"COMPARISON OF EPIDURAL DEXMEDETOMIDINE Vs MAGNESIUM SULPHATE USED AS ADJUVANT TO ROPIVACAINE FOR ANALGESIA IN POST THORACOTOMY PATIENTS"

(A prospective, controlled, double blind randomized study)

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment for the award of the degree of

DOCTOR OF MEDICINE
IN
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BRANCH X

INSTITUTE OF ANAESTHESIOLOGY AND CRITICAL CARE
MADRAS MEDICAL COLLEGE
CHENNAI- 600003

APRIL 2018

CERTIFICATE

This is to certify that this dissertation titled, **"Comparison of Epidural Dexmedetomidine Vs Magnesium Sulphate used as Adjuvant to Ropivacaine for Analgesia in Post Thoracotomy patients"** (A prospective, controlled, double blind randomized study) submitted by Dr. MILANJYOTI PATAR in partial fulfillment for the award of the degree of DOCTOR OF MEDICINE in Anaesthesiology to The Tamilnadu Dr.M.G.R Medical University, Chennai is a bonafide record of work done by him in the INSTITUTE OF ANAESTHESIOLOGY & CRITICAL CARE, Rajiv Gandhi Govt General Hospital , Madras Medical College, Chennai during the academic year 2015-2018.

Prof.Dr.ANURADHA SWAMINATHAN, MD., DA.,
Professor and Director,
Institute of Anesthesiology &
Critical care,
Madras Medical College,
Rajiv Gandhi Govt General Hospital,
Chennai – 600003.

Prof.Dr.R.NARAYANA BABU, MD, DCH
The Dean,
Madras Medical College,
Rajiv Gandhi Govt General Hospital,
Chennai – 600003.

CERTIFICATE OF THE GUIDE

This is to certify that this dissertation titled, **"Comparison of Epidural Dexmedetomidine Vs Magnesium Sulphate used as Adjuvant to Ropivacaine for Analgesia in Post Thoracotomy patients"** (A prospective, controlled, double blind randomized study) submitted by Dr. MILANJYOTI PATAR in partial fulfillment for the award of the degree of DOCTOR OF MEDICINE in Anaesthesiology, to The Tamilnadu Dr.M.G.R Medical University, Chennai is a bonafide record of work done by him in the INSTITUTE OF ANAESTHESIOLOGY & CRITICAL CARE, Rajiv Gandhi Govt General Hospital ,Madras Medical College, Chennai during the academic year 2015-2018.

Prof. Dr. M. VELLINGIRI, MD.DA,
Professor of Anaesthesiology
Institute of Anaesthesiology
& Critical care,
Rajiv Gandhi Govt General Hospital,
Madras Medical College,
Chennai – 600 003.

Date:
Place: Chennai

DECLARATION

I, Dr. MILANJYOTI PATAR, hereby declare that the dissertation titled, **"Comparison of Epidural Dexmedetomidine Vs Magnesium Sulphate used as Adjuvant to Ropivacaine for Analgesia in Post Thoracotomy patients"**(A prospective, controlled, double blind randomized study) is a bonafide work done by me under the guidance of Prof. Dr. M. VELLINGIRI, M.D.DA, Professor of Anaesthesiology, Institute of Anaesthesiology & Critical care, Madras Medical college, Chennai, and submitted to The Tamilnadu Dr.M.G.R Medical University, Chennai in partial fulfillment of the regulations for the award of the degree of MD (Anaesthesiology), examinations to be held in April 2018. This study was conducted at Institute of Anaesthesiology & Critical care, Madras Medical College, Rajiv Gandhi Govt. General Hospital, Chennai.

I have not submitted this dissertation previously to any journal or any university for the award of any degree or diploma.

Date:
Place: Chennai **Dr. MILANJYOTI PATAR**

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Dr. MILANJYOTI PATAR

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TITLE

“COMPARISON OF EPIDURAL DEXMEDETOMIDINE Vs MAGNESIUM SULPHATE USED AS ADJUVANT TO ROPIVACAINE FOR ANALGESIA IN POST THORACOTOMY PATIENTS”

INTRODUCTION

PAIN continues to be a significant problem for many patients after major surgery. In addition to improving patient satisfaction and decreasing pain scores, enhanced perioperative pain control can improve clinical outcomes. Thoracotomies are among the most painful surgical procedures. Thoracic epidural analgesia (TEA) remains a critical tool for Anesthesiologists to use in acute pain management. TEA is particularly effective for reducing pain after thoracic and upper abdominal surgery and likely permits major surgical procedures to be performed on patients with moderate to severe comorbid diseases, who several years ago may have been determined to be too great a risk for surgery. Post-thoracotomy pain management plays a very essential role in the outcome of thoracic surgery for lung resection. Use of high dose opioids for treating intense postoperative pain are associated with many side effects. Regional anaesthesia is a safe, inexpensive technique, with the advantage of prolonged postoperative pain relief. Effective treatment of postoperative pain blunts autonomic, somatic, and endocrine responses. It has become common practice to use a polypharmacological approach for the treatment of postoperative pain, because no drug has yet been identified that specifically inhibits nociception without associated side-effects. Research continues concerning different techniques and drugs that could prolong the duration of regional anaesthesia and postoperative pain relief. There are multiple

literature and studies has shown that dexmedetomidine is agonist of alpha-2 adrenergic receptors and indicated for sedation in ICU setting, postoperative pain either by I.V. or regional anesthesia.

