Dissertation on

"A STUDY ON EFFECT OF ORAL CLONIDINE PREMEDICATION ON ONSET AND DURATION OF SPINAL ANAESTHESIA BY HYPERBARIC 0.5% BUPIVACAINE"

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CERTIFICATE

This is to certify that the dissertation titled "A STUDY ON THE EFFECT OF ORAL CLONIDINE PREMEDICATION ON ONSET AND DURATION OF SPINAL ANAESTHESIA WITH 0.5% HYPERBARIC BUPIVACAINE" presented by DR.P. SURESHU is an original work done in the Department of Anaesthesiology, Govt. Stanley Medical College and Hospital, Chennai for the award of the degree of M.D. (Branch X) Anaesthesiology under the guidance and supervision during the academic period of 2003 – 2006.

Prof. Dr. M. VASANTHA, M.D.,DTCD,
DEAN
GOVT. STANLEY MEDICAL
COLLEGE AND HOSPITAL
CHENNAI.

Prof. Dr.J.RANGANATHAN,M.D.,DA
Professor & HOD,
Deparment of Anaesthesiology
GOVT. Stanley Medical College
and Hospital, Chennai.

DECLARATION

I, DR. P. SURESHU solemly declare that the dissertation titled "A STUDY ON THE EFFECT OF ORAL CLONIDINE PREMEDICATION ON ONSET AND DURATION OF SPINAL ANAESTHESIA WITH 0.5% HYPERBARIC BUPIVACAINE" is a bonafide work done by me in the department of Anaesthesiology, Stanley Medical College and Hospital, Chennai under the able guidance of Prof.J. Ranganathan,M.D.,D.A., Professor and HOD, Department of Anaesthesiology, Govt. Stanley Medical College and Hospital, Chennai – 1.

Place : Chennai

Date :

(DR.P.SURESHU)

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CONTENTS

INTRODUCTION

Among all the regional anesthesia techniques subarachnoid block is the easiest to perform because of its clearly defined end point and it is most widely used for surgeries below the umbilicus and lower extremities.

The advantages of subarachnoid block are reduced blood loss, attenuation of neuroendocrine response, increase blood flow to lower limbs, decreased platelet aggregation, well maintained airway in a conscious patients reduced mortality and marked decrease in hospital cost.

In order to prolong the duration of subarachnoid block vasoconstrictors were added to local anesthetics but one of the rare outcomes is ischemia of spinal cord.

Hence the need to find a drug which do not damage the spinal cord but at the same time should effectively prolong the duration of spinal anaesthesia could be an α2 agonist clonidine which inhibit nerve conduction in Aα and C fibers without causing ischemic damage to spinal cord.

AIM OF THE STUDY

1) To assess whether oral clonidine affects the onset and duration of subarachnoid block by 0.5% hyperbaric bupivacaine.

2)To assess whether oral clonidine affects the onset and duration of subarachnoid block by 0.5% hyperbaric bupivacaine in a dose related manner.

3) To evaluate the side effects and complications that may arise with the use of oral clonidine

ANATOMY

The vertebral column consists of 7 Cervical 12 Thoracic 5 Lumbar and 4 or 5 Coccygeal vertebrae.

The vertebral column has 4 curves of which the thoracic and sacral curves are concave anteriorly. The cervical and lumbar are secondary and are convex anteriorly. Thus, when the spine is fully flexed, the cervical and lumbar curves are obliterated.

The vertebral canal is bounded anteriorly by the bodies of the vertebrae and intervertebral discs. Posteriorly by the laminae, ligamentum flava and the arch which becomes spinous processes with ligaments between them, the interspinous ligaments, and laterally by the pedicles and laminae of the vertebrae.

CONTENTS

1. Roots of spinal nerves.

2. Spinal membranes with their enclosed cords and CSF.
3. Epidural vessels, fat and alveolar tissue of the extradural space.

4. Spinal cord begins at the level of foramen magnum as a continuation of medulla oblongata and ends below at the conus medularis. Spinal cord lies within the vertebral canal bound together by several ligaments which gives stability and elasticity. The important ligaments are supraspinous, interspinous and ligamentum flavum. The spinal cord is protected by both the bony vertebral column and the three connective tissue covering the meninges—the duramater,

the arachnoid matter and the piamater.

The subarachnoid space is filled with CSF and contains numerous trabeculae which form a delicate sponge like mass. The subarachnoid space has 3 divisions. Cranial (surrounding the brain) Spinal (surrounding the spinal cord) and Root (surrounding the dorsal and vertebral roots). All these compartments are in free communication with each other. There are 31 pairs of symmetrically arranged spinal nerves 8Cervical, 12Thoracic, 5Lumbar, 5Sacral and 1Coccygeal.

CSF

It is an ultrafiltrate of plasma and is produced by the choroid plexus in the lateral ventricle. It is a clear, colourless fluid found in the spinal and cranial subarachnoid space and in the ventricles of the brain.

At 37 degree centigrade, its specific gravity is 1003 to 1009 and its pH is 7.4-7.6. The total amount varies from 120-150ml of which 25-35ml is in the spinal subarachnoid space. In the horizontal position, the CSF pressure ranges from 60-80 mm of water.

DENSITY AND BARICITY

Density is the weight of one ml of solution at a specific temperature. Baricity is a term related to the local anaesthetic used for spinal anaesthesia.. It is the ratio of the density of the local anaesthetic at a specified temperature to the density of CSF at the same temperature. Local anaesthetic solution with a baricity of less than .9998 at 37deg. centigrade are hypobaric in all patients. While local anaesthetic solution at 37 deg. centigrade with baricity 1.008 are hyperbaric,

those between .9998 and 1.008 are isobaric .

Isobaric

These tend to remain in the vicinity of the injection site, both during and after injection and are unaffected by movement of the patient after injection.

Hyperbaric

Hyperbaric solutions are produced by mixing them with dextrose. Barker first introduced this technique in 1907. Increasing the density of local anaesthetic solution for spinal use by addition of dextrose[3,4] increase controllability as with the weighed solution. The movement is more responsive to position of patient resulting in more easily manageable levels.

Fink et al concluded that it is unnecessary to use solutions with a dextrose concentrations greater than 5% as this was found to be optimal.

CARBONATED LA SOLUTIONS

Bromage has recommended the use of a carbonated local anaesthetic solution to prolong the duration of anesthetic action. As a weak base, bupivacaine exists largely as a cation and does not readily penetrate the epineurium of nerves on alkalinizing the solution. The agent exists predominantly as an unchanged particle which readily penetrates the neuronal membrane to establish a high intraneuronal concentration where it readily ionizes in the axoplasm and blocks conduction.

VASOCONSTRICTOR AGENTS

In 1940, Pitkin stated that addition of vasoconstrictor agents would result in reduction of toxicity of local anaesthetic agents and that the duration of anesthesia would be

prolonged.

Ephedrine, Adrenaline and Phenylephrine have been used to prolong spinal anaesthesia. Ephedrine is least effective and rarely used. Adrenaline (1:1000) upto 100mg (0.1 mg) and Phenylephrine 1% solution (2.5mg) have been added to prolong subarachnoid blockade clinically and experimentally without any adverse effects. Adrenaline and Phenylephrine also have autoreceptive effects on the dorsal horn of spinal cord. Intrathecal clonidine is also effective in prolonging the local anaesthesia induced sensory and motor blockade. Racle et al[8] demonstrates that intrathecal clonidine in dose of 0.15mg, prolonged motor (38%) and sensory (46%) blockade when used as an adjunct to spinal anaesthesia using bupivacaine.

Clonidine is also effective following oral administration, reaching a peak plasma concentration within 80-90 mines of administration. Although prolongation of local anaesthetic induces spinal sensory and motor blockade is well documented after co-administration with intrathecal clonidine, the effect of oral clonidine remains controversial.

BASIC PHARMACOLOGY AND CLASSIFICATION OF ADRENERGIC RECEPTORS

Until recently , the dual receptor theory of Ahlquist was the only framework for the understanding of adrenergic receptors. Ahlquist differentiated the adrenergic receptors into α and β based on the rank order of potency of various natural and synthetic catecholamines.

Subsequently Lands and colleagues showed that the rank order of potency of a series of catecholamines for a variety of β adrenergic receptor mediated responses could used to identify two types of β adrenergic receptors β_1 and β_2 . Both these receptors stimulate the membrane bound enzyme adenylate cyclase , leading to the intracellular accumulation of 3, 5 cyclicAMP , a ubiquitous second messenger present in all tissues.

The next major breakthrough was the identification of a receptor in the presynaptic site of a adrenergic pathway which regulated the release of neurotransmitter. This led a subdivision of adrenoceptors based on the synaptic location into postsynaptic and presynaptic . A classification based strictly on anatomical location has proven to be untenable in the light of postsynaptically and even extrasynaptically located α2 adrenergic receptors not linked to neurotransmitter release. The current pharmacological classification of α2 versus α1 is based on the antagonists Yohimbine and Prazosin is more potent than Prazosin at α2 receptors.

The basic structure is similar to other neurotransmitter receptors. Each of the receptor proteins is comprised of a single polypeptide chain which weaves back and forth through the cell membrane. The main structural difference exists in the cytoplasmic side of the

receptor which predicates the characteristic adrenergic responses. By providing contact points for the host of guanine nucleotide binding proteins –the G proteins in turn signal to a discrete effector mechanism which may be a transmembrane ion channel (Efflux of K- or suppression of Ca++ entry) or second messenger cascade (cyclic AMP or Inositolphosphate) (Figure I).

