"THE EFFECT OF INTRATHECAL CLONIDINE AS AN ADJUVANT TO HYPERBARIC BUPIVACAINE ON POSTOPERATIVE ANALGESIC REQUIREMENTS IN PATIENTS UNDERGOING LOWER ABDOMINAL SURGERIES - A RANDOMISED CONTROLLED TRIAL"

BY

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DISSERTATION

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ANAESTHESIOLOGY

UNDER THE GUIDANCE OF

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KLE UNIVERSITY, BELGAUM, KARNATAKA

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"THE EFFECT OF INTRATHECAL CLONIDINE AS AN ADJUVANT TO HYPERBARIC BUPIVACAINE ON POSTOPERATIVE ANALGESIC REQUIREMENT IN PATIENTS UNDERGOING LOWER ABDOMINAL SURGERIES- A RANDOMIZED CONTROLLED TRAIL"** *is a bonafide and genuine research work carried out by me under the guidance of* **Dr. RAJESH MANE** **MD,DNB** *Associate Professor, Department of Anaesthesiology, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum-590010.*

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ABBREVIATIONS

ASA- American Society of Anaesthesiologists

aPTT- Activated partial thromboplastin time

BP- Blood pressure

C- Cervical

CNS- Central nervous system

cms- Centimeters

CSF- Cerebrospinal fluid

CVS- Cardio vascular system

DBP- Diastolic blood pressure

ECG- Electrocardiogram

G- Gauge

HR- Heart rate

Hr- Hour

Inj- Injection

IV- Intravenous

IM- Intramuscular

Kg- Kilograms

L- Lumbar

mg - Milligrams

mL- Milliliters

min - Minute

mEq- Milliequivalents

MAP- Mean arterial pressure

PT- Prothrombin time

RR- Respiratory rate

SAB- Subarachnoid block

SBP- Systolic blood pressure

T- Thoracic

µg- Micrograms

ABSTRACT

Background

Postoperative pain besides its psychological effects, causes restlessness, excitability, tachycardia and increased oxygen consumption. Opioid analgesics commonly used to provide analgesia are associated with sedation, respiratory depression and PONV. Intrathecal clonidine prolongs spinal anaesthesia by its potent anti nociceptive effect mediated by α-2 adrenergic receptors. We investigated the effect of the addition of clonidine (30µg) to hyperbaric bupivacaine on postoperative pain relief and the analgesic requirement in postoperative period.

Objective

To determine the effect of intrathecal clonidine as an adjuvant to hyperbaric bupivacaine on postoperative analgesic requirements in patients undergoing lower abdominal surgeries.

Study design

A randomized controlled trial.

Methods

Sixty ASA I-II posted for various lower abdominal surgeries under spinal anesthesia using hyperbaric 0.5% bupivacaine were randomly allocated into two groups of thirty each. Group B received 3ml of hyperbaric 0.5% bupivacaine with 0.2 ml of normal saline and Group BC received 3ml of hyperbaric 0.5% bupivacaine with 0.2ml of clonidine (30µg). Pain was assessed in the PACU and later in the ward by a trained nursing staff blinded to the study for a period of 24 hrs. Pain scores were assessed every hourly and when it exceeded 3 on VAS injection

Diclofenac 50mg IM as rescue analgesic was administered. The time to first rescue analgesic administration and total analgesic dose for 24 hrs was noted.

Results

The mean duration of analgesia in Group B and Group BC were 4.91±1.41 and 7.46±2.18 hrs respectively and the mean analgesic requirements in Group B and BC were 170.83±54.57 and 121.67±49.01 mgs respectively. There was significant difference between two groups with P value <0.001.

Conclusion

From our study we conclude that administration of clonidine as adjuvant to hyperbaric bupivacaine spinal anaesthesia for abdominal surgeries increases the duration of analgesia and reduces the postoperative analgesic requirements.

Key words

Spinal anaesthesia, intrathecal clonidine, postoperative analgesia

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INTRODUCTION

Surgery leads to severe tissue damage and surgical pain or "post operative pain" is a universal phenomenon experienced by all patients, yet paradoxically after all the efforts taken to make intraoperative period pain free and stress free, the patients experience significant pain in the postoperative period.

The surgical stress response peaks during the postoperative period and has major effects on almost all body systems. A pain and stress free postoperative period definitely reduces morbidity and mortality due to any surgery.

Spinal anaesthesia[1] is a popular and common anaesthetic for technique used worldwide for lower abdominal surgeries. The advantages of an awake patient, minimal drug cost, relatively less side effects has made this the choice of many a surgical procedure. It is also simple to perform, economical and produces rapid onset of anaesthesia and complete muscle relaxation.

Spinal anaesthesia was introduced into clinical practice by Karl August Bier in1898.[2] More than a century has passed and even today still remains one of the most popular techniques for both elective and emergency surgical procedures particularly Caesarean Sections, lower abdominal surgeries, orthopedic and urological surgeries.[3]

Hyperbaric bupivacaine is the most common local anaesthetic used for sub-arachnoid block.

The major disadvantage with spinal anesthesia using hyperbaric bupivacaine alone is relatively shorter duration of action, which means that early analgesic intervention is needed in the postoperative period. Additives like benzodiazepines, synthetic and semi synthetic opioids, NMDA receptor antagonists and anticholinesterases are the common adjuvant used for prolongation of post operative analgesia with variable benefits and side-effects. Hence the search for ideal analgesic agent still persists.

Clonidine is an alpha-2 agonist originally developed in 1962 for use as a nasal decongestant and later used as an anti-hypertensive agent. Its unique mechanism of action and ability to modify both central and peripheral adrenergic transmission prompted to investigate its therapeutic potential in providing pain relief.

There are quite a very few studies of its use through epidural route but minimal with intrathecal administration.

Hence this study is an attempt to evaluate the effectiveness of using intrathecal clonidine with hyperbaric bupivacaine on postoperative pain relief in patients undergoing lower abdominal surgeries.

OBJECTIVES

The objectives of the present study were:

To determine the effect of addition of intrathecal clonidine (30µg) to 0.5% hyperbaric bupivacaine on:

1. Duration of postoperative analgesia.

2. The analgesic requirement in first 24 hrs of post-operative period.

REVIEW OF LITERATURE

HISTORICAL REVIEW:

Spinal anaesthesia also referred to as subarachnoid block, intrathecal analgesia or central neuraxial blockade, has fascinating historical background.

In the year 1885, J. Leonard Corning, a New York Neurologist injected cocaine into the subarachnoid space by accidentally piercing the dura while experimenting on a dog. Later he deliberately repeated the intradural injection of 60 minims of 3% cocaine and suggested it might be used in surgery.

"Be the destiny of this observation, what it may. It had seemed to me, on the whole worth recording", were his words.

On 16th of August 1898, Keil August Bier performed the first planned spinal anaesthesia in man. He injected 3ml of 0.5% cocaine into the subarachnoid space of a 34 years old labourer for the operation on the lower limb. After using it on 6 patients, he and his assistant injected cocaine into each other's theca.

Heinrich Iraneus Quincke of Keil in Germany standardized the lumbar puncture

as a simple procedure in 1891.In the same year Essex Wynter described lumbar puncture in England.

Heinrich Braun, a German Surgeon in 1905 reported the use of procaine for spinal anaesthesia. He also reported the use of intrathecal epinephrine to prolong the duration of spinal anaesthesia but it was not accepted because of the fear of neurologic complications. It was only in 1945 Prickett and his associates published their report on the neurologic safety of intrathecal epinephrine to prolong the duration of spinal anaesthesia.

The technique of spinal anaesthesia was eventually well accepted all over globe and many reports were published on its usage. In the following years, the popularity of spinal anaesthesia steadily increased with the introduction of newer drugs and techniques and is the commonest method in the anaesthesia armamentarium and since then advent various methods are being tried to prolong its duration of anaesthesia.

Clonidine is a selective partial alpha 2 adrenergic agonist with a selectivity ratio of about 200:1 in favour of alpha 2 receptors. The intrinsic analgesic effect of clonidine has been demonstrated with large doses of clonidine alone given intrathecally or epidurally to control both intraoperative and postoperative pain.

Elia N, Culebras X, Mazza C, Schiffer E, conducted a metaanalysis which

included data from 22 randomised trials testing a large variety of doses of clonidine added to intrathecal bupivacaine, mepivacaine, prilocaine, or tetracaine and concluded that addition of clonidine to hyperbaric bupivacaine significantly prolonged the duration of sensory and motor blockade and lesser episodes of intraoperative pain but more episodes of arterial hypotension without evidence of dose responsiveness.[4]

Spinal clonidine is more efficacious then oral clonidine in patients posted for lower abdominal surgeries under spinal anesthesia was proved by Bonnet F et al.[5]

Dobrydnjov I, Axelsson K et al conducted a study to find out perioperative effects of intrathecal and epidural clonidine combined with local anaesthetic in sixty patients undergoing hip arthroplasty and concluded that low dose (15µg) of clonidine added to 17.5mg of plain bupivacaine for spinal anaesthesia provided a better quality of anaesthesia and long lasting analgesia with reduced consumption of rescue analgesic and decreased VAS score compared to plain bupivacaine. The maximal upper level of sensory block measured by pin-prick (T6-T7) did not differ between the groups while the partial sensory block for cold and warmth were increased by two dermatomes above pin-prick level in group with intrathecal clonidine compared to other two groups ($P< 0.05$).[6]

A study in children between the age group of 6-15 years old was conducted with 2µg/kg clonidine added to 0.5% hyperbaric bupivacaine and the quality and length of

motor and sensory blocks and side effects viz hypotension, bradycardia and sedation were assessed. Kaabachi O, Ben Rajeb A, Mebazaa M, Safi H observed that addition of clonidine led to prolongation of postoperative analgesia and insignificant motor block with a higher incidence of hypotension and bradycardia and hence concluded that intrathecal clonidine is associated with increased duration of postoperative analgesia but with moderate side effects.[7]

Clonidine in addition to clinically relevant analgesic action when administered spinally also has a hypotensive action. Niemi L et al conducted a study in which forty ASA I-II patients undergoing knee arthroscopy under spinal anaesthesia were randomised into two groups, one group received clonidine 3µg/kg mixed with 15mg 0.5% heavy bupivacaine and in the other group an identical volume of saline was mixed with bupivacaine to find out the analgesic and circulatory effects of intrathecal clonidine. They concluded that addition of clonidine prolonged the bupivacaine spinal block but marked hemodynamic changes and sedation may limit the usefulness of intrathecal clonidine.[8]

