"EFFICACY OF PREOPERATIVE ORAL MIDODRINE IN PREVENTING HYPOTENSION AFTER SPINAL ANESTHESIA IN PATIENTS UNDERGOING INFRAUMBILICAL SURGERIES - A PLACEBO CONTROLLED TRIAL "

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With reference to the above, we wish to inform you that your proposed research project titled **" EFFECTS OF STELLATE GANGLION BLOCK ON INTRAOPERATIVE HEMODYNAMIC RESPONSES TO PNEUMOPERITONEUM IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY, HOSPITAL BASED RANDOMISED CONTROLLED TRAIL".** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee.

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ABBREVATIONS

ASA	-	American Society of Anaesthesiologists
HR	-	Heart Rate (bpm)
SBP	-	Systolic Blood Pressure (mm Hg)
DBP	-	Diastolic Blood Pressure (mm Hg)
SpO_2	-	Saturation of peripheral Oxygen (%)
SD	-	Small Dose
MD	-	Medium Dose
LD	-	Large Dose
CO	-	Cardiac Output
SA	-	Spinal Anaesthesia
SAB	-	Subarachnoid Block
MAP	-	Mean Arterial Pressure
ANP	-	Atrial Natriuretic Peptide
DGM	-	Desglymidodrine
BP	-	Blood Pressure
CSF	-	Cerebrospinal fluid
BJR	-	Bezold Jarisch reflex

ABSTRACT

TITLE: "EFFICACY OF PREOPERATIVE ORAL MIDODRINE IN PREVENTING HYPOTENSION AFTER SPINAL ANESTHESIA IN PATIENTS UNDERGOING INFRAUMBILICAL SURGERIES - A PLACEBO CONTROLLED TRIAL."

CONTEXT: Spinal anaesthesia is a neuraxial blockade which is widely used for anaesthetic management of patients undergoing lower abdominal and lower limb surgeries . There are different complications described in literature following spinal anesthesia ranging from local tissue effects to systemic effects of the administered drugs. Among the systemic side effects the cardiovascular side effects predominate, with hypotension.

AIMS: To demonstrate the efficacy of Midodrine drug in oral form in preventing post spinal hypotension in patients undergoing infraumbilical surgeries.

SETTING AND DESIGN: A ONE-YEAR RANDOMISED CONTROLLED TRIAL.

MATERIALS AND METHODS:

This one-year randomized controlled trial was conducted in the Department of Anaesthesiology, KLES Dr Prabhakar Kore Charitable Hospital Belagavi, from June 2023 to June 2024 on 120 participants undergoing infraumbilical surgeries under spinal anaesthesia.

- Group S- Patients were administered Midodrine 10milligram tablets powdered and dissolved in 25 millilitre water orally one hour prior to Spinal anaesthesia.
- Group C: Patients were administered with 25 millilitre of water orally 1 hour before spinal anaesthesia.

RESULT: The hemodynamic parameters were comparable in both the groups at baseline. At Time intervals of 2 minutes to 120 minutes post spinal anaesthesia there was significant decrease in systolic blood pressure, diastolic pressure and mean arterial pressure with p value < 0.001 at several time points in study group. The number of episodes of hypotension were markedly reduced in study group when compared to control group and was statistically significant p-value< 0.001.

The frequency of rescue vasopressors used was significantly high in control group when compared with study group, depicting high statistical significance, p value < 0.001.

CONCLUSION: The hemodynamic parameters showed significant stability in study group (Midodrine) in comparison to control group, thereby aiding in preventing post spinal hypotension in infraumbilical surgeries. The number of episodes of hypotension and number of doses of rescue vasopressors (mephentermine) were significantly on the decreasing trends in the study group in comparing with control group.

KEYWORDS: Spinal anaesthesia, Midodrine, Hypotension, Infraumbilical surgeries

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INTRODUCTION:

Spinal anaesthesia is a widely employed anaesthetic technique for many surgical procedures worldwide, providing advantages such as patient awareness, reduced medication costs, and rapid patient turnover. Lower limb, perineal (e.g., genital or anal procedures), or lower abdominal wall surgeries (e.g., inguinal herniorrhaphy) may be conducted safely and successfully with a subarachnoid (spinal) block rather than general anaesthesia. Spinal anaesthesia is more favored than epidural anaesthesia, which requires large amounts of local anaesthetics and is associated with toxicity due to these huge doses.[1]

Spinal anaesthesia utilizing 0.5% hyperbaric bupivacaine is favoured for prolonged surgeries owing to its extended duration of action. A subarachnoid block serves as the sole source of anaesthesia. Subsequently, epidural and spinal anaesthesia may be employed concurrently, combining the benefits of both methods: the swift, profound sensory blocking provided by spinal anaesthesia and the ability to provide additional doses via an epidural catheter.

Spinal anaesthesia is straightforward to administer, inexpensive, guarantees extensive muscular relaxation, and facilitates a speedy onset of anaesthesia. It has superior efficiency and demands a lower medication dosage. It produces intense sensory and motor blockade as well as sympathetic blockade. Additionally, resumption of the different physiologic functions was more rapid, greater compliance and reduced hospital stay when abdominal gynaecologic surgeries were performed under spinal anaesthesia than with general anaesthesia. When compared to epidural anaesthesia, which involves instilling desired medications outside the dura mater, spinal anaesthesia seeks to introduce the necessary medications straight into the CSF. Often marked by a higher density, the sensorimotor block requires less local anaesthetics, thereby minimizing the risk of local anaesthetic toxicity.

Central neuraxial opioids whether intrathecal (IT) or/and epidural (Ep) offers the benefit of selective analgesia without motor or sensory blockade. Several drugs like midazolam, opioids, and alpha 2 adrenergic receptor agonists have been used as an adjuvant to local anaesthetics.

The advantages encompass the omission of general anaesthesia and its associated airway management issues, a diminished metabolic stress response to surgery, hemorrhage control, venous thromboembolism prevention, pulmonary protection (particularly for patients with severe lung problems), and mental status monitoring.

Sympathetic and parasympathetic nervous system function play a vital part in development of haemodynamic instability and intraoperative hypotension which is a well-established source of post operative complications. Preloading with sympathomimetic medications, volume replacement, as well as physical methods, such as compression stockings and leg bindings are among the several approaches used to avoid hypotension of spinal anaesthesia.[2]

Midodrine is a prodrug of desglymidodrine that stimulates alpha-1 adrenergic receptors. This leads to venous vasoconstriction and, consequently, an increase in blood pressure. Midodrine hydrochloride exhibits direct alpha-1 adrenoreceptor agonist action via its metabolite desglymidodrine, resulting in vasoconstriction. The net outcome is an elevation in SBP and vascular tone. The blood-brain barrier is almost completely bypassed, and cardiac beta receptors are unaffected. Midodrine has a low risk of neurological side effects, is well-absorbed orally, with good oral bioavailability and has a generally acceptable safety profile. The literature search did not uncover any studies on the efficiency of Midodrine in mitigating hypotension following spinal anaesthesia.[2]

We postulate that patients provided with Midodrine prior to spinal anaesthesia will have less intraoperative hypotension. Hence, we aim to assess the efficacy of prophylactic administration of 10mg Midodrine tablet one hour before spinal anaesthesia in prevention of hypotension,

which is defined as SBP below 90 millimetre of mercury or below 80% of baseline, in patients having lower limb or abdominal procedures.[4]

AIMS AND OBJECTIVES:

Primary objective:

To study the efficacy of preoperative oral midodrine in prevention of hypotension after spinal anaesthesia in patients undergoing lower abdominal and lower limb surgeries.

Secondary objective:

• To assess Haemodynamic parameters like SBP, DBP, MAP, HR for 2 hours after administration of Midodrine.

• To assess the number of doses of mephentermine used.

REVIEW OF LITERATURE:

Spinal anaesthesia is a neuraxial blockade extensively utilized for the anaesthetic management of patients enduring lower abdomen and lower limb surgeries. Several complications associated with spinal anaesthesia are documented in the literature, encompassing local tissue effects and systemic implications of the administered agents.

The cardiovascular side effects are the most prevalent among systemic side effects, with hypotension occurring in up to 33% of patients. Spinal anaesthesia produces sympathetic blocking, resulting in diminished vasomotor tone, which subsequently decreases preload (due to venodilatation and reduced venous return), afterload (reduced systemic vascular resistance), and ultimately cardiac output.

The autonomic nervous system's function is pivotal in contributing to the hemodynamic instability and intraoperative hypotension, which are recognized contributors to complications following surgery. Different approaches are employed to prevent low blood pressure during subarachnoid block, such as IV fluid preloading, vasoconstrictor agents, and physical interventions such as compression hosiery with limb restraints. Innovations in comprehending the mechanisms behind spinal-induced hypotension have prompted improvements in management protocols. For instance, if decreased preload is considered the primary concern, positioning and fluid therapy are prioritized; conversely, if vasodilation is identified as the cause, a vasoconstrictor is preferred.

Ahmed M Hasanin et al performed a randomised dose finding study to identify optimum dosage of Norepinephrine infusion for preventing hypotension caused by spinal anaesthesia in a double-blinding randomised controlled trial including full gestation parturient scheduled for c-section delivery, with norepinephrine infusion was initiated after the subarachnoid block. The participants were randomized into three groups which received norepinephrine with an

initial infusion rates of 0.025 microgram/kilogram/minute, 0.050 microgram/kilogram/minute, and 0.075 microgram/kilogram/minute revealed that the 0.05 microgram/kilogram/minute and 0.075 microgram/kilogram/minute rates significantly diminished post-spinal hypotension after c- sections compared to the 0.025 microgram/kilogram/minute rate.[5]

Tarek M Ashoor et al undertook a double-blinded, placebo controlled RCT comprising 110 individuals belonging to the age group of 60 years and above to assess the efficacy of intravenous Dexamethasone in averting post-spinal hypotension. They identified that a one shot intravenous dose of 8milligram Dexamethasone considerably decreased the incidence of post-spinal hypotension in contrast to placebo.[6]

A prospective cohort study by Shitemav J aimed to assess the use of prophylactic ephedrine to minimize post-spinal hypotension following spinal anaesthesia in elective caesarean-section. The study discovered that the prophylactic administration of a 10milligram intravenous bolus of ephedrine successfully diminished the incidence of post-spinal fall in blood pressure and resulted in greater arterial pressure stability among parturients undergoing elective cesarean sections.[7]

A randomized controlled trial was executed by Miodrag Z to evaluate the affects of ephedrine and phenylephrine infusion upon hemodynamic variables that follows subarachnoid anaesthesia in elderly individuals. After delivering 15 milligram of Levobupivacaine for spinal anaesthesia, subjects received infusion of either 20 milligram of ephedrine, 250 microgram of phenylephrine, or saline within a 30-minute period. They saw a substantial decline in blood pressure (BP), cardiac index (CI) and heart rate (HR) from 15 minutes before the block to 30 minutes following spinal anaesthesia in saline group compared to the other two groups. Consequently, they ascertained that the administration of ephedrine (20 milligram) or

phenylephrine (250 microgram,) offsets post-spinal hypotension while preserving cardiac index and heart rate.[8]

Amos Lal A et al performed a placebo-controlled clinical trial to determine the effectiveness in orally administering midodrine within the initial 24 hours of sepsis, aimed at decreasing the requirements for vasoconstrictor agents. In this study, 32 patients in early sepsis were randomly made to receive either oral midodrine at dose of 10 milligram for three doses or a placebo. The results indicated a substantial decrease in both the dose requirement and the duration of vasopressor use in midodrine troop compared to the control group. They observed that pre-emptive use of oral 5milligram midodrine did not significantly reduce the prevalence of orthostatic hypotension during early post operative mobilisation compared with placebo.[9]

Hemant Bhagat et al conducted a randomized control trial including 90 patients to evaluate the success rate of three regimens in preventing post spinal hypotension. Group I patients (crystalloid group) received preloading with 15 millilitre/kilogram of ringer's lactate over 20 minutes period preceding the subarachnoid block, followed by intravenous injection of placebo for next 20 minutes after spinal anaesthesia, Group II patients (vasoconstrictor group) received intravenous bolus of 5 milligram ephedrine in the first and second minute, followed by 1 milligram ephedrine at the end of each minute for next 18 minutes following spinal anaesthesia. Group III patients (combination group) received preloading with 7.5 mililitre/kilogram of ringer's lactate over 10 minute period preceding the spinal block followed by intravenous bolus of 2.5 milligram ephedrine in the first and second minute and 0.5 milligram ephedrine at the end of each minute for the next 18 minutes after spinal anaesthesia. He observed that there was a significant fall in the mean systolic blood pressure throughout the study period in group I patients, in group II significant decrease was seen during 10 and 15 minutes of the study, while in group III the decrease from the baseline value was found to be significant only at 15th minute of the study.[10]

Ahmed Ibrahim Elsakka et al and others performed a randomized controlled trial on 85 parturients, they were randomly assigned into two groups. Group Sitting remained sitting for 2 minutes post-injection, while Group Control was positioned supine immediately following the spinal anaesthesia. Both groups were given a prophylactic intravenous infusion of norepinephrine in conjunction with an intravenous ondansetron bolus prior to surgery. SBP of patients was recorded from the intrathecal injection till the delivery of the foetus. He noted that the SBP in the Sitting Group (122 ±14 mmHg) was considerably elevated compared to Control group's measurements (114 ±10 mmHg) till delivery (P = 0.004). The intraoperative SBP values of the Sitting group frequently exceeded those of the Control group. The Sitting group exhibited a diminished incidence of hypotension and a lower rate of ephedrine use in comparison to the other group; nevertheless, the incident of bradycardia were found similar in both groups.[11]

Randall L. Carpenter performed a prospective study on 952 individuals to determine the number of cases of bradycardia (HR<50 beats per minute), hypotension (SBP<90 millimetre of mercury), nausea, vomiting, and dysrhythmia during spinal anaesthesia. He found that 314 patients (33%) developed hypotension, 125 patients (13%), 175 patients (18%), and 65 patients (7%). He determined that the occurrence of deleterious consequences such as hypotension, bradycardia, nausea and vomiting were diminished by reducing peak block height and utilizing basic solutions of LA executing intrathecal administration at or beneath the L3-L4 interspace.[12]

Charlotte Hofhuizen et al and their team performed prospective cohort trial upon 64 subjects aged > 65 years old who underwent operations with spinal anaesthesia. Participants was assigned into 2 groups: one received 15 milligram of bupivacaine MD group), while the other was given 10 milligram of bupivacaine(H) along with 5 microgram of Sufentanil (low dose [LD] group). Arterial BP and cardiac output was constantly checked during entire surgery with a non invasive finger cuff apparatus. The study included 33 subjects in MD group and 31 in the LD group, with no mathematic corelation in baseline hemodynamics. On average, CO

declined by 11.6% in the MD group and 10.0% in the LD group, while systemic vascular resistance (SVR) remained stable. A reduction in stroke volume (SV) of more than 15% from baseline occurred in 67% of MD patients and 45% of LD patients ($P<0.05$). The findings indicate that spinal anaesthesia significantly reduces CO and blood pressure in elderly patients, primarily due to decreased SV rather than SVR. However, the impact on CO and blood pressure exhibited no substantial difference between the two doses of bupivacaine.[13]

Ajay K. Parsaik et al and their colleagues undertook a thorough review and meta-analysis of clinical studies on the advantageous effects of midodrine in managing orthostatic hypotension. 7 trials with 325 participants, averaging 53 years of age were studied. Compared to the control group the mean variation in systolic blood pressure was 4.9 mm mercury ($p=0.65$), while the mean difference in mean arterial pressure when shifting from supine to standing position was -1.7 millimetre of mercury ($p=0.45$). Nonetheless, following midodrine, SBP increased by 21.5 millimetre of mercury ($p<0.001$). A notable augmentation was observed in the global evaluation symptoms scale for both patients and investigators, with mean differences of 0.70 (95% CI: 0.30–1.09; $p<0.001$) and 0.80 (95% CI: 0.76–0.85; $p<0.001$), respectively. This metanalysis demonstrates that the alteration in mean blood pressure and systolic blood pressure when transitioning from a supine to an erect position was similar across the midodrine and control groups. Despite this, there was reasonable variability in results. The global assessment symptoms scale utilized by subjects and researchers indicated symptom relief with midodrine treatment.[14]

Karim Asehnoune et al conducted a prospective randomized study of 36 patients belonging to ASA grade 1 and 2 patients receiving subarachnoid anaesthesia for urologic, lower abdominal, or lower extremities surgery. The clients were split into SD and LD SA groups. The SD group got 7.5 mg of hyperbaric bupivacaine and 5 mcg of sufentanil, whereas the LD group received 12.5 mg. No significant differences were seen in baseline CO, SBP, MAP, DBP, and HR values

across groups. SD group carbon monoxide levels were far greater than LD group at 2,10, and 30 minutes post-SA. CO levels in the SD group increased significantly 2 minutes post-SA ($P < 0.0002$) and returned to baseline values (T0) after 10 and 30 minutes. In the LD group, CO significantly reduced after 10 minutes ($P < 0.001$) and 30 minutes ($P < 0.0002$) after SA. The SD group's SBP, MAP, and DBP decreased significantly from T0 to SA, whereas HR remained steady. SBP, MAP, DBP, and HR decreased significantly in LD compared to T0. They found that spinal injection of 7.5 milligram bupivacaine and 5 microgram sufentanil provides better anaesthetic and cardiovascular stability than 12.5 milligrams. Post-SD HR and DBP readings are significantly higher than LD bupivacaine, indicating hemodynamic stability. Low-dose patients had lower heart rate and diastolic blood pressure than standard-dose patients, with just two patients in each cohort having hypotension. This research shows that standard-dose bupivacaine (7.5 milligram) does not reduce cardiac output like low-dose (12.5 milligram), indicating that it may reduce cardiovascular problems.[15]

L. A. H. Critchley et al performed a RCT with 34 patients belonging to ASA grade 2 or 3 individuals necessitating SAB for urological procedures. One group was administered fluid preloading with normal saline, supplemented with additional fluid boluses as necessary; the second group got an infusion of the alpha agonist metaraminol; the third group was treated with an infusion of combination alpha and beta agonist ephedrine. Preloading with normal saline at a dosage of 16 ml/kg prior to subarachnoid administration of bupivacaine led to elevations in central venous pressure and cardiac index (CI), together with a fall in systemic vascular resistance index (SVRI). Following subarachnoid administration of bupivacaine, six out of ten patients necessitated additional fluid boluses to sustain systolic arterial pressure. Even so, this did not sustain sufficient systemic arterial pressure in five patients, necessitating a rescue infusion of ephedrine for 3 patients and metaraminol for 2 patients. Relative to baseline data, both SAP and MAP exhibited a reduction at 10 minutes following the subarachnoid

administration of bupivacaine (‘P = 0.004; P = 0.002’). In the metaraminol cohort, sufficient Systemic Arterial Pressure was preserved in all subjects, and SAP is considerably elevated compared to the fluid cohort 15 minutes after induction (P < 0.01). SAP and MAP reduced 5 minutes post-induction (P = 0.005; P = 0.03) and reverted to initial levels by 15 minutes. Heart rate declined at 10 minutes (P = 0.0001) and central venous pressure reduced at 5 minutes (P = 0.006), with both parameters reverting to baseline values by 15 minutes. Systolic and mean arterial pressures declined 5 minutes following the introduction of the subarachnoid block (both P = 0.0001), while heart rate rose 5 minutes after the block's induction (P = 0.001). Each treatment modality stabilised SBP within normal limits in 50% or more of patients, with treatment shortcomings seen in the fluid and ephedrine groups. There were discrepancies in the haemodynamic changes of treatment on stroke index, heart rate, and systemic vascular resistance index.[16]

Amrita Panda Manoja K et al conducted a 2-year, single -centre, prospective observational study. Seventy-eight patients participated in the study. Patients with high blood pressure and blood pressure within normal ranges undergoing planned surgeries receiving a subarachnoid block (SAB) were included. Group 1 comprised patients with hypertension undergoing treatment with calcium channel blockers. Group 2 comprised individuals with hypertension undergoing treatment with calcium channel blockers in conjunction with beta-blockers. Patients exhibiting blood pressure within the normal range were assigned to group 3. We gathered patients demographic data, and we analysed heart rate (HR), systolic and diastolic blood pressure, mean arterial pressure among the batches. HR, SBP, DBP and mean arterial pressure substantially diminished during time across all batches; however, no notable differences were observed when comparing data between batches. Hypotension was clearly more prevalent in group 1 (p=0.02) than in groups 2 and 3. Group 2 exhibited a significantly elevated occurrence of bradycardia (p<0.05) in comparison to groups 1 and 3. The study

revealed no significant variations in hemodynamic changes between people using antihypertensive drugs (calcium channel blockers alone or in combination with beta-blockers) and those not undergoing antihypertensive treatment after SAB.[17]

J. Jankovic et al undertook a double-blinded, placebo controlled trial featuring a one-week placebo run-in phase involving 97 patients with orthostatic hypotension. Midodrine 10 milligram has shown an increase in orthostatic SBP of 22 millimetre of mercury (28 percent, $p < 0.001$ relative to placebo). Moreover, Midodrine evidently elevated ($p < 0.05$) features associated with orthostatic hypotension, including dizziness/ lightheadedness, syncope, low energy levels, fatigue, reduced standing capacity, and depressive emotions compared to placebo. The predominant side effects ranged mainly between mild to moderate. Adverse reactions recorded in 22 percent of the placebo group and 27 percent of the midodrine treated group.[18]

BASIC SCIENCES

Applied Anatomy

For the safe and effective delivery of spinal anaesthesia, an anaesthesiologist needs a comprehensive and precise understanding of the vertebral column's structure and its contents. This knowledge is crucial not only for the procedure itself but also for understanding how the drug disperses in the sub arachnoid space and the extent of the block achieved.

Vertebral column

The primary role of the vertebral column is to protect the spinal cord. The vertebral column comprises 33 vertebrae.[19]

- Cervical - 7
- Thoracic - 12
- Lumbar - 5
- Sacrum - 5 (fused)
- Coccyx - 4 (fused)

Curves of spine[20]

In adults, the curves of the vertebral column play a crucial role in the distribution of drugs in the subarachnoid space[20], and these curves include:

- Cervical curve - Convexity anterior
- Thoracic curve - Concave anterior
- Lumbar curve - Convexity anteriorly

Cervical (C) five and lumbar (L) five are the highest points of cervical and lumbar curves in supine position and the lowest points of thoracic and sacral are at thoracic (T) five and sacral (S) two respectively.[19]

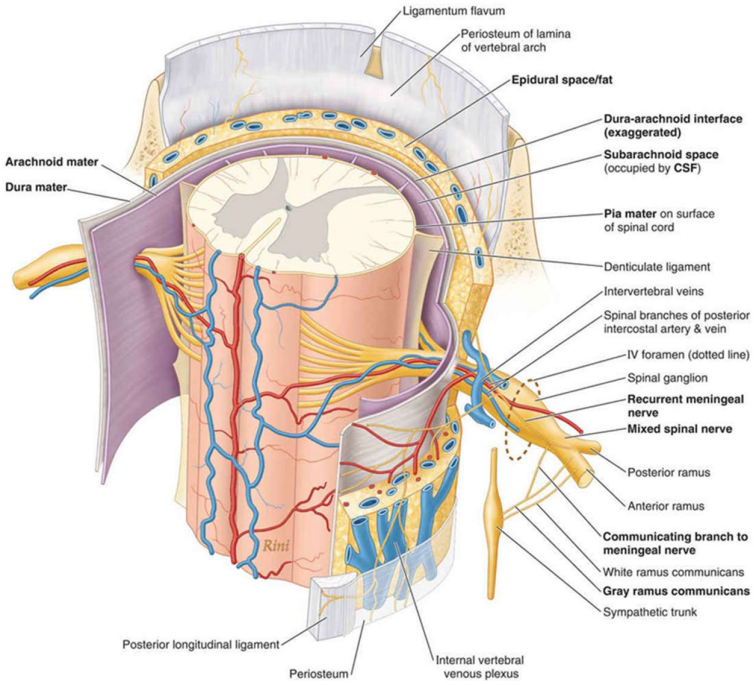


Figure 1: Vertebral Column[21]

Lumbar vertebrae

A typical lumbar vertebra consists of:

- A kidney shaped body.
- Two pedicles directed backwards from the upper part of the body.
- Two transverse processes
- Two laminae meeting posteriorly and enclosing the triangular vertebral foramen.
- Thick, broad and quadrilateral spinous processes.