The exact mechanism of magnesium on analgesia is not clear, and the study results are still controversial. Noxious stimulation causes release of excitatory amino acids such as glutamate and aspartate mediated by NMDA and non-NMDA receptors. Magnesium is a natural calcium antagonist, has been reported as an adjuvant to analgesics in the perioperative period. There are studies concerning different routes of magnesium administration such as intravenous or intrathecally, that improve anaesthetic and analgesic quality . Very minimal clinical studies have examined the effect of epidurally administered magnesium and dexmedetomidine.

Hence, this study was conducted as a prospective, randomized, controlled clinical trial with a hypothesis that the epidural injection of dexmedetomidine and magnesium to ropivacaine increases the duration of postoperative analgesia/ first epidural top up.

AIMS AND OBJECTIVES OF THE STUDY

AIM

The aim of the study was to compare the efficacy of Dexmedetomidine with Ropivacaine & Magnesium Sulphate with Ropivacaine as thoracic epidural analgesia as a single shot injection for postoperative pain relief in patients undergoing Thoracotomy under general anaesthesia.

PRIMARY OUTCOME MEASURES

- Post-operative Visual Analogue Scale for pain score.
- Duration of analgesia.

SECONDARY OUTCOME MEASURES

- Sensory block level.
- Post operative Hemodynamics .
- Complications if any.

ANATOMY OF EPIDURAL SPACE

DEFINITION

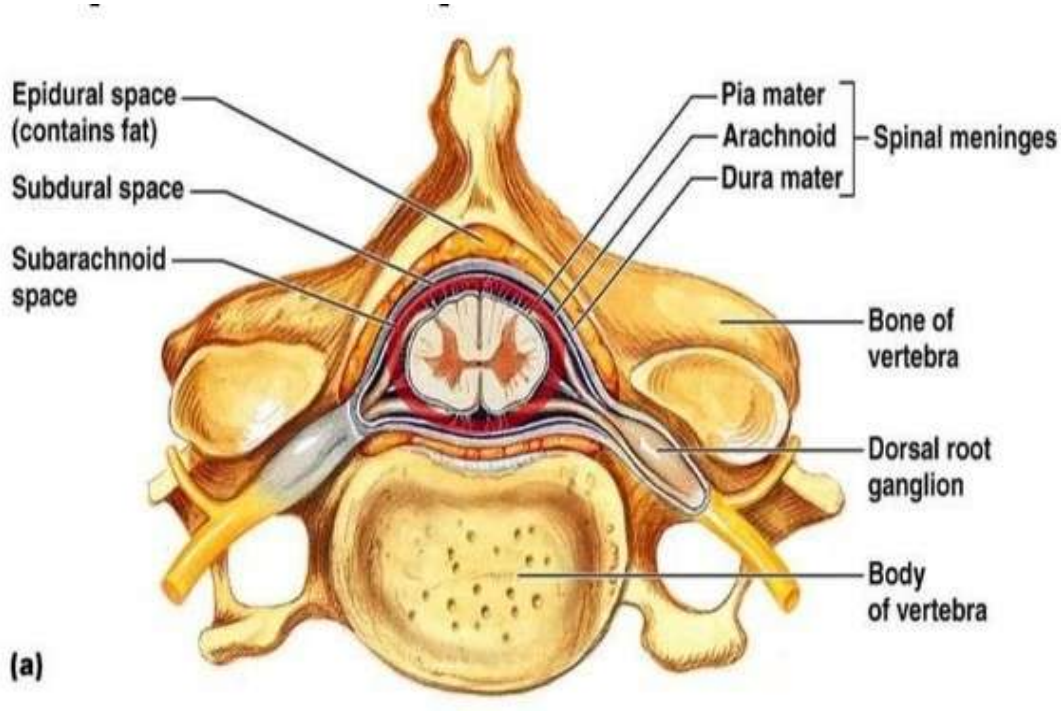
Epdidural Space is a potential space within the bony cavity of the spinal canal outside the dural sac. It extends from the foramen magnum of the skull to the sacral hiatus, communicating laterally with paravertebral space through the intervertebral formina. It was first described in 1901 by Corning J L.

The vertebral column in humans is made up of twenty four individual vertebrae comprising of seven cervical, twelve thoracic and five lumbar vertebrae. There are five sacral vertebrae which are fused together, and the 3-5 coccygeal bones though fused, remain rudimentary. These vertebrae house the subarachnoid and the epidural spaces.

BOUNDARIES

- Superiorly :- Lies the foramen magnum. Here the periosteal and spinal layers of duramater fuse together.
- Inferiorly :- It is bounded by the Sacrococygeal ligament.
- Anteriorly :- Lies the posterior longitudinal ligament covering the posterior aspect of the vertebral bodies and the intervertebral disc.
- Posteriorly :- Ligamentum flavum, capsule of facet joints and the periosteum of the laminae.

- Laterally :- The pedicles of the spinal column and the intervertebral foramina containing their neural elements.



CONTENTS OF THE EPIDURAL SPACE

The epidural space contains :

- nerve roots that traverse it from foramina to peripheral location,
- fat,
- areolar tissue,
- lymphatics and
- blood vessels,

which include the well organized Batson venous plexus. The epidural contents are contained in a series of circumferentially discontinuous compartments separated by zones where the dura contacts the wall of the vertebral canal.

Epidural Veins

The epidural venous plexus is a valveless system, well known as Batson venous plexus. The veins form a network that run in four main trunks along the space. They communicate with venous rings at each vertebral level, with the basivertebral veins on the posterior aspect of each vertebral body and with the ascending and deep cervical, intercostals, iliolumbar and lateral sacral veins. They connect the pelvic veins below with the intracranial veins above, so that air or other local anaesthetic solution injected into one of them may ascend straight to the brain.

Chronically increased intra-abdominal pressure or obstruction of the inferior vena cava (as in late trimester of pregnancy or in the presence of large intra abdominal tumour) can distend the epidural venous plexus, with important implications for epidural anaesthesia.

