"EFFICACY OF INTRAMUSCULAR EPHEDRINE IN REDUCING THE INCIDENCE OF HYPOTENSION AFTER SPINAL ANAESTHESIA"

By

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IN

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Dr Nagaraj S Kalla

LIST OF ABBREVATIONS USED

Abbreviation	Full form
ASA	American society of Anaesthesiologists
CSF	Cerebro-spinal fluid
SAB	Sub-arachnoid block
MAP	Mean arterial pressure
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
HTN	Hypertension
DM	Diabetes
SVT	Supra-Ventricular Tachycardia
MAO	Mono-amino Oxidase
CNS	Central Nervous System
IV	Intravenous
IM	Intramuscular
HR	Heart rate
BP	Blood pressure
MG	Milligram
SD	Standard deviation
mmHg	Millimeters mercury
Min	Minute

ml	Milliliter
PS	Physical status
RCT	Randomized Control Trial
Vs	Versus

ABSTRACT

"EFFICACY OF INTRAMUSCULAR EPHEDRINE IN REDUCING THE INCIDENCE OF HYPOTENSION AFTER SPINAL ANAESTHESIA"

BACKGROUND

Since its introduction into the clinical practice, spinal anaesthesia remains one of the basic and important technique in the modern period. But also associated with significant adverse effects like Hypotension, Bradycardia, post-spinal headache. Prevention of post spinal hypotension still continues to be a major problem faced by Anaesthesiologists.

Several options have been tried to prevent spinal induced hypotension like preloading with colloid/crystalloids, Leg elevation, premedication with IV Atropine 0.6mg, IM Glycopyrolate, Ondansetron, Vasopressors.

In spite of many modes of treatment which we use daily for treating spinal induced hypotension in our Hospital, problem still continues.

Therefore this study, was conducted in our hospital to observe the outcome of prophylactic intramuscular ephedrine and to reduce the further incidence of spinal induced hypotension.

OBJECTIVES

To observe the outcome of prophylactic IM ephedrine on intraoperative hemodynamic changes after spinal anaesthesia. To see the incidence of hypotension after spinal anaesthesia.

MATERIALS AND METHODS

This study is a prospective randomized controlled study conducted on 108 patients posted for elective lower abdominal and lower limb surgeries under spinal anaesthesia. Patients are then randomly divided into two groups:

Group A: received IM Ephedrine 30mg (1ml), 10 minutes before SAB.

Group B: received Injection of Normal saline as placebo 10 minutes before SAB.

Patients were monitored for intra-hemodynamic changes, to see the incidence of hypotension in both the groups and also to see any adverse side effects during intraoperative period.

RESULTS

Incidence of Hypotension was more in group B and proven to be statistically significant when compared to ephedrine group from 2 – 20 minutes.

The numbers of patients receiving the rescue vasopressor therapy was higher among in group B. There was no side effects observed in both the groups.

KEYWORDS: Intramuscular, Ephedrine, Spinal Anaesthesia, Hypotension.

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INTRODUCTION

INTRODUCTION

Spinal anaesthesia is one of the basic and important technique since it came into the daily practice. It is widely practiced regional anaesthesia technique for many lower abdominal and lower limb surgeries[1].

Advantage lies in its simplicity of administration, efficacy of the block, lesser side effects, good post-operative analgesia and decreasing blood loss while maintaining better perioperative hemodynamic stability. But also associated with significant adverse effects like hypotension, bradycardia, post-spinal headache [2].

Despite of its fast revival, prevention of post spinal hypotension still continues to be a major problem faced by Anaesthesiologists. Fall in Systolic Blood pressure by 30% from the baseline record is considered as hypotension.

Incidence of hypotension can vary depending upon the level of blockade[3], type of blockade, type and site of operation, age of the patient, comorbidities and Blood volume status.

Many methods came into existence to counter the spinal induced hypotension like preloading with colloid/crystalloids[4,5,6], leg elevation with compression bandages[7], stockings or inflatable boots, premedication with IV Atropine 0.6mg[8], IM Glycopyrolate[9], Ondansetron[10], Vasopressors[11].

For treating the hypotension after spinal anaesthesia, vasopressors are the choice. Effect of vasopressor should reduce the rise in level of sympathetic blockade, which is difficult to obtain because the alpha and beta adrenergic activities may act independently during blockade.

The sequel in the activity of sympathetic system may be due to inhibiting cardiac fibers, inhibition in the lower body and increased activity in the upper body or inhibition of catecholamine release from the adrenal medulla [12].

The Vasopressors used commonly (phenylephrine, ephedrine) have systemic effects and may have effects on organs, vascular system or fetus. One of the vasopressor is Ephedrine, which is commonly used drug in the treatment of hypotension following spinal anaesthesia. Its mechanism involves stimulating both alpha and beta adrenergic receptors and releases norepinephrine from sympathetic neurons[13].

It has slow onset and long duration of action than phenylephrine. It does not cause uterine vasoconstriction further preserving utero-placental blood flow while maintaining maternal blood pressure.

By increasing cardiac output and heart rate due to its action on beta-1 adreno receptor, it maintains arterial pressures and having less chance of utero-placental insufficiency even if we plan to go for general anaesthesia in case failure of spinal blockade[14].

Reactive increase in HR, BP in underweight patients and inadequate control of hypotension in overweight patients

are some studies observation. IM dose less than 25 mg is ineffective to prevent decrease in BP and 50 mg is associated with increased incidence of reactive rise in BP and fetal acidosis are some of the observations made by several studies[15].

When compared mephentermine, ephedrine and phenylephrine are equally effective in preventing hypotension from SAB. Requirement of less maintenance dose with ephedrine is observed[16].

In comparison, the use of phenylephrine was associated with better fetal acid-base status, but the risk of maternal bradycardia (responsive to atropine) was larger than in those women given ephedrine[17].

Daily for treating spinal induced hypotension in our hospital many treatment options have been tried, but problem still continues. This study was conducted and proven to be effective against spinal induced hypotension earlier, but found to be controversial in pregnant patients (due to its inconclusive effect on fetal outcome, this study is avoided in pregnant patients).

Therefore this study, conducted in our hospital in patients undergoing elective lower abdomen and lower limb surgeries under spinal anaesthesia to observe the outcome of prophylactic intramuscular ephedrine[13] and to reduce the further incidence of spinal induced hypotension.

OBJECTIVES

AIMS AND OBJECTIVES

- To observe the outcome of prophylactic IM ephedrine on the hemodynamic changes after spinal anaesthesia.
- To mark the incidence of spinal induced hypotension.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

HISTORY OF SPINAL ANAESTHESIA[18,19,20]

The local analgesia concept started by Koller with demonstrating the anaesthetic properties of cocaine eye drops in 1884 and in 1885, neural blockade by Halsted.

In the year 1885, Coining introduced the term "Spinal anaesthesia".

The technique of lumbar puncture was described by Quincke in 1891.

Publications subjecting to spinal anaesthesia for surgical procedures were done in 1899 by Bier, later by Tuffier. Bier applied the concept for surgeries on the lower limbs and to relieve pain of sarcoma of the leg in a young man was done by Tuffier.

In 1900 Kries, used spinal analgesia for caesarean section. In 1903, Adrenaline was added to prolong the anaesthetic effect by Dowitz.

In later part, trials were done to achieve higher level of blockade and also to make it lighter than cerebrospinal fluid, local anaesthetic was added with alcoholic mixture.

Hypotension caused due to the high level of blockade lead to introduction of vasopressor (ephedrine) in 1927 by Ockerbland and Dillon. Later passed on to western medicine by Chenn and Schmidt.

A.F. Ekenstein synthesized Bupivacaine in the year 1957 and practiced it in regional blocks in coming years.

ANATOMY [18,21,22,23]

According to Corning - "One who practices spinal anaesthesia should have the detailed knowledge about the skeleton, specially the lumbar vertebrae"[18].

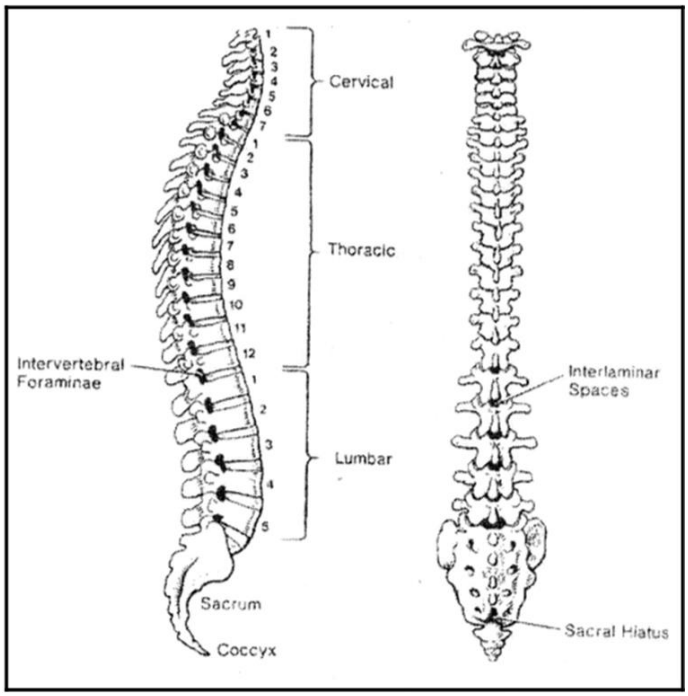


Fig. l - Vertebral Column, Lateral and Posterior view [19]

Successful spinal anaesthesia depends on how well we know the vertebral column anatomy and the contents it possesses.

The vertebral column have 33 vertebrae:

- **Cervical -** 07
- **Thoracic** -12
- **Lumbar -** 05
- **Fused sacral -** 05
- **Coccygeal -** 04

(Spaced with 23 intervertebral discs in between)

The thoracic and sacral are the primary curves, which are convex posteriorly and are present since birth. The cervical and lumbar are the secondary curves which are convex anteriorly develop after birth due to the growth differences of intervertebral discs. These curves have a role on the spread of the local anaesthetic solution injected, in turn determining the level of blockade.

LUMBAR VERTEBRAE

Typical ones are the first four vertebrae and have common features and fifth one is atypical. Identification is made easy due to its large size and due to costal facets absence on the body of the vertebrae.

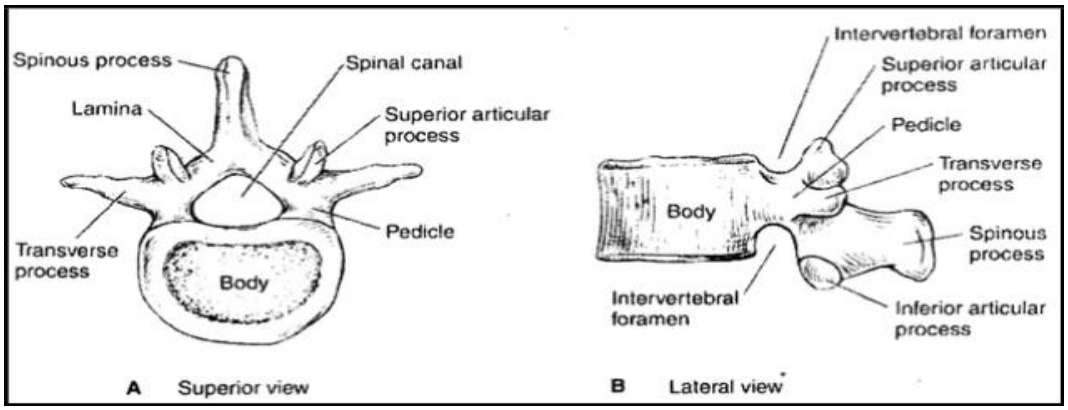


Fig.2 - Features of lumbar vertebrae[23]

Typical lumbar vertebrae is formed of:

- Typical large kidney shaped body.
- Compared to thoracic, it has triangular vertebral foramen but smaller compared to cervical. Two pedicles, directed backwards from the upper part of the body.
- The lamina directed backwards and medially to complete the vertebral foramen posteriorly.
- Thick, broad, quadrilateral spinous process and directed backwards.

- Thin and tapering transverse process.
- Two upper and two lower articular processes which prevent rotation but will have limited flexion and extension.

Fully flexed spine will show obliteration of the cervical and lumbar curves, and in supine position the 3rd lumbar vertebrae is the first point of lumbar spine curve and the fifth thoracic is the lowest point of lowest of dorsal curve.

Therefore hyperbaric solutions instilled at the third lumbar vertebrae will spread into both cranially and caudally from it.

INTERVERTEBRAL DISC

One fourth the length of vertebral column is formed by this, thickest at cervical and lumbar regions. Disc is made up of outer part by collagenous annulus fibrous and inner part by nucleus pulposes.

Its function is to acts as shock absorber making sure to have the equal compression force distribution and providing flexibility to the vertebral column.

THE VERTEBRAL CANAL

Bounded anteriorly by bodies of the vertebrae and intervertebral discs, posteriorly by the lamina, ligamentum flavum and spinous process and inter-spinous ligament, laterally by pedicles and also by laminae, size and shape varies with larger at cervical and lumbar region.

THE VERTEBRAL LIGAMENTS

The series of ligaments holds the vertebrae together, also assists in protecting the spinal cord. It includes:

(a) Anterior longitudinal.

(b) Posterior longitudinal

(c) The ligamentum flavum

(d) The Inter-spinous ligament

(e) The Supraspinous ligament connects the apices of spinous processes. Extends from the 7th cervical vertebra to the sacrum.