The efficacy of clonidine in prolongation of postoperative analgesia in unilateral spinal anaesthesia was studied by De Negri P, Borrelli F, Salvatore R, Visconti C, De Vivo P, Mastronardi P in a prospective randomised study where 56 patients underwent minor surgical procedure (spermatic vein ligature) under unilateral spinal anaesthesia with hyperbaric bupivacaine 1%. One half of patients received clonidine (105 micrograms) in addition to bupivacaine. MAP, HR, cardiac output, stroke volume,

ejection fraction, systemic vascular resistance and left cardiac work were measured. They observed that patients in the clonidine group had significant prolongation in sensory and motor block, a higher sedation level and a significant postoperative analgesia with minimal variations in hemodynamic parameters and concluded that the addition of clonidine to hyperbaric bupivacaine seems to be particularly useful in unilateral spinal anaesthesia, exerting minimal influence on hemodynamic parameters and satisfactory postoperative analgesia.[9]

Clonidine has also been shown to shorten the onset time of sensory and motor blockade. In a study G.E.Kanazi et al concluded that addition of 30 µg of clonidine to 12mg of hyperbaric bupivacaine reduced the time to reach T10 sensory block (Group Bupivacaine 9.7±4.2 mins group clonidine 7.6±4.4) with subsequent increase in sensory and motor regression times. The MAP, HR and level of sedation were similar in the three groups intropera tively and postoperative period.[10]

Clonidine is equally effacious when used with isobaric bupivacaine. Strebel Stephan, Gurzeler, Jurg A, Schneider conducted a study to evaluate the effect of clonidine (15-150µg) with isobaric bupivacaine and concluded that small doses of intrathecal clonidine <150 µg significantly prolong the anaesthetic and analgesic effects of bupivacaine in a dose dependent manner.[11]

Clonidine carries the same beneficial effects of prolongation of sensory and motor

block with minimal foetal or neonatal complications when used during Caesarean section. I. Van Tuijl, W. A. van Klei et al concluded that the addition of clonidine (75µg) to hyperbaric bupivacaine prolongs spinal anaesthesia after Caesarean section and improves early analgesia, but does not reduce the postoperative morphine consumption during the first 24hrs. No clinically relevant maternal or neonatal side-effects were detected.[12]

Spinal anaesthesia with intrathecal clonidine are known to have hypnotic effects. Jang, Inseok MD confirmed that spinal anaesthesia and intrathecal clonidine reduce the requirement of propofol for sedation. The study showed target concentrations of propofol for sedation was 1.4 to 1.7 µg/mL using local anaesthesia only, 1.1 to 1.4 µg/mL using spinal anaesthesia with bupivacaine, and 0.7 to 0.9 µg/mL using spinal anaesthesia with bupivacaine and 75µg of clonidine.[13]

Thus studies and existing literature on clonidine with regards to its effectiveness, safety and side effects opine that, it is safe and effective analgesic. The intrathecal route is a tested mode, acceptable for its administration and also reduces the requirement of Opioid during postoperative period and does not cause clinically significant side effects and complications.

Hence, after reviewing the existing literature and existing practice of postoperative analgesia for lower abdominal surgeries in our institution and as

there were few systematic study of its use in lower doses, we decided to evaluate the effects of clonidine as an adjuvant to hyperbaric bupivacaine in postoperative pain relief.

ANATOMY

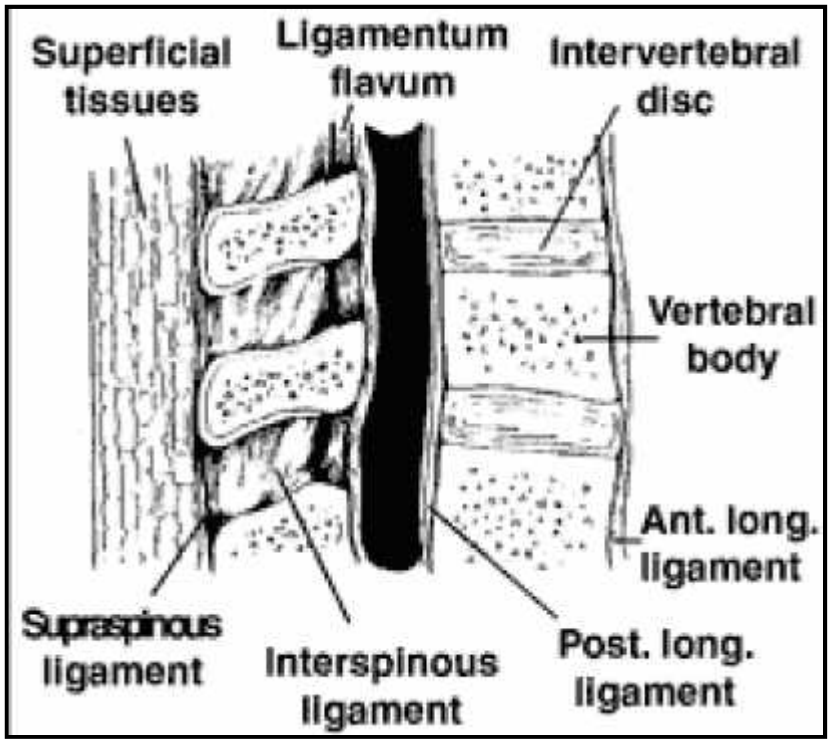


Fig 1: Vertical section at lumbar vertebra

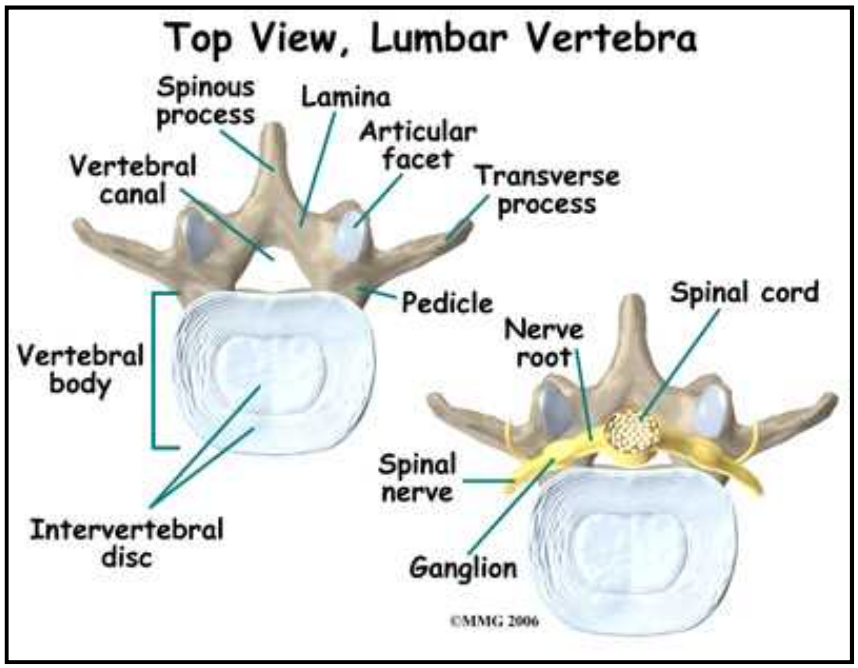


Fig 2: Typical lumbar Vertebra

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

The vertebral column comprises total of 33 vertebrae and includes 7 cervical, 12 thoracic, 5 lumbar, 5 fused sacral, and 4 coccygeal vertebrae. The vertebral column has 4 curves which have significant effect on spread of drugs in subarachnoid space. Cervical and lumbar curves are convex anteriorly whereas thoracic and sacral curves are convex posteriorly. The highest point of cervical and lumbar curves in supine position are at C5 and L5; lowest points of thoracic and sacral are at T5 and S2 respectively. Main function of vertebral column is to protect the spinal cord.

Vertebral ligaments

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

Supraspinous ligament: This is strong fibrous cord connects apices of spinous processes from sacrum to C5 where it is continued as the ligamentum nuchae.

Interspinous ligament: This is thin membranous ligament connects spinous processes blending anteriorly with ligamentum flavum and posteriorly with supraspinous ligament.

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.

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

Lumbar vertebrae

A typical lumbar vertebrae consists of

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

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 consists of spinal cord, spinal membranes, adipose tissue, blood vessels, CSF and the roots of the spinal nerves.

Spinal cord

The spinal cord which is the extension of central nervous system into the vertebral canal begins at the level of foramen magnum and ends below as conus medullaris. At birth spinal cord ends at the level of L3 but rises as the age progresses and reaches to lower border of L1 in adults. It measures about 42-45 cm.

The spinal cord receives blood supply from three arteries, one anterior and two posterior spinal arteries. Anterior spinal artery is single vessel lying in the substance of piamater overlying the anterior median fissure. It receives communications from intercostals, lumbar and other small arteries and 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 arises from posterior inferior cerebellar arteries at the level of foramen magnum. They supply posterior columns of the cord.

Spinal meninges

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

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

Arachnoid mater: It is the 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: It is the delicate highly vascular covering closely investing the spinal cord and brain.

Subarachnoid space

The space between the arachnoid and pia is called subarachnoid space and is filled with cerebrospinal fluid and contains numerous arachnoid trabaculae 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 subpial 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

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 ultrafilteration from the choroids arterial 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: 1.003-1.009 at 37˚C.

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

CSF pressure: 60-80 mm of Hg in lumbar space

pH: 7.27- 7.37

PCO2: 48 mm of Hg

HCO3:23 mEq/L

Sodium-135-145 mEq/L

Calcium:2-3 mEq/L

Phosphorous:1.6 mg/dl

Magnesium: 2-2.5 mEq/L

Chloride: 15-20 mEq/L

Proteins: 23-38 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 where as steroids have an inconsistent effect. Inhalational anaesthetics like isoflourane and vasoconstrictors decrease the CSF formation. CSF formation is decreased when the serum osmolality is increased when the serum is made hypotonic. During equilibrium rate of formation equals the rate of formation (500 ml/day).

PHYSIOLOGY OF SUBARACHNOID BLOCK

Physiological responses to intra and extra dural blockade results from autonomic blockade with its effects on both vascular beds and cardiac action from addition of somatic pain and the reflex responses associated with it and from the effects of blockade of motor fibres.

1) Autonomic blockade occurs in the following order:

Autonomic preganglionic B fibres> Temperature fibres> Pin prick fibres> Fibres conveying pain greater than pin prick> Touch fibres> Deep pressure fibres> Somatic motor fibres> Fibres conveying vibratory sense and proprioceptive impulses.

During recovery return of sensations in the reverse order assumed, but it has been suggested that sympathetic activity returns before sensation.

In SAB sympathetic fibres are blocked two to three segments higher than sensory fibres and sensory block is two segments higher than motor block effects of SAB on cardiovascular system.