Arterial Supply

Arteries enter the epidural space at each intervertebral foramen and supply adjacent vertebra, ligaments and spinal cord. These arteries are from the vertebral, deep cervical, ascending cervical, intercostal and lumbar and

iliolumbar arteries. They anastamose with their neighbors above and below, cross the midline and lie chiefly in the lateral parts of the epidural space.

Types of epidural space

The epidural space can be categorized into cervical, thoracic, lumbar and sacral epidural spaces. These spaces can be defined according to their margins.

At the cervical epidural space, there is a fusion of the spinal and periosteal layers of dura mater at the foramen magnum to lower margin of the 7th cervical vertebra. While the thoracic epidural space is formed by the lower margin of C7 to the upper margin of L1, the lumbar epidural space is formed by the lower margin of L1 vertebra to the upper margin of S1 vertebra. The sacral epidural space is formed by the upper margin of S1 to sacrococcygeal membrane.

CLINICAL IMPORTANCE OF THE EPIDURAL SPACE

The epidural space has been subjected to many clinical manipulations for purposes of anesthesia and analgesia. Injection into this space can be by a single shot, intermittent, continuous or under the control of the patient (Patient controlled epidural analgesia (PCEA). Intermittent or continuous injections into the space are carried out through an epidural catheter. The epidural space is catheterized in a wide range of clinical reasons.

Epidural space steroid injection

Epidural injection of corticosteroids is one of the most commonly used interventions in managing radicular pain caused by nerve irritation. Steroids placed in the epidural space have a very potent anti-inflammatory action that can decrease pain and allow patients to improve function. Although steroids do not change the underlying condition, they can break the cycle of pain and inflammation and, allow the body to compensate for the condition.

Postoperative pain management

The administration of local anesthetics with or without opioids into the epidural space provides and maintains pain relief during labor, abdominal surgery, thoracic surgery, pelvis or lower limb surgeries. It is also used for pain management in conditions associated with chronic pain (including back pain, and palliation for intractable pain of neoplastic origin). It has also been found useful in the extension of regional anesthesia/ analgesia during prolonged intraoperative period.

Site of action

When a solution of a local anaesthetic is injected into the epidural space, it may exert its effects :

- On the nerve roots in the epidural space.

- On the nerves in the paravertebral spaces after they have shed their dural sheaths.

- On the nerve roots in the subarachnoid space after inward diffusion of drug across the dura mater.

TECHNIQUE OF THORACIC EPIDURAL

Thoracic epidural analgesia remains a key component of anesthesia - based acute pain services and is used to treat acute pain after: thoracic surgery, abdominal surgery, and rib fractures etc. Beneficial effects of TEA require that catheter placement and the infusion be targeted at the thoracic segments innervating injured skin, muscle, and bone from which the nociceptive input originates. Most percutaneous approaches to the thoracic epidural space use needle puncture guided by surface anatomic landmarks.

The prominent C7 spinous process, the scapular spine (T3), and the inferior border of the scapula (T7) are useful landmarks used to approximate the puncture site to the intended segment. Use of these landmarks may vary among patients. Classical landmarks are root of spine of scapula at T3 and the inferior angle of the scapula at T7.[2]

Before proceeding to place a thoracic epidural fistly an intravenous access preferably with 18G venflon is obtained, monitors are placed, oxygen is administered, and sedative and analgesic drugs can be used.

Because of the extreme caudal angulation of the thoracic spinous processes, a conventional midline approach to the thoracic epidural space can be difficult. A paramedian approach is required to place the needle consistently at most other thoracic epidural segments above T11. It is preferred that patients be placed in a sitting position with neck and upper back flexion before surgery.

