dose of 3μg kg^{-1} to 6 μg kg^{-1} effectively attenuated the haemodynamic response to intubation.

Respiratory effects

Clonidine has minimal respiratory depressant effect on ventilation and do not potentiate ventilatory depressant effect of opioid[26]. It must be considered that drugs acting on the central nervous system to alleviate pain, relieve anxiety, and produce sedation are almost always accompanied by

some reduction in alveolar ventilation.

Central nervous system

Sedation commonly accompanies the use of clonidine. Clonidine increases stage I and stage II sleep with decrease in rapid eye movement. It causes anxiolysis. Anaesthetic-sparing properties of alpha$_2$-adrenergic agonists by inhibitory actions in the locus ceruleus via a G-protein mediated mechanism that involves inhibition of adenylatecyclase and decreases requirement for inhaled anaesthetic (MAC) and injected drugs. Clonidine produces dose-dependent sedation over the dose range 50-900 micro gram of rapid onset (< 20 min) regardless of route of administration.

Renal system

Clonidine hastens time to first micturition after spinal anaesthesia.Clonidine induces diuresis. Mechanism for diuresis is inhibition of release of antidiuretic hormone (ADH), antagonism of renal tubular action of ADH and increase in glomerular filtration.

Hormonal effects

Clonidine decreases plasma catecholamine levels. In stress situations, it reduces, but does not suppress, the neurohormonal secretion (norepinephrine, epinephrine, adrenocorticotrophic hormone, cortisol) secondary to sympathoadrenalhyperactivation.

Uses of Clonidine

1. Clonidine is very effective in the treatment of patient with severe hypertension or renin dependant disease.
2. Clonidine is used aspreanesthetic medication,
3. Preservative free clonidine administered into the epidural or subarachnoid space (150 to 450 μg) produces dose dependent analgesia.[9]
4. Addition of clonidine 1 μg/kg, to lidocaine for Bier's block enhances postoperative analgesia.
5. Clonidine protects against perioperative myocardial ischemia.
6. Clonidine used for the diagnosis of pheochromocytoma.
7. Used for the treatment of opioid and alcohol withdrawal syndrome.
8. Used in the treatment of shivering.

REVIEW OF LITERATURE

1. Benhamou D et al [27]in 1998 compared analgesic efficacy and side effectprofile of intrathecal clonidine and fentanyl with hyperbaric bupivacaine during elective cesarean section. Study group consisted of 78 ASA I and II pregnant women who were scheduled for elective cesarean section. Group B received hyperbaric bupivacaine 0.06 mg/cm of body height and 1 ml saline. Group BC received hyperbaric bupivacaine 0.06 mg/cm of body height with clonidine 75μg (0.5 ml) and saline (0.5 ml). Group BCF received fentanyl 12.5 μg (0.5 ml) and clonidine 75 μg with hyperbaric bupivacaine. Combined spinal epidural anaesthesia performed in 34 patients out of 78. When data were compared for patients who received only the initial spinal injection, time of regression to two segments and time to request of first analgesic were significantly longer only in group BCF. They concluded that by using small dose of intrathecal clonidine to bupivacaine improves intraoperative analgesia with no side effects. Combination of clonidine and fentanyl further improved analgesia but with moderately increased sedation and pruritis.

2. De KockM et al[28]in 2001studied the effect of intrathecalropivacaineand clonidine for ambulatory knee arthroscopy.In this study 120 ASA grade I patients scheduled for elective knee arthroscopy was divided into four groups. Group 1 patients received 8 mg of ropivacaine, group 2 patients received 8 mg of ropivacaine plus 15 μg clonidine,group 3 patients received 8 mg ropivacaine plus 45 μg clonidine and group 4 patients received

ropivacaine 8 mg plus 75µg clonidine.A combined spinal epidural technique was performed in the lateral position at L_3-L_4 interspace using a midline approach.

Intrathecalropivacaine (8 mg alone) produced short sensory anaesthesia and motor blockade (132 ± 38 min and 110 ± 35 min) and the quality of anesthesia was significantly lower than in any other group. Ropivacaine (8 mg) with 75 µg clonidine produced significantly longer sensory and motor anesthesia(195 ± 40 min and 164 ± 38 min) and was associated with systemic effects, such as sedation and reduction of arterial blood pressure, but without bradycardia. Ropivacaine (8 mg) with 45 µg clonidine increased the duration of sensoryblockade (183 ± 52 min) and had no influence on motor blockade or time to walk but was associated with delayed micturition and relative hypotension. Ropivacaine (8 mg) with 15µg clonidine did not prolong sensory or motor blockade, but produced high quality anaesthesia.

Authors concluded that the association of low dose clonidine (15 µg) with 8 mg ropivacaine for ambulatory arthroscopy significantly improves the subjective parameters that reflect the quality of intraoperative analgesia, and without compromising earlymobilization or interferring systemic side effects.

3. Dobrydnjov I et al [29]in 2003 studied clonidine combined with small dosebupivacaine during spinal anesthesia for inguinal herniorrhaphy. 45 ASA I and II patients were randomly allocated to one of the three groups, each

comprising 15 patients. Group B received 0.5% hyperbaric bupivacaine 6 mg. Patients in group BC15 received clonidine 15 µg along with 6 mg of 0.5% hyperbaric bupivacaine. Patients in group BC30 received clonidine 30 µg along with 6 mg of 0.5% hyperbaric bupivacaine. All test solutions were diluted with saline to a total volume of 3 ml. Intensity and duration of motor and sensory block, duration of analgesia, hemodynamic stability, sedation and adverse effects such as pruritis, postoperative nausea and vomiting, headache and low back pain was assessed.The authors concluded that addition of intrathecal clonidine to small dose of bupivacaine increased the spread and duration of analgesia and produced an effective spinal anesthesia. Clonidine 15 µg combined with bupivacaine 6 mg did not produce prolonged postoperative motor block and is therefore to be preferred for ambulatory inguinal herniorrhaphy.

4. Strebel S et al [30]in 2004 studied the effect of small dose intrathecalclonidine and isobaric bupivacaine for orthopedic surgery. Eighty ASA I-III patients scheduled for elective hip or knee arthroplasties were randomly assigned to receive intrathecal isobaric 0.5% bupivacaine 18 mg, plus saline (Group 1) or clonidine 37.5 µg (Group 2) or clonidine 75 µg (Group 3) or clonidine 150 µg (Group 4). All patients received a coded intrathecal drug volume of 4.6 ml.Time to regression of spinal anaesthesia below level L1 was 288±62 mins in control group, 311±101 mins in group 2, 325±69 min in group 3 and 337±78 mins in group 4.The time interval between spinal anesthesia and the first request for supplemental PCA morphine was

295±80 min in control group, 343±75 min (group 2), 381±117 min (group 3) and 445±136 min (group 4). The range of the upper level of sensory blockade was similar in all groups. A complete motor blockade of the lower extremities was observed in all patients. After 4, 5, 6 and 7 hours, the Bromage grade was significantly higher in group 4 compared in the group 1.There were no inter group differences in the number of patients with a MAP decrease ≥ 30% or in the maximal decrease of MAP. There was no significant difference in sedation scores or in the intraoperative use of midazolam among the groups.

Authors concluded that the addition of intrathecal clonidine at doses≤150 µg to isobaric bupivacaine dose dependently prolongs both sensory blockade of spinal anesthesia and time interval to first request for supplemental analgesia.

5. KanaziG E et al [31]in 2005conducted a prospective, double blindstudy in 60 patients undergoing transurethral resection of prostate or bladder tumour under spinal anaesthesia. The aim was to compare the onset and duration of sensory and motor block, hemodynamic changes and level of sedation following intrathecal administration of bupivacaine with either dexmedetomidine or clonidine.

60 patients were randomly allocated into 3 Groups. Group B received 12 mg of hyperbaric bupivacaine, Group D received 12 mg of bupivacaine supplemented with 3µg of dexmedetomidine; Group C received 12 mg of bupivacaine supplemented with 30µg of clonidine.

The mean time to reach T10 sensory block was 9.7 ± 4.2 minutes in Group B, 7.6 ± 4.4 minutes in Group C, 8.6 ± 3.7 in Group D. The mean time to reach peak sensory level was 20.2 ± 8.4 minutes in Group B, 18.7 ± 9.2 minutes in Group C, 24.5 ± 14.8 minutes in Group D. The mean time to reach Bromage 3 was 13.2 ± 5.6 in Group D, 11.7± 5.9 minutes in Group C, 20.7 ± 10.3 minutes in Group B.The time taken for regression of sensory block by two segments was 80±28 mins in Group B, 101±37 mins in Group C and 122±37 mins in Group DThe mean values of MAP and heart rate were comparable between 3 Groups throughout the intra op and post-operative period. All patients had oxygen saturation > 96% at all times and did not require additional oxygen in PACU.

They concluded that supplementation of spinal bupivacaine with low dose of intrathecal dexmedetomidine or clonidine produces significantly shorter onset of motor block and significantly longer sensory and motor block than bupivacaine alone. Dexmedetomidine 3µg and Clonidine 30µg have a equipotent effect on the characteristics of the block without any significant hemodynamic instability or sedation.

6. Kaabachi O et al[32]in 2007 studied spinal anesthesia in adolescents withplain bupivacaine and clonidine 1µg/kg with regards to safe and effective adjuvant for spinal anesthesia.The study group consisted of 83 adolescents

aged between 10 to 16 years, scheduled for orthopaedic surgeries of lower extremities. Control group received plain 0.5% bupivacaine alone and clonidine group received clonidine 1 μg /kg along with bupivacaine. Isobaric bupivacaine 0.5%, at a dose of 0.2 to 0.4 mg/kg of body weight up to 15 mg was given. Volume of injection was 0.1 to 0.5 ml larger in clonidine group due to the addition of clonidine. Non-invasive blood pressure, heart rate and arterial oxygen saturation were assessed at baseline and every 2 min for the first 10 min after spinal injection, and thereafter, every 5 minute during the surgery.Sensory and motor blocks were assessed at 15 and 30 min after intrathecal injection and every 5 min in the post anaesthesia care unit. Postoperative pain was assessed using an 100 mm visual analog scale every hour during first 6 hours and at every 3-4 hours thereafter and rescue analgesia given with tramadol 1-2 mg/kg iv if the pain score was 30 mm or higher.

They observed similar cephalic spread of the sensory block in the two groups, but the time to regression of the sensory block by two segments was significantly longer in the clonidine group. Duration of analgesia was prolonged in clonidine group (461±147 min) when compared to control group (330±138 min). Motor blockade was similar in two groups, but the time to recovery of motor block was significantly longer in clonidine group (252±79 min) when compared to placebo group (181±59 min).Authors also noted that the first dose of rescue analgesic was longer in the clonidine group than the

control group.Number of patients who developed hypotension was 29% in clonidine group and 17% in placebo group. Number of patients who developed bradycardia was 21% in clonidine group and 12% in placebo group.Authors concluded that adding clonidine 1 μ/kg to bupivacaine prolongs spinal anesthesia in adolescents without causing severe adverse effects.

7. Sethi BS et al[33]in 2007 studied the efficacy of analgesic effects of lowdose intrathecal clonidine as adjuvant to bupivacaine. 60 ASA I and II patients in the age group of 20-50 years scheduled to undergo lower abdominal surgeries were randomly divided into two groups of 30 each. Clonidine group patients received 0.5% hyperbaric bupivacaine 12.5 mg with preservative free clonidine 1μg/kg. Control group patients received 0.5% hyperbaric bupivacaine 12.5 mg with identical volume of saline. The degree of sensory block, motor block, parameters like HR,NIBP, ECG and SpO_2 were recorded at 5 min interval. They showed that decrease in mean heart rate and MAP from 45 minutes until the end of 6 hours was greater in clonidine group than in control group and was statistically significant though, no patient had a fall of MAP to <70 mmHg in both the group and hence did not require additional vasopressor and fluid therapy and no patient in both the groups had a decrease in heart rate less than 60/minute and hence did not require injection atropine sulphate. The level of sensory regression by two segments was 218 minutes in the clonidine group and 136 min in the control group. The duration of motor blockade was 205 minutes in clonidine group and 161 minutes in

control group.Duration of analgesia was 614 minutes in clonidine group and 223 minutes in control group. The number of diclofenac sodium injection required in 24 hours was higher in control group than clonidine group.The sedation score were higher in clonidine group than control group. They concluded that addition of clonidine to bupivacaine in the dose of 1 μg/kg significantly increases the duration of analgesia compared to bupivacaine alone without significant fall in MAP and heart rate requiring therapeutic intervention.

8. Grandhe RP et al[34]in2008 studied the effect of bupivacaine-clonidinecombination for unilateral spinal anaesthesia in lower limb orthopedic surgery. 45 ASA I and II patients aged 20-50 years, undergoing unilateral lower limb surgery were allocated to receive 1.5 ml of 0.5% heavy bupivacaine combined with either 1 ml of normal saline (group B) or clonidine 1 μg/kg (group BC1) or 1.5 μg/kg (group BC2). The total volume injected was 2.5 ml in all patients.The authors observed time to achieve sensory block upto T_{11} was 7.6±2.2 mins in control group and it was 7.1±4.2 mins and 8.2±3.4 mins in clonidine groups (BC1 and BC2 respectively). The time to achieve maximum sensory block was 19±2.1 mins in the control group and 18±4.6 mins and 21±3.9 mins in clonidine groups (BC1 and BC2 respectively). The mean duration of analgesia was 3.8±0.7 hours in control group, 6.3±0.8 hours when using clonidine of 1 μg/kg with a mean weight of 60.6±19.4 kg and 7.3±0.9 hours when using clonidine of 1.5 μg/kg with a mean weight of 62.7±18 kg. The authors observed the mean heart rate was significantly lower

in group BC2 compared to group B between 105 min to 8 hours following intrathecal drug administration. No bradycardia occurred in any of the patients. The incidence of hypotension was 4patients in control group, 10 patients in group BC1and 8 patients in group BC2. Authors concluded that the combination of 1-1.5 µg/kg body weight of clonidine with 1.5 ml of 0.5% hyperbaric bupivacaine for producing unilateral spinal anaesthesia effectively prolonged the sensory and motor block and postoperative analgesia while causing minimal adverse effects.