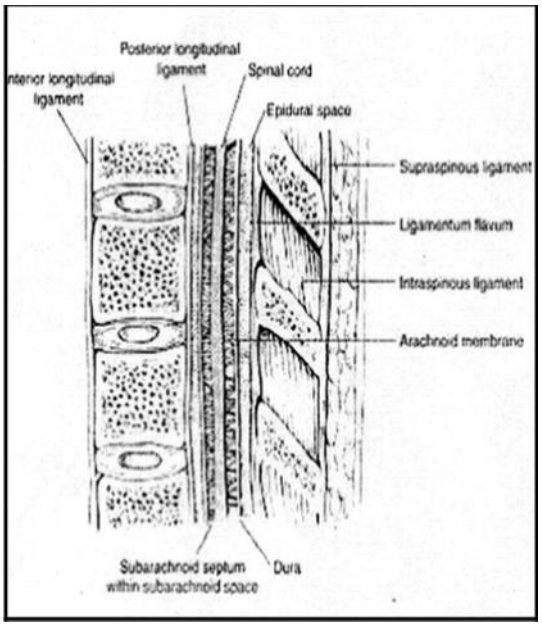


Fig 3 – showing the sagittal section taken through lumbar vertebrae[22]

THE SPINAL CORD

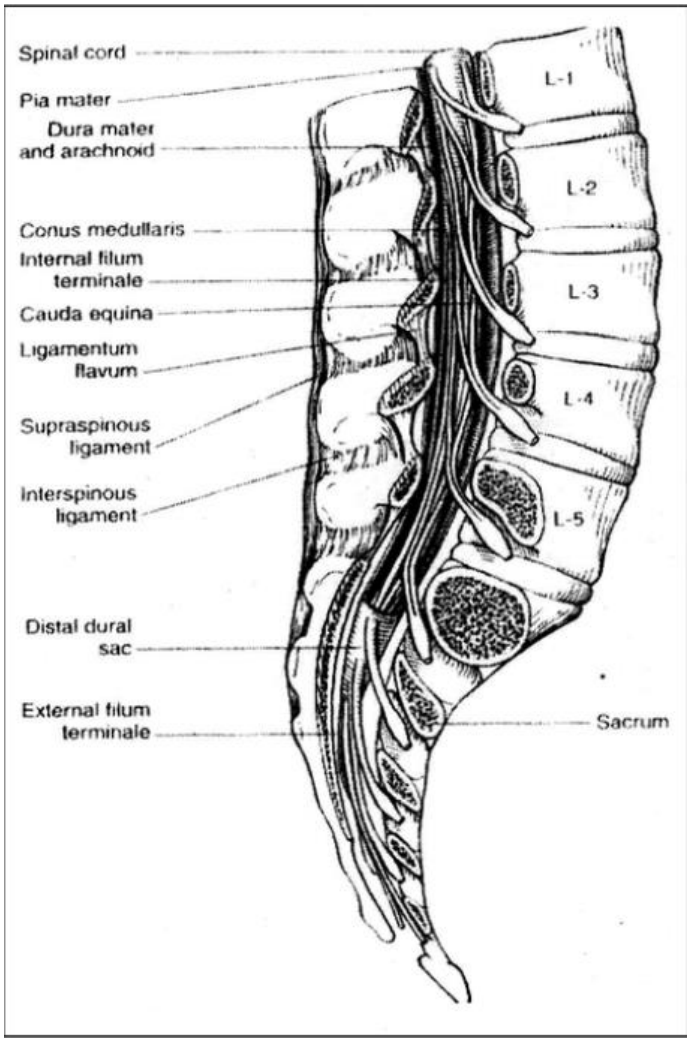


Fig. 4 - Spinal Cord[24]

It is the elongated, cylindrical part of CNS. It occupies the upper two third of the vertebral canal. Its length is about (42- 45) cm. It starts from the upper part border of the atlas to the lower rim of the 1st lumbar or upper rim of the 2nd lumbar vertebrae. The tapering lower border is called as Conus medullaris. Filum terminale is the continued apex of the conus.

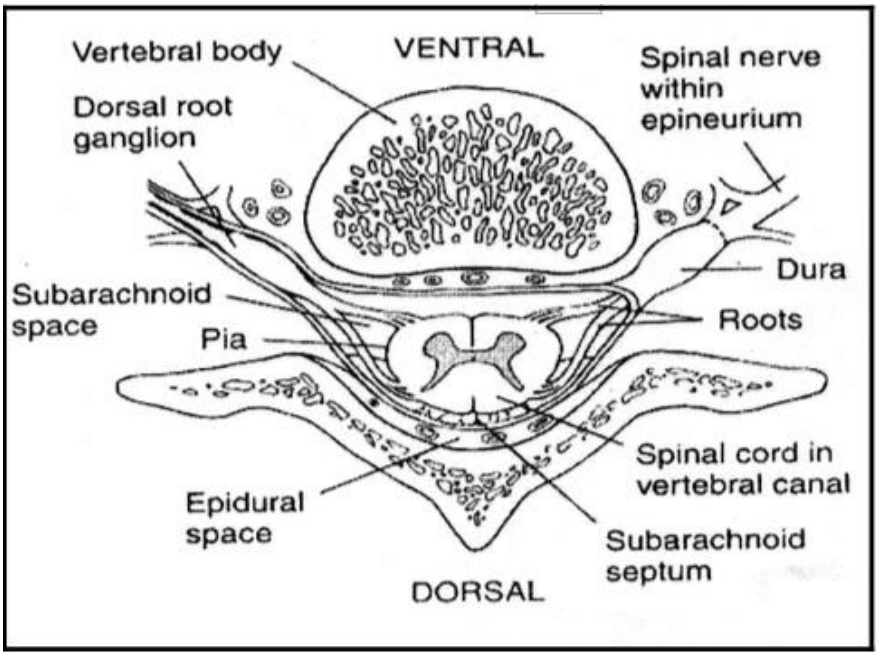


Fig. 5 – showing the exit of Spinal nerves[22]

Spinal nerves a total of 31 from the spinal cord emerges in the form of pair. Spinal nerve trunks are formed by uniting the anterior and posterior roots of the spinal nerves joining intervertebral foramina.

Nerves arise above their respective vertebra at the cervical level, but they exit below their vertebra, starting at first thoracic vertebra. From the spinal cord, nerve roots emerging and exiting from the vertebral foramina at the same level that is at the cervical and upper thoracic level.

These spinal nerves at the lower part forms the cauda equina. Hence for avoiding the needle trauma to cord it is better to perform a lumbar puncture after the first lumbar vertebra in an adult.

THE SPINAL MENINGES

The three membranes cover the spinal cord, which are as follows:

(a) Duramater: consisting of two layers, the continuation of the cerebral dura made up of dense fibrous tissue and periosteal lining the vertebral canal. Potential extradural space lies in between these two.

The extradural space extends from foramen magnum above to second sacral vertebrae below. Dural fibers run longitudinally, therefore it is important to direct the spinal needle bevel, so as to "split" the fibers rather than "cutting" them, which reduces the incidence of headache after lumbar puncture.

(b) Arachnoid matter: is adherent to the duramater. The subdural space is the space lying in the middle of dura and arachnoid.

(c)Piamater: thin vascular membrane closely layering the spinal cord. CSF lies between the pia mater and the arachnoid mater in the subarachnoid space.

BLOOD SUPPLY TO SPINAL CORD

The blood supply is from the single anterior spinal artery and paired posterior spinal arteries.

The two third of the cord anteriorly is supplied by the anterior spinal artery arising from the vertebral artery and supplies.

The one third of the cord posteriorly is supplied by the posterior spinal artery arise from the posterior-inferior cerebellar arteries.

The posterior and anterior plexus forms venous plexus, which drain into vertebral, azygous and lumbar veins through the intervertebral foramina.

THE SUBARACHNOID SPACE

The space between the arachnoid and pia mater. It includes spinal nerve roots, cerebrospinal fluid, denticulate ligaments, and reticulum of fibers connecting the arachnoid mater with the pia mater.

The nerve roots get affected by analgesics easily due to the absence of dural epineural sheath.

THE CEREBROSPINAL FLUID (CSF)

Spinal cord, Cerebral ventricles and subarachnoid spaces possesses this tissue fluid. Its production is by the choroid plexus in combination of filtration and secretion in ventricles and absorption in arachnoid granulations.

The production of total CSF normally is approximately about 21 ml per hour in adult, all the times it is of 130-150 ml. Patient lying in lateral position, the measured CSF pressure is 7-15 cm of water.

COMPOSITION OF CSF

1. Specific gravity: 1.005 (1.003- 1.007) at 37 degree centigrade.
2. pH: 7.33

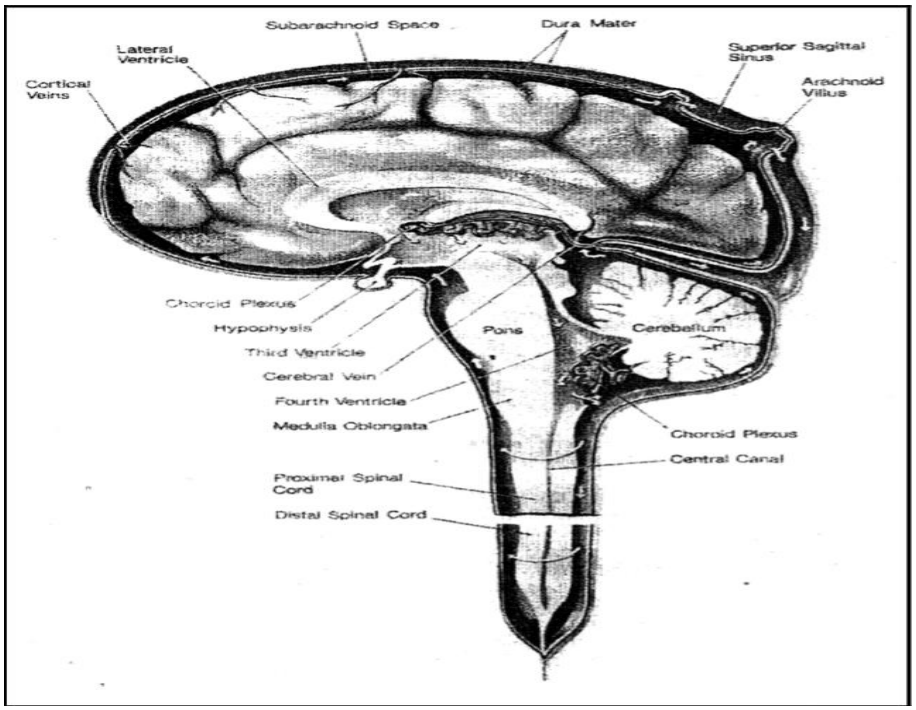


Fig.6 - Production, Circulation, and Resorption of Cerebrospinal fluid.

3. Volume: 120-140 ml
4. Glucose (Fasting): 2.5 -4.5 mmol/L
5. Sodium: 144-152 miliEq/L
6. Calcium:1.1-1.3mEq/L
7. Chloride: 123-128 mEq/L
8. Bicarbonate: 24-32 mEq/L
9. Proteins:200-400mg/1
10. Urea: 2.0-7.0 mmol/L
11. Osmolality: 289 mmoL/kg of H2O

FUNCTIONS OF CSF

1. It parts a separation between the brain, spinal cord from the skull and vertebral canal.

2. Supplies the required oxygen and nutrition to the nerve cells.

3. Metabolites drainage.

4. Regulating the pulmonary ventilation.

PHYSIOLOGY OF SPINAL HYPOTENSION [25,26]

The key to safe and appropriate management of the patients depends on the following:

- **Control of Arterial Pressure[27]**

Definition: the product of cardiac output and systemic vascular resistance.

Frank Starling law states that cardiac output is determined by the venous return. Venous return in turn is influenced by the gravity, the calf muscle pump, intra-thoracic pressure and the degree of vasomotor tone.

Sympathetic vasomotor tone and the influence of hormones such as rennin, angiotensin, aldosterone and anti-diuretic hormone determines the systemic vascular resistance.

- **Organ Perfusion**

Mechanisms which control auto-regulation and perfusion are:

- Myogenic auto-regulation acts via stretch receptors.
- Chemical auto-regulation acting via concentration of vasoactive metabolites.

- **Cerebral blood flow**

Between 50 to 180 mmHg of mean arterial pressure, auto regulation occurs. Since vessels are devoid of sympathetic nerve supply they auto-regulate by myogenic mechanism. The

increased tone of the sympathetic system and systemic vascular resistance in a try to restore arterial pressure occurs by the stimulation of vasomotor center.

- **Coronary blood flow** mediated by chemical auto-regulation between 60 to 150 mm of Hg MAP. As the hypoxia occurs, adenosine diphosphate gets accumulated. This is later converted to adenosine, a potent coronary vasodilator, restores the local blood flow.
- **Autoregulation of renal system** occurs between (60 – 160) mm of mercury of MAP. Due to stretch myogenic response occurs and constricts with hypertension and dilates with hypotension.

Physiology of Central Neural Blockade

Order of blockade of Nerve fibers[20]

- Autonomic pre ganglionic nerve fibers (B fibers).
- Temperature and pain fibers (A delta and C fibers).
- Pinprick fibers.
- Pain greater than pinprick fibers.
- Touch fibers (A beta fibers).
- Deep pressure fibers.
- Somatic motor fibers.
- Vibratory sense and proprioception impulses (A gamma fibers).

Return of sensitivity is in the reverse order during the recovery, but sympathetic activity returns before other sensation[28]. The important physiologic involves the cardiovascular system; they include hypotension and bradycardia.