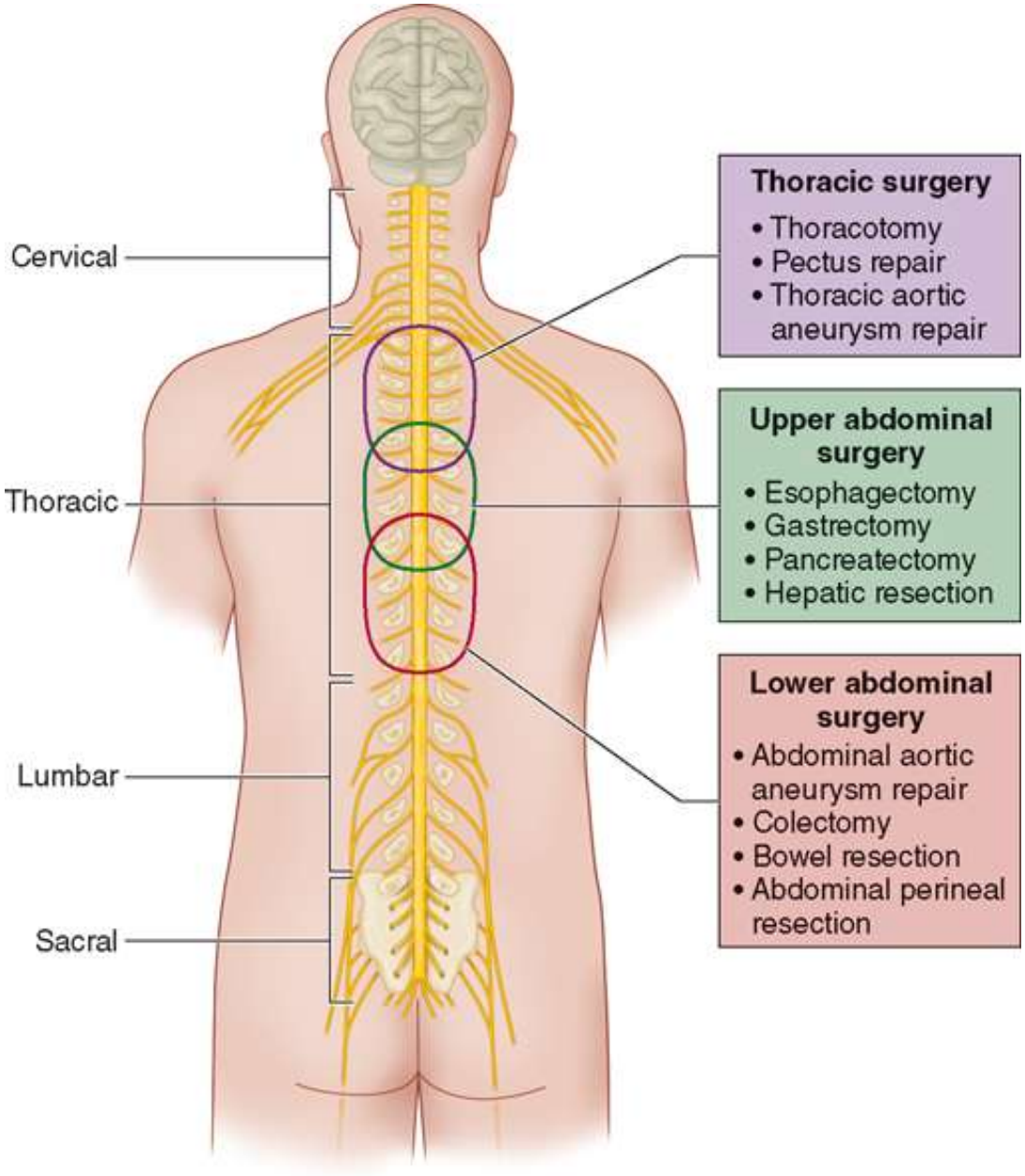


Fig: Regions of the spine that can be used to insert thoracic epidural catheters in a variety of surgeries are shown.

Two approaches exist to the thoracic epidural space -- midline or paramedian. The midline approach is no more difficult in the low-thoracic region than lumbar epidurals because of the similar angulation of the spinous processes.

However, in the mid- and high-thoracic regions, extreme upward angulation of the Tuohy needle directed through a small space makes insertion more difficult in the midline. My preference is to use the paramedian approach, as the bony lamina of the vertebra below acts as a depth finder and there is a definite `rubbery' feel as the Tuohy needle passes from bony lamina to ligamentum flavum. The inferior tip of the spinous process corresponding to the vertebra above should be palpated and, 1 cm lateral to this point, local anaesthetic injected both to the skin and lamina of vertebral body below. The approach of the needle is about 15 degrees to the midline and 60 - 65 degrees from the coronal plane. The thoracic epidural space is identified by two methods - loss of resistance to saline/air or hanging drop. Use of saline is associated with a reduced dural puncture rate and avoids the rare complications of venous air embolism and pneumocephalus. A popular misconception is that the pressure of the epidural space is negative. In fact, it is slightly positive, but large negative pressures are induced by tenting of the epidural space from the Tuohy needle and account for the rapid inward entry of saline using the hanging drop method.

STEPS[6]

(*A*). Place the patient in the sitting position with neck and upper back flexed. Preparation and draping of the targeted thoracic segments using sterile technique.

Infiltrate the skin and subcutaneous tissues with local anesthetic approximately 1 cm lateral to the inferior aspect of the targeted spinous process with a 1.5-inch 25- Gauge needle.

(*B*). With the infiltration needle, contact the ipsilateral lamina or transverse process and anesthetize the periosteum if possible. Perform local infiltration of subcutaneous tissues in both medial and cephalad directions to achieve adequate anesthesia of tissues at the intended path of the Hustead (or Tuohy) needle and epidural catheter.

(*C*). Introduce the epidural needle with the bevel directed cephalad perpendicular to the anesthetized skin and advance until the ipsilateral lamina or transverse process is contacted.