Spinal block can influence CVS in various ways. Vasodilatation of resistance and capacitance vessels. Block of cardiac efferent sympathetic fibres from T_1-T_4 resulting in loss of chronotrophic and inotropic drive and fall in cardiac output. Bainbridge reflex causing bradycardia. 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 fibres 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.

- Diminished cardiac output due to reduction of venous return to heart and lack of muscular propulsive force in veins.
- Dilatation of post arteriolar capillaries and small venules due to paralysis of vasoconstrictors.

- Paralysis of sympathetic nerve supply to heart.
- Paralysis of sympathetic nerve supply to adrenal glands with catecholamine depletion. Ischemia and hypoxia of vital centres.
- Compression of great vessels in abdomen by pregnant uterus or abdominal tumours.

Effects of SAB on respiratory system

Due to motor blockade and deafferentation with reduction of sensory input to respiratory centre breathing quiet during spinal anaesthesia. Intercostal paralysis is compensated by descent of diaphragm which is made easier by lax abdominal wall. This is not accompanied by hypoxia or hypercapnia although the ability to cough forcibly to remove secretions is impaired. Spinal anaesthesia as such does not interfere significantly with gas exchange.

Effects of SAB on gastrointestinal system

SAB up to T5 results in, narrowing of gut and active peristalsis and hence leading to increase in intraluminal pressure. It also causes relaxation of sphincters, enlargement of spleen, nausea and vomiting.

Effects of SAB on endocrine system

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

Effects of SAB on genito-urinary system

Kidney function is not affected unless severe hypotension is present. The urinary bladder is relaxed and its sphincter is contracted leading to retention of urine. Post spinal injury retention may be moderately prolonged as L2-L3 contains small autonomic fibres and their paralysis lasts longer than that of larger sensory and motor fibres.

The engorgement of flaccid penis due to paralysis of nervigentis is often the first sign of successful block. The tone of uterus is not greatly altered after spinal anaesthesia in pregnancy.

Factors affecting height of analgesia in SAB

Specific gravity of solution

Position of patient during and after injection

Volume of solution

Concentration of drug

Rate force of injection

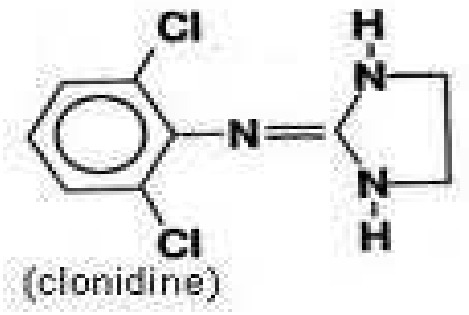
The site of injection

Pregnancy and intraabdominal tumours

CLONIDINE

Structure

Its chemical name is N-(2,6-dichlorophenyl)-4,5-dihydro-1H-imidazol-2-amine with the chemical formula $C_9H_9Cl_2N_3$.

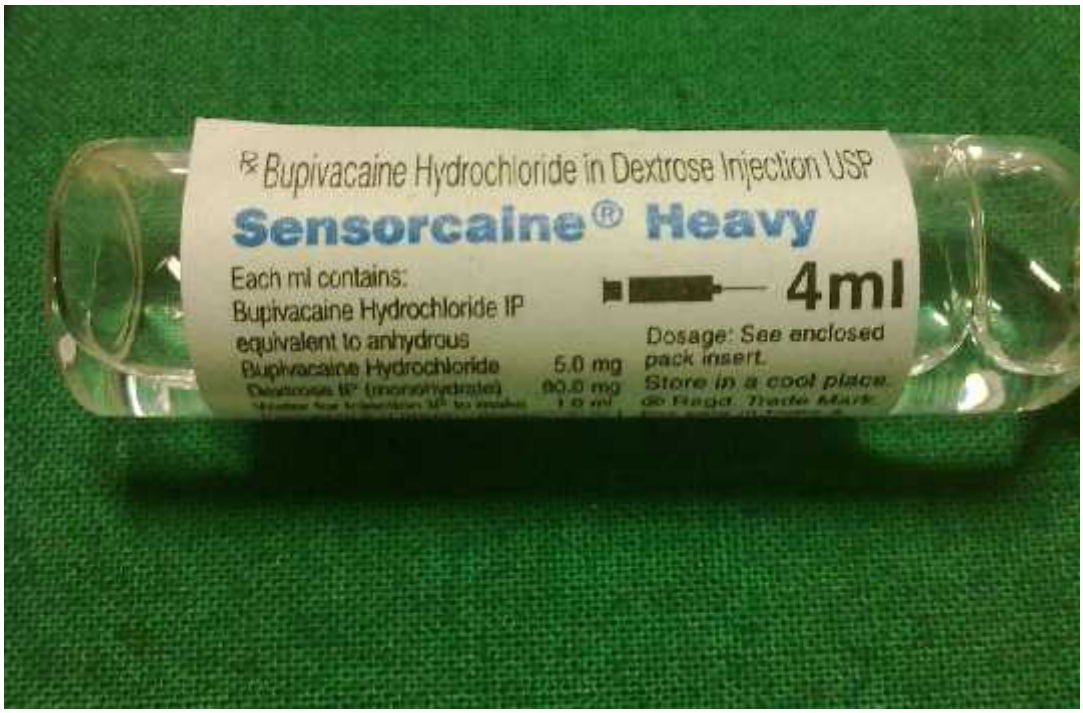


(clonidine)

Mechanism of action [14]

Clonidine is a selective partial αlpha 2 adrenergic agonist with a selectivity ratio of about 200:1 in favour of αlpha 2 receptors. It is lipid soluble and easily penetrates the blood brain barrier to reach the hypothalamus and the medulla when injected epidurally. It stimulates inhibitory αlpha 2 adrenoceptors to reduce central neural transmission in the spinal neurons. Inhibition of substance-P is believed to be involved in the analgesic effect. The analgesic action is through αlpha 2 receptors as shown by the partial reversal of the epidural clonidine analgesia and sedation, by the αlpha 2 adrenoceptor antagonists Yohimbine, although the affects on the blood pressure and heart rate were not reversed.

The αlpha 2 receptors are located on the afferent terminals of both peripheral and spinal neurons, on neurons in the superficial lamina of the spinal cord, and within several



Photograph 1: Injection Bupivacaine Hydrochloride

Photograph 2: Injection Clonidine Hydrochloride

brainstem nuclei implicated in analgesia. The possible site of analgesic action of clonidine is one or more of these locations.

Animal studies support the hypothesis of analgesic action of alpha 2 adrenergic agonists at all these sites but their relative importance is debated. The superficial lamina of the dorsal horn contains 3 groups of neurons: tonic, adapting, and single-spiking–firing; all of which are important neuronal structures for pain transmission, receiving, most of their primary sensory input from alpha, delta, and C fibres. Studies in rat model show that at clinical concentrations clonidine partially inhibits voltage gated Na+ and K+ channels and suppresses the generation of action potential in tonic firing spinal dorsal horn neurons. This may, in part, contribute to its analgesic effect.[15]

Some contribution to the analgesic effect may be through the release of acetylcholine in the neuraxial region. Acetylcholine concentration in the lumbar CSF increases after epidural clonidine by bolus or infusion; and epidural clonidine analgesia in volunteers is enhanced by the intrathecal injection of the cholinesterase inhibitor, neostigmine. This suggests that cholinergic mechanism may be involved, atleast in part, in analgesia due to neuraxially administered clonidine.

The alpha 2 adrenergic agonists also enhance analgesia from intraspinal opioids. In animals, this interaction is clearly synergistic when both drugs are administered

intrathecally. In contrast, epidural clonidine and fentanyl interact in an additive or minimal synergistic manner after bolus administration in humans and the dose of each component can be reduced by 60% when epidural clonidine and fentanyl are combined together for postoperative analgesia. The type of interaction between clonidine and opioids after the intrathecal administration has not been quantified.

Sedation usually accompanies the use of clonidine through its actions in the locus ceruleus. Sedation after epidural clonidine represents an alpha 2 adrenergic effect because it can be reversed by the antagonist, Yohimnine.[16]

Clonidine effects blood pressure in a complex fashion after neuraxial or systemic administration because of opposing actions at multiple sites. In the nucleus tractus solitaries and the locus cerelues of the brainstem, activation of the postsynaptic alpha 2 receptors reduces sympathetic drive. It also activates non-adrenergic imidazole-preferring binding sites in the lateral reticular activating system thereby producing hypotension and an anti-arrhythmogenic action. In the periphery, its action on the presynaptic alpha 2 receptors at sympathetic terminals reduces the release of norepinephrine causing vasorelaxation and reduced chronotropic drive. The brainstem and peripheral effects of alpha 2 receptors stimulation are counter balanced by direct peripheral vasoconstriction through its action on alpha 2 adrenoceptors from circulating concentrations of clonidine.[17] As a result, the dose response for clonidine by neuraxial or

systemic administration is U-shaped, with peripheral vasoconstriction from circulating drug concentrations at high doses opposing central sympatholysis.[14]

PHARMACODYNAMICS IN THE CONTEXT OF REGIONAL ANESTHESIA/ANALGESIA [14]

The analgesic effect of clonidine is more potent after neuraxial administration indicating a spinal site of action and favours neuraxial administration although it is possible to achieve analgesia from systemic administration as well. In volunteers, a single lumbar epidural bolus injection of clonidine produces analgesia in the lower, but not upper, extremity against a noxious stimulus as would be expected from a spinal action, when Clonidine was infused for 4 hrs in the lumbar epidural space in volunteers, analgesia spread to the upper extremity, suggesting that more extensive dermatomal distribution of analgesia is possible with continuous infusion.

Intrathecal injection of 150µg clonidine after caesarean section or minor orthopaedic surgery yields analgesia for 4-6hrs but injection of same dose by intramuscular or epidural routes produces no more analgesia than a placebo.

Cardiovascular System

Clonidine has a minor or no effects on responses to vasoconstrictors or atropine given to treat hypotension or bradycardia, respectively, that may occur with neuraxial anesthesia.[18] Clonidine pre-treatment delays the central nervous system and cardiovascular toxic manifestations of bupivacaine overdose in animals, without

accentuating the subsequent hypotension[19]. This does not imply that clonidine is a treatment for bupivacaine overdose but implies that should such an overdose occur, inclusion of clonidine is unlikely to exacerbate the problem.

Sedation

Clonidine produces a dose-dependent sedation at the dose of 50 µg or more in less than 20mins regardless of the route of administration. After a large epidural bolus dose of 700µg sedation is intense for 4-6 hrs. Several studies have demonstrated a reduced need for other sedatives and anxiolytics when clonidine is administered intraoperatively.[20,21]

Respiration

The αlpha 2 adrenergic agonists alone do not induce profound respiratory depression even after massive overdose, nor do they potentiate respiratory depression from opioids.[22,23,24]

Peripheral Nerves

Clonidine produces a minor degree of blockade at high concentrations with some preferences for C-fibres in the peripheral nerves and this effect may in part enhance peripheral nerve block when added to local anaesthetics, probably because the α 2 receptors are lacking on the axons of peripheral nerves.