Primary Mechanisms of Hypotension[28]

- Peripheral venous pooling and decreased venous return due to sympathetic preganglionic denervation
- Arterioles and post arteriolar capillaries vasodilation.
- Depletion of catecholamine in view of sympathetic denervation to adrenal medulla (T8 to LI).
- Splenic venous pooling
- Great vessels compression, which is exaggerated by pregnant uterus and abdominal tumors.
- Higher level of blockade

Opposing Factors Affecting Heart Rate[29]

- Baroreceptor reflex
- Changes in the preload
- Decrease in heart rate due to vagal responses
- Decrease in heart rate due to sympathetic blockade of cardio-acceleratory nerves.
- SAB cause a decrease in sensory input to the cortex, later reducing the heart rate.

If the level of blockade rise above fifth thoracic vertebrae level, it will tough to compensate the response as the (T1 to T4) fibers are involved and blocked. Decrease in BP occurs in the beginning of 10-15 minutes after giving spinal anaesthesia. There is exaggerated fall in BP in higher levels of block, elderly patients, parturient, known HTN disorder and hypovolemic states.

Prevention of Hypotension[28]

- Providing a lateral tilt of (10-15) degrees or placing a wedge under the right buttock.
- Preloading with IVfluids.
- Treating with vasopressors prophylactically.

Treatment of Hypotension[28]

1. 100% Oxygenation
2. Foot end elevation <20°, further can lead to increase in internal jugular venous pressure reducing the cerebral perfusion pressure.
3. Rapid fluid resuscitation.
4. Injection of vasopressor with effect on vaso-constriction properties excluding the effect on myocardial supply and demand.
5. If bradycardia continues to occur, treat it with

PHARMACOLOGY

LOCAL ANESTHETIC DRUGS

Drugs producing reversible depression of nerve conduction when applied to nerve fiber[30].

- **BUPIVACAINE**[30,31,32]

Bupivacaine is the choice in regional anaesthesia practice due to its onset, long duration of action, good conduction blockade, and effective separation of sensory to motor block.

- **Chemistry:** It differs in a butyl group substituted for a methyl group on the piperidine nitrogen from its homologue mepivacaine.

Chemical structure

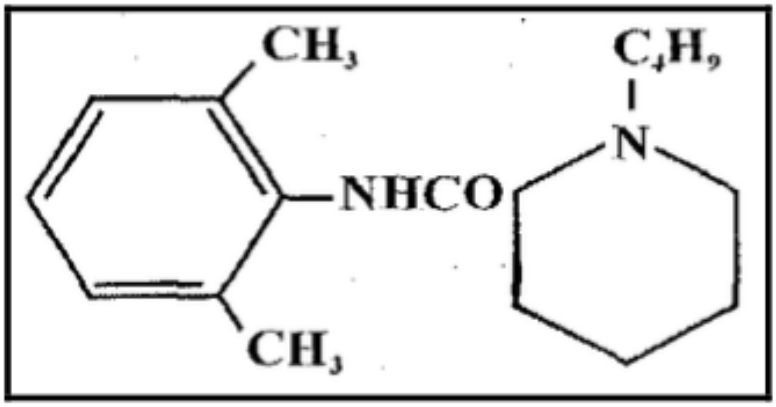


Fig.7 – showing the Chemical structure of Bupivacaine[31]

Mechanism of Action

Action on the cell membrane of the axon is its primary mechanism. The increase in the sodium ions permeability, which is must for propagation of impulses is prevented. So

there is maintenance of resting membrane potential and depolarization is inhibited. They block the sodium conductance:

a) The cationic form acts on the receptors within the sodium channels and also on the cell membrane later blocking it. The local anesthetics can reach the sodium channels either via the lipophilic pathways directly across the lipid membrane or via the axoplasmic opening.
b) Also by the membrane expansion, calling it as non- specific drug receptor interaction.

Anaesthetic Properties

a) Potency: Bupivacaine is approximately three to four times more potent than other local anaesthetics. Due to its slow penetrating potential, it leads to slow onset, prolonged duration of action due to its lipid solubility and protein binding properties.
b) pKa: is 8.2
c) pH of 5.2 (saturated solution)
d) Ratio of potency over toxicity is (3.0 to 4.0).

Pharmacodynamics

- Onset of action: 3 to 4 minutes
- Complete block attains by 6 to 8 minutes.
- The total duration of action may varies between 75 to 150 minutes.

Pharmacokinetics: Depends on

- Route of administration
- Drug concentration
- Total dose administered
- The drug absorbed is less through subarachnoid route, plasma bupivacaine concentration is (1-2) µg/ml after one to two hour of administration. Alpha half life and Beta half life is (2-7) and 28 minutes, T 1⁄2 gamma is 3-5hrs, volume of distribution is 72. It clears at the rate of 0.471t/min.
- The concentration of the drug in blood reduces as it goes through the pulmonary vasculature. Plasma Binding is about (90 to 95%), unbound form of drug is about $1/7^{th}$ that of Lidocaine and $1/5^{th}$ that of Mepivacaine.

Metabolism and Elimination

- Amide derivative
- Liver is the primary site of metabolism.
- It is metabolized by N- dealkylation and the metabolite is excreted in the urine.
- 10% of the drug is goes unchanged in the urine and the remaining part is conjugated with glucuronide and later excreted.

Dosage

- Safe limit in a 70kg adult with adrenaline: (2.5 to 3.0mg/kg) body weight.
- Without adrenaline: (2 to 2.5mg/kg) body weight.

Actions on different systems

Central nervous system: Excess dose can produce

- Visual and auditory disturbances
- Drowsiness and disorientation
- Shivering, tremors
- Lately can also lead to generalized convulsions of tonic-clonic nature.

Cardio vascular system:

- Cardiac sodium channel is blocked and altering the mitochondrial function. Because of its protein binding nature, it can prolong resuscitation and make it difficult.
- Arrythmogenic and can reduce the cardiac contractility.
- Lower concentration produces vasoconstriction
- Higher doses cause vasodilatation.

Autonomic nervous system:

- Sensitivity of myelinated beta fibers is more to local anaesthetics.
- Bupivacaine produce higher sensory than the motor blockade.

Respiratory system:

- Excess plasma level results in depression of medullary respiratory centers causing respiratory depression.
- Paralysis of respiratory muscles in case of high spinal or total spinal anesthesia can also cause respiratory depression.

Neuromuscular junction:

- Local anesthetics can affect transmission at neuro-muscular junction and block motor nerve fibers.

Toxicty

Local anesthetics are comparatively safe when administered in proper dosages in the correct position. But accidental intravascular, intrathecal injection or administration of large doses can occur and cause toxicity.

Toxicity can manifest on the CNS and CVS.

CNS toxicity includes:

- Nausea, Vomiting, Excitation or depression, nervousness, blurred vision, convulsions, loss of consiousness and lastly can cause respiratory arrest.

CVS manifestations include:

- Hypotension
- Myocardial depression

Allergic reactions: Urticaria, bronchospasm can also occur.

Treatment of toxic reactions includes:

- Mainly symptomatic treatment.
- Providing ventilation support with oxygen or controlled ventilation if required.

- Supportive treatment with IV fluids and vasopressors restore the cardiovascular stability, convulsions may be controlled with diazepam or thiopentone sodium and controlled ventilation with oxygen.
- Corticosteroids may be helpful when allergic reactions are suspected.

EPHEDRINE PHARMACOLOGY[33,34,35]

❖ HISTORY[36]

Ephedrine was introduced in 1926 by Chenn and Schmidt. Used to counter the spinal hypotension in 1927 by Ockerblad & Dillon.

Earlier only adrenaline and Methyl guanidine were available. But has the adverse effects of severe tachycardia and decrease in ratio of myocardial oxygen need to supply.

Since then many pressor agents have come and gone but Ephedrine still remains the preferred drug due to its dual action on both alpha and beta-adrenergic receptors.

For a millennium, the active mechanism of the herb Ma-Huang which belongs to the Ephedra species was only known to Chinese medicine.

But later in 1887, drug was extracted in its pure state by Naguan.

❖ Structural formula:

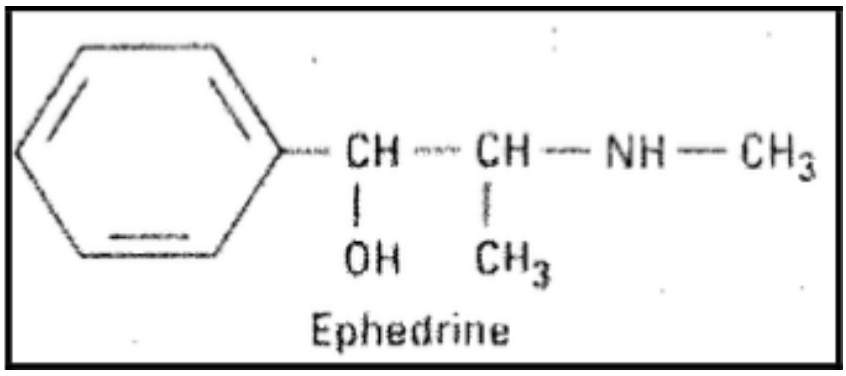


Fig.8 Structure of Ephedrine[35]

(1R,2SJ-2 Methylamino-1 Phenyl propanolol Hemi hydrate) is its chemical name.

❖ Physiochemical properties

- White crystalline in powder form or in granules form with bitter in taste.

- Odourless or can have smell of slight aromatic.

❖ 217-220 degree Celsius is its **melting point.**

❖ **Mechanism of Action**[35,37,38]

Direct Action:

Non-selective drug acting on both alpha and beta receptors.

Indirect Action:

(a) Peripheral post-sympathetic norepinephrine release

(b) Central nervous stimulation

(c) Inhibition of norepinephrine reuptake

❖ **Pharmacokinetics**[37]

- Resistant to degradation by (MAO) and (COMT)
- Distribution occurs throughout the body.
- The mean plasma half life is 6hours (3 to 11 hours),
- Clearance occurs at 13.6 to 44.3 L/hour.
- In 24 hours, 95% of drug is excreted in urine. Patients with renal disease, will have the problems with elimination of the drug.

Action on different systems:

Cardiovascular system: due to its peripheral vasoconstriction action, it increases the arterial blood pressure and also causes increase in HR and cardiac output.

Central nervous system:

It is a potent CNS stimulant:

- Increases the MAC value of anaesthetic agents
- Causing apprehension and tremors
- Causes Insomnia
- Psychoses can occur in chronic abuse.

Respiratory system:

- It relaxes bronchial smooth muscles and increases the airway conductance within one hour following administration in obstructive airway disease patients.

Alimentary and urinary tract:

- Reduces the intestinal tone and motility.
- Alpha adrenergic receptors stimulation of smooth muscle cells in the bladder base and relaxation of the detrusor muscle increases the resistance to the outflow of urine.

Uterus: It causes uterine relaxation and preserves the uterine blood flow by its beta adrenergic activity.

Musculoskeletal: It stimulates oxygen uptake and thermo genesis.

Eyes: causing mydriasis, but will not alter the light reflexes.

Therapeutic Uses

- To treat the hypotension following subarchnoid blockade
- Bronchodilatory effect
- Treating allergic disorders such as hay fever or urticaria
- Nasal decongestant

- Enuresis

Dosage : 0.5 - 0.6 mg/kg

Contraindications:

- Ischemic heart disease
- Hypertensive patients
- Benign prostatic hypertrophy patients
- Thyrotoxic patients and also in lactating mothers and for long durations in pregnant women.

Drug Interactions[39]

- Administered with (MAO) inhibitors can cause hypertensive crisis
- Half life of dexamethasone decreases when administered with ephedrine.
- Risk of arrhythmias if patient is on digoxin.
- Increased response in cocaine users.

Adverse Effects

Ephedrine when given in large doses give rise to side effects such as giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, muscular weakness and tremors, anxiety, restlessness and insomnia.

Treating the overdose

- Protection of patient's airway and to support ventilation if required with 100% oxygen.
- Monitor vital signs, blood gases, and serum electrolytes.

- Monitor ECG for SVT, administration of beta-adrenergic blocker such as Propranolol by slow intravenous infusion; however in asthmatic patients a cardio selective beta-adrenergic blocker (Acebutalol, Atenolol, Metaprolol) is considered.
- Marked hypertension to be treated with vasodilators.
- Treat convulsions using Diazepam, refractory seizures to be treated with Thiopentone and Neuro-muscular blocking agents if required.

REVIEW OF CLINICAL STUDIES

Since its use into the daily clinical practice, spinal anaesthesia is widely practiced regional anaesthesia technique. Due to its advantages[1]:

- Easy to perform
- Rapid onset
- Poly-pharmacy is avoided
- Intubation avoided
- High quality sensory and motor block
- The patient will be awake and be able to communicate.
- Cost effective

Spinal anaesthesia also has a set of disadvantages. The common adverse effects are hypotension and bradycardia and methods developed in to prevent these side effects are [2]: Foot end elevation[40], wrapping legs with bandage[7], left displacement of are the **Physical methods used to increase venous return,** but are less potential in overcoming the hypotension.

IV fluids for **volume expansion**, Crystalloids are cheaper, improves the peripheral circulation and decreases hypotension to a extent by filling up the venous capacitance vessels [41].

- But have disadvantages like hemodilution which can affect oxygen supply, leading to abnormal rise in central venous pressure[42].
- Colloids like Albumin has good efficacy on reducing hypotension but are expensive. Adding to this are the side effects like anaphylactic reaction, coagulation disturbances.