- Two upper and lower articular processes which prevent rotation but allow limited flexion and extension between contiguous vertebrae.

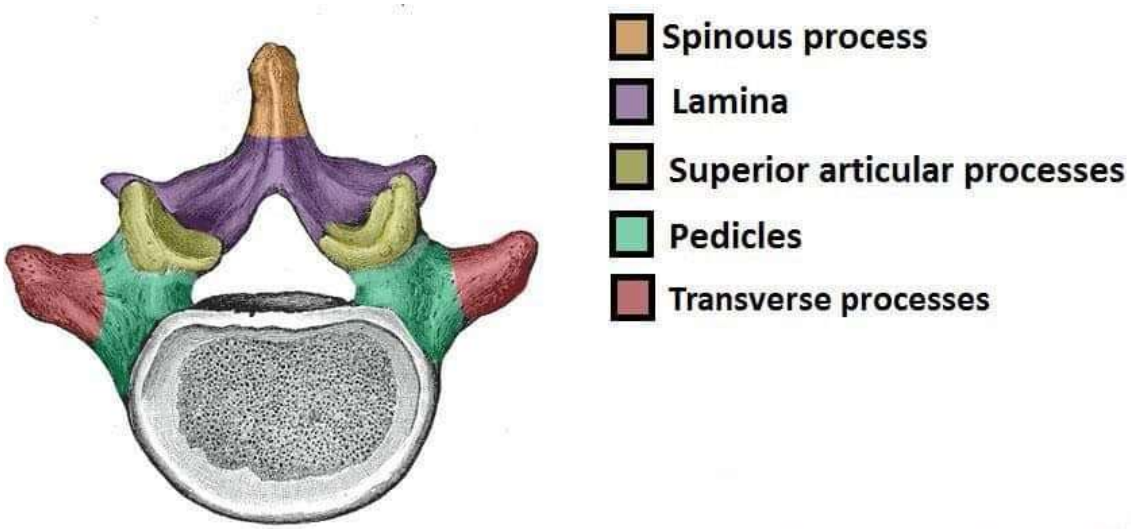


Figure 2: Typical Lumbar Vertebrae[21]

Thoracic vertebrae:

- A heart shaped body
- A small costal demi facet on superior border of lateral side of body and a larger demi facet on the inferior surface
- Shallow superior vertebral notches and deeper inferior vertebral notches
- Transverse processes are directed backwards and laterally, carrying a costal facet for articulation with ribs.

Vertebral ligaments[22]:

The following overlapping ligaments provide stability to the vertebral column and protect the spinal cord:

Supraspinous ligament: This is a strong fibrous cord which connects apices of spinous processes from sacrum to C5 where it is continued as the ligamentum nuchae. The width depends upon the width of the spinous process – in lumbar region it might be up to 1 cm wide. In elderly people and manual labourers this ligament calcifies thus making the midline approach difficult.

Interspinous ligament: This is a thin membranous ligament running obliquely and connecting spinous processes blending anteriorly with ligamentum flavum and posteriorly with supraspinous ligament. In the lumbar region, this ligament is rectangular in shape leading to the characteristic and identifiable "loss of resistance" feel to air or saline.

Ligamentum flavum: This ligament comprises of yellow elastic fibres and connects adjacent laminae. Laterally, this ligament begins at the root of articular processes and extends posteriorly and medially to the point where laminae join to form spinous process. It provides the classic springy resistance in the lumbar region.

Longitudinal ligaments: There are two longitudinal ligaments (anterior and posterior) that bind vertebral bodies together.

In spinal anaesthesia, the needle is advanced beyond the dura mater and into the subarachnoid space, which lies between the lumbar vertebrae. To access this space, the needle traverses several layers of tissue and ligaments, including the supraspinous ligament, interspinous ligament, and ligamentum flavum.[22]

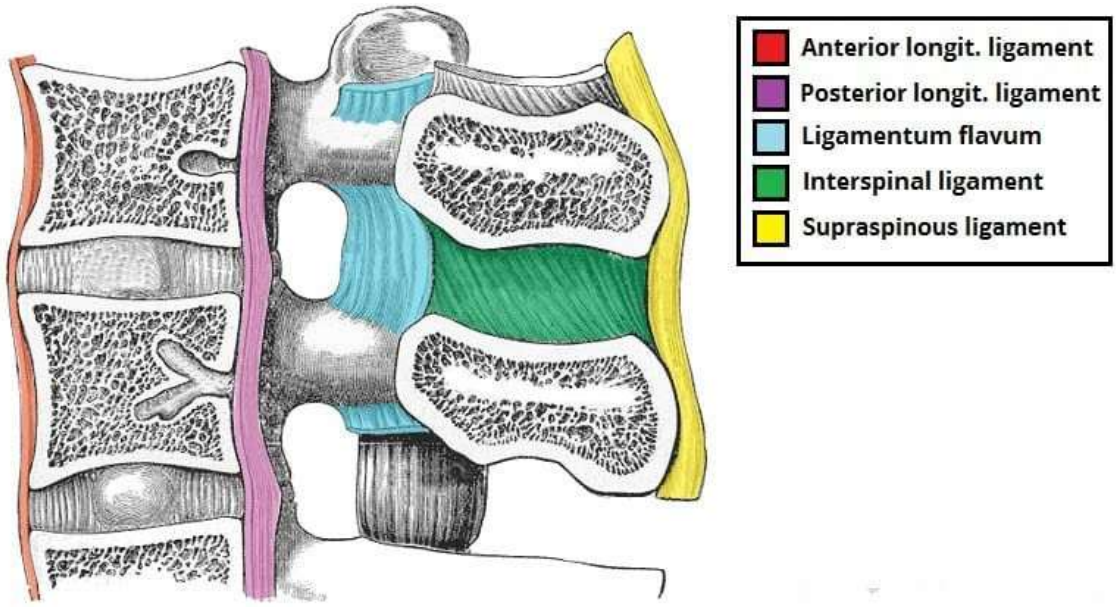


Figure 3: Vertebral Ligaments[22]

Intervertebral Discs

These are principle connecting link between vertebral bodies. They form about 25% of the length of the spine. They consist of two parts - The outer fibrous part called the *annulus fibrosus* (made up of fibrous tissue), while the *nucleus pulposus* is the softer core. The discs serve as shock absorbers and lend flexibility to the vertebral column.[19]

Topographical Line of Tuffier

This is a horizontal line across the back between the crests of the iliac bone passing over the spine of the 4th lumbar vertebra in the upright position. In a patient lying in the lateral position, it may also pass through L4 and L5 interspaces. The superior iliac crest is used to identify the L4 and L5 interspace during epidural anaesthesia.[23]

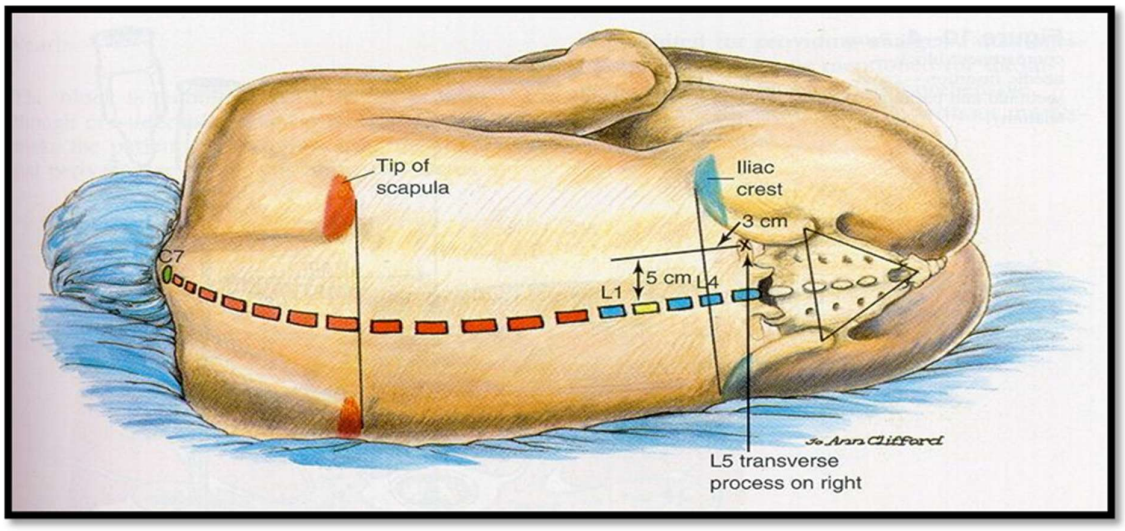


Figure 4 Topographical line of tuffier[23]

Vertebral canal:

The vertebral canal is bound by the vertebral bodies and intervertebral discs anteriorly, the laminae, ligamentum flavum and laterally by pedicles and laminae.[24]

The contents of vertebral canal are as follows:

- Spinal cord
- Spinal nerve roots
- Meninges
- Cerebrospinal fluid
- Vessels
- Fat
- Loose areolar tissue

Spinal cord[20]

The average length of the spinal cord in males is 45 centimetres (cms) and in females it is 42centimetres (cms). The average weight is approximately 30 gram.

The spinal cord is a continuation of the medulla oblongata below the level of foramen magnum and it tapers off into a conical extremity known as conus medullaris. Filum terminal descends to the back of first segment of coccyx from apex of conus medullaris.

At birth, Spinal cord ends at the level of lower border of lumbar (L) three vertebra and in adults, it is as follows;

- Lower border of L1 - 50%
- Upper border of L2 - 40%
- Upper border of L3 - 3%

From the spinal cord arise 31 pairs of spinal nerves, each made of a ventral and a dorsal root. These anterior and posterior roots after crossing the subarachnoid space, pass through the dura and extradural space independently and unite at the level of intervertebral foramen to form spinal nerve trunks, which further divide into anterior and posterior primary divisions.

The amount of white matter declines progressively from the cervical region down to the lumbar region. The grey matter is greatly increased in the both the lumbar and cervical enlargement.[25]

Blood Supply of Spinal Cord:

The spinal cord receives its blood supply from anterior and posterior spinal arteries. The anterior spinal artery is a single vessel lying in front of the anterior median fissure. It is formed by two small arteries, one given off from each vertebral artery at the level of the foramen

magnum. It receives small communications from the intercostal and lumbar arteries; to provide the extra blood supply needed in the cervical, thoracic and lumbar enlargements.[26]

There are two posterior spinal arteries-one on each side. They are derived from the vertebral artery or more often from a primary branch of each vertebral artery. They supply the posterior one-third of the spinal cord. This supply is augmented by spinal branches of vertebral, ascending cervical, posterior intercostals, lumbar and lateral sacral arteries, which pass through the intervertebral foramina.

Venous drainage is through a plexus of anterior and posterior veins in the neck, azygous veins in the thorax, lumbar veins in the abdomen, and lateral sacral veins in the pelvis. There is no anastomosis between the anterior and posterior spinal arteries.

The longest of the feeder arteries is the radicularis magna (artery of Adamkiewicz), which supplies the anterior spinal artery in the area of the lumbar enlargement of the cord. It enters by way of a single intervertebral foramen (78% of the time on the left) between the T8 and L3 foramina.[26]

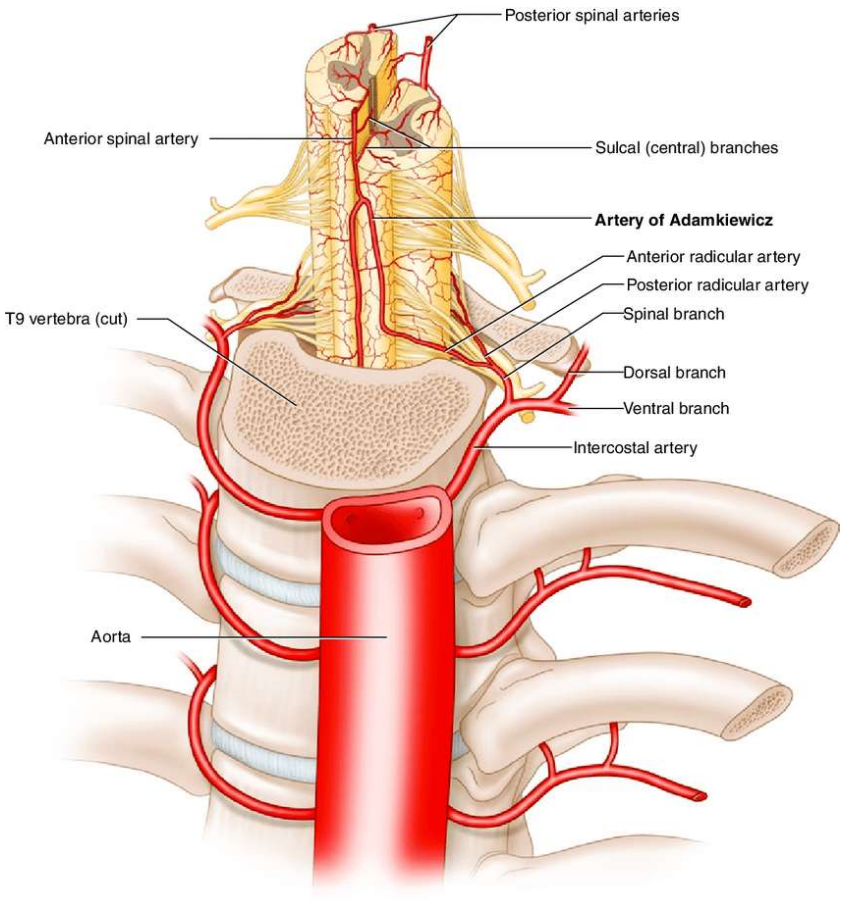


Figure 5: Blood supply of spinal cord[26]

Meninges

The spinal cord is covered by three membranes from inward to outward, they are the pia mater, the arachnoid mater and the dura mater. The dural sac is the continuation of meningeal layer of the cranial dura mater. It is a circular sac or sleeve surrounding the spinal cord. Above, it is attached firmly to the circumference of the foramen magnum[20].

Duramater

It is the outermost membrane, the fibres of which run longitudinally. Although continuous, it can be described in two parts: the cranial and the spinal. The cranial dura consists has two

layers, outer endosteal layer, which lines the skull, and an inner meningeal layer, which invests the brain and folds inward to form the falx cerebri and tentorium cerebelli.

Arachnoid Mater

The arachnoid mater is a delicate non-vascular membrane applied closely to the dura mater. The lower extent of dural sac is as follows:

Below this the dura continues as the filum terminale. The subarachnoid space is the space between the arachnoid and pia mater. This space is occupied by the cranial and spinal nerves and by the cobweb trabeculae. The space is annular in the cranial and thoracic vertebrae and is about three mm deep. Below the first lumbar vertebrae it is circular in shape.

Cerebrospinal fluid (CSF):

It is clear, colourless liquid that fills and surrounds the brain and the spinal cord and provides a mechanical barrier against shock. Formed primarily in the ventricles of the brain, the cerebrospinal fluid supports the brain and provides lubrication between surrounding bones and the brain and spinal cord. When an individual suffers a head injury, the fluid acts as a cushion, dulling the force by distributing its impact. The fluid helps to maintain pressure within the cranium at a constant level. An increase in the volume of blood or brain tissue results in a corresponding decrease in the fluid. Conversely, if there is a decrease in the volume of matter within the cranium, as occurs in atrophy of the brain, the CSF compensates with an increase in volume. The fluid also transports metabolic waste products, antibodies, chemicals, and pathological products of disease away from the brain and spinal-cord tissue into the bloodstream. CSF is slightly alkaline and is about 99 percent water.

Composition:

Volume: 120 – 150ml (25-35ml in spinal space)

Specific gravity: 1.003 – 1.009 (at 37 degree Celsius)

CSF pressure: 60-80 mm Hg in lumbar space

pH: 7.27-7.37

PCO2: 48mmHg HCO3:23mEq/L

Sodium: 135-145 mEq/L

Magnesium: 2-2.5mEq/L

Chloride: 15-20 mEq/L

Calcium: 2-3mEq/L

Phosphorous: 1.6mg/dl

Proteins: 23-38mg/dl

Physiology of Subarachnoid Block

Spread, duration, density and dose are the most important factors that determine the spread and duration of subarachnoid anaesthesia. Density is the ratio of the mass of a substance to its volume. Baricity is the ratio of two densities; here, the density of CSF and that of the injected local anaesthetic. Currently used local anaesthetics are made hyperbaric by mixing with dextrose. Plain local anaesthetic solutions are isobaric or slightly hypobaric.

Hyperbaric local anaesthetics are denser than CSF and will flow with gravity to the dependent areas of the spine, usually the upper thoracic region in supine patients. Positioning patients upright or lateral can limit the initial spread of hyperbaric local anaesthetic. But, when the patient returns to the supine position, even after 20 to 30 minutes, the sensory level reaches the usual mid-thoracic dermatomes. Bulk displacement determines the initial spread of isobaric drug. Subsequently, movement of CSF by either transmission of cardiac pulsations or gross patient movements (i.e., turning from lateral to supine position) will determine the ultimate spread of block. In nonpregnant patients, hyperbaric local anaesthetics produce more consistent levels of sensory block than isobaric drug. When used for subarachnoid anaesthesia for cesarean section, there is little difference between equal doses of isobaric or hyperbaric bupivacaine.

PHARMACODYNAMICS OF SPINAL ANESTHESIA

The pharmacodynamics of spinal injection of local anaesthesia vary widely. The following discussion covers the effects of spinal anaesthesia on the cardiovascular, respiratory, gastrointestinal, hepatic, and renal systems.

Cardiovascular Effects of Spinal Anaesthesia

It is well known that spinal anaesthesia often leads to hypotension. In fact, some degree of hypotension can reassure the anaesthesiologist that the nerve block is effective. However, this hypotension can also cause nausea and vomiting, ischemia of vital organs, cardiovascular collapse, and, in pregnant women, pose a risk to the foetus.[27] Over time, there have been changes in the definitions, proposed mechanisms, and management strategies for hypotension.

Many mechanisms have been proposed for spinal anaaesthesia-induced hypotension, including the direct circulatory effects of local anaesthetics, relative adrenal insufficiency, skeletal

muscle paralysis, ascending medullary vasomotor nerve block, and concurrent respiratory insufficiency. However, the primary cause is the preganglionic sympathetic nerve block produced by spinal anaesthesia. Since the height of the nerve block determines the extent of the sympathetic block, it consequently affects the changes in cardiovascular parameters.[34] However, this relationship is unpredictable. The sympathetic nerve block can vary between two and six dermatomes above the sensory level and may be incomplete below this level. The sudden onset of the sympathetic nerve block with spinal anaesthesia allows little time for cardiovascular compensation, which may explain why similar sympathetic nerve blocks with epidural anaesthesia result in less hypotension.

Sympathetic nerve block induces hypotension by affecting preload, afterload, contractility, and heart rate essentially the determinants of cardiac output (CO)—as well as by reducing systemic vascular resistance (SVR).[20] Preload decreases due to venodilatation caused by the sympathetic nerve block, leading to blood pooling in the peripheral areas and reduced venous return. During a sympathetic nerve block, the venous system is maximally vasodilated and depends heavily on gravity to return blood to the heart. Therefore, patient positioning and aortocaval compression, such as from a gravid uterus, significantly impact venous return during spinal anaesthesia.[27]

Sympathetic nerve block can also reduce arterial vasomotor tone, thereby lowering systemic vascular resistance (SVR) and afterload. Unlike venodilation, arterial vasodilation is not complete after a spinal block, as vascular smooth muscle retains some autonomic tone even after sympathetic denervation. This residual tone can be lost in the presence of hypoxia and acidosis, potentially leading to cardiovascular collapse following high spinal anaesthesia without cardiorespiratory support. Despite vasodilation below the level of the spinal block, compensatory vasoconstriction occurs above it, mediated by carotid and aortic arch

baroreceptors. This is crucial for two reasons: First, higher dermatomal blocks may result in reduced compensatory response. Second, using vasodilatory drugs such as glyceryl trinitrate (GTN), sodium nitroprusside, or volatile anaesthetics can eliminate this compensatory mechanism, worsening hypotension or even causing cardiac arrest.[28]

There may initially be an increase in cardiac output (CO) due to decreased afterload. Alternatively, CO might decrease because of reduced preload. Some studies have indicated that CO remains unchanged or is only slightly reduced during the onset of spinal anaesthesia.

The impact of spinal anaesthesia on contractility may be influenced by the blockade of upper thoracic sympathetic nerves. Intriguingly, a study exploring the common occurrence of ST segment depression in healthy women undergoing cesarean section (25-60%) revealed that ST depression was linked to a hyperkinetic contractile state.[29]

The effect of spinal anaesthesia on heart rate (HR) is multifaceted. HR might rise (due to hypotension triggering the baroreceptor reflex) or fall (either from the blockade of sympathetic nerve fibers originating from T1–T4 spinal segments, or through the reverse Bainbridge reflex). The reverse Bainbridge reflex leads to a decrease in HR caused by reduced venous return, sensed by stretch receptors in the right atrium, albeit it is weaker than the baroreceptor reflex. Another reflex, the Bezold-Jarisch reflex (BJR), reduces HR and has been associated with bradycardia, hypotension, and cardiovascular collapse following central neuraxial anaesthesia, especially spinal anaesthesia.[29]

While the BJR is a cardioinhibitory reflex, its association with spinal anaesthesia is likely weak. The BJR has been implicated in bradycardia after spinal anaesthesia, particularly following haemorrhage, where forceful contractions of an underfilled heart may initiate the reflex. This occurrence is more probable with ephedrine use rather than phenylephrine.[30]

Young, healthy patients (American Society of Anaesthesiologists class 1) and those using beta-blockers face a heightened risk of bradycardia. The incidence of bradycardia in the nonpregnant population is approximately 13%. Although bradycardia is generally well tolerated, it can lead to asystole and higher-degree heart nerve block, underscoring the importance of vigilant monitoring and prompt treatment post-spinal anaesthesia.

Various risk factors contribute to hypotension, including hypovolemia, preoperative hypertension, high sensory nerve block height, age over 40, obesity, combined general and spinal anaesthesia, chronic alcohol consumption, elevated BMI, and the urgency of non-obstetric surgery. Hypotension is less common in women in labor compared to those undergoing elective cesarean section.[30]

Respiratory Effects of Spinal Anaesthesia

In patients with normal lung function, spinal anaesthesia typically has minimal impact on pulmonary physiology. Parameters such as lung volumes, resting minute ventilation, dead space, arterial blood gas levels, and shunt fraction tend to remain relatively unchanged following spinal anaesthesia. The primary respiratory effect occurs during a high spinal block when active exhalation is hindered due to the paralysis of abdominal and intercostal muscles. This can result in reductions in expiratory reserve volume, peak expiratory flow, and maximum minute ventilation, particularly in patients with obstructive pulmonary disease who rely on accessory muscles for adequate ventilation. However, patients with normal lung function experiencing a high spinal nerve block may experience dyspnoea, which is typically due to the inability to sense chest wall movement during respiration. Simple reassurance is often sufficient to alleviate their distress.[33]

Arterial blood gas measurements generally remain stable during a high spinal anesthesia in patients breathing room air spontaneously. The primary effect of a high spinal anesthesia is on

expiration, as the muscles responsible for exhalation are impaired. Since a high spinal block typically spares the cervical area, the function of the phrenic nerve and the diaphragm remains normal, and inspiration is minimally affected. While some studies have shown no significant changes in vital capacity, maximal inspiratory pressure, or resting end-tidal PCO2 with spinal anaesthesia, increased ventilatory responsiveness to CO2 has been observed with bupivacaine spinal anaesthesia.[33]

Gastrointestinal Effects of Spinal Anaesthesia

Sympathetic innervation to the abdominal organs originates from T6 to L2. Following a spinal block, sympathetic blockade and the subsequent dominance of parasympathetic activity lead to increased secretions, sphincter relaxation, and bowel constriction.

