"COMPARISON OF ONSET AND DURATION OF SENSORY AND MOTOR BLOCKADE WITH INTRATHECAL ISOBARIC ROPIVACAINE VERSUS ISOBARIC ROPIVACAINE-CLONIDINE FOR INFRAUMBILICAL SURGERIES - A ONE YEAR HOSPITAL BASED RANDOMISED CONTROL TRIAL"

(R E G . N O . B A 0 1 1 1 0 0 3)

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
ANAESTHESIOLOGY

DEPARTMENT OF ANAESTHESIOLOGY,

JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELGAUM, KARNATAKA

APRIL – 2014

KLE UNIVERSITY, BELGAUM, KARNATAKA

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This is to certify that the dissertation entitled "**COMPARISON OF ONSET AND DURATION OF SENSORY AND MOTOR BLOCKADE WITH INTRATHECAL ISOBARIC ROPIVACAINE VERSUS ISOBARIC ROPIVACAINE-CLONIDINE FOR INFRAUMBILICAL SURGERIES – A ONE YEAR HOSPITAL BASED RANDOMISED CONTROL TRIAL"** is a bonafide research work done by **(REG.NO. BA0111003).**

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LIST OF ABBREVIATIONS USED

α	-	Alpha
β	-	Beta
δ	-	Delta
μ	-	Micro
^{0}C	-	Degree centigrade
ACTH	-	Adreno corticotropic hormone
APGAR	-	Appearance Pulse Grimace (reflex) Activity Respiration
ASA	-	American Society of Anaesthesiologist
BT	-	Bleeding time
BP	-	Blood pressure
bpm	-	Beats per minute
CBC	-	Complete blood count
Cm	-	Centimeter
CT	-	Clotting time
CO	-	Cardiac output
CO_2	-	Carbon di-oxide
CNS	-	Central nervous system
CVS	-	Cardiovascular system
CSF	-	Cerebrospinal fluid
DBP	-	Diastolic blood pressure
ECG	-	Electrocardiography
EEG	-	Electro encephalogram
FRC	-	Functional residual capacity
G	-	Gauge
H	-	Hour

HR	-	Heart rate
HCl	-	Hydrochloride
HCO3	-	Bicarbonate
i.e	-	That is
IHD	-	Ischaemic heart disease
INJ	-	Injection
INR	-	International normalized ratio
IV	-	Intravenous
KCl	-	Potassium Hydrochloride
Kg	-	Kilograms
MAP	-	Mean arterial pressure
MBP	-	Mean blood pressure
MCG	-	Microgram
MLAC	-	Minimum Local Anaesthetic Concentration
Min	-	Minute
mg	-	Milligrams
meq/L	-	Milli equivalents per litre
mL	-	Millilitre
mm Hg	-	Millimeters of mercury
mg/dL	-	Milligrams per deciliter
NE	-	Norepinephrine
O_2	-	Oxygen
P	-	Probability
$PaCO_2$	-	Partial pressure of carbon dioxide
PDPH	-	Post dural puncture headache
PT	-	Prothrombin time
SAB	-	Subarachnoid block

sec	-	Second
SSA	-	Selective spinal anaesthesia
SA	-	Spinal anaesthesia
SBP	-	Systolic blood pressure
SD	-	Standard deviation
Vs	-	Versus

ABSTRACT

Background and Objective

Spinal anaesthesia remains a popular technique used for surgeries involving abdomen and lower limbs providing fast onset and effective sensory and motor blockade. Clonidine a potent alpha 2 agonist is commonly used adjuvant. The present study was done to evaluate onset and duration of sensory and motor block with isobaric 0.75 % ropivacaine and 0.75 % isobaric ropivacaine with 15 mcg clonidine as an adjuvant.

Methods

This one year randomized controlled trial was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2012 to December 2012. A total of 70 patients undergoing infra umbilical surgeries were allocated into two groups namely, Group I (n=35; Patients received 3 ml of isobaric 0.75 % ropivacaine intrathecally) or Group II (n=35; Patients received 3 ml of isobaric 0.75 % ropivacaine + 15 mcg of clonidine intrathecally).

Results

In this study, demographic parameters were comparable in both the groups. Onset of sensory block was comparable in both the groups but duration of sensory block was prolonged in group II (191.7±19.21 minutes) than in group I (180.8 ±13.08 minutes). Onset of motor block was faster in group II (11.4±2.29 minutes) than in group I(13.6±2.29 minutes). Duration of motor block was prolonged in group II (271.3±18.32 minutes) than from group I (224.5±16.46 minutes). Mean heart rate

was significantly lower in group II than in group I. Mean arterial pressure was comparable in most of the recordings between both the groups.

Conclusion and interpretation

Overall, based on the findings of this study it may be concluded that, addition of clonidine to 0.75 % isobaric ropivacaine intrathecally prolonged the duration of sensory and motor block but with no effect on sensory onset but faster onset of motor block with no significant hemodynamic changes.

Key Words: Clonidine; Isobaric ropivacaine; sensory block; motor block; Spinal anaesthesia;

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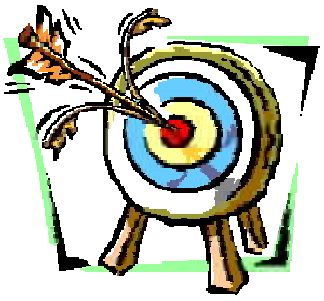

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INTRODUCTION

The main essence of anaesthesia is adequate pain relief, a need for early ambulation, rapid and a complete recovery with minimal side effects. Regional anaesthesia continuous to be the most accepted and important technique, with simplicity, effectiveness and safety as its added advantages.

Subarachnoid anaesthesia is the most popular, an effective and simpler technique for lower abdominal and lower limb surgeries. The advantages of spinal anaesthesia is that the risk of general anaesthesia is avoided like anatomical abnormalities, patients with irritable airway (bronchial asthma or allergic bronchitis) and administration of general anaesthesia or endotracheal intubation can elevates the blood pressure. It is less costly, maintains patent airway, decreased pulmonary complications, faster return of normal gastrointestinal function, decreased incidence of deep vein thrombosis and pulmonary emboli formation compared to general anaesthesia. Spinal anaesthesia is achieved when the drug (local anaesthetics) are injected in sub arachnoid space with the help of spinal needle. Spinal needles are classified as cutting and splaying type of needle. In Cutting type Quincke's (commonly used), Greene, Pitkins and Splaying type includes Whitacre and Sprotte.

Traditionally amide and ester linked local anaesthetics have been used in regional anaesthetic techniques, and bupivacaine has emerged as the most commonly used drug for spinal anaesthesia. But it also carries undesirable effects like cardio-toxicity and central nervous system toxicity.

Ropivacaine is a new amide local anaesthetic, which is the first commercially available local anaesthetic in its category as a pure S-enantiomer. Ropivacaine also belongs to the same pipecoloxylidide group; it has a propyl group on the amine portion of pipecoloxylidide whereas bupivacaine has a butyl group.[1]

Ropivacaine is known to be less toxic to central nervous system and cardiovascular system and is widely used as an alternative to bupivacaine. Ropivacaine has high pKa and with a low lipid solubility which blocks Aδ and C (pain fibers) to a greater degree than Aβ (motor fibers) leading to decreased post-operative motor blockade and thus early ambulation of the patients can be achieved[2]. But shorter duration of sensory and motor block can itself be a drawback if the surgery prolongs or the quality of motor blockade is poor , hence to overcome these deficiencies adjuvants are commonly added to ropivacaine.

Efforts to find an ideal adjuvant in regional anaesthesia are underway since long. Sedation, stable hemodynamic and an ability to provide effective and prolonged post-operative analgesia are the main desirable qualities of an adjuvant in neuraxial anaesthesia.[3]

Alpha-2 adrenergic agonists have both analgesic and sedative properties. They also potentiate the effect of local anaesthetics and allow a decrease in required doses when used as an adjuvant in regional anaesthesia[3, 4].

The anaesthetic and the analgesic requirement gets reduced to a considerable extent by the use of such adjuvants because of their analgesic properties and augmentation of local anaesthetic effects as they cause

hyperpolarization of nerve tissue by altering transmembrane potential and ion conductance at locus coeruleus in the brainstem.[3]

Clonidine is a partial α2 agonist used intrathecally with well-established safety. It prolongs duration of motor and sensory spinal blockade when used along with local anaesthetics.[5, 6]

Several studies have shown the effect of Clonidine on Bupivacaine.[5] There are only few studies showing the effect of clonidine as an adjuvant to 0.5 % isobaric ropivacaine intrathecally.[6] However there is no study evaluating the effect of clonidine on addition to 0.75 % isobaric ropivacaine.

Hence this study was attempted to compare the onset and duration of sensory and motor block following intrathecal isobaric ropivacaine and intrathecal isobaric ropivacaine supplemented with clonidine.

OBJECTIVES

The aim of the present study was to compare

1. Onset and duration of sensory and motor block

2. Changes in heart rate and mean arterial pressure

Between intrathecal isobaric 0.75 % ropivacaine and isobaric 0.75 % ropivacaine with clonidine (15 µg) in patients undergoing infraumbilical surgeries.

REVIEW OF LITERATURE

Spinal anaesthesia, also known as subarachnoid block (SAB), or intrathecal analgesia, has an interesting historical background. Spinal anaesthesia was the first major regional technique attempted and is produced when a local anaesthetic agent is injected into the subarachnoid space.

James Leonard Corning (1855–1923) in 1885, when he was experimenting with cocaine on the spinal nerves of a dog, accidentally pierced the dura mater. This was the first spinal analgesia administered[7].

August Karl Bier (1861-1949) on 16th August 1898, in Keil in Germany performed the first planned spinal anaesthesia for surgery in humans .[8] Bier and his assistant Hildebrandt injected cocaine into each other's theca and both experienced severe headache which lasted for days thus they postulated that their headache was due to loss of large volume of cerebrospinal fluid.[9]

Heinrich Braun in 1905, a German surgeon, reported the use of procaine for operative spinal anaesthesia. Barker in 1907 reported the means for controlling levels of anaesthesia by making procaine solutions hyperbaric by adding glucose or hypobaric by adding alcohol. Tetracaine was synthesized in 1931 and was introduced into clinical practice by Sise in 1935, Jones in 1930 synthesized dibucaine and introduced into clinical practice. Lemmon in 1940 and Tuohy in 1945 demonstrated continuous spinal anaesthesia. Prickett and associates in 1945 published their report on the neurologic safety of intrathecal epinephrine to prolong the duration of spinal anaesthesia.[10]

The technique of spinal anaesthesia was eventually well accepted and many reports were published on its usage and the popularity of spinal anaesthesia had steadily increased with the introduction of newer drugs and techniques.

Spinal anaesthesia has many advantages like ease of administration, rapid onset of action and good muscle relaxation. Main disadvantages are its limited duration of action and hemodynamic instability.

Albright in 1979 published an alarming editorial which associated the long acting local anaesthetics bupivacaine and etidocaine with cardiac arrest during regional anaesthesia; he reported six cases of accidental intravascular injection of either bupivacaine or etidocaine which caused sudden ventricular arrhythmias at the same time as convulsions. This flow of events acted as a catalyst for the development of a newer local anaesthetic drug [11].

This acted as an impetus for development of local anaesthetic with better safety profile. Ropivacaine has an improved safety profile over bupivacaine with decreased CNS and cardiotoxic potential together with wide clinical utility at different doses and for a wide range of indication.

A study which used ropivacaine at low concentration (25-50µmol/L) on isolated sheathed vagus and phrenic nerves of rats, produced a profound and rapid block of both Aδ and C fibers and was more potent than similar concentration of bupivacaine in blocking these fibres. Higher concentration of the drug had similar blocking activity [12].

In 1989 Barder AM et al conducted a study using an isolated rabbit vagus nerve model to compare the in vitro potency, onset and recovery from block of ropivacaine and bupivacaine. Effect of varying concentration of ropivacaine and bupivacaine and its compound action potential of A and C nerve fibres was analysed to determine, whether motor and sensory fibres have different sensitivities to the two agents and it was found that depressant effect of bupivacaine was 16 % greater than that of ropivacaine on motor fibres but only 3% greater on sensory fibres.[13]

Comparison between 3 local anaesthetic- hyperbaric solutions of bupivacaine, levobupivacaine and ropivacaine under spinal anaesthesia for elective surgery were studied by Luck LF et al and they found that, bupivacaine or levobupivacaine shows clinically indistinguishable effects whereas hyperbaric ropivacaine provides reliable spinal anaesthesia of shorter duration. Ropivacaine may be useful where prompt mobilization is required due to its faster recovery profile.[14]

One hundred and ten patients were studied by Brockway MS et al for comparing extradural Ropivacaine and Bupivacaine, they received one of the five solutions: 0.5, 0.75 or 1% ropivacaine or 0.5 or 0.75 % bupivacaine. Speed of onset of sensory block showed a little difference between the groups whereas duration of analgesia was increased by increasing the concentration of both drugs, but this has minimal effect on onset time or extent of block.[15]

Dose - response study of spinal hyperbaric ropivacaine for caesarean section reported that the maximum sensory block levels and duration of motor

block and rate of hypotension were significantly related to the ropivacaine dose. However onset of anaesthesia was not. Under the conditions of this study for caesarean delivery ED50 of spinal hyperbaric ropivacaine was 10.37 mg and ED95 was 15.39 mg. Study concluded that, ropivacaine is suitable for spinal anaesthesia in caesarean delivery.[16]

Jean marc Malinovasky et al studied one hundred patients scheduled for transurethral resection, comparison between intrathecal 15 mg isobaric ropivacaine and 10 mg isobaric bupivacaine in, mean arterial pressure, pain at surgical site requiring supplemental analgesics, onset and offset times for sensory and motor block were recorded. The study concluded that 15 mg of intrathecal ropivacaine provided similar motor and hemodynamic effects but less potent anaesthesia than 10 mg of bupivacaine for endoscopic urological surgery.[17]

In sixty – six patients undergoing total hip arthroplasty 3.5ml of 0.5% isobaric ropivacaine with 3.5ml of 0.5% bupivacaine were compared by Mc Namee DA et al. This showed that onset of motor and sensory block was rapid and similar between two groups. Ropivacaine showed more rapid postoperative recovery of sensory and motor function compared to Bupivacaine. In the ropivacaine group however median duration of complete motor block was shorter, it was 2.1 hours compared to 3.9 hours in Bupivacaine group. [18]

The clinical efficacy and safety of 3 mL 0.5% (15 mg) and 3 mL 0.75% (22.5 mg) glucose- free ropivacaine as a local anaesthetic for spinal anaesthesia in forty patients were studied by Jack W. Van Kleef et al and it was found that onset of analgesia was similar with both concentrations. The median (range)

upper level of analgesia obtained with the 0.5% solution was T11 (T5- L4) and was T10-11 (T4 – L4) with the 0.75% solution. The duration of analgesia at T12 and the total duration of analgesia were longer in the 0.75% group. Incidence of complete motor block of the lower limbs was higher and the total duration of motor block longer in the 0.75% group.[19]

In forty patients the efficacy and appropriate dosage of 3ml of 0.5% isobaric ropivacaine and 3ml of 0.75% isobaric ropivacaine for spinal anaesthesia were studied by Wahedi W et al. Onset of analgesia and onset of motor block was not statistically significant in both the groups but duration of analgesia and duration of motor block was more in 0.75 % group. Hemodynamic changes between the two groups were statistically insignificant.[20]

The efficacy and safety of two concentrations of intrathecal Ropivacaine 2.5ml of 0.75% ropivacaine and 2.5 ml of 1% ropivacaine in 104 patients undergoing total hip arthroplasty were studied by Mc Namee DA et al and the results showed that the onset of motor and sensory block was rapid with no significant differences between the groups. The median duration of sensory block was shorter (3 hours) in 0.75 % ropivacaine group when compared to 1 % group (3.4 hours). The median duration of motor block was more prolonged in 1% group (1.9 hours) when compared to 0.75% group (1.2 hours). So doses of 18.75 mg and 25 mg were well tolerated and provided effective anaesthesia for patients undergoing total hip arthroplasty.[21]

In recent years, use of intrathecal adjuvant especially to ropivacaine has gained popularity with the aim of prolonging the duration of block and for better

success rate. The quality of the spinal anaesthesia has been reported to be improved by the addition of opioids (such as morphine, fentanyl and sufentanil) and other drugs (such as clonidine, magnesium sulfate, neostigmine, ketamine and midazolam).

