A COMPARATIVE STUDY TO EVALUATE THE EFFICACY OF DEXMEDETOMIDINE AND CLONIDINE IN EPIDURAL ANAESTHESIA WITH ROPIVACAINE FOR LOWER ABDOMINAL SURGERIES

Dissertation submitted for

M.D. Degree Examination

Branch X - Anaesthesiology

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CERTIFICATE

This is to certify that this dissertation entitled

"A COMPARATIVE STUDY TO EVALUATE THE EFFICACY OF DEXMEDETOMIDINE AND CLONIDINE IN EPIDURAL ANAESTHESIA WITH ROPIVACAINE FOR LOWER ABDOMINAL SURGERIES"

is a bonafide record of the work done by DR. ARULOLI .M under my supervision and guidance in the Department of Anaesthesiology at Thanjavur medical college, Thanjavur during the period of his post graduate study from June 2009 to March 2012 for the partial fulfilment of M.D. (Branch X - Anaesthesiology) degree.

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DECLARATION

I, solemnly declare that the dissertation titled **"A COMPARATIVE STUDY TO EVALUATE THE EFFICACY OF DEXMEDETOMIDINE AND CLONIDINE IN EPIDURAL ANAESTHESIA WITH ROPIVACAINE FOR LOWER ABDOMINAL SURGERIES"** is a bonafide work done by me at Thanjavur Medical College Hospital, Thanjavur, during 2009 – 2012.

The dissertation is submitted to **"The Tamilnadu Dr. M.G.R. Medical University, Chennai",** Tamilnadu as a partial fulfillment for the requirement of **M.D** Degree examinations – Branch -X (Anaesthesiology) to be held in April 2012.

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CONTENTS

INTRODUCTION

Epidural blockade is becoming one of the most useful and versatile procedure in modern anaesthesiology. It is more versatile than spinal anaesthesia, giving the opportunity to provide analgesia and anaesthesia, as well as enabling diagnosis and treatment of chronic disease syndromes. It can be used to supplement general anaesthesia, decreasing the need for deep levels of general anaesthesia, therefore providing a more hemodynamically stable operative course.

Epidural anaesthesia can reduce the adverse physiologic response to surgery such as autonomic hyperactivity, cardiovascular stress, tissue breakdown, increased metabolic rate, pulmonary dysfunction and immune system dysfunction[1].

Epidural anaesthesia is widely regarded as a boon for patients as it can provide a relief from pain for a longer duration and the facility of further top-ups and continuous infusion of the analgesic drugs through epidural catheter thus providing an uneventful and smooth recovery.

Epidural bupivacaine has been studied extensively in the past, however, in recent years, ropivacaine has increasingly replaced bupivacaine because of its similar analgesic properties, lesser motor blockade and decreased propensity of cardio toxicity.

Though a slightly larger dose of ropivacaine is required as compared to bupivacaine to achieve the analgesic and anaesthetic effects, the addition of an adjuvant help in reduction of the local anaesthetic dose and also enhance the effectiveness of local anaesthetics by intensifying and prolonging the blockade.

α_2 adrenergic agonists have been used as an adjuvant to epidural local anaesthetics to improve the quality of analgesia after major abdominal surgeries. They produce analgesia through central and peripheral actions. Three subtypes of α_2 receptors have been described in humans; α_{2A}, α_{2B} and α_{2C}. The α_{2A} receptors are primarily distributed in the periphery, whereas α_{2B} and α_{2C} are in the brain and spinal cord. The overall response to α_2 agonists is related to the stimulation of α_2 receptors located in the brain and spinal cord which are involved in sedation, sympatholysis and anti-nociception[2].

Clonidine, an imidazoline compound, is a prototypal $\alpha_2$adrenergic agonist having 200-fold selectivity for α_2 over α_1 adrenoceptors. Clonidine has a long plasma half life of 12 to 24 hours.

Dexmedetomidine, also an imidazoline derivative, is 1600 times more selective for α_2 than α_1 receptors and with plasma elimination half life of about 2 hours.

The efficacy of adding dexmedetomidine and clonidine to ropivacaine in epidural anaesthesia is compared in this study.

AIM OF THE STUDY

The aim of the study is to compare the effects of dexmedetomidine and clonidine added to ropivacaine in epidural anaesthesia for lower abdominal surgeries with respect to onset of anaesthesia, duration of analgesia, sedation and other side effects.

EPIDURAL ANAESTHESIA

HISTORY

In 1901, two French physicians, Ferdinand Cathelin and Jean Anthanase Sicard found that injecting a dilute solution of cocaine through the sacral hiatus to be an effective treatment for severe sciatic pain and suggested the technique for surgical procedures. In 1921, a Spanish surgeon, Fidel Pages Mirave described lumbar epidural anaesthesia. In 1931, an Italian surgeon, Archile Dogliotti popularised segmental epidural anaesthesia. Few years later, in 1949, a Cuban Anaesthesiologist, Martinez Curbelo practised continuous epidural anaesthesia using Tuohy-Huber needle and silk ureteral catheter[3].

ANATOMY[4,5,6]

The epidural space extends from the base of skull to the sacral hiatus and surrounds the duramater anteriorly, laterally and posteriorly. The epidural space is bound posteriorly by the Ligamentum flavum and laterally by the pedicles and the intervertebral foramina.

The epidural space is discontinuous and is divided into posterior, lateral and anterior compartments. It is rich in fat, areolar tissue, lymphatics, nerve roots, spinal arteries and epidural plexus of veins,

which are more prominent in the lateral aspects of the space. These veins have no valves and communicate with the intracranial veins.

The epidural space is widest in the midline and tapers off laterally. It is 5-6 mm in midlumbar region, whereas, 3-5 mm in thoracic region.

Ligamentum flavum is the key landmark in epidural anaesthesia. It is composed mainly of elastic fibres, providing a unique tactile clue for epidural needle placement using the loss of resistance technique.

PHYSIOLOGICAL EFFECTS[4]

Induction of epidural anaesthesia has widespread effects on various physiological systems. Understanding these effects and the ability to manage physiologic side effects is important to the safe conduct of neuraxial anaesthesia.

1. Differential Neural blockade:

The ability to obtund sensory, motor and sympathetic nerve functions to different degrees is called ‘differential blockade’. Smaller C fibres conveying autonomic impulses are more easily blocked than the larger sensory and motor fibres. As a result, the level of autonomic blockade extends above the level of sensory blockade by two to six segments. Similarly, fibres conveying sensation are more easily blocked

than the larger motor fibres so that the sensory blockade will extend above the level of motor blockade.

2. Cardiovascular effects:

Hypotension is directly proportional to the degree of sympathetic blockade produced. Sympathetic blockade below T4 results in dilatation of arteries and venous capacitance vessels, leading to decreased systemic vascular resistance and decreased venous return also increasing baroreceptor activity produces vasoconstriction of the upper extremeties. Blockade above T4 interrupts cardiac sympathetic fibres, leading to bradycardia, decreased cardiac output, and a further decrease in blood pressure.

3. Pulmonary effects:

The effect of epidural anaesthesia on respiratory system is minimal. Blockade upto T4 spinal level does not result in impaired ventilation, but respiratory compromise may happen in patients with limited respiratory reserve or higher level of blockade.

4. Visceral effects :

a. *Bladder* – sacral blockade (S2 – S4) results in an atonic bladder that can retain large volumes of urine. Blockade of sympathetic afferent and

efferent innervations of the sphincter and detrussor muscle produces urinary retention.

b. *Intestine* – sympathetic blockade (T5 –L1) leads to contraction of the small and large intestines because of predominance of parasympathetic tone.

5. Neuroendocrine effects :

Epidural block to T5 level inhibits part of the neural component of the stress response through its blockade of sympathetic afferents to the adrenal medulla and blockade of sympathetic and somatic pathways mediating pain.

6. Thermoregulation :

Thermoregulation is impaired due to loss of vasoconstriction to preserve heat below the level of sympathectomy, resulting in shivering.

7. Central nervous system effects :

Cerebral blood flow is autoregulated; thus blood flow to the brain remains constant during neuraxial anaesthesia unless there is profound hypotension. Neuraxial anaesthesia may be associated with a decreased incidence of early postoperative cognitive dysfunction. Higher level of neuraxial blockade results in decrease in afferent input to the reticular activating system, thus producing sedation.

MECHANISM OF NEURAL BLOCKADE

The precise mode of action of an epidural drug remains unexplained fully. Theories of mechanism of action centre around one or more of the following sites[5]:

- Spinal roots within the dural root sleeves
- Dorsal root ganglia
- Mixed spinal nerves in the paravertebral spaces
- Subpial region

DISTRIBUTION OF THE DRUG GIVEN INTO THE EPIDURAL SPACE[5] :

Following epidural injection the longitudinal spread depends on the volume of the solution that escapes leak out of the epidural space. Some of this solution penetrate the epineurium and perineurium into the subperineurial space and then spreads subpially to reach the neuraxis.

High concentration of local anaesthetics in the intradural roots suggests dural root sleeves with arachnoid granulations are likely to be the principal site of penetration through the dural barrier. From here the drugs spread in the subdural space with further penetration into the subarachnoid space and with still further penetration into the subpial

space from where the local anaesthetics enter into the nerve roots and the spinal cord.

INDICATIONS FOR EPIDURAL ANAESTHESIA :

Epidural anaesthesia can be used for a variety of surgeries and conditions extending from the neck to the foot.

Common Applications for Epidural Blockade

Epidural anaesthesia is commonly used in long orthopaedic surgeries like major hip/knee surgery, repair of pelvic fractures etc.

The main use lies in Obstetrics as for Caesarean section and labour analgesia. Other applications include gynaecological surgeries, major urological surgeries involving prostate, bladder and ureters. Epidural anaesthesia is also applied in various upper and lower abdominal procedures, pediatric procedures of abdomen and lower limbs.

Various vascular reconstructions of the lower limbs are also being done in epidural anaesthesia.Other uses include postoperative analgesia, combination with GA to reduce GA requirements.

Surgeries involving thyroid and parathyroid have also been tried under epidural anaesthesia

It is also used in the diagnosis and management of chronic pain

Contraindications for Epidural Blockade

Absolute contraindications are patient refusal, uncorrected hypovolemia, increased ICP, infection at the injection site and allergic to local anaesthetics

Relative contraindications include coagulopathy, Platelet count <100,000 cells/mm^3, uncooperative patient, severe anatomic abnormalities of spine, sepsis, hypertension, and inadequate training and experience in epidural technique.

TECHNIQUE OF EPIDURAL ANAESTHESIA[4,5]:

The level of insertion and dosing of the epidural needle or catheter depends on the purpose of the epidural block. Two approaches have been classically described for epidural anaesthesia, namely the midline and the paramedian approach.

MIDLINE APPROACH

This approach is the most commonly used technique for lumbar epidural placement in the sitting position. After appropriate monitors are attached and the patient is positioned, the lumbar spine is prepared and draped in a sterile fashion. A fully prepared epidural tray should be placed to anaesthesiologist's right for right-handed, and to left for the left-handed.

The vertebral level to be entered is identified by surface landmarks (e.g., crest of iliac spines L4 to L5, entry level usually L3-4). The skin is infiltrated with local anaesthetic using 25-gauge 1 1/2 inch needle at midpoint between two adjacent vertebrae to raise a large skin wheel, followed by infiltration of the deeper tissues to alleviate pain and to assist with locating midline.

The epidural needle is inserted with stylet through same skin puncture and the dorsum of the anaesthesiologist's non injecting *hand* rests on the patient's back with the thumb and index finger holding the hub of the epidural needle (Bromage grip).

The needle is advanced through the supraspinous ligament and into the interspinous ligament (approximately 3 cm depth) at which point the needle sits firmly in the midline. The stylet is then removed and a glass syringe or a plastic 'loss of resistance' syringe with air or saline is attached to the hub of the needle and locked firmly so that a false loss of resistance is not encountered. By applying constant or intermittent pressure to the syringe plunger, the epidural needle tip crosses the ligamentum flavum and enters the epidural space which could be appreciated by the loss of resistance.

PARAMEDIAN APPROACH

This approach offers a much larger opening into the epidural space than the midline approach.

Indications for this approach are patients who cannot be positioned easily or cannot flex the spine (trauma/arthritic) when inserting the needle into the lumbar epidural space, patients with calcified interspinous ligament, Spine deformities like kyphoscoliosis, prior lumbar surgery,

Midline approach may be difficult if the desired entry level is between T3 to T7, where the angulation of the spinous processes is more oblique, the space between spinous processes is narrower and the ligaments are less dense. False loss of resistance is much more common if entered through the midline in these levels.