Heightened vagal activity post-sympathetic nerve block triggers increased gastrointestinal peristalsis, often resulting in nausea. Additionally, nausea may stem from gut ischemia induced by hypotension, which stimulates the production of serotonin and other emetogenic substances. The incidence of intraoperative and postoperative nausea and vomiting (IONV) in non-obstetric surgery can reach up to 42%, rising to as high as 80% in parturient women[33].

Hepatic and Renal Effects of Spinal Anaesthesia

Hepatic blood flow is directly linked to arterial blood flow without autoregulation. Therefore, as arterial blood flow decreases following spinal anaesthesia, so does hepatic blood flow. Maintaining the mean arterial pressure (MAP) post-spinal anaesthesia ensures the preservation of hepatic blood flow. Patients with hepatic disease require careful monitoring and blood pressure control during anaesthesia to safeguard hepatic perfusion. While no definitive studies have determined the superiority of regional versus general anaesthesia in liver disease patients, either can be administered as long as MAP remains close to baseline.[40]

Renal blood flow, on the other hand, is autoregulated, with kidneys maintaining perfusion when MAP stays above 50 millimeter of mercury. Temporary reductions in renal blood flow may occur if MAP drops below 50 mm Hg, but renal function typically returns to normal once blood pressure normalizes. Attention to blood pressure post-spinal anaesthesia is crucial to maintaining MAP close to baseline. Importantly, spinal anaesthesia does not disrupt the autoregulation of renal blood flow, as evidenced by minimal changes in renal perfusion observed in sheep following spinal anaesthesia.

COMPLICATIONS OF INTRATHECAL ANESTHESIA

1) **HYPOTENSION**: Approximately one-third of patients will suffer from hypotension following an intrathecal anaesthetic. Hypotension is more likely in the older patient, in patients with higher blocks (T5 and above), and in cases in which a high lumbar puncture site is used. It is defined as a fall in 25-30% from the preoperative blood pressure. Treatment for normalizing BP should be started at this point. The fall in blood pressure is due to the thoracolumbar sympathectomy produced by the local anaesthetic solution, which produces a decrease in systemic vascular resistance and an increase in venous pooling. Venous pooling may be corrected with intravenous fluids, elevation of the legs, or with beta-adrenergic agonists. A slight head-down tilt will encourage venous return in patients undergoing intrathecal anaesthesia. Caution may be required with head-down tilt as this may encourage further cranial spread of the local anaesthetic block if this is undertaken in the early stages of intrathecal anaesthesia . Consider administration of vasoactive drugs. Ephedrine is often the first choice of vasopressor. This drug has a predominantly beta-adrenergic agonist effect and produces an increase in heart rate, with some effect on the venous pooling but little direct effect on peripheral

resistance. This is advantageous in pregnancy, when preservation of uterine blood flow in the presence of hypotension is important.

2) **BRADYCARDIA**: Bradycardia is more likely with a high block (T5 and above), in patients with a normal heart rate of less than 60 beats per minute and patients on beta-adrenergic antagonists. If the fluctuations in blood pressure is not significant, then careful monitoring is adequate. If significant hypotension or other cardiovascular events present then treatment is indicated. If the heart rate drops to 50 beats per minute or less then treatment will be necessary for the older patient and the patient with heart disease. Intravenous glycopyrrolate, 0.2milligram or atropine 0.6 milligram, should be administered. The circulation time will be much prolonged by the bradycardia and thus patience may be required to avoid administration of further, unnecessary doses of the drugs. If hypotension and bradycardia prove resistant to treatment, administration of intravenous epinephrine should be considered.
3) **NAUSEA AND VOMITING**: Nausea and vomiting are commonly associated with hypotension, bradycardia, and a high block. Treatment of the cardiovascular problem often relieves these symptoms, but not in every case. The use of conventional antiemetics can be beneficial.
4) **POST DURAL PUNCTURE HEADACHE**: Headache has always been recognized as a side-effect of dural puncture and therefore of intrathecal anaesthesia. The headache is believed to be the result of CSF leak, both at the time of the dural puncture and more importantly, continuing afterward.

Factors known to increase the likelihood of PDPH include the size of the needle used for the dural puncture (the larger the needle, the higher the incidence), the age of the patient (younger patients are more likely to have a headache than older patients) and early ambulation. Newer

needle designs (Sprotte and Whitacre) are associated with a significantly lower incidence of PDPH especially in higher risk groups.

PDPH is characteristically throbbing in nature, is eased by lying down and returns on standing. It is unusual for the headache to present more than 48h after lumbar puncture. The conservative management of PDPH (bed rest, simple analgesia and good fluid intake) is not successful in all cases. Severe PDPH will render the patient bed bound and merits more aggressive treatment if conservative management is ineffective after 24hours.

The most reliable and effective method of treatment is the autologous extradural blood patch: 20-30mL of blood is removed aseptically from the patient and injected into the extradural space. It is usual for two doctors to be involved in this procedure, one to remove the blood and one to perform the extradural injection. The headache usually disappears within minutes of the injection with a good long-term safety record. If the patient is pyrexial it is not advisable to use this technique safety record. If the patient is pyrexial it is not advisable to use this technique.

Management of Hypotension After Spinal Anesthesia

Evolving perspectives on the underlying mechanisms of spinal-induced hypotension have led to changes in its management strategies. For instance, if reduced preload is deemed the main issue, then positioning and fluid therapy are favored treatments; likewise, if vasodilation is identified as the cause, a vasoconstrictor is preferred. This has sparked intense debates. In the 1970s, there was a suggestion to avoid vasopressors until all other methods to address hypotension had been exhausted, highlighting the emphasis on preload. This notion was supported by extrapolated evidence from flawed studies on pregnant ewes undergoing general anesthesia, which indicated potential adverse effects of vasopressors on uteroplacental circulation. The choice of vasopressor has also been a contentious topic, with ephedrine traditionally favored due to its perceived preservation of uterine blood flow in animal studies.

However, recent research, including studies by Ngan Kee and others, suggests that phenylephrine may be more suitable, particularly in elective obstetric cases.[38]

Management of hypotension post-spinal anaesthesia necessitates frequent blood pressure monitoring (initially every minute), along with electrocardiogram (ECG), oxygen saturation, and foetal monitoring in pregnant patients. Invasive blood pressure monitoring may be considered for patients with significant cardiac issues. Fluid therapy is crucial in dehydrated patients to restore volume before spinal anaesthesia.[31]

Non Pharmacological interventions such as positioning, leg compression, and uterine displacement are also effective in managing hypotension. While Trendelenburg positioning can enhance venous return, extreme angles should be avoided to prevent reduced cerebral perfusion. To mitigate the risk of altering spinal anaesthesia levels, maintaining a modest elevation of the upper body with a pillow under the shoulders is recommended. Lower limb compression has shown some benefit in pregnant women, although its efficacy varies depending on the method used. Additionally, aortocaval compression from a gravid uterus should be avoided.[32]

There have been conflicting views on fluid management during spinal anaesthesia, with early studies advocating for crystalloid preloading before the procedure, while recent research suggests minimal benefits from preloading. Colloid preloading appears to be effective but needs to be balanced against the risk of allergic reactions and increased costs. Co-loading with crystalloid immediately after spinal anaesthesia seems more effective than preloading in preventing hypotension.[32]

Reducing the dose of spinal local anaesthetic can help limit hypotension. However, lower doses may compromise anaesthetic efficacy, necessitating early top-up doses via an epidural catheter. Regarding the choice of vasopressor, ephedrine and phenylephrine have been the main

contenders, with phenylephrine gaining preference due to its superior efficacy in reducing hypotension and nausea. Although phenylephrine may decrease cardiac output and spinal nerve block height, concerns about its potential side effects, such as hypertensive crisis and drug concentration errors, persist.[32] Cardiovascular collapse following spinal anaesthesia is rare but requires prompt treatment, typically involving intravenous atropine, ephedrine, and epinephrine.

Factors affecting level of spinal block

Numerous factors have been proposed as potential determinants of spinal block level, broadly categorized into four main groups: (1) attributes of the local anaesthetic solution, (2) patient-related variables, (3) aspects of the spinal block technique, and (4) diffusion dynamics. Attributes of the local anaesthetic solution encompass factors such as baricity, dosage, concentration, and volume administered.[34] Patient-related variables include age, weight, height, gender, intra-abdominal pressure, spinal column anatomy, cerebrospinal fluid characteristics, and patient positioning. Techniques of spinal block involve considerations like injection site, injection speed, needle bevel direction, injection force, and the inclusion of vasoconstrictors. While these factors have been theorized to influence the spread of anaesthetic in the spinal region, only a few have demonstrated significant alteration in block distribution when other influencing factors remain constant.

Site of Injection

The injection site of local anaesthetics for spinal anaesthesia can influence the level of block achieved. For instance, in certain studies, the administration of isobaric spinal 0.5% bupivacaine at interspaces L2–L3, L3–L4, and L4–L5 has been associated with a sensory block reduction of two dermatomes per interspace. However, there is no discernible difference in

nerve block height when hyperbaric bupivacaine or dibucaine is injected as a spinal anaesthetic across different interspaces.[34, 35]

Age

Some studies have indicated varying alterations in nerve block height following spinal anaesthesia in elderly patients compared to younger individuals, while others have found no significant difference. These investigations involved both isobaric and hyperbaric 0.5% bupivacaine.[36]

Isobaric bupivacaine seems to elevate nerve block height, whereas hyperbaric bupivacaine shows no apparent change in nerve block height with advancing age. However, any potential correlation between age and spinal anaesthesia height alone does not appear robust enough to serve as a reliable predictor in clinical practice. Similar to the role of injection site, it seems that baricity predominantly influences nerve block height following spinal anaesthesia in older populations, with age not acting as an independent determinant.[37]

Position

The positioning of the patient is crucial in determining the level of block following hyperbaric and hypobaric spinal anaesthesia, but not for isobaric solutions. Variations in positioning such as sitting, Trendelenburg, and prone jackknife positions can significantly influence the distribution of the local anaesthetic, primarily due to the gravitational effects.[38]

The level of spinal nerve block is determined by the combination of the baricity of the local anaesthetic solution and patient positioning. For instance, sitting posture combined with a hyperbaric solution can induce analgesia in the perineum. Trendelenburg positioning also impacts the spread of hyperbaric and hypobaric local anaesthetics due to gravitational effects.

Prone jackknife positioning, typically utilized for rectal, perineal, and lumbar procedures with a hypobaric local anaesthetic, prevents upward spread of the spinal block post-injection.[38]

Flexing the hips and knees of a supine patient flattens lumbar lordosis and reduces pooling of local anaesthetic in the sacral area. When combined with Trendelenburg positioning, this may facilitate upward spread. This position may inadvertently occur during urinary catheterization following spinal insertion.[38]

Speed of Injection

The impact of injection speed on spinal nerve block height has been investigated, but findings in the literature are inconsistent. Studies using isobaric bupivacaine have shown no variation in spinal nerve block height with different injection speeds.[39] Despite the lack of effect on nerve block height, it is recommended to administer a smooth, slow injection when delivering a spinal anaesthetic. Forceful injection, especially if the syringe is not tightly connected to the spinal needle, may result in needle disconnection from the syringe and subsequent loss of local anaesthetic.[39]

Volume, Concentration, and Dose of Local Anaesthetic

Maintaining consistency in the volume, concentration, or dose of local anaesthetic while altering other variables poses a challenge, making it difficult to conduct high-quality studies investigating these factors individually. Axelsson et al demonstrated that the volume of local anaesthetic can impact both the height and duration of spinal nerve block when equivalent doses are administered.[40]

Similarly, Peng et al. found a direct correlation between the concentration of local anaesthetic and the effective anaesthesia dose. However, when it comes to determining the duration of spinal nerve block, the dose of local anaesthetic emerges as the primary determinant, with

neither volume nor concentration of isobaric bupivacaine or tetracaine affecting block duration when the dose remains constant. Numerous studies have consistently shown that higher doses of local anaesthetic lead to longer durations of spinal nerve block. It is crucial to consider not only the dose of local anaesthetic but also its volume and concentration during spinal anaesthesia to avoid over- or under-dosing the patient.[40]

The utilization of hyperbaric solutions diminishes the significance of dose and volume, except in instances where doses of hyperbaric bupivacaine equal to or less than 10 mg are employed, resulting in reduced cephalad spread and shorter durations of action. However, doses ranging between 10 and 20 mg of hyperbaric bupivacaine yield comparable nerve block heights. When employing hyperbaric solutions, it's essential to recognize that patient positioning and baricity exert the most influence on nerve block height, except in cases of low-dose hyperbaric bupivacaine usage.[41, 42]

BUPIVACAINE HYDROCHLORIDE:

C18 H28N2o, HCl(±) –1–Butyl–N–(2,6–dimethyl phenyl)–2– piperidine– decarboxamide. It was synthesized in 1957 by Ekemstan and hydrochloride monohydrate was first clinically used in 1963 by L. J. Telivuo.

PHYSICOCHEMICAL PROPERTIES:

Molecular weight (free base) 342.9 (288.4) pKa 8.115 Bupivacaine hydrochloride is a white, odourless, crystalline powder with a bitter, numbing taste. It is prepared by chemical synthesis. The hydrochloride salt is available in solution with and without epinephrine. A preparation marketed specifically for intrathecal use contains dextrose.

Chemical Structure

Bupivacaine consists of a tertiary amine attached to a substituted aromatic ring by an amide linkage. The butyl group attached to the piperidine nitrogen makes bupivacaine more lipid soluble and potent. The molecular weight is 288. It is a chiral drug that exists as two enantiomeric forms – dextrorotary (R-) and levorotatry (S-) forms. The pure levorotatry form Levobupivacaine produce less cardiotoxicity compared to that of the racemic mixture.[33]

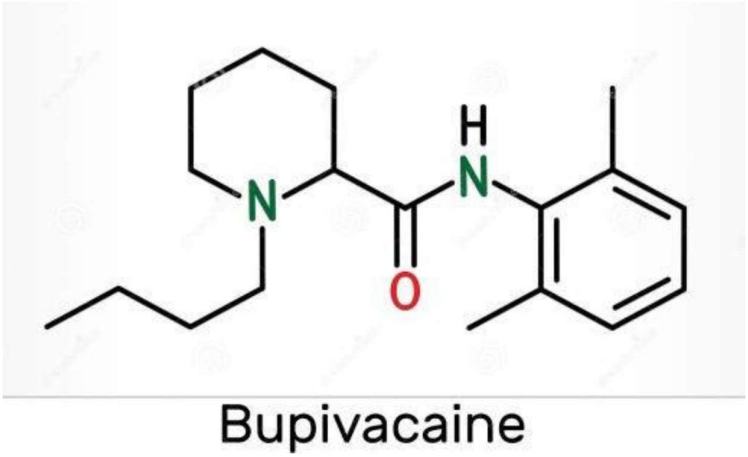


Figure 6: Chemical Structure of Bupivacaine

Presentation:

Vials of 20ml containing a clear colourless solution of 0.25% & 0.5% Bupivacaine hydrochloride. 20 ml vials of 0.25% - 0.5% Bupivacaine without preservative are also available. Ampoules containing 4ml of 0.5% (heavy) solution with dextrose for spinal anaesthesia.

Mechanism of action:

Bupivacaine, like other local anaesthetics prevents the generation and the conduction of the nerve impulse. Their primary site of action is the cell membrane. Local anaesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na+ that normally is produced by a slight depolarization of the membrane. This action of local anaesthetics is due to their direct interaction with voltage-gated Na+ channels. As the anaesthetic action progressively develops in a nerve, the threshold for electrical excitability gradually increases, the rate of rise of the action potential declines, impulse conduction slows, and the safety factor for conduction decreases. These factors decrease the probability of propagation of the action potential, and nerve conduction eventually fails.

Toxicity of Bupivacaine:

It is relatively free of side effects if administered in an appropriate dosage. It is more cardiotoxic than lignocaine and this is made worse by hypoxia, hypercapnia and by pregnancy.

1. Central nervous system toxicity[43] : The principal effect of Bupivacaine is reversible neural blockade which leads to a characteristically biphasic effect in the CNS. Initially, excitation (light headedness, dizziness, visual and auditory disturbances and fits) occurs, due to the

blockade of inhibitory pathways in the cortex. With increasing doses, depression of both facilitatory and inhibitory pathways occur leading to CNS depression (drowsiness, disorientation and coma). Disorientation and occasional feeling of drowsiness may occur. Objective signs are usually excitatory in nature which includes shivering, muscular twitching 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 enhance cerebral blood flow, so that more anaesthetic is delivered rapidly to the brain. Bupivacaine is more lipid soluble and protein bound. This limits its passage across the placenta to foetus. Bupivacaine is undetectable in neonatal plasma 24 hours after cesarean section using Bupivacaine.

2. Cardiovascular system toxicity: Bupivacaine depresses rapid phases of depolarization (Vmax) in purkinje fibres and ventricular musculature to a greater extent than lignocaine. It also decreases the rate of recovery from a dependant block than that of lignocaine. This leads to incomplete restoration of Vmax between action potential at high rates, in contrast to complete recovery by lignocaine. This explains why lignocaine has antiarrythmic property while bupivacaine has arrythmogenic potential. High level of bupivacaine prolongs conduction time through various parts of heart and extremely high concentration will depress spontaneous pacemaker activity, resulting in bradycardia and arrest. Cardiac resuscitation is more difficult following bupivacaine induced cardiovascular collapse and hypoxia along with acidosis which markedly potentiates cardiac toxicity. Bretylium but not lignocaine could raise the ventricular tachycardiac threshold that was lowered by bupivacaine. Pregnancy enhances the cardiotoxicity of bupivacaine. 0.75% is no longer recommended for use in labour analgesia. CVS toxicity includes atrio-ventricular block, ventricular arrhythmias and cardiac arrest. CC / CNS dose ratio is 3.7 ± 0.516. Cardiovascular collapse is more difficult to resuscitate and pregnant women are more sensitive to the cardiovascular effects than non- pregnant women.

Bupivacaine is used in obstetric analgesia due to its longer duration of action, limited placental transfer, high degree of sensory block than motor block, less cumulation and no tachyphylaxis.

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

4.Autonomic nervous system: Myelinated preganglionic beta fibres have a faster conduction time and are more sensitive to the action of local anaesthetic including bupivacaine. Involvement of preganglionic sympathetic fibres is the cause of widespread vasodilation and consequent hypotension that occurs in epidural and paravertebral block. When used for conduction blockade all local anaesthetic particularly bupivacaine produces higher incidence of sensory blockade than motor fibres.

Pharmacokinetics of Bupivacaine:

Bupivacaine is rapidly absorbed from the site of injection, the rate of rise in plasma concentration and the peak plasma concentration depending on the particular local anaesthetic technique being used. There is also some inter individual variation and peak systemic concentrations may occur between 5 and 30 min after administration.

1. Absorption: The site of injection, dose and addition of a vasoconstrictor determine systemic absorption of bupivacaine. The maximum blood level of bupivacaine is related to the total dose of the drug administered from any particular site.

2. Distribution: This can be described by a two compartment model. The rapid distribution phase is believed to be related to uptake by rapid equilibrating tissue (i.e., tissues that have high vascular perfusion). The slow distribution phase is mainly a function of distribution to slowly equilibrating tissue, biotransformation and excretion of the compound. More highly perfused

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

3. Biotransformation and excretion: Bupivacaine undergoes enzymatic degradation primarily in the liver. The excretion occurs via the kidney. Renal perfusion and factors affecting urinary pH affect urinary excretion. Less than 5 percent of unchanged drug is excreted via the kidney through urine. The major portion of injected agent appears in urine in the form of 2, 6, pipecolyloxylidine (PPx) which is a N-dealkylated metabolite of bupivacaine. Renal clearance of this drug is related inversely to its protein binding capacity and pH of urine.[32]

4. Dosage: Maximal dose is 2mg/kg body weight (25-30 ml 0.5% solution) and the strength used is 0.125% - 0.75%.

MIDODRINE:

Midodrine is a peripherally acting α-receptor agonist available as 2.5 mg and 5 mg tablets. It does not act preferentially on either α1, or α2-receptors, but its active metabolite, desglymidodrine, selectively stimulates α1-receptors. It causes modest increases in supine and standing blood pressure in a dose-dependent manner. Its other pharmacodynamic effects are to increase peripheral vascular resistance, increase venous tone and release of atrial natriuretic peptide and reduce circulating plasma and blood volume.

Pharmacokinetics[45] :

Midodrine has poor blood-brain barrier penetration and, therefore, no direct central nervous system activity. It has no myocardial ß-adrenoreceptor activity but indirectly increases end-diastolic volume and stroke volume, decreases heart rate and circulating noradrenaline levels via baroreceptor stimulation and causes QT prolongation. It has no significant metabolic or endocrine effects. It has no effect on serum lipids, insulin, or uric acid levels. It also does not have any established effect on pulmonary, renal, coagulation or immune function. It has been safely administered in pregnancy.

Desglymidodrine, the active metabolite, is generated from midodrine by the enzymatic cleavage of the amino acid glycine. The oral bioavailability of desglymidodrine is 93%. The mean maximum concentration in plasma for midodrine is 20–30 minutes after oral administration and 60 minutes for desglymidodrine. Binding to plasma proteins is less than 30%. Midodrine is cleared from plasma after 2 hours, with an elimination half-life of 30 minutes. The elimination half-life of desglymidodrine is 3 hours.

Midodrine undergoes extensive metabolism in various tissues including the liver (predominantly by cytochrome P450 isoforms CYP2D6 and CYP1A244), with only 4% of a

single dose excreted unchanged. Excretion of midodrine and desglymidodrine is primarily urinary. Haemodialysis can reduce the elimination half-life of desglymidodrine to 90 minutes. In end-stage chronic kidney disease, the elimination half-life can be as long as 10 hours.

Adverse effects:

Common adverse effects are related to midodrine's α -agonist properties:

- Supine hypertension, bradycardia
- Piloerection, scalp pruritus
- Nausea, abdominal pain, urinary retention, dysuria
- Paraesthesia, taste and smell disturbance

  Although up to 80% of patients may experience one or more of these adverse effects, they are dose-dependent and generally mild. Singular case reports describe midodrine use associated with takotsubo cardiomyopathy, intracerebral haemorrhage, reversible cerebral vasoconstriction syndrome, myoclonic seizures, vascular ischaemia, and ileus.

FENTANYL[44]

It is an opioid.

Molecular Formula: C22H28N2O

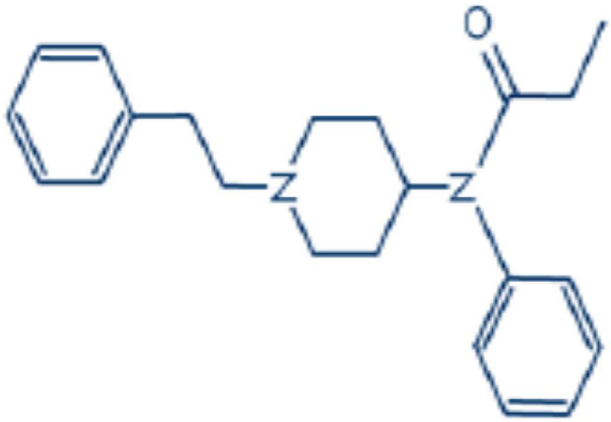


Figure 7: Chemical Structure of Fentanyl

Route of Administration: Epidural, Intrathecal, IV, Skin Patch, Sublingual.

Pharmacokinetics:

Bioavailability:

- Transdermal – 92%
- Intranasal – 89%
- Buccal – 50%
- Ingestion – 33%
- Intramuscular – 100%.