9. Al Ghanem SM et al[35]in 2009 conducted a double blind controlled studyon the effect of adding dexmedetomidine versus fentanyl to intrathecal bupivacaine on spinal block characteristics in gynaecological procedures.Seventy-six patients of ASA Grade I-III were randomly allocated to one of two groups.Group D received 10 mg of isobaric bupivacaine with 5µg dexmedetomidine and Group F received 10 mg of isobaric bupivacaine with 25 µg of fentanyl.The authors observed the time to reach T10 sensory block to be 7.5±7.4 min in Group D and 7.4±3.3 min in Group F. The time to reach the maximum sensory block was 19.34±2.87 min in Group D and 18.39±2.46 min in Group F. The time to reach S1 segment was significantly longer in group D (274.8±73.4 min) than in Group F (179.5±47.4 min).The onset time motor block was not different between group D (14.4±6.7 min) and group F (14.3±5.7 min). The regression of motor block to Bromage 0 was 240±64 mins in group D was significantly longer than that for Group F

(155±46 min).The mean values of MAP and HR were similar in both the groups. The sedation score was between 0 and 1 in both groups. Hypotension was mild to moderate in both groups except one in group F who had blood pressure less than 90 mmHg and required 36 mg ephedrine. The authors concluded that 5µg of Dexmedetomidine seems to be an attractive alternative as an adjuvant to spinal bupivacaine in surgical procedures especially in those that need quite long time with minimal side effects and excellent quality of spinal analgesia.

10. Al-Mustafa et al [36]in 2008conducted a study todetermine the effect of adding different doses of dexmedetomidine to isobaric bupivacaine for patients undergoing urological procedures under spinal anaesthesia.Sixty six patients were randomly assigned into 3 groups. Group N received Bupivacaine 12.5mg with saline. Group D5 received 12.5mg Bupivacaine with 5µg Dexmedetomidine. Group D10 received 12.5mg Bupivacaine with 10µg Dexmedetomidine. The mean time of sensory block to reach T10 dermatome was 4.7 ±2 minutes in D10 group, 6.3 ±2.7 minutes in D5 group and 9.5 ± 3 minutes in Group N .The mean time to reach Bromage 3 scale was 10.4 ± 3.4 minutes in group D10, 13.0 ± 3.4 minutes in Group D5 and 18.0 ± 3.3 minutes in GroupN. The regression time to reach S1 dermatome was 338.9 ± 44.8 minutes in Group D10, 277.1±23.2 minutes in D5 and 165.5 ± 32.9 minutes in Group N . The regression to Bromage 0 was 302.9± 36.7 minutes in D10 , 246.4± 25.7 minutes in D5 and 140.1 ± 32.3 minutes in Group N. Onset and

regression of sensory and motor block were highly significant (N verses D5,N verses D10 and D5 verses D10).They concluded that dexmedetomidine has a dose dependent effect on the onset and regression of sensory and motor block when used as an adjuvant to bupivacaine in spinal anaesthesia.

11. Saxena H et al [37]in 2010 studied the effect of low dose intrathecalclonidine with bupivacaine with regards to onset and duration of block.80 patients of ASA grade I and II, scheduled for elective surgery below umbilicus were grouped into 4 groups. Group1 received hyperbaric bupivacaine 13.5 mg and 0.3 ml saline. Group 2 received 15 µg, group 3 received 30 µg and group 4 received 37.5 µg clonidine added to bupivacaine. The total volume of drug was 3 ml in all groups.The mean time for onset of sensory block was significantly lower in all clonidine groups in a dose dependant manner compared to control group and lowest in group 4. The mean time to achieve sensory block up to T10 was 6.57±0.49 mins in control group and 2.58±0.33 mins, 2.54±0.34 mins and 2.09±0.89 mins in clonidine group (15 µg, 30 µg and 37.5 µg respectively). The mean time to achieve maximum sensory level was 7.3±1.25 mins in control group and 6.8±1.20 mins, 7.4±1.31 mins and 6.7±1.12 mins in clonidine group (15µg, 30µg and 37.5µg respectively). There was no statistical difference in the extent of block achieved in any group.The onset of motor block was 7.41±0.55 mins in control group and 2.67±0.50 mins, 2.30±0.45 mins, 2.20±0.50 mins in clonidine group (15µg, 30µg, 37.5µg respectively).The duration of analgesia was 99.75±21.91 mins in control group, 164.5±23.9 mins, 264.75±44.3 mins

and 285.60±36.59 mins in clonidine group (15µg, 30µg and 37.5µg respectively). The duration of motor blockade was 153±19.5 mins in control group, 206.75±20.16 mins, 220±47.43 mins and 235±31.9 mins in clonidine groups (15µg, 30µg and 37.5µg respectively).The haemodynamic parameters were similar in all the 4 groups at any point of time with no statistical variation. There was a 20% fall in the mean pressure from the baseline in group 4 as compared to 8% in group 1, 30 min after the injection. Authors concluded that addition of intrathecal clonidine to bupivacaine, even in very small doses, significantly improves the onset and duration of sensory and motor block with relative haemodynamic stability.

12. Gupta R et al[38]in 2011 Studied dexmedetomidine as an intrathecaladjuvant for post-operative analgesia with isobaric ropivacaine.Sixty patients were randomized into 2 groups. Group R received 3 ml of 0.75% isobaric ropivacaine with 0.5 ml normal saline, Group D received 3 ml of 0.75% isobaric ropivacaine with 0.5 ml dexmedetomidine (5µg). They showed that the duration of onset of sensory blockade in Group D was 4.8±1.2 mins and in Group R was 4.7±1.1 mins and duration to achieve maximum sensory blockade in Group D was 11.7±1.7 mins, in Group R was 12.1±1.6 mins and time to 2 segment regression of sensory blockade in Group D was 125.6±16.5 mins, in Group R was 62.7±8.3 mins and regression of sensory blockade to S2 in Group D was 468.3±36.8 mins, in Group R was 239.3±16.8 mins and time for rescue analgesia in Group D was 478.4±20.9 mins, in Group R was 241.7±21.7 mins. Time to two segment regression of sensory blockade

and regression of sensory blockade to S2 were significantly slower with intrathecal dexmedetomidine. The duration of analgesia was significantly prolonged with addition of dexmedetomidine as compared to ropivacaine alone.Intraoperative ephedrine requirement was more in group D and two patients had bradycardia was treated with 0.6 mg of IV atropine. Authors concluded that 5µg dexmedetomidine seems to be an alternative as an adjuvant to spinal ropivacaine in the surgical procedures, especially those requiring long time.

13. Eid HEA et al[39]in 2011 studied dose related effect of intrathecaldexmedetomidine with hyperbaric bupivacaine, a prospective randomized double blind study.Forty eight patients scheduled for anterior cruciate ligament reconstruction were randomized to one of the 3 groups receiving 10 µg Dexmedetomidine (Group D1), 15 µg Dexmedetomidine (Group D2) and normal saline with 3 ml of 0.5% hyperbaric bupivacaine (Group B). In all the group's total volume of drug was 3.5 ml. The onset of sensory block was 8.7±3.3 mins in Group B, 7.7±3.6 mins in Group D1 and 8±2.5 mins in Group D2. Time to two segment regression in Group B was 76.9±26.8 mins, Group D1 was 103±28.7 mins and Group D2 was 200.6±30.9 mins and regression of sensory blockade to S1 in Group B was 238±57 mins, Group D1 was 320±65.8 mins and Group D2 was 408.7±68 mins and regression to Bromage 0 in Group B was 202±41.8 mins, in Group D1 was 280±46 mins and in Group D2 was 336±58 mins.There was a dose dependent

prolongation of the duration of sensory block and motor block by the addition of intrathecal dexmedetomidine. The mean values of MAP and HR were comparable between the three groups throughout the study. They concluded that intrathecal dexmedetomidine in significantly prolonges the anaesthetic and analgesic effects of spinal hyperbaric bupivacaine in a dose dependent manner.

14. Gupta R et al[40]in 2011 conducted a comparative study of intrathecaldexmedetomidine and fentanyl as adjuvants to bupivacaine.Sixty patients scheduled for lower abdominal surgeries were randomly allocated to receive either 12.5 mg hyperbaric bupivacaine with 5µg dexmedetomidine (group D) or 25µg fentanyl (group F). They showed that there was no difference between groups D and F in the highest level of block achieved in the two groups (T_5 andT_6 respectively) or in the time to reach peak level. Block regression (476±23 min in group D and 187±12 min in group F) was significantly slower with the addition of intrathecal dexmedetomidine as compared with fentanyl. There was no difference in the onset time of motor block (11.6±1.8 min in group D and 11.2±1.3 min in group F) but the duration of motor block (421±21 min in group D and 149±18 min in group F) was significantly slower with the addition of dexmedetomidine. The time to rescue analgesic was significantly longer in group D as compared to group F.The patients in both groups remained hemodynamicallystable, the sedation score was more in group D patients. Intraoperative ephedrine requirement was more in group D (10±4 mg) as compared to group F (6±3 mg). One patient in group

D had bradycardia (HR<50/min) but it was successfully managed with atropine 0.4 mg. Authors concluded that 5µg dexmedetomidine seems to be an attractive alternative to 25µg fentanyl as an adjuvant to spinal bupivacaine in providing good quality of analgesia, hemodynamic stability and minimal side effects.

15. Shukla D et al[41]in2011 compared the effects of Intrathecaldexmedetomidine and magnesium sulfate used asadjuvants to bupivacaine.Ninety patients scheduled for lower abdominal and lower limb surgeries were randomly allocated to receive either 15 mg hyperbaric bupivacaine with 10µg (0.1 ml) dexmedetomidine (group D) or 50 mg (0.1 ml) magnesium sulfate (group M) or 0.1 ml saline (group C). The onset of sensory blockade in Group D was 2.27±1.09 mins, in Group M was 6.46±1.33 mins and in Group C was 4.14±1.06 min. The onset of motor blockade in Group D was 3.96±0.92 mins, in Group M was 7.18±1.38 mins and in Group C was 4.81±1.03 min, the mean time for regression of sensory blockade to S1 in Group D was 352±45 mins, in Group M was 265±65 mins and in Group C was 194±55 min, mean time for regression to Bromage 1 in Group D was 331±35 mins, in Group M was 251±51 mins and in Group C was 140±34 mins.The onset time of both sensory and motor block was rapid in Group D and delayed in Group M in comparison with the control Group C and was statistically significant. The regression time of both sensory and motor block

was prolonged in Group D and in Group M in comparison with the control Group C and was statistically significant. There was no significant difference in the mean values ofmean arterial pressure and heart rate intraoperatively and postoperatively.Authors concluded that intrathecal dexmedetomidine supplementation of spinal block seems to be a good alternative to intrathecal magnesium sulfate as it produces earlier onset and prolonged duration of sensory and motor block without associated significant hemodynamic alterations.

MATERIALS AND METHODS

Study design **:** Double blinded randomised case control study.

Sample size **:** 90 patients

Sampling method **:** Randomised sampling

Statistical analysis **:** Chi square test

Method of collection: All patients undergoing elective lower limb surgery

After obtaining approval from the institutional ethical committee, Thanjavur medical college, Thanjavur, the study was conducted in 90 ASA grade I or II patients undergoing elective lower limb surgeries under spinal anaesthesia. All patients were explained about the procedures and an informed written consent was obtained.

INCLUSION CRITERIA

1. Patients aged between 18 and 60 years
2. ASA I□II
3. Scheduled for elective lower limb surgeries.

EXCLUSION CRITERIA

1. Any contraindication of regional anaesthesia, or patient refusal.
2. Body weight more than 120 kg
3. Height <140 cm

4. Post spinal surgeries, spinal deformity

5. History of allergy to study drugs

6. Pregnancy

7. Coagulopathy

8. Cardiac, liver, or kidney diseases.

9. Neurological disorder.

METHODOLOGY

Ninety patients in the age group between 20 years and 60 years of either sex belonging to ASA physical status I and II posted for elective lower limb surgerieswere grouped randomly into three groups (n=30). Randomization was done using sealed envelope technique.

Group B (control group): received 15mg of 0.5% hyperbaric bupivacaine with 0.5ml normal saline.

Group C (clonidine group): received 15mg of 0.5% hyperbaric bupivacaine with 50µg clonidine.

Group D (dexmedetomidine group): received 15mg of 0.5% hyperbaricbupivacaine with 5µg dexmedetomidine.

Total volume of the injected solution was 3.5ml in all three groups.

Preoperative preparation

Preoperative assessment was done for each patient and informed written consent was taken. Patients were kept NPO for solids 6

hoursand clear fluids 2 hours before surgery. All patients were premedicated on the night before surgery with Tablet Ranitidine 150mg and Tablet Alprazolam 0.5mg.Intravenous line was secured with 18 gauge cannula and preloaded with 500 ml of Ringer lactatesolution half an hour before anaesthesia.

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. Non-invasive blood pressure monitor, pulseoximeter 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.

Intraoperative monitoring

On sitting position, the skin over the back was prepared with antiseptic solution and draped with sterile towel.Under aseptic precautions subarachanoid block was performed at level of L3-L4 through a midline approach using 25G Quincke spinal needle and study drug was injected with operative table kept flat. The patients were made to lie supine immediately and the time of injection of study drug was noted.

In the perioperative period the following parameters were studied.

- Onset of sensory blockade and motor blockade.
- Maximum level of sensory blockade and time taken for the same.
- Maximum level of motor blockade and time taken for the same.
- Two segments sensory regression time.
- Total duration of analgesia.
- Total duration of sensory blockade and motor blockade.

Sensory blockade was tested using pinprick method with a blunt tipped 27G needle at every minute for first 5 mins and every 5 mins for next 15 mins and every 10 mins for next 30 mins and every 15 mins till the end of surgery and there after every 30 mins until sensory block was resolved.

- Quality of motor blockade was assessed by Bromage scale.
- Level of sedation was noted.
- Side effects if any were noted.

Haemodynamic monitoring was done during the block every 5 mins for first 15 mins and every 10 mins for next 30 mins and once in 15 mins till the end of surgery and post operatively every hourly employing multi parameter monitor which displays heart rate (HR),

systolic blood pressure (SBP) diastolic blood pressure (DBP), mean arterial pressure (MAP), ECG and SpO_2.

Onset of sensory blockade: was defined as time taken from theinjection of study drug till loss of pin prick sensation at T10 level.

Time taken for maximum sensory blockade: was defined as the time taken fromthe injection of study drug to the maximum sensory blockade attained.

Onset of motor blockade: was defined as the time taken from theinjection of study drug till the patient was unable to move hip but was able to move knee and ankle.

Quality of motor blockade was assessed by Bromage scale

Bromage0 - able to move hip, knee and ankle.

Bromage 1- unable to move hip but able to move knee and ankle.

Bromage 2 - unable to move hip and knee but able to move ankle.

Bromage 3- unable to move hip, knee and ankle.

Time taken for maximum motor blockade: was defined as the time taken from the injection of study drug to maximum motor blockade attained (Bromage 3).

Duration of two segment sensory regression: was defined as the time taken fromthe maximum level of sensory block attained till the

sensation has regressed by 2 segments.

Duration of analgesia: was defined as the time taken frominjection of study drug till the patient requests for rescue analgesic in the post-operative period.

Duration of sensory blockade: was defined as the time taken from time of injectionof study drugtill the patient feels the sensation at S1 dermatome.

Duration of motor blockade: was defined as the time taken from time of injection of study drug tillthe patient attains complete motor recovery (Bromage 0).

Level of sedation: was assessed using subjective sedation score.