Blockade of sympathetic system gave rise to its treatment with vasopressors. Earlier epinephrine was used, but because of the cardiac adverse effects it was substituted with Ephedrine. Since then its introduction, ephedrine has remained the choice in reducing the incidence of hypotension caused spinal anaesthesia blocking sympathetic system.

Study done to assess whether prophylactic intravenous infusion of ephedrine maintains the maternal blood pressure without affecting the mother or fetus? by **Kang et al in 1982[43]**

Method: here 44 pregnant undergoing elective caesarean section under SAB were substituted in two groups. Twenty two patients received ephedrine infusion (5mg/min, 0.01% solution) and twenty two patients (control group) received 20mg of Ephedrine as an intravenous bolus.

Results: With the infusion, SBP did not change much from the baseline and reactive increase in BP did not occur. Nausea and vomiting occurred in 09 women in the control group and 01 patient in the infusion group ($p<0.001$).

Conclusion was made that prophylactic intravenous infusion of ephedrine was safe and effective in healthy parturient undergoing cesarean section under spinal anaesthesia, without any adverse effects.

In 1989, Hemmingsen C et al, conducted a study to determine the efficacy of prophylactic Ephedrine on spinal anaesthesia related hypotension[44].

Method: 48 patients undergoing lower Extremities or limb abdomen surgeries under spinal anaesthesia were allotted into three groups of 16 each. Each patient received a fluid of 7ml/kg and either ephedrine 12.5mg I.V and 37.5mg I.M or placebo.

Result: 12 patients in the placebo group had decrease in MAP exceeding 20%, 05 of them showed a decrease exceeding 33% and required treatment. In ASA III, all patients in placebo group had a decrease MAP exceeding 33%. They came to a closure that it is good to administer prophylactic ephedrine I.V and I.M. regularly at the time of induction of spinal anaesthesia.

In 1993, Gajraj et al designed a study to find out the efficacy of Ephedrine infusion with crystalloid in reducing the incidence of hypotension following spinal anesthesia[45].

Method: Fifty four patients of ASA grade I posted for postpartum tubal ligation were taken into two groups. Group 1 received ringer lactate at 15ml/kg. Group 2 received Ephedrine infusion (50mg in 50ml of ringer lactate).

Results noted are 55% hypotension was observed in the crystalloid group and 22% in the infusion group. They came to conclusion that Ephedrine infusion was found effective than preloading with crystalloids.

Study was carried on to evaluate the effect of IV bolus of Phenylephrine combined with Ephedrine and Ephedrine alone during spinal anesthesia for cesarean delivery by **Loughrey and co. in 2005** [46]

Method: 43 patients of ASA grade I and II were divided into two groups. Group E (n=20) received bolus I.V. Ephedrine l0mg and Group EP (n=20) received Ephedrine l0mg and Phenylephrine 40ug I.V.

Result: shown that 80% hypotension in group E and 95% in group EP. Thus Ephedrine alone is better in preventing hypotension in healthy parturient.

Varathan S, Ekanayake S U , Amarasinghe U in **2009**, compared the prophylactic ephedrine with preloading and preloading alone to see whether it can prevent the hypotension in patients undergoing caesarian section caused by spinal anaesthesia? [47].

Method: Forty six pregnant were allocated randomly to five groups. Group A (control group) received preloading with crystalloid 20 minutes prior to subarachnoid block. Groups B and C received IM ephedrine 15mg, 10 and 20 minutes prior to subarachnoid block whereas Groups D and E received IM ephedrine 30mg, 10 and 20 minutes prior to subarachnoid block.

Results: Crystalloid along with prophylactic IM ephedrine 15mg given 10min prior to subarachnoid block can prevent hypotension effectively during cesarean section under spinal anaesthesia.

Study using prophylactic intravenous ephedrine was done too see its efficacy on reducing spinal-induced hypotension during cesarean section was done by **Iqbal M S, Ishaq M, Masood A, Khan M Z in 2010** [48]

Method: Ninety pregnant posted for elective C-section were included in this study. Patients divided into 03 groups. Group-I received 10mg, Group-II 15mg, and Group-III received 20mg prophylactic IV ephedrine immediately after spinal anesthesia.

Results: bolus dose of 15mg IV ephedrine effectively prevents the maternal hypotension without causing any adverse effects.

Bhar D in 2011 planned to carry out a study to see the efficacy of prophylactic IM ephedrine in decreasing spinal induced hypotension in caesarian section [11].

Methods: prospective, randomized, double blind controlled study, in which 150 pregnant of ASA I, posted for elective cesarean section, were split into three groups randomly. C-group received only 15 ml/kg of ringer's Lactate pre-loading, Group E10 and Group E20 received injection ephedrine 0.5 mg/kg IM 10 minutes and 20 minutes prior to SAB with 15 ml/kg RL preloading.

Results: IM ephedrine 0.5 mg/kg given 10 minutes when given prophylactically before spinal anaesthesia has better outcome on hemodynamic stability without causing any incidence of adverse effects.

A clinical study on comparison of pre-operative IM ephedrine and mephentermine in bringing down the incidence of spinal induced hypotension during Cesarean Section was designed by **Yadav A S, Shakya M L, Dwivedi S in 2016**[49]

Methods: 90 pregnant of ASA I and II, posted for elective LSCS under SAB were taken into the study. They were randomly cleaved into 3 groups of 30 patients each. Patients of Group I - received 1 ml of injection NS (IM); patients of Group II received 30 mg mephentermine IM; patients of Group III received 30 mg ephedrine IM 5 min before block.

Results: both ephedrine and mephentermine before SAB decreases the occurrence of spinal anesthesia-induced hypotension. Group with mephentermine have lower APGAR scores.

Volume preload and ephedrine infusion were compared in a study to see their potency in reducing and preventing the spinal induced hypotension in elective cesarean section undergoing parturient by **Ahmed H O, Hossam M, Adel A** [50]

Method: Randomly divided 54 patients into two groups. Group I (F group) patients received 15 ml/kg ringer lactate preloading, and group II (E group) received IV ephedrine (5 mg in 1st minute after spinal anesthesia and 5 mg in the 2nd minute and 1mg every minute after that for 15 minutes).

Results: Ephedrine infusion after spinal anesthesia was more effective than crystalloid preloading in preventing hypotension without causing any significant increase in heart rate.

Kumari P, Tahir S, Mir A, Kumari H in 2019, has done study to see the effects of prophylactic ephedrine and phenylephrine on fetal acid-base status in patients undergoing cesarean section under SAB [51].

Methods: Patients received either ephedrine 6 mg (group E) or phenylephrine 75μg (group P) as vasopressor.

Results: Equal response on controlling the hypotension is shown by both phenylephrine and ephedrine, without causing any significant side effects affecting either mother or fetus

METHODOLOGY

MATERIALS AND METHODS

Source of data

Study was conducted on 108 patients undergoing lower abdominal and lower limb surgeries at R L Jalappa Hospital, Tamaka Kolar during the academic year from January 2018 to May 2019.

Collection of data:

- Patients undergoing lower abdominal and lower limb surgeries were randomly selected from computerized table.
- Informed consent is obtained from the patient.
- Result values are recorded in proforma.

Inclusion Criteria:

- Patients belonging to ASA 1 and 2
- Age: 20-60 years

Exclusion Criteria:

- Emergency surgeries
- Patients with comorbidities like DM, HTN
- Patients with spine abnormalities
- Patients on MAO inhibitors and beta blockers

SAMPLE SIZE

- Sample size for this study estimated based mainly on mean arterial pressure as reported in a study done by Bhar D et al. – "efficacy of prophylactic intramuscular ephedrine in prevention of hypotension during caesarean section under spinal anesthesia", with an average variance estimate of 46.4,to detect an increase of atleast

5% in M.A.P in the treatment group, with 95% confidence interval , with 80% Power , with an alpha error of 5%. The calculated sample size is 54 per group. Total of 108 patients.

The selection of patients were carried out randomly. Patients were briefed in the understandable language the anaesthesia procedure they are going to undergo.

Pre-anaesthetic checkup was done one day before the surgery which included general physical examination, systemic examination and examination of spine.

Basic investigations like haemoglobin percentage, total blood count, differential blood count, serum electrolytes, renal function tests, urine routine, bleeding and clotting time, blood Sugars (if urine sugar positive) were advised.

On the day of surgery, drugs and resuscitation equipment checked and kept ready. The baseline Heart rates (HR) Systolic blood pressure (SBP), Diastolic blood pressure (DBP) were recorded.

Patients then were randomly allocated into two groups. 18 gauge intravenous line was secured. Group A received IM ephedrine 30 mg (1ml) 10 minutes before spinal anaesthesia. Group B received injection normal saline (1ml) (placebo) 10 minutes before spinal anaesthesia along with preloading of 15ml/kg of ringer lactate in each group.

Patients then shifted to the operation theatre. The pre subarachnoid block heart rates (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) were recorded for all patients and continuous monitoring done.

Under strict aseptic precaution lumbar puncture was done using 25-gauge disposable Quincke type of spinal needle at L3-L4 spinal intervertebral space by midline approach.

After the continuous free back flow of cerebrospinal fluid, 3.2ml (0.5% 5mg/ml) heavy Bupivacaine hydrochloride plus 0.3ml (90mcg) of Buprenorphine was injected intrathecally irrespective of weight and height of the patients and the time noted.

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) were recorded in all patients at every 2 minutes interval for 10 minutes, then at every 10 minutes interval up to 45minutes and then at every 15 minutes till the end of surgery or up to 90 minutes.

Level of sensory blockade was checked using a 23G hypodermic needle, Success of the block was defined as pinprick analgesia extending cranially to the desired dermatome.

Ringer lactate was infused at the rate of 15 ml/min upto 1 hr after starting the operation in both groups then reduced to 10 ml/min if operation continued beyond 1 hr.

Following subarachnoid block, patient are monitored for any decrease in BP, nausea, vomiting, desaturation ($SpO_2<90\%$) or any other side effects. Hypotension was defined as a decrease in systolic blood pressure (SBP) more than 30% from the base line.

If hypotension occurred, then they were treated first with 200 ml rapid infusion of ringer lactate was done. If hypotension continued they were treated with rescue vasopressor (mephentermine) administered intravenously in 6mg boluses.

Injection Atropine 0.6mg was administered intravenously if the heart rate goes below 50 per minute. Tachycardia was defined as HR more than 100 beats per min, and hypertension was defined as rise of MAP more than 20 mmHg over the baseline.

RESULTS

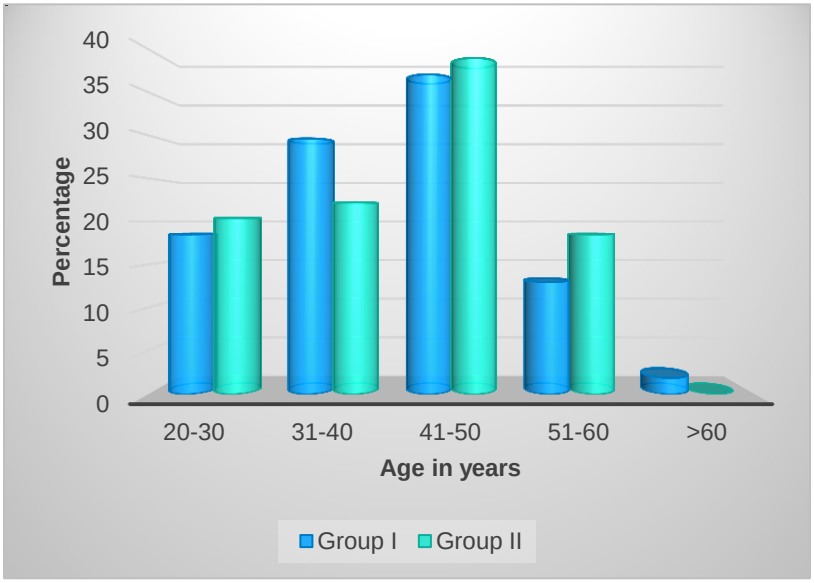
RESULTS

Age distribution of patients

Table 1:

Age in years	Total	Group I	Group II
20-30	21(19.4%)	10(18.5%)	11(20.4%)
31-40	28(25.9%)	16(29.6%)	12(22.2%)
41-50	41(38%)	20(37%)	21(38.9%)
51-60	17(15.7%)	7(13%)	10(18.5%)
>60	1(0.9%)	1(1.9%)	0(0%)
Total	108(100%)	54(100%)	54(100%)
Mean ± SD	40.75±10.85	40.48±10.62	41.02±11.16

Graph 1:



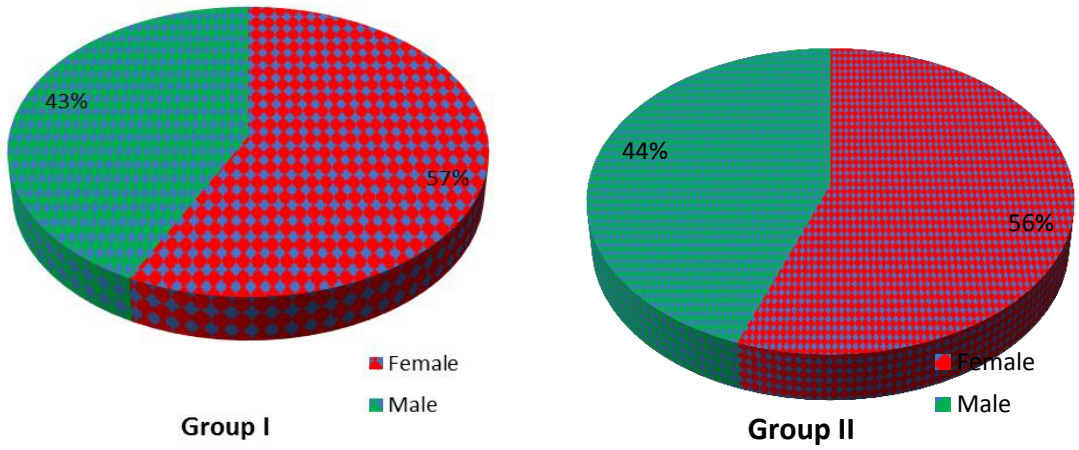
(Samples are age matched with P=0.798, Student t test)