PHARMACOLOGY OF α2 Agonists.

The α2 agonists can be grouped into 3 main classes:

1. Phenylethylamines eg α methyl noradrenaline
2. Imidazolines eg Clonidine
3. Oxaloazepines eg Azepexole.

The α adrenergic drugs can be arranged in order of their selectivity to α2 and α 1 receptors as given below:-

α2 Dexmedetomidine
Guanafacine
Clonidine
Oxymetazaoline
Epinephrine
Norepinephrine

α1 Phenylephrine

Dexmedetomidine, currently under development is most selective with α 2 to α1 ratio of 2000:1 , whereas clonidine exhibits a selectivity of 300:1.

CLONIDINE

CHEMISTRY

An imidazole compound

HISTORY

Clonidine was synthesized in 1960 and was originally developed for intranasal administration as a nasal decongestant. Since it is highly lipid soluble it is not surprising that it produced systemic effects (sedation and hypotension) and its use as a decongestant had to be

abandoned.

PHARMACODYNAMICS

Clonidine is rapidly and almost completely absorbed after oral administration and the bioavailability is nearly 100% Peak plasma concentration is reached again 60-90 minutes and maximal hypotensive effects are observed 1-3 hours after an oral dose. The elimination half-life of clonidine is between 6 and 24 hours (mean 12 hours). Approximately 50% of the drug is metabolized in the liver to inactive metabolites while the rest is excreted unchanged by the kidney.

PHARMACOLOGIC EFFECTS OF α2 ADRENERGIC AGONISTS

	Site	Effect
Cardiovascular	Brainstem; Spinalcord Peripheral vasculature Heart	Decreased BP. HR Increased BP. SVR Slowed conduction
Consciousness	Locus coeruleus	Sedation, anaesthesia
Pain transmission	Peripheral nerve endings Brainstem	Reduced sensitivity Analgesia
Respiration	Brainstem	Reduced respiratory drive
Hormonal	Hypothalamus, Pituitary	Decreased ACTH, LH
		FSH, AVP, Increased GH
	Pancreatic islets	Decreased Insulin
	Spinalcord , periphery	Decreased
		Catecholamines

EFFECTS OF ACTION OF CLONIDINE

CENTRAL NERVOUS SYSTEM

Clonidine by virtue of its action on the small discrete nucleus of noradrenergic cells in the brainstem , the locus coeruleus causes sedation and anxiolysis, clonidine is a potent analgesic by itself and acts synergistically with concomitant Opioids. Anaesthesia induced by α2 agonists is mediated through G1 protein and is dependant on inhibition of c-AMP protection.

CARDIOVASCULAR SYSTEM

Action of clonidine may be classified as peripheral or central.

PERIPHERAL.

Clonidine inhibits noradrenaline release from the peripheral prejunctional nerve endings and this may lead to bradycardia . Among the different vascular beds the effects of clonidine on the coronary circulation is important. Clonidine has been documented to release EDRF(Endothelial Derived Relaxant Factor) in coronary arteries and to enhance coronary blood flow induced by endogenous and exogenous adenosines in an INVIVO MODEL . Intravenous clonidine causes a transient hypertensive response due to its direct action on the post-synaptic α2 receptors . However this effect is not seen when clonidine is administered orally.

CENTRAL

Clonidine mediated hypotensive and bradycardia effects have been well recognized. The mechanism for these actions may involve inhibition of sympathetic outflow and the potentiation of parasympathetic nerve activity. However the precise mechanism involved in these actions is not well understood. While the nucleus tractus solitarius is an important central

site for the action of α2 agonists, other nuclei, including the locus coeruleus , the dorsal motor nucleus of vagus and the nucleus reticularis lateralis may also mediate hypotension, bradycardia or both. It has been documented that the imidazole – preferring receptors play an important role in the hypotensive effects of clonidine.

ANTI-ARRHYTHMIC PROPERTIES.

Clonidine is capable of preventing adrenaline-induced arrhythmias during halothane anaesthesia.

CEREBRAL CIRCULATION.

Clonidine has been shown to decrease cerebral blood flow. This action may be favourable in protecting the brain from an abrupt increase in intracranial tension..

RESPIRATORY SYSTEM.

α2 agonists may produce mild respiratory depression by three mechanisms.

a.) Sedation or analgesia can produce a small decrease in respiratory rate due to anxiolysis or pain relief

. b.) By acting at the α2 receptors close to the respiratory centre in the brainstem.

c.) By interference of the thermoregulatory control mechanism.

Respiratory depression is not common and there are only anecdotal reports in literature . It may occur if massive doses of clonidine is used. There is no potentiation of opioid induced respiratory depression by clonidine.

Nebulized clonidine causes bronchial constriction is asthmatics.

ENDOCRINE SYSTEM

α2 agonists can decrease stress induced ACTH release and hence cortisol synthesis.

α2 agonists activate growth hormone release and has been used as a diagnostic tool to test for the pituitary glands ability to release growth factor in children.

Clonidine also inhibits the release of Insulin from the pancreatic β cells directly.

α2 agonists decrease circulating Norepinephrine and Epinephrine by central and peripheral mechanisms. Centrally they diminish sympathetic outflow by actions in the brainstem and spinalcord. Peripherally, they stimulate classical presynaptic autoinhibitory α2 adrenergic receptors to decrease norepinephrine release.

GASTROINTESTINAL SYSTEM.

Hyposalivation is one of the advantages of clonidine as a premedicant . Clonidine is also supposed to prevent intestinal ion and water secretion in the large bowel.

RENAL SYSTEM.

Clonidine induces diuresis by

a. Inhibition of ADH release
b. Antagonism of the renal tubular action of ADH.
c. Increase in the GFR.
d. Release of atrial natriuretic factor

HAEMATOLOGICAL SYSTEM

Clonidine induces platelet aggregation. It also enhances the aggregatory effects of other drugs.

CLINICAL USES.

The ADVANTAGES of α2 agonists over other agents used for anaesthesia and analgesia

are

a. lack significant respiratory depression
b. low abuse potential
c. ability to rapidly reverse therapeutic and pharmacological effects with specific α2 antagonists.

The DISADVANTAGES of α2 agonists over other agents include

a. Dry mouth
b. Sedation
c. Bradycardia and
d. Hypotension

PRE MEDICATION

As a premedicant 90-120 minutes prior to induction produces good sedation, maintains cardiovascular stability intraoperatively without respiratory depression..

Clonidine decreases intraocular pressure both before and during surgery.

Combination of oral and transdermal Clonidine at therapeutic levels to provide greater haemodynamic stability.

INTRAOPERATIVE USE

Intrathecal clonidine (150mcg) to potentiate local anaesthetic agents to prolong bupivacaine spinal anaesthesia in elderly patients undergoing hip surgery.

Postoperative administration of extradural clonidine to produce effective analgesia in a dose dependant fashion – 100-900 mcg in patients after knee orthroplasty or abdominal surgery.

Extradural clonidine for the relief of neuropathic pain (100 – 900 mcg) and as a therapeutic

adjunct in the management of refractory reflex sympathetic dystrophy.

Intrathecal clonidine in combination with morphine for attenuation of cancer pain and terminal pain especially in patients who have developed tolerance to intrathecal morphine.

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OTHER USAGES.

The major advantage over other general anaesthetic or supplements is providing haemodynamic stability . Increases in blood pressure and heart rate during tracheal intubation and surgical stress are blunted or abolished by α2 adrenergic agonists.

Clonidine induced sedation is counterbalanced by reduced requirement for other general anaesthetics and therefore the recovery time is actually reduced.

Clonidine may diminish myocardial ischaemia intra and postoperatively after a single dose, providing an important indication in high risk patients

Systemic clonidine for postoperative analgesia 5mcg/kg intramuscularly

CONSIDERATIONS FOR USE OF α2 ADRENERGIC AGONISTS IN ANAESTHESIA

	Advantages	**Disadvantages**	**Potential Advantages**
Major	Preservation of haemodynamic stability (prevent wild swings in HR & BP) Anxiolysis/Sedation/Analgesia without respiratory depression	Hypertension (parenteral bolus administration)	Preservation of renal function in presence of insult. Limitation of increase in ICP/IOP. Decrease of narcotic induced muscle rigidity. Bronchodilatation.
Minor	Limitation of the use of	Hypotension	

	potentially toxic anesthetic/adjunctive agents. Induced hypotension.	Bradycardia 'rebound' (only after prolonged use.)	

REVERSAL

Clinical effects of clonidine can be reversed by atipamezole. .

PHARMACOLOGY OF BUPIVACAINE

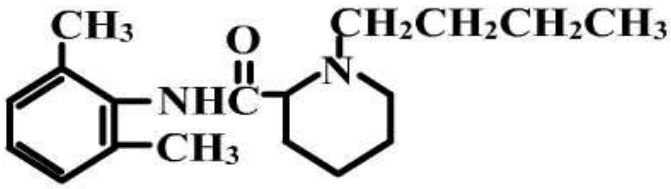
HISTORY

It is an amide linked local anesthetic synthesized by B.A.F Ekenstam in 1957 and introduced into clinical practice by Talivuo in 1963.

STRUCTURE

An amino amide local anesthetic having aromatic moiety (benzene ring), which offers liphophilicity at one end of the molecule. It is linked by an amide to a tertiary amine, which is hydrophilic on the other end of the molecule.