The paramedian procedure involves placement of a skin wheal 1.5–2.0 cm lateral to the midline opposite the centre of the selected interspace in the lumbar and lower thoracic levels. The epidural needle is advanced at that site perpendicular to the skin until the lamina is encountered. The needle is redirected and advanced at a 10 to 25 degree angle toward the midline.

If bone is encountered, the needle is "walked off" the bone into the ligamentum flavum. The epidural needle penetrates paraspinous muscles with little resistance before entering the ligamentum flavum and then into the epidural space.

IDENTIFICATION OF THE EPIDURAL SPACE[5]:

Two classic methods of identifying the epidural space have been described.

a. Loss of resistance to injection- the test of Sicard, Dogliotti:

This technique is based on the fact that there is considerable loss of resistance to injection through the epidural needle as it advances from the interspinous ligament and ligamentum flavum into the epidural space. Either a gas filled or liquid filled system can be used to identify the loss of resistance. Liquid filled system is advantageous in that liquid being incompressible, changes in the resistance are more accurately transmitted to the anaesthetist's fingers. But the problem with it is difficult to differentiate CSF and the liquid used for testing. However, in the air filled system, air being compressible, does not reflect the changes in the resistance.

Various mechanical aids were used to facilitate the appreciation of loss of resistance namely, MACINTOSH'S needle with spring loaded stylet, BRUNNER and ILKE'S spring loaded syringe, MACINTOSH'S balloon indicator and ZELENKA'S "U" tube and balloon indicator.

b. <u>Negative pressure sign:</u>

A negative pressure is present in the epidural space.

This negative pressure can be appreciated by:

<u>Hanging drop sign of Gutterrez</u>: The epidural needle is placed in the interspinous ligament and a drop of liquid is placed in the hub of the needle. As the needle is advanced into the epidural space, due to the negative pressure, the liquid will be sucked in.

Various mechanical aids were used to identify this negative pressure namely, "U" tube manometer, ANEROID manometer, ZORRAQUIN'S bulb indicator, ODOM'S indicator, BROOK'S indicator, ZELENKA'S balloon indicator and DAWKIN'S gravity indicator.

COMPLICATIONS OF EPIDURAL ANAESTHESIA:

Though epidural anaesthesia is a safe technique, it is not without complications.

Major complications associated with epidural anaesthesia are direct trauma to the nerves, systemic toxicity associated with inadvertent intravascular injection, subdural injection of drugs, total spinal anaesthesia, epidural abscess and meningitis.

Minor complications include backache, nausea and vomiting, postdural puncture headache, pneumocephalus, shivering .and urinary retention**.**

PHARMACOLOGY OF DRUGS USED

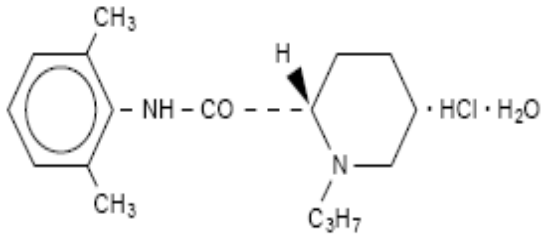
ROPIVACAINE[7]

Ropivacaine is a long acting local anaesthetic belonging to amino amide group. Injection form is a sterile isotonic solution that contains enantiomerically pure drug substance containing sodium chloride for isotonicity and water for injection.

It comes as preservative free and is available in 0.2%, 0.5%, 0.75% and 1.0% concentrations in 4 ml, 10ml and 20ml ampoules.

Physiochemical properties:

Ropivacaine is chemically described as S-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate



Chemical structure of Ropivacaine

- Molecular weight-274 daltons
- pKa - 8.07, pH - 7.4
- Protein binding - 94%
- Partition coefficient (lipid solubility) - 8.7.

- T1/2 - 111 minutes,
- clearance -10.3 L/minute

Pharmacodynamic properties*:*

Ropivacaine is an optically pure S(-) enantiomeric form of the parent chiral molecule propivacaine. It causes reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the cell membrane of the nerve fibres. Ropivacaine has both anaesthetic and analgesic effects. At higher doses it produces surgical anaesthesia, while at lower doses it produces sensory block (analgesia) with limited and non progressive motor block. The duration and intensity of ropivacaine block are not improved by the addition of adrenaline

Ropivacaine is less lipophilic than bupivacaine and that, together with its stereoselective properties contributes to ropivacaine having a significantly higher threshold for cardiotoxicity and CNS toxicity than Bupivacaine in animals and healthy volunteers.

Ropivacaine has been shown to inhibit platelet aggregation in plasma at concentrations of 3.75 and 1.88 mg/mL (0.375% and 0.188%), which correspond to those that could occur in the epidural

space during infusion. Hypotension and bradycardia are uncommon after caudal epidural block in children.

Pharmacokinetic properties*:*

Absorption:

The plasma concentration of ropivacaine depends upon the dose, the route of administration and the vascularity of the injection site.

Ropivacaine follows linear pharmacokinetics and the maximum plasma concentration is proportional to the dose.

Distribution:

After intravascular infusion, ropivacaine has a steady state volume of distribution of 41±7 liters. It is 94% protein bound, mainly to a1-acid glycoprotein. Ropivacaine readily crosses the placenta.

Metabolism:

Ropivacaine is extensively metabolized in the liver, predominantly by aromatic hydroxylation mediated by cytochrome P450 1A to 3-hydroxy ropivacaine, approximately 37% of the total dose is excreted in the urine as both free and conjugated 3-hydroxy ropivacaine. Low concentrations of 3-hydroxy ropivacaine have been

found in the plasma. An additional metabolite, 2-hydroxymethyl-ropivacaine, has been identified but not quantified in the urine. N-de-alkylated metabolite of ropivacaine and 3-OH-ropivacaine are the major metabolites excreted in the urine during epidural infusion.

Elimination:

The kidney is the main excretory organ for most ropivacaine metabolites. In total 86 % of the Ropivacaine dose is excreted in the urine after intravenous administration of which only 1% relates to unchanged drug.

Indications:

For Surgical anaesthesia: Epidural block for surgery, including Caesarean section, nerve blocks and infiltration anaesthesia

In Acute pain management: Continuous epidural infusion or intermittent bolus administration for postoperative or labour pain. Also in minor nerve block and infiltration analgesia

Acute pain management in paediatrics: as in Caudal epidural block, Peripheral nerve block for intra and postoperative pain management.

Chronic pain management: *as in cases of c*hronic low back pain and cancer pain relief

Contraindications:

Ropivacaine solutions are contra-indicated in patients with known hypersensitivity to local anaesthetic of the amide-type, Intravenous regional anaesthesia (Bier's block), and obstetric para cervical block.

Dosage and Toxic manifestation

Upper limit of safe dosage in adult is 3mg/kg body weight up to 275mg. Adverse reactions are associated mainly with excess plasma levels of the drug, which may be due to over dosage, unintentional intravascular injection or slow metabolic degradation.

Central nervous system manifestations include restlessness, circumoral numbness, light headedness, confusion, tremors, convulsions, respiratory failure.

Cardiovascular system involvement like cardiovascular collapse, bradycardia, pallor, sweating, hypotension, acute circulatory failure.

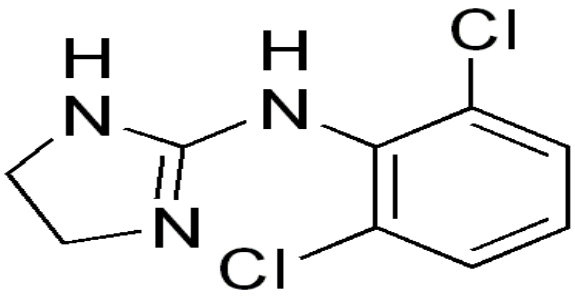
Respiratory system manifestations include medullary depression leading to apnoea , respiratory muscle paralysis and delayed respiratory depression..

The mean doses at which CNS symptoms of toxicity begin to occur in human beings are 4.3 and 0.6μg/ ml of total and free plasma

concentrations respectively. When prolonged blocks are used, either through continuous infusion or through repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury are increased.

CLONIDINE

Clonidine hydrochloride is an imidazoline derivative with α_2 adrenergic agonist that has a variety of different actions including antihypertensive effects as well as the ability to potentiate the effects of local anaesthetic. It can provide pain relief by an opioid -independent mechanism.



Chemical structure of Clonidine

Preparations available:

Oral 0.1, 0.2, 0.3 mg tablet

IV 1ml ampoule containing 150µg of clonidine as preservative free solution.

Transdermal patches 0.1, 0.2, 0.3 mg /24 hrs

Pharmacodynamics[8]:

Clonidine is a selective partial α_2 adrenergic agonist with a selectivity ratio of about 200: 1 in favour of α_2 receptors.

It is lipid soluble and easily penetrates the blood brain barrier to reach the hypothalamus and medulla when injected epidurally.

It stimulates inhibitory α_2 adrenoreceptors to reduce central neural transmission in the spinal nerves.- Inhibition of substance P release is believed to be involved in the analgesic effect. .α_2 - adrenoreceptors are located on the afferent terminals of both peripheral neurons and neurons in the superficial laminae of the spinal cord and within several brainstem nuclei implicated in analgesia.

Hypothesis of analgesic action of clonidine in spinal cord:

The superficial laminae of the dorsal horn contain 3 groups of neurons: tonic, adapting and single-spike firing; all of which are important neuronal structures for pain transmission, receiving most of their primary sensory input from Aδ and C fibres. Clonidine partially inhibits voltage gated Na^+ and K^+ channels and suppresses the generation of action potentials in tonic-firing dorsal horn spinal neurons.

Epidurally administered clonidine produces dose-dependent analgesia not antagonized by opiate antagonists.
The analgesia is limited to the body regions innervated by the spinalsegments where analgesic concentrations of clonidine are present. Clonidine is thought to produce analgesia at presynaptic and

postjunctional α_2-adrenoceptors in the spinal cord by preventing pain signal transmission to the brain.

Some contribution to the analgesic effect of Clonidine may be through release of Ach in the neuraxial region.

Pharmacokinetics:

Clonidine is relatively well absorbed by most routes. Concentrations in blood peak in 2 -4 hours after oral clonidine.. Its pKa is 8.05. It is a lipid soluble drug rapidly crosses blood brain barrier. About 20 - 40% of the drug bound to plasma proteins. The volume of distribution is 150L /70 kg (2.1 $\pm$0.4L/kg). The plasma clearance is 12.6L/hr/70 kg. 1/2 to 2/3 of an oral dose is excreted unchanged in urine, the rest as metabolites p-.hydroxyclonidine.. 60 -70% of the parent drug is excreted in the urine. Plasma t ½ 8-12 hrs. Effect of single dose lasts for 6 - 24 hours.

Elimination t1/2 is 9$\pm$ 2 hrs. It is severely affected in severe renal dysfunction (41 hour).

Pharmacological actions:

Cardiovascular system:

Stimulation of α_{2A} receptors present mainly post junctionally in medulla (Vasomotor centre) decreases sympathetic outflow leads to reduced

release of nor epinephrine causes fall in BP and bradycardia (also due to enhanced vagal tone). This activation of the Post synaptic α_2 adrenoreceptors in the Nucleus Tractus Solitarius and locus ceruleus of the brain stem reduces sympathetic drive. It also activates non - adrenergic imidazoline preferring binding sites in the lateral reticular nucleus thereby producing hypotension and an anti arrhythmogenic actions.

Central nervous system:

Being lipophilic it crosses blood brain barrier rapidly and cause analgesic action by its action with in several brain nuclei. Sedation is a dose dependent response of clonidine by its action in the locus ceruleus.

Respiratory system: Not induce Respiratory depression even after massive overdose nor they potentiate respiratory depression from opioids.Peripheral nerves: Some preference over C fibres in the peripheral nerve may enhance peripheral nerve block when added to local anaesthetics

Renal: Dose should be adjusted according to the degree of renal impairment Decreased sympathetic flow to the kidney results in reduced renin release.

Pregnancy and lactation:

Clonidine readily crosses the placental barrier and may lower the fetal heart rate. Maternal perfusion of the placenta is critically dependent on blood pressure so use of clonidine as an analgesic during labor and delivery is not indicated.

In human breast milk, concentration of clonidine are approximately twice those in maternal plasma. So it is not recommended during lactation.

Uses:

Clonidine is used as an anxiolytic, sedative in anaesthesia. It was earlier used in the treatment of hypertensive crisis**.**

It also prolongs the duration of analgesia when given in various routes (Intrathecal/epidural/peripheral nerve blocks/ Intraarticular) along with local anaesthetics. It is also used in the prevention and treatment of shivering. 1-2 µg/kg body weight of clonidine is administered along with local anaesthetics in caudal epidural analgesia to prolong the duration of analgesia in children. Whereas in adults, for epidural anaesthesia, 1-3µg/kg of clonidine have been used in various studies for prolongation of epidural analgesia.