The efficacy of intrathecal morphine and clonidine in 15 patients was studied by Siddall P J et al for treatment of pain after spinal cord injury and it was demonstrated that administration of morphine or clonidine into the spinal fluid can provide substantial pain relief in people with this type of pain and combination is more effective than either drug administered alone.With intrathecal morphine mean reduction in pain levels was 80% and with intrathecal clonidine it was 83%.[22]

In twenty five parturient comparisons between intrathecal isobaric 0.5% bupivacaine- morphine and isobaric 0.5% ropivacaine-morphine for caesarean delivery were studied by Ogun CO et al. Both provided effective sensory and motor block. In the bupivacaine-morphine group time to reach complete motor block was shorter and time to recover from motor block was longer than in the ropivacaine-morphine group.[23]

The efficacy of low dose of intrathecal clonidine as adjuvant to bupivacaine in gynecological surgeries were studied by B.S.Sethi et al, they added 1µg/kg of clonidine to 2.5ml of bupivacaine and compared it with plain bupivacaine. The duration of anaesthesia was 614 minutes in clonidine group when compared to 223 minutes in control group. Also the 2 segment regression time and the duration of motor blockade was significantly prolonged in clonidine

group. They concluded that by adding clonidine the post-operative analgesia is significantly prolonged.[24]

The analgesic effects of intrathecal clonidine (50 mcg) along with 0.5% bupivacaine (8 mg) and plain 0.5% (12.5 mg) bupivacaine in cesarean section were compared in a study done by Kothari N et al. Result showed that addition of intrathecal clonidine causes some sedation in the postoperative period, but it provides adequate analgesia and motor paralysis at lower dose of Bupivacaine i.e. duration of analgesia in lower Bupivacaine dose - clonidine group was 246 mins versus 146 mins in higher Bupivacaine dose group. It also significantly prolongs postoperative pain relief.[25]

A study done by De Kock M et al compared the efficacy of low dose (15mcg) of intrathecal clonidine as an adjuvant to (8mg) ropivacaine in knee arthroscopy surgeries Intrathecal ropivacaine (8 mg alone) produced short sensory anaesthesia and motor blockade (132 ± 38 min and 110 ± 35 min; mean ± SD). However, the quality of anaesthesia was significantly lower than in any other group ($P < 0.05$). Ropivacaine (8 mg) plus 75 μg clonidine produced significantly longer sensory and motor anaesthesia (195 ± 40 min and 164 ± 38 min; $P < 0.05$). However, this was associated with systemic effects, such as sedation and reduction of arterial blood pressure. Ropivacaine (8 mg) plus 15 μg clonidine did not prolong sensory or motor blockade, afforded high quality anaesthesia, and was not associated with detectable systemic effects. Thus it was concluded that it produced adequate and short-lasting anesthesia for knee arthroscopy.[26]

In fifty parturient the effects of intrathecal isobaric 0.5% ropivacaine and isobaric 0.5% ropivacaine-clonidine combination undergoing caesarean deliveries were studied by Ogun CO et al. Twenty-five parturient received 17.5 mg ropivacaine and twenty five parturient received 15 mg ropivacaine and 30 µg clonidine for spinal anaesthesia. Results showed that intrathecal ropivacaine and ropivacaine-clonidine provided effective sensory anaesthesia and motor block. S2 dermatome regression time was longer in ropivacaine-clonidine combination. Umbilical venous pH and fifth minute APGAR scores were similar between the groups. Postoperative analgesia was prolonged by clonidine. Although intraoperative ephedrine requirements (mg) were higher in ropivacaine-clonidine group, the number of patients requiring ephedrine and the number of hypotension episodes were similar. Dry mouth was observed more with clonidine .It was concluded that, intrathecal 17.5 mg 0.5% isobaric ropivacaine provides efficient and safe anaesthesia for caesarean section delivery. The addition of 30 µg clonidine to 15 mg 0.5% isobaric ropivacaine results in longer complete and effective analgesia with similar block properties. In both groups, hypotension was easily treated with ephedrine and did not affect maternal and neonatal outcome.[6]

The effects of adding various doses of clonidine to ropivacaine in spinal anaesthesia were studied by Gonul Sagiroglu et al. Seventy-five patients who were to undergo elective lower extremity surgery were randomly divided into three groups and were given Group I: % 1 ropivacaine 12 mg, group II: % 1 ropivacaine 12 mg + clonidine 15 µg, group III: % 1 ropivacaine 12 mg + clonidine 30 µg. Results showed mean arterial pressure recorded in group III decreased significantly at 75, 105 and 120 min compared to groups I and II. In

group I, time to two segment regressions and time to sensory block to S2 was shorter when compared to the other groups. The time to voiding and the duration of motor blockade was significantly longer in group I in comparison to the other groups. The need for atropine in group III was significantly higher. The incidence of hypotension and the requirement for ephedrine were significantly higher in groups II and III as compared to group I. Similarly, sedation in group III was significantly higher compared to the other groups. It was concluded that that clonidine can be added to ropivacaine for spinal anaesthesia in surgical interventions to obtain deeper and longer sensory and motor block. However, hypotension, bradycardia and sedation should be monitored closely. [27]

BASIC SCIENCES

Subarachnoid (spinal) block is a safe and effective alternative to general anaesthesia when the surgical site is located on the lower extremities, perineum, or lower abdominal wall. Spinal anaesthesia was the dominant form of neuraxial anaesthesia well into the 20th century.[28]

Spinal anaesthesia produces intense sensory and motor blockade as well as sympathetic blockade. The goal of spinal anaesthesia is to instil the desired medications into the cerebrospinal fluid (CSF). The block produced requires smaller doses of local anaesthetics (hence, local anaesthetic toxicity is rarely a concern) and is often more dense in character.

Advantages include avoidance of general anaesthesia and the airway management concerns that accompany general anaesthesia. Additional benefits may include reducing the metabolic stress response to surgery, reduction in blood loss, decrease in the incidence of venous thromboembolism, reduction in pulmonary compromise (particularly in patients with advanced pulmonary disease), and the ability to monitor the patient's mental status.

Strong contraindications include patient refusal, lack of patient cooperation, difficulties with positioning, and increased intracranial pressure. Other contraindications include situations that require some risk-benefit analysis, like spinal abnormalities, hypovolemia, coagulation disturbances, stenotic valvular disease, bacteremia, and infection at the site of needle insertion.

Spinal anaesthesia has also been noted to result in symptomatic deterioration in patients with multiple sclerosis.[29] Allergy to local anaesthetics may also be a contraindication, but true allergies are usually found with ester-based local anaesthetics (tetracaine), not the amide-based local anaesthetics (bupivacaine)

ANATOMY

Sound knowledge of anatomy of vertebral column and its contents is essential to all the anaesthesiologists for safe and successful administration of spinal anaesthesia, not only in terms of performance but also in terms of spread of drug in CSF and level of block achieved.

Vertebral column

Main function of the vertebral column is to protect the spinal cord (figure 1). The vertebral column comprises of 33 vertebrae and includes[30]

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

Curves of spine

In adult, the vertebral column has four curves which have significant effect on spread of drugs in sub arachnoid space namely[30]

- Cervical and lumbar curve - Convexity anterior
- Thoracic and sacral curve - Concave anterior

In adults the curves of the spine are important when patient is supine. The highest point of cervical and lumbar curves in supine position are at cervical (C) five and lumbar (L) five; lowest points of thoracic and sacral are at thoracic (T) five and sacral (S) two respectively.[30]

Vertebral ligaments[30]

Vertebral column is bound together by following ligaments which give stability and elasticity.

Supraspinous ligament: This is a strong fibrous cord which connects apices of spinous processes from where it continues as the ligamentum nuchae (Figure 2).

Interspinous ligament: This is a thin membranous ligament which connects spinous processes blending anteriorly with ligamentum flavum and posteriorly with supraspinous ligament (Figure 2).

Ligamentum flavum: This ligament comprises yellow elastic fibres and connects adjacent lamina. 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 (Figure 2).

Longitudinal ligaments: There are two longitudinal ligaments (anterior and posterior) that bind vertebral bodies together (Figure 2).

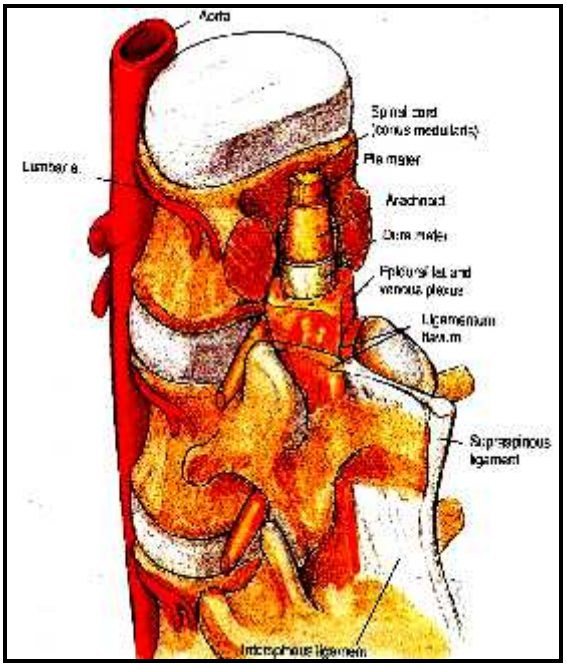

Figure 1. Vertebral Column

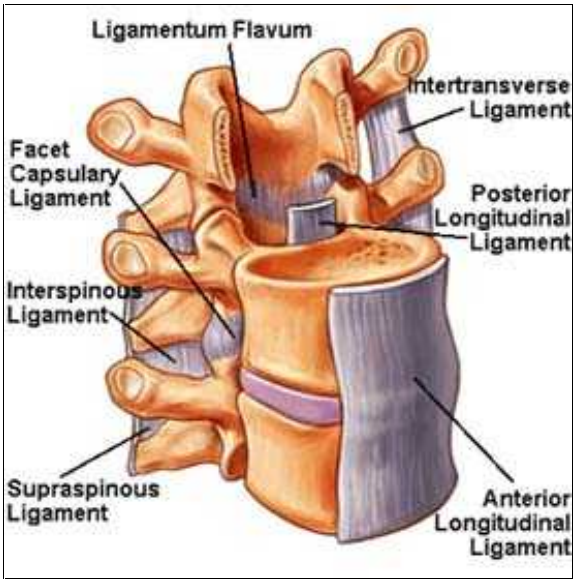

Figure 2. Spinal Ligaments

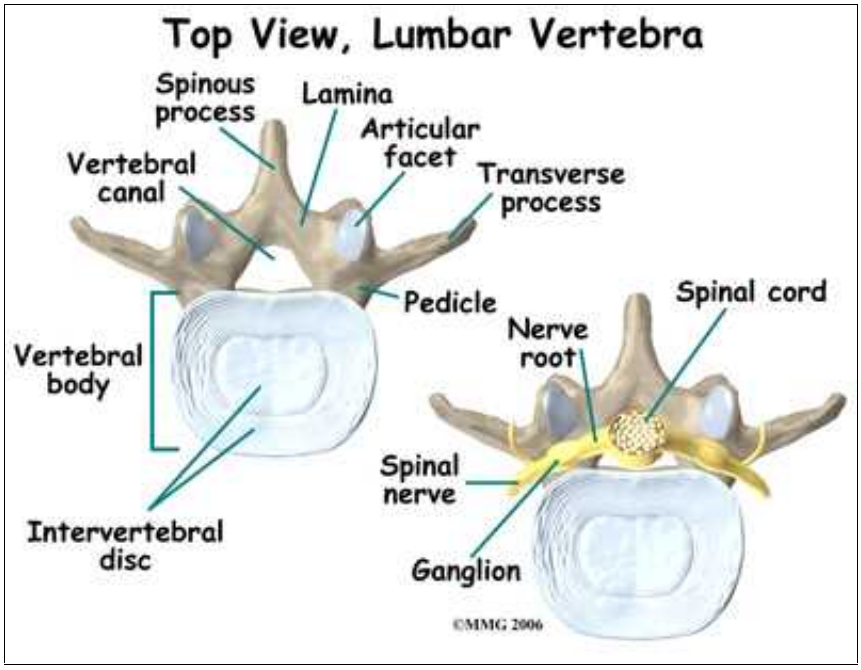

Figure 3. Typical Lumbar Vertebra

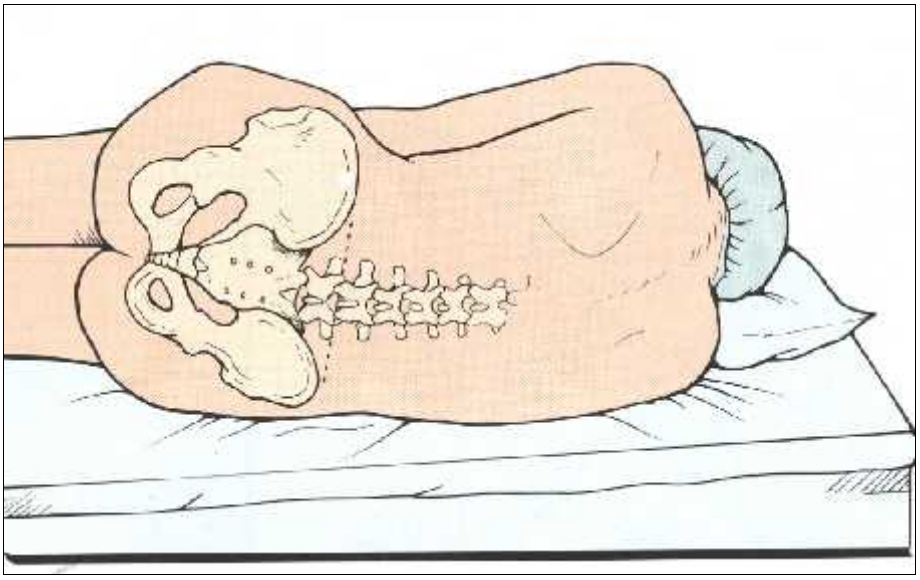

Figure 4. Line of Tuffier

Lumbar vertebrae[31]

A typical lumbar vertebra consists of (Figure 3);

- A kidney shaped body.
- Two pedicles directed backwards from the upper part of the body.
- Two transverse processes which are slender
- Two laminae meeting posteriorly and enclosing the triangular vertebral foramen.
- Spinous processes which are thick, broad and quadrilateral in shape.
- Two upper and lower articular processes which prevent rotation but allow limited flexion and extension between contiguous vertebrae.

Topographical Line of Tuffier[30]

This is a horizontal line across the back between the crests of the ilia 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 spinal anaesthesia (Figure 4).

Vertebral canal

Vertebral canal is bounded posteriorly by spinous processes and interspinous ligaments, laterally by the pedicles and posterolaterally by the laminae and ligamentum flavum. This ends superiorly in the foramina magnum

and inferiorly in the sacral hiatus. The vertebral canal contains the spinal cord, spinal membranes, adipose tissue, blood vessels, CSF and the roots of the spinal nerves.

Spinal cord[29]

The average length of the spinal cord in males is 45 centimeter (cm) and females it is 42 cm (figure 5).

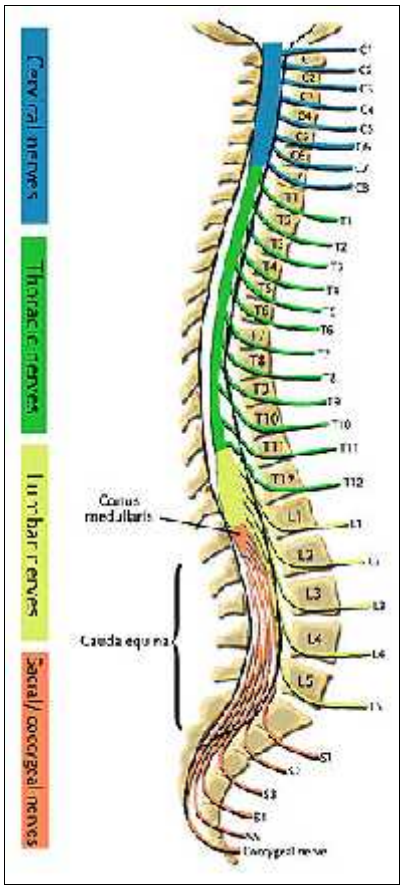

Figure 5. Spinal nerve roots

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. A delicate fibrous filament descends to the back of first segment of coccyx from apex of conus medullaris. This is known as the filum terminale.

At birth spinal cord ends at the level of L3 but rises as age progresses and reaches the lower border of L1 in adults.

Blood Supply of Spinal Cord[29]

The spinal cord receives blood supply from three arteries, one anterior and two posterior spinal arteries (figure 6).

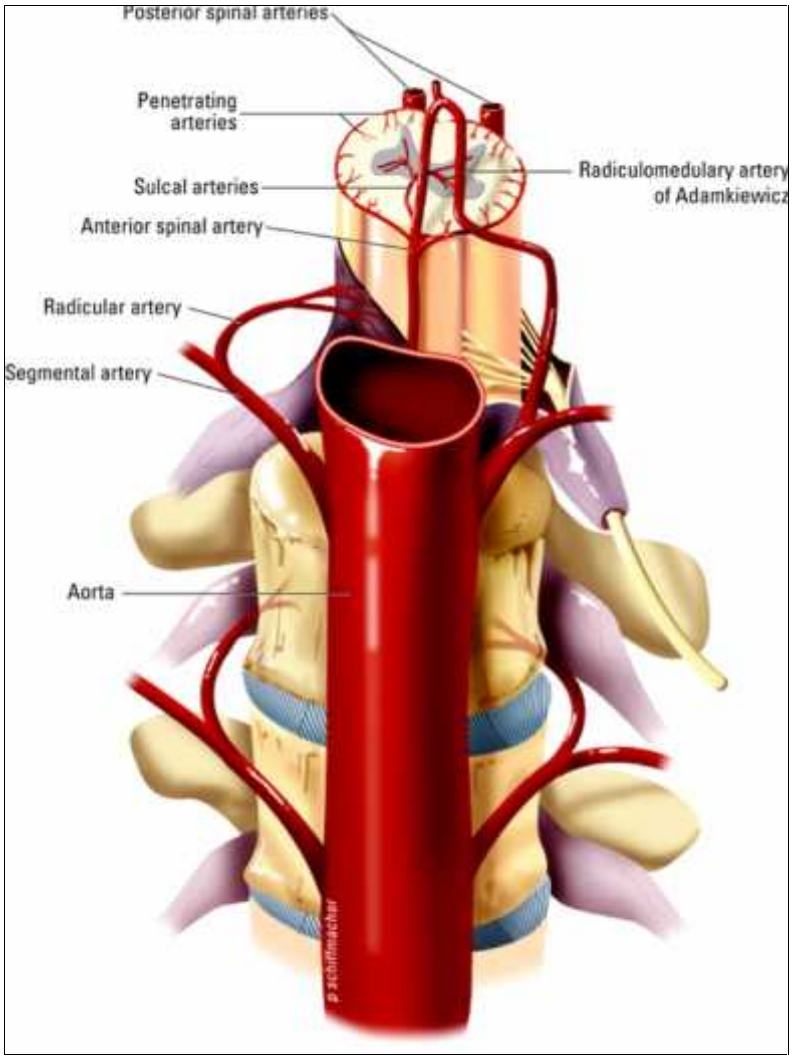

Figure 6. Blood Supply of Spinal Cord

Anterior spinal artery is a single vessel lying in the substance of pia matter overlying the anterior median fissure. It supplies the lateral and anterior columns, comprising three quarters of substance of the cord. Thrombosis of this artery causes anterior spinal artery syndrome.

There are two pairs of posterior spinal arteries, one pair on each side arising from posterior inferior cerebellar arteries at the level of foramen magnum. They supply posterior column of the cord.