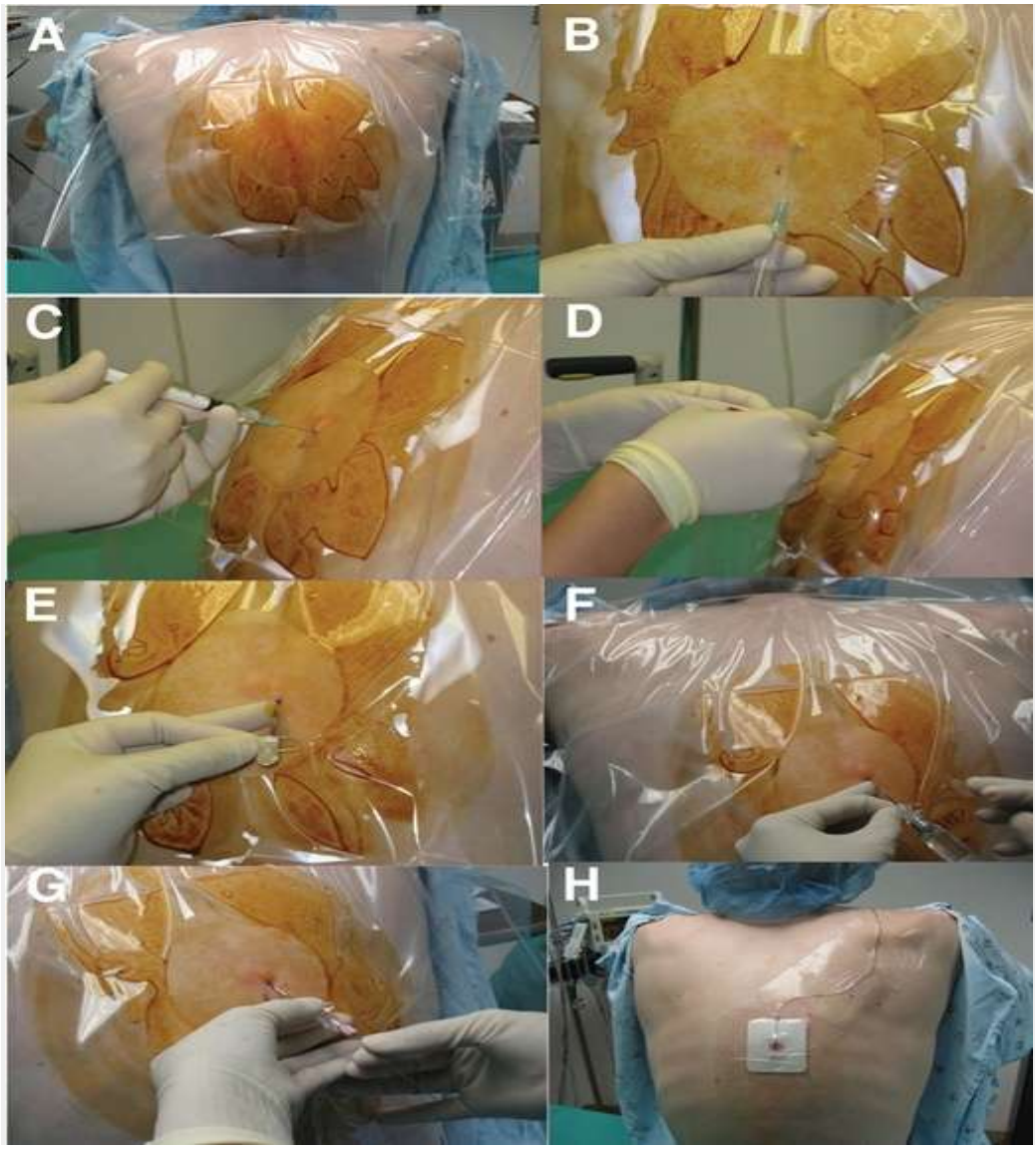
(*D*). If lamina is not contacted, care may be taken to avoid advancing the needle laterally, which will place the needle in the paravertebral space. The needle depth to the lamina is then noted, and the needle is withdrawn back to skin and advanced again slightly medially. This step is repeated until the needle contacts bone at a slightly more superficial (approximately 2–5 mm) depth than the original depth at the lateral lamina. This suggests the epidural needle tip is midline at the junction of the lamina and spinous process. The needle is withdrawn and advanced with the same medial angle but in small increments cephalad to the same depth.

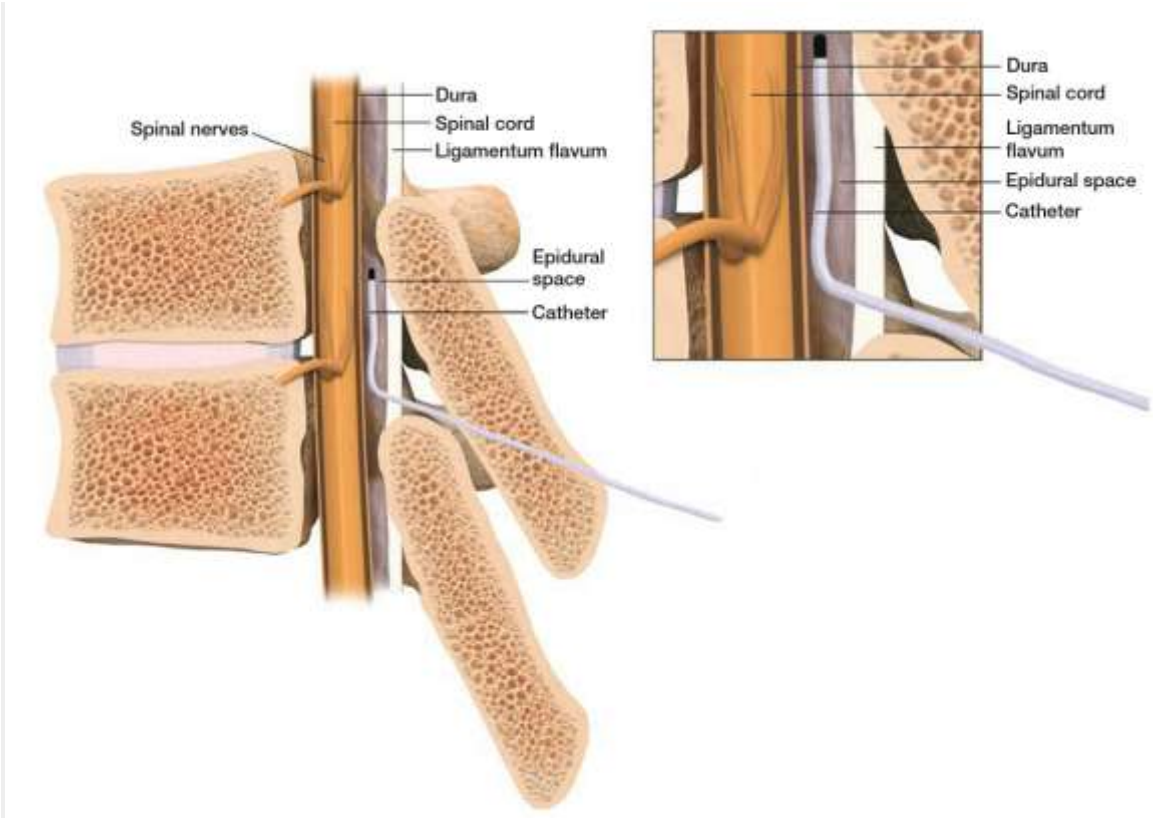
(*E*). Either bone or ligamentum flavum is contacted. If bone is contacted, the needle is redirected cephalad and advanced. If bone is no longer contacted and

the depth exceeds the depth previously noted, the epidural needle stilette is removed. The luer lock loss-of-resistance syringe is attached to the needle for loss of resistance.