Clonidine has been extensively used for withdrawal from addictive drugs (Narcotics, alcohol or smoking).

Other uses include Chronic pain syndromes, - In diabetic diarrhea due to autonomic neuropathy, to reduce menopausal hot flushes.

Contraindications include hypersensitivity to clonidine, Bradyarrhythmia or AV block patients, severe cardiovascular diseases, In patients with haemodynamic instability, pregnant and lactating woman**.**

Adverse effects:

Clonidine can cause hypotension which usually responds to intravenous fluids, if necessary parenteral ephedrine. Bradycardia may also occur and it responds to atropine. Sedation produced by clonidine can sometimes be an undesirable effect. Other adverse effects include mental depression, disturbed sleep, dryness of mouth, constipation, confusion, headache, skin reactions etc.

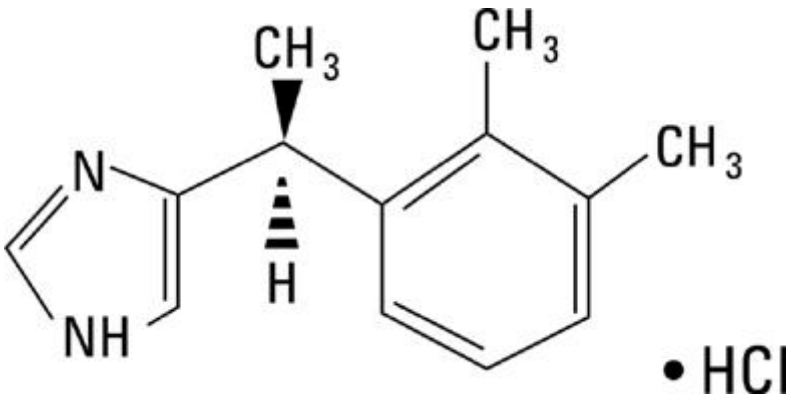
Overdosage:

No specific antidote for Clonidine overdosage.Treatment mainly involves supportive care.An overdosage can produce Vasospasm and hypertension. For hypertensive emergency- IV furosemide, diazoxide or α-blocking agents may be used. Hypertension may develop early and may be followed by hypotension, bradycardia, hypothermia, drowsiness, irritability and miosis can occur.

DEXMEDETOMIDINE

Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine, and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride.

. The empirical formula is $C_{13}H_{16}N_2$.HCl and the structural formula is



Chemical structure of Dexmedetomidine.

It is available as preservative free, clear, colourless, isotonic solution in 1ml or 2ml ampoules. Each ml contains 118 µg of dexmedetomidine hydrochloride equivalent to 100 µg of dexmedetomidine and 9mg of sodium chloride in water.

Physiochemical properties:

Molecular weight – 236.7 daltons

pKa – 7.1

Partial coefficient in octanol : water at pH 7.4 – 2.89

Mechanism of action :

Dexmedetomidine is a selective α_2 adrenergic agonist with α2 : α1 ratio of 1600 : 1. α_2 receptors are found in the peripheral and central nervous systems, platelets and many other organs including liver, pancreas, kidney and eye. Stimulation of these receptors in the brain and spinal cord inhibits neuronal firing causing hypotension, bradycardia, sedation and analgesia. The responses from other organs include decreased salivation, decreased secretion and decreased bowel motility, inhibition of renin release, increased glomerular filtration, increased secretion of sodium and water in the kidney, decreased intraocular pressure and decreased insulin release from the pancreas.

Pharmacokinetics:

Following intravenous administration, dexmedetomidine exhibits linear pharmacokinetics in the dosage range of 0.2 to 0.7µg/kg/hr. It has a rapid distribution half life (t1/2α) of approximately 6 minutes and a terminal elimination half life (t1/2β) of approximately 2 hours and a steady state volume of distribution (Vss) of approximately 118 litres. Clearance is estimated to be approximately 39litres/hour for a 70 kg adult. There were no differences in the pharmacokinetics of dexmedetomidine in young (18 – 40 years), middle age (41 – 65 years) and elderly (>65 years) subjects.

Distribution:

The average protein binding of dexmedetomidine is 94% and is constant across different plasma concentration. Protein binding is similar in males and females and is significantly decreased in subjects with hepatic impairment compared to healthy subjects.

Metabolism:

Dexmedetomidine undergoes almost complete biotransformation with very little unchanged drug excreted in urine and faeces. Biotransformation involves direct glucuronidation as well as cytochrome P 450 mediated metabolism.

Elimination:

The main route of elimination of dexmedetomidine is through kidneys. There is a theoretical possibility of accumulation of metabolites of biotransformation in patients with renal failure.

Indications:

Dexmedetomidine is used for ICU sedation of intubated patients and mechanically ventilated patients and for procedural sedation of non intubated patients prior to or during surgery.

In operating room, it is used as a premedicant and a sole anaesthetic in MAC. It is also used as an adjunct for local anaesthetics in regional anaesthesia: i.e., in epidural anaesthesia, subarachnoid block, peripheral nerve block and intravenous regional anaesthesia.

Use in specific population:

Dexmedetomidine should be used cautiously in patients with pre-existing severe bradycardia and conduction abnormalities, reduced ventricular function (ejection fraction < 30%) and patients who are hypovolemic or hypotensive

Pregnancy and lactation warrants its cautious use.

The drug is not approved for use in patients < 18 years.

Adverse effects:

Major adverse effects include hypotension, hypertension, haemorrhage, bradycardia, atrial fibrillation, sinus tachycardia, ventricular tachycardia, myocardial infarction, agitation, confusion, delirium, hallucination, illusion

Dosage and administration:

For adults, dexmedetomidine is administered intravenously at a loading dose of 0.5 to 1 µg/kg given over 10 minutes followed by a

maintenance infusion of 0.2 to 0.7 µg/kg/hr. Dexmedetomidine should be diluted in 0.9 % saline for infusion. The bolus dose should not be infused rapidly as it can cause paradoxical increase in blood pressure. Dexmedetomidine is recommended for infusion lasting upto 24 hours only.

Dexmedetomidine has been used in epidural anaesthesia as an adjuvant to local anaesthetics at a dose ranging from 1-2µg/kg.

Overdosage:

Overdosage may cause first degree or second degree atrioventricular block. By omitting or reducing the loading dose these adverse effects can be reduced.

Sedative and analgesic effects of dexmedetomidine can be terminated by Atipemazole

Drug interactions:

Anaesthetics, hypnotics, sedatives and opioids if co-administered with dexmedetomidine lead to an enhancement of effects. So reduction in dose with these agents may be required.

REVIEW OF LITERATURE

Sukhminder Jit Singh Bajwa et al[9] (2011) conducted a prospective randomised study in 50 female patients between the ages 45 and 65 years who underwent vaginal hysterectomy. They compared epidural 0.75% ropivacaine 17 ml + dexmedetomidine 1.5 µg/kg with epidural 0.75% ropivacaine 17 ml + clonidine 2 µg/kg. They observed that addition of dexmedetomidine to ropivacaine resulted in earlier onset (8.52±2.36 min) of sensory analgesia at T10 as compared to addition of clonidine (9.72±3.44 min), p=0.032. Sedation score of dexmedetomidine was better and statistically significant ($p<0.05$) than that of clonidine, the mean time for two segment regression and motor regression were prolonged in dexmedetomidine group. Also the time for first rescue top up was significantly prolonged in dexmedetomidine group when compared with the clonidine group (342.88±29.16 vs. 310.76±23.76). They concluded that dexmedetomidine is a better adjuvant than clonidine in epidural anaesthesia as far as patient comfort, stable cardio-respiratory parameters, intraoperative and postoperative analgesia is concerned.

Mausumi Neogi et al[10] (2010) conducted a randomised prospective study to compare the efficacy of clonidine 1 µg/kg and dexmedetomidine 1 µg/kg used as adjuvant to ropivacaine for caudal analgesia in 75 paediatric patients who underwent elective inguinal herniiotomy. They observed that the mean duration of analgesia was 6.32±0.46 hours in group R, 13.17±0.68 hours in group C and 15.26±0.86 hours in group D. The prolongation of duration of analgesia was significant ($p<0.05$) in both group C and group D in comparison to group R but not between group C and group D. They concluded that addition of both clonidine and dexmedetomidine with ropivacaine administered caudally significantly increased the duration of analgesia.

Shobana Gupta , Dipak Raval et al[11] (2010) conducted a randomised double blinded comparative study in 60 adult patients who received epidural analgesia for postoperative pain relief after total knee replacement surgery. They compared bupivacaine 1.5 mg/kg + clonidine 1 µg/kg with bupivacaine alone and observed that the onset of sensory anaesthesia was faster (493.8±31.66 seconds vs. 686.4±47.42 seconds, $p<0.05$) and the duration was significantly longer in clonidine group (334.2±38.61 minutes vs. 161.4±26.98, $p<0.05$). They also observed for side effects and found that 26% in clonidine group had significant hypotension when compared to 6% in control group, 48% in

clonidine group complained of dryness of mouth as compared to 18% in control group. They concluded that addition of clonidine to epidural bupivacaine prolonged the motor and sensory block with increased incidence of side effects.

Elhakim M, Abdelhamid D et al[12] (2010) conducted a comparative study in 50 adults who underwent thoracic surgery with epidural analgesia and one lung ventilation. They concluded that epidural dexmedetomidine 1µg/kg with bupivacaine 0.5% decreased the intra-op anaesthetic requirements, prevented awareness during anaesthesia and improved intra-op oxygenation and post-op analgesia.

Obayah GM, Refaie A et al[13] (2010) did a randomised controlled trial to evaluate the efficacy of adding 1µg/kg of dexmedetomidine to bupivacaine for post-op analgesia with bilateral greater palatine nerve block after cleft palate repair in 30 children and concluded that the combination of bupivacaine and dexmedetomidine increased the duration of analgesia by 50% with no clinically relevant side effects.

Salgado PF, Sabbag AT et al[14] (2008) conducted a randomised control study in 40 patients who underwent hernia repair or varicose vein surgeries under epidural anaesthesia. They compared

0.75% ropivacaine (20 ml) with 0.75% ropivacaine (20 ml) + dexmedetomidine 1 µg/kg. They observed that epidural dexmedetomidine did not affect the upper level of anaesthesia ($p>0.05$), however it prolonged sensory and motor block duration time ($p<0.05$) and post operative analgesia ($p<0.05$). Values of bispectral index were lower in dexmedetomidine group ($p<0.05$). There was no difference in incidence of hypotension and bradycardia ($p>0.05$). Occurence of side effects namely shivering, vomiting and respiratory depression was low and similar between groups ($p>0.05$). They concluded that there is synergism between epidural dexmedetomidine and ropivacaine without additional side effects.

Oriol-Lopez, Maldonado Sanchez et al[15] (2008)

conducted a prospective, descriptive study in 40 patients who were subjected to abdominal surgery under epidural anaesthesia. Dexmedetomidine at a dose of 1 µg/kg added to epidural lignocaine produced Ramsay sedation score of 3 in 17% of the patients within 5 minutes, 90% of the patients had sedation level of 3-4 from 15-90 minutes, 4 patients had sedation level of 5 from 30-60 minutes. They concluded that adequate sedation (Ramsay sedation level of 3-4) $p=0.05$, was maintained between 10-120 minutes with a single bolus epidural dose of dexmedetomidine.

Antonio Mauro Vieira et al[16] (2004) conducted a randomised, double-blind study in 40 patients who underwent subcostal cholecystectomy under combined lumbar epidural and general anaesthesia. They compared epidural clonidine 2µg/kg and dexmedetomidine 2µg/kg with 20 ml of 0.75% ropivacaine for sedation and post-operative analgesia. They observed that clonidine and dexmedetomidine provided similar sedation (Filos'score 0) and pain scores (VAS 0) during initial two hours post-op period. However, clonidine provided analgesia at 24 hours post-op significantly better when compared to dexmedetomidine.

MATERIALS AND METHODS

This prospective, randomised, double blinded, case control study was conducted at Thanjavur Medical College Hospital,Thanjavur between June 2010 and July 2011 after obtaining approval from the institutional ethical committee.