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.

Spinal Meninges[32]

Along with the bony vertebral column spinal cord is also protected with three connective tissue coverings called meninges.

Duramater[32]

This is a tough outermost fibro elastic covering consisting of outer endosteal layer and inner meningeal layer. Fibers of dura run longitudinally, thus it is important to insert the spinal needle so as to split these fibers and not to cut them. Dural sac ends at lower border of S2, where it is pierced by filum terminale.

Arachnoid Mater[32]

It is a delicate, non-vascular, middle covering and is closely attached to the dura. There is a capillary interval or potential space between dura and arachnoid mater called subdural space and contains serous fluid.

Pia Mater[32]

The pia mater, the innermost membrane is a vascular sheath which closely invests the brain and spinal cord.

Subarachnoid Space[32]

The space between the arachnoid and pia is called the subarachnoid space and is filled with cerebrospinal fluid and contains numerous arachnoid trabeculae which form delicate sponge like mass. . This space has three divisions which are free communication to each other: cranial (surrounding the brain), spinal (surrounding the spinal cord) and root (surrounding the dorsal and ventral nerve roots). In the spinal cord these nerve roots are covered only by pia and bathed in CSF. As these spinal nerve roots pass beyond the spinal dura and traverse the epidural space, they carry with them all the three meningeal layers and have a distinct epidural, subdural, subarachnoid and sub pial spaces. The subarachnoid space extends separately along both the dorsal and ventral roots to the level of dorsal root ganglion, where arachnoid and pia continue as perineural epithelium of peripheral nerve.

Cerebrospinal Fluid[32]

It is a clear colourless fluid found in the cranial and spinal subarachnoid spaces and in the ventricles. CSF is mainly formed by either secretion or ultrafiltration from the choroidal plexus of lateral ventricles. CSF flows from the lateral ventricles into the third ventricle through the foramina of Monro into the fourth ventricle through the Aqueduct of Sylvius into the cerebromedullary cisterna (cisterna magna) through foramen of Magendie and foramina of Luschka. From the cisterna magna, CSF enters subarachnoid space circulating around brain and spinal cord before being absorbed into the arachnoid granulations over the cerebral hemispheres.

Composition of cerebrospinal fluid

- Specific gravity : 1.003 to 1.009 at 37^0C.
- Volume : 120 ml to 150 ml (25 ml to 35ml in spinal space).
- CSF pressure : 60 to 80 mm Hg in lumbar space.
- pH : 7.27 to 7.37
- PCO_2 : 48 mm Hg
- HCO_3 : 23 mEq/L
- Sodium : 135 to 145 mEq/L
- Calcium : 2 to 3 mEq/L

- Phosphorous : 1.6 mg/dl
- Magnesium : 2 to 2.5 mEq/L
- Chloride : 15 to 20 mEq/L
- Proteins : 23 to 38 mg/dl

It is important to know that certain drugs alter the rate of formation of CSF. Carbonic anhydrase inhibitors like acetazolamide reduce the rate of CSF formation by as much as 50%. Furosemide in large doses may reduce the CSF formation. Inhalational anaesthetics like isoflurane and vasoconstrictors decrease the CSF formation. CSF formation is decreased when the serum osmolality increases and is increased when the serum is made hypotonic. During equilibrium, rate of formation equals the rate of absorption (500 mL/day).

PHYSIOLOGY OF SUB ARACHNOID BLOCK

The well recognized physiological effects of subarachnoid block are often wrongly termed as complications. The various factors, which control the different effects of a spinal anaesthetic technique are[33]

- Amount and type of drug
- Volume of solution
- Site of injection
- Rate of injection
- Specific gravity of solution – density and baricity
- Barbotage

The various factors which affect the spread of local anaesthetics include; [34, 35]

1) Patient factors:

- Age
- Height
- Position
- Spinal column configuration
- Cerebrospinal fluid volume

2) Technical factors

- Site of injection
- Direction of needle
- Local anaesthetic dose
- Local anaesthetic baricity
- Local anaesthetic volume

The sensory and motor blockade results from direct effects of local anaesthetic on the spinal nerve roots. The primary site of action is on both anterior and posterior nerve roots, affecting smaller nerve fibers first, and thick large motor fibers last. Generally, the sympathetic paralysis is more diffuse and will extend to two to four segments above motor block. The sympathetic fibers

are affected first and are last to recover. On the other hand, motor nerve blockade is usually last to be affected and first to recover.

Sequence of spinal anaesthesia (SA) [36]

- Vasomotor block: Dilatation of skin vessels and increase cutaneous blood flow
- Temperature fibers: Cold first and then warmth
- Loss of temperature discrimination
- Pain – pin prick fibers first
- Loss of tactile sensation
- Motor paralysis
- Pressure sensation
- Proprioception and vibratory sensation.

Sympathetic blockade is the major determinant of physiologic response to spinal anaesthesia.

Sympathetic blockade

Because the level of sympathetic denervation determines the magnitude of cardiovascular responses to SAB, it might be anticipated that the higher the level of neural blockade, the greater would be the change in the cardio-circulatory parameters. In the presence of partial sympathetic blockade, a reflex increase in

sympathetic activity occurs in sympathetically intact areas. The result is vasoconstriction that tends to compensate for the peripheral vasodilatation-taking place in the sympathetically denervated areas. This can be seen in the changes in the arterial pressure waveforms and in the cutaneous blood flow in the upper extremities in the presence of low or midthoracic sensory levels of spinal anaesthesia. Most cephalad preganglionic sympathetic fibers exit the spinal cord at the level of T1. Since sympathetic denervation is complete at the T1 level, cardiovascular changes are no greater with mid cervical sensory levels of anaesthesia than they are with T1 levels. Sympathetic fibers are blocked usually two to three segments higher than sensory fibers and sensory block is two segments higher than motor block.

Cardiovascular effects of spinal anaesthesia[37]

They are mediated by the combined effects of autonomic denervation and, with higher levels of neural blockade, added effects of vagal innervation. Spinal block can influence CVS in various ways.

a. Vasodilatation of resistance and capacitance vessels.

b. Block of cardiac efferent sympathetic fibers from T1-T4 resulting in loss of chronotropic and inotropic drive and fall in cardiac output.

c. Bainbridge reflex causing bradycardia.

d. Depression of vascular smooth muscle and beta adrenergic blockade of myocardium with fall in cardiac output following systemic absorption of local anaesthetic drug.

Block extending above T4 is associated with fall in BP. Slowing of HR is caused if any of anterior roots carrying sympathetic cardiac accelerator fibers are blocked as may happen in high spinals above T4-T5. Bradycardia may also be due to lowering of BP in the right atrium consequent to diminished venous return.

Theories of causation of fall in BP.

a. Diminished cardiac output due to reduction of venous return

b. Dilatation of post arteriolar capillaries and small venules

c. Paralysis of sympathetic nerve supply to heart.

d. Paralysis of sympathetic nerve supply to adrenal glands with consequent catacholamines depletion.

e. Ischemia and hypoxia of vital centres.

f. Compression of great vessels in abdomen by pregnant uterus or abdominal tumors.

Myocardial Oxygen Demand:

Myocardial oxygen demands decrease during hypotension associated with spinal anaesthesia due to decrease in afterload, preload and heart rate.

Cerebral Blood Flow

Cerebrovascular auto regulatory mechanisms maintain cerebral blood flow in humans at constant levels.

Respiratory System

Phrenic nerve paralysis can occur. During spinal analgesia breathing becomes quiet and tranquil. This is not only due to motor blockade but also due to differentiation with reduction of sensory input to the respiratory center. Lowered arterial and venous tone also lessens the work of the heart and tends to relieve any existing pulmonary congestion. The pulmonary gas-exchange is preserved. Intercostal paralysis is compensated for by increased descent of the diaphragm, which is made easier by a lax abdomen.

Gastrointestinal System

Pre-ganglionic sympathetic fibers from T5-Ll are inhibitory to the gut. There is no effect on oesophagus, the innervation of which is vagal. The small gut is contracted as sympathetic inhibitory impulses are removed, the vagus being dominant. Pressure within the bowel lumen is increased. Handling of small bowel by the surgeon may cause it to dilate, as may the injection of atropine before the operation. Nausea and vomiting due to the hypotension may occur and usually comes on in waves lasting a minute or so and passes away spontaneously. Relaxation of sphincters also occurs.

<u>Causes of Nausea and Vomiting</u>

- Hypotension
- Hypoxia
- Increased peristalsis
- Traction on nerve endings, especially vagus

- Presence of bile in stomach due to relaxation of pyloric sphincters
- Narcotic analgesics used in pre medication
- Psychological effects

Spleen

The spleen enlarges 2-3 times in high blocks when its sympathetic efferent fibers are paralyzed.

Liver

If the liver is diseased, a decrease in the mean arterial pressure (MAP) affects the liver blood flow and also the metabolism of amide anaesthetics.

Endocrine System

The stress response to surgery results in rise in blood sugar, cortisol and catecholamine level sufficiently high and prolonged spinal blockade can minimize or even prevent these changes.

Genitourinary System

Renal blood flow due to hypotension is decreased but does not cease until blood pressure has fallen to about 80 mm Hg. These changes are transient. The penis is often engorged and flaccid due to paralysis of nervi erigenti (S2 to S3) and this is also a positive sign of a successful block. Post spinal retention of urine may be moderately prolonged as S2 to S3 contain small autonomic fibers and their paralysis lasts longer than that of larger sensory and motor fibers.

Uterus

The tone of uterus is not greatly altered after spinal analgesia in pregnancy. Block of nerves from T11 downwards results in painless labour.

Body Temperature

Vasodilatation favors heat loss, absence of sweating favors hyperpyrexia in hot environment, catecholamine secretion is depressed hence heat loss is prevented by metabolism. Spinal anaesthesia also reduces the threshold for shivering.

PHARMACOLOGY[38]

Local anaesthetics are drugs that produce reversible blockade of conduction of nerve impulses.

The primary desirable properties of an ideal local anaesthetic agent are:

1. Short latency
2. High potency or anaesthetic activity
3. Superior penetration or diffusion
4. Low toxicity
5. Complete reversibility of action
6. Prolonged duration of action
7. No tachyphylaxis
8. Stability and ability to withstand heat sterilization

Classification:

Clinically useful agents can be classified into two groups depending on the link between the aromatic portion and the intermediate chain. The aminoester groups have an ester link and include procaine, chloroprocaine and amethocaine. The amino amides have an amide link between the aromatic head and the intermediate chain and include lignocaine, bupivacaine, mepivacaine, prilocaine, etidocaine and ropivacaine.

ROPIVACAINE

Pharmacology of Ropivacaine

Introduction

Ropivacaine is a new long acting local anaesthetic drug belonging to the amino amide group. Though it was synthesized by Ekenstam [39] in 1957 and belongs to the same group as that of bupivacaine and mepivacaine, pipecoloxylidides local anaesthetics, ropivacaine was introduced to clinical practice in 1996.

Historically bupivacaine was used as it had a long duration of action, but subsequently it was found “propyl derivatives” of pipecoloxylidides were less toxic than “butyl derivatives” (bupivacaine).Thus Ropivacaine was developed after bupivacaine was noted to be associated with significant number of cardiac arrests. Despite being in the market for close to three decades internationally, it was only introduced into the Indian market very recently.

It is the first local anaesthetic to be presented as an almost pure S – enantiomer (>99% pure) [40]. It is used as local anaesthetic including infiltration, nerve block, epidural and recently for intrathecal anaesthesia in adults and children over 12 years of age. It is also used for peripheral nerve blocks and caudal epidural in children 1 to 12 years of age for surgical pain relief.

Chemical structure

Ropivacaine is an amino-amide class of local anaesthetic chemically described as S-(-)-1-propul-2', 6'-pipecoloxylidide hydrochloride monohydrate. The International Union of Pure and Applied Chemistry name is(S)-N-(2,6-dimethylphenyl)-1-propylpiperdine-2-carboxamide. The drug substance is a white crystalline powder, with a molecular formula of $C_{17}H_{26}N_2O.HCl.H_2O$ and a molecular weight of 328.89.The chemical structure is given in the below figure 7.

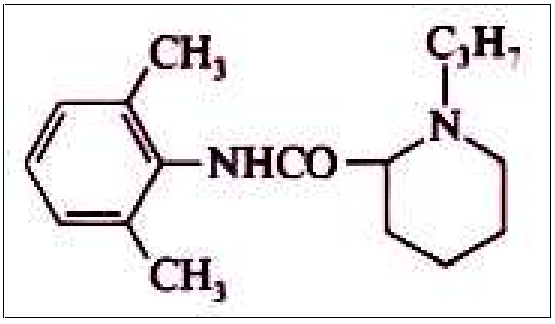

Figure: 7

Physical properties

At 25^o C ropivacaine HCl has a solubility of 53.8 mg/ml in water, a distribution ratio between n-octanol and phosphate buffer at pH 7.4 of 14:1 and a pKa of 8.07 in 0.1M KCl solution. The pKa of ropivacaine is approximately the

same as bupivacaine (8.1). However, ropivacaine has a lower lipid solubility owing to (substitution of pipecoloxylidine with a 3-carbon side chain instead of a 4- carbon side chain) [41] compared to bupivacaine and mepivacaine. Usually sodium hydroxide or hydrochloric acid is added to adjust pH of the compound. Ropivacaine is preservative free and is available in single dose containers in 2(0.2%), 5(0.5%), 7.5(0.75%) and 10mg/ml (1%) concentrations. The specific gravity of solutions ranges from 1.002 to 1.005 at 25^{o}C.

Mechanism of Action

Ropivacaine reversibly interferes with the entry of sodium in nerve cell membranes, leading to decreased permeability to sodium and thus

a) Block generation and conductance of nerve impulses.

b) Slows propagation of nerve impulses.

c) Reduce the rate of rise of action potential

Most local anaesthetics block the unmyelinated C and myelinated Aδ fibers that transmit pain impulses at the same rate . However the rate of blockade of Aα and Aβ (that carry motor impulses) depends on the physiochemical properties, pKa and lipid solubility of the individual local anaesthetic drugs. As Ropivacaine is less soluble when compared to bupivacaine , the blockade of Aα and Aβ is slow and hence produce less motor blockade than bupivacaine. Studies of lumbar epidural block in humans have confirmed that equal volumes and concentrations of bupivacaine and ropivacaine produce similar degree of sensory block while the motor block produced by ropivacaine is slower in onset, less

intensity and short duration. Clinically the order of blockade of nerve fibers is autonomic, sensory and motor, while the disappearance occurs in reverse order. The order of loss of nerve function is

1. Pain
2. Temperature
3. Touch
4. Proprioception and
5. Skeletal muscle tone.

Pharmacokinetics

Absorption

The systemic concentration of ropivacaine is dependent on the total dose and concentration of drug given, the route of administration, the patient's hemodynamic condition and vascularity of the site of administration. Ropivacaine shows a complete and biphasic absorption from the epidural space. The half-lives of the 2 phases (mean ±SD) are 14±7 minutes and 4.2±0.9 h, respectively.

Distribution

After intravascular infusion, ropivacaine has a steady state of distribution of 41±7 liters. It is a 94 % protein bound, mainly to α1-acid glycoprotein. Ropivacaine readily crosses the placenta.

Metabolism

Ropivacaine is extensively metabolized in the liver, predominantly by aromatic hydroxylation mediated by cytochrome P450 1A to 3- hydroxyl ropivacaine. After a single IV dose, approximately 37% of the total dose is excreted in the urine as both free and conjugated 3- hydroxy ropivacaine. Low concentration of 3- hydroxy ropivacaine has been found in the plasma. An additional metabolite, 2- hydroxyl-methyl-ropivacaine has been identified but not quantified. N-de-alkylated metabolite of ropivacaine and 3-OH-ropivacaine are the major metabolite excreted in urine during epidural infusion.

Elimination

Ropivacaine metabolites are mainly excreted via kidney. After IV administration 86% of the dose is excreted in urine of which only 1% is in unchanged form. Following IV administration ropivacaine has a mean ± SD total plasma clearance of 387± 107 ml/min, an unbound plasma clearance of 7.2±1.6 L/min and a renal clearance of 1ml/min. The mean ± SD terminal half-life is 1.8± 0.7 h and 4.2±1.0 h after IV and epidural administration respectively.

Potency [41]

Lipid solubility appears to be the primary determinant of intrinsic anaesthetic potency. Chemical compounds which are highly lipophilic tend to penetrate the nerve membrane more easily, so that fewer molecules are required for conduction blockade resulting in enhanced potency. For this reason, a strict correlation between the lipid solubility of local anaesthetic and its potency and

toxicity exists. Mc Donald et al[42] compared three intrathecal doses of ropivacaine and bupivacaine (4, 6 and 8mg) in healthy volunteers and reported that ropivacaine is half as potent as bupivacaine.

Using the same up-down sequential technique for determining the minimum local anaesthetic concentration (MLAC) producing adequate pain control in 50% of patients receiving an epidural for labour pain[43] and found nearly 50% higher MLAC values[44] for ropivacaine when compared to bupivacaine. A study[45] determined the minimal volume of local anaesthetic to produce an effective block of femoral nerve in 50% of patients within 20 minutes after the injection similar to that required when using 0.5 % bupivacaine.

With ropivacaine 7.5 mg/ml a volume of two to three ml injected into the sub arachnoid space (Dose 15-22.5mg) results in sensory block as high as T5 and T4 respectively. Anaesthesia to pin prick begins in sacral dermatomes in two to three minutes extends to T10 in 10 to 13 minutes and lasts for approximately two hours.

Intrathecal administration

Intrathecal anaesthesia is useful for ambulatory anaesthesia, requirements of which are a sensory and motor block of adequate duration for the procedure and a fast regression of motor block to assist mobilisation. The majority of data relating to the efficacy of intrathecal ropivacaine for regional anaesthesia are usually derived from studies of patients undergoing caesarean section or orthopaedic surgery. Ropivacaine has also shown efficacy in several trials in

other types of surgery such as perineal surgery[46], inguinal herniorrhaphy[47], other lower abdominal or gynaecological procedures[48] and anorectal surgery[49].