0 awake, conscious, no sedation to slightly restless

1 calm and composed

2 awakens on verbal commands

3 awakens on gentle tactile stimulation

4 awakens only on vigorous shaking

5 unarousable

Hypotension was defined as reduction of systolic blood pressure more than 30%below baseline value and was treated with increased rate of intravenous fluids and incremental doses of injection ephedrine.

Bradycardia was defined as heart rate less than 60/minute and was treated withinjection atropine 0.6mg IV.

Adverse effects: Any discomfort like nausea, vomiting, shivering, pruritus and adverse events such as hypotension, bradycardia, respiratory depression and ECG changes were noted.

STATISTICAL ANALYSIS

30 patients were selected for each group in our study. The data collected was subjected to statistical analysis using Statistical Package for Social Sciences (SPSS). Results were expressed as range, mean, and standard deviations.The comparison of normally distributed continuous variables between the groups was performed using one-way analysis of variance (ANOVA). Nominal categorical data between study groups were compared using the chi-square test or Fisher's exact test. Ordinal categorical variables and non-normal distribution continuous variables were compared using the Mann-Whitney U-test. 'P' value < 0.05 was considered to be significant.

OBSERVATION AND RESULTS

All 90 patients completed the study without any exclusion. Inter group analysis was done and the collected data was analysed by chi square test. Results were obtained in the form of range, mean and standard deviation. The probability value ‘p’ of less than 0.05 considered statistically significant.

Table 1: Age distribution

AGE IN YEARS	GROUP B		GROUP C		GROUP D	
	NO	%	NO	%	NO	%
21-30	16	53.3	14	46.7	18	60.0
31-40	9	30.0	6	20.0	2	6.7
41-50	5	16.7	6	20	8	26.7
51-60	0	0	4	13.3	2	6.7
TOTAL	30	100	30	100	30	100
RANGE	20-50		20-59		20-55	
MEAN	31.17		36.60		33.07	
SD	9.752		11.082		11.585	

Graph 1: Age distribution

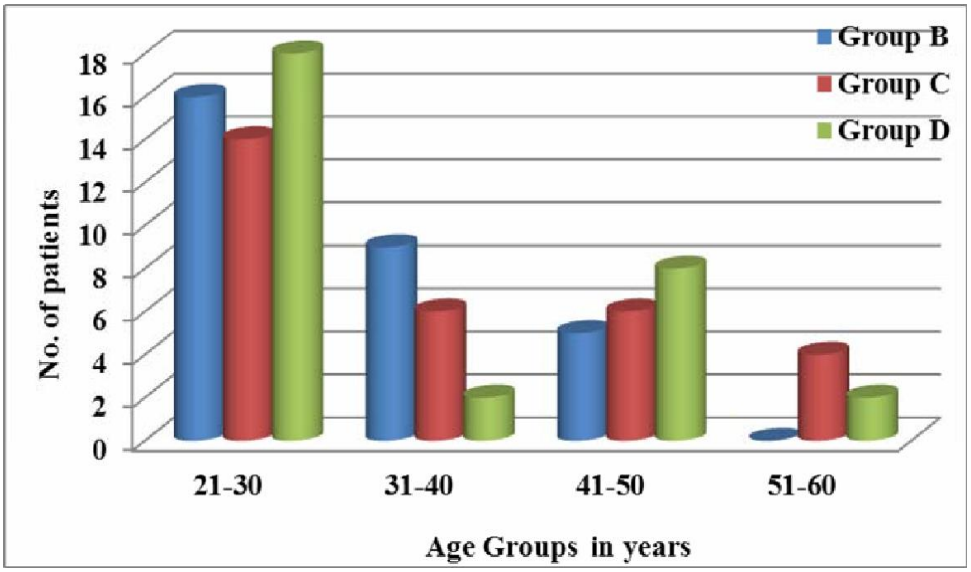


Table 1 shows the age distribution of the patients in all the three groups. The minimum age in group B (control group), group C (clonidine group) and group D (dexmedetomidine group) were 20 years. The maximum age in group B is 50 years, in group C is 59 years and in group D is 55 years. The mean age in group B is 31.17 ± 9.75 years, group C is 36.6 ± 11.08 years and group D is 33.07 ± 11.58 years. There is no significant difference in the age of patients between the groups. All the three groups were similar with respect to age distribution ($p>0.05$).

Table 2: Sex distribution

SEX	NO OF PATIENTS		
	GROUP B	GROUP C	GROUP D
MALE	15	20	24
FEMALE	15	10	6
TOTAL	30	30	30

Graph 2: Sex distribution

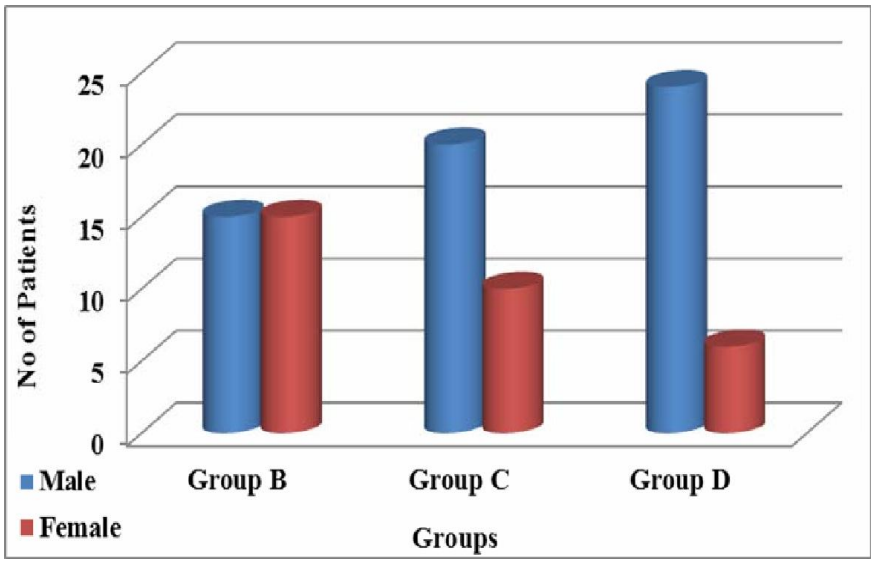


Table 2 shows the sex distribution of the patients in all the three groups. There is no significant difference in the sex distribution of the patients between the groups. (P>0.05).

Table 3: Height distribution

Height in cm	Group B	Group C	Group D
n	30	30	30
RANGE	152-168	150-170	150-170
MEAN	159.4	161.03	161.6
SD	4.76	6.18	5.14

Graph 3: Height distribution

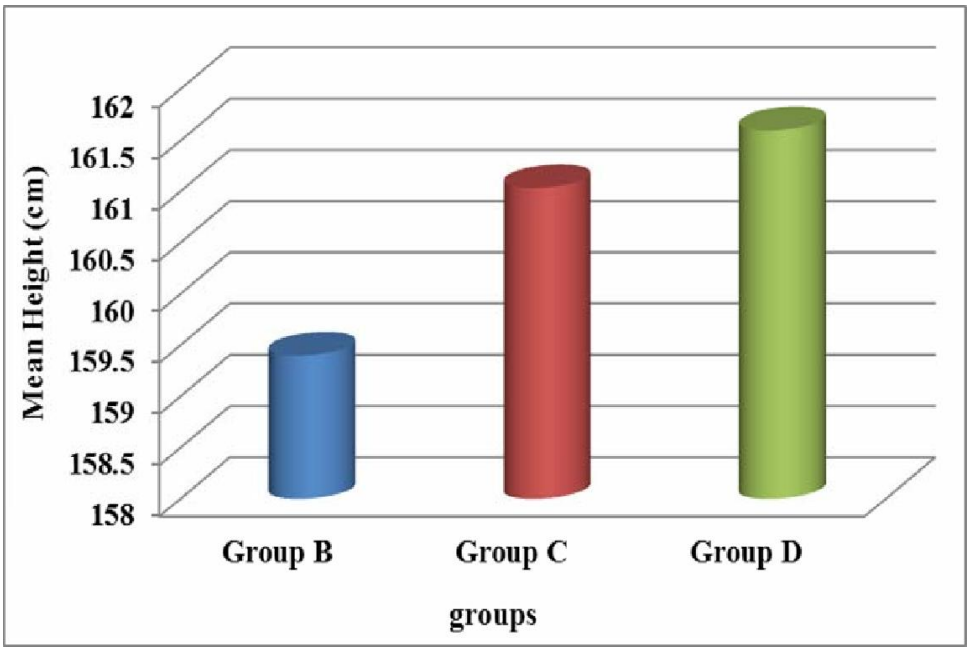


Table 3 shows the height distribution of patients. The mean height in group B (control group) is 159.4±4.7cm, group C (clonidine group) is 161.03± 6.18 cm and group D (dexmedetomidine group) is 161.6±5.14cm. The minimum height is 152cm in group B, 150cm in group C and 150cm in group D. The maximum height was 168 cm in group B and 170cm in both the groups D and C. There is no significant difference in the height of patients between the groups ($p>0.05$).

Table 4: Body weight distribution

Weight In Kg	Group B	Group C	Group D
MEAN	60.9kg	61.33 kg	60.7 kg
SD	4.62 kg	5.53 kg	5.74 kg
RANGE	50-68	50-70	50-70

Graph 4: Body weight distribution

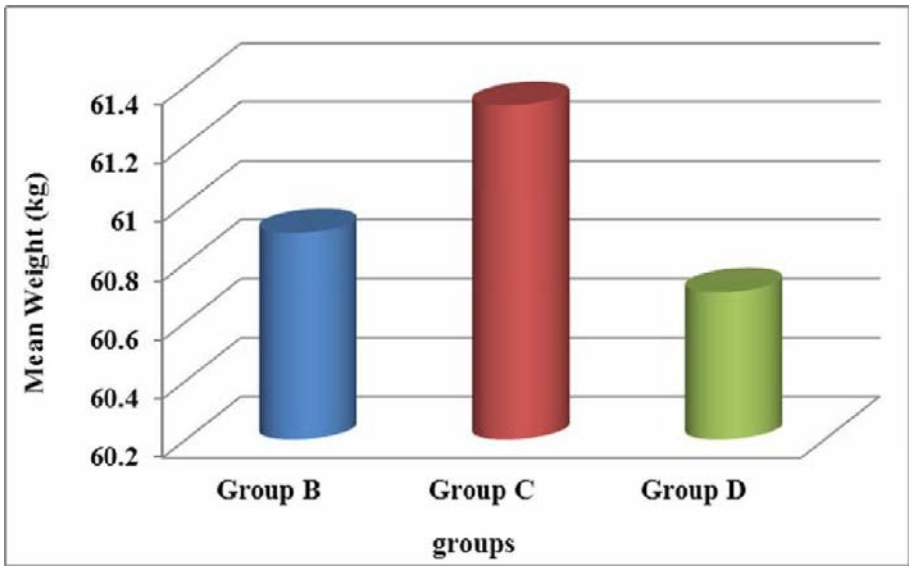
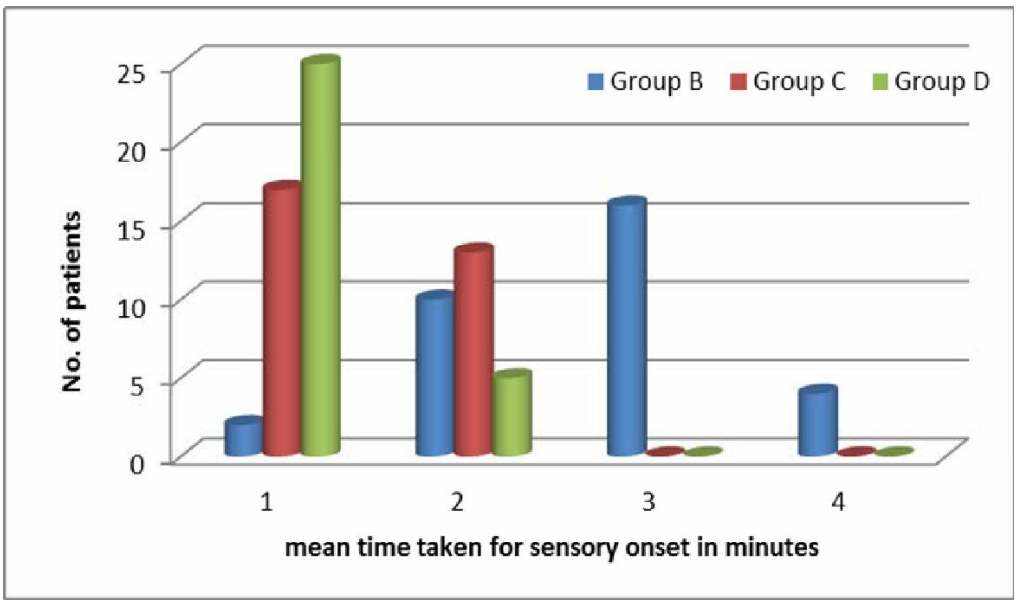


Table 4 shows the body weight distribution of patients. The mean body weight in group B (control group) is 60.9 ± 4.62 kg, in group C (clonidine group) is 61.33 ± 5.53kg and in group D (dexmedetomidine group) is 60.7±5.74 kg. The minimum body weight in the groups were 50kg. The maximum body weight in the group B was 68 kg and in group C and group D were 70kg. There is no significant difference in the body weight of patients between the groups ($p>0.05$).

Table 5: Mean time taken for sensory onset in minutes

Time takenfor sensoryonset in mins	RANGE	MEAN	SD	P value B vs C	P value B vs D	P value C vs D
Group B	2-4	2.80	0.664	0.000	0.000	0.024
Group C	1-2	1.43	0.504			
Group D	1-2	1.17	0.379			

Graph 5: Mean time taken for sensory onset in minutes

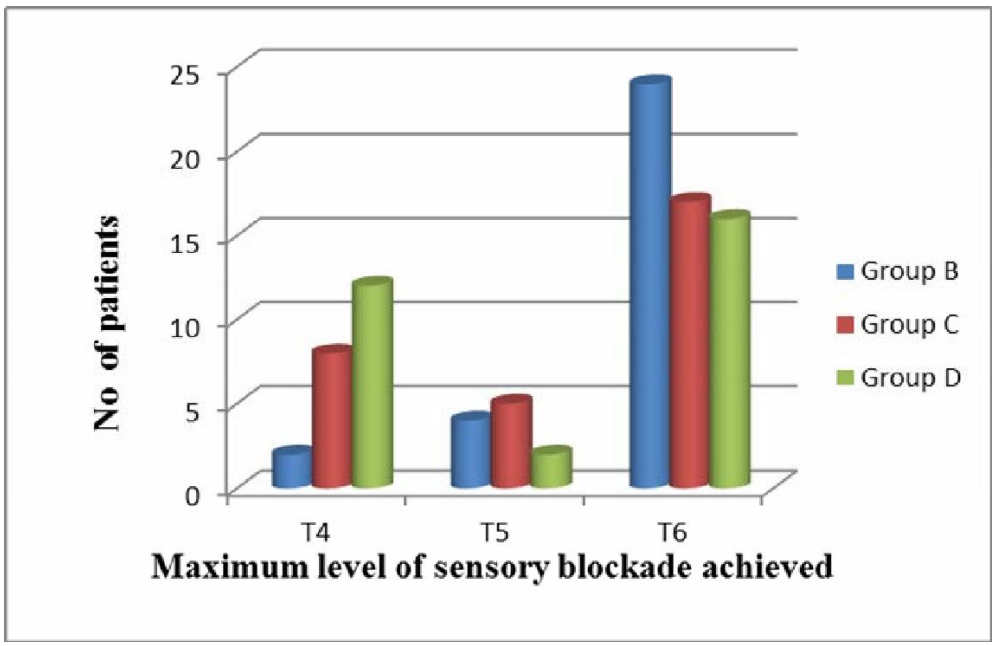


The mean time of onset of sensory blockade in group B (control group) is 2.8±0.66 mins, in group C (clonidine group) is 1.4±0.5mins and in group D (dexmedetomidine group) is 1.17±0.37mins. There is a statistically highly significant difference when group B was compared with group C and with group D (p=0.000) and there is statistically significant difference between group C and group D (p=0.024). However there is no clinical significance between group C and group D regarding mean time taken for onset of sensory blockade.