Protein Binding: 80-85%

Metabolism: Liver primarily by CYP3A4

Onset Of Action: 5 minutes

Duration Of Action: 30-60 minutes

Excretion: Mostly by kidney

Fentanyl is given intrathecally as a part of spinal anaesthesia or epidurally for epidural anaesthesia and analgesia. The greater potency and rapid onset of action reflect the greater lipid solubility of fentanyl compared with that of morphine which facilitates its passage across the blood brain barrier. In obstetrics the dose must be closely regulated in order to prevent large amount of transfer from mother to foetus.

Side Effects of Fentanyl[44]

- Depression of ventilation
- Hypotension
- Nervousness
- Increase in intracranial pressure to head injury patients
- Seizure activity following rapid IV administration.

MATERIALS AND METHODS:

Site of research: The present trial was done on One hundred twenty individuals undergoing elective procedures Lower abdomen and lower limb surgeries performed under spinal anaesthesia at KLES Prabhakar Kore Hospital & Medical Research Centre, Nehru Nagar, Belagavi from June 2023 to June 2024.

Study Design: Hospital Based Randomised Controlled Trial

Study period : One year

SAMPLE SIZE CALCULATION:

Sample size is calculated with 95% confidence interval with 80% power. The minimum sample size formula based on mean and standard deviation is:

$$n = (Z1-\alpha/2 + Z1-\beta)2 (SD12 + SD22)$$

$$(\bar{x}1-\bar{x}2)2$$

Where zα is linked with the level of significance and zβ is linked with the power of the test. For 5% level of the significance zα =1.96 and zβ =0.84 for 80% power of the test.

Ref: $\bar{x}1$ is the mean of the first group (87.4) and $\bar{x}2$ is the mean of the second group (83).

SD1 is the standard deviation of the first group (8.1) and the standard deviation of the second group (8.1).

n= 55 in each group

Total n= 55.2

n= 110~120

n= 60

With these values the sample size obtained is 120.

There will be two groups with 60 cases in each group.

INCLUSION CRITERIA:

• Age: 18 – 60 years

• ASA 1& 2

• Subjects undergoing lower abdominal and lower limb surgeries

• Subjects without local anaesthetic allergy

• Either gender

EXCLUSION CRITERIA:

• Patients with history of hypertension, cardiovascular disease, cerebrovascular disease, baseline SBP >140 millimeter of mercury before administration of drug

• Patients with any contraindications to spinal anaesthesia

• History of coagulopathy, pheochromocytoma.

• Patients on vasoconstrictors.

• Pregnancy

METHODOLOGY:

- After obtaining approval of the ethical committee and written informed consent. A total of 120 patients undergoing lower abdominal and lower limb surgeries under spinal anaesthesia were included in the study.
- After having met inclusion and exclusion criteria and having obtained informed consent, patients were randomised into 2 groups according to computer generated randomization table.

Group S- Patients were administered Midodrine 10mg tablets powdered and dissolved in 25 ml water given orally one hour before Spinal anaesthesia.

Group C: Patients were administered with 25 ml of plain water orally 1 hour before spinal anaesthesia.

- A detailed Pre-Anaesthetic Evaluation was done one day prior to surgery, and vital parameters were noted on the day of the surgery.
- After confirming NBM status.
- The vital parameters were noted which Systolic, Diastolic & Mean arterial pressure and the Heart rate.
- The patients in Group S received 25 ml of water in which Midodrine 10mg powder was dissolved and the patients in Group C received plain water 25 ml 1 hour before administration of spinal anaesthesia.
- The patients were blinded to the group to which they belong.
- Then an 18 Gauge IV canula was inserted to patients in either group and they received 10ml/kg Ringer's lactate before administering Spinal anaesthesia.
- On arrival at the operating room the patients were monitored using, ECG, NIBP, pulse oximeter, spinal anaesthesia was performed in sitting position, by injecting

0.5% (H) Bupivacaine 15mg (3cc) & 25 mcg Fentanyl, total (3.5cc) in L3-L4 or L4-L5 Space using 23-gauge Quincke's Needle, patient were put in supine position.

- The highest sensory level of the spinal block was tested by the pinprick method every 5 minutes for 20 minutes and recorded after 20 minutes. Hemodynamic variables comprising SBP, DBP, MAP and HR were recorded at 2, 5, 10, 15, 20, 25, 30, 45, and 60 minutes after spinal anaesthesia, every 15 mins until 2 hours.
- Hypotension (MAP < 70 mm Hg or 80% of base line) was treated with an IV bolus of 6mg mephentermine, repeated if hypotension persists, and increasing infusion rate of lactated Ringer's solution. Severe hypotension (MAP <60 mm Hg) was treated with an IV bolus of 10-mg mephentermine and a bolus of lactated Ringer's solution 100 ml. Bradycardia (HR<50 beats /min) was treated with IV atropine 0.5 mg, repeated as appropriate. A single measurement of MAP or HR below the respective threshold is sufficient to qualify as hypotension, severe hypotension, or bradycardia. The occurrence of vasovagal attacks (bradycardia and hypotension with fainting) during spinal needle insertion, post spinal hypotension, severe hypotension, bradycardia, reactive hypertension (SBP higher than 140 mm Hg), nausea and vomiting, shivering, intraoperative requirements of mephentermine and atropine, and total volume of fluids infused were recorded.

RESULTS:

TABLE1: DISTRIBUTION OF PARTICIPANTS BETWEEN CONTROL AND STUDY GROUPS

Group	Frequency	Percent
Control	60	50
Study	60	50
Total	120	100

GRAPH 1: DISTRIBUTION OF PARTICIPANTS BETWEEN CONTROL AND STUDY GROUPS

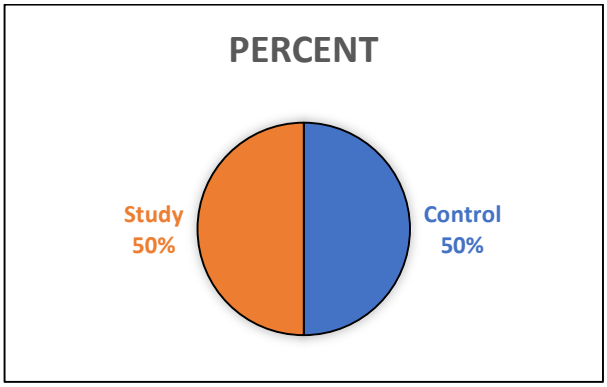


TABLE 2: SEX DISTRIBUTION ACROSS CONTROL AND STUDY GROUPS

	Group		Total
Sex	Control	Study	
Female	17	15	32
Male	43	45	88
Total	60	60	120
Pearson chi-square = 0.170, p-value = 0.680			

GRAPH 2: SEX DISTRIBUTION ACROSS CONTROL AND STUDY GROUPS

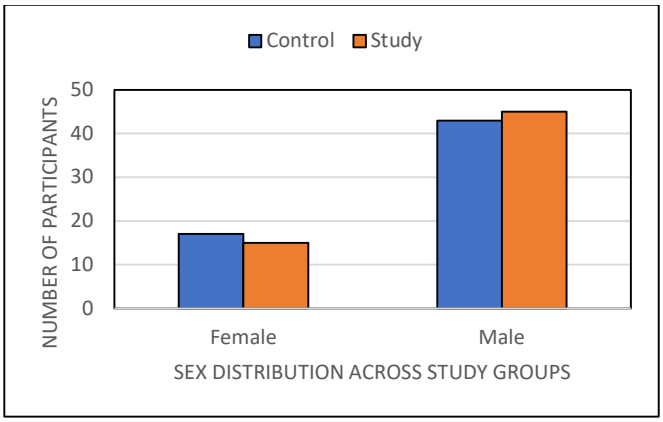


TABLE 3: COMPARISON OF AGE AND WEIGHT BETWEEN CONTROL AND STUDY GROUPS

	Group	N	Mean	Std. Deviation	P value
Age	Control	60	45.3	13.642	0.069
	Study	60	42.52	11.998	
Weight	Control	60	68.68	10.028	0.376
	Study	60	71.57	11.504	

GRAPH 3: COMPARISON OF AGE AND WEIGHT BETWEEN CONTROL AND STUDY GROUPS

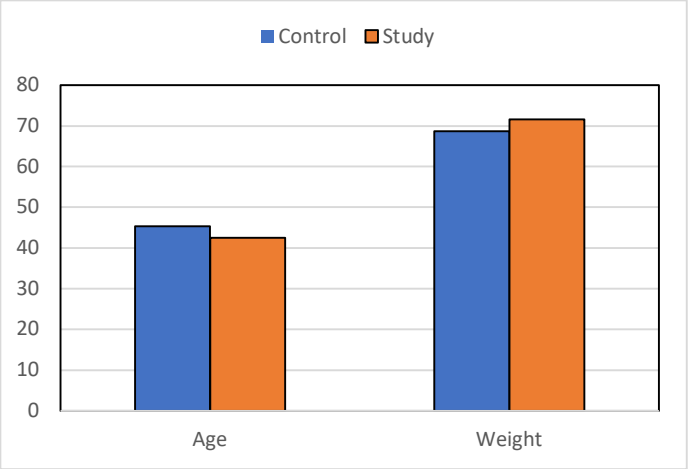


TABLE :4 ASA GRADE DISTRIBUTION ACROSS CONTROL AND STUDY GROUPS

	ASA Grade		Total
ASA Grade	Control	Study	
1	35	45	80
2	25	15	40
Total	60	60	120

GRAPH :4 ASA GRADE DISTRIBUTION ACROSS CONTROL AND STUDY GROUPS

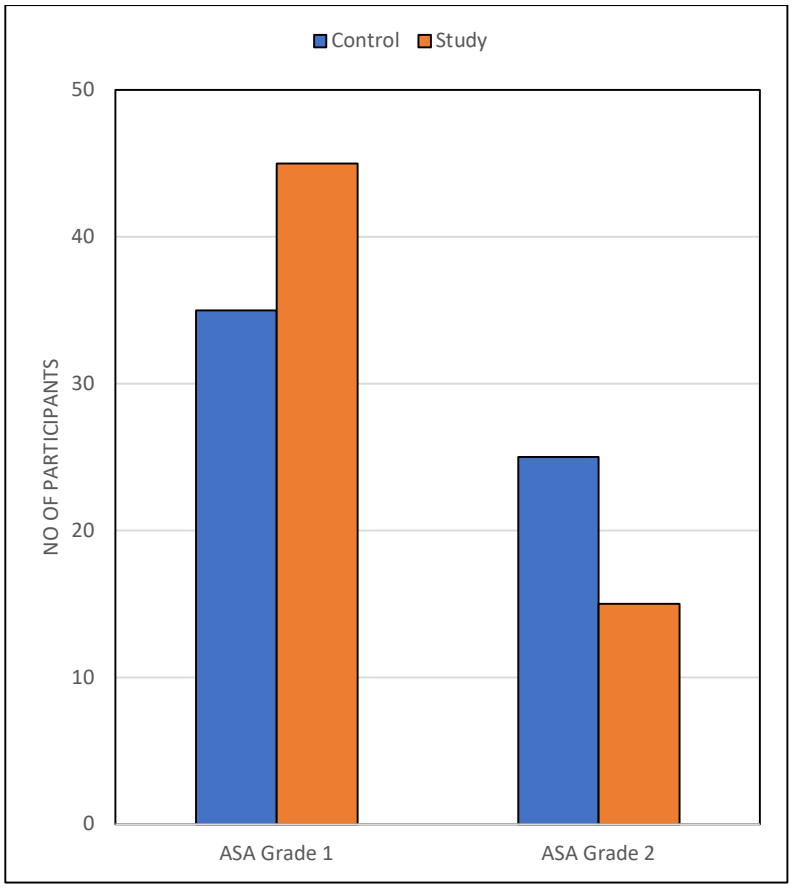


TABLE 5 : COMPARISON OF SBP ACROSS STUDY AND CONTROL GROUPS

	Control		Study		
Group	Mean	SD	Mean	SD	P-value
Baseline	126.00	10.92	125.23	12.37	0.372
T2	107.13	12.41	121.28	13.49	0.920
T5	101.50	9.98	118.35	13.39	0.045
T10	100.13	7.22	117.97	12.84	0.166
T15	99.95	6.72	115.60	10.96	0.000
T20	101.13	7.39	113.60	10.65	0.006
T25	100.87	7.70	114.00	11.32	0.002
T30	104.78	8.44	114.25	11.72	0.028
T45	104.38	8.20	117.18	11.27	0.034
T60	105.55	7.80	117.68	10.82	0.025
T75	107.25	8.04	119.02	10.68	0.046
T90	108.12	7.70	120.48	9.42	0.511
T105	109.78	8.71	121.05	8.44	0.429
T120	116.03	7.10	121.80	8.91	0.167

GRAPH 5 : COMPARISON OF SBP ACROSS STUDY AND CONTROL GROUPS

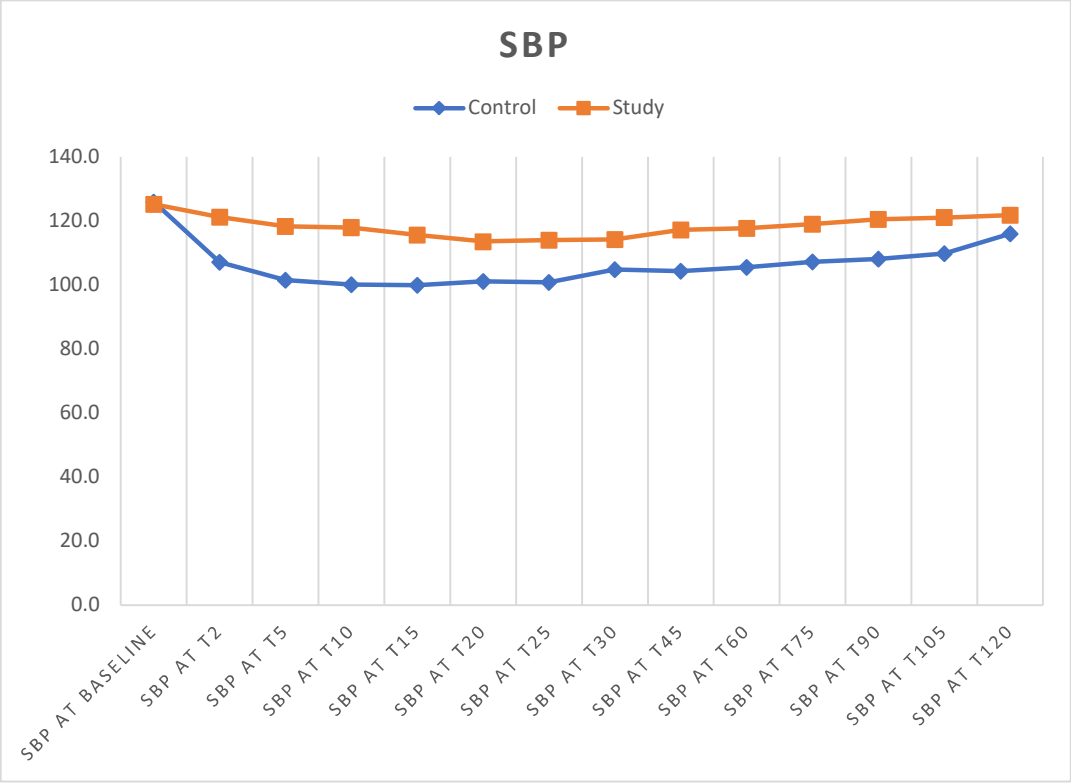


TABLE 6 : COMPARISON OF DBP ACROSS STUDY AND CONTROL GROUPS

Group	Mean	SD	Mean	SD	P-value
Baseline	70.42	9.76	81.13	10.02	0.926
T2	62.48	8.28	76.47	9.96	0.042
T5	58.60	6.36	73.10	9.56	0.005
T10	58.05	5.05	72.83	9.92	0.000
T15	57.68	5.49	71.65	10.18	0.001
T20	58.48	4.79	70.85	9.09	0.000
T25	58.20	4.93	72.67	9.89	0.000
T30	58.55	4.40	74.60	10.08	0.000
T45	60.27	5.10	76.30	10.29	0.000
T60	60.07	4.74	75.13	9.75	0.000
T75	59.90	5.87	76.65	9.98	0.000
T90	61.25	4.90	77.45	8.00	0.001
T105	62.77	4.98	77.12	9.34	0.000
T120	66.55	4.79	74.58	6.80	0.034

GRAPH 6 : COMPARISON OF DBP ACROSS STUDY AND CONTROL GROUPS

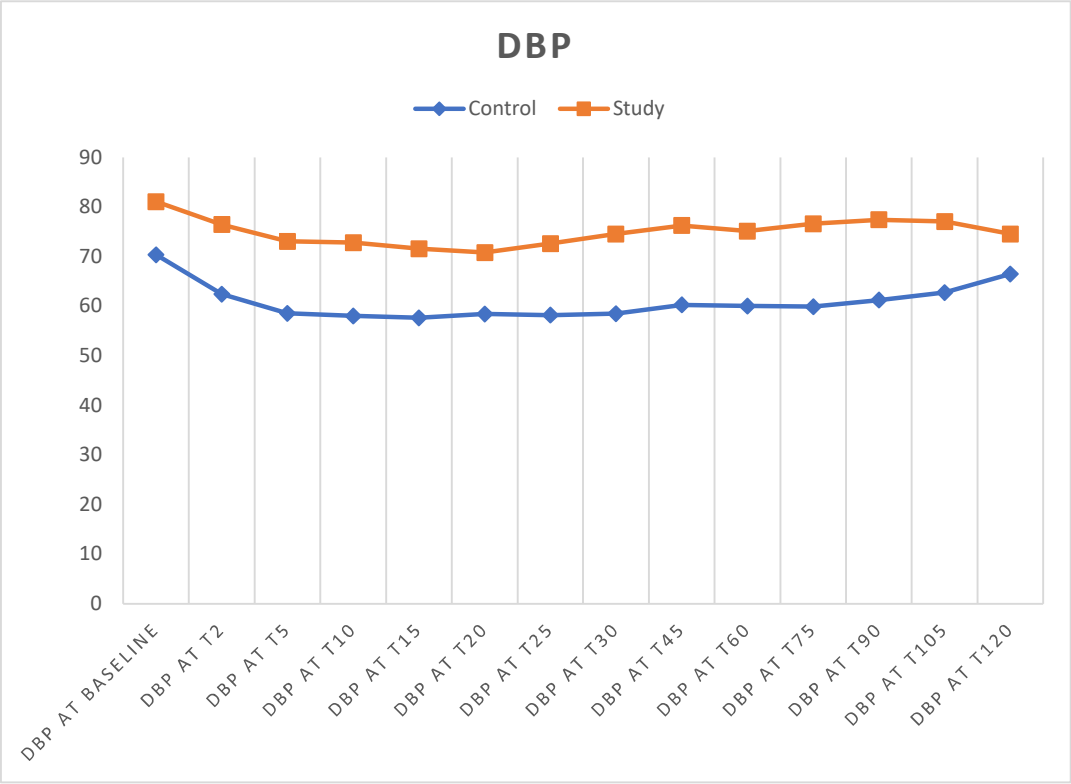


TABLE 7: COMPARISON OF MAP ACROSS STUDY AND CONTROL GROUPS

Group	Mean	SD	Mean	SD	P-value
Baseline	86.49	9.16	95.83	9.72	0.934
T2	77.37	8.50	91.41	9.96	0.040
T5	72.90	6.74	88.18	9.72	0.047
T10	72.08	5.04	87.88	9.13	0.400
T15	71.77	5.12	86.30	8.91	0.001
T20	72.70	4.61	85.10	8.26	0.000
T25	72.42	4.68	86.44	8.76	0.000
T30	73.96	4.07	87.82	9.47	0.000
T45	74.97	5.04	89.93	9.10	0.000
T60	75.23	4.54	89.32	8.35	0.000
T75	75.68	4.76	90.77	8.53	0.000
T90	76.87	4.56	91.79	7.06	0.010
T105	78.44	5.60	91.76	7.46	0.025
T120	83.04	4.87	90.32	6.24	0.129

GRAPH 7: COMPARISON OF MAP ACROSS STUDY AND CONTROL GROUPS

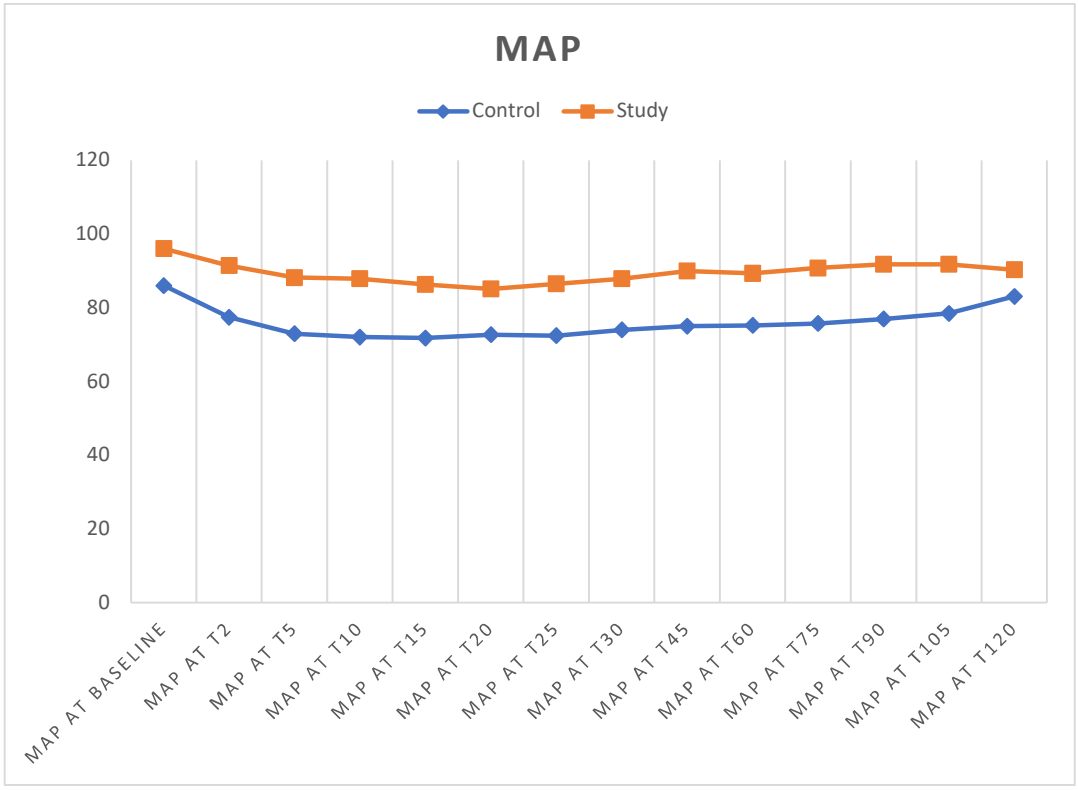


TABLE 8: COMPARISON OF HEART RATE ACROSS STUDY AND CONTROL GROUPS

Group	Mean	SD	Mean	SD	P-value
Baseline	94.83	8.79	78.05	12.20	0.015
T2	94.30	9.07	77.52	10.30	0.481
T5	96.62	8.64	74.87	11.24	0.192
T10	96.15	8.13	73.45	14.53	0.040
T15	95.48	7.71	73.63	10.18	0.114
T20	94.92	9.53	71.62	9.84	0.794
T25	94.50	8.96	72.93	9.77	0.534
T30	93.43	8.54	72.55	10.27	0.210
T45	94.45	8.91	72.63	10.61	0.492
T60	95.17	8.94	72.02	10.06	0.643
T75	96.48	9.00	71.98	9.71	0.561
T90	94.23	9.92	72.80	9.74	0.195
T105	97.83	8.32	74.18	10.80	0.036
T120	88.37	8.33	69.27	9.19	0.573