Adverse effects

Excessive plasma levels are due to over dosage, unintentional intravascular injection or slow metabolic degradation. The mean doses at which CNS symptoms of toxicity begin to occur in human beings are 4.3 and 0.6 µg/ml of total and free plasma concentrations respectively. When prolonged blocks are used the risks of reaching a toxic plasma concentration or inducing local neural injury are increased. Various possible side effects include

a) Injection site pain

b) Cardiovascular system toxicity: Vasovagal reaction, syncope, postural hypotension, non-specific ECG abnormalities

c) Gastrointestinal system toxicity: Fecal incontinence, tenesmus, nausea, vomiting.

d) Central nervous system toxicity: Tremor, Horner's syndrome, dyskinesia, neuropathy, vertigo, convulsion and coma. Because of depressant effect of ropivacaine in medulla, excitatory stage of CNS might not occur.

e) Liver and Biliary system toxicity: Jaundice

f) Metabolic disorders: Hypomagnesemia.

Management of complications

Discontinuation of ropivacaine should be done at the first sign of toxicity. As no specific antidote is available, symptomatic and supportive management should be done promptly. Any change in mentation needs oxygen administration. Secure airway and provide assisted ventilation if any signs of respiratory depression are observed. Convulsions can be treated with barbiturates, specific anticonvulsants or neuromuscular blockers. In case of cardiac arrest, prolonged resuscitative efforts might be required.

Drug interactions

Ropivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide type local anaesthetics, as these are additives. Strong inhibitors of cytochrome P4501A2, such as fluvoxamine can interact with ropivacaine leading to increased ropivacaine plasma levels. Sixteen possible interactions with drug known to be metabolized by CYP1A2 via competitive inhibition such as theophylline and imipramine may also occur.

Advantages over other local anaesthetics

Ropivacaine produces a more differential blockade allowing better separation between sensory and motor block and hence a better choice for use in labour analgesia and post op pain relief. When compared to bupivacaine it produces less motor blockade of shorter duration and hence permitting earlier mobilization and discharge. It has a low systemic toxicity than bupivacaine and a

better cardiotoxic profile. Ropivacaine has been developed to offer a safer alternative to bupivacaine while retaining the desirable blocking properties of racemic bupivacaine.

The extensive clinical use of ropivacaine through various routes for a variety of surgeries has confirmed a long lasting block similar to that provided by racemic bupivacaine. Another clinically relevant advantage with ropivacaine is greater differentiation between sensory and motor blockade, which is particularly useful if early mobilization is needed to enhance postoperative recovery. Though 40 to 50 % less potent than bupivacaine, ropivacaine in an equipotency ratio of 1.5:1 produces results in a similar clinical profile with good preservation of motor function. Ropivacaine is the only local anaesthetic that is specifically approved for use by infusion.[50]

CLONIDINE

Clonidine is Alpha-2 adrenoceptor agonists and has analgesic properties when given parenterally, epidurally or intrathecally. Stimulation of alpha-2 adrenoceptors in the substantia gelatinosa of the dorsal horn of the spinal cord by specific agonists inhibits the firing of nociceptive neurons stimulated by peripheral Aδ and C fibres.[51]

Structure

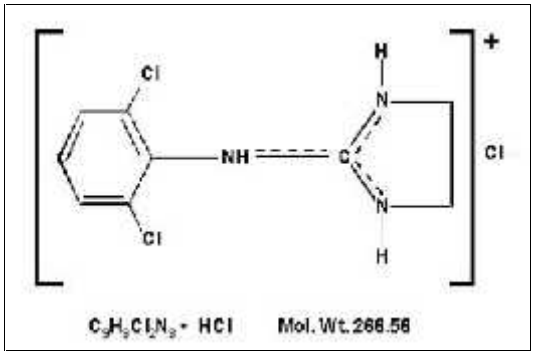

Figure 8. Chemical structure of clonidine

Clonidine decreases peripheral norepinephrine release by stimulation of prejunctional inhibitory alpha-2 adrenoceptors and by inhibition of neural transmission in different brainstem areas, such as the nucleus tractus solitarius and lateral reticular nucleus in the ventrolateral medulla. Hypnotic-sedative, analgesic and anxiolytic actions of clonidine may be modulated via the alpha 2A adrenoceptor subtype.[52] It is a partial agonist with an alpha-2a to alpha-1 selectivity ratio of 39. The alpha-2a-to-imidazoline selectivity ratio is 16.[53] Clonidine is an imidazoline and is the alpha-2 adrenoceptor agonist currently available for use in anaesthetic practice.

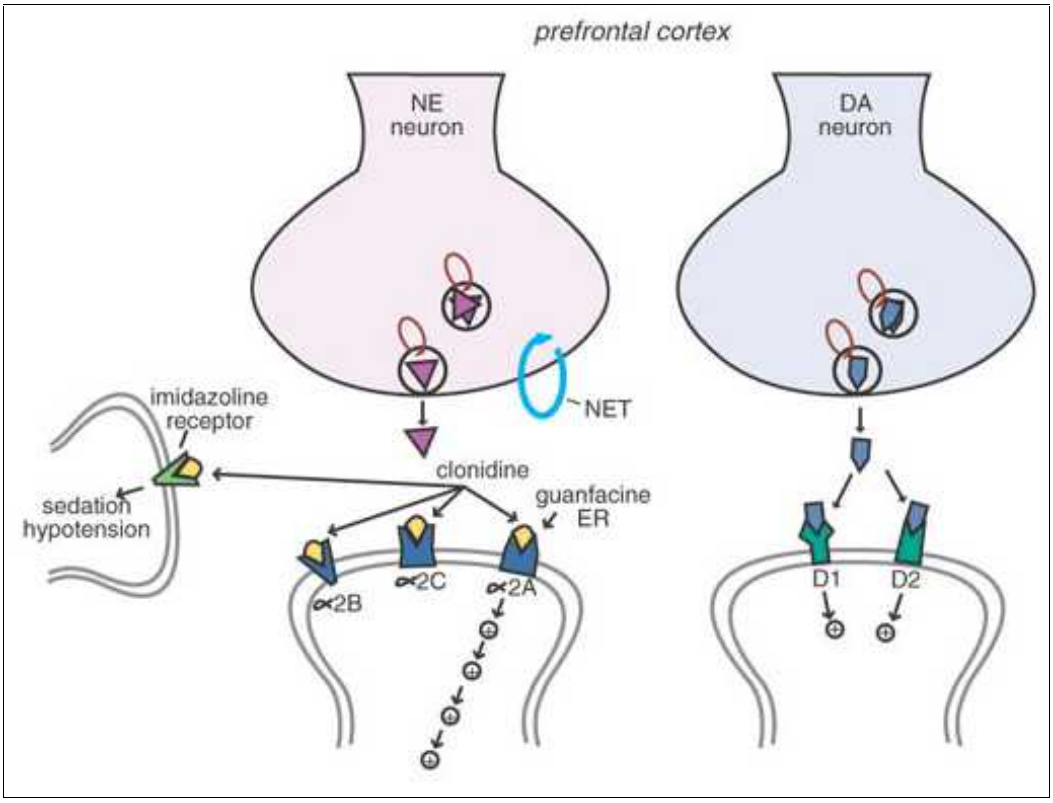

Figure 9. Clonidine - Mechanism of action

Pharmacokinetics

Clonidine is lipid soluble and so has both rapid and complete absorption after oral administration, reaching peak plasma level in 60 to 90 min. Time release transdermal patches are available and two days of administration are required before therapeutic plasma concentrations are achieved. Because of its high lipid solubility Clonidine crosses the blood–brain barrier and disappears rapidly from the CSF. The elimination half-life after epidural injection of Clonidine 150 mcg is 30 min. It is 20% bound to plasma proteins and the volume of distribution is 1.7 to 2.5 L/kg. Clonidine is less than 50% metabolised in the liver to inactive metabolites, the remaining drug being excreted unchanged in the kidney and about 20% is excreted in the faeces. The elimination half-life is

around 6 to 23 h and is prolonged if renal impairment exists. The clearance is 1.9 to 4.3 mL/min/kg.

Preparation and Route of Administration

- Available as 100 / 250 / 300 mcg tablets for oral administration
- Transdermal patch releasing 100/200/300 mcg over 24 hour and

Injectable solution containing 150 mcg/ml for intravenous, intramuscular, local and regional use is available. The adult oral dose is 100 to 600 mcg administered 8 hourly; the corresponding intravenous dose is 150 to 300 mcg, a dose of 150 mcg has been used epidurally.[54]

Central alpha-2 adrenoceptor agonists attenuate sympathoadrenal activation and provide greater perioperative stability. Selective and nonselective alpha-2 adrenoceptor agonists are;

Nonselective Alpha-2 Adrenoceptor Agonists	**Selective Alpha-2 Adrenoceptor Agonists**
Noradrenaline	Dexmedetomidine
Adrenaline	Mivazerol
	Clonidine
	A-Methyl dopa

Pharmacodynamics

Central Nervous System Effects

When adrenaline has been administered intracerebroventricularly, so that the blood–brain barrier is avoided, sedation ranging from sleep to surgical anaesthesia has been described. The use of clonidine as an antihypertensive has been limited by its sedative effects, but offers advantages in anaesthetic practice. When clonidine was given in a sufficient dose to produce sleep, the EEG showed an increase in stage 1 and 2 sleep and decrease in rapid eye movement sleep. Alpha-2 adrenoceptor agonists and benzodiazepines produce comparable anxiolysis. Clonidine at high doses can be anxiogenic owing to alpha-1.[54]

Cardiovascular system effects

There are both alpha-1 and alpha-2 postjunctional receptors in the arterial and venous vasculature where they both mediate vasoconstriction.[55] The alpha-1 and alpha-2 adrenoceptors differ in their location and their utilisation of calcium. In the arterial vasculature, the alpha-1 adrenoceptors are junctional and the alpha-2 adrenoceptors are extra-junctional, while the reverse is true of the venous vasculature. Alpha-1 adrenoceptor stimulation produces vasoconstriction by utilizing intracellular calcium while the alpha-2-adrenoceptor-mediated vasoconstriction uses extracellular calcium.[56] This makes the alpha-2 adrenoceptor agonist's pressor response more sensitive to calcium antagonists.

Clonidine lowers the ‘set point’ around which arterial blood pressure is regulated. It also increases the gain of the baroreceptor system, resulting in lower

heart rates for a given increase in blood pressure, and broadens the range of heart-rate responses to changes in blood pressure.

The bradycardia commonly seen after administration of alpha-2 adrenceptor agonists may be due to the central sympatholytic action of these drugs leaving vagal tone unopposed. It may also be due to presynaptic-mediated reduction of noradrenaline release or a direct vagomimetic action.

There are no known directly mediated alpha-2 adrenoceptor effects on the myocardium. Alpha-2 adrenoceptor reduction in sympathetic tone and increase in parasympathetic tone results in a reduced heart rate, systemic metabolism, myocardial contractility and systemic vascular resistance. All these result in a decrease in the myocardial oxygen requirements. This may be the reason behind the success of Clonidine in the treatment of angina pectoris.

Renal System Effects

Activation of alpha-1 receptors in the kidney results in a redistribution of blood from the cortical to medullary areas due to an increase in renal vascular resistance. Stimulation of alpha-2 adrenoceptors has a number of effects that promote diuresis and natriuresis. They decrease the secretion of vasopressin and antagonise its action on renal tubules. Alpha-2 adrenoceptors are also thought to inhibit the release of renin and increase the release of atrial natriuretic factor.[54]

Neuroendocrine System Effects

The alpha-2 adrenoceptor agonists have a number of neuroendocrine effects, mainly related to their inhibition of sympathetic outflow and the decrease

in plasma levels of circulating catecholamines. Stimulation of alpha-2 adrenoceptors located on the β cells of the islets of Langerhans can temporarily cause direct inhibition of insulin release; clinical hyperglycaemia has not proved to be a problem. Alpha-2 receptor agonists also increase the release of growth hormone and inhibit adipose tissue lipolysis. Clonidine can inhibit the secretion of adrenocorticotropic hormone (ACTH) and cortisol during surgery.[54]

Effects on Platelets

Selective alpha-2 adrenoceptor agonists, as well as adrenaline, are known to stimulate platelet aggregation by stimulating alpha-2c receptors on platelets. High concentrations of alpha-2 adrenoceptor agonists are required to cause platelet aggregation, as low concentrations of these drugs decrease plasma adrenaline concentration; the net effect may be a reduction in platelet aggregation. Alpha-2 receptor stimulation also results in the release of nitric oxide, a potent inhibitor of platelet aggregation. Clonidine does not promote platelet aggregation; it also blocks adrenaline-induced platelet aggregation.[54]

Respiratory system effects

Alpha-2 adrenoceptors have a minimal effect on ventilation. Clonidine in doses up to 300 mcg, seems to cause a small reduction in resting minute ventilation and an increase in expired carbon dioxide.[57]

The locus coeruleus, is an important site for the action of alpha-2 adrenoceptor agonists. The locus coeruleus is involved in arousal reactions; suppression of its activity by alpha-2 adrenoceptor agonists can result in a state

similar to sleep with mild respiratory depression. There is no significant effect on hypercapnic or hypoxic ventilatory drive with alpha-2 adrenoceptor stimulation. The combination of alpha-2 adrenoceptor agonists with opioids does not lead to further ventilatory depression.

Gastrointestinal system effects

Alpha-2 adrenoceptors regulate vagally mediated increases in gastric and intestinal motility and secretions. It has been postulated that gastric cholinergic prejunctional alpha-2 adrenoceptors inhibit gastric secretions during stress. Activation of alpha-2 adrenoceptors inhibits water secretion and increases net absorption in the large bowel. This is the mechanism by which clonidine has been used to successfully treat diarrhoea. Stimulation of alpha-2 adrenoceptors is known to reduce salivary secretions and may lead to a dry mouth.[58]

Drug and receptor interactions

Alpha-2 adrenoceptor agonists and opioids have some similar pharmacological effects. It is known that they have a similar distribution in the brain and that they function through the activation of the same transduction and effector mechanisms that is by G-proteins and coupling to potassium channels. Therefore, if alpha-2 adrenoceptor agonists and opioids are administered together they may exhibit a synergistic action. It may also be possible to reduce the opioid dose and therefore decrease the respiratory and addictive side-effects.

Alpha-2 adrenoceptor agonists also have a synergistic action with benzodiazepines.[59]

METHODOLOGY

The present study titled "COMPARISON OF ONSET AND DURATION OF SENSORY AND MOTOR BLOCKADE WITH INTRATHECAL ISOBARIC ROPIVACAINE VERSUS ISOBARIC ROPIVACAINE-CLONIDINE FOR INFRAUMBILICAL SURGERIES - A ONE YEAR HOSPITAL BASED RANDOMISED CONTROL TRIAL**"** was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2012 to December 2012.

Source of Data

A total of 70 patients between the age group of 18-60 years of either gender, belonging to ASA Grade I and II scheduled for infraumbilical surgeries were divided into two groups using computer randomization.

Group I- 3ml of 0.75 % isobaric ropivacaine.

Group II– 3 ml of 0.75 % isobaric ropivacaine + 15 mcg clonidine.

Sampling procedure

Using the results of previously conducted study and standard statistical formula, time for duration of motor block was taken to determine the sample size.

$$\text{Sample Size} = \frac{2\,(Z\alpha + Z\beta)^2\,(S_1^2 + S_2^2)}{(\bar{x}_1 - \bar{x}_2)^2}$$

Level of significance is taken as 5%

Power of the test used is taken as 80%

Hence, $Z\alpha = 1.96$ $\bar{x}_1 = 112$

$Z\beta = 0.84$ $\bar{x}_2 = 127$

$S_1 = 11.1$

$S_2 = 19.5$

Where:

- S_1 is S.D of Ropivacaine group
- S_2 is S.D of Ropivacaine-clonidine group
- $\bar{x}_1$ is duration of motor block in Ropivacaine group
- $\bar{x}_2$ is duration of motor block in Ropivacaine-clonidine group

$$\text{Sample Size (n)} = \frac{2 \times (1.96+0.84)^2 \ (11.1^2 + 19.5^2)}{(15)^2}$$

$$= 7894.25/225 = 35.08$$

The sample size obtained was 35 in each group.

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Selection Criteria:

Inclusion

- Patients undergoing infraumbilical surgeries under spinal anaesthesia.
- Age: 18 to 60 years.
- ASA Grade I and Grade II patients.
- Height: 150 cm - 180 cm

Exclusion

- Patient's refusal.
- Contraindications to subarachnoid block like coagulopathy, local skin infection, raised intracranial pressure, spinal deformity, etc.
- ASA grade III or IV patients.
- Patient allergic to study drugs.

Methodology:

After obtaining institutional ethical committee clearance and written informed consent, seventy patients having met inclusion criteria's were randomized based on computer generated randomization table into one of the two groups.

- Group I**:** Received 3ml of 0.75% Ropivacaine
- Group II: Received 3ml of 0.75% Ropivacaine + 15mcg Clonidine.

Investigations like complete Blood count, RBS, Serum Creatinine, urine routine, if patients age is >40 years Chest X-ray, ECG were done.

Preoperatively the patient's intravenous (IV) line was secured with either 18 G or 20 G branula and IV ringer lactate solution was started at 15 ml/kg half an hour before spinal anaesthesia. The patient was then shifted to the Operation Theatre and monitors like electrocardiograph (ECG), pulse oximeter and non-invasive blood pressure were attached and baseline heart rate and blood pressure reading was taken. The patient was then placed in the right lateral position.

Under strict aseptic precautions spinal puncture was performed at L_3-L_4 sub arachnoid space with 23 G Quinckes spinal needle and the study drug was injected at a rate of 1 ml/ 15 seconds. Patient was then placed in supine position immediately.

Sensory block was assessed using alcohol swab bilaterally in mid clavicular line. Onset of sensory block was defined as time taken to achieve T_{10} level block and duration of sensory blockade was defined as two dermatome regression of anaesthesia from highest level. Motor block was assessed using a modified bromage scale.