Table 6: Maximum level of sensory block attained

Maximumlevel ofsensory blockattained	No of patients			Total
	T4	T5	T6	
Group B	2	4	24	30
Group C	8	5	17	30
Group D	12	2	16	30

Graph 6: Maximum level of sensory blockade attained



Two out of 30 patients in group B (control group), 8 out of 30 patients in group C (clonidine group) and 12 out of 30 patients in group D (dexmedetomidinegroup) had T4 level of sensory blockade.

Four out of 30 patients in group B, 5 out of 30 patients in group C and 2 out of 30 patients in group D had T5 level of sensory blockade.

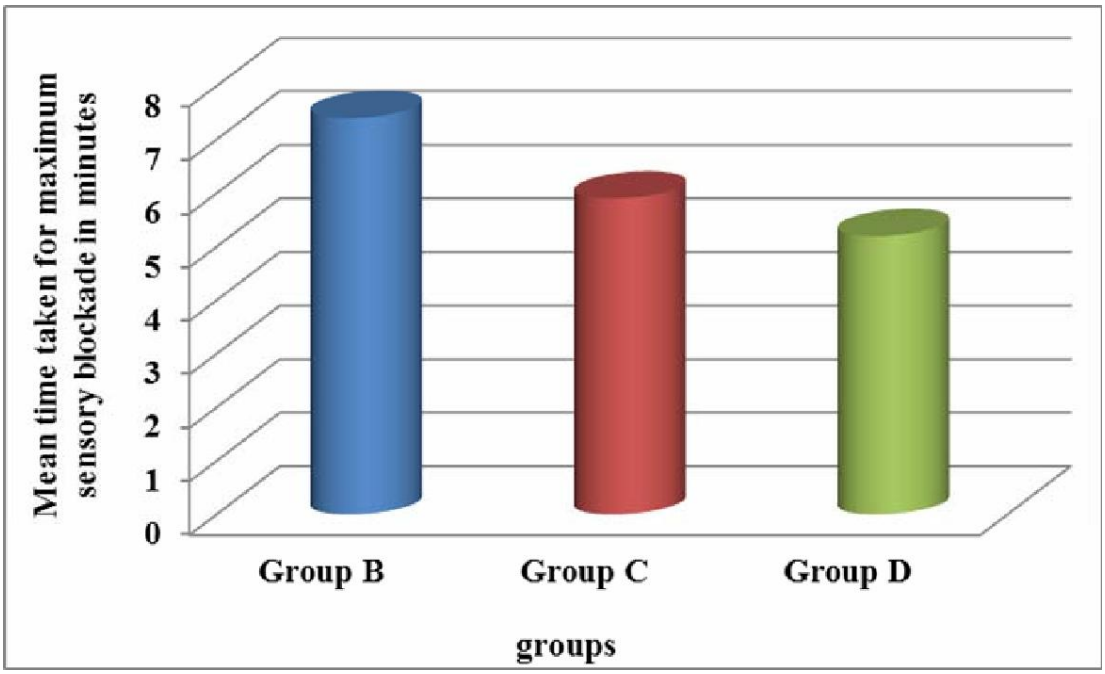
Twenty-four out of 30 patients in group B, 17 out of 30 patients in group C and 16 out of 30 patients in group D had T6 level of sensory blockade.

There is no statistically significant difference between the groups (p=0.24).

Table 7: Mean time taken for maximum sensory blockade in minutes

Time takenfor maximum sensory block in mins	RANGE	MEAN	SD	P value B vs C	P value B vs D	P value C vs D
Group B	6-9	7.4	1.102	0.000	0.000	0.001
Group C	5-7	5.9	0.803			
Group D	4-7	5.2	0.714			

Graph 7: Mean time taken for maximum sensory blockade in minutes

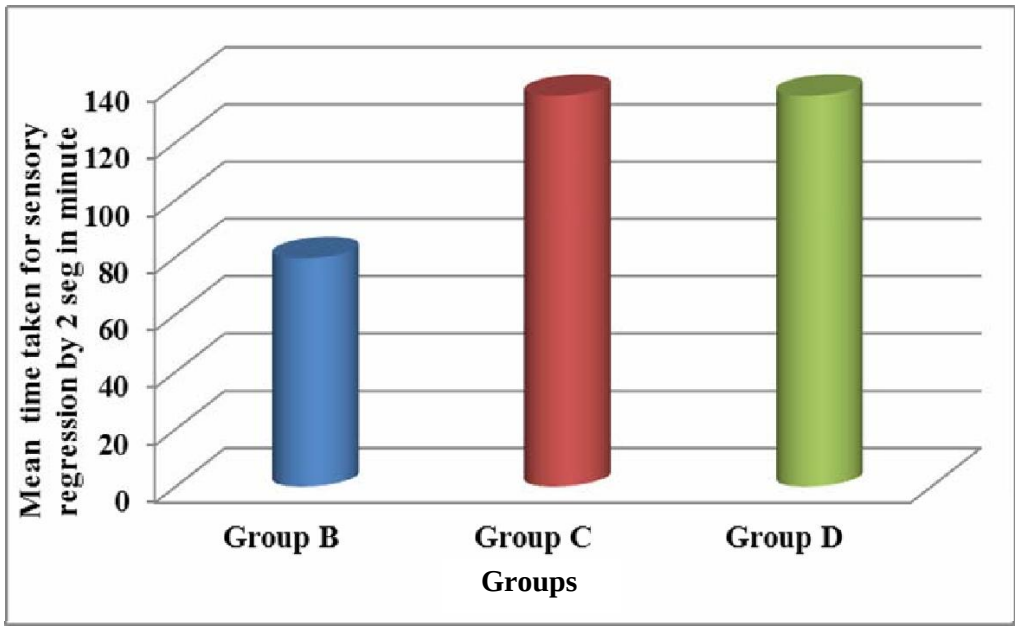


The mean time taken for attaining the maximum sensory blockade is 7.4±1.10mins in group B (control group), 5.90±0.80mins in group C (clonidinegroup) and in group D (dexmedetomidine group) is 5.20±0.7mins . There is a statistically highly significant difference when group B compared with group C and with group D (p=0.000) and there is a statistically significant difference between group C and group D (p=0.001). However there is no clinical significant difference between group C and group D regarding the mean time taken for attaining the maximum sensory blockade.

Table 8 : Mean time taken for regression of sensory block by two segments

Time takenfor two segment sensory regression in mins	RANGE	MEAN	SD	P value B vs C	P value B vs D	P value C vs D
Group B	60-95	79.46	10.16	0.000	0.000	1.000
Group C	120-155	136.33	10.90			
Group D	120-150	136.33	11.59			

Graph 8 : Mean time taken for regression of sensory block by two segments

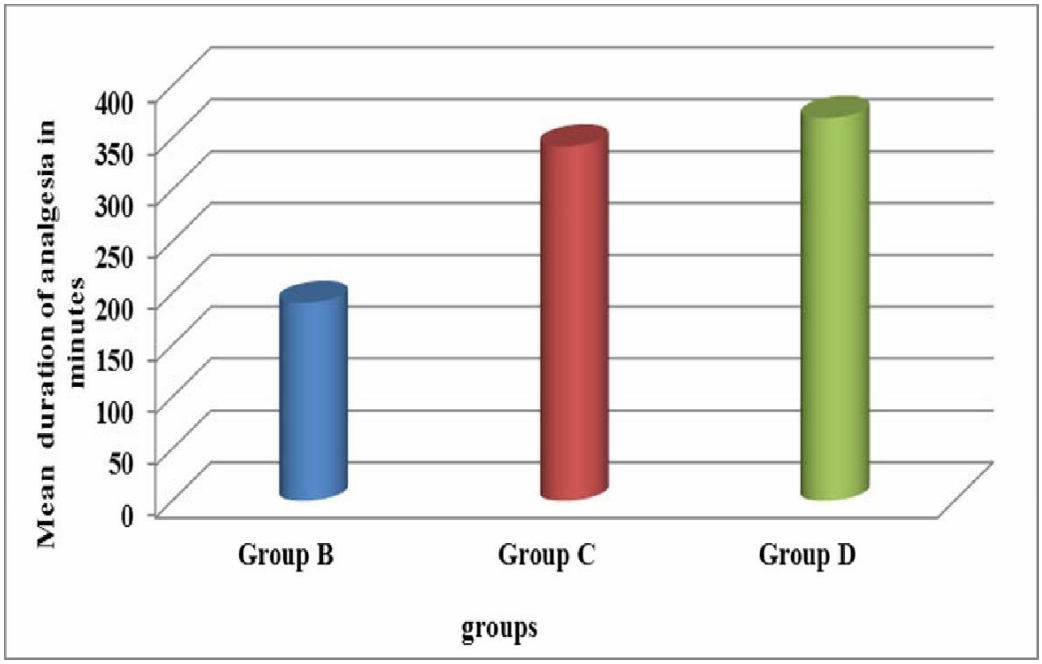


The mean time taken for regression of sensory block by two segments is 79.46±10.16mins in group B (control group),136.33±10.9 mins in group C(clonidine group). and 136.33±10.9 mins in group D (dexmedetomidine group) There is a statistically highly significant difference between group B and group C and between group B and group D (p=0.000). There is statistically no significant difference between group C and group D (p=1.000).

Table 9: Mean duration of analgesia

Duration of analgesia in mins	RANGE	MEAN	SD	P value B vs C	P value B vs D	P value C vs D
Group B	150-240	191	22.94	0.000	0.000	0.001
Group C	300-390	342.33	28.12			
Group D	300-420	369.33	34.13			

Graph 9: Mean duration of analgesia

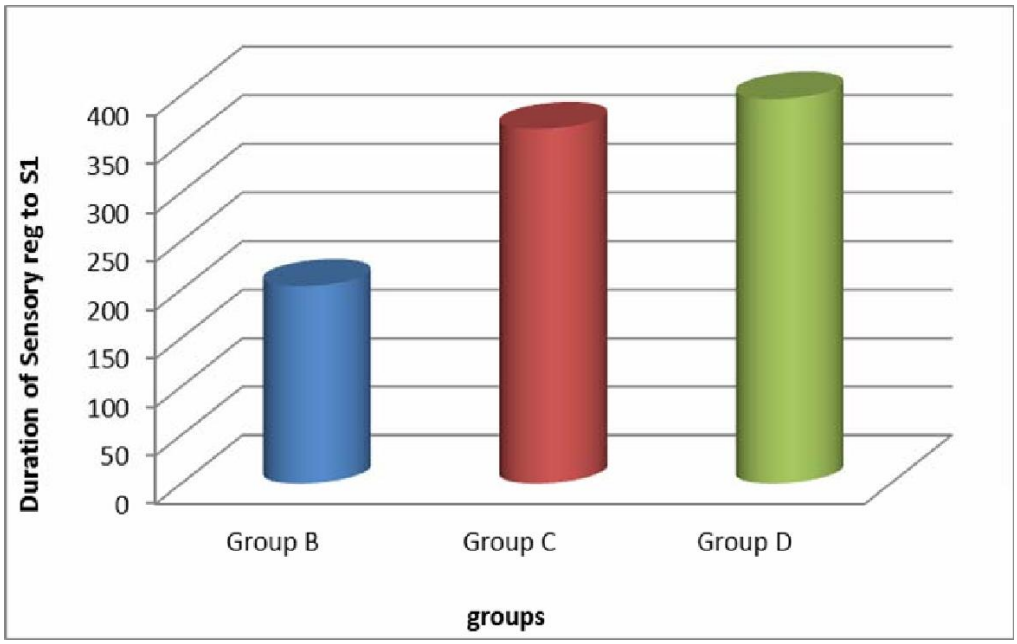


The mean duration of analgesia is 191±22.94 mins in group B (controlgroup), 342.33±28.12 mins in group C (clonidine group) 369.33±34.13 mins in group D (dexmedetomidine group). There is a statistically highly significant difference between group B and group C (p=0.000) and between group B and group D (p=0.000) and between group C and group D (p=0.001). However there is no clinical significant difference between group C and group D.