MOLECULAR FORMULA



It displays stereoisomerism: marketed as a racemic mixture containing optically active enantiomers, R and S. S-enantiomer has been noted to have a slightly longer duration of action and lower systemic toxicity when compared to its R-type.

MECHANISM OF ACTION

The base form is in equilibrium with cationic form outside the axoplasmic membrane. Base form diffuses inside the cell and recalibrates with cationic form. It then reaches the local anesthetic receptor in the Na^+ channel by reversing channel pore while it is in an open state. It prevents Na^+ ions moving intracellularly.

In addition to this simple sodium channel blockade, it also affects second messenger system such as adenylate cyclase and guanylate cyclase and also inhibits synaptic transmission by modification of post synaptic receptor (or) presynaptic calcium channel blockade in epidural / subarachanoid blockade.

PHYSIOCHEMICAL PROPERTIES

Property	Value
Molecular weight	288
Potency ratio	15
Toxicity ratio	10
pKa(25.C)	8.16
Protein binding in %	
Maternal	95
Fetal	66
% non ionized at	
pH 7.4	17
pH 7.2	11
Partition co-efficient	
(25.C, pH 7.4)	346
Anesthetic index	3.0-4.0

ABSORPTION

A biphasic absorption pattern has been found for epidural Bupivacaine. The rapid initial absorption following epidural administration is most likely related to high concentration gradient between the drug in the solution and in the blood. In addition profound increases in epidural blood flow observed during epidural administration of Bupivacaine may contribute to its fast initial absorption rate.

Later on, after the local anaesthetic has been taken up into local tissues such as epidural fat, absorption will become dependent on tissue blood partitioning, resulting in marked slowing of absorption. Estimated total fraction of the dose ultimately absorbed into general circulation is 0.94 with mean absorption time 8.6 hours.

Absorption of local anesthetic is directly related to the amount of drug injected, vascularity, site injected and tissue binding of local anesthetic at injection site. Bupivacaine will produce lower C_{max} than less potent and less lipid soluble agents.

DISTRIBUTION

Distribution of local anesthetic has special emphasis in the pregnant patient, because one of the organs that will be exposed to the absorbed drug is fetoplacental unit.

PHARMACOKINETICS OF BUPIVACAINE

Elimination half-life t1/2β - 162 minutes

Volume of distribution VDSS - 73 lit

Clearance (lit/min) - 0.6

Hepatic extraction - 0.4

BIODEGRADATION AND ELIMINATION

Liver is the site of metabolism. Two major factors controlling the clearance of the amide-linked local anesthetic are hepatic blood flow and hepatic function. The principal pathways are N-dealkylation, aromatic hydroxylation and amide hydrolysis.

CLINICAL CHARACTERISTICS OF BUPIVACAINE

Property	Value
Penetrance	Moderate
Duration	6-8 hrs
Infiltration	0.05%
Field block	0.1%
Pudendal / paracervical	0.125%
Epidural analgesia	0.125 – 0.25%
Extradural motor	0.5 – 0.75%
Maximal dose	2mg/kg body weight

ADVERSE EFFECT AND COMPLICATIONS

Central Nervous System Toxicity

Potentially toxic blood level can occur when a drug is injected intravenously, intra arterially or a large dose of drug is given into highly vascular area. Risk of CNS toxicity is more because Bupivacaine is a highly protein bound drug. Pregnancy is associated with 30% reduction in protein binding. This allows for higher brain level of Bupivacaine for a given dose of drug.

Symptoms

Slow speech, jerky movements, tremors, hallucination, and seizure.

Cardiovascular Toxicity[36,37]

1. Dose dependant depression of contractility
2. Dose dependent depression of conduction and velocity in all conducting tissues. Progressive prolongation of ventricular conduction.
3. Predisposition to reentry phenomenon followed by sudden onset of ventricular fibrillation.
4. More affinity for cardiolipin

Toxic plasma concentration is 4-5µg/ml.

REVIEW OF LITERATURE

Administration of first spinal anaesthesia was by Corning in the year 1885. He attempted to anaesthetise the lower half of the body of a patient by injecting Cocaine into subarachnoid space.

ORAL CLONIDINE PRETREATMENT AND SPINAL ANAESTHESIA

Pouttu at al studied the effect of oral clonidine premedication on concentrations of cortisol and monoamine neurotransmitters and their metabolites in cerebrospinal fluid and plasma[10]. Forty two healthy male patients aged 19 to 40 years undergoing orthopaedic surgery under spinal anaesthesia were studied.

They were divided into 4 groups: clonidine 4.5microgram/kg orally either 2 hours before surgery (group I) or 4 hours before surgery (group II), diazepam 0.15 mg/kg orally (group III) or placebo tablet (group IV). Plasma concentration of cortisol, noradrenaline, adrenaline, 3,4 dihydroxyphenyl glycol (DHPG) dihydroxyphenyl acetic acid (DOPAC) were assayed from venous samples just before premedication and just before spinal block. The plasma noradrenaline concentrations of patients in groups receiving clonidine clearly decreased as compared with other groups. In group I, the sensory blockade lasted significantly longer than in group III and mean duration of motor blockade was longer in group I than in groups III and IV.

Bonnet et al studied the effects of oral and subarachnoid clonidine on spinal anaesthesia with bupivacaine[1]. Their study was designed to determine the analgesic properties of clonidine and its

effects on the minimum alveolar concentration of inhaled anaesthetics and the quality and duration of spinal anaesthesia with bupivacaine. The comparative effects of oral and subarachnoid clonidine on spinal anaesthesia with bupivacaine were studied in 36 patients scheduled for orthopaedic surgery. Patients were allocated randomly into four groups to receive either oral diazepam (10mg in groups I and II) or oral clonidine (150 microgram and 300 micrograms in group III and IV respectively) as premedication. Spinal anaesthesia was performed with 15mg hyperbaric bupivacaine 0.5% plus either 1ml isotonic saline in groups I,III and IV, or 150 microgram clonidine in group II. They concluded that subarachnoid but not oral clonidine significantly prolonged the duration of sensory blockade (time for regression to L1 was 157+ /- 21 minutes in group I, 267+/-75 minutes in group II, 168 +/-59 minutes in group III and 157+/-22 minutes in group IV) and the duration of motor blockade (duration of grade III motor block – Bromage scale was 103 +/- 20 minutes in group I, 175+/-68 in group II, 145+/-43 in group III and 120+/- 19 in group IV).

Ota et al studied the effects of oral clonidine on the duration of isobaric tetracaine spinal anaesthesia [11]. They studied 30 patients who were divided into 3 groups.

Group I (n = 10) received 0.25 mg of oral triazolam

Group II (n = 10) received 0.15 mg of oral clonidine

Group III (n = 10) received 0.25 mg of oral triazolam and -.75 mg of intrathecal phenylephrine.

All the groups received 15 mg of tetracaine intrathecally in isobaric saline solution. While the regression time in groups II and III were significantly longer than those in group I, the regression times were not different between groups II and III. The authors concluded that sensory blockade produced by the intrathecal administration of tetracaine could be prolonged by premedication with 0.15 mg of clonidine given orally. The prolongation is similar to that produced by intrathecal

phenylephrine.

Singh et al studied the effect of oral clonidine and intrathecal fentanyl on the onset and duration of spinal anaesthesia produced by hyperbaric tetracaine[12]. They studied 40 adult males undergoing elective surgery. All patients received a crystalloid preload of 300 to 400 ml with lactated Ringer solution followed by 5 to 10 ml/kg/hr intraoperatively. The patients were divided randomly into 4 treatment regimens: Group I: Placebo per os (PO) + tetracaine 12 mg intrathecally (IT); group II: Placebo (PO) + tetracaine 12 mg (IT) + fentanyl 10 micrograms IT: group III: Clonidine 200 micrograms (PO) + tetracaine 12 mg IT; group IV: Clonidine 200 microgram (PO) + tetracaine 12 mg IT + fentanyl 10 microgram IT

They found that the intrathecal administration of 10 micrograms fentanyl did not change the onset or duration of tetracaine-induced spinal anaesthesia. Furthermore, there was no significant interaction between clonidine and fentanyl in group IV. They concluded that oral clonidine (200 micrograms) shortened the onset time of sensory blockade produced by tetracaine and prolonged the duration of sensory and motor blockade. However, clonidine premedication increased the risk of hypotension and bradycardia.

Ota et al conducted a study to evaluate the optimal time for administration of oral clonidine as premedication for prolonging the duration of tetracaine induced spinal anaesthesia in humans[13]. Forty male patients scheduled for urologic surgery were studied. Patients were allocated randomly into 4 groups who were given 15 mg of 0.5% isobaric tetracaine. Patients in group I were given 250 micrograms triazolam orally 1 hour before anaesthesia while those in groups II, III and IV were administered 150 micrograms oral clonidine just before anaesthesia, 1 hour and 3 hours before anaesthesia respectively. Sensory block was assessed by pin prick. Patients in group II and III had a significantly longer duration of sensory blockade (74% to 94%) when compared to patients in group I.

However this prolonging effect of oral clonidine was not apparent in patients in group IV.

They concluded that when administered orally 1 hour before anaesthesia clonidine in a dose of 150 micrograms produced a significant prolongation of Spinal anaesthesia produced by tetracaine without producing adverse effects.