Gender distribution

Table 2:

Gender	Total	Group I	Group II
Female	31(28.7%)	31(57.4%)	30(55.6%)
Male	47(43.5%)	23(42.6%)	24(44.4%)
Total	108(100%)	54(100%)	54(100%)

Graph 2:



(Samples are gender matched with P=0.846, Chi-Square test)

Heart rate in two groups

Table 3:

Heart Rate (beats/min)	Total	Group I	Group II	P value
Basal	83.32±12.32	85.74±14.23	80.91±9.58	0.041*
Immediately after sab	84.03±13.83	87.07±16.26	80.98±10.14	0.021*
2 mins	82.96±14.48	87.04±17.12	78.89±9.82	0.003**
4 mins	82.26±14.16	86.74±16.37	77.78±9.81	0.001**
6 mins	80.2±12.81	84.22±14.3	76.19±9.7	0.001**
8 mins	78.99±12.65	82.7±14.02	75.28±9.91	0.002**
10 mins	78.56±14.54	83.22±16.68	73.91±10.23	0.001**
20 mins	78.55±13.4	82.94±14.55	74.15±10.56	<0.001**
30 mins	78.64±12.71	82.98±11.7	74.3±12.28	<0.001**
40 mins	78.21±11.85	81.04±11.93	75.39±11.18	0.013*
60 mins	78.16±12.38	81.17±13.71	75.15±10.16	0.011*
80 mins	77.85±10.9	79.87±11.29	75.79±10.19	0.053+
90 mins	78.1±11.31	80.19±11.76	76.02±10.54	0.055+

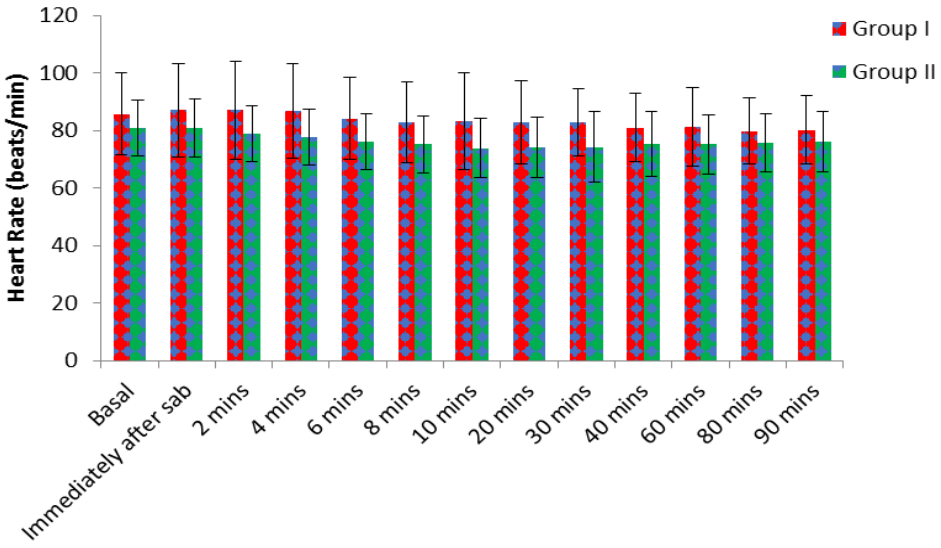
Student t test applied (two tailed and independent test)

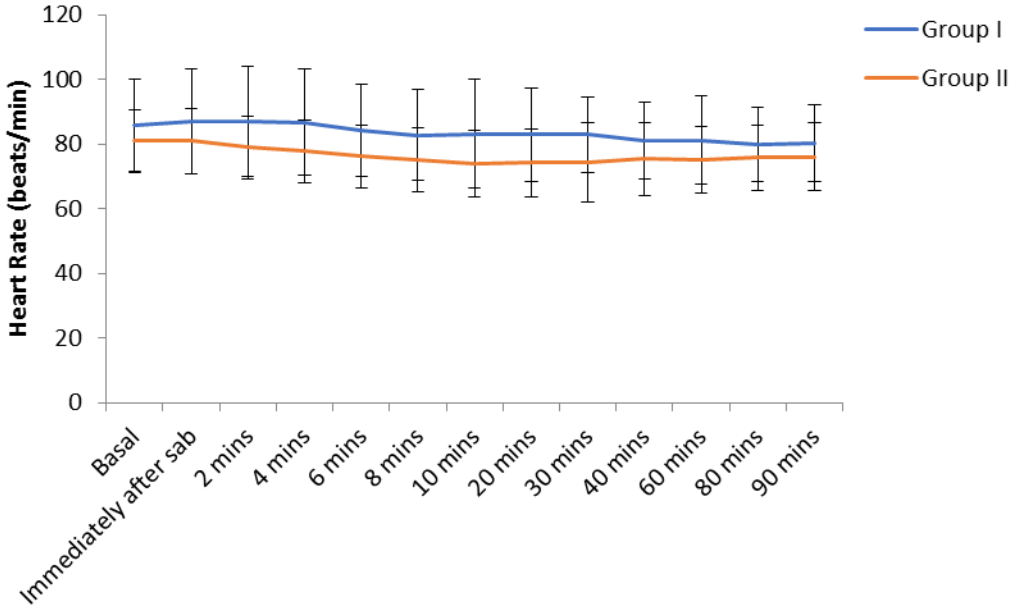
+ Suggestive significance (P value: 0.05<P<0.10)

*** Moderately significant (P value:0.01<P</=0.05)**

**** Strongly significant (P value: P</=0.01)**

Graph 3:


120
100
80
60
40
20
0
Heart Rate (beats/min)
Group I
Group II
Basal
Immediately after sab
2 mins
4 mins
6 mins
8 mins
10 mins
20 mins
30 mins
40 mins
60 mins
80 mins
90 mins


120
100
80
60
40
20
0
Heart Rate (beats/min)
Group I
Group II
Basal
Immediately after sab
2 mins
4 mins
6 mins
8 mins
10 mins
20 mins
30 mins
40 mins
60 mins
80 mins
90 mins

Comparison of SBP (mmHg) in two groups

Table 4:

SBP (mm Hg)	Total	Group I	Group II	P value
Basal	133.2±15.38	133.7±14.54	132.7±16.29	0.737
Immediately after sab	130.93±14.55	133.28±13.1	128.57±15.63	0.093+
2 mins	125.7±15.84	130.09±14.73	121.31±15.83	0.004**
4 mins	120.99±20.54	128.87±18.45	113.11±19.61	<0.001**
6 mins	118.03±17.93	124.43±18.36	111.63±15.12	<0.001**
8 mins	115.83±17.6	123.7±17.56	107.96±13.82	<0.001**
10 mins	115.33±16.06	121.87±15.65	108.8±13.73	<0.001**
20 mins	113.81±14.91	120.11±14.48	107.52±12.57	<0.001**
30 mins	115.04±13.71	119.06±13.99	111.02±12.28	0.002**
40 mins	116.1±13.42	117.26±14.77	114.94±11.96	0.373
60 mins	115.35±15.49	117.13±13.2	113.57±17.43	0.235
80 mins	117.41±11.14	117.17±11.92	117.65±10.42	0.824
90 mins	119.69±12.15	119.93±14.05	119.44±10.04	0.838

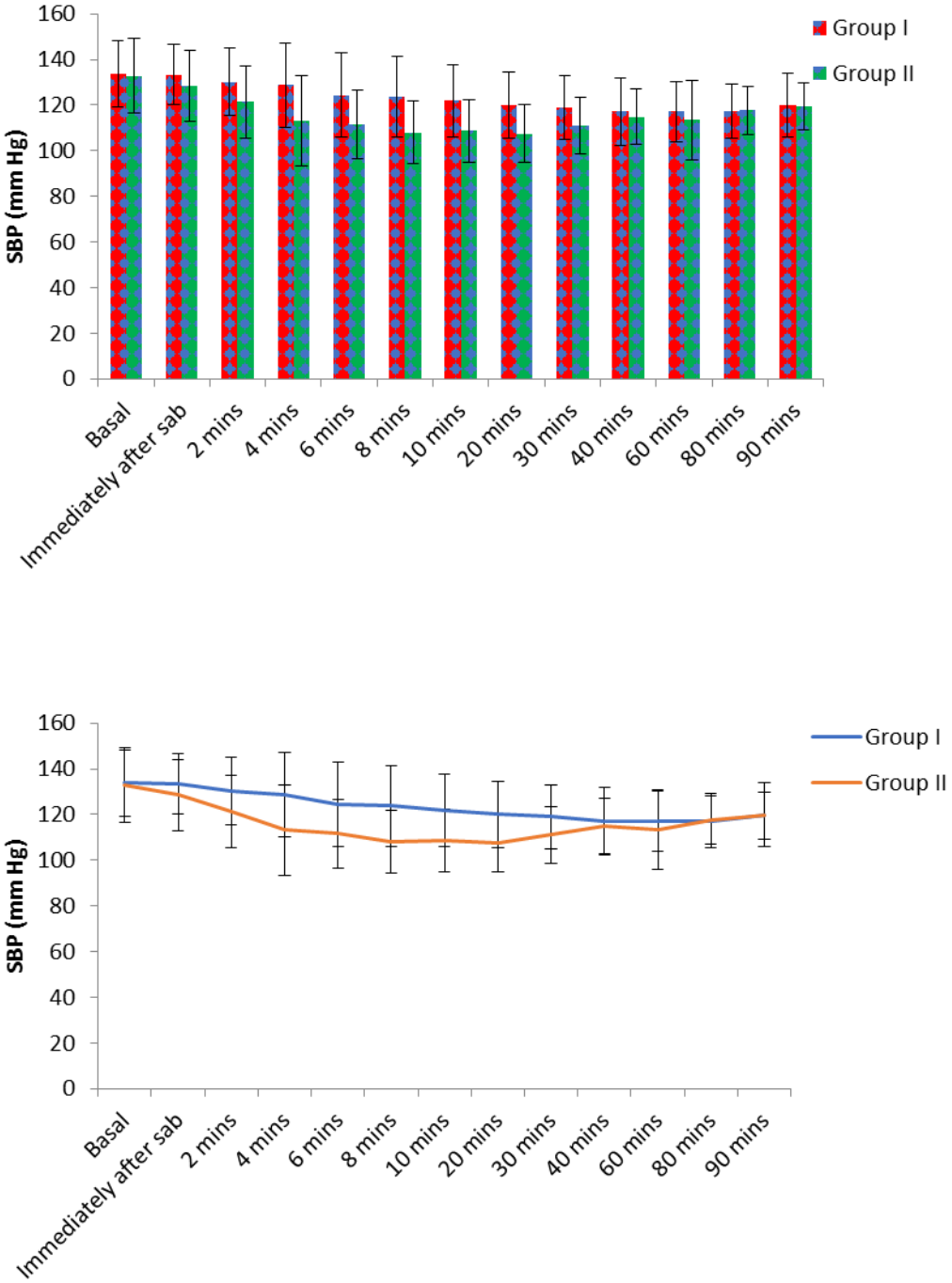
Student t test was applied (two tailed and independent test)

+ Suggestive significance (P value: 0.05<P<0.10)

*** Moderately significant (P value:0.01<P</=0.05)**

**** Strongly significant (P value: P</=0.01)**

Graph 4: Showing SBP comparision among two groups



Comparison of DBP(mmHg) in two groups

Table 5:

DBP (mm Hg)	Total	Group I	Group II	P value
Basal	78.73±9.32	79.11±9.66	78.35±9.03	0.674
Immediately after sab	77.06±9.39	77.69±9.9	76.44±8.91	0.495
2 mins	73.63±8.98	74.74±8.43	72.52±9.45	0.200
4 mins	71.6±10.09	72.67±9.98	70.54±10.18	0.275
6 mins	69.19±9.95	70.76±10.2	67.63±9.53	0.102
8 mins	67.78±9.97	69.93±9.27	65.63±10.25	0.024*
10 mins	67.11±9.37	68.74±9.74	65.48±8.78	0.071+
20 mins	67.68±8.77	69.54±9.02	65.81±8.17	0.027*
30 mins	67.49±8.68	68.07±9.56	66.91±7.75	0.487
40 mins	68.97±7.84	68.26±8.45	69.69±7.19	0.347
60 mins	69.43±7.16	68.96±8.08	69.89±6.13	0.504
80 mins	69.94±7.20	68.93±8.35	70.94±5.72	0.146
90 mins	71.00±7.75	70.20±8.57	71.80±6.82	0.288