Dosage guidelines for intrathecal route

A 15-30 µg of clonidine added to local anaesthetic agent provides most of the benefits without any significant side effects. The maximum dose is 1ug/kg body weight.

Drug interactions

Clonidine may potentiate the CNS depressive effect of alcohol, barbiturates or other sedating drugs. Narcotic analgesics may potentiate the hypotensive effects of clonidine. Tricyclic antidepressants may antagonize the hypotensive effects of clonidine. The effects of tricyclic antidepressants on clonidine's analgesic actions are not known. Concomitant administration of drugs with a negative chronotropic or dromotropic effect can cause or potentiate bradycardia and rhythm disturbances. Beta-blockers may exacerbate the hypertensive response seen with clonidine withdrawal.

Patients receiving clonidine with agents known to affect sinus node function or AV nodal conduction (such as digitalis, calcium channel blockers, and beta-blockers) may experience potentially additive effects such as bradycardia and AV block.Epidural clonidine may prolong the duration of pharmacologic effects of epidural local anaesthetics, opioids, neostigmine and other similar drugs; on both sensory and motor blockade.

Contraindications

- Patients with a known hypersensitivity to clonidine or components of the product
- Hemodynamic instability, Bradycardia, arrhythmia or heart block
- Local infection at site of epidural injection
- Patients with a bleeding diathesis
- Level above C4 is contraindicated because there are no safety data to support such use

Precautions

- Use with caution in patients with cerebrovascular or coronary insufficiency.
- Treatment with clonidine should be monitored carefully in patients with heart failure.
- In patients with renal insufficiency a lower dose is needed and careful monitoring is required. Very less amount of clonidine is removed by haemodialysis.
- Intrathecal/epidural clonidine causes bradycardia that if symptomatic can be treated with atropine. Rarely, atrioventricular block greater than first degree may occur.
- Clonidine does not alter the hemodynamic response to exercise, but may mask the increase in heart rate associated with hypovolemia.
- During hypertensive crisis a transient hypotension may precede hypotension if the intravenous clonidine is administered too rapidly.
- Sudden withdrawal of prolonged clonidine continuous epidural infusion may cause a rise in blood pressure and symptoms like agitation, nervousness, headache, and tremors.

Use in renal impairment

- Dose to be adjusted according to degree of renal impairment and patient to be monitored carefully.
- Only a minimal amount of clonidine is removed by haemodialysis and hence, there is no need to give supplemental clonidine following dialysis.

Pregnancy, Labour and Lactation

Included in category C. Clonidine readily crosses placenta and its levels are equal in maternal and umbilical cord plasma. The amniotic fluid concentration can be 4 times those found in the serum. Use in early pregnancy is not supported since no well controlled studies are available. Clonidine should not be used in pregnancy because it crosses the placental barrier causing foetal bradycardia.

There are no adequate studies evaluating the safety, efficacy, and dosing of clonidine in obstetrical settings. Because maternal perfusion of the placenta is critically dependant on blood pressure, use of clonidine as an adjuvant is not indicated. If used, a transient rise in BP in new born may occur. Concentrations of clonidine in human breast milk are approximately twice those found in maternal plasma. Because of the potential for severe adverse reactions in nursing infants, the use of clonidine during lactation is not recommended.

Carcinogenicity

In animal clonidine was not found mutagenic or carcinogenic in standard tests.

Fertility and teratogenicity

In animal studies fertility of female rats appeared to be affected at oral dose levels of 500-2000 ug/kg. In pregnant rats there were increased resumptions when treated continuously from 2 months prior to matching.

Adverse effects

Hypotension may occur and usually responds to intravenous fluids and if necessary, IV ephedrine. Hypotension has been observed more frequently in women and in lower weight patients. Bradycardia may occur and responds to atropine. Sedation which may occur which is a desirable effect during the intra and postoperative period.

Other effects reported in patients while on continuous epidural infusion of clonidine are constipation, dyspnoea, fever, infection, skin ulcer, vomiting, anxiety, confusion, hyperesthesia, headache, orthostatic complaints as well as skin reactions such as rash, urticaria, and pruritus.

Overdose and Treatment

No specific antidote available. Most cases require general supportive measures. Atropine will help in bradycardia. Fall in blood pressure may require intravenous fluids and/or ephedrine. An overdose can produce significant vasospasm and hypertensive emergency. Hypertension associated with over dosage has been treated with intravenous furosemide. Diazoxide or alpha blocking agents such as phentolamine.

Hypertension may develop early and may be followed by hypotension, bradycardia, respiratory depression, hypothermia, drowsiness, decreased or absent reflexes, irritability, and miosis.

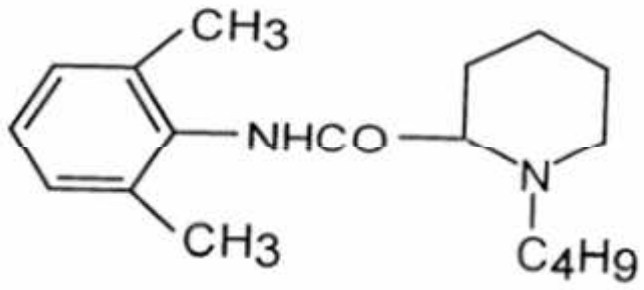
BUPIVACAINE [25,26,27,28]

INTRODUCTION

- It is an aminoamide local anaesthetic.
- It is chemically known as 1-butyl 2-piperidyl formo – 2'6'- xylidine hydrochloride.
- It was first synthesized by Swedish investigator Boaf Ekenstam et al.

CHEMICAL STRUCTURE:-

BUPIVACAINE:



PHYSICAL AND CHEMICAL PROPERTIES

- It is a white crystalline powder soluble in water
- Chemically it is an amide – 2,6 methyl amide
- Molecular weight - 325
- PH of saturated solution - 5.2
- Specific gravity - 1.025 at 37° C
- Stability and sterilization - highly stable, can withstand repeated autoclaving
- Melting point - 247 to 258°C

MECHANISM OF ACTION

Mechanism of action of bupivacaine is similar to that of any other local anaesthetics. The primary action of local anaesthetic is on the cell membrane of the axon on which it produces electrical stabilization. The large transient increase in permeability to sodium ions necessary for propagation of the impulse is prevented. Thus the resting membrane potential is maintained and depolarization in response to stimulation is inhibited. Initially the threshold for electrical excitation is raised, the rate of rise of action potential reduced and conduction slowed. Eventually propagation of the impulse fails. The mechanism by which local anaesthetics block sodium conductance is as follows:-

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

DOSAGES AND PREPARATION

As with all local anaesthetics the dosage of bupivacaine varies and depends upon:

- Area to be anaesthetized.
- The vascularity of the tissue to be blocked.
- The number of neuronal segments to be blocked.

- Individual tolerance.
- Technique of local anaesthesia.

Available concentrations:-

- 0.25%, 0.5%, 0.75%.
- 0.25% and 0.5% solutions in isotonic saline.
- O.5% solution in 8% dextrose.

Type of block	Concentration	Volume (ml)	Doses (mg)
Local infiltration	0.25%-0.5%	5-20	125-175
Brachial block	0.25%-0.5%	15-30	75-225
Intercostal block	0.25%-0.5%	3-5	15-20
Epidural block	0.25%-0.5%	15-30	50-200
Caudal block	0.25%-0.5%	15-30	75-150
SAB	0.5%-0.75%	2-4	10-20

Table 1: Shows concentration, volume and dose of bupivacaine for various blocks

These doses may be repeated in 3-4hrs but 400mg is the maximum dose in 24hrs. Bupivacaine can be used with or without epinephrine. The addition of vasoconstrictor

produces a very slight increase in the duration of action. However, the peak blood level is significantly reduced, thereby minimizing the systemic toxicity.

PHARMACOLOGICAL ACTION

Central nervous system

Over dose of bupivacaine produces light headedness and dizziness followed by visual and auditory disturbances such as difficulty to focus and tinnitus. Disorientation and drowsiness can also occur. Shivering, muscular tremors and tremors of muscles of face and distal part of extremities can occur.

Ultimately generalized convulsions of tonic clonic nature occur. Further increase in doses causes respiratory arrest. Since bupivacaine is a potent drug, smaller doses can cause rapid onset of toxic symptoms when compared to other drugs.

Autonomic nervous system

Bupivacaine does not inhibit the noradrenaline uptake and hence has no sympathetic potentiating effect. Myelinated preganlionic β fibers have a faster conduction time and are more sensitive to the action of local anaesthetics including bupivacaine. Involvement of preganglionic sympathetic fibres is the cause of widespread vasodilatation and consequent hypotension that occurs is epidural and paravertebral block. When used for conduction blockade, all local anaesthetics particularly bupivacaine produces higher incidence of sensory than motor fibres.

Neuro-muscular junction

Bupivacaine like other local anaesthetics can block motor nerves if present insufficient concentration but has no effect on the neuromuscular junction as such.

Cardiovascular system

The primary cardiac electro physiologic effect of local anaesthetic is a decrease in the maximum rate of depolarization in purkinje fibres and ventricular muscle. This is due to decrease in the availability of sodium channels. Action potential duration and the effective refractory period is also decreased. The depression of rapid phase of depolarization (V-max) in purkinje fibres and ventricular muscle by bupivacaine is far greater compared to lignocaine. Also the rate of recovery of the block is slower with bupivacaine. Therefore, there is incomplete restoration of V-max between action potential particularly at higher heart rates. Therefore, bupivacaine is highly arrhythmogenic, the cardiac contractility is reduced, and this is by blocking the calcium transport. Low concentrations of bupivacaine produce vasoconstriction, while higher doses cause vasodilatation.

Respiratory system

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

PHARMACOKINETICS OF BUPIVACAINE

Absorption of local anaesthetics is determined by site of injection, dosage and addition of a vasoconstrictor. Absorption is faster in regions of higher vascularity and also in some regions e.g. absorption of drug after intercostals block is faster than after brachial plexus block. Higher dosage leads to faster absorption. Addition of vasoconstrictor does not prolong the duration of action of bupivacaine significantly but decrease its absorption.

DISTRIBUTION

Bupivacaine is distributed throughout all body tissues. $T_{1/2}$ α of bupivacaine is 2-7 mins $T_{1/2}$ β of bupivacaine is 28 mins and $T_{1/2}$ γ of bupivacaine is 3-5 hrs. The more highly perfused organs show higher concentration of the drug. The blood concentration of the drug decreases markedly as it passes through the pulmonary vasculature. Because of the mass of skeletal tissue, it makes it the largest reservoir of bupivacaine.