The same group did a study on the dose related prolongation of tetracaine spinal anaesthesia by oral clonidine in humans[14] Forty seven healthy patients were divided randomly into 4 groups. All patients received 15 mg tetracaine intrathecally in isobaric saline. Patients in group I received 0.25 mg triazolam orally while those in groups II , III & IV received 75 mg , 150 mg and 300 mg of oral clonidine respectively. These drugs were administered one hour before anaesthesia sensory block was evaluated by pin prick. Regression time was prolonged significantly in all the groups as compared to the control group. The prolongation produced by oral clonidine increased in a dose dependent manner and reached a maximal effect at 150 micro grams. 4 patients in group IV developed bradycardia (heart rate < 45 BPM), suggesting that the does of 300 micro grams of oral clonidine may promote bradycardia during spinal anesthesia .

Liu et al studied the effect the oral clonidine on the duration of spinal anaesthesia produced by lignocaine in human volunteers[15] . Eight volunteers received 50 mg of lignocaine (1.5 % dextrose free) both with and with out 0.2 mg oral clonidine 1.5 hour before spinal anaesthesia. Sensory block was assessed by pin prick, transcutaneous electric stimulation equivalent to surgical incision and duration of tolerance to pneumatic thigh tourniquet. Motor block at quadriceps and gastronemius muscles was assessed by isometric force dynamometry. They concluded that pre medication with oral clonidine prolonged sensory and motor blockade from lignocaine induced spinal anesthesia .

Omote et al evaluated the effects of oral triazolam , tizanidine and clonidine as premedication for tetracaine spinal anesthesia[16].Sixty two patients were randomly allocated to one of

the six groups . Patients in group I (n = 7) group II (n = 8) and group III (n = 7) received 13 mg of tetracaine intrathecally in 10% glucose solution 2.6 ml. Patients in group IV (n = 13), group V (n = 14) and group VI (n = 13) received 13 mg of tetracaine intrathecally in a volume of 2.8 ml in 10% glucose solution which contained 0.6 mg of phenylephrine. Patients in groups I and IV received 0.25 mg of oral triazolam while those in groups II and V received 3 mg of oral tizanidine. Patients in groups III and VI received 0.15 mg of oral clonidine.

Patients in groups II and V or group III and VI needed a significantly longer time for regression of sensory blockade as compared to patients in groups I and IV. Heart rate and blood pressure of patients in group VI (clonidine – tetracaine – phenylephrine group) showed significant decreases ($P < 0.05$) after spinal anaesthesia. Hence they concluded that oral premedication with clonidine and tizanidine prolonged tetracaine-induced spinal anaesthesia. From the viewpoint of prolongation of spinal anaesthesia and the haemodynamic stability, oral premedication with tizanidine seems to be useful.

Goyagi et al studied the effect of oral clonidine premedication on the quality of postoperative analgesia by intrathecal morphine[17]. Twenty six patients were randomly allocated into 2 groups. Coniine group (n = 13) received oral clonidine 5 micrograms / kg and the control group (n = 13) received no clonidine. All patients received hyperbaric tetracaine 12 mg dissolved in 10% dextrose and morphine 0.2 mg of spinal anaesthesia. The duration of analgesia (time to the first request for supplemental analgesics) and motor block were noted. The duration of analgesia in the clonidine group was longer than the control group. They concluded that preanaesthetic medication with oral clonidine enhances the postoperative analgesia produced by intrathecal morphine plus tetracaine without increasing the intensity of side effects from morphine.

Filos et al studied the effects of orally administered clonidine as premedication in the elderly[18]. To pursue this approach, sedation, intraocular pressure (IOP), and haemodynamic profile of two doses of oral clonidine premedication were compared in 60 elderly patients, aged 65 to 82 years, who underwent elective ophthalmic surgery under local anaesthesia. Group I (n = 20) received placebo, group II (n = 20) received 150 microgram of clonidine (2 to 2.5microgram/kg) and group III (n~20) received 300 microgram of clonidine (4 to 4.5 I1g/kg) in a randomized, double blind fashion . Decreases in mean arterial blood pressure were more pronounced and occured earlier after 300microgram of clonidine (31.4 +/-12.1%, P<0.001) as compared to 150 microgram of clonidine (18.1 + 10.9% P <0.001) Throughout the study, 6 patients (30%) in group III (300 microgram clonidine treated group), were treated atleast once for hypotension, while no patient in groups I or II required any such treatment (P<0.05). Heart rate decreased significantly 18.5 +/- 8.1% (P<0.001) only after 300 micro gram of clonidine. Clonidine 150 microgram and 300 microgram decreased IOP 32.1 +/- 14.3% (P<0.001) and 47.8 +/- 17.2% (P<0.001) respectively. After 150 micro gram of clonidine, patients were significantly more sedated as compared to those given placebo (pc0.01) but significantly less sedated than after 300 micro gram of clonidine (P<0.01), where sedation persisted more than 6 hours postoperatively. The authors concluded that a dose of 150 micro gram of clonidine given orally 90 to 120 minutes preoperatively to elderly patients managed with local anaesthesia is as effective as a dose of 300 micro gram in decreasing IOP perioperatively without causing excessive haemodynamic depression and sedation.

NEURAXIAL ADMINISTRATION OF CLONIDINE

Acalovschi at al studied the effect of added α adrenergic agonists, adrenaline versus clonidine on spinal anaesthesia with pethidine[19]. Forty five patients scheduled for orthopaedic surgery were divided into three groups. They received spinal anaesthesia with 1 mg/kg of 5% pethidine alone or with 200 microgram of adrenaline or 2 microgram/kg clonidine. The onset, extent and duration of

sensory block (to pin prick) and duration and degree of motor block (Bromage scale) were assessed as were the haemodynamic responses, duration of postoperative analgesia and degree of sedation. The addition of adrenaline to the pethidine solution prolonged the sensory block ($P<0.01$) but did not affect its onset or extent. A similar potentiation was demonstrated for clonidine ($P<0.001$). The duration and degree of motor block were increased by addition of both adrenaline and clonidine. A tendency towards bradycardia and a decrease of mean arterial pressure was potentiated by clonidine but not by adrenaline.

Only the addition of Clonidine prolonged the postoperative analgesia ($P<0.001$), but was associated with an increased sedation score. The authors concluded that co-administration of adrenaline or clonidine with pethidine enhances the intensity and duration of spinal anaesthesia and that addition of clonidine prolongs the duration of postoperative analgesia.

Mercier at al studied the effect of addition of mini-dose of clonidine to sufentanil on combined spinal and epidural analgesia for first stage of labour[20]. Group I received sufentanil 5 micrograms + clonidine 30 micrograms intrathecally (n = 10) and group II only intrathecal sufentanil 5 micrograms (n = 11). Analgesia evaluated with the VAS pain scores was better in group I compared with group II ($P = 0.02$) and decreased somewhat slower. Side effects such as hypotension, pruritis and sedation were not statistically different between the groups. Nausea and motor blockade did not occur. The authors concluded that the addition of mini dose of clonidine (30 micro grams) to sufentanil (5 micrograms) given intrathecally seems to markedly potentiate the analgesia obtained during the early first stage of labour.

Klimscha et al compared the haemodynamic and analgesic effects of spinal versus epidural clonidine alone and after repetitive dosing.[23] Forty patients scheduled for lower extremity

orthopaedic surgery under continuous spinal or epidural anaesthesia with bupivacaine 0.5% (initial dose 5 mg and 50 mg respectively) were studied. In either spinal or epidural technique, one half of patients received clonidine 150 micrograms in addition to bupivacaine. Repeat doses of the same anaesthetic mixture were allowed in cases of subsequent pain. Mean arterial pressure (MAP) and heart rate were recorded for 6 hours after each injection. Duration of clinically useful anaesthesia was defined as the time from drug administration to first sensation of pain. Intrathecal but not epidural clonidine decreased MAP significantly compared with bupivacaine alone. Mean arterial pressure after intrathecal clonidine with bupivacaine was lower than epidural clonidine 5 and 6 hours after injection. Onset time required to surgical anaesthesia (sensory blockade of T11) did not differ among the four groups. Duration of spinal and epidural anaesthesia was increased more than twofold by clonidine.

Girace et al studied the postoperative analgesia after co-administration of clonidine and morphine by the intrathecal route in patients undergoing hip replacement.[24] Postoperative analgesia after intrathecal co-administration of clonidine hydrochloride (75 micrograms) and morphine sulphate (0.5mg) was compared with analgesia produced after either intrathecal morphine 0.5mg or 0.9% sodium chloride in 90 patients undergoing total hip replacement under bupivacaine spinal anaesthesia. Patient controlled morphine requirements were significantly reduced ($P<0.001$) postoperatively by both by clonidine or morphine and morphine compared with control (saline). However, no significant additional reduction in postoperative analgesic requirements was seen with the clonidine/morphine combination compared with morphine alone. Visual analog pain scores, although good in all groups at all times, were significantly poorer in the control group at 2 hours ($P<0.04$) and 4 hours ($P<0.001$) after operation compared with both treatment groups, and significantly poorer than the clonidine/morphine group at 6 hours ($P<0.002$) and 24 hours ($P<0.008$) following surgery. Mean arterial blood pressure was significantly lower in the clonidine/morphine group than in the other two groups ($P<0.001$) between 2 and 5 hours after operation.