- Bromage 0, free movement of legs and feet, with ability to raise extended leg.
- Bromage 1, inability to raise extended leg and knee flexion is decreased, but full flexion of ankle and feet is present.

- Bromage 2, inability to raise leg or flex knees, flexion of ankle and feet present.

- Bromage 3, inability to raise leg, flex knee or ankle, or move toes.

Onset of motor block was defined as the time taken to reach modified bromage score 3 and duration of motor block was defined as the time taken for return to modified bromage score 0.

Sensory and motor block was assessed at time intervals: 0, 5, 10, 15, 20, 25 and every 15 minutes till there was two segment regression in sensory block and motor block regressed completely (i.e. modified bromage score= 0). All durations were calculated considering the time of injection as time zero.

Blood pressure and Heart rate were recorded at 2, 4, 6, 8, 10, 15, 20, 25, 30 minutes and every 10 minutes till the end of surgery. Hypotension was defined as decrease in systolic B.P by 30% from baseline values or a systolic B.P less than 90 mm of Hg and was treated with a bolus administration of intravenous fluids and with incremental intravenous boluses of Inj Mephentermine sulphate 3 mg. Bradycardia was defined as decrease in heart rate less than 60 beats per minute and was treated with intravenous Inj Atropine Sulphate 0.6 mg. Supplementary oxygen was given through face mask. Side effects of clonidine like hypotension, bradycardia, sedation and dry mouth were observed for.

Statistical Analysis:

All data were expressed as mean ±standard deviation.

Quantitative data were compared using student's unpaired t test while qualitative data were compared using chi- square test.

The p value of <0.05 was considered significant.

RESULTS

The present one year clinical trial was conducted in the Department of Anaesthesiology, during the period of January 2012 to December 2012 at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum attached to Jawaharlal Nehru Medical College, Belgaum.

A total of 70 patients undergoing infra umbilical surgeries under spinal anaesthesia were randomly allocated into one of the two groups by computer generated randomization that is

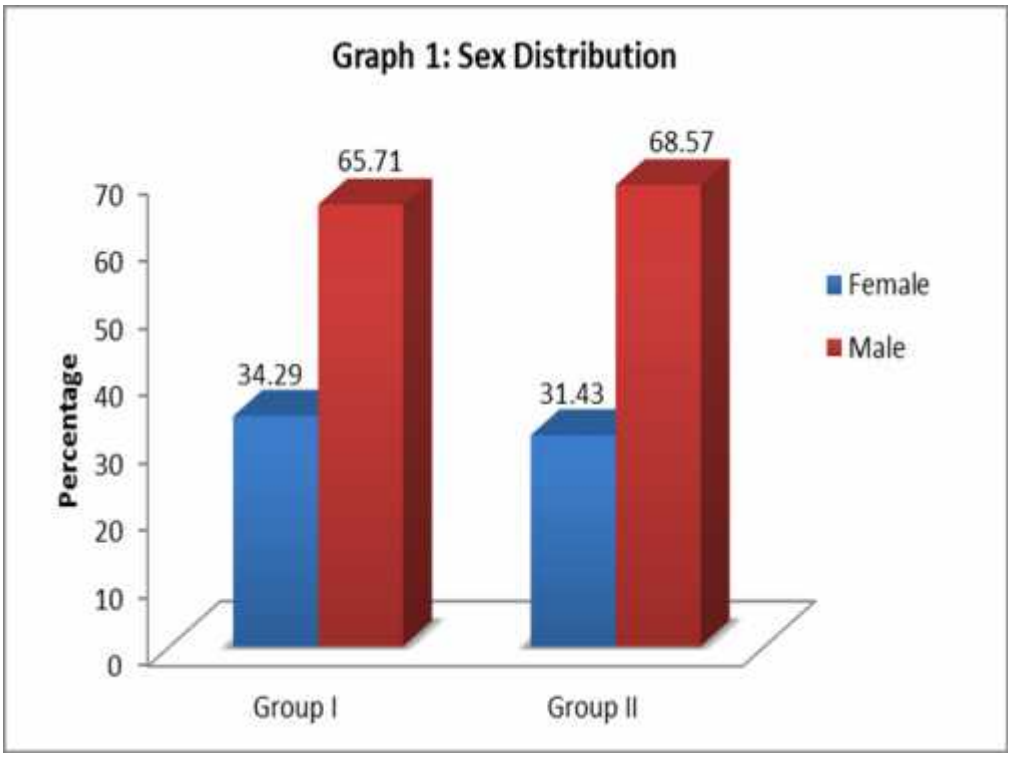
- Group I (n=35) Patients received 3 ml of 0.75 % isobaric ropivacaine intrathecally.
- Group II (n=35) Patients received 3 ml of 0.75 % isobaric ropivacaine + 15 µg clonidine intrathecally.

Data obtained were analyzed and final results are tabulated as below.

Table 1. Sex Distribution

Sex	Group I (n=35)		Group II (n=35)	
	Number	**Percent**	**Number**	**Percent**
Female	12	34.29	11	31.43
Male	23	65.71	24	68.57
Total	35	100.00	35	100.00

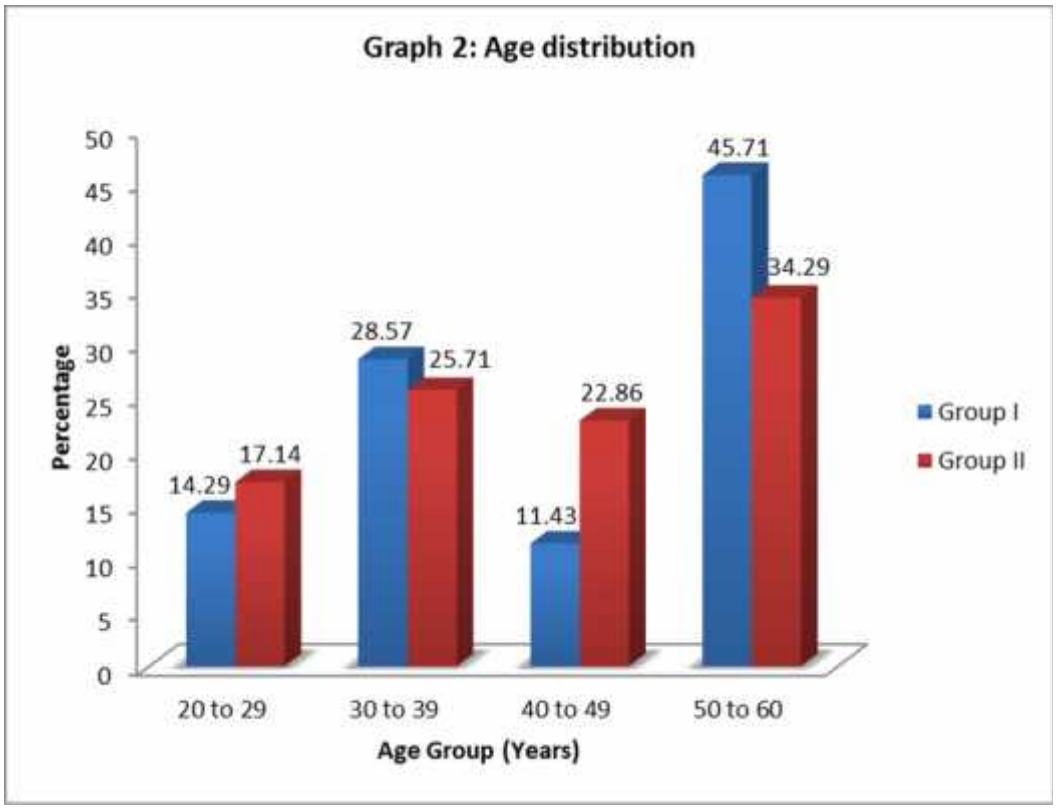
x^2=0.065 **p=0.065**



In this study 65.71% were males and 34.38% were females in group I and 68.57% were males and 31.42% were females in group II, suggesting both the groups had comparable demographic characteristics (p=0.799).

Table 2. Age Distribution

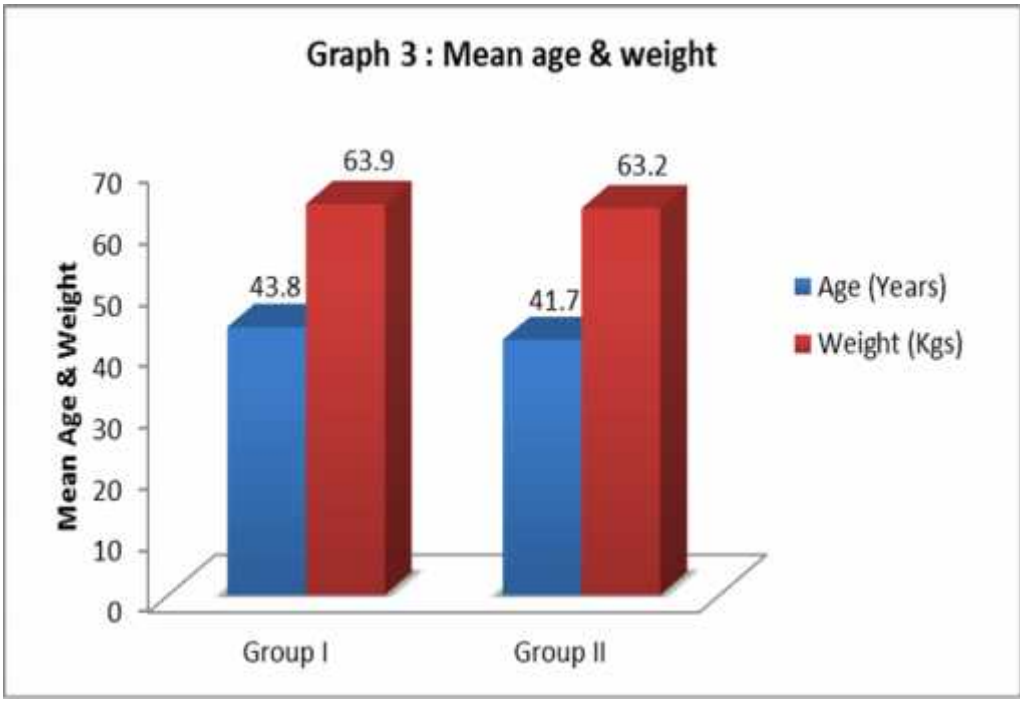
Age group (Years)	Group I (n=35)		Group II (n=35)	
	Number	**Percent**	**Number**	**Percent**
20 to 29	5	14.29	6	17.14
30 to 39	10	28.57	9	25.71
40 to 49	4	11.43	8	22.86
50 to 60	16	45.71	12	34.29
Total	35	100.00	35	100.00



In both group I (45%) and group II (34 %) most of the patients were aged between 50 to 60 years. In both groups, less than 20% of the patients were aged less than 30 years .The mean age in group I was 43.8 ± 13.78 years and in group II was 41.7 ± 12.01 years suggesting both the groups had comparable demographic characteristics (p=0.502).

Table 3. Mean age and weight

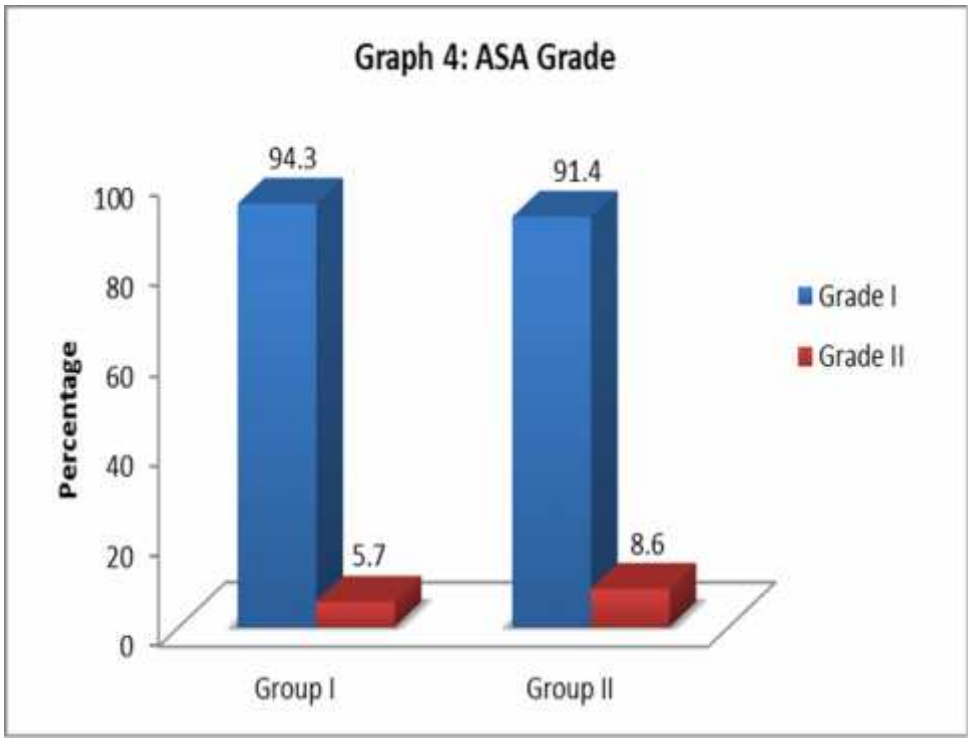
Parameters	Group I (n=35)		Group II (n=35)		p' value
	Mean	SD	Mean	SD	
Age (Years)	43.8	13.78	41.7	12.01	0.502
Weight (Kgs)	63.9	9.67	63.2	6.99	0.693



The mean weight in group I was 63.9 ± 9.67 kgs and in group II it was 63.2 ± 6.99 kgs (p=0.693), suggesting mean weight in both the groups were comparable.

Table 4. ASA grade

ASA grade	Group I (n=35)		Group II (n=35)	
	Number	**Percent**	**Number**	**Percent**
Grade I	33	94.3	32	91.4
Grade II	2	5.7	3	8.6
Total	35	100.00	35	100.00
x^2=0			p=1	

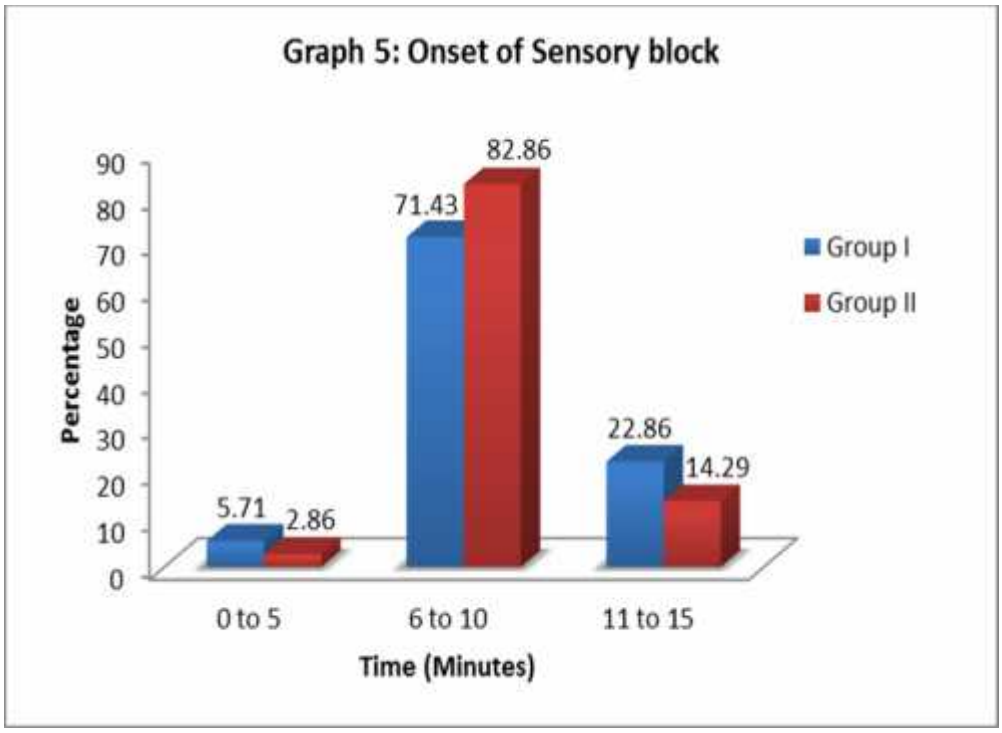


In group I, 94.3% patients were ASA Grade I and 2% were ASA Grade II. In group II, 91.4% patients were ASA Grade I and 8.6% were ASA Grade II, suggesting that ASA Grades in both groups were comparable (p=1).

Table 5. Onset of sensory block

Time (Minutes)	Group I (n=35)		Group II (n=35)	
	Number	**Percent**	**Number**	**Percent**
0 to 5	02	05.71	01	02.86
6 to 10	25	71.43	29	82.85
11 to 15	08	22.86	05	14.29
Total	**35**	**100.00**	**35**	**100.00**

P=0.067

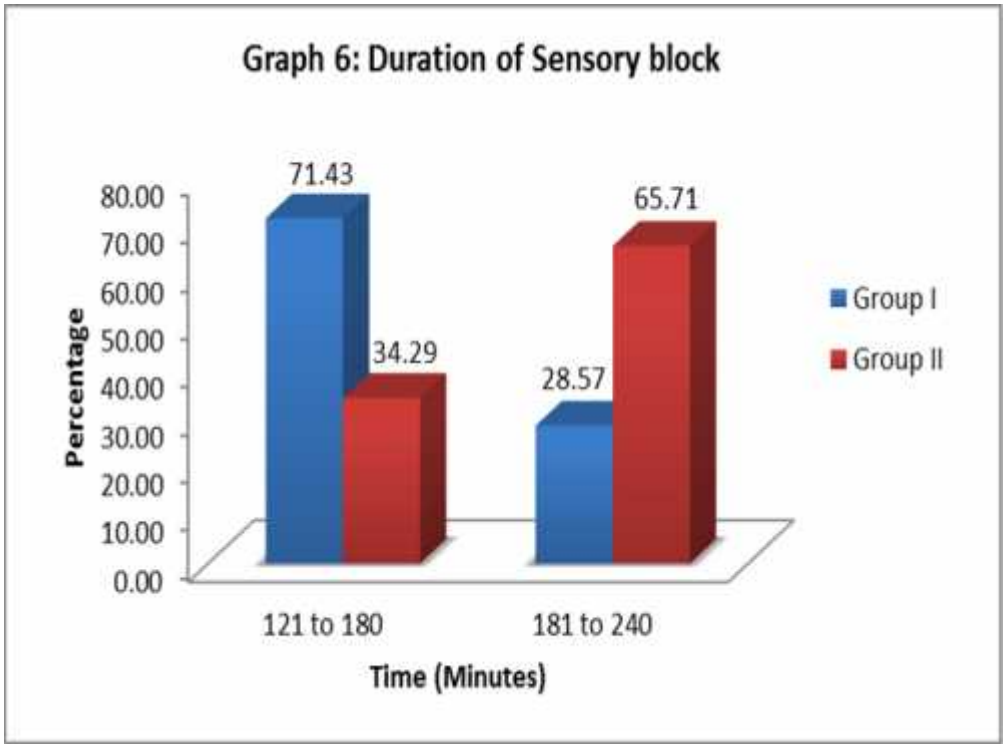


The mean onset of sensory block in group I was 10.8±2.56 minutes and in group II was 10.6±2.02 minutes. The result was not statistically significant and both group had almost similar onset of sensory block.