BIOTRANSFORMATION AND EXCRETION

Bupivacaine is metabolized in the liver. Here it undergoes N-dealkylation and hydroxylation and then conjugation to form a water soluble compound. The drug is excreted by kidneys.

TOXICITY

In humans bupivacaine is about 4-5 times more toxic than lignocaine. The acute toxicity is about the same as that of tetracaine and approximately 3-4 times higher than that of mepivacaine and the toxic plasma concentration is set at 4-5mg/ml.

Non specific local irritant effects on nerve tissue have been noted in human subjects. No evidence of permanent damage has been found in clinical dosage. There is no alteration in blood picture of methaemoglobin formation due to this drug.

PRECAUTIONS

- The lowest dose that gives adequate anaesthesia should be used to avoid high plasma levels and serious systemic side effects.
- Debilitated elderly patients and acutely ill patients should be given reduce doses.
- Should be used cautiously in patients with known drug allergies and sensitivities.
- Repeated doses should be given cautiously in patients with severe liver diseases.

ADVERSE REACTIONS:-

Adverse reactions occur with excessive plasma levels which may be due overdose, inadvertent IV injections or slow metabolic degradation. These manifest by effects on CNS and CVS and other systems.

The CNS effects: can be excitation or depression, nervousness, dizziness, blurring of vision, tremors, drowsiness, convulsions, unconsciousness and respiratory arrest.

The CVS manifestations: can be myocardial depression, hypotension and cardiac arrest.

Others: In obstetrics, foetal bradycardia may occur. Nausea, vomiting, chills, constriction of pupils and tinnitus. Allergic reactions like urticaria, bronchospasm and hypotension.

TREATMENT OF ADVERSE REACTIONS

Treatment is mainly symptomatic.

- One should be prepared to maintain circulation and to support ventilation with oxygen or controlled ventilation if required.
- Supportive treatment with IV fluids and vasopressors restore the cardiovascular stability.
- convulsions may be controlled with diazepam or a muscle relaxant and controlled ventilation with oxygen. Corticosteroids may be helpful where allergic reactions are suspected.

MATERIALS AND METHODS

The present study titled "THE EFFECT OF INTRATHECAL CLONIDINE AS AN ADJUVANT TO HYPERBARIC BUPIVACAINE ON POSTOPERATIVE ANALGESIC REQUIREMENTS IN PATIENTS UNDERGOING LOWER ABDOMINAL SURGERIES- A RANDOMISED CONTROLLED TRIAL." was conducted in KLES Prabhakar Kore Hospital and MRC between December 2008 to December 2009

After obtaining the Institutional Ethical committee clearance and informed consent the study was undertaken on 60 ASA grade 1/11 patients scheduled for lower abdominal surgeries.

INCLUSION CRITERIA

- ASA Grade I &II
- Age 20-60 years
- Height 140-160 cms
- Weight 40-60 kgs

EXCLUSION CRITERIA

- Patient refusal
- Allergy to Bupivacaine
- History of bleeding diathesis
- Infection at the site of spinal needle insertion
- Severe spinal abnormalities like spina bifida, meningocele etc.
- On treatment with alpha adrenoreceptor antagonists

SAMPLE SIZE CALCULATION

Using the results of previously conducted study and considering an α error of 0.001 and β error of 1.282, with the power of 90% and p1 as 98 and p2 as 90, in the below stated formula the sample size of 30 in each group was derived.

$$n = \frac{2(Z\alpha+Z\beta)2\ (S1^2 +S2^2)}{(x_1-x_2)^2}$$

Zα=3.29, Zβ=1.282, power =90% , , q=6

S1= standard deviation of Clonidine group

S2= standard deviation of placebo group

X1= mean of Clonidine group.

X2 = mean of Conventional /Placebo group.

DESIGN

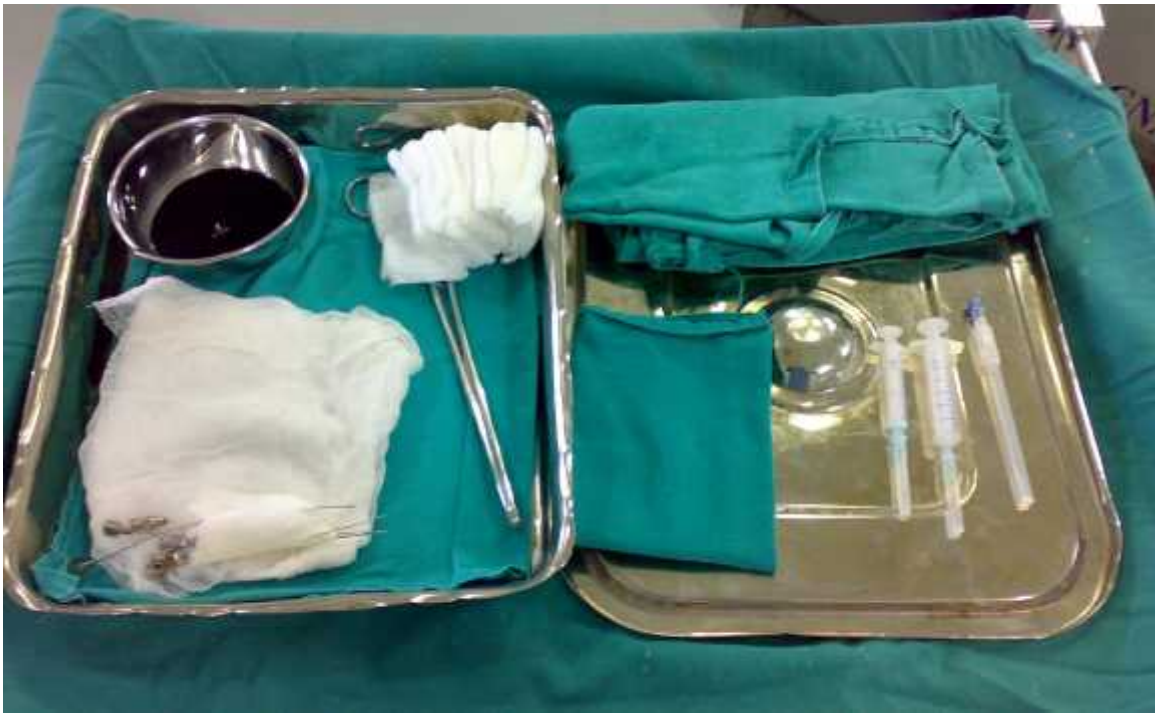
Randomized Controlled Trial.

METHODOLOGY

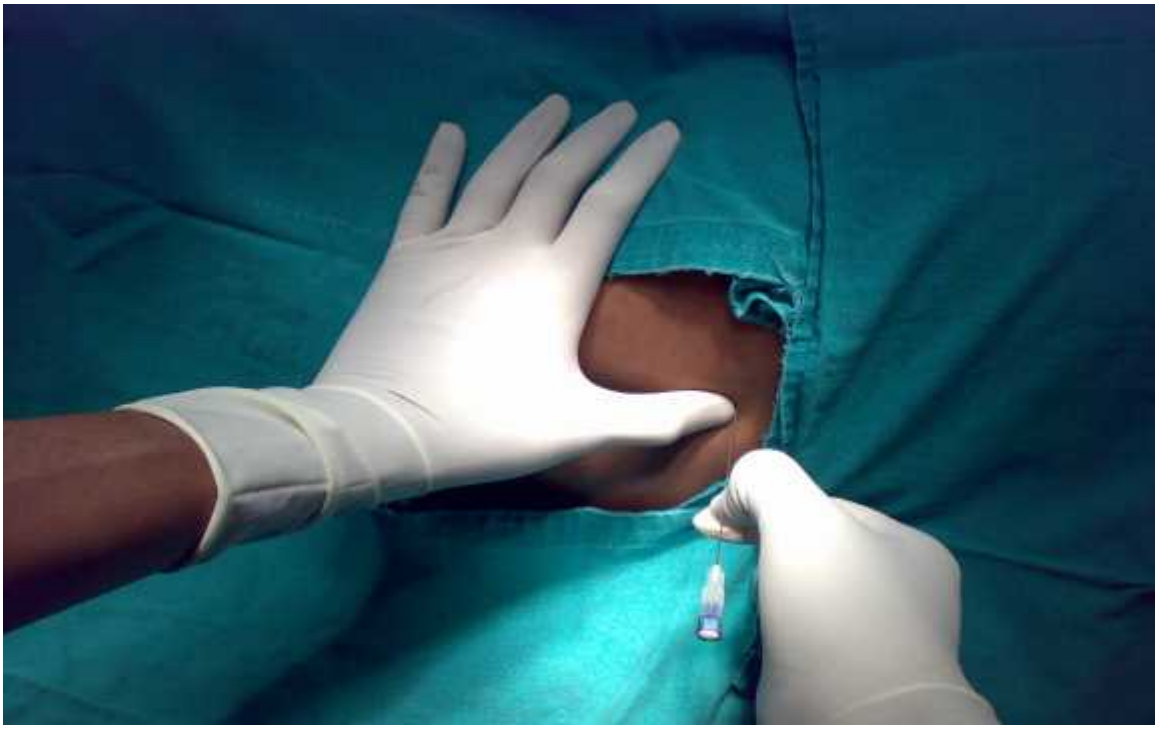
In our study a sample size of 60 (30 in each group) was taken. After having met the inclusion and exclusion criteria and having obtained written informed consent patient were randomised into one of the two groups. A intravenous line was secured using appropriate IV cannula and all patients were preloaded with 15ml/kg of Ringer lactate . Monitoring consisted of heart rate , non-invasive blood pressure and oxygen saturation.

Under strict aseptic precautions a 23G Quinkes spinal needle was inserted at L3-L4 intervertebral space and after confirming free flow of CSF, a mixture containing 3ml of 0.5% Heavy Bupivacaine and 0.2ml of clonidine was injected into the subarachnoid space in Group BC and a mixture containing 3ml of 0.5% Heavy Bupivacaine and 0.2ml of normal saline in group B.

Intraoperatively patients HR, BP and MAP were measured and noted. Hypotension defined as a decrease in systolic blood pressure by 30% from baseline, or a systolic blood pressure lower than 90 mmHg, was treated with a bolus administration of



Photograph 3: Spinal tray



Photograph 4: Procedure of spinal anaesthesia

250 ml Ringer Lactate solution over 10 mins and incremental doses of intravenous ephedrine (6mg). Bradycardia defined as HR <50 beats/min, and will be treated with 0.6 mg of intravenous atropine. The vitals will be monitored every 15 mins till the end of the surgery.