Fifty patients who were posted for elective Lower abdominal surgery (hernia repair, appendicectomy, abdominal hysterectomy) of age between 20 and 60 years and categorised under ASA I and ASA II physical status were included in the study

EXCLUSION CRITERIA were patient refusal to participate in this study, patients with weight > 120 kg, height < 150 cm, history of Diabetes mellitus, Hypertension, Psychiatric illness, ECG changes showing any degree of heart block, patients on beta blockers or Alpha 2 antagonists, patients with coagulation abnormality, Pregnant and lactating mothers and those who are allergic to any of the drug used in this study

After obtaining informed written consent, patients were randomly divided into two groups namely GROUP RD and GROUP RC. Distribution of sample was done by drawing lots. Each patient had an equal chance of being selected in either of the group.

Group RD (n = 25) received 0.75% Ropivacaine 16ml + Dexmedetomidine 1µg/kg.

Group RC (n = 25) received 0.75% Ropivacaine 16ml + Clonidine 1µg/kg.

MATERIALS USED for performing an epidural block were placed in a sterile tray which contained antiseptic solution in a bowl, gauze sponges, sponge holding foreceps and sterile towel and drapes to prepare the area for asepsis.

A sterile epidural kit was kept ready with a 18G Tuohy needle, 19G calibrated epidural catheter, a 5 ml glass syringe for appreciating loss of resistance.

Lignocaine 2% vial, 25G 1.5 inch needle and 3ml disposable syringes were used for local infiltration and freshly prepared 2% lignocaine with adrenaline (5µg/ml) solution for test dose

Emergency drugs and equipments were kept ready.

METHODS

All patients were fasted for eight hours and were premedicated with Tab. Ranitidine 150 mg the night before and two hours before the surgery. Tab. Diazepam 10 mg was given the night before surgery to reduce anxiety. Peripheral venous line was accessed using an 18G

intravenous cannula and all patients were preloaded with 10 ml/kg of Ringer lactate solution[17] before performing the epidural block. ECG, pulsoximeter and NIBP monitors were connected and baseline parameters namely heart rate, blood pressure, SpO2, respiratory rate were recorded.

Epidural block was performed by anaesthesia resident who was blinded to this study. The block was done using 18G Tuohy needle in L3-L4 or L4-L5 interspaces and 3-5 cm of 19G epidural catheter was inserted into the epidural space. Test dose of 3ml of 2% lignocaine with 15µg adrenaline (1:200000) was given. After ruling out intravascular and intrathecal placement, the bolus drug solution of either group was administered slowly. Vital parameters were continuously monitored and recorded every 5 minutes for the first 30 minutes, then every 10 minutes upto 1hour, and every 15 minutes from 1 to 2 hours. Intravenous fluids were given based on the surgical requirements.

Hypotension[4] (SBP < 100 mmHg) was treated with Ephedrine 6mg i.v. Bradycardia[4] (HR<60 beats/minute) was treated with atropine 0.3mg i.v. Respiratory depression (RR< 8 breaths/min or SpO2 < 90%) was managed with intermittent positive pressure ventilation with 100% O2..Nausea or vomiting was treated with Ondansetron 4mg i.v..

Sensory level of block was assessed bilaterally by pin prick method from distal to proximal dermatome level.

Motor level of block was assessed by **Modified Bromage Scale**

SCALE	MOTOR BLOCK
1	Full flexion of knees and feet possible
2	Just able to flex knees, full flexion of feet possible
3	Unable to flex knees, full flexion of feet possible
4	Unable to move legs and feet

Sedation level was assessed by **Ramsay Sedation Scale**[18]

SCALE	RESPONSE
1	Patient is anxious and agitated or restless, or both
2	Patient is cooperative, oriented and tranquil
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
6	Patient exhibits no response

Surgical incision was made only after achieving total loss of sensation at T10 level. At the end of surgery patients were shifted to the recovery room and subsequently to the post operative ward. The patients were instructed to inform the onset of incisional discomfort to the post operative ward nurse who was blinded to the study.

Duration of analgesia was recorded from the onset of block to the time of incisional discomfort as reported by the patient

Epidural top up of 8 ml of 0.2% ropivacaine was given as rescue analgesia when the patient reported of incisional discomfort.

Side effects like shivering, dryness of mouth, nausea, vomiting, urinary retention and respiratory depression were observed.

The following details were noted.

1. Time to reach sensory block of T10 level
2. Peak sensory level
3. Time to reach peak sensory level
4. Time to reach complete motor block
5. Duration of analgesia.

Statistical Tools

The information collected regarding all the selected cases were recorded in a Master Chart. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's chi square test was used for qualitative variables. A 'p' value less than 0.05 was taken to denote a significant relationship.

OBSERVATIONS AND RESULTS

A : PROFILE OF CASES STUDIED

Both the groups were comparable demographically with respect to age and sex distribution, height and weight characteristics.

Table 1 : Age distribution

Age group	Group RD		Group RC	
	No.	%	No.	%
Less than 30 years	6	24	6	24
30 – 39 years	6	24	7	28
40 – 49 years	7	28	6	24
50 years & above	6	24	6	24
Total	25	100	25	100
Range	23 – 58 years		20 -58 years	
Mean	39.4 years		39.4 years	
S.D.	11.7 years		11.4 years	
S.E.	2.307		2.254	
Difference	3.225			
'p' value	0.9923			

Persons aged 20 years to 58 years were included in the study. Group RD had a mean age of 39.4 $\pm$11.7 years and Group RC had a mean age of 39.4 $\pm$11.4 years. The standard error was 2.307 in Group RD and 2.254 in Group RC. There was no significant difference in the age composition between the two groups ($p>0.05$).

Table 2 : Sex distribution

Sex	Group RD		Group RC	
	No	%	No	%
Male	15	60	16	64
Female	10	40	9	36
Total	25	100	25	100
‘p’ value	0.773			

15 out of 25 cases in Group RD (60%) and 16 out of 25 cases in Group RC (64%) were males. There was no statistically significant difference in the sex composition of the two groups ($p>0.05$).

Table 3 : Physical parameters

Para-meters	Group RD			Group RC			Diff-erence	'p' value
	Mean.	S.D.	S.E.	Mean	S.D.	S.E.		
Height (in cm)	158.0	5.9	1.16	157.3	6.0	1.19	1.667	0.6126
Weight (in kg)	55.2	8.4	1.65	56.3	8.7	1.72	2.392	0.8155

The mean height in Group RD was 158.0±5.9 and that of Group RC was 157.3±6.0. The mean weight in Group RD was 55.2±8.4 and that of Group RC was 56.3±8.7. There was no statistically significant difference ($p>0.05$) between the two groups with respect to height and weight.

Table 4 : Distribution of Surgery

Surgery done	Group RD		Group RC	
	No	%	No	%
Appendicectomy	8	32	8	32
Hernioplasty	13	52	12	48
Hysterectomy	4	16	5	20
Total	25	100	25	100

52% of cases in Group RD and 48% of cases in Group RC were Hernioplasty, 32% of cases in either group were Appendicectomy, rest of the cases were Hysterectomy.

Table 5: Duration of surgery

Duration of surgery in minutes	Group RD			Group RC			Difference	'p' value
	Mean	S.D.	S.E.	Mean	S.D.	S.E.		
	79.2	11.1	2.189	78.6	16.9	3.351	4.002	0.5233

The mean duration of surgery in Group RD was 79.2±11.1 and that in Group RC was 78.6±16.9. The difference was statistically not significant ($p>0.05$).

B: EFFICACY OF THE DRUGS

Table 6: Onset of Block

Time (in minutes)	Group RD			Group RC			Difference	'p' value
	Mean	S.D	S.E.	Mean	S.D	S.E.		
Time to reach T 10 sensory level	10.7	2.1	0.407	11.4	1.8	0.357	0.542	0.1429
Time to reach peak sensory level	14.3	2.8	0.55	15.4	2.4	0.471	0.724	0.0512
Time to reach complete motor block	19.2	3.8	0.743	20.6	3.3	0.646	0.985	0.0677

The onset of analgesia at T10 level was 10.7±2.1 minutes in Group RD and 11.4±1.8 minutes in Group RC. Peak sensory level was achieved in 14.3±2.8 minutes in Group RD and 15.4±2.4 minutes in Group RC. Maximum motor block was achieved in 19.2±3.8 minutes in Group RD and 20.6±3.3 minutes in Group RC. The difference in onset of sensory and motor blockade was not significant ($p>0.05$) when comparing both the groups.

Table7: Peak sensory level

Peak sensory level	Group RD		Group RC	
	No	%	No	%
T4	3	12	3	12
T6	17	68	18	72
T8	5	20	4	16
Total	25	100	25	100

Peak sensory level of T6 was achieved in 68% of cases in Group RD and 72% in Group RC. T4 level was achieved in 12% of cases in both the groups. Thus both the drugs did not vary much in their height of block.

Table 8: Duration of analgesia

Time (in minutes)	Group RD			Group RC			Difference	'p' value
	Mean	S.D.	S.E.	Mean	S.D.	S.E.		
Duration of analgesia	277.7	30.4	6.0	261.0	33.6	6.7	9.0	**0.0426**

Duration of analgesia for the Group RD was 277.7±30.4 minutes and for the Group RC it was 261.0±33.6 minutes. This difference was statistically significant ($p<0.05$). This proves that dexmedetomidine provides prolonged analgesia when compared to clonidine.

Table 9: Changes in heart rate

Time in minutes	Value (Mean±SD) for		'p' value
	Group RD	Group RC	
0	80.0±8.0	77.9±7.0	0.3057
5	78.2±8.7	74.3±6.3	0.1316
10	74.0±6.8	71.1±6.0	0.1898
15	69.9±6.8	68.2±6.1	0.2964
20	66.6±5.7	66.3±5.2	0.7619
25	65.3±5.5	63.9±4.4	0.3688
30	66.8±7.5	63.4±5.9	0.0719
40	66.6±7.6	63.0± 7.1	0.0837
50	65.6±5.9	64.5±7.6	0.2974
60	67.2±5.5	65.5±7.0	0.1596
75	67.5±4.2	66.8±5.6	0.4181
90	67.5±3.8	65.9±4.8	0.1462
105	68.8±3.8	66.9±3.4	0.0628
120	69.9±8.3	65.9±6.4	0.1014
Decrease in HR	10.2±8.4	12.0±7.3	0.4757

Mean heart rate at various time intervals did not have any statistically significant difference between the two groups ($p>0.05$). The mean decrease in heart rate was 10.2±8.4mmHg in Group RD and 12.0±7.3mmHg in Group RC. This variation was not clinically and statistically significant ($p>0.05$).

Table 10: Changes in Blood pressure

Time in minutes	SBP (Mean±SD)		'p' value	DBP (Mean±SD)		'p' value
	RD	RC		RD	RC	
0	120.7± 9.6	117.6± 9.1	0.2385	71.9± 6.5	71.0± 5.7	0.7615
5	115.9± 10.2	114.5± 7.9	0.792	68.9± 5.9	68.6± 5.0	0.9141
10	112.2± 8.8	111.3± 8.2	0.5779	65.4± 6.2	65.5± 5.1	0.8758
15	107.4± 7.6	106.4± 7.1	0.5256	62.3± 5.6	64.1± 5.8	0.2475
20	102.9± 8.0	104.0± 6.0	0.3582	60.3± 5.4	61.4± 4.6	0.252
25	101.0± 6.5	104.3± 5.3	0.06	58.9± 6.1	61.0± 4.2	0.1396
30	102.2± 5.2	101.5± 5.3	0.5289	59.3± 5.3	60.0± 4.2	0.5562
40	104.1± 6.6	101.9± 5.4	0.1929	60.5± 4.6	59.0± 4	0.4089
50	104.3± 4.3	103.6± 4.5	0.8512	61.4± 3.7	59.8± 3.2	0.1158
60	104.0± 3.7	104.9± 3.7	0.3689	61.2± 4.8	60.7± 3.3	0.8901
75	105.1± 3.1	104.8± 3.5	0.8266	61.6± 4.0	60.6± 3.6	0.2843
90	106.2± 3.2	105.4± 2.6	0.5341	63.0± 4.1	61.0± 3.0	0.0646
105	107.4± 3.9	105.2± 3.3	0.0537	63.0± 4.2	60.6± 4.7	0.0704
120	107.4± 2.8	106.2± 2.6	0.0658	62.9± 3.7	61.1± 3.5	0.0598
Decrease in BP	13.3± 9.2	11.4± 9.0	0.4356	9.0± 6.1	9.8± 4.8	0.6524

Systolic BP decreased by 13.3±9.2 mmHg in Group RD and 11.4±9.0 mmHg in Group RC. Diastolic BP decreased by 9.0±6.1 mmHg in Group RD and 9.8±4.8 mmHg in Group RC. Thus, blood pressure at various time intervals did not have any statistically significant difference between the two groups ($p>0.05$). Both dexmedetomidine and clonidine at the given dose maintained hemodynamic parameters close to the baseline values.