Table6. Duration of sensory block

Time (Minutes)	Group I (n=35)		Group II (n=35)	
	Number	**Percent**	**Number**	**Percent**
60 to 120	0	0.00	00	0.00
121 to 180	25	71.43	12	34.29
181 to 240	10	28.57	23	65.71
Total	**35**	**100.00**	**35**	**100.00**

P=0.007

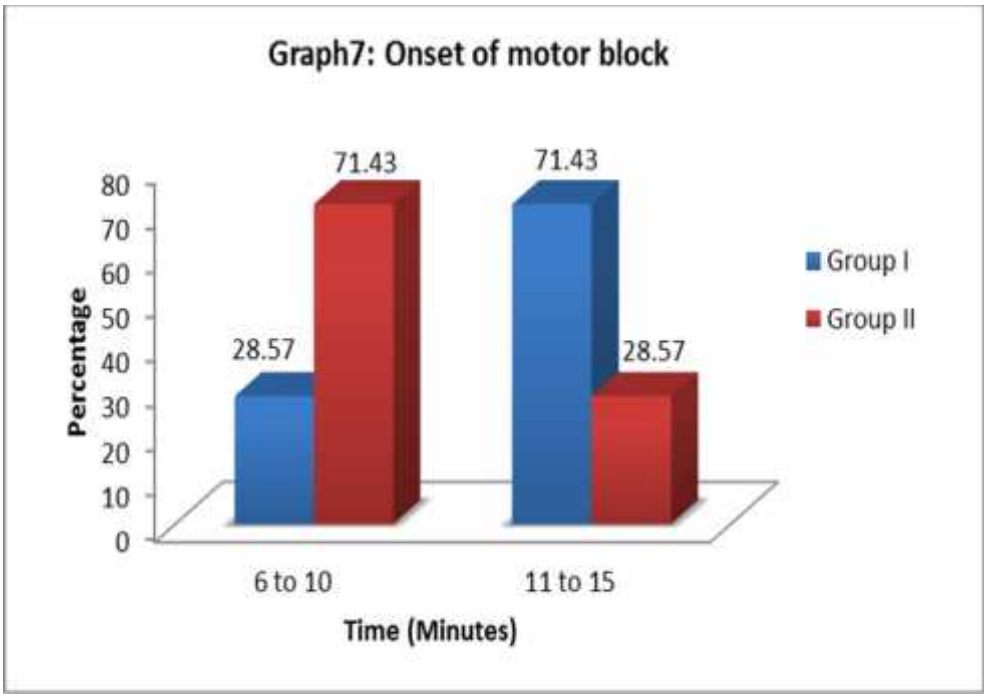


The mean duration of sensory block in group I was 180.8±13.08 minutes and in group II was 191.7±19.21 minutes and the result is statistically significant with longer sensory duration in group 2.

Table 7. Onset of motor block

Time (Minutes)	Group I (n=35)		Group II (n=35)	
	Number	**Percent**	**Number**	**Percent**
6 to 10	10	28.57	25	71.43
11 to 15	25	71.43	10	28.57
Total	**35**	**100.00**	**35**	**100.00**

P<0.001

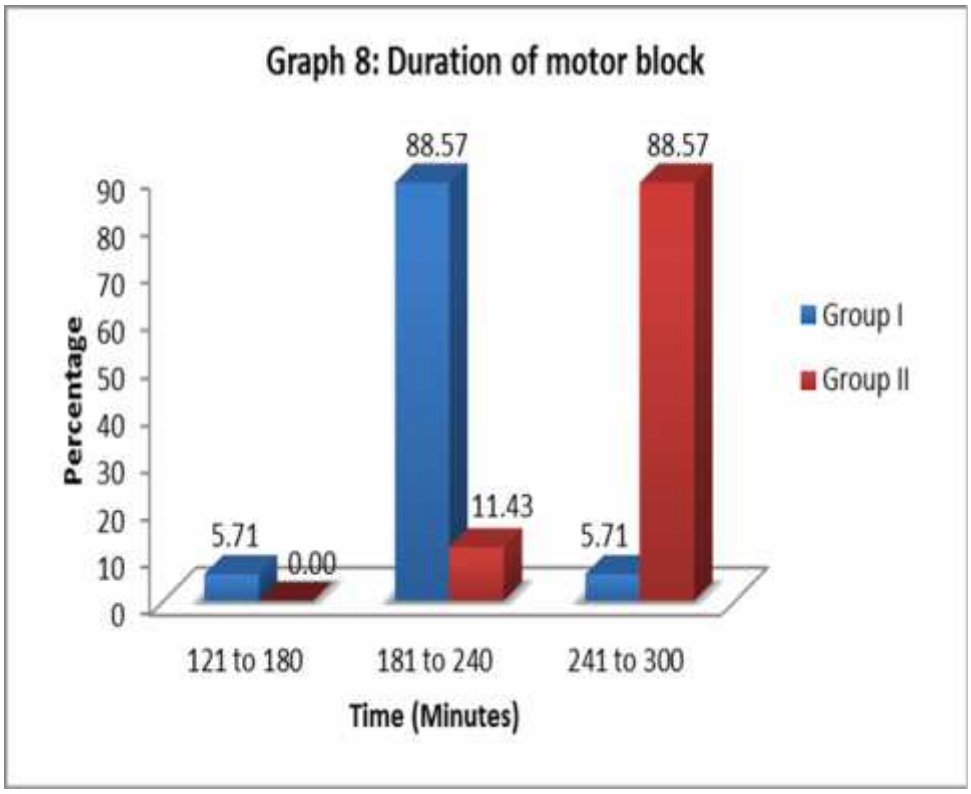


The mean onset of motor block in group I was 13.6±2.29 minutes and in group II were 11.4±2.29 minutes. The result was statistically significant and faster onset was seen in group 2

Table8. Duration of motor block

Time (Minutes)	Group I (n=35)		Group II (n=35)	
	Number	**Percent**	**Number**	**Percent**
121 to 180	02	05.71	00	00.00
181 to 240	31	88.57	04	11.43
241 to 300	02	05.71	31	88.57
Total	**35**	**100.00**	**35**	**100.00**

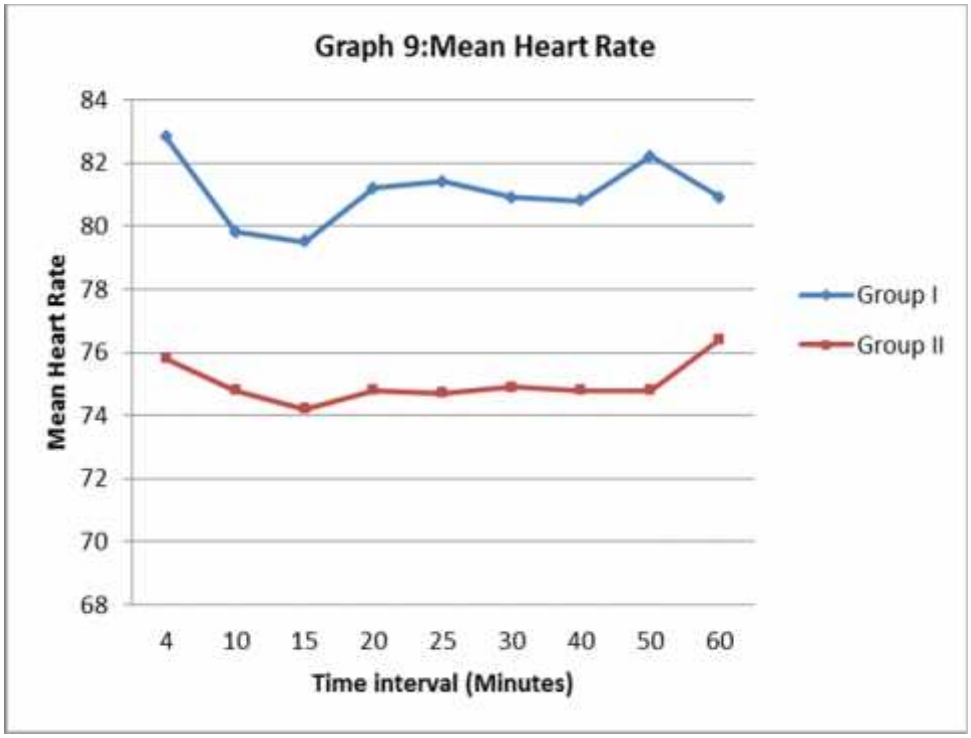
P<0.001



The mean duration of motor block in group I was 224.5±16.46 minutes and was 271.3±18.32 minutes in group II. This result signifies that there is prolonged duration of motor block in group II.

Table 9. Haemodynamic parameters - Heart rate

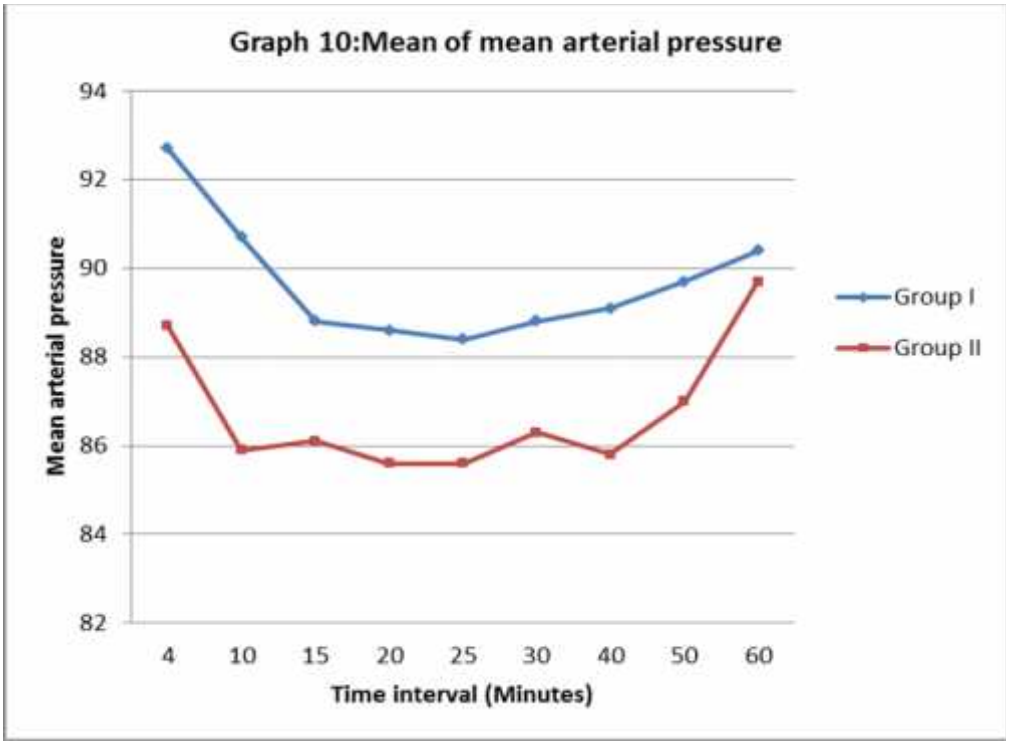
Time interval	Group I (n=35)		Group II (n=35)		p' value
	Mean	**SD**	**Mean**	**SD**	
Baseline	88.13	13.88	77.87	8.03	0.936
4 minutes	82.80	12.27	75.80	07.52	0.005
10 minutes	79.80	09.91	74.80	06.31	0.014
15 minutes	79.50	10.25	74.20	06.85	0.014
20 minutes	81.20	10.56	74.80	07.61	0.005
25 minutes	81.40	09.84	74.70	07.24	0.002
30 minutes	80.90	09.71	74.90	06.89	0.004
40 minutes	80.80	09.51	74.80	07.02	0.004
50 minutes	82.20	09.65	74.80	07.56	0.001
60 minutes	80.90	08.31	76.40	07.04	0.017



The mean heart rate in group II was lesser compared to group I and the difference was statistically significant.

Table 10. Haemodynamic parameters – Mean arterial pressure

Time interval	Group I (n=35)		Group II (n=35)		p' value
	Mean	**SD**	**Mean**	**SD**	
Baseline	97.63	05.24	97.70	06.95	0.961
4 minutes	92.70	09.84	88.70	06.76	0.004
10 minutes	90.70	09.47	85.90	07.06	0.021
15 minutes	88.80	11.11	86.10	07.25	0.236
20 minutes	88.60	10.51	85.60	06.24	0.145
25 minutes	88.40	11.07	85.60	07.43	0.214
30 minutes	88.80	11.87	86.30	07.21	0.289
40 minutes	89.10	10.37	85.80	05.68	0.109
50 minutes	89.70	09.96	87.00	05.83	0.170
60 minutes	90.40	09.93	89.70	06.67	0.336



The mean of MAP at 4 and 10 minutes in group I was significantly higher ($p<0.05$) compared to group II. The Mean of MAP in both groups was found to be comparable at baseline, 15, 30, 40, 50, 60 minutes ($p>0.05$).

No other side effects like sedation, delayed mobilization and micturition were seen.

DISCUSSION

Subarachnoid block is the anaesthetic technique of choice because of its rapid onset, superior blockade, less failure rates and cost-effectiveness, but has the drawbacks of shorter duration of block and lack of adequate postoperative analgesia.

It also has added advantages such as amelioration of hypercoagulable states associated with surgery thus reducing venous thrombosis and sympathectomy mediated increase in tissue blood flow.

Till recently hyperbaric Bupivacaine 0.5% was the most common drug used since it gave a reliable spinal anaesthesia but had disadvantages like cardiotoxicity and CNS toxicity.[60]

Ropivacaine another amino-amide local anaesthetic having all the advantages of bupivacaine along with lower cardiac and CNS toxicity than that of Bupivacaine has been introduced. It is the first new local anaesthetic to be introduced in more than 25 years after Bupivacaine.

Ropivacaine is a first single enantiomer-specific compound, which has similar sensory blocking properties compared to Bupivacaine with a reduced risk of cardio toxicity, neurotoxicity, and rapid recovery of motor function. It is a long acting enantiomerically pure(S) amide local anaesthetic with a low lipid solubility which blocks Aδ and C (pain fibers) to a greater degree than Aβ (motor fibers).[2] Bupivacaine also belongs to the same group as Ropivacaine but it has two optically active isomers, R enantiomer which is more cardiotoxic and S

enantiomer. It blocks the cardiac sodium channel and depresses the automaticity and conduction of cardiac fibers hence causing re-entrant type ventricular dysrhythmias and also since Bupivacaine dissociates from cardiac sodium channel more slowly, it has a prolonged cardiac depressant effect. Ropivacaine is available as a pure S enantiomer hence it is less cardiotoxic than bupivacaine.[11] Ropivacaine is commercially available in isobaric form which is known to have a variable response since the spread of the drug is dependent on the current produced by injection and simple diffusion. [61]

The characteristics of intrathecal isobaric Ropivacaine, mainly prolonged sensory with lesser quality motor blockade is dose dependent as demonstrated in a study by Van Kleef et al[19], who observed a longer duration and better quality of blockade with 1.5 ml of 0.75% compared to that of 0.5% ropivacaine. Also in another study, McNamee et al[21], observed comparable quality of blockade with 2.5ml of 0.75% and 1% Ropivacaine in patients for orthopaedic surgeries but with increased cardiovascular side effects with regard to 1% Ropivacaine.

Therefore, in our study 0.75 % isobaric Ropivacaine (3ml) was used but a larger volume (3ml) was chosen as infra umbilical abdominal surgeries may require larger volume than used for lower limb surgeries for better quality of motor blockade.

The use of intrathecal adjuvant with isobaric Ropivacaine has gained popularity to improve the efficacy of blockade, better success rate and better patient satisfaction[62].

Clonidine, a potent and selective α2-adrenoceptor agonist is the newer drug under evaluation as a neuraxial adjuvant as it provides stable hemodynamic conditions, good quality of intraoperative and prolonged postoperative analgesia. It also has minimal side effects when compared to opioids.[63]

In our study 15mcg of Clonidine was used as an adjuvant to 3ml of 0.75% Ropivacaine as higher doses are associated with significant side effects as demonstrated in a study by De Kock et al[26] who observed comparable effects on the objective parameters of anaesthesia, *i.e.,* duration of sensory and motor blockade on addition of 15, 45, and 75 µg of Clonidine to isobaric Ropivacaine but dose of 45 and 75 µg Clonidine were associated with increased cardiovascular and other side effects. D'Angelo[64] considered a dose of 15µg Clonidine as low or mini dose.

This one year randomized controlled trial was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2012 to December 2012. A total of 70 patients undergoing infra umbilical surgeries under spinal anaesthesia were randomly allocated into one of the two groups by computer generated randomization that is, Group I (n=35; patients received 3 ml of 0.75 % Ropivacaine) or Group II (n=35; Patients received 3 mL of 0.75 % Ropivacaine + 15 mcg Clonidine).