Table 10: Mean duration of sensory regression to S1

Duration of sensory regin mins	RANGE	MEAN	SD	P value B vs C	P value B vs D	P value C vs D
Group B	170-280	203.33	42.41	0.000	0.000	0.000
Group C	320-410	365	24.60			
Group D	335-445	396.16	30.61			

Graph 10: Mean duration of sensory regression to S1



The mean duration of sensory regression to S1 is 203.33±42.41 mins ingroup B (control group), 365±24.60 mins in group C (clonidine group)396.16±30.61 mins in group D (dexmedetomidine group). There is a statistically highly significant difference between group B and group C and between group B and group D and between group C and group D (p=0.000). However there is no clinical significant difference between group C and group D regarding the mean duration of sensory regression to S1

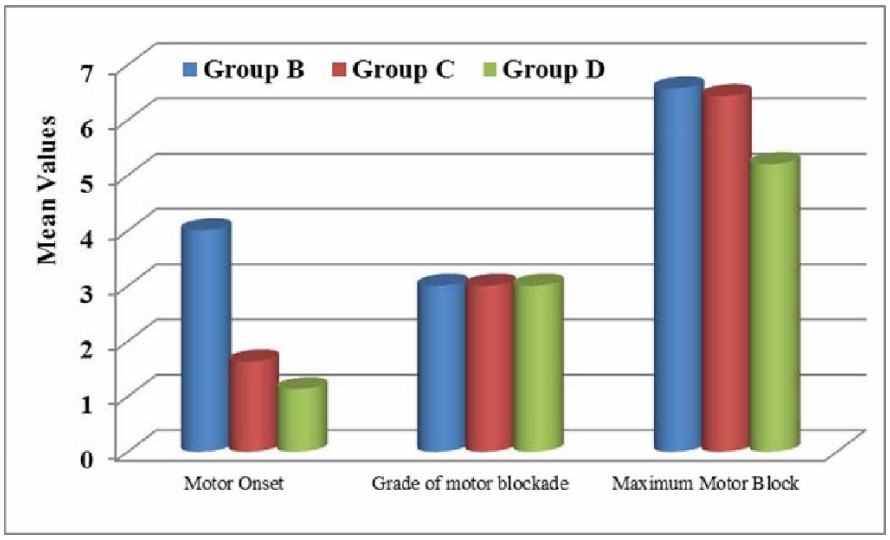
Table 11: Time taken for onset of motor blockade

Time takenfor motoronset in mins	RANGE	MEAN	SD	P value B vs C	P value B vs D	P value C vs D
Group B	3-5	4	0.695	0.000	0.000	0.000
Group C	1-2	1.63	0.49			
Group D	1-2	1.13	0.346			

Table 12: Time taken for maximum motor blockade

Time TakenFor maximum motor block In Mins	RANGE	MEAN	SD	P value B vs C	P value B vs D	P value C vs D
Group B	5-9	6.57	0.935	0.000	0.000	0.000
Group C	5-8	6.43	1.04			
Group D	4-7	5.2	0.887			

Graph 11: Motor characteristics



The mean time taken for the onset of motor blockade is 4.00±0.69mins ingroup B (control group), 1.63±0.49mins in group C (clonidine group) and ingroup D (dexmedetomidine group) is 1.13±0.346mins. There is a statistically highly significant difference between group B and group C and between group B and group D and between group C and group D. (p=0.000). However there is no clinical significant difference between group C and group D.

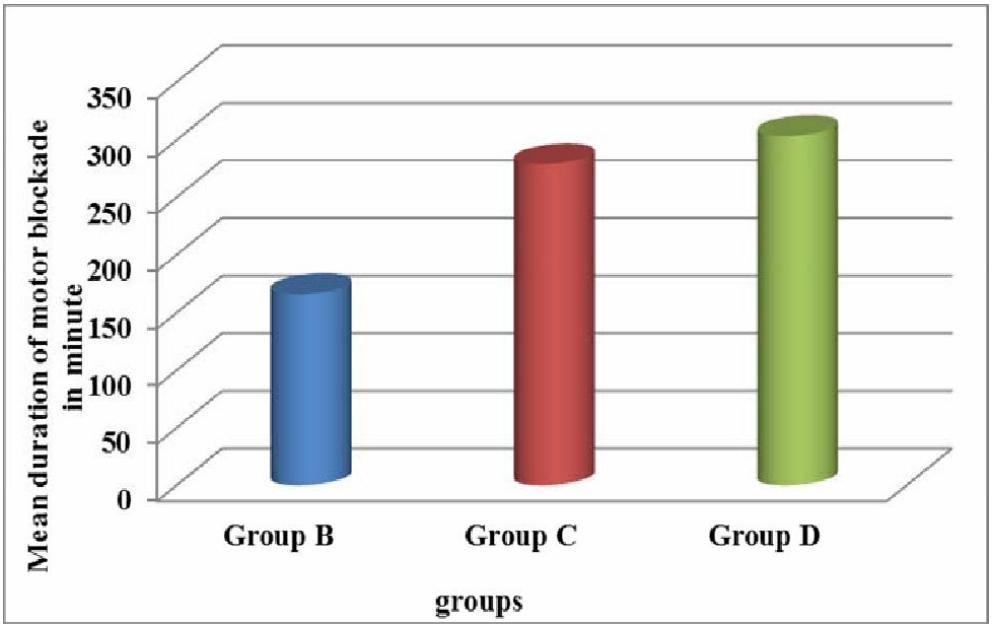
The quality of motor blockade is similar in all the groups (Bromage grade3).

The mean time taken for attaining maximum motor blockade is 6.57±0.93mins in control group, 6.43±1.045mins in clonidine group and 5.20±0.887mins in dexmedetomidine group. There is a statistically highly significant difference between group B and group C and between group B and group D and between group C and group D (p=0.000).

Table 13: Mean duration of motor blockade

Duration of motor block In Mins	RANGE	MEAN	SD	P value B vs C	P value B vs D	P value C vs D
Group B	135-210	166.16	20.95	0.000	0.000	0.003
Group C	240-330	279	24.68			
Group D	240-360	303.66	35.95			

Graph 12: Mean duration of motor blockade

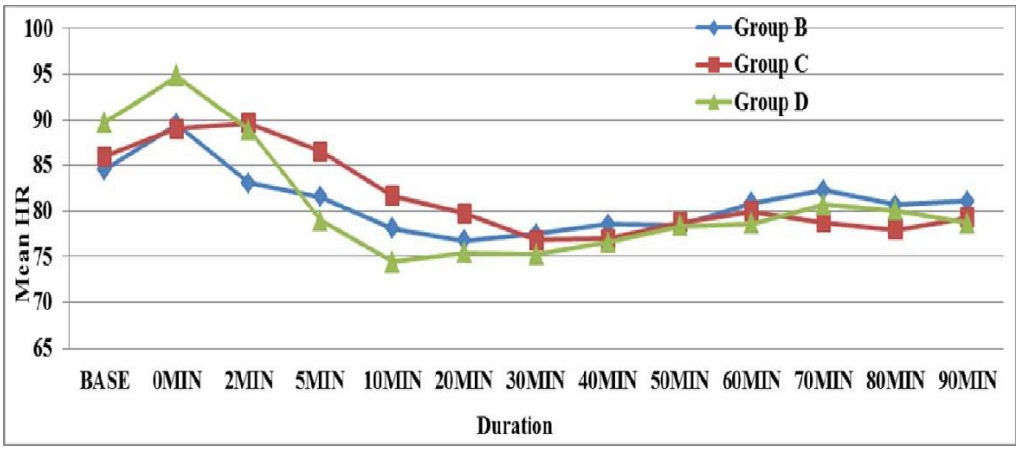


The mean duration of motor blockade is 166.16±20.95mins in group B(control group), 279±24.68 mins in group C (clonidine group). And303.66±35.95mins in group D (dexmedetomidine group) There is a statistically highly significant difference between group B and group C (p=0.000) and between group B and group D (p=0.000). However there is no clinical significant difference between group C and group D.

Table 14: Mean heart rate in bpm at various intervals

HR in min	Group B	Group C	Group D	P Value B vs C	PValue B vs D	P Value C vs D
Basal	84.53± 6.32	86.00±12.3	89.73±17.27	0.563	0.126	0.339
0min	89.53±6.31	89.03±11.82	94.83±16.65	0.839	0.109	0.125
2min	83.06±5.35	89.66±14.74	88.90±18.48	0.286	0.100	0.860
5min	81.53±6.61	86.50±18.19	78.96±17.39	0.164	0.44	0.107
10min	78.06±5.59	81.66±19.47	74.40±13.88	0.330	0.184	0.101
20min	76.73±4.50	79.76±14.01	75.40±11.47	0.270	0.550	0.192
30min	77.46±4.57	76.80±14.65	75.23±9.24	0.814	0.240	0.622
40min	78.53±4.75	76.93±12.68	76.56±9.48	0.520	0.313	0.900
50min	78.46±3.18	78.76±9.35	78.33±11.52	0.860	0.950	0.874
60min	80.90±4.85	79.93±9.39	78.63±11.86	0.125	0.470	0.640
70min	79.26±4.96	78.76±9.26	80.70±11.59	0.560	0.180	0.478
80min	79.66±5.737	77.96±9.89	80.06±11.16	0.535	0.143	0.444
90min	81.06±5.08	79.26±10.45	78.70±9.84	0.304	0.420	0.830

Graph 13: Mean heart rate at various interval in bpm



In the group B (control group) the basal value of mean heart rate is 84.53±6.32 bpm and we observed a decrease in mean heart rate which is maximum of 7.80 bpm from basal value at 20th min (9.32% decrease from basal value)

In the group C (clonidine group) the basal value of mean heart rate is 86 ± 12.34 bpm and we observed a decrease in mean heart rate which is maximum of 9.26 bpm from basal value at 30th min (10.68% decrease from basal value).

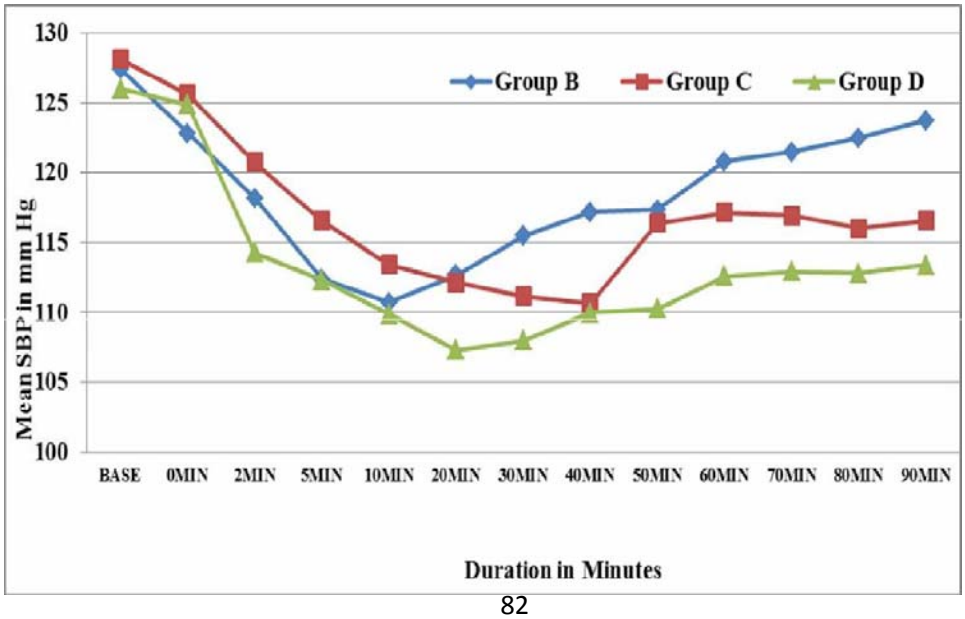
In the group D (dexmedetomidine group) the basal value of mean heart rate is 89.73 ± 17.27 bpm and we observed a decrease in mean heart rate which is maximum of 15.33 bpm from basal value at 10th min (17.08% decrease from basal value).

The mean heart rate from basal to 90th minute recording is statistically not significant between the groups

Table 15: Mean SBP at various time intervals in mm Hg

SBP in min	Group B	Group C	Group D	P Value B vs C	P Value B vs D	P Value C vs D
Basal	127.40±5.308	128.13±7.82	126.00±8.48	0.673	0.447	0.316
0min	122.80±5.18	125.60±9.83	124.86±10.30	0.173	0.330	0.779
2min	118.20±5.88	120.73±9.05	114.30±17.84	0.204	0.485	0.748
5min	112.40±4.76	116.53±8.64	112.33±11.46	0.025	0.977	0.114
10min	110.73±5.023	113.46±8.05	109.86±10.14	0.120	0.676	0.133
20min	112.70±5.22	112.13±11.63	107.33±11.09	0.809	0.020	0.107
30min	115.46±6.078	111.20±12.60	108.00±10.66	0.100	0.002	0.293
40min	117.20±6.35	110.66±12.63	109.96±9.286	0.014	0.001	0.808
50min	117.33±6.48	116.400±10.6	110.26±9.780	0.683	0.002	0.024
60min	120.80±8.49	117.13±9.493	112.60±9.00	0.120	0.001	0.063
70min	121.46±8.01	116.93±8.30	112.933±8.70	0.036	0.000	0.074
80min	122.46±7.137	116.00±9.82	112.80±7.76	0.005	0.000	0.167
90min	123.73±7.73	116.53±9.51	113.40±6.74	0.002	0.000	0.147

Graph 14: Mean SBP at various time intervals in mm Hg



In the group B (control group) the basal value of mean SBP is 127.4±5.3mmHg and we observed a fall in mean SBP which is maximum of 16.66 mmHg from mean basal SBP at 10^{th} min (13.08% fall from basal SBP).In the group C (clonidine group) the basal value of mean SBP is 128.13±7.82mmHg and we observed a fall in mean SBP which is maximum of 17.46mmHg from mean basal SBP at 40^{th} min (13.63% fall from basal SBP).In the group D (dexmedetomidine group) the basal value of mean SBP is 126±8.48mmHg and we observed a fall in mean SBP which is maximum of 18.66mmHg from mean basal SBP at 20^{th} min (14.81% fall from basal SBP).

However this is clinically not significant as hypotension is considered as a fall in systolic blood pressure more than 30% from basal value or SBP less than 90 mmHg.

The mean SBP from basal to 70^{th} minute recording is statistically not significant between group B and group C. The mean SBP from 70th to 90^{th} minute recording is statistically highly significant between group B and group C.

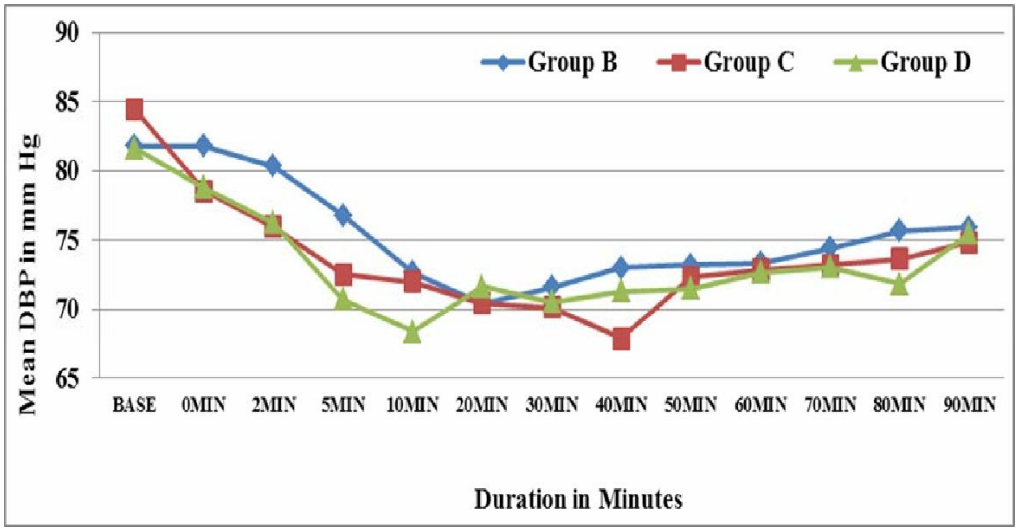
The mean SBP from basal to 10^{th} minute recording is statistically not significant between group B and group D. The mean SBP from 20^{th} to 90^{th} minute recording is statistically highly significant between group B and group D.

The mean SBP from basal to 90^{th} minute recording is statistically not significant between group C and group D.