(*F*). Once loss of resistance is attained, stabilize the epidural needle and threading of the catheter is done.

(*G*). Next securing of the catheter using a sterile locking device and adherent dressings is done. For thoracotomies or thoracoscopies, placing the dressings on the same side as the surgery is avoided.





In some cases, patients may not be able to be placed in a sitting position for thoracic epidural placement. This situation can be encountered in ventilated intensive care unit patients and those in the recovery room immediately after surgery.

The same technique can be used in patients in a lateral decubitus position. Briefly, the patients are placed on the lateral edge of the bed or cart. In the lateral decubitus position, the approach of the needle can be from the floor toward the midline. Subsequent steps identifying midline and cephalad angulation are repeated.

COMPLICATIONS AND ADVERSE EVENTS

Epidural placement in the thoracic spine is thought to be more hazardous than lumbar epidural placement because of the perceived increased risk of neurologic injury to the spinal cord. However, complications associated with TEA are relatively rare. This included unsuccessful catheter placement, dural puncture, postoperative radicular pain, and peripheral nerve lesions. Unintentional dural perforation was observed more often during lower thoracic, than during mid or upper thoracic spine placements. Epidural hematomas or abscesses can occur.

Rare but devastating complications of epidural analgesia include neurologic injury from hemorrhagic and infectious etiologies. The incidence of epidural hematoma appears to be less than 1 in 150,000 patients and usually occurs in the presence of impaired coagulation.[2]

The most traumatic event likely to cause bleeding is epidural catheter placement followed by catheter removal, needle placement, and daily catheter management. Consensus statements for the administration of neuraxial techniques in the presence of anticoagulants have been published by the American Society of Regional Anaesthesia. Careful consideration of the properties of the specific anticoagulant before placement and removal of epidural catheters is important.

The incidence of epidural abscesses appears to be low. An epidural catheter colonization rate as great as 28% has been found, and usually staphylococcus is identified. However, few cases of epidural abscess associated with TEA have

been reported. Factors likely influencing infection may include perioperative antibiotic use and duration of TEA use. The risk of infection appears to increase after the second day of epidural catheterization, and a longer duration of use has an incidence of local infection that approaches that of intravascular devices.

It is recommended that patients be monitored daily for signs and symptoms of infection and that the benefit-to-risk ratio be evaluated closely after catheterization day four. Vigilance for epidural hematoma and epidural abscess followed by early intervention if detected may limit sequelae.

Other complications of epidural analgesia also apply to TEA, including postdural puncture headache, back pain, and catheter migration (intravascular or intrathecal). Adverse effects related to medications used in TEA include nausea, vomiting, pruritus, hypotension, urinary retention, sedation, and respiratory depression. Reports of dysesthesia, paresthesias, weakness, and local anesthetic toxicity are rare. Recent evidence suggests that use of a urinary catheter throughout the duration of TEA increases the incidence of urinary tract infection without causing a decrease in urinary retention. Pleural puncture and pneumothorax, although likely underreported, appear to be rare.

PAIN PATHWAY

Pain is basically a protective mechanism bestowed by nature to warn us about impending injury to our body. It induces one to withdraw from damaging situations or to protect an injured body part while it heals. It is both a sensory and emotional experience, affected by psychological factors such as past experiences, beliefs about pain, fear or anxiety.

NOCICEPTORS[5]

Nociceptors are the specialised sensory receptors responsible for the detection of noxious (unpleasant) stimuli, transforming the stimuli into electrical signals, which are then conducted to the central nervous system.

They are the free nerve endings of primary afferent Aδ and C fibres.Distributed throughout the body (skin, viscera, muscles, joints, meninges) they can be stimulated by mechanical, thermal or chemical stimuli. Inflammatory mediators (egbradykinin, serotonin, prostaglandins, cytokines, and H+) are released from damaged tissue and can stimulate nociceptors directly. [2,5]

They can also act to reduce the activation threshold of nociceptors so that the stimulation required to cause activation is less

Primary afferent fibres[5]

- *Aβ fibres* are highly myelinated and of large diameter, therefore allowing rapid signal conduction. They have a low activation threshold and usually respond to light touch and transmit non noxious stimuli.
- *Aδ fibres* are lightly myelinated and smaller diameter, and henceconduct more slowly than Aβ fibres. They respond to mechanical and thermal stimuli. They carry rapid, sharp pain and are responsible for the initial reflex response to acute pain.
- *C fibres* are unmyelinated and are also the smallest type of primary afferent fibre. Hence they demonstrate the slowest conduction. C fibres are polymodal, responding to chemical, mechanical and thermal stimuli. C fibre activation leads to slow, burning pain.