GRAPH 8: COMPARISON OF HEART RATE ACROSS STUDY AND CONTROL GROUPS

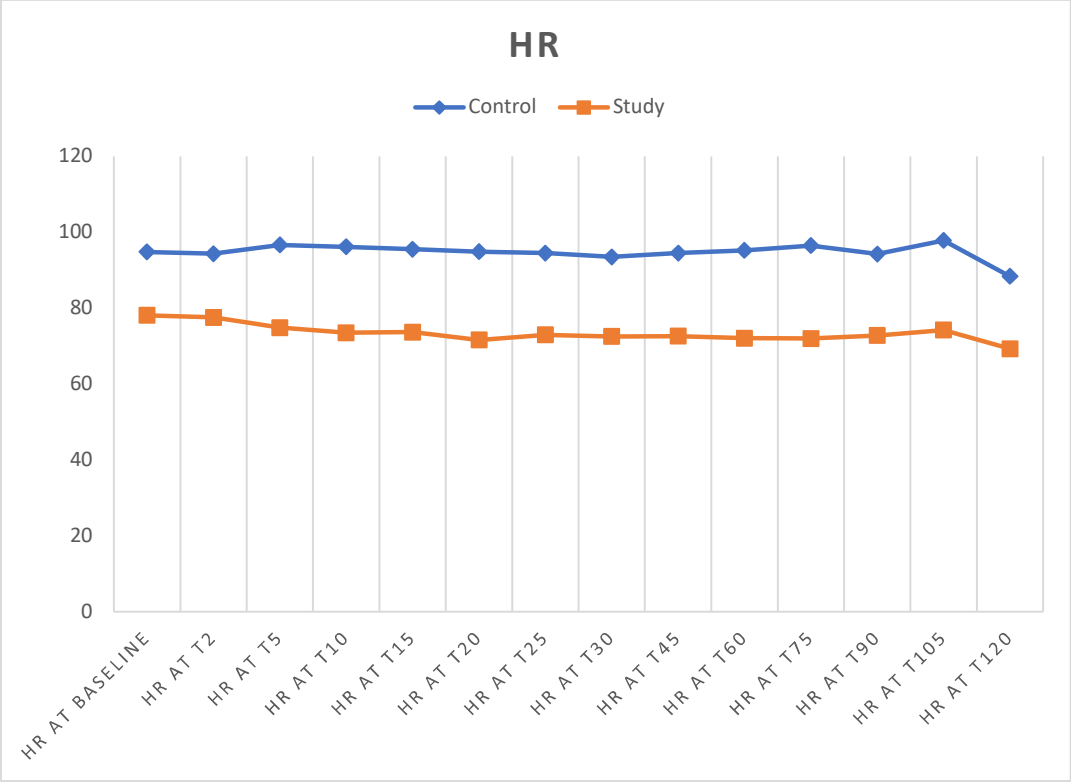


TABLE 9: COMPARISON OF NUMBER OF DOSES OF MEPHENTERMINE USED ACROSS STUDY AND CONTROL GROUPS

	Group		Total
No of doses of mephentermine	Control	Study	
10mg	3	0	3
12mg	19	3	22
18mg	8	0	8
20mg	3	0	3
24mg	3	0	3
6mg	12	5	17
NIL	12	52	64
Total	60	60	120
Pearson chi-square = 56.519, p-value = 0.000			

GRAPH 9: COMPARISON OF NUMBER OF DOSES OF MEPHENTERMINE USED ACROSS STUDY AND CONTROL GROUPS

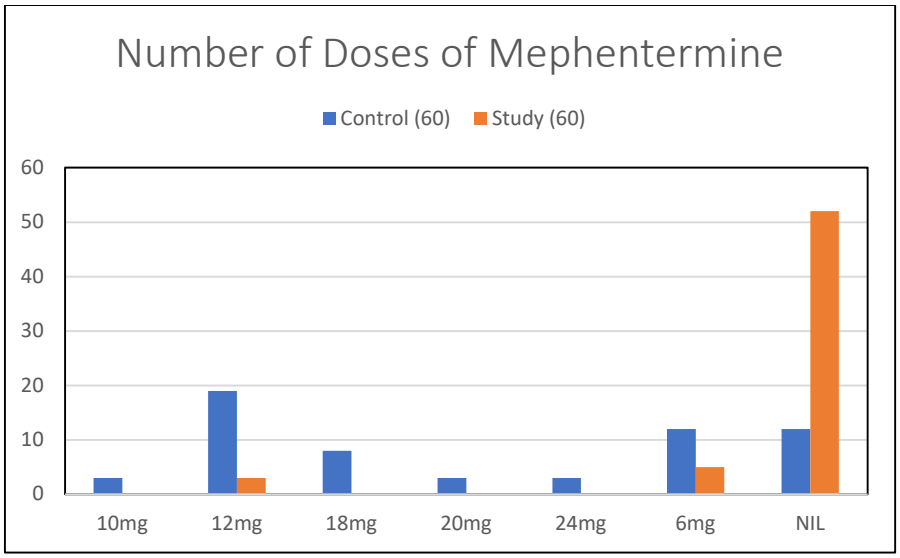
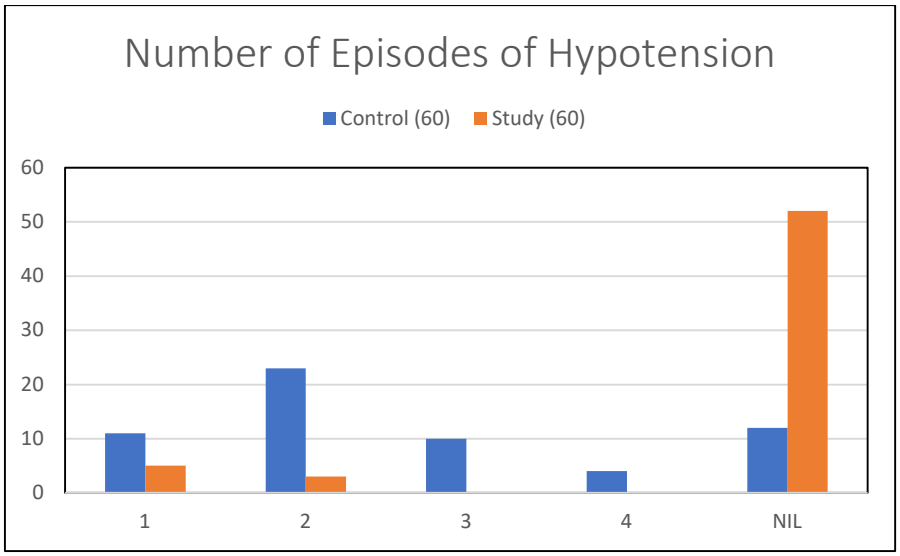


TABLE 10: COMPARIOSN OF NUMBER OF EPISODES OF HYPTENSION ACROSS STUDY AND CONTROL GROUPS

	Group		Total
No of episodes of hypotension	Control	Study	
1	11	5	16
2	23	3	26
3	10	0	10
4	4	0	4
NIL	12	52	64
Total	60	60	120
Pearson chi-square = 56.635, p-value = 0.000			

GRAPH 10: COMPARIOSN OF NUMBER OF EPISODES OF HYPTENSION ACROSS STUDY AND CONTROL GROUPS



DISCUSSION:

This study investigates the efficacy of preoperative oral midodrine in preventing hypotension following spinal anaesthesia in patients undergoing infraumbilical surgeries. It is prospective, double blinded, randomised controlled trial involving 120 patients. The study cohort consisted of 120 participants, evenly distributed between the control and study groups, with each comprising 60 individuals (50.0%). Utilizing a software-based randomization mechanism, 120 patients undergoing spinal anaesthesia for infraumbilical procedures were randomly allocated into two groups.

Group S:- Patients received 25ml of water containing Midodrine 10mg.

Group C:- Patients were given 25ml of plain water.

Study group receiving midodrine and a control group receiving placebo, were assessed on multiple hemodynamic parameters—namely systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR)—at various time points up to 120 minutes after administration of spinal anaesthesia. We further recorded the number of hypotensive episodes and the doses of rescue vasopressor (mephentermine) required.

In this trial, the study and control populations were comparable in terms of age and weight and ASA grade.

Both the control and research groups had similar sex distributions, with 17 females (28.3%) and 43 males (71.7%) in control group, while study group had 15 females (25.0%) & 45 males (75.0%). Overall male-to-female ratio in the study was 88:32 (73.3% male, 26.7% female), reflecting a predominance of male participants. The ‘Pearson chi-square test’ ($\chi 2 = 0.170$, $p = 0.680$) demonstrates no mathematical corelation in variance in sex distribution amongst the

two groups, supporting the accuracy of the randomization technique and suggesting that sex did not confuse the investigation.

(p=0.005), and MAP (p=0.047). The control group's SBP and DBP dropped more than in the midodrine group, echoing the protective effect of prophylactic alpha-1 agonists.

The comparison of age and weight between the control and study groups demonstrates that the mean age was 45.30 ± 13.64 years in the control group and 42.52 ± 11.99 years in the study group, with a p-value of 0.069, indicating no statistically significant difference. Similarly, the mean weight was 68.68 ± 10.03 kg in the control group and 71.57 ± 11.50 kg in the study group, with a p-value of 0.376, confirming comparability between the groups. The lack of significant differences in these baseline characteristics ensures that the observed effects of midodrine are independent of age or weight variations.

At baseline the study group had slightly higher mean SBP (125.23 vs. 118.63 mmHg) and MAP (95.83 vs. 86.49 mmHg), though these differences were statistically non-significant (p=0.372 and p=0.934, respectively). The only notable difference was the baseline HR, which was lower in the study group (78.05 vs. 94.83 bpm; p=0.015). A series of time points (T2, T5, T10, T15, T20, T25, T30, T45, T60, T75, T90, T105, T120) were evaluated to capture acute and sub-acute changes in SBP, DBP, MAP, and HR.

At T2, significant inter-group differences in DBP (p=0.042) and MAP (p=0.040) but not in SBP (p=0.920) were noted. By T5, a significant difference emerged in SBP (p=0.045), DBP (p=0.005), and MAP (p=0.047). The control group's SBP and DBP dropped more than in the midodrine group, echoing the protective effect of prophylactic alpha-1 agonists.

At T10, while SBP differences were not mathematically co-relating (p=0.166), DBP variations remained highly significant (p=0.000), depicting sustained vascular tone in the midodrine

group. Heart rate differences became significant here (p=0.040), reflecting a trend of lower HR in the midodrine group likely due to baroreceptor stimulation.

By T15, SBP (p=0.000), DBP (p=0.001), and MAP (p=0.001) differences were highly substantial, marking a clearer hemodynamic separation between the two groups. This time point coincides with the typical peak effect of spinal anaesthesia induced sympathectomy.

From T20 to T30, statistically significant disparities in SBP, DBP, and MAP remained in favor of the midodrine group. For instance, at T20, SBP (p=0.006), DBP (p=0.000), MAP (p=0.000) were all better maintained, while HR differences were not always statistically significant.

By T45, the pattern was consistent (SBP p=0.034, DBP p=0.000, MAP p=0.000), demonstrating the sustained effect of midodrine. In previous studies focusing on midodrine in orthostatic hypotension, the pharmacodynamic duration was noted to extend up to 2–3 hours, supporting the continued benefit of the drug well into the operative window.

At T60, T75, T90, and T105, differences in SBP, DBP, and MAP largely persisted (many p-values < 0.05), confirming prolonged hemodynamic support. By T120, while SBP differences did not reach the value (p=0.167), DBP (p=0.034) remained significantly higher in the midodrine group. The MAP changes was not evident at T120 (p=0.129), suggesting a gradual tapering of midodrine's efficacy at around two hours.

In the current trial heart rate (HR) was lower in the study group (72.80 ± 9.73 bpm) compared to the control group (94.23 ± 9.92 bpm), though the difference was not mathematically corelating (p = 0.195). Outcomes of Rahul Costa-Pinto Daryl A. Jones in their narrative review support the idea that midodrine does not activate myocardial β-adrenoreceptors, but it does indirectly raise end-diastolic and stroke volumes, reduce heart rate and circulating noradrenaline levels through stimulation of baroreceptors, and cause QT prolongation.

Consistently with previous midodrine safety research, our participants did not experience any adverse events due to bradycardia.[46]

Research undertaken by Joseph Jankovic studied the potency and safety of midodrine in treating 97 individuals with orthostatic hypotension caused by autonomic dysfunction. The research was prospective, double-blinded, placebo-controlled. He stated that in comparison to the placebo, Midodrine (10 mg) increased standing systolic blood pressure by 22 mm Hg (28%, $p < 0.001$ versus placebo). Midodrine improved ($p<0.05$) the following symptoms of orthostatic hypotension compared to placebo: dizziness/lightheadedness, weakness/fatigue, syncope, low energy level, impaired ability to stand, and feelings of depression. The overall side effects were mainly mild to moderate. They concluded that midodrine is an effective and well-tolerated treatment for moderate-to-severe orthostatic hypotension associated with autonomic failure.[47]

Suma Prakash, Amit X. Garg, A. Paul Heidenheim, and Andrew A House performed an extensive review of research involving five or more haemodialysis patients, including observational trials, randomised controlled trials, crossover studies, and studies with a pre- and post-intervention design. Nine out of 37 full-text papers (plus one unpublished research) fulfilled the inclusion criteria. Doses of midodrine varied from 2.5 to 10 milligram, with the optimum interval between 15 and 30 minutes prior to dialysis. In comparison with the control group, those who received midodrine after dialysis had a 12.4 millimetre mercury rise in SBP and a 7.3 millimetre mercury increase in DBP. 6 out of 10 trials discovered that midodrine alleviated intradialytic hypotension symptoms, and the drug was not associated with any serious adverse reactions. Revealing that midodrine may be useful in addressing intradialytic hypotension (IDH) in haemodialysis patients.[48]

Sarah undertook a randomised controlled trial on 56 elderly, with 29 patients belonging to midodrine group, who were given 5mg of oral midodrine 90 mins before administering spinal

anaesthesia in patients undergoing hip arthroplasty. He observed that the midodrine group had a decreased risk of intraoperative hypotension (P = 0.001) and a lower intake of intraoperative ephedrine (P = 0.002) in comparison to control group. Both groups had similar rates of hypertension and bradycardia.[49]

Maxime Lamarre-Cliché et al in a prospective, randomized, single-blind, 2-period, crossover study in which a single, oral, 5-mg dose of midodrine was compared with placebo in healthy volunteers to characterize the effects of midodrine on BP, plasma catecholamines, plasma atrial natriuretic peptide (ANP), and power spectral analysis of heart rate (HR). The study parameters included plasma DGM, systolic and diastolic BP, HR, plasma catecholamines, plasma ANP, also known as venous return, and low- and high-frequency HR variation. The study demonstrated midodrine decreased dose of norepinephrine required (P = 0.011) and HR from 57.2±7.3 to 54.9 ± 6.6 bpm (P = 0.022). No significant effects of midodrine on BP were observed. This study found that midodrine has sympatholytic influences that are independent of BP but related to augmented venous return.[50]

P A Low, J L Gilden amongst 171 individuals diagnosed with orthostatic hypotension who took part in RCT. The 6-week experiment included a single blinding run in (week 1), washout period (weeks 5 and 6), followed by double blind phase (weeks 2 to 4), following which participants were randomly divided to receive either a 10-mg dose of midodrine or a placebo three times daily. By the finish of the second week of therapy, it turned out that Midodrine boosted standing systolic pressure at all recorded intervals. P<.001 during visits 2, 3, 4, and 5, together with reported symptoms (P=.001).[51]

In our study on comparison of mephentermine doses used between the control and study groups demonstrates a evident difference in the requirement of vasopressors. In the control group, a significant proportion of patients required various doses of mephentermine (ranging

from 6 mg to 24 mg) to manage hypotension, with the most common doses being 12 mg (19 patients) and 6 mg (12 patients). In contrast, in the study group, 52 patients (86.7%) required no mephentermine at all (NIL), compared to only 12 patients (20%) in the control group. This difference was deemed to be highly crucial (Pearson chi-square = 56.519, p = 0.000).

In a randomized placebo-controlled research, 67 patients, ranging in age from 18 - 40 years, who underwent scheduled knee surgery employing spinal anaesthesia included Mahmoud Mohammed Alseoudy, Mohamed Osama Nasr, and Tamer Ahmed Abdelsalam. He noticed that out of the patients who were administered 10 milligram tablets of midodrine or placebo, the proportion of patients who developed hypotension following spinal anaesthesia was 5 or 14.7% in the midodrine group and 14 or 42.4% in the placebo group. Furthermore, he stated that midodrine, an α1-adrenoceptor agonist that does not stimulate β-receptors, was discovered to decrease the incidence of hypotension following spinal anaesthesia more potently than a placebo, validating our idea.[52]

This study by Ajay K. Parsaik, Balwinder Singh, Osama Altayar, and colleagues to examine the effectiveness and adequate protection of midodrine in treating orthostatic hypotension (OH). An efficacy analysis was performed with data from seven studies, which enrolled 325 patients with average age of 53 years. The study suggested that change in MBP and SBP from supine to standing position did not differ between midodrine and control group. Although there was a trend towards the improvement of MBP and SBP after the midodrine, the effect did not reach a statistical significance. After the intervention, the midodrine group showed an impressive rise in standing systolic blood pressure in comparison to the control batch.[53]

In our trial comparing number of episodes of hypotension between the control and study group reveals a marked reduction in hypotensive events in the study group following

midodrine administration. Among control group, 48 of 60 patients (80%) experienced at least one episode of hypotension, with 23 patients (38.3%) requiring intervention for two episodes and 10 patients (16.7%) experiencing three or more episodes. Conversely, in the study group, 52 out of 60 patients (86.7%) had no hypotension at all (NIL), compared to only 12 patients (20%) in the control group. Demonstrating highly significant difference (Pearson chi-square = 56.635, p = 0.001.

Olivind Jans Jesper Mehelson in a double-blind, randomised trial performed on 120 patients aged ≥ 18 years, posted for THR under spinal anaesthesia, to receive either 5 mg of midodrine hydrochloride or a placebo orally one hour prior to mobilization at 6 and 24 hours postoperatively. At 6 hours, 14 individuals of midodrine group exclaimed of orthostatic hypotension compared to 23 individuals in the placebo group. Their findings indicated that the prophylactic administration of 5 milligram oral midodrine couldn't markedly decrease incidence of orthostatic hypotension during early postoperative mobilization in comparison to placebo.[54]

Matthew H. Anstey Bradley Wibrow Tharusan Thevathasan conducted the MIDAS experiment, an worldwide, multicenter, randomized, double-blinded, placebo controlled research study examining efficacy of midodrine alongside intravenous vasopressor regimen in apparently stable ICU patients. Adults hospitalized to the intensive care unit who are rescued and who have been sustained on intravenous vasopressors at low doses for a minimum of 24 hours are eligible to participate in the selection procedure. Patients were randomly allocated to either midodrine 20 milligram group or a placebo group thrice daily alongside normal treatment. In this trial, the incidence of vasopressor administration fell by 38% following the introduction of midodrine. The incorporation of oral vasopressor, such as midodrine, alongside intravenous vasopressors in revived and stable intensive care patients has multiple benefits. Initially, it is beneficial to avoid some potential complications associated with the

administration of IV vasopressors, such as the complications of central catheter placement and catheter associated sepsis. Furthermore, they may reduce the time frame intravenous vasopressor therapy, hence decreasing the period of stay in the critically ill unit and the incidence of ICU-acquired problems.[55]

A critical endpoint in our study was the requirement for rescue doses of mephentermine to treat clinically significant hypotension and number of its occurences overall. The control group required more frequent and higher cumulative doses of mephentermine than the midodrine group (p=0.000). Furthermore, 64 out of 120 patients had no hypotensive episodes at all, and the vast majority of these were in midodrine batch (52 vs 12 in the control group).

These findings strongly suggest a protective effect of midodrine. Hypotension episodes were minimal in the midodrine group, with fewer patients requiring multiple vasopressor doses. This is entirely congruent with the findings of Freedman which was also evidenced by a Study from Gomaa who compared oral midodrine to IV phenylephrine prophylaxis in spinal anaesthesia for cesarean sections. Both groups receiving alpha-1 agonists had substantially reduced vasopressor consumption compared to controls. Notably, in this study, no patient in the midodrine group required three or more rescue doses of mephentermine, underscoring the robust prophylactic efficacy of this oral agent.[56]

SUMMARY:

The current research was carried out to determine the potency of preoperative oral midodrine in avoiding hypotension in patients that are undergoing infraumbilical surgery under spinal anaesthesia. Hypotension is a substantial risk factor for spinal anaesthesia, typically resulting in important perioperative complications if not dealt with properly. Midodrine, an agonist of the alpha-1 adrenergic receptor, was predicted to counteract the risk of this complication by the mechanism of vascular tone increase and thus stabilization of blood pressure. This was a placebo-controlled trial involving 120 patients, equally allocated to study and control groups, to generate strong data on the efficacy of the intervention.

The demographic evaluation verified that, both groups were similar in terms of Age, weight, sex distribution, such that the results could be ascribed to the intervention and not to inherent differences in population characteristics. The preliminary outcome of the trial was to examine the frequency of hypotension episodes and number of doses of rescue vasopressor support(mephentermine) required. The secondary outcome was to observe several hemodynamic measures like systolic and diastolic blood pressure, mean arterial pressure, and heart rate assessed at several time points over the perioperative period. The data illustrated that patients in the midodrine group consistently had improved stability in these parameters, specifically with fewer instances of hypotension than the placebo group.

Statistical comparison also confirmed the efficacy of midodrine. There were considerable distinctions in the rate of hypotension, with the study group demonstrating increased resistance to spinal anaesthesia-induced hypotension. This was supplemented by the decreased need for vasopressor support in those pre-medicated with midodrine, which indicates its ability to improve patient safety and comfort during and after surgery.

The research, however, has limitations. Its single-site design and lack of patients with major cardiovascular comorbidities may restrict generalizability to other populations. In spite of these limitations, the findings in this trial give strong evidence to inculcate the applications of midodrine to avoid hypotension in a defined surgical population.

CONCLUSION:

In conclusion, our study demonstrated preoperative oral midodrine effectively prevents the hypotension in patients having infraumbilical surgeries under spinal anaesthesia.

The study showed decrease in number of episodes of hypotension, thereby reducing the number of doses of rescue vasopressor support (mephentermine) required in study group in comparison to control group.

LIMITATIONS:

It is a single-centre design, which may affect the generalizability of the results. Additionally, exclusion of patients with significant cardiovascular comorbidities restricts the generalizability of our results to a wider surgical population.

Future studies could explore the effects of midodrine across different surgical procedures and include patients with varying degrees of baseline cardiovascular risk to enhance.

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ANNEXURE- I

KAHERs JNMC
BELAGAVI
INFORMED CONSENT FORM

CONSENT STATEMENT

I am making a voluntary decision to participate in the study ""**"EFFICACY OF PREOPERATIVE ORAL MIDODRINE IN PREVENTING HYPOTENSION AFTER SPINAL ANESTHESIA IN PATIENTS UNDERGOING INFRAUMBILICAL SURGERIES- A PLACEBO CONTROLLED TRIAL"**

My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

"EFFICACY OF PREOPERATIVE ORAL MIDODRINE IN PREVENTING HYPOTENSION AFTER SPINAL ANESTHESIA IN PATIENTS UNDERGOING INFRAUMBILICAL SURGERIES- A PLACEBO CONTROLLED TRIAL"

Introduction: Spinal anaesthesia is a common anesthestic practice which is widely used for anaesthetic management of patients undergoing lower abdominal and lower leg surgeries[1]. There are many different complications following spinal anesthesia one of common side effect is sudden fall in blood pressure seen in 33% of the patients

Many techniques are used in prevention of low blood pressure of spinal anesthesia which includes infusing intravenous IV fluid before spinal anesthetic procedure, drugs that increase Blood pressure and physical methods like compression stockings and leg bindings.