Table 16: Mean DBP at various time intervals in mm Hg

DBP in min	Group B	Group C	Group D	P Value B vs C	P Value B vs D	P Value C vs D
Basal	81.80±3.12	84.46±6.51	81.67±9.728	0.048	0.943	0.195
0min	81.80±3.12	78.53±7.314	78.80±8.19	0.028	0.066	0.895
2min	80.33±3.11	76.00±5.87	76.26±8.415	0.001	0.016	0.887
5min	76.80±3.34	72.53±8.06	70.73±10.58	0.010	0.004	0.462
10min	72.66±2.98	72.00±8.18	68.33±12.36	0.677	0.067	0.181
20min	70.46±3.98	70.46±6.31	71.66±10.25	10.000	0.553	0.587
30min	71.60±5.10	70.13±7.62	70.53±9.15	0.385	0.579	0.855
40min	73.00±6.09	67.86±.576	71.33±8.276	0.016	0.378	0.138
50min	73.20±5.39	72.33±12.09	71.53±7.13	0.721	0.312	0.756
60min	73.33±5.73	72.86±10.52	72.66±5.68	0.832	0.653	0.927
70min	74.40±5.96	73.23±11.90	73.06±6.51	0.627	0.412	0.946
80min	75.66±4.95	73.63±12.40	71.86±5.940	0.408	0.009	0.485
90min	75.93±6.180	74.86±13.65	75.50±8.182	0.698	0.818	0.828

Graph 15: Mean DBP at various time intervals in mm Hg



In the group B (control group) the basal value of mean DBP is 81.8±3.12mmHg and we observed a fall in mean DBP which is maximum of 11.33mmHg from mean basal DBP at 20th min (13.85% fall from basal DBP).

In the group C (clonidine group) the basal value of mean DBP is 84.6±6.51mmHg and we observed a fall in mean DBP which is maximum of 16.6mmHg from mean basal DBP at 40th min (19.65% fall from basal DBP).

In the group D (dexmedetomidine group) the basal value of mean DBP is 81.6±9.76mmHg and we observed a fall in mean DBP which is maximum of 13.3mmHg from mean basal DBP at 10th min (16.32% fall from basal DBP).

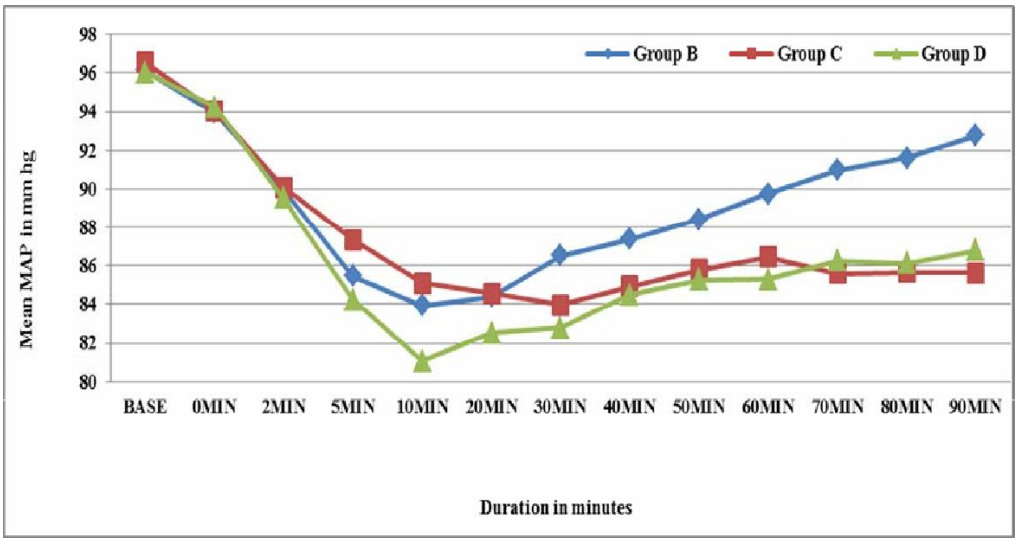
The mean DBP from basal to 5th minute recording is statistically not significant between group B and group C. The mean DBP from 10th minute to 90th minute recording is statistically significant between group B and group C.

The mean DBP from 2th minute to 10th minute and from 20th minute to 90th minute recordingis statistically significant between group B and group D. The mean DBP from basal to90th minute recording is statistically not significant between group C and group D

Table 17: Mean MAP at various intervals in mm Hg

MAP in min	Group B	Group C	Group D	P Value B vsC	P Value B vs D	P Value C vs D
Basal	96.13±6.47	96.53±8.43	96.03±9.05	0.838	0.961	0.826
0min	93.96±4.97	94.89±6.37	94.26±8.32	0.946	0.866	0.917
2min	89.93±4.96	90.06±6.38	89.50±8.49	0.928	0.810	0.771
5min	85.46±4.52	87.36±7.76	84.23±10.50	0.251	0.559	0.196
10min	83.93±4.60	85.10±7.70	81.06±12.40	0.479	0.240	0.136
20min	84.40±4.87	84.56±6.11	82.53±10.45	0.908	0.379	0.362
30min	86.53±3.94	83.96±6.93	82.80±8.762	0.083	0.038	0.570
40min	87.40±5.15	84.93±11.0	84.50±8.02	0.274	0.101	0.863
50min	88.43±4.86	85.80±9.46	85.26±7.36	0.180	0.054	0.808
60min	89.73±5.53	86.46±8.43	85.30±06.22	0.081	0.005	0.544
70min	90.96±4.97	85.60±7.06	86.26±6.564	0.001	0.003	0.706
80min	91.60±5.462	85.67±8.84	86.16±5.123	0.003	0.000	0.808
90min	92.76±5.41	85.63±8.97	86.80±5.162	0.000	0.000	0.540

Graph 16: Mean MAP at various intervals in mm Hg



In the group B (control group) the basal value of mean MAP is 96.3±6.47 mmHg and we observed a fall in mean MAP which is maximum of 12.2mmHg from mean basal MAP at 10^{th} min (12.69% fall from basal MAP). In the group C (clonidine group) the basal value of mean MAP is 96.53±8.43 mmHg and we observed a fall in mean MAP which is maximum of 12.56 mmHg from mean basal MAP at 30^{th} min (13.01% fall from basal MAP).

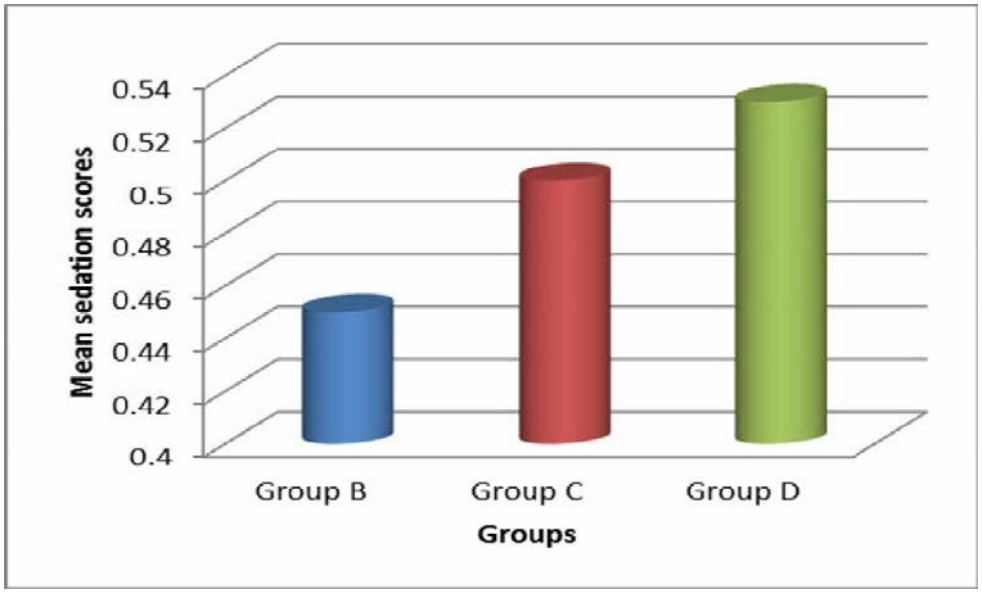
In the group D (dexmedetomidine group) the basal value of mean MAP is 96.03±9.05 mmHg and we observed a fall in mean MAP which is maximum of 14.96 mmHg from mean basal MAP at 30^{th} min (15.58% fall from basal MAP).

The mean MAP from basal to 60^{th} minute recording is statistically not significant between group B and group C. The mean MAP from 70^{th} to 90^{th} minute recording is statistically highly significant between group B and group C.

The mean MAP from basal to 50^{th} minute recording is statistically not significant between group B and group D. The mean MAP from 60^{th} to 90^{th} minute recording is statistically highly significant between group B and group D.

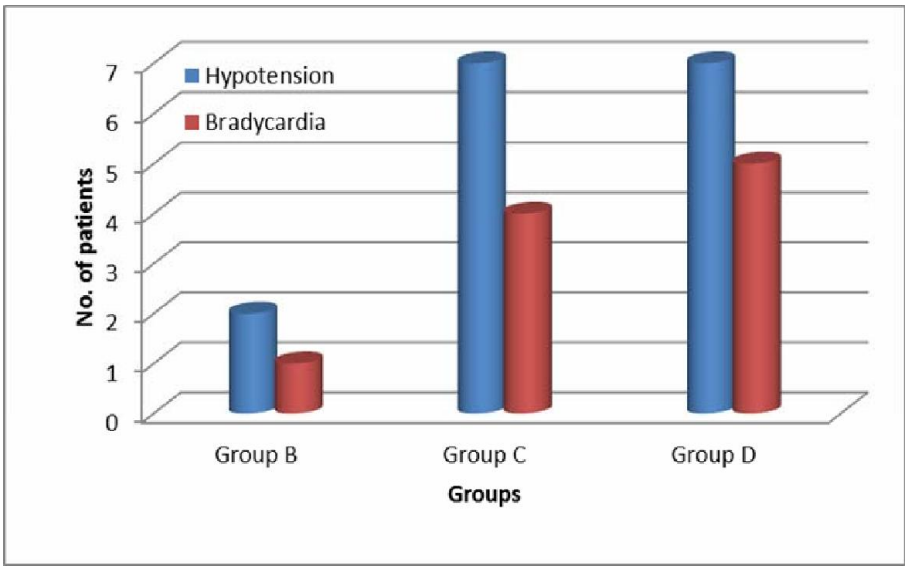
The mean MAP from basal to 90^{th} minute recording is statistically not significant between group C and group D.

Graph 17: Mean sedation scores



The mean sedation score is 0.4±0.49 in group B (control group), 0.50±0.682 in group C (clonidine group), 0.53±0.681 in group D (dexmedetomidine group). There is a statistically highly significant difference between group B and group C and between group B and group D (p=0.000). There is statistically no significant difference between group C and group D (p=0.850).

Graph 18: Hypotension and bradycardia



In group B (control group) two out of thirty patients, in group C (clonidine group) seven out of thirty patients and in group D (dexmedetomidine group) seven out of thirty patients developed hypotension, which is statistically not significant ($p>0.05$). All the patients who developed hypotension could be easily treated with intravenous fluids and vasopressor.

In group B (control group) one out of thirty patients, in group C (clonidine group), four out of thirty patientsand in group D (dexmedetomidine group) five out of thirty patients developed bradycardia, which is statistically not significant ($p>0.05$). All the patients who developed bradycardia were treated by single dose of 0.6 mg of atropine.

DISCUSSION

Subarachnoid block with bupivacaine has been most extensively used for lower limb surgeries today. It has the definitive advantage of profound nerve block produced in a large part of the body by the relatively simple injection. Commonly used local anaesthetics for intrathecal anaesthesia are lignocaine and bupivacaine. Bupivacaine 0.5% heavy has more prolonged action compared to lignocaine.However, a single intrathecal injection of bupivacaine alone provides analgesia for only 2 – 2.5 hours. Other method of prolonging anaesthesia is using a continuous epidural analgesia, which is technically more difficult and more expensive. To overcome this, various adjuvants have been tried and used successfully.

Hence, an intrathecal additive to these local anaesthetics forms a reliable and reproducible method of prolongedduration of anaesthesia and also to provide post-operative analgesia. This technique being simple and less cumbersome has gained a wide acceptance worldwide.A number of adjuvants to local anesthetics for spinal anaesthesia like opioids (fentanyl and buprenorphine), benzodiazepines (midazolam), ketamine and neostigmine have been used. The most common agents used are opioids and they have formed a cornerstone option for the treatment of post-operative pain.[43]

Spinal opiates prolong the duration of analgesia, but they do have drawbacks of late and unpredictable respiratory depression, pruritus, nausea, vomiting and urinary retention.[40,44,45] which requires constant postoperative monitoring and urinary catheterisation. Hence opioids are not ideally suited

for all patients and for ambulant surgeries.

Intrathecal alpha 2 agonists are found to have antinociceptive action for both somatic and visceral pain.[9] So in this context alpha 2 agonists may be a very useful drug along with the local anesthetic0.5% hyperbaricbupivacaine for spinal anaesthesia.[43]

Ninety patients of ASA Grade-I and Grade-II posted for elective lower limb surgeries were selected randomly into 3 groups (n=30). Randomization was done using simple sealed envelope technique.

Demographic data: demographic data comparing age, sex, height, weight showsno statistical difference among the groups.

Hypothesis done before the study: It was hypothesised that both clonidine anddexmedetomidine prolongs the duration of postoperative analgesia compared to the control. There will be no difference regarding the duration of analgesia between clonidine and dexmedetomidine as equipotent doses are used.

Dosages of drugs selected

In our study 50 μg of clonidine and 5 μg of dexmedetomidine were used.**Asano T et al**[47] showed that binding affinity to spinal alpha-2 receptors of dexmedetomidine compared with clonidine is approximately 1:10. In a study conducted by Kanazi GE et al[31]the doses of dexmedetomidine and clonidine used was 3μg and 30μg respectively.

In a study conducted by Sarma et al[48] the doses of dexmedetomidine and clonidine used was 5µg and 50µg respectivelyThe doses of dexmedetomidine and clonidine were found to be equipotent in the ratio of 1:10 and would produce similar effects on the characteristics of bupivacaine spinal anaesthesia.[42,43,35,39] Hence in our study we selected 10 times the dose of dexmedetomidine as clonidine that is 50 µg.

Analysis of data between the groups

Sensory block characteristics

Onset of sensory blockade

In our study the mean time taken for onset of sensory block is 2.8±0.6 mins in the control group, 1.43±0.5mins in the clonidine group and 1.17±0.379mins in the dexmedetomidine group. There is a statistically significant decrease in the onset of sensory blockade in clonidine group and in the dexmedetomidine group compared to the control group.