Seah et al studied the prolongation of hyperbaric bupivacaine spinal anaesthesia with Clonidine.[28] Forty ASA class I and II patients scheduled for transurethral prostatic resection were randomly allocated into two groups of twenty each. In the saline group, 3 ml of 0.5% hyperbaric bupivacaine plus 1 ml normal saline was given. In the clonidine group, 1 ml (0.15 mg) clonidine in addition to 3ml 0.5% bupivacaine was given. Assessment of the sensory blockade by pin prick, motor blockade by Bromage scale and measurement of blood pressure and heart rate were performed after injection. The highest level of sensory blockade and the time required for maximal spread of the sensory blockade were not significantly different in the two groups. The mean time for two segment regression and mean time for regression to L2 were significantly greater in the clonidine group than in the saline group ($P<0.001$). Motor blockade LL was also prolonged in the clonidine group than in the control group. Side effects such as hypotension (10 in clonidine group versus 4 in saline group) and bradycardia (4 clonidine versus 2 in saline) occurred commonly in the clonidine group, but all patients could be effectively treated with ephedrine and atropine respectively.

Bonnet et al studied the dose related prolongation of hyperbaric tetracaine spinal anaesthesia by clonidine in humans.[30] Forty four ASA physical status I and II patients scheduled for orthopaedic surgery were randomly allocated into three groups. All the three groups received 15 mg of 0.5% hyperbaric tetracaine. Group I($n = 14$) received 1 ml isotonic saline while group II ($n = 15$) received 0.5 ml saline with 0.5ml clonidine (75 micrograms). Group III ($n = 15$) received 1 ml clonidine (150 micrograms). Sensory blockade was evaluated by pin prick and motor blockade according to Bromage's scale. The level of sensory blockade was comparable in the three groups, but the duration was different. The group receiving 75 micrograms clonidine had a 25% prolongation of sensory blockade. Coniine in a dose of 150 micrograms prolonged the duration of sensory blockade at

L2 by 72% and grade III motor blockade by 96%. Colloid infusion and the decrease in diastolic blood pressure were significantly greater in the clonidine (150 microgram) group compared to the control group. The authors concluded that clonidine produces a dose related prolongation of spinal anaesthesia.

Racle et al studied the prolongation of isobaric bupivacaine spinal anaesthesia with adrenaline and clonidine for hip surgery in elderly.[8] Sixty ASA class II or III patients aged 75 years or more who were scheduled for orthopedic hip surgery under spinal anaesthesia were included in the study. The subjects were randomly allocated into one of the three groups. All patients received 15 mg bupivacaine in 4 ml in the horizontal position. Group I patients, received bupivacaine plus 1 ml normal saline, group II patients received bupivacaine plus 0.15 mg clonidine. The segmental level of sensory loss was tested using forceps. The time course required for maximal spread of the sensory blockade did not differ in the three groups. No difference was observed between mean highest levels of sensory anaesthesia. The mean time to two segment regression from the highest level was significantly longer in group III than in Group I and II. Mean time for regression to the L2 segment was also significantly longer in groups II and III than in group I. This time tended to increase more with bupivacaine plus clonidine solution than with bupivacaine plus adrenaline solution. Significant prolongation of motor block was also associated with the addition of clonidine.

MATERIALS AND METHODS

This is a prospective, randomized, double blinded, control study. Prior approval was obtained from the ethical committee of **GOVERNMENT STANLEY MEDICAL COLLEGE AND HOSPITAL.** The procedure and complications of regional analgesia was explained to them in detail and written consent was obtained from them.

Inclusion criteria:

1 Patients belonging to ASA I and ASA II
2 Age 20-50 yrs
3 Elective lower limb and lower abdominal surgeries under spinal anaesthesia

Exclusion criteria:

1. DM, bleeding disorder or other systemic disorders.
2. Patients who have already received any Opioid drugs or systemic analgesics within prior 24 hours.
3. Any contraindication for central neuraxial techniques.
4. Patients with known allergy to local anaesthetic or other drugs.
5. Patient refusal for regional technique.
6. Patients belonging to ASA3 and ASA4

The patients were randomy divided into three groups of thirty each.

Group I – placebo (n =30)	Received placebo per oral + 12.5mg of hyperbaric Bupivacaine 0.5% (2.5 ml)
Group II - clonidine (n =30)	Received clonidine per orals 100microgram + 12.5 mg of hyperbaric bupivacaine 0.5% (2.5 ml).
Group III – clonidine (n =30)	Received clonidine per orals 150microgram+12.5 mg of hyperbaric bupivacaine 0.5% (2.5ml).

Clonidine or placebo was administered sixty minutes prior to entering the operating room.

An informed written consent was obtained from each patient prior to the procedure. No patient received any other premedication.

Procedure

The patients were explained about the procedure of spinal anaesthesia. An 18 gauge intravenous cannula was inserted and patients were preloaded with 500 ml of lactated Ringer's solution.

The baseline blood pressure and heart rate were recorded using an automated non-invasive monitor (L&T). The patients were placed in the lateral decubitus position for lumbar puncture. Under strict aseptic precautions, a lumbar puncture was performed through a midline approach using 23 gauge spinal needle at the L 3-4 intervertebral space. Once a free flow of cerebrospinal fluid was obtained, the local anaesthetic was injected at the rate of 1 ml/3 seconds. After the injection the patient was returned to the supine position and retained in that position for at least 20 minutes before being positioned for surgery. The table was kept in a horizontal position throughout the procedure. Dermatomal levels of sensory anaesthesia were evaluated by pin prick. The levels of pin prick analgesia were studied every minute for the first twenty minutes and then at 10 minute intervals until analgesia to pin prick recovered to the L1 segment.

The highest sensory levels were noted and the following parameters were evaluated and noted in the proforma (Appendix 1).

a) Time from injection to attainment of highest level of sensory blockade
b) Time for two segment regression of sensory blockade
c) Time for four segment regression of sensory blockade
d) Time for regression of sensory blockade to L1 segment
e) Time for onset of complete motor blockade. This was assessed and graded at the Same time intervals as sensory blockade using the following criteria previously described by Bromage.

Here the number of joints completely blocked in both lower limbs was scored. Only an

all-or-none decision need then be made at each joint. Thus a score of 0 is assigned for no block and 1 for complete block.

6 points = Complete block in both lower limbs

f) Time for recovery of motor blockade to L2 level (hip flexion)

g) Central effects: Sedation was studied and graded as described by Ramsay et al[35]

1.Patient is anxious and agitated or restless,or both.

2.Patient is cooperative, oriented and tranqualized.

3.Patient responds to commands only.

4.Patient exhibits brisk response to light glabellar tap or loud auditory stimulus.

5.Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus.

Intraoperatively, the blood pressure and heart rate were monitored at 1 minute intervals for the first ten minutes and later every 10 minutes for one hour.

All parameters were statistically analysed using the Students 't' test for unpaired observations between the groups. The sedation score was analysed using the Chi square test with Yates correction.

A P value of > 0.05 was taken to be statistically not significant (NS), a P value of <0.05 as statistically significant (S), a P value of <0.01 as statistically highly significant (HS) and a P value of <0.001 as statistically very highly significant (VHS).

All the observations recorded are presented in the master charts. (Appendices 2A, 2B,2C, 3A,3B and 3C)

OBSERVATION AND RESULTS

Age, Weight and Gender

The mean age of patients in the placebo group was 38.93+/-12.38 years, while that in the clonidine-A group was 39.53 +/- 10.82 years and clonidine-B group was 39.40+/-10.60. The mean weight of the patients in the Placebo group was 58.33 +/- 6.29 kg as compared to that in the clonidine-A group which was 55.63 +/- 5.56 and in clonidine-B was 56.30+/-5.90 (Table I).

Table I: age, and weight in the two groups studied

Group	Age (years) Mean +/- SD	Weight (kg) Mean +/- SD
Placebo	38.93+/-12.38	58.33+/-6.29
Clonidine-A	39.53+/-10.82	55.63+/-5.56
Clonidine-B	39.40+/-10.60	56.30+/-5.90

Anova F-test for age F=0.03 P=0.97

Anova F-test for weight F=1.67 P=0.19

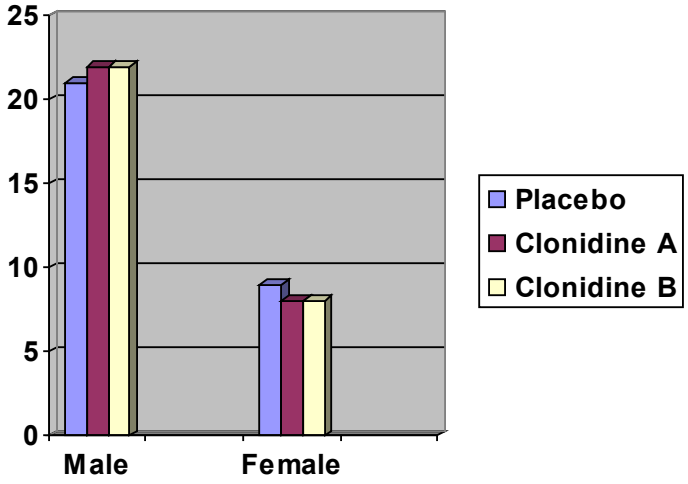
There was no statistically significant differences in the two groups with respect to age and weight.

The distribution of male and female patients in the two groups (with percentage) is given in Table II.