Table 11: Sedation

Time in minutes	Ramsay Sedation Score (Percentage of cases)												'p' value
	Group RD						Group RC						
	1	2	3	4	5	6	1	2	3	4	5	6	
0	12	88	-	-	-	-	12	88	-	-	-	-	1.0
5	4	88	8	-	-	-	4	92	4	-	-	-	0.6546
10	-	28	72	-	-	-	-	48	52	-	-	-	0.1493
15	-	12	76	12	-	-	-	16	84	-	-	-	0.2204
20	-	12	68	20	-	-	-	12	64	24	-	-	0.7987
25	-	4	20	72	4	-	-	4	36	60	-	-	0.1951
30	-	4	20	68	8	-	-	4	20	76	-	-	0.6393
40	-	-	20	72	8	-	-	-	20	80	-	-	0.6018
50	-	-	24	72	4	-	-	-	24	76	-	-	0.8089
60	-	-	28	72	-	-	-	-	44	56	-	-	0.2433
75	-	-	36	64	-	-	-	-	60	40	-	-	0.0927
90	-	4	88	8	-	-	-	-	96	4	-	-	0.9142
105	-	24	76	-	-	-	-	16	84	-	-	-	0.4839
120	-	24	76	-	-	-	-	12	88	-	-	-	0.2743

Most of the patients were sedated to a Ramsay sedation score of 3 and 4 from 10 to 90 minutes in both the groups, however, few patients (24%) in Group RD were deeply sedated to a Ramsay sedation score of 5 between 25 to 50 minutes. But overall, Ramsay sedation score of the Group RD and Group RC did not exhibit any statistically significance at all time intervals ($p > 0.05$).

Table 12 : Side effects

Side effects	Group RD		Group RC		'p' value
	No	%	No	%	
Dry mouth	6	24	3	12	0.2317
Nausea	3	12	2	8	0.5
Vomiting	1	4	-	-	0.5
Shivering	2	8	1	4	0.5
Urinary retention	0	0	0	0	
Respiratory depression	0	0	0	0	

24% of cases in Group RD and 12% in Group RC had dry mouth. Nausea was present in 12% of cases in Group RD and 8% in Group RC, but vomiting was present only in Group RD (4%). Shivering was noted in 2 cases of Group RD and in 1 case of Group RC. Overall side effects were present in 48% of cases in Group RD and 24% of cases in Group RC. But the difference was not statistically significant ($p>0.05$). None of the patient had urinary retention or respiratory depression.

DISCUSSION

Epidural analgesia has become the cornerstone for postoperative pain relief after abdominal surgery due to easy accessibility, reliability, prolongation of analgesia, early recovery, fewer side effects, and patient satisfaction and so on. Epidural clonidine has been studied in various doses ranging from 1µg/kg to 3µg/kg. Epidural dexmedetomidine has been studied in doses ranging from 1µg/kg to 2µg/kg. However no studies have found the equivalent dose of these two drugs when given epidurally or intrathecally.

Epidural dexmedetomidine at less than 1µg/kg concentration has been found not effective in prolonging block of plain ropivacaine[19, 20, 21].

Epidural clonidine in 1µg/kg dose has been suggested as optimal dose in prolonging the analgesia without producing unwanted side effects like hypotension and bradycardia[22, 23, 24, 25, 26, 27]. Hence, in our study, we used equal and low concentration (1µ/kg) of clonidine and dexmedetomidine in epidural route.

To determine the efficacy of drugs injected into epidural space, we need to understand that the uptake into neural tissue is a function of the CSF concentration and perineural concentration in the epidural space, which is determined by the distribution of the drug in various

tissues. Elimination of drug from subarachnoid and epidural space determines the duration of action. Since it is difficult to find the epidural and CSF concentrations of drugs directly, we clinically estimate their effects on onset, distribution and duration of anaesthesia[6].

In this prospective randomised control study, we compared the two available α_2 agonists, namely clonidine and dexmedetomidine with ropivacaine in epidural route for lower abdominal surgeries with respect to onset, duration and side effects.

This study was conducted in fifty patients. Twenty five of them were randomly assigned to Group RD and received dexmedetomidine 1µg/kg with 16 ml of 0.75% ropivacaine. The remaining twenty five patients were assigned to Group RC and received clonidine 1µg/kg with 16 ml of 0.75% ropivacaine.

Both the groups were comparable with respect to age, sex, weight, height and duration of surgery, but the difference was statistically insignificant ($p>0.05$).

Onset of anaesthesia:

In our study, the onset of sensory blockade at T10 level in dexmedetomidine group was 10.7±2.1min when compared to 11.4±1.8 min in clonidine group with insignificant difference ($p=0.143$). The time

to reach complete motor block was 19.2±3.8 min in dexmedetomidine group and 20.6±3.3 min in clonidine group with p=0.067. However these differences in the onset of sensory and motor block was not significant statistically and clinically.

Sukhminder Jit Singh Bajwa et al, compared dexmedetomidine 1.5µg/kg and clonidine 2µg/kg with ropivacaine and found that the onset at T10 sensory level was significantly ($p<0.05$) earlier in dexmedetomidine group (8.52±2.36 min) than the clonidine group (9.72±3.44 min). The onset of complete motor block was also significantly ($p<0.05$) earlier in dexmedetomidine group (17.24±5.16 min vs. 19.52±4.06 min)

For onset of anaesthesia, the determinants are diffusion through meningeal layers, penetration of neural tissue and distribution of the drug in various tissues. Dexmedetomidine being more lipophilic and having a favourable pKa produces earlier onset than clonidine.

Dexmedetomidine alters its own pharmacokinetics at higher concentration by causing vasoconstriction,[28, 29] and decreasing volume of distribution thereby allowing more drug for penetration of neural tissue. This also explains the transient hypertension after rapid intravenous bolus dose of dexmedetomidine. However, vasoconstriction is not seen with lower concentrations of dexmedetomidine. But the concentration at which

this change in pharmacokinetics occurs is not yet found. Clonidine doesn't have this property. *Sukhminder Jit Singh Bajwa et al*, in their study used a higher concentration of dexmedetomidine (1.5µ/kg) when compared to that in our study (1µg/kg). Vasoconstrictive property of dexmedetomidine at higher dose possibly explains the significant difference in onset time between dexmedetomidine and clonidine in their study, but non-significant difference of onset in our study.

Duration of analgesia:

In our study, the duration of analgesia was more in dexmedetomidine group (277.7±30.4 min) than in clonidine group (261.0±33.6 min) which was statistically significant ($p<0.05$)

In the study done by *Sukhminder Jit Singh Bajwa et al*, the time for first rescue top up was 342.88±29.16 minutes in dexmedetomidine group and 310.76±23.76 minutes in clonidine group and the difference was statistically significant ($p<0.05$). They also used onset of incisional pain to indicate analgesia time, however higher doses of dexmedetomidine (1.5µg/kg) and clonidine (2µg/kg) can be considered to explain prolonged action when compared to our study.

Mausumi Neogi et al, compared three groups, clonidine 1µg/kg and dexmedetomidine 1µg/kg with plain ropivacaine for post-op caudal analgesia in children and found that the mean duration of analgesia was

significantly prolonged in clonidine (13.17±0.68 hours) and dexmedetomidine group (15.26±0.86 hours) when compared to ropivacaine group (6.32±0.46 hours). However, there was no statistical significance between clonidine and dexmedetomidine groups ($p>0.05$). In their study, caudal analgesia was given as a supplement to general anaesthesia and they used CRIES score of 4 or above to denote the duration of analgesia.

Sedation:

In our study, we assessed the intra-op sedation using Ramsay sedation score. We observed that patients in both the groups were sedated to Ramsay sedation scores of 3 and 4 levels from 10 minutes to 90 minutes after drug administration. A few patients were sedated deeply to a score of 5 in dexmedetomidine group between 25 minutes to 50 minutes. However, the difference in sedation scores was not statistically significant between the two groups ($p>0.05$).

Oriol-Lopez et al conducted an observational study to find the anxiolytic and sedative property of dexmedetomidine. Epidural dexmedetomidine 1µg/kg was given with lignocaine in 40 patients who underwent various abdominal surgeries. They used Ramsay sedation score and concluded that 90% of the study group were sedated to a score of 3 and 4 from 15 to 90 minutes after drug administration.

Antonio Mauro Vieira et al, in their study comparing clonidine 2µg/kg and dexmedetomidine 2µg/kg via epidural for post-op analgesia and sedation in 40 patients who underwent cholecystectomy under general anaesthesia, observed that by using Filos' scale (1-conscious and nervous, 2-conscious and quiet, 3- sleepy but arousable, 4- sleepy and difficult arousal) there was no statistical difference in sedation ($p>0.05$) between the two groups for 2 hour post-op period.

Both these studies correlated similar to our study with insignificant difference ($p>0.05$) in sedation between dexmedetomidine and clonidine given at 1µg/kg dose in epidural route.

Side effects:

In our study, we observed that the changes in hemodynamic parameters were similar in both dexmedetomidine and clonidine groups.

Dryness of mouth was observed in 6 patients (24%) of group RD compared to 3 patients (12%) of group RC. 3 patients (12%) in group RD compared to 2 patients (8%) in group RC had nausea. Only one patient in group RD had vomiting. Shivering was observed in 2 cases (8%) of group RD and in 1 case (4%) of group RC. The incidence of side effects was statistically insignificant between the two groups ($p>0.05$).

Sukhminder Jit Singh Bajwa et al, in their study population of 50 patients observed similar incidence of side effects. 6 patients in group D and 7 patients in group C had dry mouth, 4 patients in group D and 3 patients in Group C had nausea, 1 patient in group C and 2 patients in group D had shivering. However no significant difference ($p>0.05$) in incidence of side effects were observed between the two groups.

Mausumi Neogi et al, in their study comparing three groups of 25 patients each observed no incidence of urinary retention or respiratory depression. 3 patients in dexmedetomidine group, 2 patients in clonidine group and 1 patient in ropivacaine group had nausea and vomiting. But the difference was insignificant ($p>0.05$).

Our study findings correlated with these two studies with regards to side effects.

SUMMARY

Fifty adult patients of ASA I and II physical status who presented for lower abdominal surgery were enrolled in this double blinded study. They were equally and randomly allotted into two groups namely, Group RD and Group RC.

Patients in Group RD received epidural 0.75% ropivacaine 16 ml with dexmedetomidine 1µg/kg

Patients in Group RC received epidural 0.75% ropivacaine 16 ml with clonidine 1µg/kg

They were observed for onset of anaesthesia, duration, sedation and side effects. The collected data was analysed using chi square test and a 'p' value <0.05 was considered significant.

Dexmedetomidine and clonidine when added to epidural ropivacaine produced similar onset of anaesthesia, sedation and other side effects. However, dexmedetomidine produced a significant prolongation of analgesia when compared to clonidine.

CONCLUSION

From this study, we conclude that dexmedetomidine 1µg/kg is an alternative to clonidine 1µg/kg in providing similar onset of anaesthesia, prolonged duration of analgesia, similar sedation, side effects and hemodynamic profile, when given via epidural route with ropivacaine for lower abdominal surgeries.

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PROFORMA

To compare the efficacy of dexmedetomidine and clonidine in epidural anaesthesia with ropivacaine for lower abdominal surgeries.