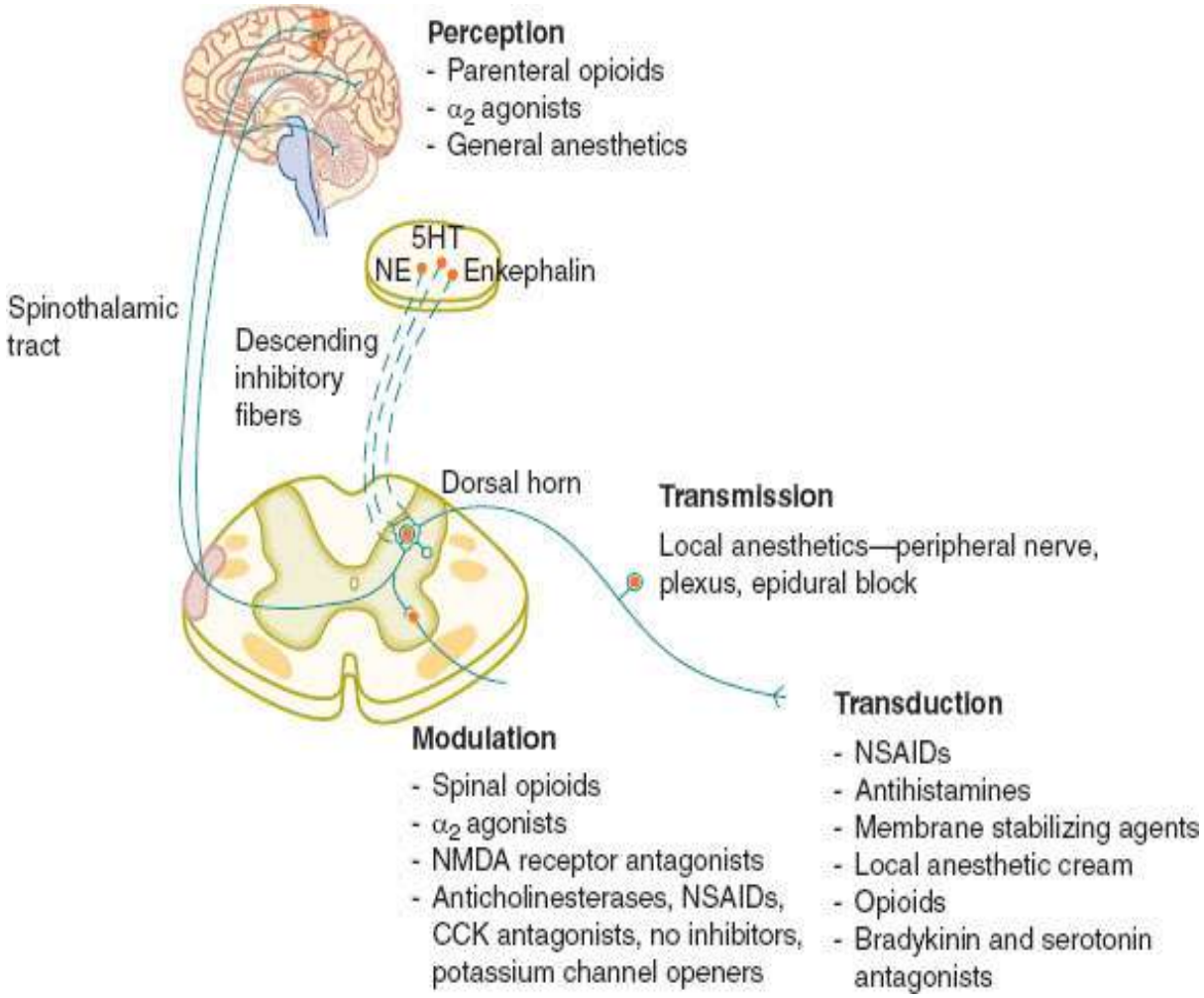
	Aαfibres	**Aβfibres**	**C fibres**
Diameter	Large	Small 2-5 mm	Smallest <2mm
Myelination	Highly	Thinly	Unmyelinated
ConductionVelocity	>40 m/s	5-15 m/s	< 2m/s
Receptoractivation thresholds	Low	High and low	High
Sensation onstimulation	Light touch, non noxious	Rapid, sharp, localised pain	Slow, diffuse, dull pain

PAIN PROCESSING[5]

Functionally comprises of four steps: transduction, transmission, modulation, perception. These processes are clinically relevant as each provides targets for pain treatment and prevention.

Transduction is the generation of an action potential from a noxious chemical, mechanical or thermal stimulus. Nociceptors are located in the skin, mucosa, muscle, fascia, joint capsules, dura, viscera, and adventitia of blood vessels. Activation causes opening of voltage sensitive sodium and calcium channels, starting an action potential.

Transmission is the propagation of the signal through the afferent pathway from the nociceptor to the sensory cortex. It occurs via a three neuron afferent pathway, beginning in the periphery. First order cell bodies are located in the dorsal root ganglia with fibers projecting to peripheral tissue where the receptors are located. Fibers enter the spinal cord and travel up or down through the posterolateral tract before entering the dorsal horn to synapse on second order neurons. Axons transmitting somatic nociception decussate and ascend via the contralateral spinothalamic tract, while axons transmitting visceral nociception ascend via the ipsilateral dorsal column medial lemniscus. Both synapse on the third order neurons in the thalamus, the axons of which terminate in the sensory cortex.



Modulation is the positive or negative modification of the pain signal along the afferent pathway. Activity between first and second order neurons is decreased by feedback from interneurons and descending inhibition from the periaqueductal gray matter, rostral ventromedial medulla, and the dorsolateral pontinetegmentum. Axonal sprouting causes crosstalk between different fibers, causing nonnoxious stimuli to become painful. Also, neuromas and axonal sprouting may be associated with upregulation of potassium channels, which causes destabilized cell membranes to become more prone to form an action potential.

Perception is the integration of the pain signal into consciousness. The primary and secondary somatosensory cortices are involved with sensory discrimination of pain. The anterior cingulated gyrus is related to emotional significance of pain, while the lentiform nucleus and cerebellum are involved in self protective reflexes related to pain.