Table II: Distribution of number (%) of male and female patients in each group

		Groups			Total
		Placebo	Clonidine A	Clonidine B	
sex	male	21	22	22	65
	female	9	8	8	25
Total		30	30	30	90

$\chi 2=0.11$ P=0.95

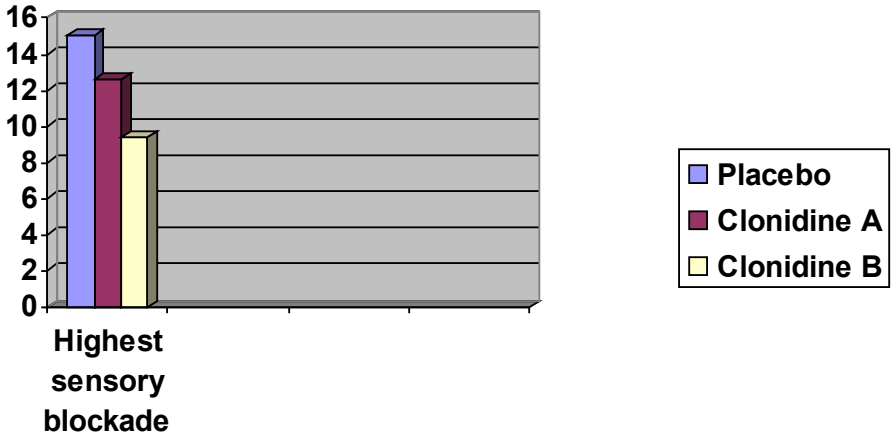


Time from injection to attainment of highest sensory blockade

The mean time from injection to attainment of highest sensory blockade in the Placebo group was 15.03 +/- 4.15 minutes while that in the clonidine-A group was 12.57+/- 2.30 minutes while that in clonidine-B was 9.37+/-2.34 (Table IIIa).

Table IIIa: Time taken for attainment of highest sensory blockade

Observed parameter	Groups	Mean	Std. Deviation	ANOVA F-test
Time from injection to attainment of highest sensory blockade.	Placebo	15.03	4.156	F=25.9 P=0.001
	Clonidine A	12.57	2.300	
	Clonidine B	9.37	2.341	



Intergroup comparision showed a statistically significant difference in the time from injection to attainment of highest sensory blockade between the three groups is highly significant. (Table IIIb).

Table IIIb: Intergroup comparison of time taken to attainment of highest sensory blockade
Bonferroni t-test

Observed parameter	Groups compared		Mean differance	Sig.
Time from injection to attainment of highest sensory block (min)	Placebo	Clonidine A	2.47(*)	.007
		Clonidine B	5.67(*)	.000
	Clonidine A	Placebo	-2.47(*)	.007
		Clonidine A	3.20(*)	.000
	Clonidine B	Placebo	-5.67(*)	.000
		Clonidine B	-3.20(*)	.000

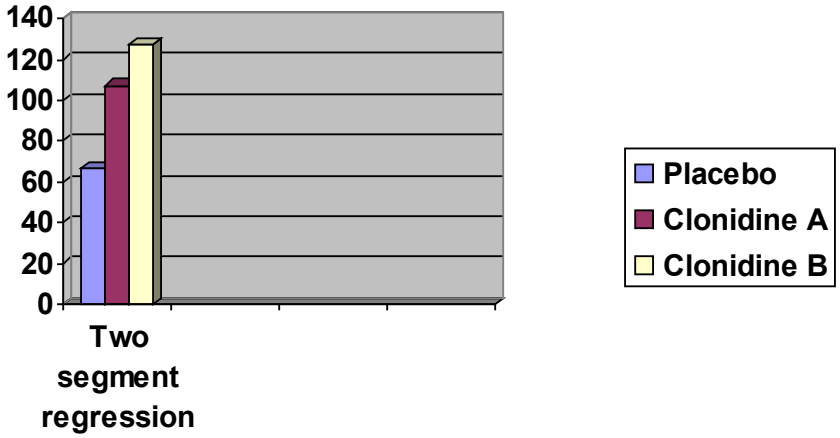
* The mean difference is significant at the .05 level.

Time for two segment regression of sensory blockade

The mean time for two segment regression of sensory blockade in the placebo group was 66.43 +/- 8.18 minutes while that in the clonidine-A group was 107.23 +/- 14.19 minutes while that in clonidine-B group was 127.47+/-15.22 (Table IVa).

Table IVa: Time for two segment regression of sensory blockade

Observed parameter	Groups	N	Mean	Std. Deviation	ANOVA F-test
Time for two segment regression of sensory block (min)	Placebo	30	66.43	8.182	F=173.8 P=0.001
	Clonidine A	30	107.23	14.197	
	Clonidine B	30	127.47	15.222	



Intergroup comparision of the two segment regression of sensory blockade showed a statistically very highly significant difference between the placebo and clonidine-A and clonidine-B groups. (P<0.001) (Table IVb).

Table IVb: Intergroup comparision of two segment regression of sensory blockade

Bonferroni t-test

Parameter observed	Groups compared		Mean Difference	Sig.
Time for two segment regression of sensory block (min)	Placebo	Clonidine A	-40.80(*)	.000
		Clonidine B	-61.03(*)	.000

	Clonidine A	Placebo	40.80(*)	.000
		Clonidine B	-20.23(*)	.000
	Clonidine B	Placebo	61.03(*)	.000
		Clonidine A	20.23(*)	.000

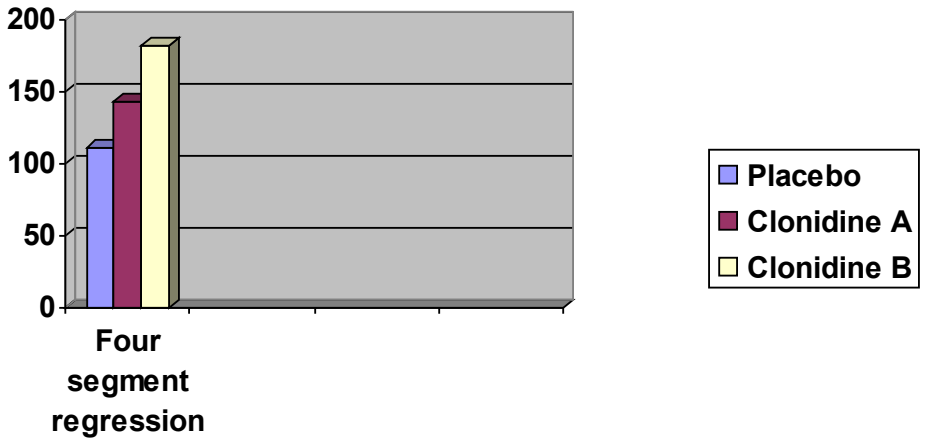
* The mean difference is significant at the .05 level.

Time for four segment regression of sensory blockade

The mean time for four segment regression of sensory blockade in the placebo group was 110.87 +/- 14.98 minutes, while that in the clonidine-A group was 142.97+/- 16.51 minutes, while that in clonidine-B was 181.83+/-18.84 (Table Va).

Table Va: Time for four segment regression of sensory blockade

Observed parameter	Groups	N	Mean	Std. Deviation	ANOVA F-test
Time for four segment regression of sensory blockage (min)	Placebo	30	110.87	14.989	F=133.3 P=0.001
	Clonidine A	30	142.97	16.508	
	Clonidine B	30	181.83	18.841	



Intergroup comparison of the four segment regression of sensory blockade showed a statistically very highly significant difference between the placebo and clonidine-A and clonidine-B groups (P<0.001) (Table Vb).

Table Vb: Intergroup comparison of four segment regression of sensory blockade

Bonferroni t-test

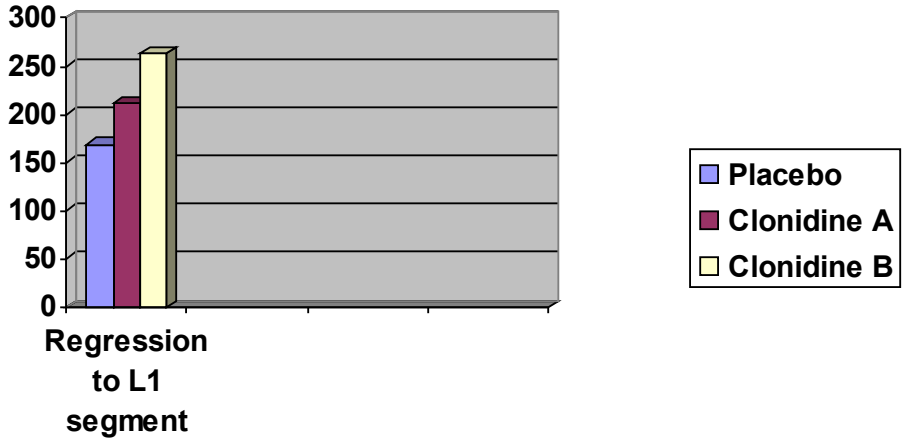
Parameter observed	Groups compared		Mean Difference	Sig.
Time for four segment regression of sensory blockage (min)	Placebo	Clonidine A	-32.10(*)	.000
		Clonidine B	-70.97(*)	.000
	Clonidine A	Placebo	32.10(*)	.000
		Clonidine B	-38.87(*)	.000
	Clonidine B	Placebo	70.97(*)	.000
		Clonidine A	38.87(*)	.000

Time for regression of sensory blockade to L1 seg

The mean time for regression of sensory blockade to L1 segment in the placebo group was 168.27 +/- 21.26 minutes, while that in the clonidine-A group was 211.40+\- 19.38 minutes, while that in clonidine-B group was 263.33 +/-27.51 (Table VIa).