Pain was assessed in the PACU and later in the ward by a trained nursing staff blinded to the study for a period of 24 hrs. Pain score was assessed every hourly and when it exceeded 3 on VAS. Rescue analgesic was administered. The time to first rescue analgesic administration and total analgesic dose for 24 hrs was noted. Injection Diclofenac 50mg IM was used rescue analgesic. The level of significance was taken as $p< 0.001$.

RESULTS

The objective of the present study to determine the effect of intrathecal clonidine as an adjuvant to hyperbaric bupivacaine on postoperative analgesic requirements in patients undergoing lower abdominal surgeries.

The present study was conducted on 60 patients undergoing elective lower abdominal surgeries under spinal anaesthesia belonging to ASA Grade I and Grade II physical status.

The study was carried out in KLES Prabhakar Kore Hospital & Medical Research Centre, Belgaum during the period of December 2008 to December 2009.

Each group consisted of 30 patients and were divided as Group B (Bupivacaine group, n =30) and Group BC (Bupivacaine and Clonidine, n =30) by a computer generated randomization table.

Results and observations of both the groups were analyzed and are presented as mean ± standard deviation in the tabular form.

DEMOGRAPHIC PROFILE

	Group B	**Group BC**
Age (yrs)	26.80 ± 1.68	26.88 ± 1.73
Weight (kg)	55.03 ± 4.08	55.30 ± 5.10
Height (cms)	151.34 ± 1.72	151.47 ± 6.17

Table 2 : Age, weight and height in both the groups.

Group B = Hyperbaric Bupivacaine+ Normal saline

Group BC = Hyperbaric Bupivacaine+Clonidine

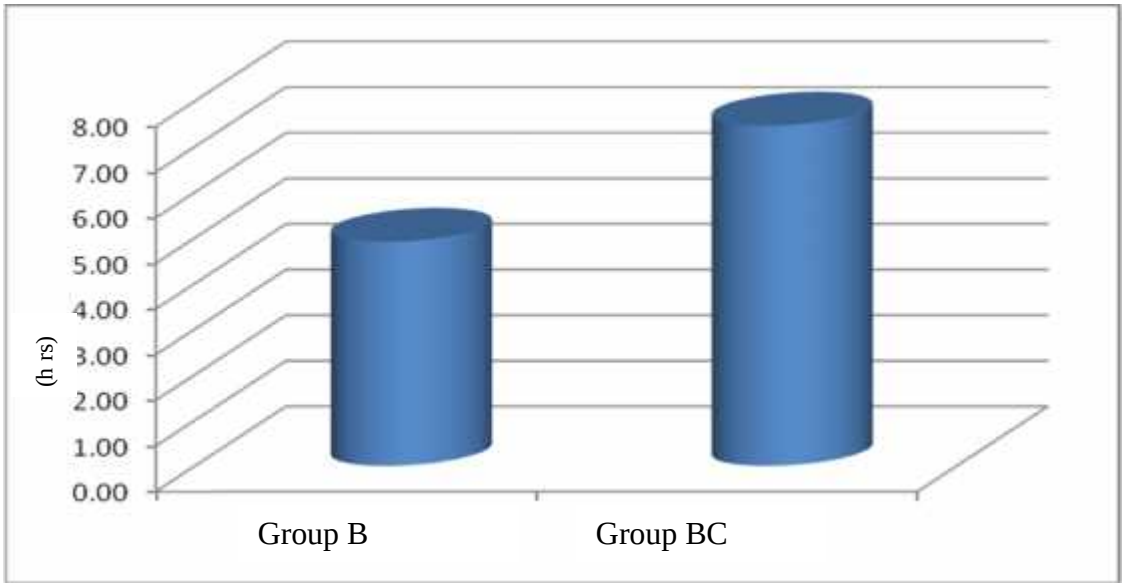
The age, weight and height were comparable in both the groups.

	Group B	**Group BC**
Heart rate (bpm)	89.52 ± 11.89	92.20 ± 11.56
SBP (mm Hg)	123.52 ± 7.84	123.14 ± 8.98
DBP (mm Hg)	80.94 ± 8.10	81.18 ± 9.12
MAP (mm Hg)	95.00 ± 7.20	95.00 ± 8.26

Table 3 : **Baseline parameters in both the groups.**

- The mean values of baseline heart rate in group B and BC were 89.52 ± 11.89 and 92.20 ± 11.56 respectively.

- The mean SBP values obtained in the two groups were 123.52 ± 7.84 and 123.14 ± 8.98 respectively.
- Similarly, diastolic blood pressure values in the two groups B and BC were 80.94±8.10 and 81.18±9.12 respectively
- Baseline mean arterial pressure in the two groups B and BC were 95.00 ± 7.20 and 95.00 ± 8.26 mm of Hg respectively. Thus, the two study groups were comparable with respect to the baseline parameters.

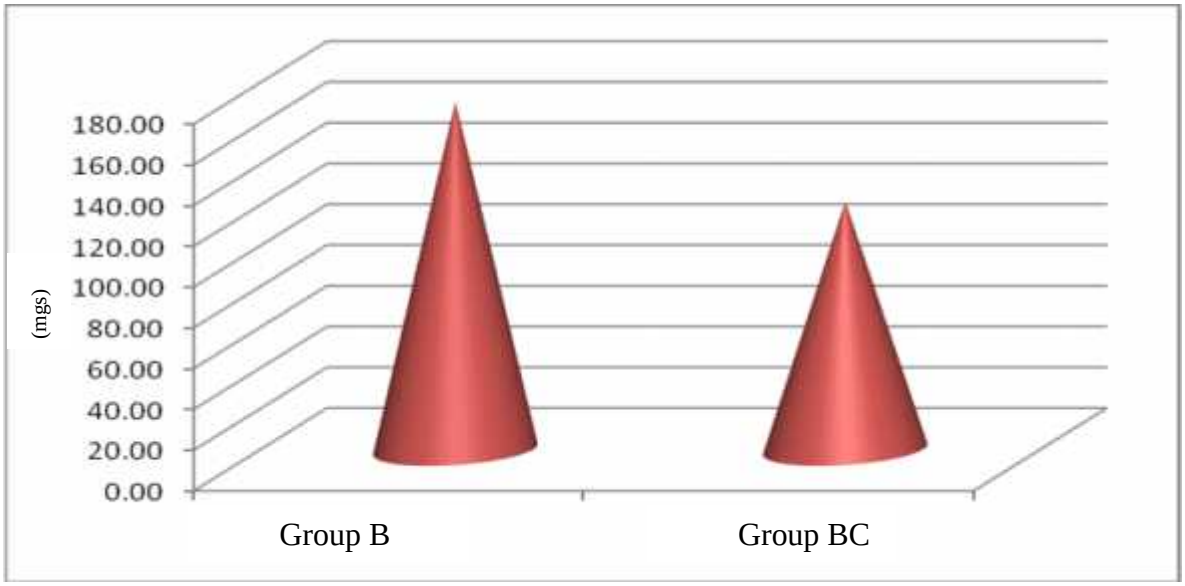


Graph 1 : Mean duration of postoperative analgesia (hrs)

Time	Group B	Group BC	p
Duration of analgesia(Hrs)	4.91±1.41	7.46±2.18	0.00000143

Table 4 : Mean duration of postoperative analgesia

The data of duration of analgesia in two groups were compared. Statistically significant difference was found between the two groups ($p < 0.001$).



Graph 2 : Mean analgesic requirements (mgs) in 24 hrs.

	Group B	Group BC	p
Mean analgesic in 24 hrs(mgs)	170.83±54.57	121.67±49.01	.00052

Table 5 : Mean amount of analgesic required in 24 hrs.

The data of mean analgesic requirement in 24hrs after surgery were compared. Statistically significant difference was found between the two groups ($p<0.001$)

DISCUSSION

Subarachnoid block is one of the most commonly used anaesthetic techniques for lower abdominal surgeries because of its simplicity, rapid onset of action, intense analgesia, awake patient and less complications.

Adequate pain relief in postoperative period has been shown to restore the normal respiratory function by preventing atelectasis and infection. With good analgesia adverse effects due to sympathetic stimulation are prevented. Wound healing is better and so early mobilisation is possible.

Alpha 2 agonists administered together with local anaesthetics intrathecally, reduce the requirement of local anaesthetic, resulting in shorter duration of motor block and also provides significantly extended postoperative analgesia without prolonging the recovery.

60 patients were included in the present study 30 in each group. In the clonidine group 30µg of clonidine was added to 0.5% hyperbaric bupivacaine. The dose of clonidine used in the present study was 30µg as previous studies have demonstrated unstable hemodynamic response with higher doses and insignificant increase in duration with lower doses.

The data obtained from our studies indicate that addition of 30µg of clonidine to 15mg of 0.5% hyperbaric bupivacaine significantly prolongs the duration of postoperative analgesia(448±131 mins) compared to plain hyperbaric bupivacaine (295±85mins).

Our findings are in accordance with the study by L Niemi in which 3 µg/kg of clonidine was added to 15mg of 0.5% hyperbaric bupivacaine administered intrathecally in patients undergoing knee arthroscopy [17] . However it is pertinent to mention that Niemi used almost six times the amount of clonidine as compared to our study. Despite that, the mean time to administration of first analgesic from test drug administration was similar to our study (613 min). Chiari et al in a dose response study using intrathecal clonidine as sole analgesic during first stage of labour found that 50-200 µg of intrathecal clonidine produces dose dependant analgesia although the duration and quality of analgesia were more pronounced with 100µg and 200 µg. In another study by Dobrydnjov et al found that addition of intrathecal clonidine (150µg) prolonged analgesia and decreased morphine consumption postoperatively more than with oral clonidine.

Subarachnoid clonidine has a potent anti nociceptive effect mediated by αlpha 2 adrenergic receptors in descending medullary pathways to the dorsal horn of the spinal cord and the pharmacokinetic profile is consistent with rapid onset and limited distribution.

Because of the lipophilicity of clonidine, its spinal effects are more pronounced and selective after intrathecal than epidural administration. Clonidine has been demonstrated to prolong sensory and motor block from intrathecal local anaesthetics.[29,30,31]

Clonidine has analgesic effect at spinal level mediated by postsynaptically situated α 2 adrenoreceptors in dorsal horn of spinal cord. The intrathecal administration of clonidine achieves a high drug concentration in the vicinity of α2 adrenoreceptors in the spinal cord and by blocking the conduction of C and Aδ fibres and increasing potassium conductance also intensifies conduction block of local anaesthetics.