In this study demographic parameters like age, sex, weight and ASA status were comparable between the two groups.

In our study, the mean onset of sensory blockade was 10.8± 2.5 minutes in plain Ropivacaine (group I) and10.6±2.02 minutes in Ropivacaine with clonidine (group II) , this difference was statistically insignificant (p=0.067).The results correlated with results of studies done by G Sagiroglu et al[27] where even on addition of 15µg or 30µg Clonidine to 12 mg Ropivacaine (20.04±9.10 mins and 19.56±7.09 mins respectively) had a similar sensory onset time compared to plain 12 mg Ropivacaine(18.88±9.28 mins). Also in another study, De Kock et al[26] observed addition of 15 µg Clonidine to 8 mg Ropivacaine (23±16 mins) had similar onset of sensory block when compared to plain 8 mg Ropivacaine (19±15 mins).

The duration of sensory blockade in our study was 180.8±13.08 minutes in group I and191.7±19.21 minutes in group II (with Clonidine) and this difference was statistically significant (p= 0.007). Similar findings were reported in a study done by G Sagiroglu et al[27] where both time for two segment regression and time to reduction to S2 segment were shorter in Clonidine free group (96 mins±14.20 and 200 mins±21.82 respectively) and on addition of Clonidine 15µg (111.00±19.84 mins and 238.00±25.21 mins respectively)and 30µg Clonidine (119.20±18.47 mins and 246.60±18.69 mins respectively) blockade was prolonged whereas a study done by C Ogun et al[6] in 50 parturient showed that the time to regression of two dermatomes was similar but the time for the block to recede to S2 dermatome was longer in group with lower dose Ropivacaine and Clonidine (123.0±19.5) than higher dose plain Ropivacaine (112.0±11.1) .

In our study the mean onset of motor blockade was 13.6±2.29 minutes in plain Ropivacaine group and was 11.4±2.29 minutes in Ropivacaine with Clonidine and the difference was statistically significant ($p<0.001$). However another study done by C Ogun et al [6] didn't find any statistically significant difference because study compared a lower dose Ropivacaine with an adjuvant with that of higher dose Ropivacaine i.e between 15mg Ropivacaine with 30 µg Clonidine and 17.5 mg Ropivacaine (higher dose of ropivacaine).

The mean duration of motor block (complete motor recovery) was 224.5±16.46 minutes in Ropivacaine group and 271.3±18.32 minutes in Ropivacaine with Clonidine group and the difference was statistically significant ($p<0.001$). Similar findings were found in study done by De Kock et al[26] in patients undergoing knee arthroscopy surgeries when an addition of 15 µg Clonidine to 8 mg Ropivacaine had a prolonged duration of motor block compared to plain 8 mg Ropivacaine (137±32 mins vs. 110±35 min). Further in a study done by G Sagiroglu et al [27] the duration of 12mg plain 1 % isobaric Ropivacaine was 138±20.26 min and on addition of 15 µg and 30 µg Clonidine (162.60±35.03 mins and 172.20±37.78 mins respectively) observed prolonged duration of motor block.

Intrathecal Clonidine when added to isobaric Ropivacaine increases both the quality and the duration of the anaesthesia provided by local anaesthetic. The analgesic effect following its intrathecal administration is mediated spinally through the activation of postsynaptic α-2 receptors in substantia gelatinosa of the spinal cord. It also increases the motor blockade as a result of local anaesthetic administration [65, 66, 67].

In our study mean heart rate was significantly lower in Ropivacaine with Clonidine group than the plain Ropivacaine group throughout the surgery but there was no incidence of bradycardia in both the groups requiring treatment with Inj Atropine. However in a study by C Ogun et al[6], no statistical difference in heart rate was observed between 17.5 mg Ropivacaine and 15 mg Ropivacaine with 30 µg Clonidine. This may be due to higher dose of Ropivacaine used in one of the groups in their study.

In our study, no significant effects on the systolic and diastolic blood pressure were observed in both groups at all time intervals after the spinal block. However in another study done by G Sagiroglu et al [27] there was statistically significant difference in mean arterial blood pressure at 15 to 210 minutes after the block in group with 30 µg Clonidine added to Ropivacaine and readings were significantly lower than the plain Ropivacaine group. In another study done by De Kock et al [26] there was significant hypotension in groups which had 45 µg and 75 µg Clonidine added to Ropivacaine. However in our study only 15µg clonidine was used and hence was not associated with significant hypotension.

Clonidine is well recognised to have central mediated hypotensive effects. Clonidine decreases peripheral norepinephrine release by stimulation of prejunctional inhibitory alpha-2 adrenoceptors and by inhibition of neural transmission in different brainstem areas, such as the nucleus tractus solitarius and lateral reticular nucleus in the ventrolateral medulla.[52] The mechanism of actions may also involve inhibition of sympathetic outflow and the potentiation of parasympathetic nervous activity [68, 69] Although Clonidine does not produce an additional hypotensive effect when combined with local anaesthetics, there is a

potential for exacerbating haemodynamic depression from the combination of intrathecal Clonidine with opioids [70]

In our study no other significant side effects were observed in both the groups. Similar results were observed in a study done by De Kock et al[26]

Side effects of Clonidine are related with the route of administration and dose. Larger Clonidine doses are associated with hypotension, bradycardia and transient sedation via intrathecal or epidural route [68]. Addition of 150 µg intrathecal Clonidine produces notable side effects including hypotension, sedation and dry mouth. Sedation is one of the most consistent effects mediated by central alpha- 2 receptors[69].

Limitation of study was that different doses of Clonidine and Ropivacaine were not studied to compare the varying effects of concentration on the level and duration of sensory and motor block. In future studies can be done comparing the effects of spinal anaesthesia between intrathecal Ropivacaine and levobupivacaine with Clonidine added as an adjuvant.

Overall the present study showed that, the administration of intrathecal 15µg Clonidine as an adjuvant to 0.75 % isobaric Ropivacaine prolonged the duration of sensory and motor block which was statistically significant, with similar onset of sensory block (statistically insignificant) and without any significant side effects compared to intrathecal plain 0.75 % isobaric Ropivacaine.

CONCLUSION

Our study showed that addition of 15 µg of clonidine to 22.5 mg of isobaric ropivacaine (3 ml of 0.75 %) intrathecally provides adequate anaesthesia for infra umbilical surgeries. The onset of sensory blockade were similar but onset of motor block was faster and the duration of sensory and motor blockade was significantly prolonged with hemodynamic stability when clonidine was added as an adjuvant.

SUMMARY

Spinal anaesthesia remains a popular technique used in abdomen, pelvis and lower limbs surgeries providing fast onset and effective sensory and motor blockade. Clonidine is a relatively newer drug to be added as an adjuvant intrathecally. The present study was taken up to assess the onset and duration of sensory and motor block between intrathecal isobaric 0.75 % ropivacaine and 0.75% ropivacaine with 15µg clonidine.

This one year randomized controlled trial was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2012 to December 2012. A total of 70 patients undergoing infra umbilical surgeries under spinal anaesthesia were randomly allocated into one of the two groups by computer generated randomization that is, Group I (n=35. Patient received 3 ml of isobaric 0.75 % ropivacaine) or Group II (n=35. Patient received 3ml of isobaric 0.75 % ropivacaine + 15 µg clonidine). Sensory characteristics like onset and duration and motor characteristics like onset and duration were studied. Hemodynamic parameters like heart rate, MAP and oxygen saturation were monitored.

Demographic parameters in both groups were comparable. Onset of sensory block was comparable in both groups (Group I -10.8±2.56 minutes ,Group II -10.6±2.02 minutes) whereas duration of sensory block at T 10 level was longer in Group II (in Group II- 191.7±19.21 minutes and Group I - 180.8±13.08). Onset of motor blockade was faster and duration of blockade was prolonged in Group II (Onset-11.4±2.29 minutes, Duration-271.3±18.32 minutes)

when compared to Group I (Onset-13.6±2.29 minutes, Duration- 224.5±16.46 minutes). However all the patients in both the groups attained complete sensory and motor blockade. The mean heart rate was lesser in group II when compared to group I but there was no bradycardia seen in both the groups. Mean arterial blood pressure was comparable in both the groups.

Thus, based on the results of our study it may be concluded that, adding clonidine 15mcg to ropivacaine provides adequate spinal anaesthesia with prolonged duration of blockade without any significant effects on hemodynamic parameters.

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ANNEXURE I – CONSENT FORM

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr/Mrs/Miss. _____ we are requesting you to enroll yourself in study titled "COMPARISON OF ONSET AND DURATION OF SENSORY AND MOTOR BLOCKADE WITH INTRATHECAL ISOBARIC ROPIVACAINE VERSUS ISOBARIC ROPIVACAINE-CLONIDINE FOR INFRAUMBILICAL SURGERIES- A ONE YEAR HOSPITAL BASED RANDOMISED CONTROL TRIAL", conducted by Post Graduate in M.D. Anaesthesiology under the guidance of Professor, Department of Anaesthesiology, J.N. Medical College, Belgaum under KLE university, Belgaum.

Respected Sir/Madam we request you to enroll yourself to participate in our study as you are eligible for participating in the study. During the study you will be asked some questions regarding your present complaint and you are supposed to answer to the best of your knowledge.

Your participation in research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J.N. Medical College. If you decide to participate you are free to withdraw at any time.

The purpose of research is to compare efficacy between Ropivacaine and Ropivacaine -clonidine on onset and duration of motor block, onset and duration of sensory block, hemodynamic changes in infraumbilical surgeries under spinal anaesthesia.

Procedure Involved:

If you agree to enroll yourself in my study, you will be interviewed regarding your present, past and family history, then you will he clinically examined in detail and investigated accordingly. You will be randomly allocated either into study Group I or Group II, and be given the study drug as per

the randomisation protocol. You will receive 3 ml of 0.75% Ropivacaine (Plain) or 3 ml of 0.75% Ropivacaine (plain) plus 15mcg of Clonidine by spinal anaesthesia.

Risks and Benefits:

The benefits of taking part in this research are that we can avoid General Anaesthesia with good quality of Analgesia. The risks are minimal which include, hypotension, bradycardia, headache, backache, syncope, paraesthesia, sedation.

Voluntary Participation/Withdrawal:

Taking part in the study is voluntary. You may choose not to enroll yourself in this study. Your decision will not change present or future health care services offered to you at K.L.E.S hospital.

Alternatives:

Even if you decline the participation in the study, you will get the routine line of management.

Privacy and Confidentiality:

The only people to know that you are a research subject are members of the research team. No information about you or information provided by you during the research will be disclosed to other without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

Authorization to Publish Results:

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will remain confidential.

Financial Incentives for participation:

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

Compensation:

In the event of injury related to the study, treatment will be made available through KLES Hospital & MRC, Belgaum. There is no compensation or payment for such medical treatment by law.

Questions:

In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact Dept. Of Anaesthesiology, KLES Hospital and MRC, Belgaum.

Consent for participation in research trial

I, _____ voluntarily agree for the participation as a subject of study. By signing this consent form I am not giving up any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read form in vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name : _____

Signature or the Left Thumb Print of Subject : _____ Date :

Witness Name : _____ Signature: _____ Date :

Investigators Name: _____ Signature: _____ Date :

Place : _____

ANNEXURE II – PROFORMA

"COMPARISON OF ONSET AND DURATION OF SENSORY AND MOTOR BLOCKADE WITH INTRATHECAL ISOBARIC ROPIVACAINE VERSUS ISOBARIC ROPIVACAINE-CLONIDINE FOR INFRAUMBILICAL SURGERIES- A ONE YEAR HOSPITAL BASED RANDOMISED CONTROL TRIAL".

Name & Address of the patient:

Age of the Patient:_____ IP. No:_____

Weight of Patient:_____ Random No._____

Anaesthesiologist : _____ Surgeon : _____

PREANAESTHETIC EVALUATION :

Chief Complaints:

Past History:

1. HTN/ DM/Asthma/Drug allergy:
2. Drug therapy:
3. Previous exposure to anaesthesia

Family History

I. General Physical Examination:

Weight: Temperature:

Pallor/ Icterus/ Cyanosis/Clubbing/ Lymphadenopathy/ Oedema

Pulse : B.P: RR:

M.P Grading

Teeth: Mouth opening:

Jaw examination:

SYSTEMIC EXAMINATION:

Respiratory System:

Cardiovascular System:

Central Nervous system:

Per Abdomen:

Spine assessment:

INVESTIGATIONS:

Complete Blood count: RBS: Serum

Creatinine: Urine routine:

Chest X-ray:

ECG:

Any others:

Pre-operative physical status: ASA grade I II

Diagnosis:

Proposed Surgery:

Selection Criteria:

Inclusion

- Patients undergoing infra umbilical surgeries.
- Age: 18 to 60 years.
- ASA Grade I and Grade II patients
- Height: 150 cm - 180 cm

Exclusion

- Patient's refusal.
- Contraindications to sub arachnoid block like coagulopathy, local skin infection, raised intracranial pressure, spinal deformity.
- ASA grade III or IV patients.
- Patient allergic to study drugs.

Procedure:

After having met inclusion and exclusion criteria's and having obtained informed consent, patients will be randomized based on computer generated randomization table into one of the two groups.

- Group I: Will receive 3ml of 0.75% Ropivacaine
- Group II: Will receive 3 ml of 0.75% Ropivacaine + 15mcg Clonidine.

Anaesthesiologist involved in the data collection as well as the patient will be blinded to the content of the study solution.

Preoperatively the patient's intravenous (IV) line will be secured with either 18 G or 20 G branula and IV ringer lactate solution is started at 15 ml/kg half an hour before spinal anaesthesia. The patient then will be shifted to the operation theater and monitors like electrocardiograph (ECG), pulse oximeter and non-invasive blood pressure will be attached and baseline reading is taken. The patient will be placed in the lateral position.

Under strict aseptic precautions spinal puncture will be performed at L_3-L_4 sub arachnoid space with 23 G Quinckes spinal needle and the study drug is injected at a rate of 1 ml/ 15 seconds. Patient is then placed in supine position immediately.

Sensory block will be assessed using alcohol swab in mid clavicular line. T_{10} will be taken as the level for onset of sensory blockade and recovery time for sensory blockade will be defined as two dermatome regression of anaesthesia from highest level. Motor block will be assessed immediately after sensory block assessment using a modified bromage scale.

- Bromage 0- free movement of legs and feet, with ability to raise extended leg.
- Bromage 1- inability to raise extended leg and knee flexion is decreased, but full flexion of ankle and feet is present.
- Bromage 2- inability to raise leg or flex knees, flexion of ankle and feet present.
- Bromage 3, inability to raise leg, flex knee or ankle, or move toes.

Motor block onset will be taken as the time to reach modified bromage score 3 and total duration of motor block will be taken as the time for return to modified bromage score 0.

Sensory and motor block will be assessed at time intervals: 0, 5, 10, 15, 20, 25 and every 15 minutes till there is two segment regression in sensory block and motor block regress completely (i.e. modified bromage score= 0). All durations will be calculated considering the time of injection as time zero.

Blood pressure and Heart rate will be recorded at 2, 4, 6, 8, 10, 15, 20, 25, 30 minutes and every 10 minutes till the end of surgery. Hypotension will be defined as decrease in systolic B.P by 30% from baseline values or a systolic B.P less than 90 mm of Hg and will be treated with a bolus administration of intravenous fluids and with incremental intravenous boluses of Inj mephentermine sulphate 3

mg. Bradycardia will be defined as decrease in heart rate less than 60 beats per minute and will be treated with intravenous Inj Atropine sulphate 0.6 mg IV. Supplementary oxygen will be given through face mask.