Table VIa: Time for regression of sensory blockade to L1 segment

	Groups	N	Mean	Std. Deviation	
Time for regression of sensory block to L1 segment (min)	Placebo	30	168.27	21.260	
	Clonidine A	30	211.40	19.383	F=128.7 P=0.001
	Clonidine B	30	263.33	27.510	



Intergroup comparison of the regression of sensory blockade to L1 segment showed a statistically very highly significant difference between the placebo and clonidine-A and clonidine-B groups. (P<0.001) (Table VIb).

Table VIb: Intergroup comparison of regression of sensory blockade to L1 segment

Bonferroni t-test

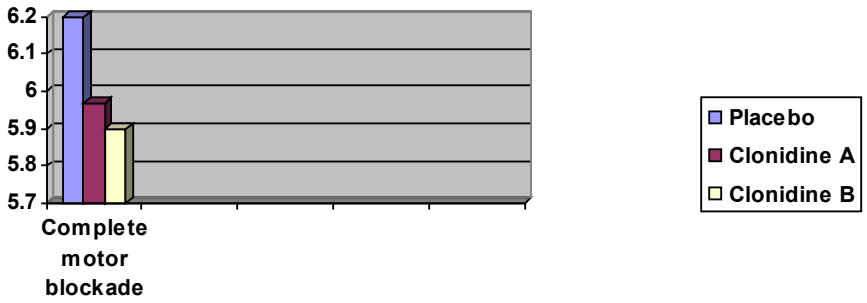
Dependent Variable	Groups compared		Mean Difference	Sig.
Time for regression of sensory block to L1 segment (min)	Placebo	Clonidine A	-43.13(*)	.000
		Clonidine B	-95.07(*)	.000
	Clonidine A	Placebo	43.13(*)	.000
		Clonidine B	-51.93(*)	.000
	Clonidine B	Placebo	95.07(*)	.000
		Clonidine A	51.93(*)	.000

Time for onset of complete motor blockade

The mean time for onset of complete motor blockade in the placebo group was 6.20 +/2.55 minutes while that in the clonidine-A group was 5.90 +/- 2.21 minutes, while that in clonidine-B group was 5.97+/-1.45minutes (Table VIIa).

Table VIIa: Onset of complete motor blockade

Parameter observed	Groups	N	Mean	Std. Deviation	ANOVA F-test
Time for onset of complete motor block (min)	Placebo	30	6.20	2.552	F=0.17 P=0.85
	Clonidine A	30	5.90	2.218	
	Clonidine B	30	5.97	1.450	



Intergroup comparison showed no statistically significant difference in the time of onset of complete motor blockade between the placebo and clonidine-A and clonidine-B groups (P>0.1) (Table VIIb).

Table VIIb: Intergroup comparison of the onset of complete motor blockade

Bonferroni t-test

Parameter observed	Groups compared		Mean Difference	Sig.
Time for onset of complete motor block (min)	Placebo	Clonidine A	.30	1.000
		Clonidine B	.23	1.000
	Clonidine A	Placebo	-.30	1.000
		Clonidine B	-.07	1.000
	Clonidine B	Placebo	-.23	1.000
		Clonidine A	.07	1.000

Time for recovery of motor block to L2 (hip flexion)

The mean time for recovery of motor blockade to L2 in the placebo group was113.90 +/- 26.26 minutes, while that in the clonidine-A group was 144.10+/- 23.24 minutes, while that in

clonidine-B was 150.13+/-39.49 minutes (Table VIIIa).

Table VIIIa: Time to recovery of motor blockade to L2 (hip flexion)

Parameter observed	Groups	N	Mean	Std. Deviation	ANOVA F-test
Time for recovery of motor block to L2 [hip flexion] (min)	Placebo	30	113.90	26.258	
	Clonidine A	30	144.10	23.240	F=12.16 P=0.001
	Clonidine B	30	150.13	39.485	

Intergroup comparision showed a statistically significant difference in recovery of motor blockade to L2 between the placebo and clonidine-A and placebo and clonidine-B groups (Table VIIIb),but there is no statistical difference between clonidine-A and clonidine-B group.

Table VIIIb: Intergroup comparison of the time to recovery of motor blockade to L2 (hip flexion)

Bonferroni t-test

Parameter observed	Groups compared		Mean Difference	Sig.
Time for recovery of motor block to L2 [hip flexion] (min)	Placebo	Clonidine A	-30.20(*)	.001
		Clonidine B	-36.23(*)	.000
	Clonidine A	Placebo	30.20(*)	.001
		Clonidine B	-6.03	1.000
	Clonidine B	Placebo	36.23(*)	.000
		Clonidine A	6.03	1.000

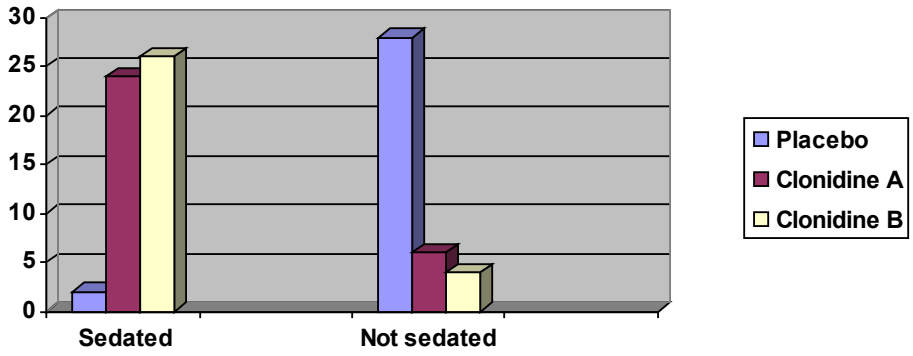
Sedation

Most of the patients in the clonidine group were sedated intraoperatively while only one patient was sedated in the placebo group. The sedation score achieved in these patients was 3, i.e., these patients were drowsy but responsive to verbal stimulus. None of the patients had a sedation score of four, five or six. This data was analysed using the Chi square test with Yates correction, which indicated a statistically very highly significant difference between the two groups ($P<0.001$) (Table IX).

Table IX: Number of patients who had intraoperative sedation

Parameter observed	group			Total
	Placebo	Clonidine A	Clonidine B	
Not Sedated	28	6	4	38
Sedated	2	24	26	52
Total	30	30	30	90

$\chi 2=48.5$ $P=0.001$



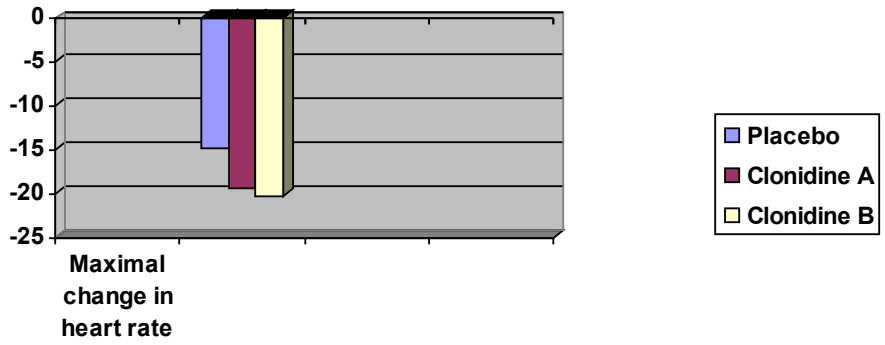
Maximal change in heart rate (Δ HR_{max})

The baseline heart rate and the lowest heart rate achieved during the study period were tabulated as shown in Appendix 3A,3B and 3C. The maximal change in heart rate (ΔHR_{max}) from the baseline was then derived and the mean and standard deviation of ΔHR_{max} calculated in the placebo and the clonidine-A and B groups. The ΔHR_{max} in the placebo group was -14.73 +/- 8.35 beats/minute while that in the clonidine-A group was -19.33 +/- 10.04, while that in clonidine-B was -20.32+/-11.37 (Table Xa).

Table Xa: Maximal change in heart rate (Δ HR_{max}) from the baseline (+ indicates increase, - indicates decrease)

Parameters observed	Groups	N	Mean(BPM)	Std. Deviation	Std. Error
HR_Change	Placebo	30	-14.73	8.346	
	Clonidine A	30	-19.33	10.039	F=2.02 P=0.14
	Clonidine B	30	-20.32	11.370	

BPM = beats per minute



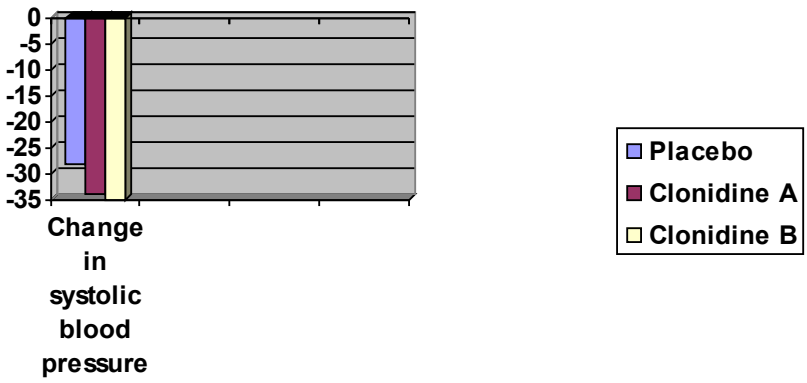
Maximal Change in systolic blood pressure (Δ SBP_{max})

The baseline systolic blood pressure and the lowest systolic blood pressure achieved during the study period were tabulated as shown in Appendix 3A, 3B and 3C. Maximal change in systolic blood pressure (Δ SBP_{max}) from the baseline was then derived and the mean and standard deviation of Δ SBP_{max} calculated in the placebo and clonidine-A and B groups. The ΔSBP_{max} in the placebo group was -28.23 +/- 12.97 mmHg while that in the clonidine-A group was -33.97+/-41.34mmHg, while that in clonidine-B group was - 34.83+/-44.10mmHg. (Table XIa).