Midodrine hydrochloride act as an agonist on alpha 1 adrenoreceptor causing an increase in blood pressure. In healthy persons, an oral dose of 10mg can rise the blood pressure 10 to 30mm Hg in one hour and stay elevated for some time. Midodrine is completely absorbed through oral route and a relatively favourable safety profile with minimal CNS side effects.

Our study is that the post spinal fall in Blood Pressure will be less in patients given Midodrine before spinal anaesthesia. Hence this study is to estimate the efficacy of administration of 10mg Midodrine tablets 1 hour before spinal anaesthesia in prevention of low blood pressure defined as SBP<90mm Hg or <80% of baseline, in patients undergoing Lower abdominal and Lower limb surgeries.

Explanation of procedure: I, request you to take part in my study. If you agree to take part in this study, I will ask you present, past and family history. Then you will be clinically examined in details. You will be allocated into one of two groups, you will not know to which group you will be allocated to. One group will be taking Midodrine 10mg tablet, powdered and dissolved in 25ml plain water, next group will be receiving plain water alone.

Withdrawal from participation in the study: Participation in this study in voluntary. You will be free to decide whether to participate in this study or

continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so.

Possible benefits from participating in the study: To prevent low blood pressure post spinal anaesthesia which is a common adverse effect and to provide better haemodynamic stability

Possible risks from participating in the study: There are no risks involved in participating in this study.

Privacy and confidentiality: The information collected from you will be coded, to prevent any person to identify you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Cost of investigations done during the course of study will be paid by the conducting post graduate.

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purpose and or presented to scientific groups. However, your identity will never be revealed.

Legal rights: By signing this consent form, we are not waiving any of your legal rights.

ANNEXURE II

PROFORMA

TITLE: "EFFICACY OF PREOPERATIVE ORAL MIDODRINE IN PREVENTING HYPOTENSION AFTER SPINAL ANESTHESIA IN PATIENTS UNDERGOING INFRAUMBILICAL SURGERIES- A PLACEBO CONTROLLED TRIAL"

Name: Address:

Age: Anaesthesiologist:

Gender: IP no. :

Date of Examination:

Pre anaesthetic evaluation:

Chief Complaints :

Past History:

- H/o co morbidities and drug intake :

- H/o previous surgery/(s):

Family history:

General physical examination:

Weight (Kg) :	Height:	BMI:
Pallor:	Icterus:	Cyanosis:
Clubbing:	Edema:	
PR :	BP :	RR:

Systemic examination:

RS : CNS:

CVS : GIT:

Airway Examination:

Teeth:

Jaw movements :

MPG:

Spine:

Preoperative physical status ASA Grade I II III IV V

Investigations:

Hb(gm/dl): TLC: Platelet count:

Serum Creatinine: FBS: Prothrombin time:

INR: Serology:

Diagnosis:

Proposed surgery:

Anaesthetic Procedure: Subarachnoid block

Inclusion Criteria:

• Age: 18 – 60 years

• ASA 1

• Patients undergoing lower abdominal and lower limb surgeries

• Patients without local anaesthetic allergy

• Either gender

Exclusion Criteria:

• Patients with history of hypertension, cardiovascular disease, cerebrovascular disease, baseline SBP>140mm Hg before administration of drug

• Patients with any contraindications to spinal anaesthesia

• History of coagulopathy, pheochromocytoma.

• Patients on vasoconstrictors.

• Pregnancy.

Methodology:

- After obtaining approval of the ethical committee and written informed consent. A total of patients undergoing lower abdominal and lower limb surgeries under spinal anaesthesia will be included in the study.
- After having met inclusion and exclusion criteria and having obtained informed consent, patients will be randomised into 2 groups according to computer generated randomization table.

    - ❖ Group A- Patients will be administered Midodrine 10mg tablets powdered and dissolved in 25 ml water orally one hour before Spinal anaesthesia.
    - ❖ Group B: Patients will be administered with 25 ml of plain water orally 1 hour before spinal anaesthesia

- A detailed Pre-Anaesthetic Evaluation will be done, one day prior to surgery, and vital parameters will be noted on the day of the surgery.
- After confirming NBM status.
- The vital parameters are noted which Systolic, Diastolic & Mean arterial pressure and the Heart rate.

- The patients in Group A will receive 25 ml of water in which Midodrine 10mg powder is dissolved and the patients in Group B will receive plain water 25 ml 1 hour before administration of spinal anaesthesia.
- The patients will be blinded to the group to which they belong.
- Then an 18 Gauge IV canula will be inserted to patients in either group and will receive 10ml/kg Ringer's lactate before administering Spinal anaesthesia.
- On arrival at the operating room the patients will be monitored using, ECG, NIBP, pulse oximeter, spinal anaesthesia will be performed in sitting position, by injecting 0.5% (H) Bupivaciane 15mg (3cc) & 25 mcg Fentanyl, total (3.5cc) in L3-L4 or L4-L5 Space using 23-gauge Quincke's Needle, patient will be put in supine position.
- The highest sensory level of the spinal block will be tested by the pinprick method every 5 minutes for 20 minutes and recorded after 20 minutes. Hemodynamic variables comprising SBP, DBP, MAP and HR will be recorded at 2,5, 10, 15, 20, 25, 30, 45, and 60 minutes after spinal anesthesia, every 15 mins until the end of the surgery.
- Hypotension (SBP <90 mm Hg or 80% of base line) will be treated with an IV bolus of 6mg mephentermine, repeated if hypotension persists, and increasing infusion rate of lactated Ringer's solution. Severe hypotension (SBP <80 mm Hg) will be treated with an IV bolus of 10-mg mephentermine and a bolus of lactated Ringer's solution 100 ml. Bradycardia (HR<50 beats /min) will be treated with IV atropine 0.5 mg, repeated as appropriate. A single measurement of MAP or HR below the respective threshold is sufficient to qualify as hypotension, severe hypotension, or bradycardia. The occurrence of vasovagal attacks (bradycardia and hypotension with fainting) during spinal needle insertion, post spinal hypotension, severe hypotension, bradycardia, reactive hypertension (SBP higher than 140 mm Hg), nausea and vomiting, shivering, intraoperative requirements of mephentermine and atropine, and total volume of fluids infused will be recorded**.**

PARAMETERS:

Data analysis table:

	SBP	**DBP**	**MAP**	**HR**
0 mins				
2 mins				
5 mins				
10 mins				
15 mins				
20 mins				
25 mins				
30 mins				
45 mins				
60 mins				
75 mins				
90 mins				
120 mins				

- Total Duration of surgery:
- Number of doses of mephentermine required:
- Number of episodes of hypotension:
- Total IV fluids infused:

ANNEXURE III

PHOTOGRAPHS

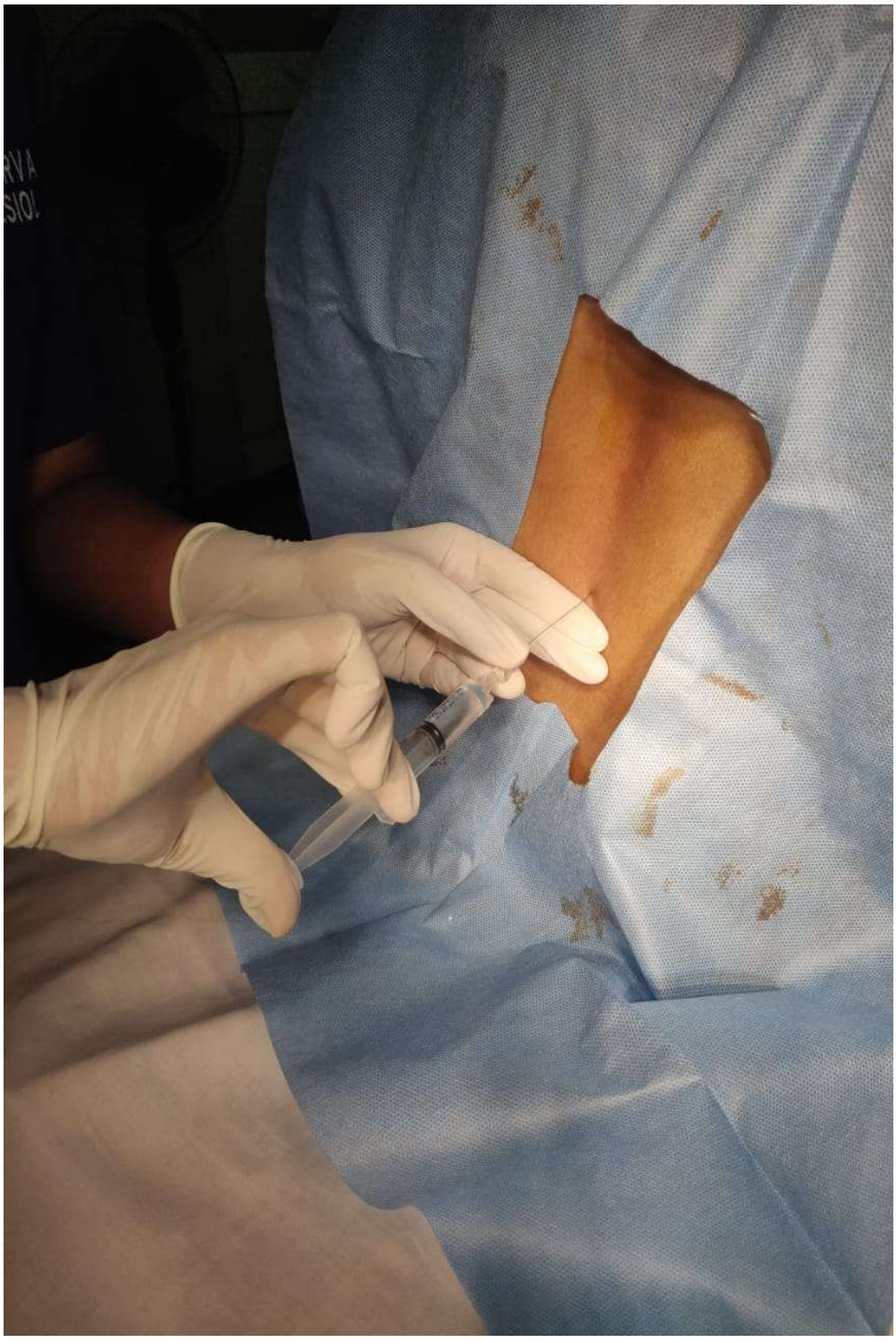

FIGURE 1: SPINAL ANESTHESIA PROCEDURE

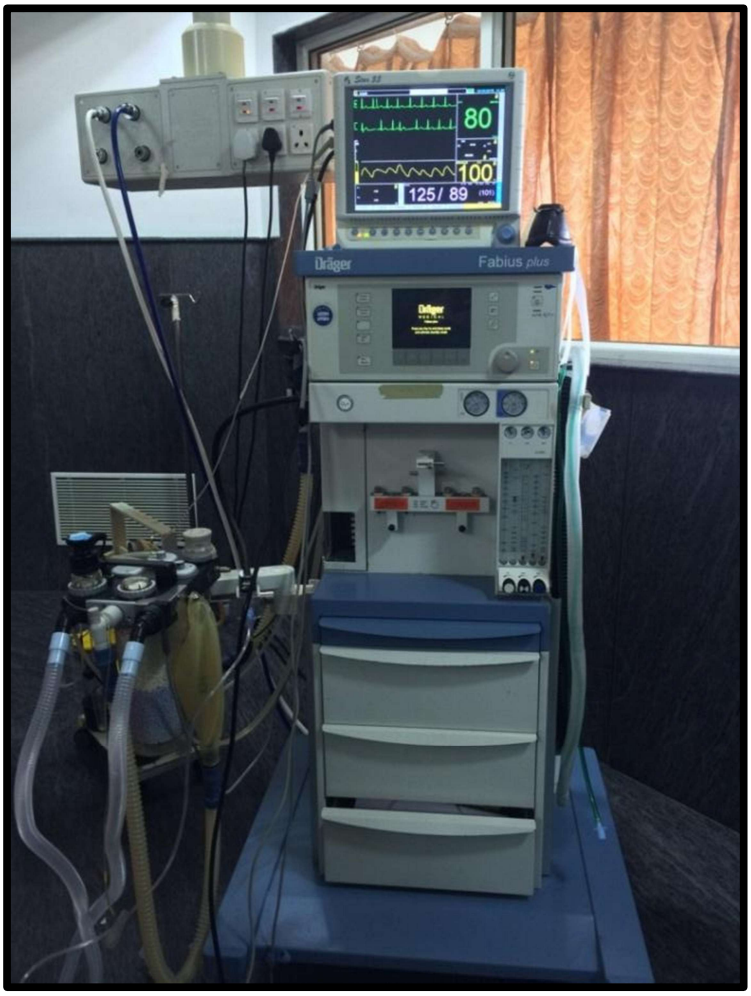

FIGURE 2: MONITORING DURING SURGERY

FIGURE 3: 0.5 % BUPIVACAINE HYPERBARIC AMPOULE

FIGURE 4: FENTANYL AMPOULE

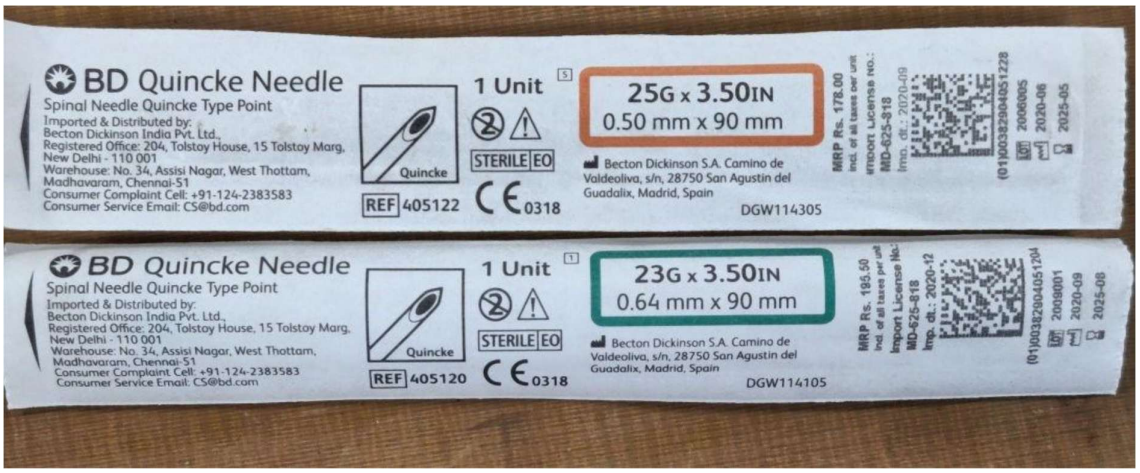

FIGURE 5: SPINAL NEEDLES

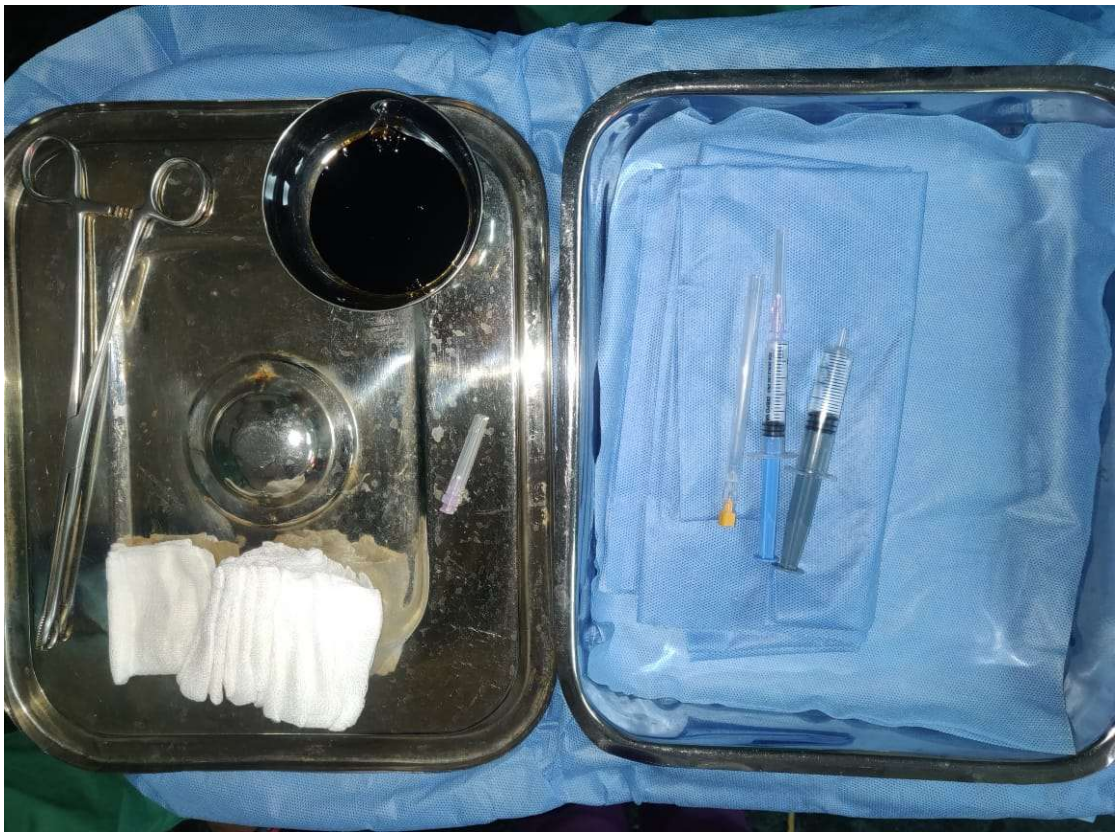

FIGURE 6: SPINAL TRAY

FIGURE 7: TABLET MIDODRINE 10mg

ANNEXURE IV

MASTER CHART

Age	Sex	ASA Grade	Weight	Baseline	T2	T5	T10	T15	T20	T25	T30	T45	T60	T75	T90	T105	T120	No of doses of mephentermine	No of episodes of hypotension
				SBP	SBP	SBP	SBP	SBP	SBP	SBP	SBP	SBP	SBP	SBP	SBP	SBP	SBP		
STUDY GROUP																			
29	Male	1	78	120	118	130	114	110	109	126	123	117	132	135	111	135	130	NIL	NIL
25	Male	1	60	130	117	109	131	127	121	113	123	125	134	141	140	134	125	NIL	NIL
42	Male	1	68	140	133	128	131	118	114	107	96	105	112	117	123	128	120	NIL	NIL
57	Female	1	75	130	126	127	114	120	108	102	108	125	115	121	134	124	118	NIL	NIL
33	Male	1	74	115	100	103	108	108	114	125	126	133	133	135	122	114	120	NIL	NIL
43	Male	2	70	140	129	123	118	103	114	95	119	120	111	110	123	128	118	NIL	NIL
26	Male	1	60	130	135	126	123	108	112	115	121	126	120	127	119	121	119	NIL	NIL
52	Male	1	59	130	124	122	114	119	115	123	117	130	147	139	130	122	120	NIL	NIL
41	Female	1	60	130	147	124	122	119	114	123	130	115	117	127	124	130	124	NIL	NIL
45	Female	2	68	138	118	120	122	117	113	116	118	108	104	102	104	103	99	NIL	NIL
58	Male	1	69	130	120	124	119	114	117	126	108	104	132	122	131	112	110	NIL	NIL
46	Male	1	66	130	127	120	101	118	108	132	121	141	130	124	137	118	115	NIL	NIL
35	Male	1	70	131	127	130	132	134	133	126	139	141	136	141	140	129	120	NIL	NIL
34	Female	1	68	140	141	137	147	118	124	138	130	146	144	147	150	145	140	NIL	NIL
40	Female	2	75	134	143	130	128	129	132	131	143	128	124	128	127	133	130	NIL	NIL
45	Male	1	68	110	109	97	106	114	99	114	113	117	115	120	117	120	123	12mg	2
55	Male	2	78	129	135	133	123	121	117	117	115	114	113	110	111	107	96	NIL	NIL
37	Male	1	80	134	135	133	137	130	125	122	133	124	127	131	126	123	120	NIL	NIL
26	Male	1	98	120	138	120	111	108	105	113	118	115	112	101	99	105	110	NIL	NIL
23	Female	1	58	112	105	97	118	119	113	112	121	123	126	127	122	118	116	NIL	NIL
58	Female	1	90	130	135	131	127	125	121	116	119	112	108	113	118	122	118	NIL	NIL
46	Male	1	80	140	133	135	132	127	121	123	116	108	113	109	104	107	115	NIL	NIL
50	Male	1	60	134	125	127	130	121	128	117	113	116	121	117	127	131	122	NIL	NIL
60	Male	2	98	130	128	123	117	118	112	108	106	103	94	103	108	113	120	NIL	NIL
42	Male	1	80	137	130	131	128	124	132	134	132	135	131	137	129	127	123	NIL	NIL
52	Male	1	70	140	129	125	121	127	132	122	116	105	111	106	113	101	119	NIL	NIL
44	Male	1	68	100	90	107	102	106	97	109	103	111	112	120	118	124	130	NIL	NIL
57	Female	2	68	135	141	140	127	130	119	126	120	125	128	116	123	126	130	NIL	NIL
56	Male	1	90	140	135	130	126	122	128	118	121	126	121	127	126	129	120	NIL	NIL
19	Male	1	57	120	115	114	121	119	114	110	114	118	126	122	126	120	110	NIL	NIL
47	Female	2	47	110	96	83	99	104	100	112	118	127	119	123	128	130	121	6mg	1
25	Male	1	85	130	128	120	126	124	118	116	128	120	110	116	118	120	110	NIL	NIL
32	Male	1	51	120	110	112	111	108	109	116	96	97	104	111	121	119	120	NIL	NIL
55	Male	2	72	110	100	108	106	98	97	100	101	111	110	112	114	118	109	NIL	NIL
38	Male	1	85	130	120	118	116	110	112	108	120	126	116	128	110	120	130	NIL	NIL
29	Male	1	80	140	130	120	138	132	130	128	124	123	113	116	120	123	114	NIL	NIL
35	Female	1	55	110	108	112	114	108	106	100	98	108	104	103	119	129	121	NIL	NIL
26	Female	2	70	100	99	86	90	110	108	98	99	110	110	112	118	120	140	6mg	1
36	Male	1	70	110	120	114	116	118	112	116	120	119	110	122	119	110	129	NIL	NIL
46	Male	1	78	90	102	110	96	102	95	91	97	108	115	109	114	107	110	6mg	1
54	Male	2	60	120	110	112	108	106	100	98	88	99	115	116	119	128	138	NIL	NIL
60	Male	1	80	140	120	124	132	122	113	103	106	107	110	113	119	120	129	NIL	NIL
32	Male	1	66	140	121	116	125	120	116	107	113	118	125	130	132	127	117	NIL	NIL
22	Male	2	67	120	127	124	118	114	108	103	108	111	116	119	124	126	120	NIL	NIL
29	Male	1	68	110	105	101	99	103	100	97	92	105	110	126	119	124	136	NIL	NIL
60	Female	1	88	123	124	116	110	100	105	94	104	108	111	116	122	128	113	NIL	NIL
37	Male	2	70	120	130	133	140	135	131	128	130	140	138	132	128	122	132	NIL	NIL
45	Male	1	73	130	120	124	119	130	128	126	120	118	114	110	111	129	135	NIL	NIL
52	Male	1	70	110	102	86	98	93	99	105	108	112	108	114	118	121	128	12mg	2
34	Male	1	40	120	120	115	113	106	115	119	124	118	108	112	116	120	116	NIL	NIL