In a study conducted by Saxena H et al.[37] authors observed the onset of sensory blockade to be 6.57±0.49 mins in control group and 2.58±0.33 mins, 2.54±0.34mins and 2.09±0.89 mins in clonidine group (15 µg, 30 µg and 37.5 µg respectively) and in this study there was a significant reduction in the onset time which concurs with our study. But compared to our study the onset time of sensory block is higher and this could be possibly due to the dose of clonidine used being less than compared to our study.

In a study conducted by Al-Mustafa MM et al.[36] authors observed the

onset of analgesia to be 9.5±3mins in control group and 6.3±2.7 mins and 4.7±2 mins in dexmedetomidine group (5 µg and 10 µg respectively) and in this study there was a significant reduction in the onset time of sensory block which is comparable to our study.

In studies conducted by Dobrydnjov I et al.,[29]Benhamou D et al.,[27]Grandhe RP et al.[34] and De Kock M et al.[28] in clonidine group and study conducted by Shukla D et al[41] in dexmedetomidine group, authors observed a significant reduction in the onset time of sensory blockade which concurs with our study.

In a study conducted by Kanazi GE et al.[31] authors observed the onset of sensory block to be 9.7±4.2 mins in control group, 7.6±4.4 mins in clonidine group and 8.76± 3.7 mins in dexmedetomidine group, which is more than the value in our study and there is no significant reduction in the onset time of sensory blockade .This could be due to the less doses of clonidine and dexmedetomidine used.

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Time taken for maximum sensory blockade

The mean time taken for maximum sensory blockade in the present study is 7.4±1.1 mins in the control group, 5.9±0.8 mins in the clonidine group and 5.2±0.71 mins in dexmedetomidine group. There is a statistically significant decrease in the mean time taken for the maximum sensory blockade in the clonidine group and dexmedetomidine group compared to the control group.

In a study conducted by Saxena H et al.[37] authors observed the mean time to achieve maximum sensory level in control group was 7.3±1.25mins which almost concurs with our study in the control group and 6.8±1.20 mins, 7.4±1.31 mins and 6.7±1.12mins in clonidine groups (15µg, 30µg, 37.5µg respectively)which is more than our study in clonidine group and this may be due to less dose of clonidine used in their study.

Our study is comparable with the study conducted by Shukla D et al[41] who also observed a significant decrease in the meantime taken for the maximum sensory blockade in the dexmedetomidine group.

Maximum level of sensory blockade achieved

In our study the maximum level of sensory blockade achieved is T4. Two out of 30 patients in control group, 8 out of 30 patients in clonidine group and 12 out of 30 patients in dexmedetomidinegroup had T4 level of sensory blockade. There is no statistical significant difference in the maximum level of sensory blockade in the clonidine group and dexmedetomidine group compared to the control group.

In a study conducted by Kanazi GE et al.,[31]the median and range of the peak sensory level reached were T6 in group B(control group), T6.5 in group C(clonidine group) and T6in group D(dexmedetomidine group) without significant differences between the groups.

In studies conducted by Al-Ghanem SM et al.,[35]Gupta R et al.,[38] Gupta R et al.[40] and Eid HEA et al.[39] with dexmedetomidine and study conducted by

Strebel S et al.[30] with clonidine there was no statistically significant difference in the maximum level of sensory blockade which also concurs with our study.

The time taken for regression of sensory block by two segments

The time taken for regression of sensory block by two segments in the present study is 79.46±10.1 mins in the control group, 136.33±10.90 mins in the clonidine group and 136.33±11.590 mins in dexmedetomidine group. There is a statistically significant increase in the mean time taken for regression of sensory block by two segments in clonidine group and dexmedetomidine group compared to the control group.

In a study conducted by Kanazi GE et al.[31] authors observed the time taken for regression of sensory block by two segments to be 80±28 mins in control group, 101±37 mins in clonidine group and 122±37 mins in dexmedetomidine group, where they also found a significant prolongation of two segment regression compared to the control group which compares with our study.

Our study is also consistent with studies done by Dobrydnjov I et al.,[29]Saxena H et al.,[37]Sethi BS et al.[33] in clonidine group and studies done by Gupta R et al.[40] and Eid HEA et al.[39] in dexmedetomidine group. Here authors observed a statistically significant increase in the mean time taken for regression of sensory block by two segments.

The time taken for sensory block to regress to S1

The time taken for sensory block to regress to S1 in the present study is 203.33±42.41 mins in the control group, 365.0±24.6 mins in the clonidine group and 396.16±30.61 mins in the dexmedetomidine group. There is a statistically significant increase in the mean time taken for regression of sensory block to S1 in clonidine group and dexmedetomidine group compared to the control group.

This compares with the study conducted by Kanazi GE et al.[31] where the time taken for regression of sensory block to S1 to be 190±48 mins in control group, 272.±38 mins in clonidine group and 303±75 mins in in dexmedetomidine group which is less than the value in our study. This could be due to the less doses of clonidine and dexmedetomidine used in their study.

In studies conducted by Al-Ghanem SM et al.[68] Al-Mustafa MM et al.[69] Gupta R et al.,[40] Gupta R et al,[38] Eid HEA et al.[39] and Shukla D et al.[41] authors observed a statistically significant increase in the mean time taken for regression of sensory block to S1 dermatome in dexmedetomidine group which concurs with our study.

Duration of analgesia

The mean duration of analgesia in our study is 191±22.9 mins in control group,342.33±28.12 mins in clonidine group and 369.33±34.13 mins in dexmedetomidine group. There is a statistically highly significant increase in

the duration of analgesia in dexmedetomidine and clonidine group compared to the control group.

Our study concurs with the study conducted by Grandhe RP et al.,[34] where authors observed the mean duration of analgesia of 3.8 ±0.7 hours in the control group and 6.3±0.8 hours when using clonidine of 1µg/kg with a mean weight of 60.6±19.4 kg.

In studies conducted by Dobrydnjov I et al.[29] and Benhamou D et al.[27] in the clonidine group the duration of analgesia was 247±75 mins , 153 ± 80 mins respectively. StrebelS et al[30]et andSaxena H at al[37]showed that duration of analgesia with Clonidine Groupwas proportional to its dose.In studies conducted by Gupta R et al.,[38] Gupta R et al.[40]in dexmedetomidine group the duration of analgesia was 478.4±20.9 min and 251.7 ± 30.69 resectively, Eid HEA et at al[39]showed that duration of analgesia with dexmedetomidine Groupwas proportional to its dose.They also observed a statistically significant increase in the mean duration of analgesia.

Motor block characteristics

Onset of motor blockade

In our study the mean time for onset of motor block is 4 ±0.69 mins in control group, 1.63±0.49 mins in clonidine group and 1.13±0.346 mins indexmedetomidine group. There is a statistically highly significant decrease in the mean time for onset of motor blockade in the dexmedetomidine group and clonidine group compared to the control group.

In studies conducted byKanazi GE et al [31].,Al-Mustafa MM et al.,[36]Gupta R et al.[40] and Shukla D et al.[41] in the dexmedetomidine group and studies done by Saxena H et al.[37] and De Kock M et al.[28] in the clonidine group authors observed a significant decrease in the mean time for onset of motor blockade which correlates with our study.

Time taken for maximum motor blockade and grade of motor blockade

The mean time taken for maximum motor blockade in our study is 6.57±0.9 mins in control group, 6.43±1.04 mins in clonidine group and 5.20±0.88 mins in dexmedetomidine group. There is a statistically significant decrease in the time taken for maximum motor blockade in dexmedetomidine and clonidine group compared to the control group. But the grade of motor blockade in the study groups did not differ. All the groups had a motor blockade of Bromage grade 3.

In a study conducted by Kanazi GE et al.,[31]the time taken for maximum motor block was significantly shorter in dexmedetomidine group(13.2±5.6 min) and clonidine group (11.7±5.9 min) than in control group(20.7±10.3 min). There was no significant difference between dexmedetomidine and clonidine group

This concurs with study conducted by Al-Mustafa MM et al.[36] and Shukla D et al.[41] where the time taken for maximum motor blockade is significantly shorter in dexmedetomidine group compared to the control

group.

This is also consistent with the studies done by Sethi BS et al.[33] and Saxena H et al.[37] who observed the complete motor blockade of the lower extremity in all patients in clonidine group.

In study conducted by Dobrydnjov I et al.[29] authors found a better quality of block in all the three clonidine groups, where no supplementation with general anaesthesia for relaxation request from surgeons was needed intraoperatively.

Duration of motor blockade

In our study the mean duration of motor blockade was 166.16±20.95 mins in control group, 279±24.68 mins in clonidine group and 303.66±35.95 mins in dexmedetomidine group. There is a statistically highly significant increase in the duration of motor blockade in dexmedetomidine group and clonidine group compared to the control group.

This compares with study conducted by Kanazi GE et al.[31] where the mean duration of motor blockade is 163±47 mins in control group, 216±35 mins in clonidine group and 250±76 mins in dexmedetomidine group which is less than the value in our study. This could be due to the less doses of clonidine and dexmedetomidine used. Our study almost concurs with the study conducted by Kaabachi O et al.[32] who observed the mean duration of motor blockade to be 252±79mins when using clonidine of 1μg/kg.

Our study also correlates with studies conducted by Al-Mustafa MM et al.,[36]Al-Ghanem SM et al.,[35] Gupta R et al.,[40] Gupta R et al.,[38] Eid HEA et

al.[39] and Shukla D et al.[41] in dexmedetomidine group and in studies conducted by Saxena H et al.,[37]Strebel S et al.,[30]Dobrydnjov I et al.,[29]Sethi BS et al.,[33]Grandhe RP et al.[34] and Benhamou D et al.[27] in the clonidine group, here authors observed a significant increase in the duration of motor blockade.

Hemodynamics

Systolic Blood Pressure

In the control group we observed a maximum fall in mean systolic blood pressure of 16.66 mmHg from mean basal systolic blood pressure at 10th min, in the clonidine group it was 17.46mmHg at 40th min and in the dexmedetomidine group it was 18.66mmHg at 20th min.

There was no statistically significant difference in any of the three groups. However it was found that there was a delay in maximum fall in systolic blood pressure in the clonidine group compared to the dexmedetomidine group and the control group.

Diastolic Blood Pressure

In the control group we observed a maximum fall in mean diastolic blood pressure of 11.33mmHg from mean basal diastolic blood pressure at 20th min, in the clonidine group it was 16.6 mmHg at 40th min and in the dexmedetomidine group it was 13.3 mmHg at 10th min.

There was no statistically significant difference in any of the three groups. However it was found that there was a delay in maximum fall in

diastolic blood pressure in the clonidine group compared to the dexmedetomidine group and the control group.

Mean Arterial Blood Pressure

In the control group we observed amaximum fall in mean arterial pressure of 12.2 mmHg from mean basal MAP at 10^{th} min, in the clonidine group it was 12.56 mmHg at 30^{th} min and in the dexmedetomidine group it was 14.96 mmHg at 30^{th} min.

There was no statistically significant difference in any of the three groups regarding fall in MAP. However it was found that there was a delay in maximum fall in MAP in the clonidine group and the dexmedetomidine group compared to the control group.

In a study conducted by Sethi BS et al.[33]authors observed lowest mean mean arterial pressure (70 mmHg) in clonidine group (1 µg/kg, mean weight 57.93±4.75 kg) which is less than that in our study (76.05±2.54 mmHg).

In a study conducted by Strebel S et al.[30] the maximum decrease in mean arterial pressure was 25%±14%, 26%±12% and 25±13%, who received clonidine 37.5 µg, 75 µg and 150 µg respectively.

In a study conducted by Grandhe RP et al.[34] the incidence of hypotension (fall in mean arterial pressure of>20% of pre-induction value) was 10/15 patients in clonidine group (clonidine 1 µg/kg, mean weight 60.6±19.4 kg) and 8/15 patient in clonidine group (clonidine 1.5 µg/kg, mean weight 62.7±18 kg).

In a study conducted by Al-Ghanem SM et al.[35] authors observed that the hypotension (fall in mean arterial pressure of>30% of pre-induction value) was mild to moderate in both dexmedetomidine and fentanyl group. 4/38 patients in dexmedetomidine group and 9/38 patient in fentanyl group had hypotension but it did not reach a significant difference.

Heart Rate

In the control group we observed a maximum decrease in the mean heart rate of 7.8 bpm from basal value at 20th min, in the clonidine group it was 9.26 bpm at 30th min and in the dexmedetomidine group it was 15.33 bpm at 10th min.There was no statistically significant difference in any of the three groups regarding decrease in the mean heart rate.Five patients in dexmedetomidine group, four patients in clonidine group and one patient in control group had bradycardia which was not statistically significant.Bradycardia was easily reversed with 0.6mg intravenous atropine in all the patients.

In a study conducted by Kaabachi O et al.[32] the authors observed the incidence of bradycardia to be 30% in clonidine (2 µg/kg) group which is higher compared to our study and this may probably due to larger dose of clonidine (2µg/kg) used compared to our study (17.77%).

Our study is consistent with the studies done by Kanazi GE et al.,[31]Al-Ghanem SM et al.[35] and Al-Mustafa MM et al.[36] who observed that there was no significant difference in mean value of heart rate throughout the

intraoperative and postoperative period.

Adverse effects

Sedation

In our study, sedation is assessed using a subjective sedation scale at the end of surgery.In our study, in the dexmedetomidine group 10% of patients had grade 2 sedation, 33.33% had grade 1 sedation and remaining 56.7% had grade 0 sedation and in the clonidine group 36% of patients had grade 2 sedation, 30% had grade 1 sedation and remaining 60% had grade 0 sedation compared to 40% of patients in control group having grade 1 sedation and 60% having grade 0 sedation. No patients in control group had grade 2 sedation and there was a statistical significance in mean sedation scores between control group and clonidine group and between control group and dexmedetomidine group. There was no statistical significance between clonidine group and dexmedetomidine group.

In a study conducted by Saxena H et al.[37] higher incidence of sedation was seen in the clonidine group (37.5 μg) compared to our study. The authors found 90% of the patients were asleep but arousable in the clonidine group (37.5μg).However in a study conducted by Gupta R et al.[40] there was significant difference in mean sedation scores among the groups.

In a study conducted by Strebel S et al.,[30] Al-Ghanem SM et al.[35] and Al-Mustafa MM et al.[36] there was no significant difference in mean sedation scores among the groups.

Hypotension

Two patients in control group, seven patients in clonidine group and seven patients in dexmedetomidine group developed hypotension and were easily managed with intravenous fluids and vasopressor.

Our study is comparable with the studies done by Sethi BS et al.[33]Strebel S et al.[30]Grandhe RP et al.[34] Al-Ghanem SM et al.[35] in which patients had hypotension but there was no significant difference throughout the intraoperative and postoperative period.

Bradycardia

Five patients in dexmedetomidine group, four patients in clonidine group and one patient in control group had bradycardia which was not statistically significant.Bradycardia was easily reversed with 0.6mg intravenous atropine in all the patients.

Our study is consistent with the studies done by Kanazi GE et al.,[31] Al-Ghanem SM et al.[35] and Al-Mustafa MM et al.[36] who observed that there was no significant difference in mean value of heart rate throughout the intraoperative and postoperative period.