Table XIa: Maximal change in systolic blood pressure (Δ SBP_{max}) from the baseline (+ indicates increase, -indicates decrease)

Parameter observed	Groups	N	Mean(mmHg)	Std. Deviation	Std. Error
SBP_Change	Placebo	30	-28.23	12.971	
	Clonidine A	30	-33.97	41.342	F=0.43 P=0.65
	Clonidine B	30	-34.83	44.108	

mmHg = millimeters of mercury



Maximal change in diastolic blood pressure (Δ DBP_{max})

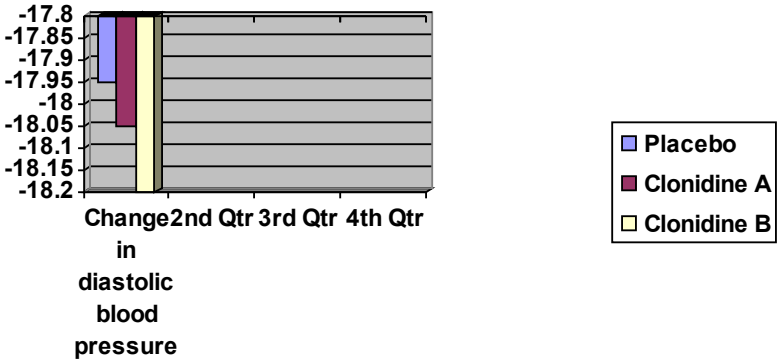
The baseline diastolic blood pressure and the lowest diastolic blood pressure achieved during the study period were tabulated as shown in Appendix 3A, 3B and 3C. Maximal change in diastolic blood pressure (ΔDBP_{max}) from the baseline was thenderived and the mean and standard deviation of Δ DBP_{max} calculated in the placebo and clonidine-A and B groups. The ΔDBP_{max} in the placebo group was -17.93 +/- 13.77 mm Hg while that in the clonidine-A group was -16.83 +/- 10.26 mmHg, while that in clonidine-B was -18.04+/-15.03mmHg (Table XIIa).

Table XIIa: Maximal change in diastolic blood pressure (Δ DBP_{max}) from the baseline

(+ indicates increase, - indicates decrease)

		N	Mean(mmHg)	Std. Deviation	Std. Error
DBP_Change	Placebo	30	-17.95	13.771	
	Clonidine A	30	-18.05	10.256	F=0.08 P=0.93
	Clonidine B	28	-18.20	15.027	

mmHg = millimeters of mercury



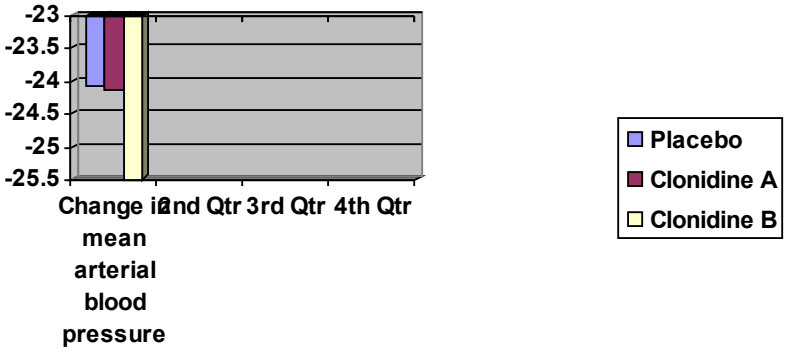
Maximal change in the mean arterial pressure (Δ MAP_{max})

The baseline mean arterial pressure and the lowest mean arterial pressure achieved during the study period were tabulated as shown in Appendix 3A, 3B and 3C. Maximal change in mean arterial pressure (ΔMAP_{max}) from the baseline was then derived and the mean and standard deviation of Δ MAP_{max} calculated in the placebo and clonidine-A and B groups. The Δ MAP_{max} in the placebo group was -24.07 +/- 10.19mmHg while that in the clonidine-A group was -24.13 +/- 11.06 mmHg, while that in clonidine-B group was -25.47+/-10.86mmHg (Table XIIIa).

Table XIIIa: Maximal change in mean arterial pressure (Δ MAP_{max}) from the baseline (+ indicates increase, -indicates decrease)

Parameter observed	Groups	N	Mean(mmHg)	Std. Deviation	Std. Error
MAP_Change	Placebo	30	-24.07	10.191	
	Clonidine A	30	-24.13	11.057	F=0.16 P=0.85
	Clonidine B	30	-25.47	10.859	

mmHg = millimeters of mercury


-23
-23.5
-24
-24.5
-25
-25.5
2nd Qtr
3rd Qtr
4th Qtr
Change in mean arterial blood pressure
Placebo
Clonidine A
Clonidine B

DISCUSSION

Vasoconstrictors have been used as adjuncts to prolong the duration of local anaesthetic-induced subarachnoid blockade. Prolongation of the local anaesthetic blockade has been attributed to localized vasoconstriction, thereby decreasing the uptake of local anaesthetics from the subarachnoid space. Collins et al suggested that intrathecal adrenaline directly stimulated α_2 adrenergic receptors in the spinal cord dorsal horn and exerted an antinociceptive effect through the descending inhibitory pathways in the spinal cord[33]. In these descending inhibitory adrenergic pathways, noradrenaline is the neurotransmitter responsible for suppressing the activation of spinal cord dorsal horn neurons by noxious stimuli.

In addition to vasoconstrictors, intrathecal clonidine is also effective in prolonging the local anaesthetic-induced sensory and motor blockade .While Ota et al[11] reported that oral clonidine (0.15 mg), prolonged the duration of tetracaine sensory analgesia by 93%, Bonnet et al[11] failed to demonstrate significant prolongation of the bupivacaine-induced sensory and motor blockade following clonidine 0.15 mg or 0.3mg orally. We found that oral clonidine 0.10mg, 0.15mg prolonged the duration of bupivacaine-induced sensory blockade (regression to L1 segment) by 44%, 61% and motor block by 44%, 46% respectively. We also observed that oral clonidine 0.10mg, 0.15mg decreased the time taken for attainment of the highest level of sensory blockade, it was 12.57 minutes& 9.37 minutes respectively, when compared to the placebo group which was 15.03 minutes. However, oral clonidine did not affect the onset of complete motor blockade. These findings are in concurrence with those observed in earlier studies[10,12,15,17,18]. Racle et al demonstrated that intrathecal clonidine (0.15mg) prolonged motor (38%) and sensory (46%) blockade when used as an adjunct to spinal anaesthesia with bupivacaine in humans[8] However, the effect of oral clonidine on subarachnoid local anaesthetic blockade in humans is controversial. .Although there is clinical and experimental evidence that alpha$_2$ adrenergic agonists produce their central effects by binding to alpha$_2$ adrenergic receptors in the spinal

cord, Butterworth and Strichartz have demonstrated in animal experiments that analgesia after neuraxial administration of alpha $_2$ adrenergic agonists may in fact result from direct inhibition of impulse conduction in Aα and C fibres.[34]

Clonidine has been demonstrated to potentiate inhibitory effects of local anaesthetics on C fibre activity. Previous studies suggest that clonidine also may affect peripheral sensory nerves as a sole agent or in combination with local anaesthetics. Therefore, oral clonidine may exert its effects within the central nervous system, at peripheral nerve roots, or by potentiation of effects of local anaesthetics.

Haemodynamic consequences such as bradycardia and hypotension were seen more frequently when the dose of oral clonidine exceed 150µg.[14] In our study, the dose of oral clonidine was restricted to 100µg & 150µg. This could have resulted in the lower incidence of bradycardia (one patient) and hypotension (one patient). Both these patients responded effectively to intravenous atropine (0.6 mg) or ephedrine (6 mg) respectively.

Crystalloid preloading in a dose of 300 to 400 ml followed by 5 to10 ml/kg/hr intraoperatively could not prevent significant bradycardia and hypotension associated with spinal anaesthesia following oral clonidine premedication.[12] The use of a larger volume for preloading (500 ml of lactated Ringer's solution) prior to the administration of anaesthesia as performed in our study could probably have resulted in an extremely low incidence of bradycardia and hypotension (one patient each).

In our study, we noticed that patients premedicated with clonidine had a very high incidence of mild sedation when compared to the placebo group. This finding is in agreement with the results of previous studies where oral clonidine was used as a premedicant. [18]

CONCLUSION

Pretreatment with 100 micrograms & 150 micrograms of clonidine hydrochloride administered orally 60 minutes prior to spinal anaesthesia with 0.5% hyperbaric bupivacaine.

1) Hastens the onset of sensory blockade but does not affect the onset of motor blockade.

2) Prolongs the duration of both sensory and motor blockade.

3) Produces significantly higher incidence of mild sedation intraoperatively

4) The duration of both sensory and motor blockade is increased when premedicated with 150 microgram of clonidine compare to 100 microgram of clonidine with the side effects comparable in both the groups

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5) Is not associated with any greater change in heart rate and blood pressure than that seen following spinal anaesthesia without clonidine premedication.

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