Name: Age: Sex: I.P.no.:

Pre-op diagnosis: Proposed surgery:

Pre-op

Height: Weight: PR: BP: CVS: RS: ASA:

Hb: BT: CT: RBS: Urea: Creatine: ECG:

Regional technique: CEA

Position: Site: Needle: Catheter length in epidural space:

Test dose: Time: Volume:

Per-op	0 min	5	10	15	20	25	30	40	50	60	75	90	105	120
HR														
BP														
RR														
SpO2														
Sedation														

Duration of surgery: Blood loss: Ephedrine: Atropine:

Urine output: IV fluids:

Side effects: nausea & vomiting, sedation, resp.depres'n, dry mouth, shivering, urine retent'n

Postop	2 hrs	4	6	8	10	12	16	24
HR								
BP								

Variables analysed:

Time to reach T10: Peak sensory level:

Time to reach peak sensory level: Time to reach complete motor block:

Duration of analgesia::

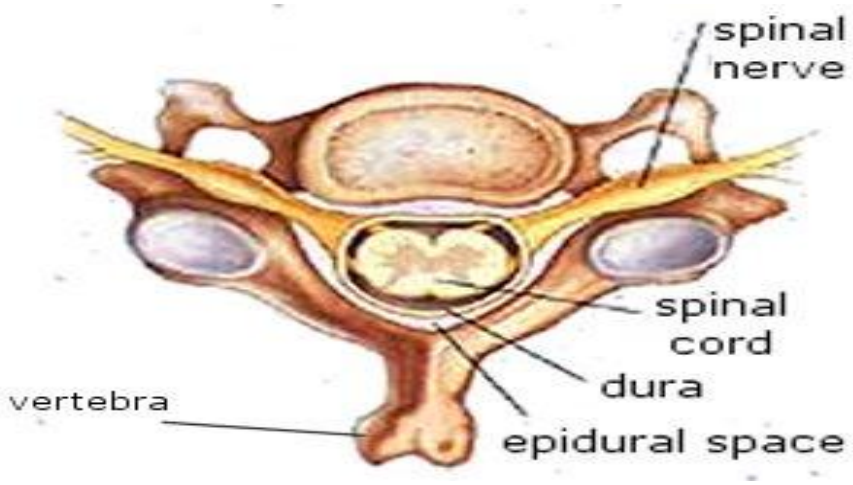


Fig.1: Cross section showing the epidural space

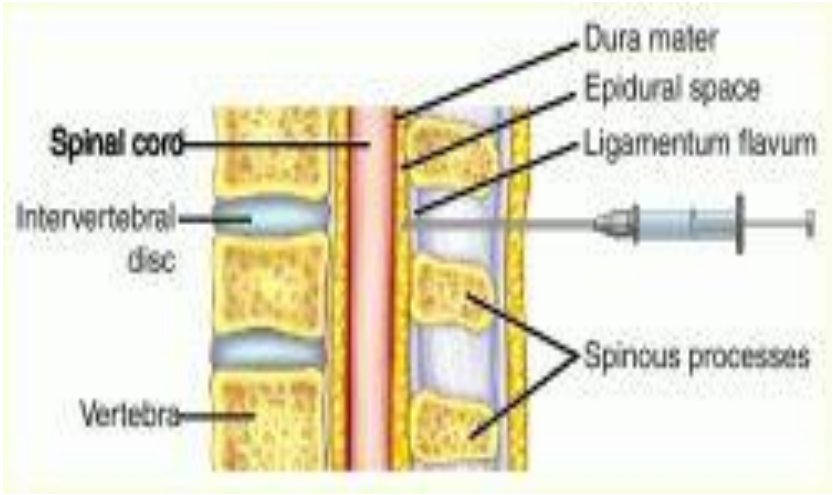


Fig 2: Longitudinal section showing the epidural space

FIG.3. BAR COLUMN TO SHOW AGE DISTRIBUTION

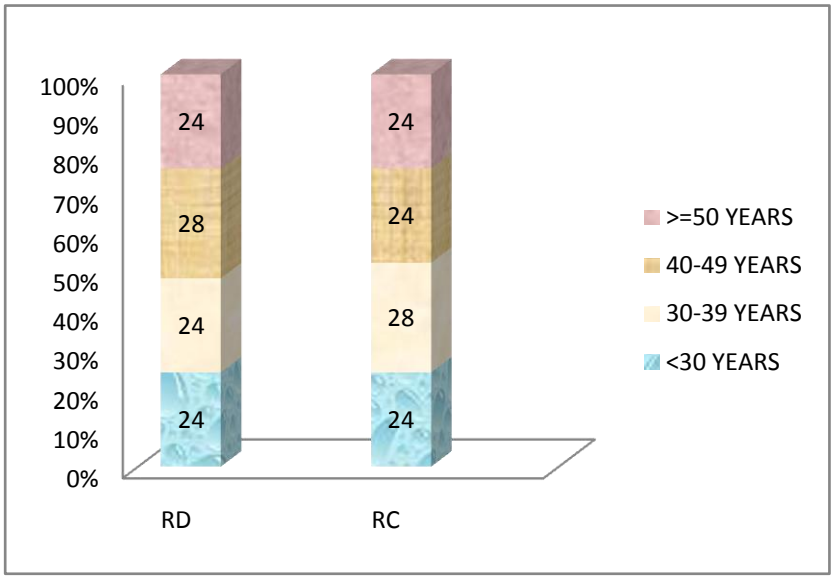