60	Male	1	80	140	130	125	130	128	118	123	110	124	125	116	127	120	128	NIL	NIL
45	Male	2	80	130	124	120	118	110	107	100	98	111	115	105	110	120	130	6mg	1
57	Male	1	68	132	128	126	123	120	118	116	113	115	119	120	110	111	123	NIL	NIL
55	Female	1	60	120	119	110	115	113	108	105	107	100	98	113	117	120	130	NIL	NIL
60	Male	2	82	140	142	138	136	133	130	128	120	126	124	118	119	117	120	NIL	NIL
22	Female	1	68	110	108	100	98	96	89	97	100	98	110	108	104	112	120	6mg	1
47	Female	1	88	130	120	128	124	119	120	118	110	125	126	119	121	123	128	NIL	NIL
53	Male	2	80	120	100	110	90	99	105	109	111	103	110	109	111	120	130	NIL	NIL
47	Male	1	68	130	128	126	124	116	110	120	100	108	109	110	121	110	123	NIL	NIL
35	Male	1	82	100	98	88	96	86	98	100	110	120	110	108	118	120	128	12mg	2

Age	Sex	ASA Grade	Weight	Baseline	T2	T5	T10	T15	T20	T25	T30	T45	T60	T75	T90	T105	T120	No of doses of mephentermine	No of episodes of hypotension
				SBP	SBP	SBP	SBP	SBP	SBP	SBP	SBP	SBP	SBP	SBP	SBP	SBP	SBP		
CONTROL GROUP																			
26	Male	1	79	104	117	103	90	93	94	96	103	117	98	97	107	104	114	18mg	3
57	Male	2	73	100	99	96	97	106	99	111	113	120	113	112	108	109	113	12mg	2
56	Male	1	52	122	104	93	99	99	106	110	95	94	95	108	112	96	100	6mg	1
60	Male	2	64	103	97	101	98	100	100	94	123	118	108	116	102	99	110	NIL	NIL
60	Male	1	70	113	100	97	106	115	99	110	117	111	115	120	116	126	116	NIL	NIL
55	Female	2	75	113	104	89	109	110	97	110	115	117	109	110	120	118	128	12mg	2
27	Male	1	77	110	106	103	109	110	92	84	107	99	110	112	114	103	120	18mg	3
37	Female	2	65	133	127	123	110	105	122	118	111	95	121	117	121	120	139	NIL	NIL
54	Male	1	78	111	106	113	1088	97	100	99	115	120	117	123	116	126	120	NIL	NIL
34	Male	1	65	121	124	114	115	109	111	116	123	121	117	121	120	110	112	NIL	NIL
37	Male	1	64	113	94	100	98	102	109	103	98	104	110	108	110	117	115	6mg	1
60	Male	2	70	127	111	106	87	98	103	97	99	102	99	98	105	110	119	12mg	2
55	Male	1	68	136	120	110	93	97	107	106	117	104	104	96	108	113	122	12mg	2
60	Male	1	80	130	125	108	101	97	102	94	109	112	110	104	111	110	114	NIL	NIL
50	Male	1	75	110	100	92	88	96	99	93	114	94	108	96	100	110	121	18mg	3
58	Male	1	65	133	128	123	118	111	107	115	118	106	109	100	110	108	119	NIL	NIL
53	Male	2	66	138	122	103	88	92	94	96	90	99	109	99	107	110	120	24mg	4
57	Male	2	50	111	89	113	93	94	98	90	100	99	101	100	109	106	110	12mg	2
48	Male	1	66	128	117	112	110	108	106	110	95	105	118	115	118	123	120	NIL	NIL
57	Female	2	63	125	115	113	96	104	95	112	109	110	113	109	115	120	121	NIL	NIL
35	Female	1	55	120	110	95	90	96	99	99	108	110	99	98	105	110	117	6mg	1
55	Male	2	70	114	91	100	93	91	88	101	107	100	100	98	99	103	110	12mg	2
60	Male	2	61	118	105	86	106	95	101	94	92	90	92	121	98	106	113	20mg	3
45	Female	1	78	112	98	96	98	102	106	91	96	95	110	107	96	98	115	18mg	3
54	Male	2	71	123	118	108	98	93	101	99	103	96	105	104	119	120	122	18mg	3
24	Male	1	65	113	103	96	101	107	100	106	109	103	97	98	117	109	115	12mg	2
59	Male	1	70	126	98	88	94	101	93	99	114	106	114	112	109	116	120	18mg	4
44	Male	1	77	114	85	96	99	90	101	94	106	100	94	98	105	110	121	10mg	2
56	Male	2	85	113	96	99	107	90	95	103	92	97	103	109	106	113	120	12mg	2
58	Female	2	45	103	114	94	97	100	98	97	106	94	98	116	103	96	109	24mg	4
43	Female	2	58	101	92	98	104	97	115	112	99	111	100	115	115	119	124	6mg	2
56	Male	2	66	134	123	99	94	102	96	105	108	110	98	109	112	116	120	12mg	2
56	Male	2	70	126	103	89	95	95	96	100	103	110	105	113	116	120	119	20mg	3
23	Male	1	68	99	85	95	91	99	95	100	109	114	108	103	110	122	121	12mg	2
60	Male	2	58	105	90	90	98	84	104	99	101	107	98	107	100	115	126	12mg	2
50	Male	2	70	114	105	110	99	100	98	98	93	99	100	104	111	102	106	6mg	1
30	Male	1	70	122	96	95	103	105	99	106	102	108	113	101	99	108	117	6mg	1
27	Female	1	55	140	127	116	110	96	100	101	91	100	112	123	119	120	128	NIL	NIL
55	Female	2	60	132	99	101	90	100	99	101	92	101	121	105	114	125	123	12mg	2
25	Male	1	76	114	100	96	107	100	111	106	109	100	99	106	96	102	114	6mg	1
34	Female	1	66	108	110	98	96	105	99	103	110	119	124	116	120	126	124	6mg	1
38	Male	1	80	127	117	109	100	109	116	98	106	112	117	120	112	118	122	NIL	NIL

50	Female	2	60	98	100	99	95	107	97	92	98	100	109	112	109	104	110	12mg	2
53	Male	2	55	123	127	117	93	97	100	92	121	105	107	99	104	103	113	12mg	2
26	Male	1	79	130	120	111	101	93	99	108	112	117	98	99	110	109	114	10mg	2
60	Male	2	69	116	110	100	97	99	96	103	110	109	106	99	119	93	97	12mg	2
55	Male	1	73	107	95	88	105	110	99	106	100	111	98	113	103	99	110	18mg	3
31	Female	1	50	120	110	100	90	85	100	111	107	103	107	100	97	102	110	20mg	3
60	Male	1	80	110	99	91	103	99	98	87	97	100	104	100	100	108	114	12mg	2
20	Female	1	65	119	120	114	100	114	100	99	91	94	99	100	110	108	112	6mg	1
60	Female	2	70	110	99	101	98	104	99	100	109	100	99	101	97	102	110	6mg	1
21	Male	1	60	129	95	88	99	98	107	99	110	108	112	116	112	120	118	12mg	2
35	Male	1	70	110	89	84	104	102	78	89	104	110	108	102	96	105	115	12mg	2
27	Female	1	86	130	123	115	110	107	110	98	97	99	102	109	98	104	110	NIL	NIL
40	Male	2	80	129	116	109	95	98	98	97	109	92	97	99	102	110	118	12mg	2
56	Male	2	89	137	127	119	110	104	110	91	98	100	99	119	110	99	110	6mg	1
23	Male	1	90	111	100	90	103	95	116	105	99	92	97	100	91	94	106	18mg	3
39	Male	1	85	122	90	93	108	97	116	100	99	103	110	112	96	102	110	6mg	1
20	Female	1	54	132	123	115	110	94	95	88	100	100	99	114	108	113	123	10mg	2
54	Female	1	67	126	115	90	104	94	100	111	99	91	91	97	115	100	103	24mg	4

Age	Sex	ASA Grade	Weight	Baseline	T2	T5	T10	T15	T20	T25	T30	T45	T60	T75	T90	T105	T120	No of doses of mephentermine	No of episodes of hypotension
				DBP	DBP	DBP	DBP	DBP	DBP	DBP	DBP	DBP	DBP	DBP	DBP	DBP	DBP		
STUDY GROUP																			
29	Male	1	78	80	94	85	84	88	83	88	83	78	75	71	82	82	76	NIL	NIL
25	Male	1	60	85	83	96	96	89	80	77	81	72	61	71	85	93	84	NIL	NIL
42	Male	1	68	90	84	84	74	69	76	79	83	88	93	93	87	98	80	NIL	NIL
57	Female	1	75	85	75	80	80	93	68	79	85	85	75	90	78	88	74	NIL	NIL
33	Male	1	74	76	59	81	77	76	83	89	89	88	90	90	86	77	70	NIL	NIL
43	Male	2	70	90	90	82	74	69	79	69	91	100	89	97	84	72	68	NIL	NIL
26	Male	1	60	70	73	69	62	62	68	73	81	88	84	94	89	97	87	NIL	NIL
52	Male	1	59	80	91	78	80	72	78	74	86	69	70	80	90	90	84	NIL	NIL
41	Female	1	60	80	91	80	78	72	71	76	86	74	64	72	67	61	75	NIL	NIL
45	Female	2	68	83	71	70	69	67	66	68	70	65	67	65	67	66	70	NIL	NIL
58	Male	1	69	60	66	70	67	75	80	87	78	85	78	85	82	69	73	NIL	NIL
46	Male	1	66	99	88	80	71	76	74	81	81	86	83	73	79	70	72	NIL	NIL
35	Male	1	70	81	87	81	88	88	88	79	91	92	92	93	91	82	72	NIL	NIL
34	Female	1	68	81	81	79	79	70	73	79	83	85	85	90	94	91	92	NIL	NIL
40	Female	2	75	78	84	82	78	77	78	80	81	84	75	78	77	84	80	NIL	NIL
45	Male	1	68	75	75	54	74	78	53	80	79	61	84	88	85	86	80	12mg	2
55	Male	2	78	77	81	75	72	74	75	75	74	70	70	70	70	69	78	NIL	NIL
37	Male	1	80	88	87	91	86	81	86	86	88	75	83	79	79	77	70	NIL	NIL
26	Male	1	98	98	90	84	83	81	80	84	89	86	87	83	80	82	73	NIL	NIL
23	Female	1	58	64	63	56	59	64	66	66	77	65	71	75	72	84	80	NIL	NIL
58	Female	1	90	90	79	74	70	66	64	69	65	67	72	75	79	84	76	NIL	NIL
46	Male	1	80	80	75	81	77	73	66	69	60	65	67	69	72	74	70	NIL	NIL
50	Male	1	60	69	69	62	67	60	72	68	73	77	87	95	89	89	78	NIL	NIL
60	Male	2	98	80	74	67	65	72	67	58	66	63	63	72	82	89	70	NIL	NIL
42	Male	1	80	89	81	76	72	68	72	75	81	79	85	85	80	82	75	NIL	NIL
52	Male	1	70	90	84	80	84	79	76	82	86	71	71	76	78	73	70	NIL	NIL
44	Male	1	68	70	70	67	60	61	58	64	71	74	79	83	78	65	70	NIL	NIL
57	Female	2	68	93	81	71	81	74	89	83	71	76	90	80	78	70	80	NIL	NIL
56	Male	1	90	90	93	89	84	71	72	74	71	76	69	70	73	75	69	NIL	NIL
19	Male	1	57	80	74	69	69	73	71	67	80	86	74	77	74	69	69	NIL	NIL
47	Female	2	47	80	66	62	77	80	80	92	95	87	81	77	71	71	76	6mg	1
25	Male	1	85	91	90	80	84	92	79	80	78	80	78	84	90	80	75	NIL	NIL
32	Male	1	51	80	70	72	68	70	60	58	68	70	82	84	79	64	70	NIL	NIL
55	Male	2	72	60	68	70	60	69	70	80	78	80	70	70	70	80	76	NIL	NIL
38	Male	1	85	89	90	80	60	68	78	80	70	78	80	90	73	80	73	NIL	NIL
29	Male	1	80	90	80	70	60	70	82	62	60	63	72	76	79	69	64	NIL	NIL
35	Female	1	55	70	68	72	80	64	76	68	64	90	92	89	78	64	70	NIL	NIL
26	Female	2	70	70	60	52	60	74	70	64	66	80	78	84	90	80	76	6mg	1
36	Male	1	70	90	80	70	78	84	64	70	80	78	68	64	70	80	76	NIL	NIL
46	Male	1	78	60	63	69	64	69	64	53	66	59	60	64	68	71	65	6mg	1
54	Male	2	60	70	80	78	88	62	66	72	65	82	64	73	84	90	99	NIL	NIL
60	Male	1	80	90	80	74	82	94	73	84	76	78	70	74	84	90	88	NIL	NIL
32	Male	1	66	90	71	76	81	74	67	61	75	89	84	80	73	70	65	NIL	NIL
22	Male	2	67	70	70	66	63	60	62	66	69	73	69	63	73	66	60	NIL	NIL
29	Male	1	68	70	67	60	60	55	55	63	62	69	69	73	79	86	76	NIL	NIL
60	Female	1	88	90	86	74	69	74	58	61	64	57	63	67	59	69	75	NIL	NIL
37	Male	2	70	90	93	94	100	98	92	87	90	93	91	88	81	82	76	NIL	NIL
45	Male	1	73	90	80	78	80	62	64	74	62	78	72	60	68	84	74	NIL	NIL
52	Male	1	70	70	63	58	63	50	60	66	61	67	71	75	69	74	70	12mg	2
34	Male	1	40	80	64	70	69	73	80	88	83	88	83	83	77	73	68	NIL	NIL
60	Male	1	80	100	81	77	67	72	56	60	76	89	90	59	63	70	78	NIL	NIL
45	Male	2	80	77	67	70	58	60	62	67	50	56	62	61	69	70	75	6mg	1
57	Male	1	68	80	78	70	68	74	64	84	63	65	70	72	79	68	70	NIL	NIL
55	Female	1	60	90	60	63	73	64	72	58	60	70	61	74	60	64	70	NIL	NIL
60	Male	2	82	80	60	63	60	53	58	60	72	78	61	62	70	84	80	NIL	NIL
22	Female	1	68	80	60	65	72	60	58	60	70	68	63	61	74	68	76	6mg	1

47	Female	1	88	90	80	72	60	64	62	56	60	59	62	67	70	72	68	NIL	NIL
53	Male	2	80	80	70	62	68	70	65	69	70	72	65	71	72	80	78	NIL	NIL
47	Male	1	68	90	80	70	80	62	72	60	63	64	66	67	90	80	78	NIL	NIL
35	Male	1	82	60	70	56	58	60	70	79	80	88	78	68	78	60	65	12mg	2

Age	Sex	ASA Grade	Weight	Baseline	T2	T5	T10	T15	T20	T25	T30	T45	T60	T75	T90	T105	T120	No of doses of mephentermine	No of episodes of hypotension
				DBP	DBP	DBP	DBP	DBP	DBP	DBP	DBP	DBP	DBP	DBP	DBP	DBP	DBP		
CONTROL GROUP																			
26	Male	1	79	71	51	62	60	57	64	52	54	51	62	57	51	60	65	18mg	3
57	Male	2	73	63	53	53	57	55	50	51	60	61	58	60	52	60	70	12mg	2
56	Male	1	52	67	55	51	55	50	54	50	60	61	63	51	60	53	67	6mg	1
60	Male	2	64	63	60	60	54	60	55	59	70	62	55	60	54	58	65	NIL	NIL
60	Male	1	70	83	62	59	59	70	61	58	54	52	62	52	54	68	60	NIL	NIL
55	Female	2	75	84	60	51	54	62	50	62	60	58	68	57	65	60	69	12mg	2
27	Male	1	77	60	55	51	58	52	55	60	60	63	63	61	67	61	67	18mg	3
37	Female	2	65	71	51	65	61	64	63	62	54	66	52	54	60	63	78	NIL	NIL
54	Male	1	78	50	71	61	58	58	68	62	60	64	62	55	59	62	70	NIL	NIL
34	Male	1	65	80	65	59	63	58	61	65	60	63	64	56	67	68	66	NIL	NIL
37	Male	1	64	60	53	54	56	54	57	53	57	64	62	58	63	64	68	6mg	1
60	Male	2	70	90	71	60	55	56	59	58	61	65	60	52	62	58	60	12mg	2
55	Male	1	68	92	78	65	54	56	53	57	52	52	54	57	64	66	70	12mg	2
60	Male	1	80	80	69	60	65	56	55	65	66	66	62	70	64	70	72	NIL	NIL
50	Male	1	75	70	64	60	53	65	64	54	51	50	59	62	69	67	72	18mg	3
58	Male	1	65	86	70	74	70	68	62	69	65	68	57	61	60	63	67	NIL	NIL
53	Male	2	66	76	71	64	60	53	60	58	55	50	57	58	64	68	70	24mg	4
57	Male	2	50	62	55	52	58	53	60	66	62	62	60	62	64	59	60	12mg	2
48	Male	1	66	79	80	70	72	73	68	62	57	64	60	64	62	68	64	NIL	NIL
57	Female	2	63	78	70	62	68	64	60	64	63	68	60	59	63	69	70	NIL	NIL
35	Female	1	55	70	66	63	51	58	66	58	60	64	60	66	68	65	68	6mg	1
55	Male	2	70	63	61	55	53	61	53	64	60	61	55	57	59	63	65	12mg	2
60	Male	2	61	67	62	45	63	53	60	58	65	60	51	51	59	60	65	20mg	3
45	Female	1	78	60	56	51	53	55	58	57	58	57	50	55	58	59	63	18mg	3
54	Male	2	71	86	76	53	52	54	59	50	56	57	58	59	63	68	70	18mg	3
24	Male	1	65	54	54	54	55	58	52	60	53	57	57	62	51	53	60	12mg	2
59	Male	1	70	83	68	55	57	58	51	52	54	55	50	53	53	64	68	18mg	4
44	Male	1	77	64	56	58	60	57	55	62	60	64	59	62	60	63	67	10mg	2
56	Male	2	85	61	51	57	54	61	52	56	66	57	60	50	55	60	66	12mg	2
58	Female	2	45	64	68	52	58	52	56	50	55	52	57	52	54	57	60	24mg	4
43	Female	2	58	64	62	52	55	52	55	60	55	60	62	67	64	70	68	6mg	2
56	Male	2	66	64	55	55	51	59	53	58	60	65	70	72	68	73	75	12mg	2
56	Male	2	70	74	68	53	59	50	61	57	60	63	67	64	67	70	73	20mg	3
23	Male	1	68	61	51	58	60	57	55	57	60	62	65	61	64	68	64	12mg	2
60	Male	2	58	53	50	60	56	53	54	55	54	58	60	54	60	63	61	12mg	2
50	Male	2	70	61	69	68	50	55	58	62	63	60	58	60	65	63	64	6mg	1
30	Male	1	70	70	65	60	54	50	55	59	60	58	59	58	57	65	70	6mg	1
27	Female	1	55	80	75	70	68	61	65	65	61	63	67	69	70	72	76	NIL	NIL
55	Female	2	60	65	50	57	56	55	60	64	54	60	65	65	66	62	68	12mg	2
25	Male	1	76	63	60	50	56	60	63	52	60	56	60	50	59	57	63	6mg	1
34	Female	1	66	60	57	60	54	54	58	54	60	66	69	63	66	70	68	6mg	1
38	Male	1	80	75	68	62	65	69	70	66	59	73	69	71	69	63	67	NIL	NIL
50	Female	2	60	70	65	62	55	59	56	50	56	59	57	64	65	60	67	12mg	2
53	Male	2	55	70	63	56	53	56	57	56	50	51	55	57	60	62	67	12mg	2
26	Male	1	79	70	68	62	63	54	59	61	64	67	62	68	69	63	70	10mg	2
60	Male	2	69	63	66	51	56	60	54	60	64	68	62	68	60	61	57	12mg	2
55	Male	1	73	60	53	54	63	60	60	60	64	60	60	55	53	55	57	18mg	3
31	Female	1	50	77	66	69	51	50	59	65	54	58	59	60	62	54	60	20mg	3
60	Male	1	80	70	60	53	60	60	64	50	57	60	63	67	60	55	60	12mg	2

20	Female	1	65	69	71	61	60	59	60	60	51	58	58	57	60	65	60	6mg	1
60	Female	2	70	71	60	57	52	60	63	60	58	60	60	57	65	54	64	6mg	1
21	Male	1	60	80	61	55	57	53	58	57	60	67	70	68	63	67	70	12mg	2
35	Male	1	70	70	63	53	58	55	53	63	60	62	63	68	60	68	70	12mg	2
27	Female	1	86	90	85	76	71	68	70	60	63	60	65	66	64	60	78	NIL	NIL
40	Male	2	80	80	70	68	59	50	59	51	50	63	58	60	62	64	68	12mg	2
56	Male	2	89	74	68	65	60	67	60	53	63	62	50	68	62	62	68	6mg	1
23	Male	1	90	66	52	66	57	65	60	52	52	56	56	57	62	59	64	18mg	3
39	Male	1	85	74	50	57	60	56	53	57	58	58	60	63	57	54	64	6mg	1
20	Female	1	54	84	60	55	58	53	57	52	59	59	60	54	60	65	70	10mg	2
54	Female	1	67	60	56	55	60	50	59	62	56	50	58	50	52	65	60	24mg	4