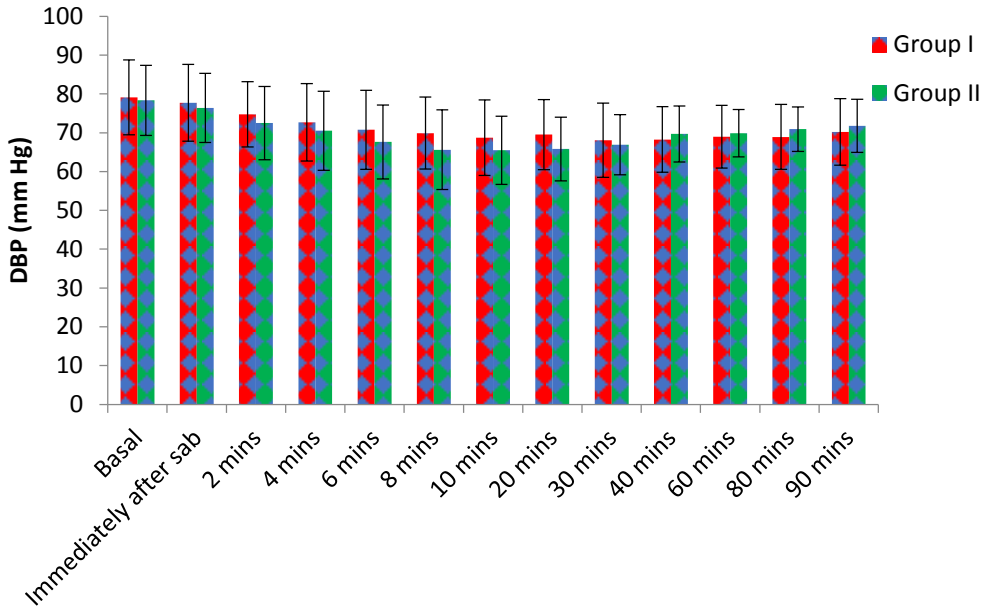
Student t test was applied (two tailed and independent test)

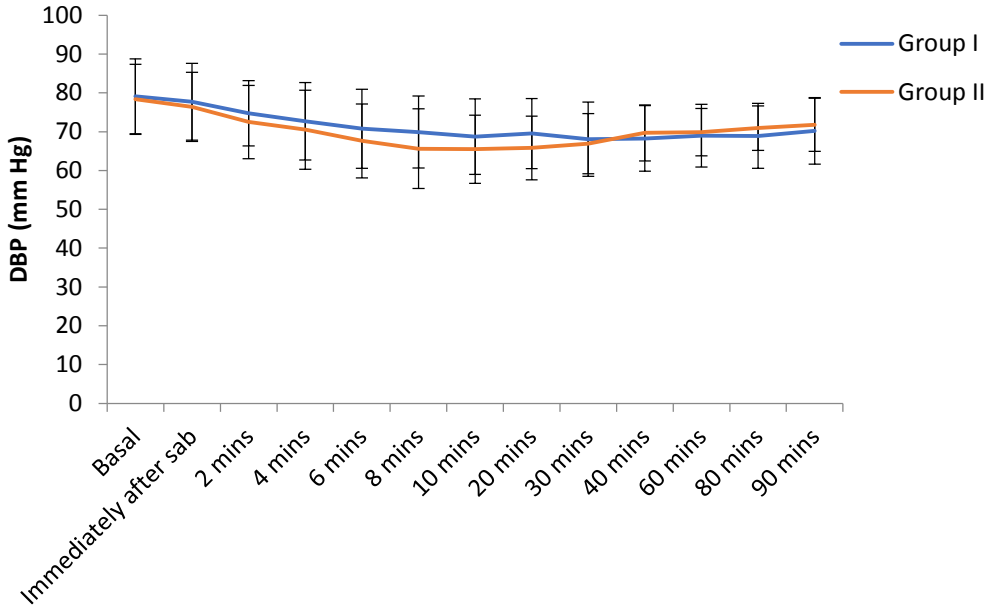
+ Suggestive significance (P value: 0.05<P<0.10)

*** Moderately significant (P value:0.01<P</=0.05)**

**** Strongly significant (P value: P</=0.01)**

Graph 5: Showing DBP among both the groups





Mean arterial pressures in two groups

Table 6:

MAP (mm Hg)	Total	Group I	Group II	P value
Basal	96.89±10.07	97.3±9.81	96.48±10.41	0.676
Immediately after sab	94.99±10.23	96.2±9.89	93.78±10.5	0.219
2 mins	90.99±10.25	93.2±9.22	88.78±10.82	0.024*
4 mins	88.06±11.99	91.43±11.15	84.69±11.94	0.003**
6 mins	85.48±11.55	88.65±11.45	82.31±10.85	0.004**
8 mins	83.80±11.59	87.8±10.91	79.80±10.94	<0.001**
10 mins	83.20±10.63	86.44±10.53	79.96±9.79	0.001**
20 mins	83.03±9.94	86.39±9.62	79.67±9.17	<0.001**
30 mins	83.35±9.49	85.07±10.00	81.63±8.71	0.059+
40 mins	84.67±8.79	84.56±9.65	84.78±7.94	0.896
60 mins	84.70±8.24	85.00±8.79	84.41±7.73	0.711
80 mins	85.72±7.51	84.98±8.37	86.46±6.53	0.308
90 mins	87.22±8.19	86.81±9.28	87.63±7.00	0.608

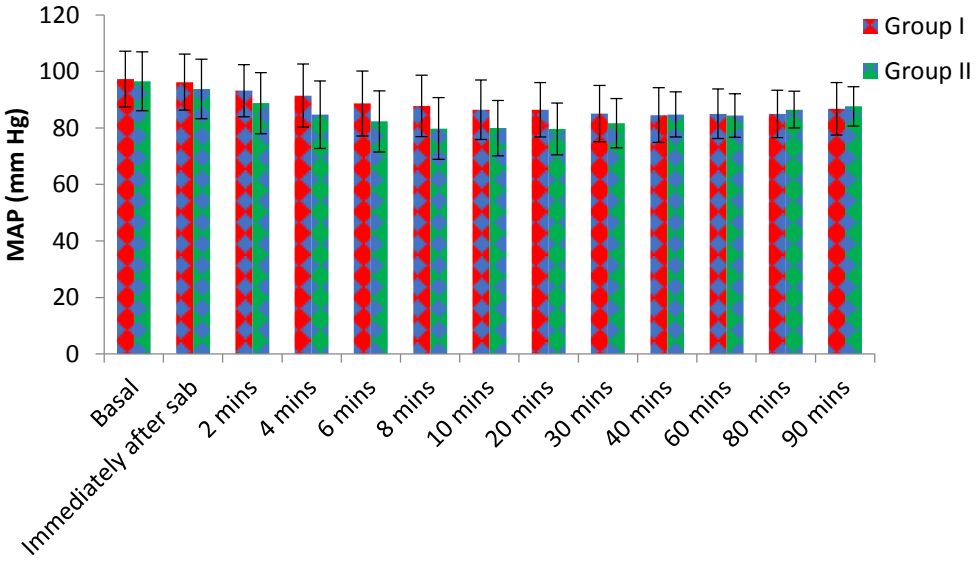
Student t test was applied (two tailed and independent test)

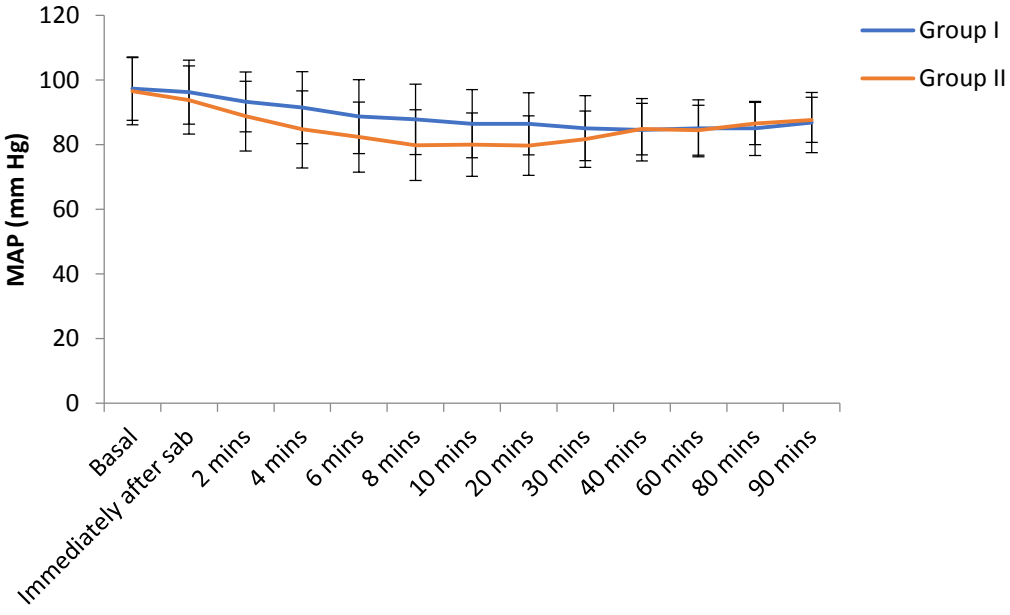
+ Suggestive significance (P value: 0.05<P<0.10)

*** Moderately significant (P value:0.01<P</=0.05)**

**** Strongly significant (P value: P</=0.01)**

Graph 6: shows MAP among two groups





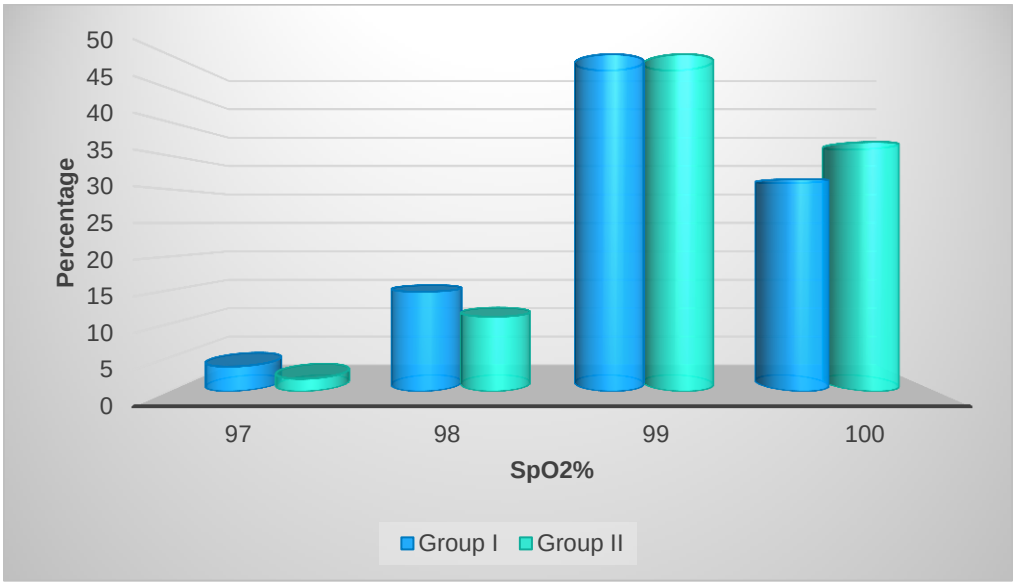
Comparision of Oxygen saturation

Table 7:

SpO2%	Total	Group I	Group II
97	3(2.8%)	2(3.7%)	1(1.9%)
98	14(13%)	8(14.8%)	6(11.1%)
99	54(50%)	27(50%)	27(50%)
100	37(34.3%)	17(31.5%)	20(37%)
Total	108(100%)	54(100%)	54(100%)

(P=0.372, Not Significant, Fisher Exact Test)

Graph 7:



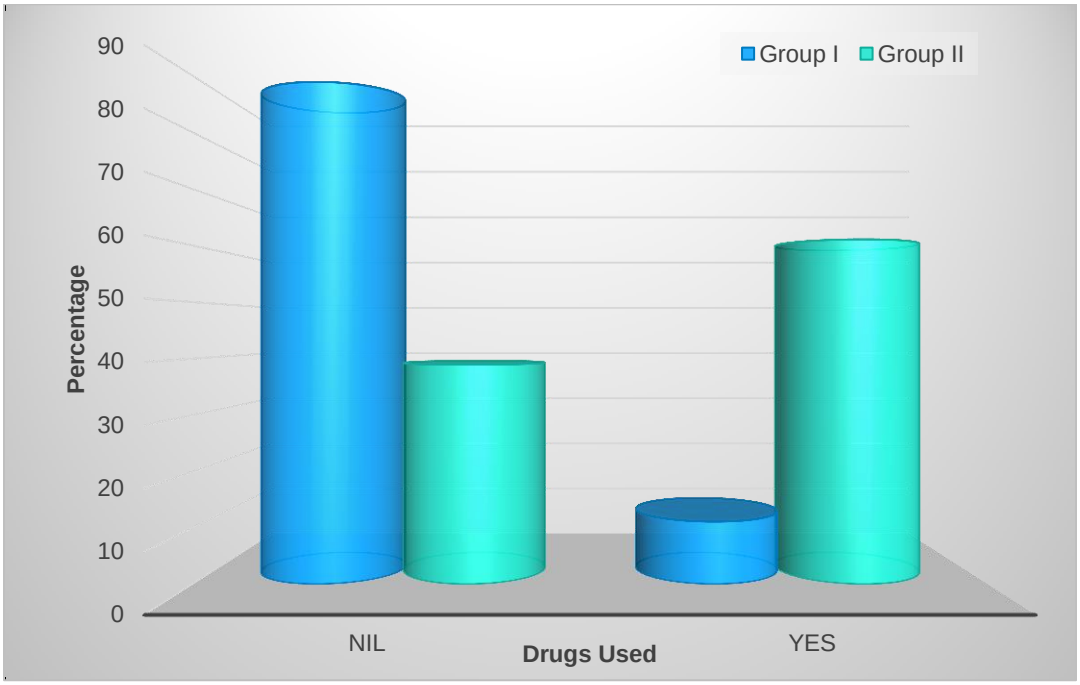
Rescue agent used in two groups

Table 8:

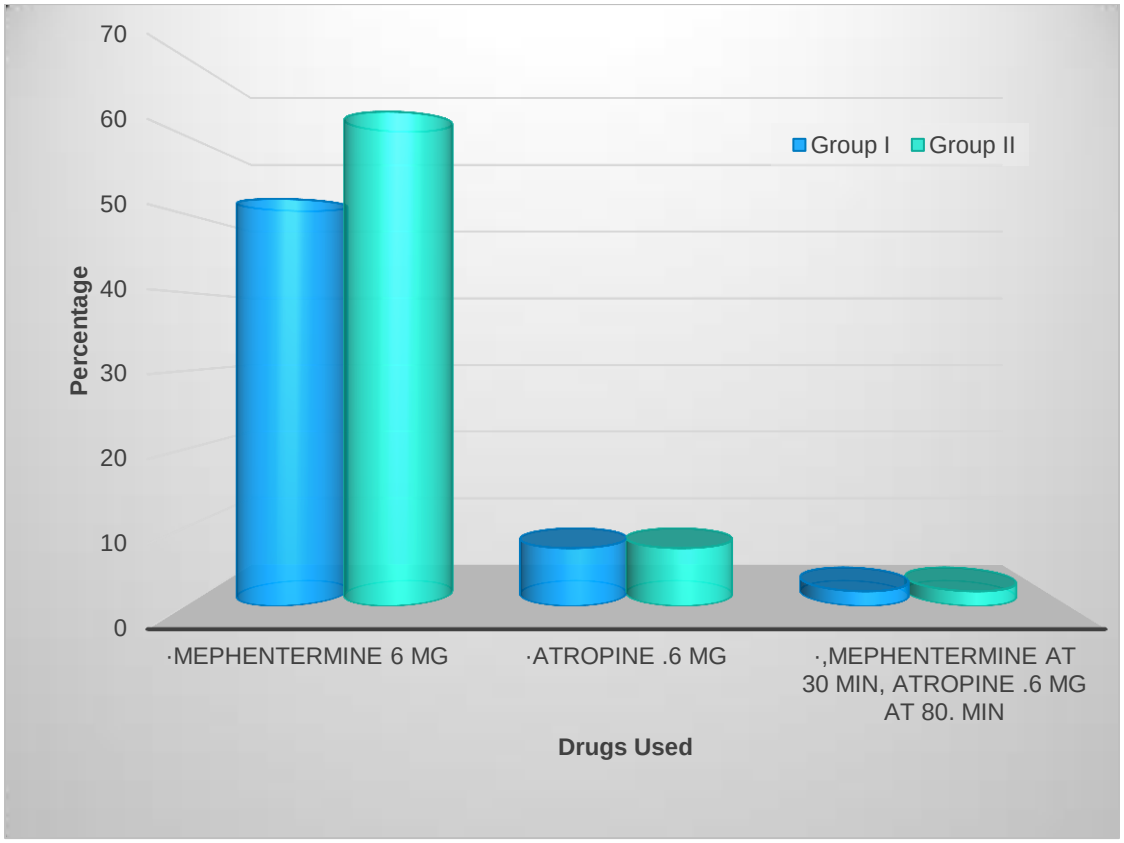
Drugs Used	Total (n=108)	Group I (n=54)	Group II (n=54)
Nil	69(63.9%)	48(88.9%)	21(38.9%)
Yes	39(36.1%)	6(11.1%)	33(61.1%)
Mephentermine 6 mg	6(5.6%)	28(51.9%)	34(63%)
Atropine .6 mg	0(0%)	4(7.4%)	4(7.4%)
Mephentermine at 30 min, atropine .6 mg at 80. Min	0(0%)	1(1.9%)	1(1.9%)

P=0.001, Significant, Chi-Square Test**

Graph 8: shows groups where drugs used and where drug is not used



Graph 9: shows different drugs used and their percentage



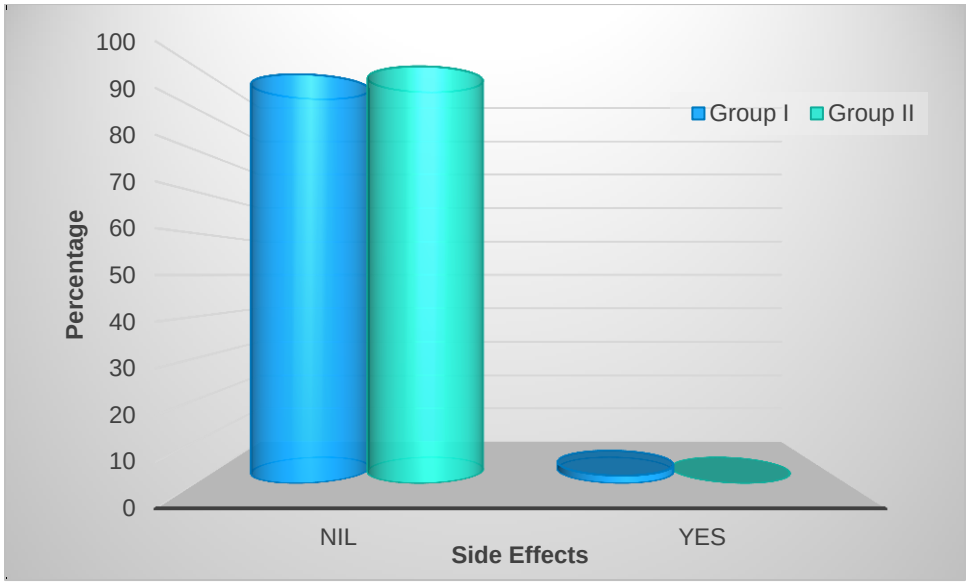
Side effects comparision in two groups

Table 9:

Side Effects	Total (n=108)	Group I (n=54)	Group II (n=54)
Nil	107(99.1%)	53(98.1%)	54(100%)
Yes	1(0.9%)	1(1.9%)	0(0%)
• Tachycardia	1(0.9%)	1(1.9%)	0(0%)

(P=0.615, Not Significant, Chi-Square Test)

Graph 10:



STATISTICAL ANALYSIS[52,53.54,55]

- Descriptive and inferential analysis is carried out.
- Continuous measurements plotted on (Mean+/-SD).
- Categorical measurements are plotted in Number (%).
- Assessment of significance done at 5 % level of significance.
- The data assumptions made are:
    1. Normal distribution of dependent variables.
    2. Random samples should be made.
    3. Cases of the samples shall be independent.

To find the significance on continuous scale between two groups, Student t test was used.

Leven`s test used to find the homogeneity of variance.

Chi-square/ Fisher Exact test: used for significance of categorical scale study parameters between the groups, Fisher exact test is applied when samples are very small.

Significant figures

+ Suggestive significance (P value: 0.05<P<0.10)

*** Moderately significant (P value:0.01<P</=0.05)**

**** Strongly significant (P value: P</=0.01)**

DISCUSSION

DISCUSSION

Since its use into the daily clinical practice, It is widely accepted and practiced regional anaesthesia technique for many lower abdominal and lower limb surgeries.

Advantage lies in its simplicity of administration, effectiveness of the block, lesser side effects, good post- operative analgesia and decreasing blood loss while maintained better peri-operative hemodynamic stability. But also associated with significant adverse effects like hypotension, bradycardia, post-spinal headache.

Hypotension is because of added effects of autonomic denervation and vagal nerve predominance. These leads to:

- Decrease in preload caused by peripheral venous pooling.
- Decrease in afterload caused by arterial vasodilation.
- Bradycardia will be due to sieling of cardio-accelerator fibers (T1-T4).
- Decrease in contractility in turn reducing the blood pressure.

Risk factors include:

- Higher level of blockade.
- Aorto-caval compression in obstetric patients leading to the drop in venous return.
- Lumbar puncture above L3-4 intervertebral space.

Spinal induced hypotension is corrected by improving the venous return so as to increase the preload thereby restoring the cardiac output physiologically.

1. Mechanical methods includes - leg elevation [40] (10-15 degrees) or wrapping leg with bandages [7], but doesnot reduces the incidence of hypotension.

2. <u>Volume preloading</u> stratergies are undertaken but colloids are not better than crystalloids in reducing the occurrence of hypotension and also shows some added limitations [42]:

- Increased cost in comparison to crystalloids
- Anaphylactic reactions
- Interfering in coagulation cascade

3. <u>Crystalloids</u> on the other part are required in large number of volumes (>15ml/kg) to bring down the incidence of hypotension. The requirement of large volumes have side effects like [42]:

- Increased Central venous pressure
- Hemodilution decreases oxygen carrying capacity
- Atrial natriuretic peptide release initiating diuresis, diminishing the effect of volume load on blood pressure.

In view of lesser efficacy of mechanical and volume expansion methods to correct spinal induced hypotension, pharmacological methods have come into practice to reduce the occurrence of spinal induced hypotension.

Several studies have done and proven that administration of vasopressors prophylactically in correcting hypotension are effective.

Among the Vasopressors Ephedrine, has better results in correcting the non-cardiac circulatory complications of spinal anaesthesia than a single alpha or beta-adrenergic agonist.

But intramuscular use of vasopressor is in borderline particularly when given before spinal anaesthesia because of rise in blood pressure risk and placental perfusion inadequacy, if subarachnoid block fails. But spinal anaesthesia procedure is easy to perform and <1% is its failure rate[56] and thus we excluded those patients who have spine anomalies to perform subarachnoid block in turn limiting the chances of block failure.

Ephedrine maintains arterial pressure by increasing cardiac output and heart rate. Due to its action on beta1 adreno receptor there is small chance of utero-placental insufficiency even if we have to go for general anaesthesia due to spinal anaesthesia failure.

Dosage

IM dose less than 25 mg is ineffective to prevent hypotension and 50 mg is found with increased incidence of hypertension and fetal acidosis[15].

Administration of 37.5mg Ephedrine I.M. was not associated with reactive increase in HR and BP in women posted for cesarean section[57].

But in past studies, it is nowhere considered to use ephedrine in relating to body weight. We have used prophylactic IM ephedrine 30 mg, in lesser dose when compared to other studies which have shown positive effect and also to see the potency of the drug in reducing the spinal induced hypotension and to look after any adverse side effects associated with it.

Changes in Oxygen saturation

All patients were monitored clinically in the intraoperative period in our study. It was noticed that none of the patients in both the groups had changes in oxygen saturation.

(P=0.372, Not Significant, Fisher Exact Test)

Incidence of Hypotension

Various authors have quoted several definitions for hypotension after subarachnoid block. Some of the authors have considered SBP of < 100 mmHg or (20% - 30%) drop from the baseline or 30 mmHg drop in SBP for defining hypotension.

Bhar d etal[11] study in 2011, **Ahmed H**[50] study in 2016 defined hypotension as 20-30% decrease in MAP from the baseline.

Yadav A S, Shakya M L, Dwivedi S in their study in 2016, comparing ephedrine and mephentermine have quoted hypotension as SBP less than 90 mmHg or more than 20% fall from baseline [49].

SBP less than 100 mmHg was taken by **Rout I.C.C in 1993** [58], **Hiroshi Ueyama in 1999** [59], **Vercauteren in 1998** [60].

We defined hypotension as 30% decrease in mean arterial pressures from baseline. We observed that occurrence of hypotension was more in placebo group when compared to ephedrine group and proven to be significant.

It was observed that hypotension occurred more in the first 20 minutes (from 2 minute after subarachnoid block in placebo group.

Preloading with crystalloid along with prophylactic IM ephedrine 15mg given 10min before to subarachnoid block will effectively prevent hypotension was the observation noted in 2009 by **Varathan S, Ekanayake S U, Amarasinghe U**, in cesarean section patients [47].

Frequency of hypotension is more in group C (preloaded with RL 15ml/kg) compared to group E10 and E20 (received ephedrine 0.5mg/kg along preloading with RL at 15ml/kg,

10 and 20 minutes before SAB).There was no notable rise in the HR and BP in any group, was some of the observations made by **Bhar D et al 2011**[11].

In both the above studies, it was shown that prophylactic ephedrine along with preloading has proven to be effective in reducing the occurrence of hypotension caused by spinal block and is statistically remarkable.

Even in our study, ephedrine has proven to be effective but the difference is above studies have compared between the dosages and timing of giving ephedrine along with preloading. Results showed that giving ephedrine 10 minutes before SAB is more effective.

Intraoperative rescue agents:

In our study, the rescue agent used is mephentermine 6mg IV boluses when the MAP is less than 30% from the baseline. Whenever the baseline MAP is between 20-30%, initially resuscitated with crystalloids. But when the MAP is below 30% of the baseline, rescue agent was given in IV bolus and observed for the pressures to improve. But even if pressures fail to improve, patient was given the repeated IV bolus of mephentermine 6mg.

Drugs Used	Total (n=108)	Group I (n=54)	Group II (n=54)
Nil	69(63.9%)	48(88.9%)	21(38.9%)
Yes	39(36.1%)	6(11.1%)	33(61.1%)
Mephentermine 6 mg	6(5.6%)	28(51.9%)	34(63%)

We noticed that the requirement of rescue agent is seen in 39 patients, in which 6 patients were from ephedrine group and 33 patients were from placebo group. Our study is similar to the below studies done with prophylactic ephedrine.