Preoperative baseline values

HR: **SBP:** **DBP:** **MAP:**

Monitors attached

Pulse oximetry : NIBP :

ECG:

II. Vital parameters:

Time	**HR**	**Blood pressure**			**$Sp0_2$**
		SBP	**DBP**	**MAP**	
2 min					
4 min					
6 min					
8 min					
10 min					
15 min					
20 min					
25 mm					
30 min					
40 min					
50 min					
↓					
↓					

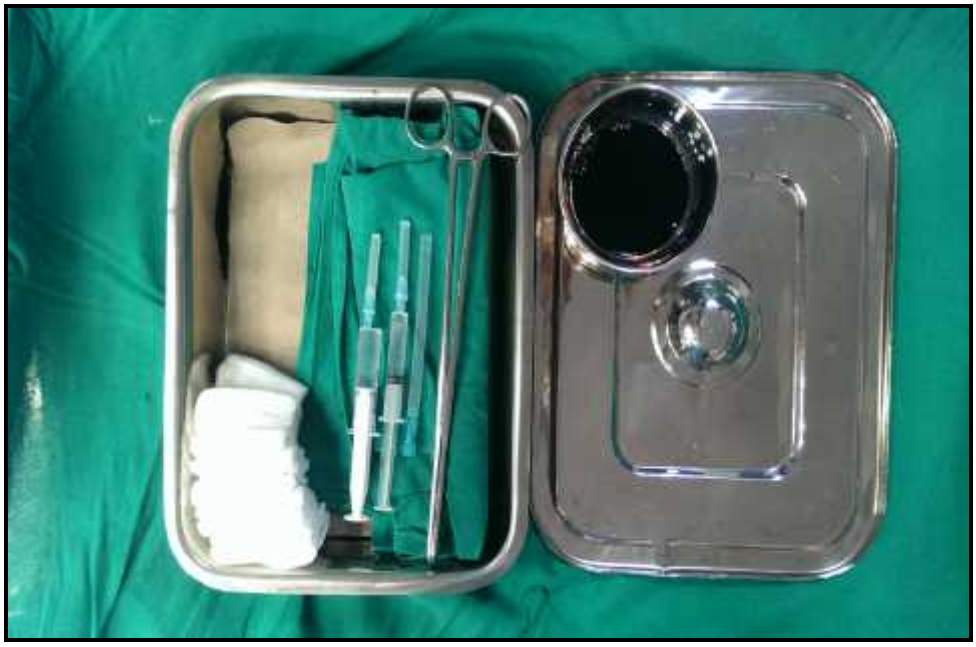
↓ Recovery from spinal anaesthesia					

Time(mins)	Sensory blockade	Motor blockade
0 mins		
5 mins		
10 mins		
15 mins		
20 mins		
30 mins		
45 mins		
60 mins		
75 mins		
90 mins		
↓		
Till recovery from spinal anaesthesia		

ANNEXURE III – PHOTOGRAPHS

Photograph 1. Isobaric Ropivacaine 0.75%

Photography 2. Clonidine Hydrochloride



Photograph 3. Spinal tray

Photograph 4. Spinal anaesthesia

Photograph 5. Monitoring haemodynamic parameters

Serial Number	In Patient Number	Gender	Age (Years)	Weight (Kg)	ASA Grade	Sensory block		Motor block		Observations at regular intervals (Time in minutes)																																			
										4				10				15				20				25				30				40				50				60			
						Onset (Min)	Duration (Min)	Onset (Min)	Duration (Min)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg	HR (/Min)
1	489455	M	60	70	1	10	180	15	225	136	80	99	116	105	64	78	62	95	56	69	60	125	85	98	87	113	68	83	71	112	68	83	78	108	72	84	84	110	63	79	88	108	72	84	84
2	480085	F	30	48	1	10	165	15	210	112	70	84	64	108	70	83	66	96	58	71	62	113	54	74	63	91	52	65	62	94	51	65	60	92	53	66	62	100	64	76	61	94	51	65	63
3	495796	F	35	49	1	5	195	10	240	113	72	86	72	107	68	81	73	104	69	81	78	107	66	80	82	104	71	82	71	109	80	90	88	107	66	80	80	113	72	86	81	104	69	81	84
4	484320	F	30	60	1	10	180	15	225	99	66	77	78	104	72	83	78	103	70	81	76	116	76	89	78	119	88	98	77	114	68	83	78	109	65	80	76	107	62	77	77	114	68	83	77
5	481793	M	25	70	1	10	195	10	240	112	78	89	62	110	80	90	68	110	69	83	64	108	70	83	66	104	68	80	66	104	66	79	68	102	64	77	70	110	64	79	72	128	80	96	80
6	481468	M	25	68	1	10	210	15	255	117	64	82	92	120	90	100	90	121	96	104	89	110	63	79	90	108	72	84	91	120	90	100	92	121	96	104	90	107	72	84	89	110	63	79	88
7	470196	F	40	50	1	10	180	15	225	145	86	106	74	145	86	106	80	150	89	109	84	152	89	110	88	145	86	106	84	148	100	116	79	138	94	109	88	148	100	116	84	145	86	106	88
8	473292	M	58	60	1	15	195	15	240	120	90	100	89	110	63	79	92	107	66	80	90	104	69	81	89	110	71	84	87	114	74	87	86	113	72	86	88	107	68	81	88	110	70	83	88
9	484320	M	18	56	1	10	165	10	225	139	91	107	103	126	79	95	88	125	82	96	88	113	73	86	96	113	68	83	88	112	68	83	84	110	63	79	80	115	71	86	88	113	73	86	84
10	473416	F	35	56	1	10	180	15	225	135	87	103	76	133	82	99	76	133	82	99	77	139	81	100	76	138	83	101	78	144	83	103	74	136	87	103	78	133	82	99	75	140	82	101	75
11	473628	M	59	60	1	10	165	10	210	133	84	100	77	138	84	102	78	139	81	100	77	140	82	101	80	142	86	105	84	135	87	103	88	133	82	99	79	142	87	105	89	135	87	103	76
12	479628	M	60	80	2	15	180	15	180	134	84	101	77	129	80	96	87	129	76	94	87	132	82	99	88	118	76	90	82	124	75	91	80	117	77	90	78	118	77	91	87	134	84	101	74
13	472218	F	32	42	1	10	165	10	225	125	85	98	74	108	72	84	70	110	63	79	68	115	71	86	72	114	71	85	74	105	64	78	78	115	71	86	76	114	70	85	77	125	85	98	77
14	472737	M	55	54	1	10	180	15	210	129	80	96	77	117	77	90	83	118	77	91	87	124	75	91	82	134	84	101	80	115	71	86	77	114	71	85	78	105	64	78	72	124	76	92	77
15	479194	F	59	64	1	15	195	15	240	121	96	104	92	120	92	101	88	110	63	79	83	107	72	84	90	105	73	84	91	106	73	84	92	113	72	86	90	114	74	87	89	115	90	98	88
16	477098	F	37	54	1	10	180	15	225	90	61	71	108	98	66	77	106	91	66	74	109	90	58	69	110	93	61	72	107	77	49	58	108	92	59	70	107	97	68	78	108	100	68	79	102
17	473160	M	54	74	1	10	165	15	180	139	81	100	78	144	83	103	80	142	86	105	81	140	82	101	80	142	87	105	88	140	82	101	84	133	82	99	86	135	87	103	87	134	88	103	87
18	481791	F	55	64	1	10	180	10	210	107	66	80	74	110	71	84	70	106	70	82	72	104	69	81	74	107	66	80	86	105	73	84	82	107	66	80	84	113	72	86	83	106	72	83	85
19	480962	M	54	70	1	15	195	15	225	114	86	95	110	109	80	90	109	105	73	84	104	106	73	84	103	118	77	91	104	118	76	90	103	114	86	95	102	115	88	97	104	117	86	96	101
20	481876	M	48	80	1	10	165	15	240	127	88	101	83	118	83	95	75	119	84	96	74	115	73	87	84	110	63	79	88	108	72	84	82	107	72	84	84	118	83	95	80	110	70	83	82
21	483644	M	32	70	1	15	180	15	225	143	88	106	66	148	86	107	69	148	86	107	62	140	84	103	61	142	86	105	69	140	82	101	70	142	83	103	62	144	81	102	68	140	83	102	68
22	462321	M	60	74	2	10	195	15	225	105	58	74	88	101	67	78	76	118	78	91	81	120	76	91	62	118	78	91	70	113	75	88	66	116	74	88	62	116	76	89	68	116	77	90	70
23	481889	M	22	74	1	10	165	15	210	138	84	102	78	133	82	99	80	140	82	101	81	142	86	105	78	135	87	103	77	142	87	105	79	140	82	101	80	133	82	99	81	136	88	104	80
24	471692	M	23	70	1	10	180	10	240	142	87	105	82	135	87	103	84	142	86	105	82	140	82	101	83	133	82	99	84	136	87	103	82	139	81	100	81	138	84	102	80	138	84	102	79
25	484395	M	53	74	1	10	165	15	210	113	72	86	72	107	68	81	73	104	69	81	78	107	66	80	82	104	71	82	88	109	80	90	80	107	66	80	87	113	72	86	82	112	80	91	80
26	484395	M	32	64	1	15	195	10	225	110	72	85	85	108	70	83	84	110	70	83	80	115	72	86	83	112	71	85	84	112	77	89	82	115	75	88	80	115	74	88	87	112	77	89	81
27	473218	F	49	48	1	10	180	15	225	112	71	85	74	110	70	83	74	108	70	83	76	110	80	90	77	100	60	73	74	110	70	83	76	112	77	89	77	115	84	94	87	114	67	83	80
28	480358	M	35	72	1	10	165	15	240	113	72	86	80	107	68	81	76	104	69	81	78	107	69	82	77	107	66	80	78	104	71	82	80	109	80	90	82	113	72	86	87	108	65	79	81
29	483614	M	53	70	1	10	180	15	225	115	75	88	82	110	70	83	88	108	70	83	82	108	72	84	83	110	80	90	84	100	66	77	88	114	73	87	82	116	85	95	86	112	76	88	85
30	480967	M	60	60	1	10	180	15	225	123	82	96	88	138	84	102	82	139	81	100	80	133	82	99	88	140	82	101	84	142	86	105	83	135	87	103	82	142	87	105	88	136	85	102	88
31	480350	F	60	64	1	15	180	15	225	116	75	89	82	106	70	82	77	107	68	81	73	104	69	81	72	107	66	80	74	104	71	82	70	109	80	90	68	107	66	80	69	108	75	86	72
32	483110	M	40	76	1	10	195	10	210	122	77	92	81	115	74	88	82	103	74	84	88	96	61	73	89	108	68	81	90	105	68	80	88	104	66	79	84	108	68	81	83	106	76	86	85
33	480259	F	34	64	1	15	165	15	240	133	82	99	88	136	87	103	72	138	84	102	78	142	87	105	82	140	82	101	83	139	81	100	80	138	84	102	81	133	82	99	82	134	80	98	80
34	486936	M	52	62	1	5	210	10	255	111	68	82	93	116	87	97	82	112	84	93	81	110	72	85	78	104	87	93	86	119	85	96	84	112	86	95	88	112	76	88	84	114	76	89	80
35	480967	M	60	68	1	10	180	15	225	122	77	92	83	115	74	88	76	103	64	77	72	103	60	74	69	96	61	73	66	108	68	81	64	105	68	80	72	104	66	79	66	98	63	75	64

Serial Number	In Patient Number	Gender	Age (Years)	Weight (Kg)	ASA Grade	Sensory block		Motor block		Observations at regular intervals (Time in minutes)																																			
										4				10				15				20				25				30				40				50				60			
						Onset (Min)	Duration (Min)	Onset (Min)	Duration (Min)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg	HR (/Min)	SBP (mm Hg)	DBP (mm Hg	MBP (mm Hg	HR (/Min)	SBP (mm Hg)	DBP (mm Hg	MBP (mm Hg	HR (/Min)	SBP (mm Hg)	DBP (mm Hg	MBP (mm Hg	HR (/Min)	SBP (mm Hg)	DBP (mm Hg	MBP (mm Hg	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg)	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg	HR (/Min)	SBP (mm Hg)	DBP (mm Hg	MBP (mm Hg	HR (/Min)
1	#####	M	40	70	1	10	180	15	270	120	90	100	80	117	64	82	78	121	96	104	78	107	72	84	74	121	96	104	78	120	90	100	77	110	64	79	80	120	96	104	84	120	90	100	88
2	#####	M	30	64	1	10	195	10	285	119	81	94	85	115	75	88	88	112	71	85	83	115	77	90	92	117	64	82	91	120	90	100	89	119	81	94	88	112	71	85	84	115	75	88	85
3	#####	M	30	60	1	15	165	10	270	84	55	65	60	95	66	76	66	94	63	73	72	95	62	73	72	91	60	70	76	94	55	68	66	95	66	76	68	95	62	73	64	94	55	68	65
4	#####	F	32	54	1	10	195	10	300	115	75	88	78	110	70	83	74	108	70	83	72	108	72	84	74	110	80	90	76	100	60	73	78	110	70	83	77	110	70	83	79	110	70	83	78
5	#####	F	37	54	1	10	210	15	255	110	70	83	88	112	71	85	80	112	77	89	82	108	74	85	80	110	73	85	78	114	72	86	74	114	70	85	76	112	70	84	77	118	81	93	74
6	#####	M	50	60	2	10	195	10	270	108	80	89	72	112	77	89	76	115	75	88	74	110	82	91	72	108	80	89	70	119	81	94	72	112	77	89	74	115	75	88	76	120	80	93	84
7	#####	M	28	72	1	15	225	15	240	109	65	80	60	106	63	77	69	108	61	77	68	113	65	81	70	104	61	75	70	104	59	74	69	114	65	81	65	122	66	85	69	114	65	81	69
8	#####	M	52	70	1	10	195	10	270	103	70	81	83	99	64	76	82	106	68	81	88	119	88	98	84	99	66	77	82	116	75	89	83	114	75	88	82	116	75	89	80	119	88	98	86
9	#####	M	55	60	1	10	195	10	255	124	80	95	77	114	74	87	77	112	70	84	74	110	88	95	76	112	88	96	74	114	74	87	76	110	76	87	77	112	74	87	78	114	74	87	77
10	#####	M	35	62	1	15	225	10	270	113	65	81	88	107	62	77	84	108	61	77	86	106	63	77	80	104	59	74	78	104	61	75	76	106	63	77	74	114	65	81	76	110	80	90	74
11	#####	M	24	64	1	10	210	15	300	116	76	89	70	115	75	88	76	112	77	89	68	122	83	96	66	119	81	94	68	122	76	91	66	120	80	93	68	122	76	91	69	130	80	97	78
12	#####	M	54	74	1	10	165	15	255	115	77	90	88	120	80	93	82	119	80	93	70	114	77	89	72	115	74	88	74	112	78	89	72	112	71	85	73	115	77	90	74	122	76	91	78
13	#####	M	60	62	1	10	180	10	270	110	80	90	73	115	77	90	77	110	70	83	76	108	70	83	78	108	72	84	77	110	80	90	74	110	60	77	78	110	70	83	78	120	70	87	78
14	#####	M	39	70	1	15	195	10	300	137	86	103	67	139	92	108	62	130	80	97	64	128	80	96	66	132	80	97	64	130	80	97	62	130	80	97	62	132	80	97	65	128	80	96	96
15	#####	M	45	70	1	10	210	15	300	107	62	77	65	113	65	81	61	108	61	77	62	107	62	77	63	109	65	80	64	114	68	83	65	114	65	81	66	122	64	83	67	114	68	83	65
16	#####	M	50	66	1	5	210	10	300	108	80	89	84	112	77	89	78	112	71	85	77	115	75	88	72	110	70	83	77	116	75	89	74	116	75	89	76	110	70	83	86	116	75	89	73
17	#####	M	28	72	1	10	195	10	270	123	72	89	80	120	71	87	76	116	69	85	74	118	72	87	72	120	70	87	70	124	74	91	76	123	72	89	68	121	72	88	66	114	74	87	78
18	#####	M	60	64	1	10	180	10	255	112	71	85	72	122	83	96	77	119	81	94	78	122	76	91	77	110	70	83	76	110	80	90	74	108	70	83	78	110	70	83	77	119	81	94	74
19	#####	M	52	70	1	10	195	10	270	122	66	85	84	104	59	74	82	104	61	75	88	113	65	81	84	106	63	77	82	108	61	77	88	107	62	77	84	109	65	80	82	113	65	81	84
20	#####	M	20	62	1	10	210	15	285	122	64	83	68	104	61	75	62	113	65	81	62	106	63	77	57	108	61	77	55	107	62	77	68	109	65	80	60	114	68	83	54	108	61	77	60
21	#####	M	47	65	2	10	225	10	300	115	77	90	76	112	77	89	74	110	70	83	74	114	68	83	76	113	65	81	72	114	65	81	70	122	64	83	72	122	66	85	71	120	80	93	74
22	#####	M	40	72	1	10	195	10	270	115	75	88	72	110	70	83	77	119	81	94	72	118	81	93	78	117	80	92	76	110	70	83	77	110	80	90	68	110	78	89	66	110	80	90	77
23	#####	M	25	70	1	15	195	10	255	110	80	90	72	118	81	93	78	119	81	94	78	110	70	83	77	115	77	90	78	112	71	85	74	115	75	88	78	112	77	89	70	115	75	88	75
24	#####	M	53	63	1	10	180	10	270	108	70	83	76	118	77	91	74	116	74	88	76	112	76	88	80	104	78	87	88	104	77	86	86	103	74	84	84	104	77	86	88	120	80	93	74
25	#####	F	42	62	1	10	210	10	240	118	76	90	76	108	77	87	66	106	76	86	64	104	64	77	62	104	68	80	64	106	77	87	66	104	70	81	68	104	70	81	68	104	77	86	70
26	#####	F	32	56	1	10	195	10	270	108	70	83	80	120	74	89	77	114	77	89	80	112	76	88	84	110	64	79	86	114	76	89	88	112	68	83	88	110	66	81	74	112	76	88	80
27	#####	M	60	70	1	10	195	10	240	115	75	88	74	110	70	83	78	108	70	83	70	108	70	83	68	112	71	85	70	112	77	89	77	112	74	87	78	108	70	83	76	115	75	88	78
28	#####	M	58	72	2	10	180	10	285	110	70	83	83	114	77	89	80	120	88	99	82	114	70	85	80	122	74	90	74	116	76	89	70	124	78	93	74	130	77	95	82	122	74	90	74
29	#####	F	60	60	1	10	165	15	270	108	80	89	73	106	70	82	77	104	70	81	78	110	70	83	76	112	77	89	77	115	75	88	76	112	71	85	78	115	77	90	77	115	75	88	76
30	#####	F	45	52	1	10	140	15	240	116	76	89	64	100	66	77	70	99	64	76	67	99	66	77	68	106	68	81	68	115	75	88	68	112	77	89	69	115	77	90	70	119	88	98	65
31	#####	F	36	54	1	10	195	10	270	99	66	77	70	104	72	83	74	103	70	81	70	116	76	89	88	119	88	98	84	120	80	93	86	110	70	83	88	119	81	94	90	119	81	94	78
32	#####	F	30	60	1	10	165	15	285	120	80	93	82	122	78	93	70	120	74	89	68	118	74	89	66	118	76	90	70	120	74	89	72	120	80	93	73	124	80	95	77	120	80	93	74
33	#####	F	42	52	1	10	180	10	255	116	70	85	76	118	80	93	68	120	80	93	74	110	76	87	78	110	78	89	76	110	78	89	77	118	80	93	74	118	80	93	78	130	80	97	78
34	#####	F	25	49	1	10	195	10	270	114	75	88	77	115	71	86	77	114	71	85	78	105	64	78	84	112	68	83	78	113	68	83	78	114	71	85	74	114	71	85	74	124	88	100	75
35	#####	F	45	54	1	10	165	10	285	110	70	83	80	115	77	90	72	119	81	94	70	110	78	89	74	110	80	90	73	110	70	83	78	122	83	96	77	110	80	90	72	122	76	91	83

ANNEXURE IV – KEY TO MASTER CHART

ASA	-	American Society of Anaesthesiologists
DBP	-	Diastolic blood pressure
F	-	Female
HR	-	Heart rate
Kg	-	Kilogram
M	-	Male
MAP	-	Mean arterial pressure
Min	-	Minute
mm Hg	-	Millimeter of mercury
SBP	-	Systolic blood pressure