FIG.4. BAR COLUMN TO SHOW SEX DISTRIBUTION

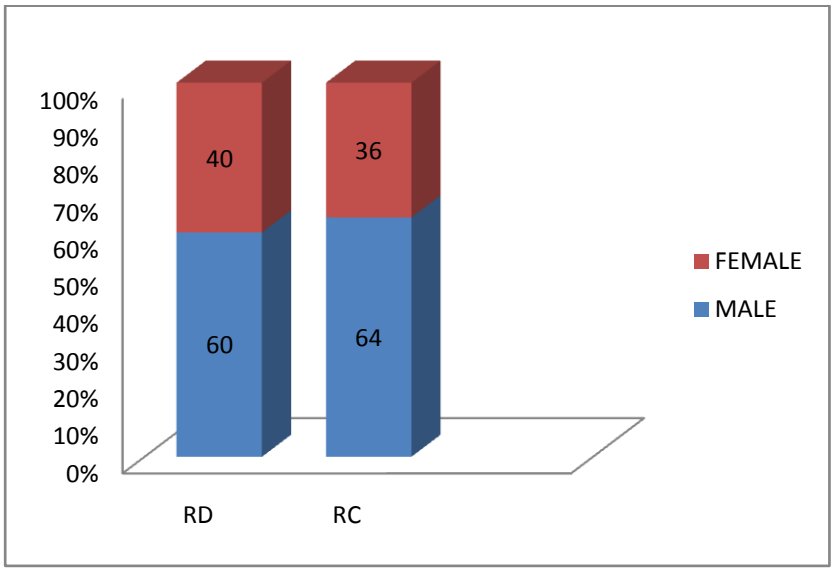


FIG.5. CONE CHART TO SHOW PATIENT PHYSICAL CHARACTERISTICS

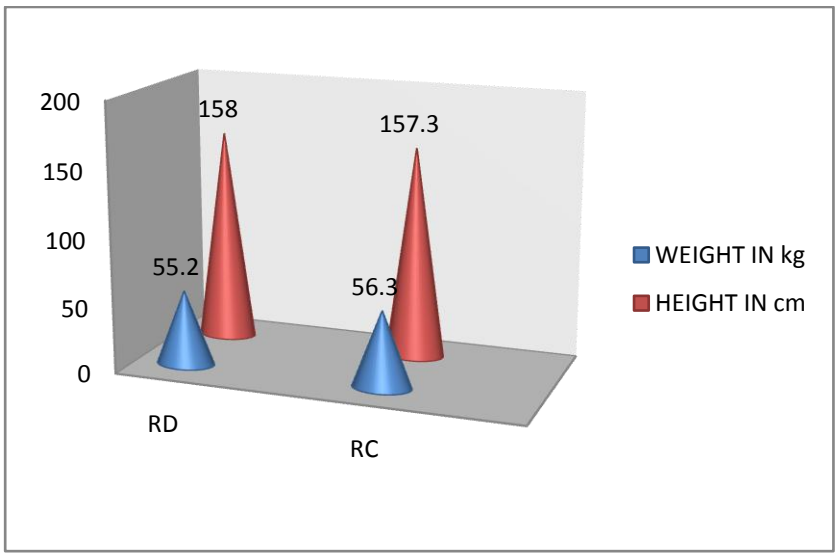


FIG.6. CYLINDER COLUMN TO SHOW DISTRIBUTION OF SURGERY

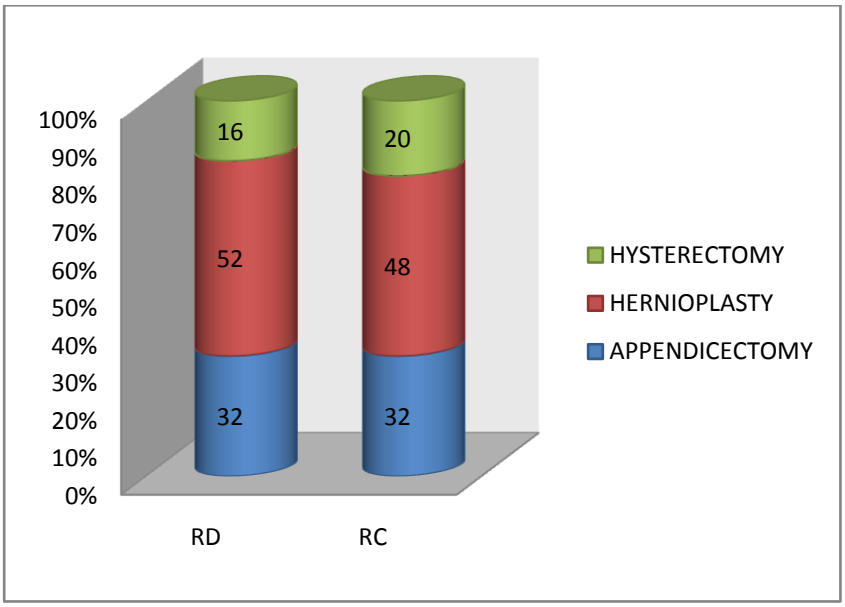


FIG.7. BAR COLUMN TO SHOW DURATION OF SURGERY

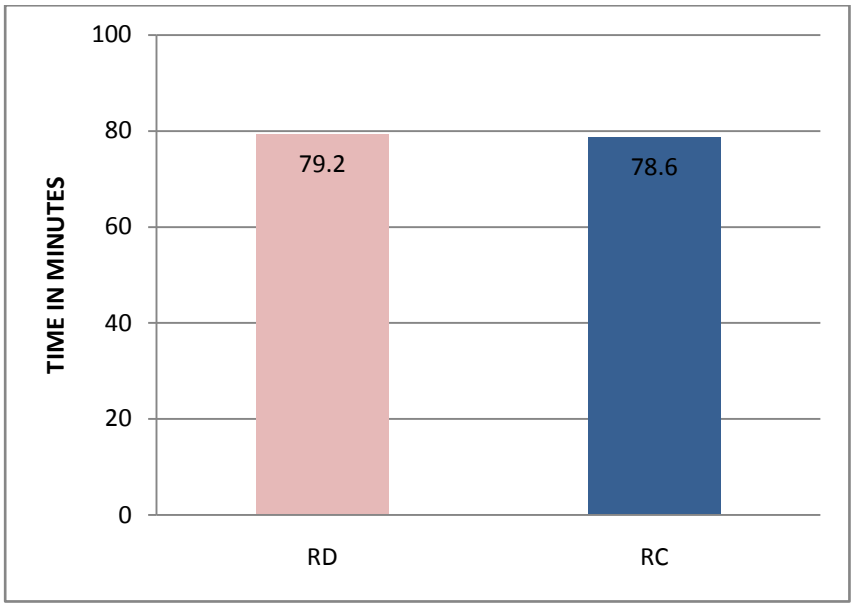


FIG.8. BAR CHART SHOWING ONSET CHARACTERISTICS OF EPIDURAL BLOCK

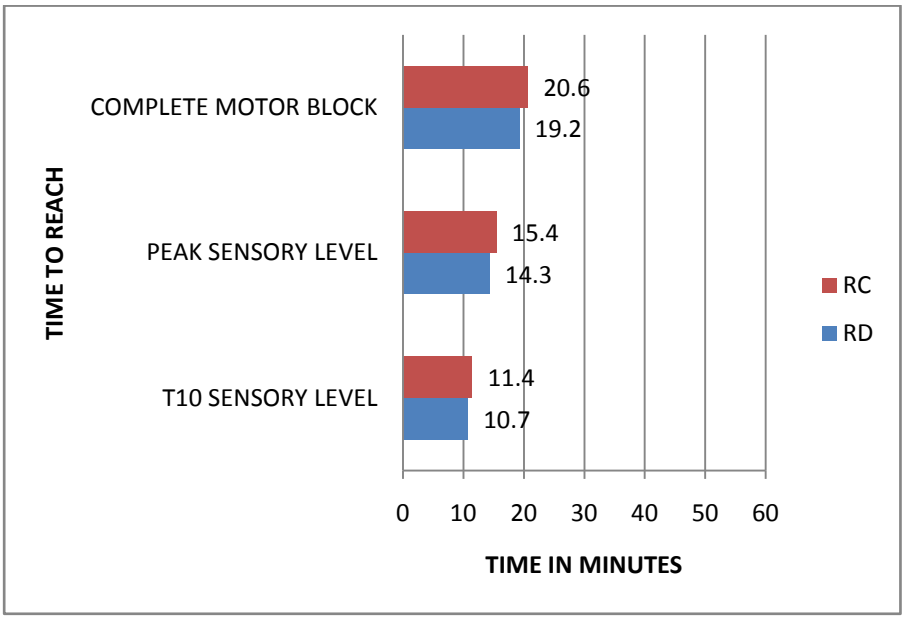


FIG.9. CONE CHART TO SHOW PEAK SENSORY LEVEL

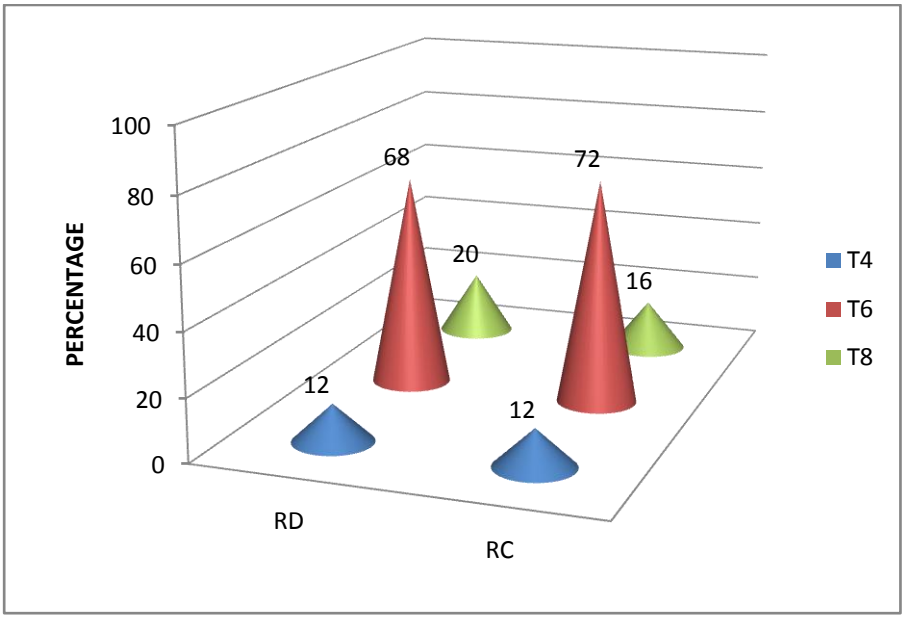


FIG.10. BAR COLUMN TO SHOW DURATION OF ANALGESIA

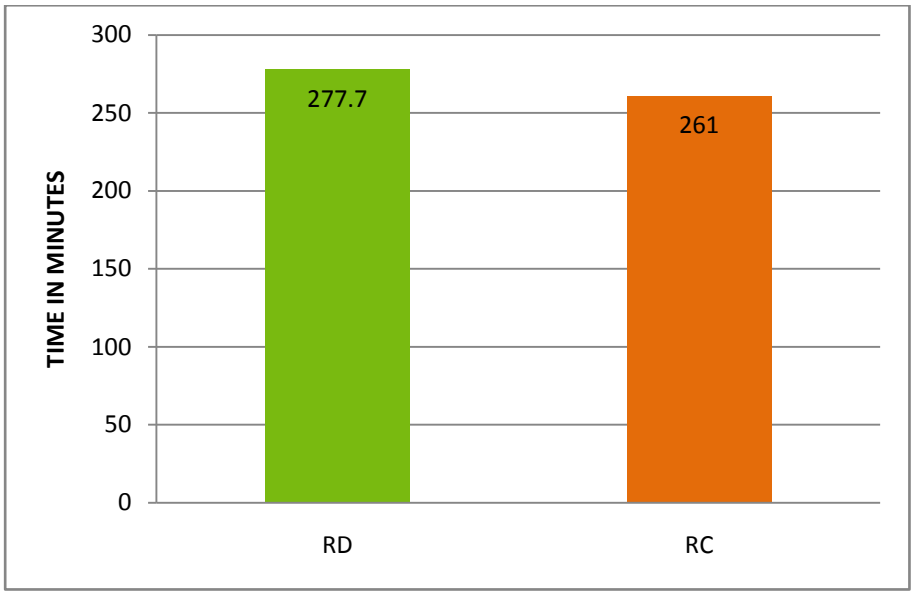


FIG.11.SCATTER DIAGRAM TO SHOW CHANGES IN HEART RATE

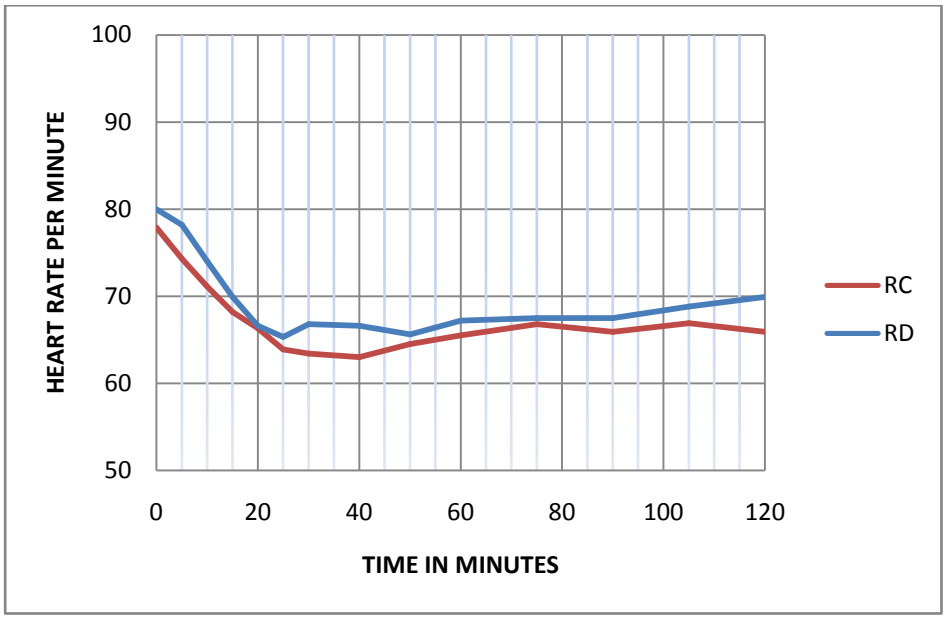


FIG.12. SCATTER DIAGRAM TO SHOW CHANGES IN BLOOD PRESSURE

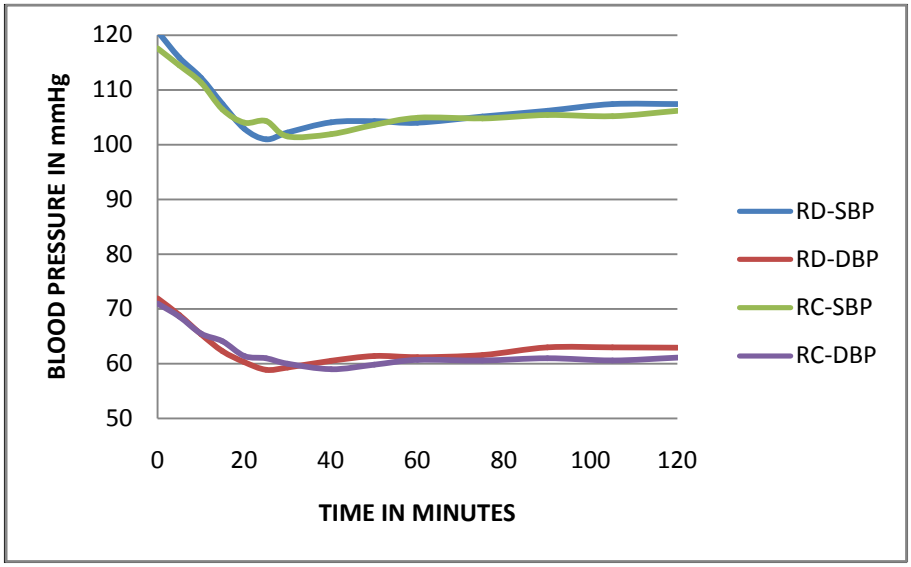
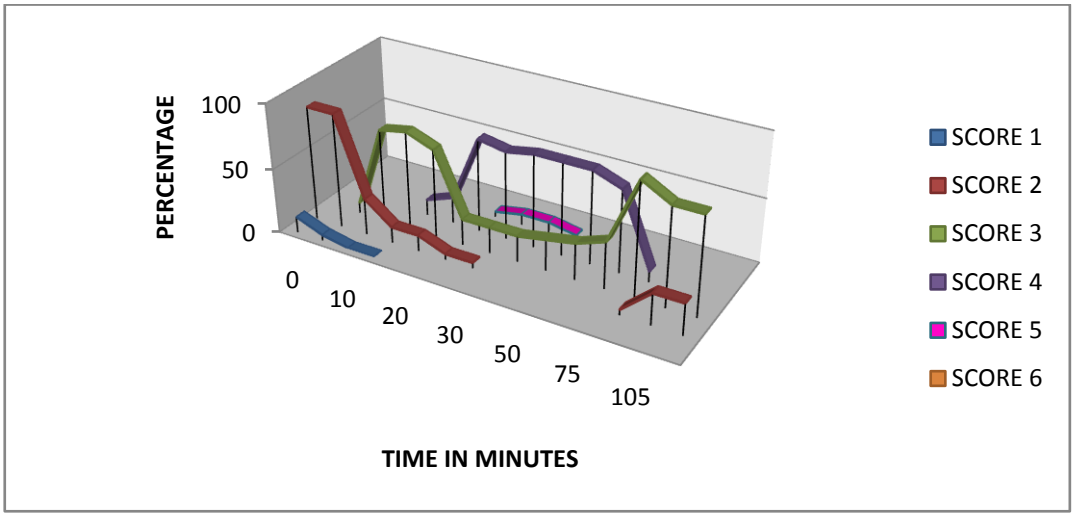


FIG.13. LINE DIAGRAM TO SHOW RAMSAY SEDATION SCORE

A. GROUP RD



B. GROUP RC

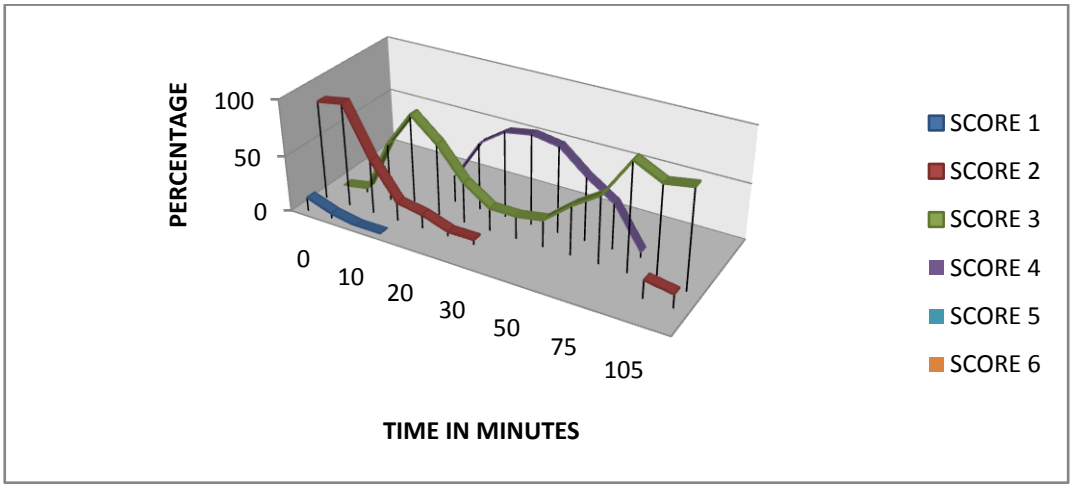
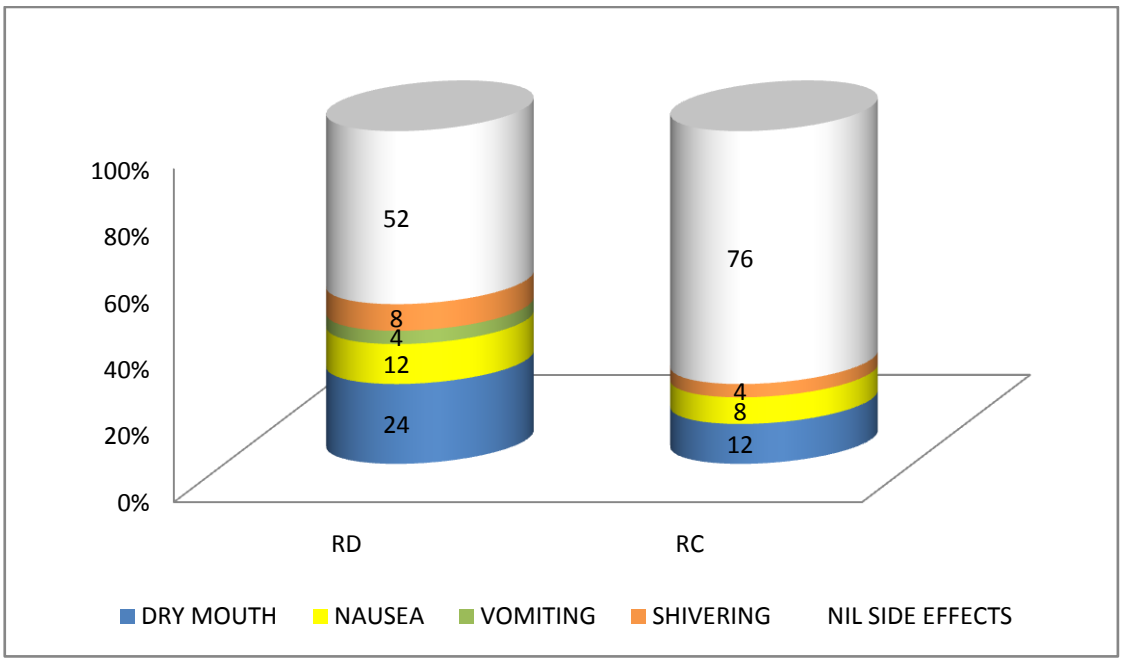