SUMMARY

The present study entitled “a comparative study of intrathecal dexmedetomidine and clonidine as an adjuvant to intrathecal bupivacaine in elective lower limb surgeries” was undertaken to evaluate the efficacy and the safety of dexmedetomidine and clonidine as adjuvant to intrathecal hyperbaric 0.5% bupivacaine.

Ninety patients were randomly divided into three groups, each group consisting of thirty patients (n=30):

Group B (control group): received 15mg of 0.5% hyperbaric bupivacaine with0.5 ml normal saline.

Group C (clonidine group): received 15 mg of 0.5% hyperbaric bupivacainewith 50 µg clonidine.

Group D (dexmedetomidine group): received 15mg of 0.5% hyperbaricbupivacaine with 5µg dexmedetomidine.

All patients in the age group 20 to 60 years, of either sex belonging to ASA class I and II posted for elective lower limb surgeries under spinal anaesthesia were included in the study. The onset, maximum level, duration of sensory blockade and motor blockade andhaemodynamic parameters were studied

Results obtained in our study

- The time taken for onset of sensory blockade in group B was 2.8±0.6 mins, in group C 1.43±0.5 mins and in group D 1.17±0.379 mins.
- The time taken for maximum sensory blockade in group B was 7.4±1.1 mins, in group C 5.9±0.8 mins and in group D 5.2±0.71 mins.
- The time taken for two segment regression of sensory blockade in group B was 79.46±10.1 mins, in group C 136.33±10.9 mins and in group D 136.33±11.59 mins.
- The time taken for regression of sensory block to S1 in group B was 203.33±42.41 mins, in group C 365±24.6 mins and in group D 396.16±30.6 mins.
- The duration of analgesia in group B was 191±22.9 mins, in group C 342.33±28.12 mins and in group D 369.33±34.13 mins.
- The time taken for onset of motor blockade in group B was 4±0.69 mins, in group C 1.63±0.49 mins and in group D 1.13±0.346 mins.
- The time taken for maximum motor blockade in group B was 6.57±0.9 mins, in group C 6.43±1.04 mins and in group D 5.2±0.88 mins.
- The duration of motor blockade in group B was 166.16±20.95 mins, in group C 279±24.68 mins and in group D 303.66±35.95 mins.

It was found that there is an early onset of both sensory and motor blockade with prolonged duration of analgesia in dexmedetomidine and clonidine group when compared to the control group with minimal side effects. Small percentage of patients developed significant fall in blood pressure and heart rate which were easily managed without any untoward effects. Seven patients each in dexmedetomidine group and clonidine group and two patients in control group developed hypotension requiring treatment. Five patients in dexmedetomidine group, four patients in clonidine group and one patient in control group developed bradycardia requiring treatment.

More number of patients in the dexmedetomidine group and clonidine group were sedated and was easily arousable. No patient had any respiratory depression, nausea, vomiting or shivering in either of the groups.

In the present study the efficacy of intrathecal dexmedetomidine and clonidine were compared and we noticed that there was significantly shorter onset of motor and sensory block and a significantly longer sensory and motor block than bupivacaine alone.

CONCLUSION

From the present study it can be concluded that the supplementation of bupivacaine with dexmedetomidine 5 μg or clonidine 50 μgin spinal anaesthesia produces significant shorter onset of motor and sensory block with longer duration of sensory and motor block when compared to bupivacaine alone. The 50 μg of clonidine or 5 μg dexmedetomidine dose provides maximum benefit with minimum side effects. These doses has minimal effect on sedation level, heart rate and mean arterial pressure without requiring any therapeutic intervention and hence can be advocated as an adjuvant to bupivacaine in spinal anaesthesia for lower limb surgeries.

BIBLIOGRAPHY

1. Brown DL. Spinal, epidural and caudal anesthesia. 6th ed. Chapter 43. In: Miller's Anesthesia, Miller RD, ed. Philadelphia: Elsevier Churchill Livingstone; 2005. pp. 1653-60.

2. Corbey MP, Bach AB. Transient radicular irritation (TRI) after spinal anaesthesia in day-care surgery. ActaAnaesthesiolScand 1998;42:425–9.

3. Henderson DJ, Faccenda KA, Morrison LM. Transient radicular irritation with intrathecal plain lignocaine. ActaAnaesthesiolScand 1998;42:376–8.

4. Colin VJ. Spinal anesthesia – principles. 3rded. In: Principles of anesthesiology. Philadelphia: Lea &Febiger; 1993. pp. 1445-52.

5. Saxena AK, Arava SK. Current concepts in Neuraxial administration of opiods and non opiods: An overview and future perspectives. Indian J Anaesth 2004;48 (1):13-24.

6. Etches RC, Sandler A N, Daley MD. Respiratory depression and spinal opiods. Can J Anaesth 1989;36:165-85.

7. Morgan M The rationale use of intrathecal and extradural opiods. Br J Anaesth 1989;63:165-88.

8. Crone L-AL, Conly J M, Clark KM. Crichlow AC, Wardell CC, Zbitnew A et al. Recurrent herpes simplex virus labialis and the use of epidural morphine in obstetric patients. AnesthAnalg1988;67:318

9. Eisenach James C, De Kock Marc, Klimscha, Walter. Alpha sub 2- adrenergic agonist for regional anesthesia. A clinical review of clonidine. Anesthesiology 1996;85 (3):655-74.

10. Dobrydnjov I, Axelsson K, Samarutel J, Holmstrom B. Postoperative pain relief following intrathecal bupivacaine combined with intrathecal or oral clonidine. ActaAnaesthesiolScand 2002 Aug;46 (7):806-14

11. Dobrydnjov I, Samarutel J. Enhancement of intrathecallidocaine by addition of local and systemic clonidine. ActaAnaesthesiolScand 1999;43:556-62.

12. Filos KS, Goudas LC, Patroni O, Polyzou V:Hemodynamic and analgesic profile after intrathecal clonidine in humans: A dose-response study. Anesthesiology 1994;81:591-601.

13. Ralph Getler, Clieghton H Brown, Mitchel H, Silvius N. Dexmedetomidine: a novel sedative analgesic agent. Baylor University Medical Centre Proceedings. 2001;14(1).

14. Harold Ellis, Anatomy for anaesthetist: Blackwell publishing 8th edition:Part 3, page 95-136.

15. Quinn H. Hogan, Anatomy of Neuraxis: Cousins and Bridenbaug'sneuraxial blockade in clinical anaesthesia and pain medicine: Lippincott Williams and Wilkins chapter 9, page 181-212.

16. B.D, chaurasia's human anatomy: volume 3; chapter 31, page 383-384

17. Robert K. stoelting, Simon C. Hillier pharmacology and physiology inanaesthesia practice. Lippincott Williams and Wilkins: chapter 7, page 179-207.

18. Hamilton CA. The role of midazoline receptors in blood pressure regulation. PharmacolTher 1992;54:231

19. Guyenet PG, Cabot GB. Inhibition of sympathetic preganglionic neurons by catecholamines and clonidine: Mediation by an alpha adrenergic receptor.Neuroscience 1981;1:908.

20. Atkinson RS, Rushman GB, Davies NJH, "Lee's synopsis of Anaesthesia", Spinal analgesia: intradural& extradural in Regional techniques. 11th edition. Butterworth-Heinemann Ltd Oxford; 1993: 698-704.

21. Madhur Gupta, NeeruGoyal, Pain update 2005 Neurophysio-pharmacodynamics, Neuropathic and chronic pain and multimodal approach to pain management, Published by MSRMC and ISPRAT, 2005;19-25.

22. Sunil Sharma, pain update 2005 Neurophysio-pharmacodynamics, Neuropathic and chronic pain and multimodal approach to pain management, Published by MSRMC and ISPRAT,2005:71-81.

23. Melzack R and Wall PD, pain mechanisms: a new theory, science, 150:971-979.

24. J.G.Reves,PeterS.A.Glass: Intravenous anestheticsDexmedetomidine: Miller's Anesthesia 7th ed: Churchill Livingstone Elsevier 751-757.

25. Edward Morgan. Jr. adjuvants to anaesthesia Morgan 4th Edition McGraw Hill Publication:Chapter 15 page 284.

26. Stoelting RK, Hillier SC, Antihypertensive drugs. 4th ed. Chapter 15. In: Pharmacology & Physiology in Anesthetic Practice: Philadelphia: Lippincott Williams & Wilkins; 2006. pp. 340-4.

27. Benhamou D, Thorin D, Brichant JF, Dailland P, Milon D, Schneider M. Intrathecal clonidine and Fentanyl with hyperbaric bupivacaine improves analgesia during cesarean section AnesthAnalg 1998;87:609-13.

28. De Kock Marc, Gautier, Philippe, Fanard, Luc Hody, Jean, LavandHomme, Patricia: Intrathecalropivacaine and clonidine for ambulatory knee arthroscopy: A dose responses duty Anesthesiology:April 2004;94:574-578.

29. Dobrydnjov I, Axelsson K, Thorn SE, Matthieson P, Klockhoff H, Holmstroma B and Gupta A: Clonidine combined with small dose bupivacaine during spinal anesthesia for inguinal herniorrhaphy: A randomized double-blinded study. AnesthAnalg 2003;96:1496-503.

30. Strebel S, Gurzeler JA, Schneider MC, Aeschbach A, Kindler CH. Small dose intrathecal clonidine and isobaric bupivacaine for orthopedic surgery. A dose response duty. AnesthAnalg 2004;99:1231-8.

31. Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al JazzarMD,Alamedine MM, Al- yaman R, et al. effect of low dose dexmedetomidine or clonidine on the characteristics of spinal block.ActaAnaesthesiolscand. 2006;50:222-7.

32. Kaabachi O, Zarghouni A, Ouezini R, Abdelaziz AB, Chattaoui O, Kokki H. Clonidine 1 mg/kg is a safe and effective adjuvant to plain bupivacaine in spinal anesthesia in adolescents.

33. Sethi BS, Samuel M, Sreevastava D. Efficacy of Analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine. Indian Journal of Anaesthesia 2007;51 (5):415-9.

34. Grandhe RP, Wig J, Yaddanapudi L N:Evaluation of bupivacaine-clonidine combination for unilateral spinal anesthesia in lower limb orthopedic surgery. J AnaesthClinPharmacol 2008;24 (2):155-8.

35. Al-Ghanem SM, Massad IM, Al-Mustafa MM, Al-Zaben KR, Qudaisat IY, Qatawneh AM, et al. Effect of Adding Dexmedetomidine versus Fentanyl to Intrathecal Bupivacaine on Spinal Block Characteristics in Gynecological Procedures: A Double blind Controlled Study. American Journal of Applied Sciences 2009;6(5):882-7.

36. Al-Mustafa MM, Abu-Halaweb SA, Aloweidi AS, Mursbidi MM, Ammari BA, Awawad ZM, et al. Effect of Dexmedetomidine added to spinal Bupivacaine for Urological procedures. Saudi Med J 2009;30(3):365-70.

37. Saxena H, Singh SK, Ghildiyal S. Low dose intrathecal clonidine with bupivacaine improves onset and duration of block with

haemodynamic stability. The Internet Journal of Anaesthesiology 2010;23:1.

38. Gupta R, Bogra J, Verma R, Kohli M, Kushwaha JK, Kumar S. Dexmedetomidine as an intrathecal adjuvant for postoperative analgesia. Indian J Anaesth 2011;55(4):347-51.

39. Eid HEA, Shafie MA, Youssef H. Dose-Related Prolongation of Hyperbaric Bupivacaine Spinal Anesthesia by Dexmedetomidine. Ain Shams Journal of Anesthesiology 2011 Jul;4(2):83-95.

40. Gupta R, Verma R, Bogra J, Kohli M, Raman R, Kushwaha JK. A Comparative study of intrathecal Dexmedetomidine and Fentanyl as adjuvants to Bupivacaine. J AnaesthesiolClinPharmacol 2011;87:835-41.

41. Shukla D, Verma A, Agarwal A, Pandey HD, Tyagi C. Comparative study of intrathecal dexmedetomidine with intrathecal magnesium sulfate used as adjuvants to bupivacaine. J AnaesthClinPharmacol 2011;27:495-9.

42. Post C, Gordh T, Minor G, Archer T, Freedman J. Antinociceptive effects and spinal cord tissue concentrations after intrathecal injection of guanfacine or clonidine intorats. AnesthAnalg 1987;66:317-24

43. Kanazi GE, Aonad MT, JabbourKhonry SI, AJ-Jazzar MD, Alameddine MM, AL-Yaman R, et al. Effect of small dose

dexmedetomidine or clonidine on the characteristics of bupivacaine – spinal block. ActaAnaesthesiolScand 2005; 50:222-7.

44. Filos KS, Goudas LC, Patroni O, Polyzou V. Intrathecal Clonidine as a sole analgesic for pain relief after cesarean section. Anesthesiology 1992; 77:267-74.

45. Shukla D, Verma A, Agarwal A, Pandey HD, Tyagi C. Comparative study of intrathecal dexmedetomidine with intrathecal magnesium sulfate used as adjuvants to bupivacaine. J AnaesthClinPharmacol 2011;27:495-9.

46. Kalso E, Poyhia R, Rosenberg P. Spinal antinociception by dexmedetomidine, a highly selective α_2-adrenergic agonist. PharmacolToxicol 1991;68:140-3.

47. Asano T, Dohi S, Ohta S, Shimonaka H, Iida H. Antinociception by epidural and systemic alpha 2 adrenoreceptor agonists and their binding affinity in rat spinal cord and brain. AnesthAnalg 2000;90:400-7.

48. Sarma J, Narayana PS, GanapathiP,Shivakumar MC. A comparative study of intrathecal clonidine anddexmedetomidine on characteristics of bupivacaine spinal blockfor lower limb surgeries. Anesth Essays Res 2015;9:195-207

PROFORMA

NAME: AGE: SEX:

IP NO:

HT: WT:

DIAGNOSIS:

SURGERY:

ASA Physical Status:

Co-Morbidity:

Any drugs:

GROUP:B/C/D

SUB ARACHANOID BLOCK:

Pre- OP:

PR: SBP: DBP: MAP: SPO2:

SENSORY BLOCKADE

Time of onset (T10):

Time for maximum sensory blockade and level:

Time for two dermatome sensory regression:

Duration of sensory blockade:

MOTOR BLOCKADE

Time of onset (Bromage 1):

Time for maximum motor blockade (Bromage 3):

Duration of motor blockade:

Level of sedation (sedation scale)

Duration of analgesia:

HAEMODYNAMICS:

TIME(MIN)	PR	SBP	DBP	MAP	SP02
0					
2					
5					
10					
20					
30					
40					
50					
60					
70					
80					
90					

SIDE EFFECTS AND COMPLICATIONS:

Nausea/vomiting:

Shivering:

Hypotension (ephedrine required):

Bradycardia (atropine required):