Eroglu et al 2003, has used Inj. Ephedrine I.V. when there was drop in blood pressure and did not rush fluids and any form of measures which was used in my study. Patients in group 1 received 3.42±0.97mg I.V. Ephedrine and Group II received 8.86±1.24mg I.V. Ephedrine which was statistically significant ($p<0.0001$) [61].

Varathan S , Ekanayake U S, Amarasinghe U in 2009, made a note that, the hypotension and the requirement of rescue agent is more patients receiving preloading alone than in ephedrine with preloading group[47].

Bhar D in 2011, noted that ephedrine requirement was significantly less ($p<0.05$) in group E10 compared to other groups. Total dose of rescue IV ephedrine and delayed hypotension was less in both group E10 and E20 compared to group C but no difference was seen in E10 and E20 group. Time of first requirement of ephedrine was more in both group E10 and E20 compared to group C [11].

Ahmed H O, Hossam M, Adel A in 2016, made observations that hypotension was significantly more in fluid group when compared to ephedrine group. P value was 0.03. Ephedrine bolus dose required to correct hypotension was significantly lower in ephedrine group (0.3 ±0.54) when compared to fluid group (0.6 ±0.8) P value 0.046* [50].

Heart rate

In our study, it is observed that heart rate when compared to two groups, placebo group shows drop in heart rate between (2 to 30) minutes and proven to be statistically significant using student t test.

Kafle et al 1994, found that tachycardia occurred in patients receiving intravenous ephedrine to treat the drop in BP and none of the patients who received oral ephedrine had rise in HR [62].

Eroglu et al 2003, recorded six cases of bradycardia in Group II (control group) who responded to Inj. Atropine 0.6mg intraoperative. These cases of bradycardia may be due to the high level of sensory block (T4 level). None of the participants who was given with oral ephedrine had episodes of tachycardia [61].

Varathan S, Ekanayake U S, Amarasinghe U in 2009 made note on heart rate in groups at 5, 8, 10, 15 and 20 minutes. The HR was best maintained by the control group A (Fluids) throughout the surgery without showing any significant changes. All the test groups (ephedrine) shown with a significant rise in heart rate at 5, 8, 10 and 20 min. Along with that, group D (30mg of drug ephedrine at 10 min before block) had shown the rise in HR at 20min time interval ($P>0.01$). Except group D, all the other groups did not show a significantly rise in HR at 15 minute interval [47].

Bhar D in the year 2011, noticed that HR intraoperatively was more in ephedrine group E10 and E20 significantly compared to group C ($p<0.05$). No difference was seen among group E10 and E20 [11].

Heart rate was higher in Ephedrine group when compared to Fluid group. But it was not statistically significant, P value more than 0.05 was the observations made by **Ahmed H O, Hossam M, Adel A in 2016 [50].**

Non-Hemodynamic side effects

Nausea and Vomiting side effects may because of the decrease in flow of blood to the trigger zone, and Ephedrine is the drug which increases mean arterial pressure and tries to improve the medullary blood flow.

Due to the preganglionic sympathetic denervation, increase in peristalsis may also stimulate during spinal anesthesia, but whether Ephedrine could prevent or reduce this action is unknown.

Double blinded randomized prospective study done by **Iqbal M S, Ishaq M, Masood A, Khan M Z in 2010** drawn a conclusion that the occurrence of nausea and vomiting was more in group-I (ephedrine 10 mg IV) and was related to hypotension (53%) when compared to other groups with 15 mg and 20 mg IV prophylactically [48].

In 2011, Bhar D in his study noted that due to improved hemodynamic stability in E10 group (Ephedrine 30 mg, 10 minutes before SAB), occurrence of nausea and vomiting was significantly less compared to other groups [11].

Ahmed H O, Hossam M, Adel A in 2016, conducted the prospective randomized study on pregnant females to see any side effects. Observations made was incidence of nausea and vomiting was higher in F group (preloading with fluids) when compared to E group (prophylactic ephedrine IV), but it was not statistically significant, and there were no chest pain symptoms in both the groups.

With above studies conducted and stating that with better stability of hemodynamic status, the occurrence of nausea and vomiting is reduced. In our study we didn't notice any occurence of nausea and vomiting in both the groups [50].

Comparison of Vasopressor Agents

Veeser M in 2012, conducted meta-analysis in elective cesarean sections between ephedrine and phenylephrine. They have come to a conclusion that, there was decreased risk of fetal acidosis with phenylephrine. But phenylephrine had a risk for bradycardia in pregnant females. There was no difference observed between vasopressors in terms of hypotension and hypertension [63].

Golakiya H N in 2016 , in their randomized double blinded parallel study on 150 parturient with comparison between mephentermine, ephedrine, and phenylephrine. It was noted that, there is no difference between mephentermine, ephedrine and phenylephrine immediately after the SAB. It was found that, there was less requirement of maintenance dose with ephedrine. Phenylephrine have shown episodes of maternal bradycardia [64].

Yadav A S, Shakya M L, Dwivedi S in 2016, on their comparative evaluation of prophylactic IM ephedrine and mephentermine made the observations that ephedrine and mephentermine when given IM prophylactically before SAB reduces the occurrence of hypotension. Apgar score was lower in mephentermine group [50].

Kaur D, Khan A L, and Pathak A in 2018, on the comparative study between the three vasopressors, Phenylephrine, ephedrine, mephentermine concluded that phenylephrine is fast-acting and short-lived normotensive effect added with a bradycardia effect. However, ephedrine and mephentermine had a steady progression and stable normotensive effect with no bradycardia effect. Hence, mephentermine and ephedrine were similar in performance, had a better hemodynamics control and had less recurrence when compared to phenylephrine [65].

When topic comes to the standard vasopressor for the treatment of spinal induced hypotension, the above studies have concluded their observations of the advantages and disadvantages. In our hospital we traditionally use mephenterine intra-operatively to treat hypotension. There were lot of studies conducted on phenylephrine with its advantages being on good fetal outcome. But studies regarding ephedrine were reduced, may be because of poor fetal outcome which was still controversial. But when compared to ephedrine and phenylephrine, both have shown their efficacy on reducing the incidences on hypotension but with regard to phenylephrine, it has shown episodes of bradycardia and also the requirement of maintenance rescue agent is more. Hence we used prophylactic ephedrine IM 30 mg aiming to reduce the incidence of post spinal

hypotension and also to have good hemodynamics intra-operatively. Our study have shown the expected results.

Effects on Fetal Outcome

A Randomized control trial was done between ephedrine and phenylephrine in cesarean delivery patients by **Lee in 2002**. They noted that 11 out of 19 patients in the Phenylephrine group and 2 of 19 women in the Ephedrine group HR demanded them to give atropine. Phenylephrine group patients are under risk of developing bradycardia.

At 1st min, one neonate with an Apgar score of <7 in the Ephedrine group compared with no neonate in the Phenylephrine group. At 5th min, no neonate in the Ephedrine or Phenylephrine groups had an Apgar score of <7. There was no change in the risk of low Apgar scores between the Phenylephrine and Ephedrine groups at 1st min and at 5th min [66].

Study conducted on comparison between prophylactic ephedrine and preloading with fluids by **Varathan S, Ekanayake U S, Amarasinghe U in 2009**, in patients undergoing elective cesarean section under spinal anesthesia have come with conclusion that APGAR scores at 1min and 5min was found to be in the normal range in either of the groups. No association was found between the I.M ephedrine and fetal acidosis [47].

Varghese N, Gurumurthy T in 2013, studied the effect of prophylactic ephedrine infusion and compared it with crystalloid preloading on neonatal acid-base outcome in elective caesarean section following SAB and concluded that, the APGAR score at 1 min and 5 min were good in both the groups. There were no case of fetal acidosis. There was

($p > 0.05$) no difference significantly in the umbilical blood gas values between Group I and Group II [67].

With the above conclusions made on the efficacy of ephedrine on fetal outcome by various studies, it is still inconclusive to use ephedrine in pregnant females undergoing cesarean section under spinal anesthesia.

Therefore we have carried out this study on ephedrine in patients undergoing lower abdominal and lower limb surgeries under spinal anaesthesia excluding cesarean sections.

SUMMARY

SUMMARY

This study was designed in prospective randomized controlled manner, to study the efficacy of prophylactic IM ephedrine in bringing down the incidence of hypotension following spinal anaesthesia.

Patients belonging to ASA Grade I & II posted for lower abdominal and lower limb surgeries under spinal anaesthesia was randomly allocated into ephedrine group and placebo group.

Group-A: Received prophylactic IM Ephedrine 30mg (1ml) 10 minutes before spinal anaesthesia.

Group-B: Received a Placebo (1ml normal saline) 10 minutes before spinal anaesthesia.

- Intra-operatively and postoperatively no significant changes were noted in oxygen saturation levels in any of the patients in both the groups.
- Incidence of Hypotension was more in group B and proven to be statistically significant when compared to ephedrine group from 2 – 20 minutes.
- The numbers of patients receiving the rescue vasopressor therapy was higher among in group B (31 patients in placebo group and 6 patients in ephedrine group)
- Heart rate is comparatively lower placebo group from 2-30 minutes and proved to be significant.
- No observations was made on the non-hemodynamic side effects like nausea, vomiting, chest pain.

CONCLUSION

CONCLUSION

The prophylactic administration of IM Ephedrine in ASA Grade I & II patients undergoing lower abdominal and lower limb surgeries under spinal anaesthesia, is a potent measure in bringing down and arresting the incidence of hypotension without causing any predicted side effects like central nervous system stimulation, tachycardia or arrhythmias.

To conclude, this study demonstrates that prophylactic IM Ephedrine is a simple, easy, effective and reliable method in reducing the occurrence of hypotension.

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BIBLIOGRAPHY

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ANNEXURES

ANNEXURES

PROFORMA

Efficacy of prophylactic IM Ephedrine in reducing the incidence of hypotension after spinal anesthesia

Investigators: Dr Nagaraj S Kalla / Dr Ravi M

1. **Name of the patient:**
2. **Age/Sex:**
3. **IP No :**

4. Ward:

5. ASA grade:

General physical examination:

Height: Weight: Pulse rate: BP:

Pallor/icterus/cyanosis/clubbing/lymphadenopathy/edema

Systemic examination:

RS -

CVS -

CNS -

P/A -

Investigations:

Blood group: Hb: WBC: Platelets:

RBS: Blood urea: Sr. Creatinine: Sodium:

Potassium: ECG:

Diagnosis:

Surgery:

Group A: IM ephedrine 30 mg given 10 minutes before spinal anaesthesia

Group B: Normal saline given 30 minutes before spinal anesthesia

Regional anesthesia procedure:

Dosage for SAB:

Baseline vitals:

HR:

BP:

MAP:

SPO2:

TIME	HR	SBP	DBP	MAP	SPO2	DRUGS USED	SIDE EFFECTS
0 MIN							
2 MIN							
4 MIN							
6 MIN							
8 MIN							
10 MIN							
20 MIN							
30 MIN							
40 MIN							
60 MIN							
80 MIN							
90 MIN							

PATIENT INFORMATION SHEET

Study: "Efficacy of IM ephedrine in reducing hypotension after spinal anaesthesia"

Investigators: Dr Nagaraj S Kalla / Dr Ravi M

Study location: R L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

Details: All Patients posted for lower abdominal and lower limb surgeries under spinal anaesthesia will be included in this study. Patients with co morbid conditions will be excluded from the study.

This study aims to reduce the incidence of hypotension after spinal anaesthesia. Patients will have to undergo routine investigations. Patient and the attenders will be completely explained about the procedure being done i.e Prophylactic IM ephedrine 30 mg will be given 30 minutes before spinal anaesthesia and patients will be randomly selected by computerized table and later put into in 2 groups - group A and group B.

Ephedrine will be avoided in patients with comorbid conditions. Most common side effects associated with high dose like nausea, headache, dizziness, anxiety, loss of appetite, restlessness, sweating, palpitations, tachycardia which are transient and for which anxiolytics such as midazolam will be given.

Please read the information and discuss with your family members. You can ask any question regarding the study. If you agree to participate in the study we will collect information. Relevant history will be taken. This information collected will be used only for dissertation and publication.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. There is no compulsion to agree to this

study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

For further information contact

Dr.Nagaraj S Kalla

Post graduate

Dept of Anaesthesia, SDUMC Kolar

Mobile no: 9972345777

INFORMED CONSENT FORM

Efficacy of prophylactic IM Ephedrine in reducing the incidence of hypotension after spinal anaesthesia

Investigators: Dr Nagaraj S Kalla/ Dr Ravi M

Date:

I, _____ aged _____ ,after being explained in my own vernacular language about the purpose of the study and the risks and complications of the procedure, hereby give my valid written informed consent without any force or prejudice for taking prophylactic IM Ephedrine 30 mg. The nature and risks involved have been explained to me to my satisfaction.

I have been explained in detail about the study being conducted. I have read the patient information sheet and I have had the opportunity to ask any question. Any question that I have asked, have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research. I hereby give consent to provide my history, undergo physical examination, undergo the procedure, undergo investigations and provide its results and documents etc to the doctor / institute etc. All the data may be published or used for any academic purpose. I will not hold the doctors / institute etc responsible for any untoward consequences during the procedure / study.

A copy of this Informed Consent Form and Patient Information Sheet has been provided to the participant.

_____

(Signature & Name of Pt. Attendant) Patient/Guardian)

(Relation with patient)

Witness: 1.

2.

Investigator signature