Age	Sex	ASA Grade	Weight	Baseline	T2	T5	T10	T15	T20	T25	T30	T45	T60	T75	T90	T105	T120	No of doses of mephentermine	No of episodes of hypotension
				MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP		
STUDY GROUP																			
29	Male	1	78	93	102	100	94	95	92	101	96	91	94	92	92	100	94	NIL	NIL
25	Male	1	60	100	94	100	108	102	94	89	95	90	85	94	103	107	98	NIL	NIL
42	Male	1	68	107	100	99	93	85	89	88	87	94	99	101	99	108	93	NIL	NIL
57	Female	1	75	100	92	96	91	102	81	87	93	98	88	100	97	100	89	NIL	NIL
33	Male	1	74	89	73	88	87	87	93	101	101	103	104	105	98	89	87	NIL	NIL
43	Male	2	70	107	103	96	89	80	91	78	100	107	96	101	97	91	85	NIL	NIL
26	Male	1	60	90	94	88	82	77	83	87	94	101	96	105	99	105	98	NIL	NIL
52	Male	1	59	97	102	93	91	88	90	90	96	89	96	100	103	101	96	NIL	NIL
41	Female	1	60	97	110	95	93	88	85	92	101	88	82	90	86	84	91	NIL	NIL
45	Female	2	68	101	87	87	87	84	82	84	86	79	79	77	79	78	80	NIL	NIL
58	Male	1	69	83	84	88	84	88	92	100	88	91	96	97	98	83	85	NIL	NIL
46	Male	1	66	109	101	93	81	90	85	98	94	104	99	90	98	86	86	NIL	NIL
35	Male	1	70	98	100	97	103	103	103	95	107	108	107	109	107	98	88	NIL	NIL
34	Female	1	68	101	101	98	102	86	90	99	99	105	105	109	113	109	108	NIL	NIL
40	Female	2	75	97	104	98	95	94	96	97	102	99	91	95	94	100	97	NIL	NIL
45	Male	1	68	87	86	68	85	90	68	91	90	80	94	99	96	97	94	12mg	2
55	Male	2	78	94	99	94	89	90	89	89	88	85	84	83	84	82	84	NIL	NIL
37	Male	1	80	103	103	105	103	97	99	98	103	91	98	96	95	92	87	NIL	NIL
26	Male	1	98	105	106	96	92	90	88	94	99	96	95	89	86	90	85	NIL	NIL
23	Female	1	58	80	77	70	79	82	82	81	92	84	89	92	89	95	92	NIL	NIL
58	Female	1	90	103	98	93	89	86	83	85	83	82	84	88	92	97	90	NIL	NIL
46	Male	1	80	100	94	99	95	91	84	87	79	79	82	82	83	85	85	NIL	NIL
50	Male	1	60	91	88	84	88	80	91	84	86	90	98	102	102	103	93	NIL	NIL
60	Male	2	98	97	92	86	82	87	82	75	79	76	73	82	91	97	87	NIL	NIL
42	Male	1	80	105	97	94	91	87	92	95	98	98	100	102	96	97	91	NIL	NIL
52	Male	1	70	107	99	95	96	95	95	95	96	82	84	86	90	82	86	NIL	NIL
44	Male	1	68	80	77	80	74	76	71	79	82	86	90	95	91	85	90	NIL	NIL
57	Female	2	68	107	101	94	96	93	99	97	87	92	103	92	93	89	97	NIL	NIL
56	Male	1	90	107	107	103	98	88	91	89	88	93	86	89	91	93	86	NIL	NIL
19	Male	1	57	93	88	84	86	88	85	81	91	97	91	92	91	86	83	NIL	NIL
47	Female	2	47	90	76	69	84	88	87	99	103	100	94	92	90	91	91	6mg	1
25	Male	1	85	104	103	93	98	103	92	92	95	93	89	95	99	93	87	NIL	NIL
32	Male	1	51	93	83	85	82	83	76	77	77	79	89	93	93	82	87	NIL	NIL
55	Male	2	72	77	79	83	75	79	79	87	86	90	83	84	85	93	87	NIL	NIL
38	Male	1	85	103	100	93	79	82	89	89	87	94	92	103	85	93	92	NIL	NIL
29	Male	1	80	107	97	87	86	91	98	84	81	83	86	89	93	87	81	NIL	NIL
35	Female	1	55	83	81	85	91	79	86	79	75	96	96	94	92	86	87	NIL	NIL
26	Female	2	70	80	73	63	70	86	83	75	77	90	89	93	99	93	97	6mg	1
36	Male	1	70	97	93	85	91	95	80	85	93	92	82	83	86	90	94	NIL	NIL
46	Male	1	78	70	76	83	75	80	74	66	76	75	78	79	83	83	80	6mg	1
54	Male	2	60	87	90	89	95	77	77	81	73	88	81	87	96	103	112	NIL	NIL
60	Male	1	80	107	93	91	99	103	86	90	86	88	83	87	96	100	102	NIL	NIL
32	Male	1	66	107	88	89	96	89	83	76	88	99	98	97	93	89	82	NIL	NIL
22	Male	2	67	87	89	85	81	78	77	78	82	86	85	82	90	86	80	NIL	NIL
29	Male	1	68	83	80	74	73	71	70	74	72	81	83	91	92	99	96	NIL	NIL
60	Female	1	88	101	99	88	83	83	74	72	77	74	79	83	80	89	88	NIL	NIL
37	Male	2	70	100	105	107	113	110	105	101	103	109	107	103	97	95	95	NIL	NIL
45	Male	1	73	103	93	93	93	85	85	91	81	91	86	77	82	99	94	NIL	NIL
52	Male	1	70	83	76	67	75	64	73	79	77	82	83	88	85	90	89	12mg	2
34	Male	1	40	93	83	85	84	84	92	98	97	98	91	93	90	89	84	NIL	NIL
60	Male	1	80	113	97	93	88	91	77	81	87	101	102	78	84	87	95	NIL	NIL
45	Male	2	80	95	86	87	78	77	77	78	66	74	80	76	83	87	93	6mg	1
57	Male	1	68	97	95	89	86	89	82	95	80	82	86	88	89	82	88	NIL	NIL
55	Female	1	60	100	80	79	87	80	84	74	76	80	73	87	79	83	90	NIL	NIL
60	Male	2	82	100	87	88	85	80	82	83	88	94	82	81	86	95	93	NIL	NIL
22	Female	1	68	90	76	77	81	72	68	72	80	78	79	77	84	83	91	6mg	1
47	Female	1	88	103	93	91	81	82	81	77	77	81	83	84	87	89	88	NIL	NIL

53	Male	2	80	93	80	78	75	80	78	82	84	82	80	84	85	93	95	NIL	NIL
47	Male	1	68	103	96	89	95	80	85	80	75	79	80	81	100	90	93	NIL	NIL
35	Male	1	82	73	79	67	71	69	79	86	90	99	89	81	91	80	86	12mg	2

Age	Sex	ASA Grade	Weight	Baseline	T2	T5	T10	T15	T20	T25	T30	T45	T60	T75	T90	T105	T120	No of doses of mephentermine	No of episodes of hypotension
				MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP	MAP		
CONTROL GROUP																			
26	Male	1	79	82	73	76	70	69	74	67	70	73	74	70	70	75	81	18mg	3
57	Male	2	73	75	68	67	70	72	66	71	78	81	76	77	71	76	84	12mg	2
56	Male	1	52	85	71	65	70	66	71	70	72	72	74	70	77	67	78	6mg	1
60	Male	2	64	76	72	74	69	73	70	71	88	81	73	79	70	72	80	NIL	NIL
60	Male	1	70	93	75	72	75	85	74	75	75	72	80	75	75	87	79	NIL	NIL
55	Female	2	75	94	75	64	72	78	66	78	78	78	82	75	83	79	89	12mg	2
27	Male	1	77	77	72	68	75	71	67	68	76	75	79	78	83	75	85	18mg	3
37	Female	2	65	92	76	84	77	78	83	81	73	76	75	75	80	82	98	NIL	NIL
54	Male	1	78	70	83	78	401	71	79	74	78	83	80	78	78	83	87	NIL	NIL
34	Male	1	65	94	85	77	80	75	78	82	81	82	82	78	85	82	81	NIL	NIL
37	Male	1	64	78	67	69	70	70	74	70	71	77	78	75	79	82	84	6mg	1
60	Male	2	70	102	84	75	66	70	74	71	74	77	73	67	76	75	80	12mg	2
55	Male	1	68	107	92	80	67	70	71	73	74	69	71	70	79	82	87	12mg	2
60	Male	1	80	97	88	76	77	70	71	75	80	81	78	81	80	83	86	NIL	NIL
50	Male	1	75	83	76	71	65	75	76	67	72	65	75	73	79	81	88	18mg	3
58	Male	1	65	102	89	90	86	82	77	84	83	81	74	74	77	78	84	NIL	NIL
53	Male	2	66	97	88	77	69	66	71	71	67	66	74	72	78	82	87	24mg	4
57	Male	2	50	78	66	72	70	67	73	74	75	74	74	75	79	75	77	12mg	2
48	Male	1	66	95	92	84	85	85	81	78	70	78	79	81	81	86	83	NIL	NIL
57	Female	2	63	94	85	79	77	77	72	80	78	82	78	76	80	86	87	NIL	NIL
35	Female	1	55	87	81	74	64	71	77	72	76	79	73	77	80	80	84	6mg	1
55	Male	2	70	80	71	70	66	71	65	76	76	74	70	71	72	76	80	12mg	2
60	Male	2	61	84	76	59	77	67	74	70	74	70	65	74	72	75	81	20mg	3
45	Female	1	78	77	70	66	68	71	74	68	71	70	70	72	71	72	80	18mg	3
54	Male	2	71	98	90	71	67	67	73	66	72	70	74	74	82	85	87	18mg	3
24	Male	1	65	74	70	68	70	74	68	75	72	72	70	74	73	72	78	12mg	2
59	Male	1	70	97	78	66	69	72	65	68	74	72	71	73	72	81	85	18mg	4
44	Male	1	77	81	66	71	73	68	70	73	75	76	71	74	75	79	85	10mg	2
56	Male	2	85	78	66	71	72	71	66	72	75	70	74	70	72	78	84	12mg	2
58	Female	2	45	77	83	66	71	68	70	66	72	66	71	73	70	70	76	24mg	4
43	Female	2	58	76	72	67	71	67	75	77	70	77	75	83	81	86	87	6mg	2
56	Male	2	66	87	78	70	65	73	67	74	76	80	79	84	83	87	90	12mg	2
56	Male	2	70	91	80	65	71	65	73	71	74	79	80	80	83	87	88	20mg	3
23	Male	1	68	74	62	70	70	71	68	71	76	79	79	75	79	86	83	12mg	2
60	Male	2	58	70	63	70	70	63	71	70	70	74	73	72	73	80	83	12mg	2
50	Male	2	70	79	81	82	66	70	71	74	73	73	72	75	80	76	78	6mg	1
30	Male	1	70	87	75	72	70	68	70	75	74	75	77	72	71	79	86	6mg	1
27	Female	1	55	100	92	85	82	73	77	77	71	75	82	87	86	88	93	NIL	NIL
55	Female	2	60	87	66	72	67	70	73	76	67	74	84	78	82	83	86	12mg	2
25	Male	1	76	80	73	65	73	73	79	70	76	71	73	69	71	72	80	6mg	1
34	Female	1	66	76	75	73	68	71	72	70	77	84	87	81	84	89	87	6mg	1
38	Male	1	80	92	84	78	77	82	85	77	75	86	85	87	83	81	85	NIL	NIL
50	Female	2	60	79	77	74	68	75	70	64	70	73	74	80	80	75	81	12mg	2
53	Male	2	55	88	84	76	66	70	71	68	74	69	72	71	75	76	82	12mg	2
26	Male	1	79	90	85	78	76	67	72	77	80	84	74	78	83	78	85	10mg	2
60	Male	2	69	81	81	67	70	73	68	74	79	82	77	78	80	72	70	12mg	2
55	Male	1	73	76	67	65	77	77	73	75	76	77	73	74	70	70	75	18mg	3
31	Female	1	50	91	81	79	64	62	73	80	72	73	75	73	74	70	77	20mg	3
60	Male	1	80	83	73	66	74	73	75	62	70	73	77	78	73	73	78	12mg	2
20	Female	1	65	86	87	79	73	77	73	73	64	70	72	71	77	79	77	6mg	1

60	Female	2	70	84	73	72	67	75	75	73	75	73	73	72	76	70	79	6mg	1
21	Male	1	60	96	72	66	71	68	74	71	77	81	84	84	79	85	86	12mg	2
35	Male	1	70	83	72	63	73	71	61	72	75	78	78	79	72	80	85	12mg	2
27	Female	1	86	103	98	89	84	81	83	73	74	73	77	80	75	75	89	NIL	NIL
40	Male	2	80	96	85	82	71	66	72	66	70	73	71	73	75	79	85	12mg	2
56	Male	2	89	95	88	83	77	79	77	66	75	75	66	85	78	74	82	6mg	1
23	Male	1	90	81	68	74	72	75	79	70	68	68	70	71	72	71	78	18mg	3
39	Male	1	85	90	63	69	76	70	74	71	72	73	77	79	70	70	79	6mg	1
20	Female	1	54	100	81	75	75	67	70	64	73	73	73	74	76	81	88	10mg	2
54	Female	1	67	82	76	67	75	65	73	78	70	64	69	66	73	77	74	24mg	4

Age	Sex	ASA Grade	Weight	Baseline	T2	T5	T10	T15	T20	T25	T30	T45	T60	T75	T90	T105	T120	No of doses of mephentermine	No of episodes of hypotension
				HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR		
STUDY GROUP																			
29	Male	1	78	64	70	78	7	70	68	74	64	68	76	84	88	80	70	NIL	NIL
25	Male	1	60	80	76	74	62	66	60	63	73	75	86	77	87	90	80	NIL	NIL
42	Male	1	68	88	90	70	76	71	68	60	63	69	73	75	80	82	78	NIL	NIL
57	Female	1	75	70	75	70	72	60	61	68	70	64	65	66	62	52	55	NIL	NIL
33	Male	1	74	73	83	64	63	64	57	86	83	85	83	81	76	89	69	NIL	NIL
43	Male	2	70	68	72	80	78	77	74	72	80	85	84	81	82	80	65	NIL	NIL
26	Male	1	60	98	96	97	98	88	86	85	84	83	73	76	78	81	71	NIL	NIL
52	Male	1	59	70	68	66	80	73	70	83	93	76	78	72	70	71	64	NIL	NIL
41	Female	1	60	70	68	66	80	73	70	83	93	76	78	80	81	85	75	NIL	NIL
45	Female	2	68	74	85	83	89	76	76	72	83	60	60	60	64	70	62	NIL	NIL
58	Male	1	69	83	84	91	90	87	84	87	88	90	91	93	90	92	80	NIL	NIL
46	Male	1	66	78	77	70	65	80	78	90	73	70	74	75	65	67	60	NIL	NIL
35	Male	1	70	71	73	70	73	74	77	72	76	74	80	80	76	73	68	NIL	NIL
34	Female	1	68	57	71	65	60	57	62	58	55	51	53	53	55	52	59	NIL	NIL
40	Female	2	75	86	80	66	68	68	75	78	75	71	73	70	69	66	60	NIL	NIL
45	Male	1	68	90	91	89	84	77	80	82	98	105	100	102	99	91	82	12mg	2
55	Male	2	78	103	82	66	64	77	62	61	60	60	60	70	80	100	80	NIL	NIL
37	Male	1	80	82	80	86	83	84	91	94	93	96	76	73	72	70	60	NIL	NIL
26	Male	1	98	90	87	83	81	82	80	82	81	80	79	77	78	73	63	NIL	NIL
23	Female	1	58	73	69	67	67	69	62	69	70	77	75	85	80	82	76	NIL	NIL
58	Female	1	90	92	98	90	88	80	83	88	78	76	73	74	70	69	70	NIL	NIL
46	Male	1	80	100	90	93	81	88	80	79	73	75	70	68	69	71	80	NIL	NIL
50	Male	1	60	68	70	67	60	61	58	63	68	69	66	64	60	61	68	NIL	NIL
60	Male	2	98	62	60	61	57	56	58	60	61	67	63	64	70	69	64	NIL	NIL
42	Male	1	80	68	69	73	71	68	66	63	60	59	63	67	70	69	70	NIL	NIL
52	Male	1	70	90	89	87	85	92	91	83	82	81	91	78	77	79	87	NIL	NIL
44	Male	1	68	90	89	81	70	87	77	78	71	70	72	79	82	81	89	NIL	NIL
57	Female	2	68	90	88	92	86	85	87	80	78	77	78	76	80	81	78	NIL	NIL
56	Male	1	90	70	67	63	64	60	75	76	77	78	79	80	78	78	70	NIL	NIL
19	Male	1	57	82	90	88	87	89	80	79	78	76	70	69	71	75	67	NIL	NIL
47	Female	2	47	70	69	67	63	71	72	69	66	62	72	70	69	68	60	6mg	1
25	Male	1	85	68	60	64	62	63	58	57	60	68	69	71	70	69	61	NIL	NIL
32	Male	1	51	80	79	78	88	84	83	78	77	84	67	70	72	79	70	NIL	NIL
55	Male	2	72	104	110	120	118	100	80	88	90	96	93	99	97	100	95	NIL	NIL
38	Male	1	85	80	88	70	74	73	70	71	68	69	70	71	67	88	72	NIL	NIL
29	Male	1	80	80	88	81	83	78	79	75	76	70	68	63	70	74	67	NIL	NIL
35	Female	1	55	90	80	78	79	64	65	66	63	64	69	70	72	78	65	NIL	NIL
26	Female	2	70	89	81	79	76	68	61	63	69	70	72	72	74	79	70	6mg	1
36	Male	1	70	60	64	68	70	69	72	73	76	79	80	82	84	86	80	NIL	NIL
46	Male	1	78	88	80	62	70	68	71	79	80	73	67	69	70	79	75	6mg	1
54	Male	2	60	60	62	66	70	69	65	63	64	58	57	59	60	62	67	NIL	NIL
60	Male	1	80	66	68	58	54	66	64	60	62	68	69	70	65	66	60	NIL	NIL
32	Male	1	66	80	70	71	73	68	69	74	75	79	63	65	66	68	70	NIL	NIL
22	Male	2	67	76	67	69	72	75	80	82	77	87	78	66	69	70	80	NIL	NIL
29	Male	1	68	76	69	68	72	75	77	64	66	67	78	69	73	75	80	NIL	NIL
60	Female	1	88	98	80	78	70	73	69	67	71	79	85	80	77	74	68	NIL	NIL
37	Male	2	70	80	81	83	90	91	89	83	85	86	83	79	80	82	78	NIL	NIL
45	Male	1	73	80	78	79	75	76	68	64	66	69	58	62	64	66	60	NIL	NIL
52	Male	1	70	72	70	60	61	65	57	59	60	60	63	69	65	66	69	12mg	2
34	Male	1	40	90	84	80	73	75	70	79	70	71	68	65	67	60	56	NIL	NIL
60	Male	1	80	60	70	72	58	57	62	63	55	56	60	61	69	69	60	NIL	NIL
45	Male	2	80	70	80	76	74	79	69	65	60	66	64	61	60	59	55	6mg	1
57	Male	1	68	60	62	56	57	60	63	69	60	61	55	54	59	57	59	NIL	NIL
55	Female	1	60	68	70	64	72	66	67	60	56	59	61	63	64	68	62	NIL	NIL
60	Male	2	82	80	78	76	74	76	70	69	67	68	63	60	62	61	59	NIL	NIL
22	Female	1	68	80	78	70	73	76	77	82	70	69	68	70	74	76	70	6mg	1
47	Female	1	88	60	68	70	72	69	60	63	64	58	57	60	55	62	59	NIL	NIL

53	Male	2	80	78	70	73	69	60	56	66	69	63	61	63	64	66	60	NIL	NIL
47	Male	1	68	100	90	80	98	97	96	89	80	82	83	84	96	95	85	NIL	NIL
35	Male	1	82	60	70	80	78	68	62	68	70	74	78	73	75	70	64	12mg	2

Age	Sex	ASA Grade	Weight	Baseline	T2	T5	T10	T15	T20	T25	T30	T45	T60	T75	T90	T105	T120	No of doses of mephentermine	No of episodes of hypotension
				HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR		
CONTROL GROUP																			
26	Male	1	79	86	102	110	102	88	96	81	103	110	95	109	84	83	75	18mg	3
57	Male	2	73	107	88	85	101	86	82	86	90	104	107	92	105	93	80	12mg	2
56	Male	1	52	91	106	80	108	101	105	83	92	89	101	88	85	91	87	6mg	1
60	Male	2	64	93	92	92	101	93	89	82	94	87	101	83	107	106	86	NIL	NIL
60	Male	1	70	84	100	107	85	100	99	107	85	89	82	81	104	105	70	NIL	NIL
55	Female	2	75	93	108	98	103	99	96	89	94	94	86	105	100	88	70	12mg	2
27	Male	1	77	101	89	109	99	109	93	85	85	97	94	90	110	101	91	18mg	3
37	Female	2	65	97	108	106	84	102	89	91	87	94	81	101	107	85	80	NIL	NIL
54	Male	1	78	105	98	88	92	102	81	89	90	84	95	105	89	105	95	NIL	NIL
34	Male	1	65	109	86	103	101	93	94	100	95	83	88	109	107	98	94	NIL	NIL
37	Male	1	64	100	87	88	102	99	88	93	99	106	85	110	104	89	80	6mg	1
60	Male	2	70	86	80	91	105	82	99	92	109	105	99	89	90	96	90	12mg	2
55	Male	1	68	87	98	100	105	99	80	87	107	94	98	95	97	100	98	12mg	2
60	Male	1	80	110	104	90	95	84	106	82	98	86	108	91	84	109	100	NIL	NIL
50	Male	1	75	95	93	88	96	93	102	101	90	100	109	94	80	96	90	18mg	3
58	Male	1	65	80	88	108	108	94	80	91	80	82	88	86	81	104	88	NIL	NIL
53	Male	2	66	105	81	101	107	87	110	109	81	101	101	100	80	87	90	24mg	4
57	Male	2	50	89	93	99	90	88	93	103	84	89	96	87	105	107	100	12mg	2
48	Male	1	66	90	108	85	89	96	97	91	101	87	87	86	82	98	88	NIL	NIL
57	Female	2	63	92	92	100	105	91	89	100	99	106	110	99	105	93	90	NIL	NIL
35	Female	1	55	109	88	93	83	91	110	110	99	100	88	102	86	81	82	6mg	1
55	Male	2	70	100	88	105	86	100	89	104	83	101	87	106	98	100	96	12mg	2
60	Male	2	61	80	93	80	96	105	106	85	92	93	97	110	82	93	83	20mg	3
45	Female	1	78	80	97	86	94	101	107	104	99	94	99	98	88	98	84	18mg	3
54	Male	2	71	95	91	100	86	86	87	83	96	103	80	109	98	110	100	18mg	3
24	Male	1	65	96	90	107	106	106	105	90	102	86	102	105	95	108	100	12mg	2
59	Male	1	70	106	104	85	90	85	83	104	103	109	88	89	108	110	98	18mg	4
44	Male	1	77	82	108	106	85	101	94	98	81	93	110	101	97	95	90	10mg	2
56	Male	2	85	92	82	91	92	96	86	97	90	95	100	86	103	107	100	12mg	2
58	Female	2	45	102	87	100	89	82	81	96	99	84	109	110	84	100	95	24mg	4
43	Female	2	58	99	85	87	107	98	106	83	102	87	103	105	110	92	100	6mg	2
56	Male	2	66	104	107	94	97	86	105	99	99	109	95	90	101	103	94	12mg	2
56	Male	2	70	82	81	92	102	109	108	97	110	106	90	94	104	103	87	20mg	3
23	Male	1	68	91	92	84	95	93	88	87	85	102	81	87	84	100	92	12mg	2
60	Male	2	58	106	100	106	81	98	103	85	101	90	82	87	94	95	85	12mg	2
50	Male	2	70	87	98	103	95	105	89	91	92	103	84	93	103	90	80	6mg	1
30	Male	1	70	107	80	106	99	104	89	101	92	81	92	99	86	95	79	6mg	1
27	Female	1	55	94	106	109	85	93	81	108	102	94	103	104	80	110	99	NIL	NIL
55	Female	2	60	97	107	81	97	93	104	101	95	110	100	95	109	84	76	12mg	2
25	Male	1	76	91	90	104	98	88	86	105	80	97	97	105	85	98	88	6mg	1
34	Female	1	66	105	92	100	98	102	91	81	107	87	89	110	83	109	74	6mg	1
38	Male	1	80	96	87	91	91	102	84	100	83	90	85	110	104	100	92	NIL	NIL
50	Female	2	60	101	85	84	110	102	105	82	82	87	81	90	80	96	78	12mg	2
53	Male	2	55	104	107	96	88	88	86	82	92	103	98	92	93	107	83	12mg	2
26	Male	1	79	87	107	110	91	105	99	109	80	90	100	94	99	109	97	10mg	2
60	Male	2	69	104	85	97	100	84	91	102	87	108	107	108	91	80	78	12mg	2
55	Male	1	73	110	98	104	99	96	110	84	90	83	109	85	93	105	95	18mg	3
31	Female	1	50	106	108	95	81	102	84	101	80	82	87	84	109	104	95	20mg	3
60	Male	1	80	84	95	100	99	97	107	99	88	81	107	85	100	98	88	12mg	2
20	Female	1	65	86	108	93	90	99	86	84	86	84	93	84	89	90	88	6mg	1

60	Female	2	70	94	80	96	100	107	99	88	109	94	91	92	83	107	97	6mg	1
21	Male	1	60	87	105	87	96	106	94	101	85	93	88	84	91	81	75	12mg	2
35	Male	1	70	93	96	95	83	81	99	110	93	104	88	107	80	101	91	12mg	2
27	Female	1	86	92	95	106	109	99	108	105	105	98	107	98	103	101	98	NIL	NIL
40	Male	2	80	90	81	89	108	89	87	86	93	86	109	89	104	104	93	12mg	2
56	Male	2	89	84	82	105	83	85	82	93	106	98	93	89	91	107	97	6mg	1
23	Male	1	90	100	91	96	107	106	109	105	103	80	84	105	103	89	87	18mg	3
39	Male	1	85	97	91	105	93	90	89	90	86	104	97	108	90	86	76	6mg	1
20	Female	1	54	90	102	108	100	86	103	96	95	106	103	102	87	94	84	10mg	2
54	Female	1	67	80	88	93	102	97	107	102	91	85	96	98	80	96	86	24mg	4

ANNEXURE V

KEY TO MASTER CHART

ASA	-	American Society of Anaesthesiologists
HR	-	Heart Rate (bpm)
SBP	-	Systolic Blood Pressure (mm Hg)
DBP	-	Diastolic Blood Pressure (mm Hg)
MAP	-	Mean Arterial Pressure