There was no statistically significant decrease in mean arterial pressure (MAP) and heart rate in the Clonidine group compared to the Control group and none of the patients required any therapeutic intervention except for one case of bradycardia due to accidental head low soon after the spinal injection of the drug. It implies that 30µg intrathecal clonidine used in our study did not produce excessive hemodynamic effects in healthy patients between 20 and 50 years of age. Dobrydnjov et a in their studyl confirmed the lesser incidence of hypotension with intrathecal clonidine.

Negri et al studied the interactions and effects on the cardiovascular system on addition of 100 µg clonidine to hyperbaric bupivacaine 1% in unilateral spinal anaesthesia which resulted in minimal influence on hemodynamic parameters and a

satisfactory postoperative analgesia.[9] Racle et al in their study using isobaric bupivacaine spinal anaesthesia with epinephrine and clonidine for hip surgery in elderly found that intrathecal clonidine (150 µg) for patients aged 75 years or more resulted in a decrease in systolic blood pressure of only 15% from resting values.[34]

Sedation is a well known side effect of clonidine and in our study patients who received clonidine were more sedated than those in the control group without any significant respiratory depression. This again underlines the safety of low dose intrathecal clonidine. Grubb, et al in their study on video assisted thoracic surgery for lobectomy or pleurectomy found that use of narcotics for pain relief may result in respiratory depression requiring prolonged intubation whereas intrathecal clonidine may provide adjunct analgesia without any respiratory depression.[33] Dryness of mouth, atypical side effects of clonidine[17] although insignificant were reported in few patients.

In conclusion, our study has demonstrated that addition of 30 µg clonidine to 15mg 0.5% hyperbaric bupivacaine significantly increases the duration of analgesia following its placement in subarachnoid space as compared to bupivacaine alone. This dose has an effect on sedation level, heart rate and mean arterial pressure which does not however, require any therapeutic intervention. The results of our study show that addition of clonidine to intrathecal bupivacaine is safe and likely to be as effective as higher dosages minimizing the side effects.

CONCLUSION

The conclusions of our present study are as follows:

The addition of 30µg intrathecal clonidine to hyperbaric bupivacaine provided increased duration of postoperative analgesia which was statistically significant.

The postoperative analgesic consumption was reduced in the clonidine group compared to the control group which was statistically significant.

Intrathecal clonidine in dose of 30µg can be used along with hyperbaric bupivacaine to provide effective and adequate post operative analgesia with minimal adverse effects in patients posted for lower abdominal surgeries.

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SUMMARY

The present study titled "The effect of intrathecal clonidine as an adjuvant to hyperbaric bupivacaine for postoperative pain relief in patients undergoing lower abdominal surgeries – A Randomized Controlled Trial" was carried out in the Department of Anaesthesiology , KLES Prabhakar Kore Hospital and MRC, Belgaum .

The study included 60 ASA grade 1 and 11 patients posted for elective lower abdominal surgeries, were divided into two groups consisting of 30 each after randomisation by a computer generated randomisation table .

Group B – 3cc of 0.5% (H) sensorcaine and 0.2 ml of NS.

Group BC –3cc of 0.5% (H) sensorcaine and 30 µg of clonidne.

Pain was assessed using Verbal Analogue Scale by trained nursing staff in the recovery room who were blinded to the groups.

Our study revealed that the patients belonging to clonidine group had a significant increase in the duration of postoperative analgesia and also a significant reduction in requirement of rescue analgesic (I.M. Diclofenac) without any complications.

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INFORMED CONSENT

YOUR PARTICIPATION

A study, " THE EFFECT OF INTRATHECAL CLONIDINE AS AN ADJUVANT TO HYPERBARIC BUPIVACAINE ON POSTOPERATIVE ANALGESIC REQUIREMENTS IN PATIENTS UNDERGOING LOWER ABDOMINAL SURGERIES- A RANDOMISED CONTROLLED TRIAL." is being conducted by Dr. Sangamesh Kunakeri, post graduate in anaesthesiology at J. N. Medical College Belgaum, Karnataka. Under guidance of Dr. Rajesh Mane Associate professor Dept. of Anaesthesiology, J. N. Medical College, Belgaum, under K.L.E.'s academy of Higher Education, Belgaum.

Respected _____ we request you to participate in our study as you are eligible to be included. During the study you will be asked questions regarding your present and past medical history and you are requested to answer to the best of your knowledge.

Your participation in this study is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J.N.M.C. If you decide to participate you are free to withdraw at any point of time. The purpose of the study is to compare the effect of addition of intrathecal clonidine to hyperbaric bupivacaine on post operative analgesic requirements.

Objective of the study:

Objective of my study is to compare the effect of addition of intrathecal clonidine as an adjuvant to hyperbaric bupivacaine on post operative analgesic requirements.

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 be clinically examined in detail and investigated accordingly. You will be randomly allocated either into study Group A or Group B, if you are in Group A then 3ml hyperbaric bupivacaine will be used for spinal anaesthesia and 30 micrograms of clonidine will be added if in group B then 0.2ml of normal saline will be added to 3ml of 0.5% hyperbaric bupivacaine. The duration of the analgesia will be evaluated in the two groups.

Benefits and Risks:

The benefits of taking part in this research is that we can avoid general anaesthesia with good quality of analgesia . The risks associated are minimal which include hypotension , bradycardia, headache, meningitis, nerve injury and backache.

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 .

Confidentiality:

All information collected about you during the course of the study will be kept confidential to the extent permitted by law. The code numbers will identify you in this study records and the information from this study may be published but your identity will be confidential in any publication.

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 at KLES Hospital & MRC, Belgaum. No reimbursement, compensation or free medical care will be given, by law. If you are injured, you may contact Dr. Sangamesh Kunakeri at Department of Anaesthesiology, KLE's Hospital & MRC or by Ph. No. 9964748462.

Queries/ Contact details

If you have any queries, in future or in case of study related injury or illness, you may contact. Dr. Sangamesh Kunakeri at Department of Anaesthesiology, KLES Hospital & MRC, Ph No. 0831-2473777 or on phone 9964748462.

If you have any queries about your rights as a study subject, you may call Dr. V.D. Patil. Principal and Chairman. J.N. Medical College Institutional Ethical Committee for Human Subjects Research, Ph. 0831-2473777 at J.N. Medical College, Belgaum.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY:

I, Mr./Mrs._____ voluntarily agree to take part in this study, by signing this consent form I am not giving up my legal rights. I may withdraw at any time. I am signing after having read, or been read to me in the vernacular language including risks and the benefits and having all queries cleared.

Signature of the participant :_____

Witness name: _____

Signature of the witness :_____

Signature of Investigator :_____

Date :_____

Place :_____

PROFORMA

Title: " THE EFFECT OF INTRATHECAL CLONIDINE AS AN ADJUVANT TO HYPERBARIC BUPIVACAINE ON POSTOPERATIVE ANALGESIC REQUIREMENTS IN PATIENTS UNDERGOING LOWER ABDOMINAL SURGERIES- A RANDOMISED CONTROLLED TRIAL."

Patients Name : I.P. No:

Age: Weight:

Sex: Height:

Occupation: Address:

Anaesthesiologist: Date of operation:

PRE-ANAESTHETIC EVALUATION:

Chief Complaints:

Past History:

a) HTN/D.M/Asthma/Epilepsy/Drug allergy.

b) Drug therapy.

c) Previous exposure to anaesthesia.

Family History:

General Physical Examination:

Pallor / Icterus / Clubbing / Lymphadenopathy / edema

P.R: B.P:

R.R:

Musculoskeletal System Examination:

Jaw movements: Teeth:

Airway assessment: Spine:

Systemic Examination:

a. R.S b. CNS

c. C.V.S d. GIT

Investigations:

Hb %: Total count:

Bleeding time: Differential count:

Clotting time: Urine routine

PT: aPTT:

INR:

Any others:

Pre operative physical status: ASA grade I II III IV V

Inclusion criteria

Patients of either sex aged between 20-60 years undergoing lower abdominal surgeries.

Patients undergoing lower limb surgery.

Exclusion criteria

Patient refusal.

Infection at the site of spinal needle insertion.

Severe Spine abnormalities like spina bifida, meningocele

Vertebral implant

Raised intracranial tension.

Known case of hydrocephalus

Severe convulsive disorders.

Diagnosis:

Proposed surgery:

Patients will be allocated by computer generated randomization into group B and group BC. On the day of surgery, I.V line secured in a peripheral vein, and will be pre-loaded with 15ml/kg of Ringer lactate .

Preoperative baseline

Heart rate:

Blood pressure:

Monitors attached:

Pulse oximeter: Non invasive blood pressure:

ECG: ETCO2:

23 G Quinke's needle used for spinal anaesthesia. In Group BC 3ml of 0.5 % Heavy Bupivacaine and 0.2ml of clonidine will be injected for spinal anaesthesia and in group B 3ml of 0.5% Heavy Bupivacaine and 0.2ml of normal saline will be used for spinal anaesthesia.

The patients of both the groups will be observed immediately for HR , BP after giving the above mentioned drug every 5mins for initial 30mins then every 15mins intraoperatively till the end of surgery.

Time	Heart rate	Blood pressure	SPO2
5 mins			
10 mins			
15mins			

20 mins			
25 mins			
30 mins			
45 mins			
60 mins			
1 h 15 mins			
1 h 30 mins			
1 h 45 mins			
2 h			
2 h 15 mins			
2 h 30 mins			
2 h 45 mins			
3 h			

Time of first rescue analgesic:

Total dose of analgesic in 24 hours:

Signature of the Staff incharge:

GROUP B

PATIENTS NAME	AGE	SEX	IP	WEIGHT	HEIGHT	SURGERY	DURATION	ANALGESIC IN 24 HRS
KAMALLAWA SUNDRAPPA	45	F	312842	56	161	VAGINAL HYSTRECTOMY	5.33	200
MALLAPPA	32	M	312362	58	158	APPENDICECTOMY	4.50	100
KALLAPPA	28	M	321623	58	159	VAGINAL HYSTRECTOMY	5.25	225
RUDRAWWA	43	F	323421	58	152	VAGINAL HYSTRECTOMY	5.33	150
PRABHA SAPHARE	45	F	312642	66	158	HERNIA REPAIR	5.17	150
FAKIRAPPA	36	M	316248	52	143	APPENDICECTOMY	6.00	150
KEERTHI MALI	18	F	312653	52	160	VAGINAL HYSTRECTOMY	5.17	225
ANNAPURNA KATTI	48	F	312698	58	156	VAGINAL HYSTRECTOMY	6.00	150
RAVI KAMMAR	48	M	326148	48	152	HERNIA REPAIR	7.50	150
GEETA HUDDALI	32	F	328621	58	152	VAGINAL HYSTRECTOMY	2.50	150
KASHAPPA SANGOLI	28	M	325862	58	168	HERNIA REPAIR	3.50	225
BHADRAPPA	40	M	324324	50	159	HERNIA REPAIR	5.00	150
BALLAWWA	42	F	324321	52	162	APPENDICECTOMY	5.09	225
INAGATOLLA REHMAN	28	M	323351	59	176	HAEMORRHOIDECTOMY	6.50	225
BASSAWA	43	F	326251	58	148	VAGINAL HYSTRECTOMY	4.50	150
SATYAWWA	48	F	324123	52	150	VAGINAL HYSTRECTOMY	4.09	225
NIVARUTI PATIL	59	M	323778	56	160	HERNIA REPAIR	6.00	200
VINAYAK	23	M	323573	54	156	APPENDICECTOMY	4.00	50
SURESH AGOLKAR	32	M	326212	56	154	APPENDICECTOMY	8.17	25
SHIVLING	59	M	324247	52	156	BILATERAL ORCHIDECTOMY	4.00	150
YALLAWWA	50	F	324575	48	144	CYST EXCISION	7.09	200
BHARMAPPA	59	M	324173	56	155	HERNIA REPAIR	5.09	150
MAHANTESH MALAPPA	38	M	323667	58	155	HAEMORRHOIDECTOMY	6.09	150
SHIVAPPA	54	M	318637	59	152	BELOW KNEE AMPUTATION	3.50	150
SHOBHA PATIL	28	F	318912	50	142	APPENDICECTOMY	2.00	300
SUJATHA METARE	19	F	316824	50	142	APPENDICECTOMY	3.75	150
CHANAWWA	55	F	317981	56	152	VAGINAL HYSTRECTOMY	3.17	200
MAHADEVI	35	F	317984	50	142	VAGINAL HYSTRECTOMY	3.50	200
GEETANJALI WANDRE	50	F	317199	55	142	VAGINAL HYSTRECTOMY	4.50	200
SUSHEELA	52	F	318443	58	150	VAGINAL HYSTRECTOMY	5.09	150
MEAN	40.56666667	16		55.03	153.87		4.91266666666667/295	170.83
S.D.	11.93280998	14		4.08	7.98		1.41089585952925/85	54.57
MINIMUM	18			48.00	142.00		2.00	25.00
MAXIMUM	59			66.00	176.00		8.17	300.00
					GROUP BC			
PATIENT NAME	**AGE**	**SEX**	**IP**	**WEIGHT**	**HEIGHT**	**SURGERY**	**DURATION**	**ANALGESIC IN 24 HRS**

UDAY KUMAR	25	M	316925	48	148	APPENDICECTOMY	10.00	150
SHANTA BANHATTI	43	F	315624	58	152	HERNIA REPAIR	7.25	150
NIRMALA	42	F	305262	56	150	VAGINAL HYSTRECTOMY	8.50	150
MALLAWWA	40	F	325826	52	148	VAGINAL HYSTRECTOMY	8.33	100
PULAVVA BHARMAPPA	50	F	325079	50	150	VAGINAL HYSTRECTOMY	10.09	100
VENKATESH	40	M	298652	48	142	PERINEAL ABSCESS DRAINAGE	12.50	100
GANGAWWA	47	F	325039	50	145	ABDOMINAL HYSTRECTOMY	10.17	100
LAXMI PATIL	55	F	323948	56	156	VAGINAL HYSTRECTOMY	8.00	100
RUDRAWWA	48	F	324089	58	152	VAGINAL HYSTRECTOMY	8.00	125
ANITA NARAYAN	42	F	323942	58	152	VAGINAL HYSTRECTOMY	6.00	100
VINAPUR B	60	M	324239	59	162	HERNIA REPAIR	5.00	100
ALSHAM KHAN	58	M	325053	59	158	HERNIA REPAIR	5.00	200
RENUKA AMBAJI	42	F	325375	56	148	ABDOMINAL HYSTRECTOMY	6.00	150
GANGAWWA	48	F	325396	48	152	VAGINAL HYSTRECTOMY	7.50	100
RUDRAWWA	35	F	324449	52	152	VAGINAL HYSTRECTOMY	6.00	200
MEERA RAJU	48	F	334212	56	152	VAGINAL HYSTRECTOMY	10.00	100
KAMALLAWA	48	F	324321	58	148	VAGINAL HYSTRECTOMY	8.00	50
BASSAWA	45	F	326212	56	156	APPENDICECTOMY	8.42	50
PRADEEP PANTH	45	M	325624	58	152	HERNIA REPAIR	7.33	100
YALLAWWA	25	F	323198	52	152	APPENDICECTOMY	9.00	100
SASHIDHAR	31	M	307399	53	158	APPENDICECTOMY	8.00	100
GANGUBAI	55	F	315877	56	144	VAGINAL HYSTRECTOMY	7.00	150
SATYANARAYAN MALLAPPA	19	M	317194	71	173	APPENDICECTOMY	8.09	100
KAMALLAWA	45	F	318867	56	148	VAGINAL HYSTRECTOMY	5.00	100
GANGUBAI MALAI	48	F	317556	52	143	VAGINAL HYSTRECTOMY	4.75	150
BHAGIRATHI NINGAPPA	47	F	282651	60	152	VAGINAL HYSTRECTOMY	4.92	300
VEERANNA DODDAMANI	42	M	282576	60	148	HAEMORRHOIDECTOMY	7.00	150
SHIVA HALKATTI	22	M	283652	62	156	HERNIA REPAIR	6.17	100
DUNDAPPA	52	M	282516	46	150	POPLITEAL CYST EXCISION	10.00	75
NAGAWWA UNDI	30	F	317233	55	145	VAGINAL HYSTRECTOMY	1.82	100
MEAN	42.56666667	20		55.30	151.47		7.461 (448)	121.67
S.D.	10.43760883	10		5.10	6.17		2.18194263860463/131	49.01
MINIMUM	19			46.00	142.00		1.82	50.00
MAXIMUM	60			71.00	173.00		12.50	300.00
STUDENT'S UNPAIRED t TEST								
p VALUE	0.492336322	0.2918		0.823844346	0.197526826		1.43997E-06	0.000526885
	NS	NS		NS	NS		HS	HS
							<0.0001	

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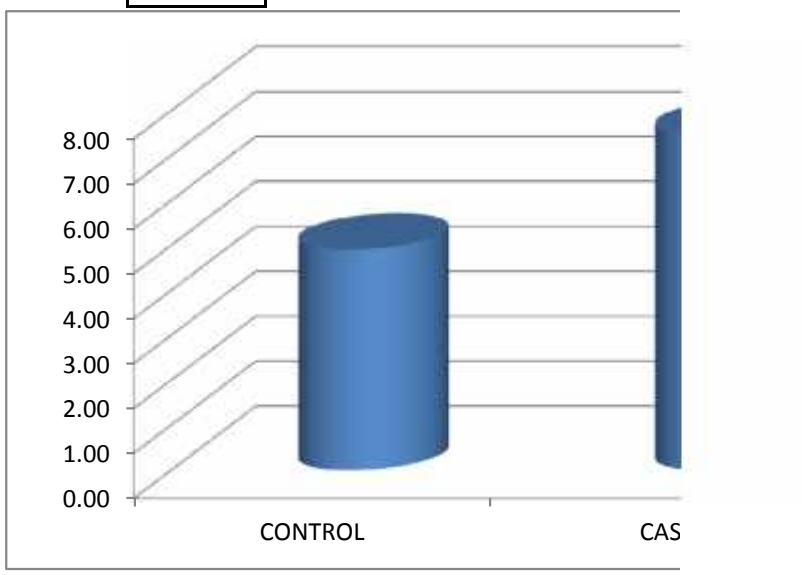
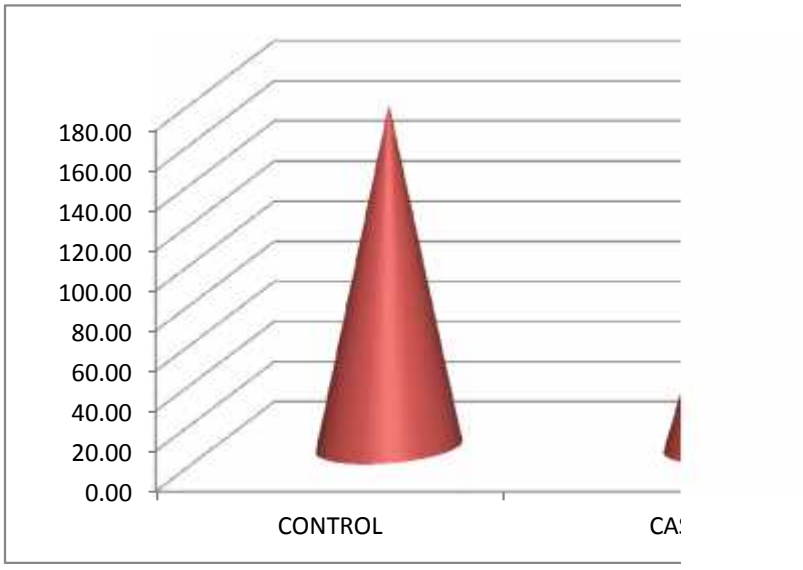
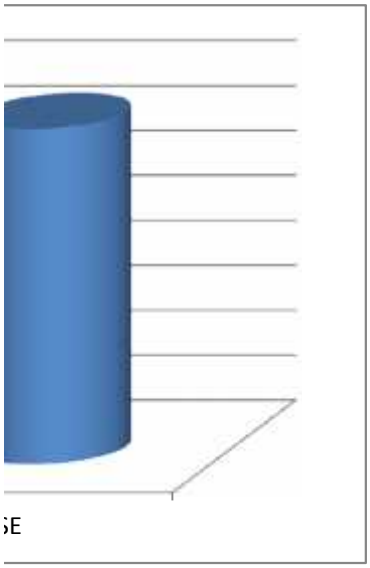
CONTROL	4.91
CASE	7.46



CONTROL	170.83
CASE	121.67

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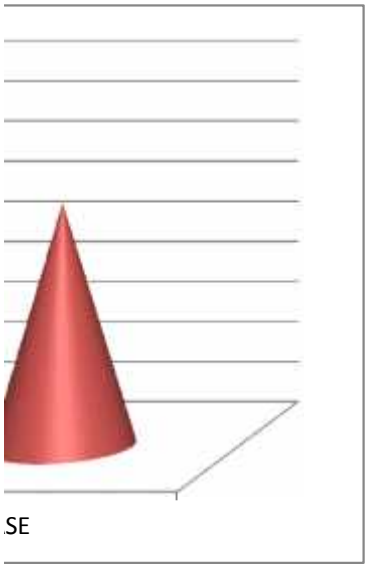
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