FIG.14. CYLINDER COLUMN TO SHOW SIDE EFFECTS



MASTER CHART

GROUP RD

sl.no	name	age	sex	ht	wt	asa	surg	dur	Tt10	peak	Tpeak	TMBS3	duration	SED													side effects
														0	5	10	15	20	25	30	40	50	60	75	90	105	120	
1	RAMASAMY	58	M	156	58	2	HER	75	10	T6	13	20	290	1	2	2	3	3	3	3	4	4	4	3	3	3	3	
2	SARAVANAN	23	M	164	65	1	APP	60	12	T8	15	18	258	2	2	3	3	4	4	4	4	4	4	3	3	2	2	dry mouth
3	MATHIYALAGAN	40	M	165	70	2	HER	90	10	T6	15	18	230	2	2	3	3	3	4	4	4	4	4	4	3	3	3	
4	VEERAMUTHU	50	M	156	55	1	HER	75	8	T6	12	20	322	2	2	3	3	3	4	4	4	4	4	4	4	3	3	
5	MEGAVARANAM	36	F	148	52	2	HER	90	10	T6	15	18	240	2	2	3	3	3	3	3	3	3	3	3	3	2	2	
6	ANBUSELVI	23	F	150	51	1	APP	75	13	T4	20	25	317	2	2	3	3	4	5	5	5	4	4	4	3	3	3	naus, vomit
7	ANANTHAYEE	46	F	150	46	2	HYS	90	15	T6	20	30	315	2	2	2	3	3	3	3	3	3	3	3	3	3	3	
8	JAYA	48	F	152	47	2	HYS	90	10	T6	12	18	290	2	2	3	3	3	4	4	4	4	4	4	3	3	3	dry mouth
9	MANIKANDAN	32	M	164	70	1	HER	75	8	T8	12	15	292	2	2	3	3	3	4	4	4	4	4	4	3	3	3	
10	VEERAMUTHU	54	M	160	45	1	HER	90	8	T6	10	15	292	2	2	3	3	3	4	4	4	4	4	4	3	3	3	
11	DHARMARAJ	38	M	154	50	2	HER	75	10	T6	15	20	320	1	2	2	2	2	3	3	3	3	3	3	3	3	3	nausea
12	VIJAYA	42	F	152	40	2	APP	75	12	T4	18	25	288	2	2	3	3	3	4	5	5	5	4	4	3	3	3	dry mouth
13	RAMANATHAN	30	M	160	54	1	APP	60	10	T6	15	18	290	2	2	3	3	3	4	4	4	4	4	4	3	3	3	
14	VADIVU	55	F	154	46	2	HYS	90	8	T6	12	15	292	2	2	2	3	3	4	4	4	4	3	3	3	3	3	shivering
15	GOVINDAN	25	M	158	54	1	APP	60	13	T6	15	20	317	2	2	3	4	4	4	4	4	4	4	4	4	3	3	dry mouth
16	MARIMUTHU	45	F	158	60	2	HER	90	10	T8	12	15	260	2	2	3	3	3	4	4	4	4	4	4	3	2	2	
17	ABDULLA	25	M	156	54	1	APP	75	10	T6	13	20	260	2	2	3	3	3	4	4	4	4	4	4	3	3	3	
18	MOORTHY	52	M	165	53	1	HER	90	12	T8	15	20	258	1	1	2	2	2	2	2	3	3	3	3	3	2	2	dry mouth
19	MAHESHWARI	23	F	158	55	1	APP	75	10	T6	12	18	230	2	2	3	4	4	4	4	4	4	4	4	3	3	3	dry mouth
20	KANNAN	30	M	162	56	2	HER	90	13	T6	15	20	257	2	2	2	2	2	3	3	3	3	3	3	2	2	2	
21	KOKILAM	56	F	151	44	2	HYS	90	15	T4	20	25	285	2	3	3	3	3	4	4	4	4	4	4	3	3	3	nausea
22	KASTHURI	34	F	158	60	1	APP	60	8	T6	12	15	292	2	2	2	3	3	4	4	4	3	3	3	3	2	2	
23	KIRUBHA	48	M	168	67	1	HER	75	10	T8	12	18	230	2	2	3	3	3	4	4	4	4	4	4	3	3	3	
24	MATHAN KUMAR	27	M	170	68	1	HER	75	10	T6	12	15	230	2	3	3	4	4	4	4	4	4	4	4	3	3	3	nausea
25	NALLAMUTHU	45	M	160	60	1	HER	90	12	T6	15	20	288	2	2	3	3	3	4	4	4	4	4	4	3	3	3	shivering

GROUP RC

sl.no	name	age	sex	ht	wt	asa	surg	dur	Tt10	peak	Tpeak	TMBS3	duration															side effects
														0	5	10	15	20	25	30	40	50	60	75	90	105	120	
1	ARUMUGAM	37	M	164	62	1	HER	120	12	T6	15	22	198	1	1	2	2	2	3	3	3	3	3	3	3	3	3	
2	MOORTHY	26	M	156	50	1	APP	60	10	T6	13	20	230	2	2	3	3	4	4	4	4	4	3	3	3	2	2	
3	VADIVELU	34	M	152	48	1	HER	75	8	T6	10	15	202	2	2	3	3	4	4	4	4	4	3	3	3	3	3	
4	KAVITHA	26	F	156	62	2	APP	75	10	T6	15	15	230	2	2	2	3	3	4	4	4	4	4	3	3	3	3	dry mouth
5	VIJAYAKUMARI	32	F	150	52	1	HYS	90	8	T8	12	18	262	2	2	3	3	3	3	3	3	3	3	3	3	3	3	
6	KUMAR	43	M	165	64	2	HER	90	13	T8	20	25	257	2	2	3	3	4	4	4	4	4	3	3	3	3	3	
7	LAVANYA	44	F	155	47	2	HER	75	12	T6	18	25	288	2	2	2	2	3	3	3	3	3	3	3	3	3	3	
8	MANIMEGALAI	34	F	150	45	1	APP	60	10	T6	15	20	230	2	2	2	2	3	4	4	4	4	4	4	3	3	3	dry mouth
9	SARASWATHI	56	F	150	50	2	HYS	90	12	T6	15	25	258	1	2	2	3	3	4	4	4	4	4	4	3	3	3	
10	NAGAMBAL	52	F	150	48	2	HYS	90	10	T4	15	18	230	2	2	2	3	4	4	4	4	4	3	3	3	3	3	nausea
11	SARAVANAN	35	M	164	60	1	HER	75	12	T6	15	25	258	2	2	2	3	2	3	3	3	3	3	3	3	3	3	
12	VATCHALA	58	F	151	48	2	HYS	90	12	T6	15	20	258	2	2	2	3	3	4	4	4	4	4	4	3	3	3	dry mouth
13	VIJAY	28	M	160	65	1	HER	75	10	T6	15	20	230	2	2	2	3	3	3	4	4	4	4	3	3	3	3	
14	KANAGARAJ	44	M	156	54	1	HER	75	10	T4	18	20	260	2	2	2	3	3	3	4	4	4	3	3	3	3	3	
15	MANIKANDAN	27	M	165	65	1	APP	60	13	T6	15	20	257	2	2	3	3	4	3	4	4	4	4	3	3	3	3	
16	MARUTHAMBAL	56	F	153	50	2	HYS	90	12	T6	18	25	318	2	2	3	3	3	4	4	4	4	4	4	3	2	2	
17	KARTHIKEYAN	20	M	155	54	1	APP	60	13	T6	18	20	287	2	2	3	3	3	4	4	4	4	4	4	3	3	3	
18	LEELAVATHY	35	F	152	55	1	APP	60	10	T6	13	20	290	2	2	3	3	2	2	2	3	3	3	3	3	2	2	
19	PARTHIBAN	48	M	167	70	2	HER	75	15	T8	18	25	285	2	2	3	3	3	3	3	4	4	4	4	3	3	3	
20	VEERAPANDI	54	M	160	55	2	HER	75	12	T4	15	18	288	2	2	3	3	4	4	4	4	4	4	4	4	3	3	
21	KATHIR	30	M	170	80	1	APP	60	13	T6	15	20	227	2	2	3	3	3	3	4	4	4	4	4	3	3	3	
22	MARKANDEYAN	24	M	162	68	1	APP	75	10	T6	13	15	260	2	2	2	3	3	4	4	4	3	3	3	3	2	3	nausea
23	SUBBURAJ	45	M	155	50	1	HER	90	12	T6	15	20	318	2	3	3	3	3	4	4	4	4	4	3	3	3	3	shivering
24	GOVINDASAMY	52	M	160	56	2	HER	120	15	T6	20	25	315	1	2	2	2	3	4	4	4	4	4	4	3	3	3	
25	KARUPPAYA	44	M	154	50	1	HER	60	12	T8	15	20	288	2	2	3	3	3	4	4	4	4	4	4	3	3	3	

RD

sl.no	HR														SBP														DBP											
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1	82	86	76	70	64	62	65	76	64	68	70	70	72	76	130	134	126	120	116	110	112	108	108	112	110	110	112	108	80	76	70	64	60	64	58	54	60	62	60	62	62	64
2	76	78	76	77	74	68	64	66	70	63	60	63	66	68	126	124	116	112	116	106	100	102	106	104	98	102	104	108	76	72	68	64	66	60	54	56	58	56	60	58	60	60
3	80	76	75	72	70	65	64	68	62	60	66	64	68	72	114	106	102	100	94	98	106	102	108	106	108	106	106	108	82	78	74	70	72	64	68	64	60	62	64	68	70	64
4	88	80	76	72	70	72	74	72	75	76	70	72	75	76	126	120	114	106	98	102	104	100	106	102	104	100	106	108	76	72	68	66	60	56	60	62	60	58	64	68	66	64
5	70	74	73	72	70	73	75	70	68	72	66	75	78	80	132	128	120	116	104	106	100	106	104	104	106	116	110	112	82	76	70	72	64	66	62	68	64	60	62	64	62	66
6	68	66	60	56	62	64	66	68	70	62	60	65	68	63	110	104	100	96	90	110	102	104	106	110	106	110	106	108	68	66	64	60	56	60	62	58	60	62	60	62	60	62
7	90	88	84	80	76	70	64	66	60	62	65	67	70	72	122	118	114	110	106	100	94	108	102	104	104	106	104	108	66	68	62	60	56	54	50	62	60	58	60	62	60	60
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19	76	75	70	65	64	62	60	62	58	66	66	64	68	68	120	116	116	110	106	100	96	98	94	102	106	104	110	106	78	76	76	70	68	70	66	64	68	70	68	70	72	70
20	86	88	78	70	68	64	60	56	68	74	76	70	70	68	116	108	102	100	102	100	96	94	106	108	102	106	106	104	68	64	60	58	56	56	54	56	60	62	58	60	60	62
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24	72	67	66	60	55	76	78	74	68	70	70	65	70	74	110	106	102	100	94	102	104	100	102	100	102	106	110	106	68	66	60	56	58	60	62	60	60	58	62	60	62	60
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RC

sl.no	HR														SBP														DBP											
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1	90	86	80	76	70	66	65	60	64	68	70	68	72	76	140	134	136	130	122	120	116	108	104	100	98	110	112	108	80	72	70	68	62	60	58	60	60	58	60	62	62	64
2	86	78	76	70	74	68	64	66	70	66	64	62	66	68	116	110	112	112	110	106	100	96	106	110	106	102	104	104	62	64	60	58	60	60	58	56	60	60	58	58	60	58
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