DRUGS ACTING AT VARIOUS SITES OF PAIN PATHWAY:

- PERIPHERAL LEVEL - Local anaesthetics, NSAIDS, Opioids
- SPINAL CORD- Opioids, Alpha 2 agonists, Local anaesthetics
- CORTICAL LEVEL - Opioids

ASSESSMENT OF PAIN

Pain is a highly subjective expression and affects many aspects of life. Hence measuring it is an important task for a physician. Many validated scales are available. It cannot be stressed more that patient's self report should be accepted and acted upon. In rare cases, there may be an exaggeration by the patient, so the physician must exert vigilance. Because pain is dynamic, it should be reassessed regularly and adjustments to therapy made as appropriate.

Unidimensional self report scales are very simple, useful, valid method to assess pain.

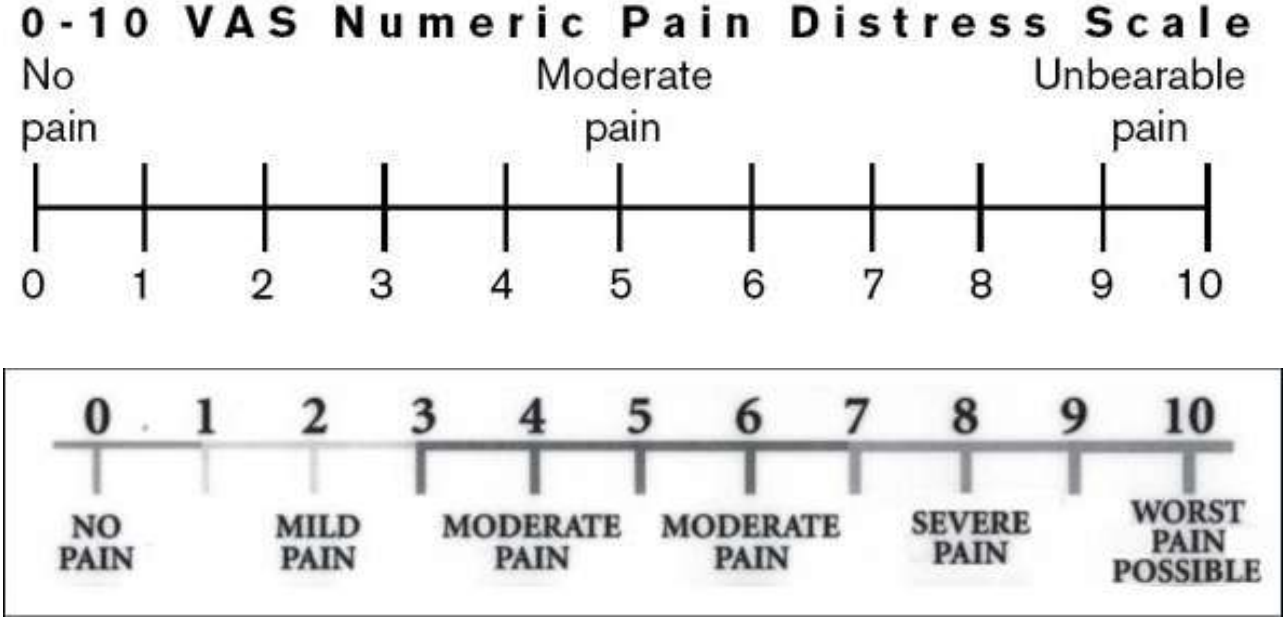
A visual analogue scale (VAS) consists of a 10 cm line, which has no pain at the beginning and worst pain at the end.

A Numeric Rating Scale (NRS) has 0-10 numbers marked on a 10 cm line. Zero corresponds to "no pain" and 10 corresponds to "Worst possible pain". In clinical practice, pain intensity can be interpreted as Mild (0-4), Moderate (4-7) and severe (7-10). Patients are asked to rate their pain along the line that best represents the intensity of pain.

The Wang Baker Faces Scale is used for patients who are three upwards. It shows faces depicting emotions from smiling to crying.[2]

The FLACC tool (Face, Legs, Activity, Cry and Consolability) is used for children upto 7 years of age who cannot verbalize their pain intensity. It is divided into five parts assessing the face, legs, activity, cry and consolability, with each part given a score ranging from 0 to2. The final score can be grouped as Score 0 for relaxed and comfortable; Score 1-3 for mild discomfort; Score 4-6 for moderate pain; Score 7-10 for severe discomfort.

The scales are very helpful in deciding the plan of treatment as well as assessing the response to the treatment.



ADDITIONAL PAIN ASSESSMENT TOOLS

These are multidimensional pain assessment tools. The Brief Pain Inventory (BPI) assesses pain severity and the degree of interference with functioning using 0-10 NRS.

The McGill Pain Questionnaire (MPQ) and the short form MPQ (SF-MPQ) evaluate sensory, affective- emotional, evaluative and temporal aspects of the patient's pain condition.

The pain DETECT questionnaire (PDQ) helps to identify neuropathic components in individuals suffering from chronic pain. Initial and periodic assessment of pain is essential to achieve relief and gauge the outcomes of therapy.

For our study we will use the Visual Analogue Scale for assessment of post operative pain.

PHAMACOLOGY OF ROPIVACAINE

ROPIVACAINE [4,1]

It is a new, long-acting local amide anesthetic with similarities in structure, pharmacology and pharmacokinetics to that of Bupivacaine. Ropivacaine is a pure (S-isomer) enantiomer.

Formula: $C_{17}H_{26}N_2O$

STRUCTURAL FORMULA

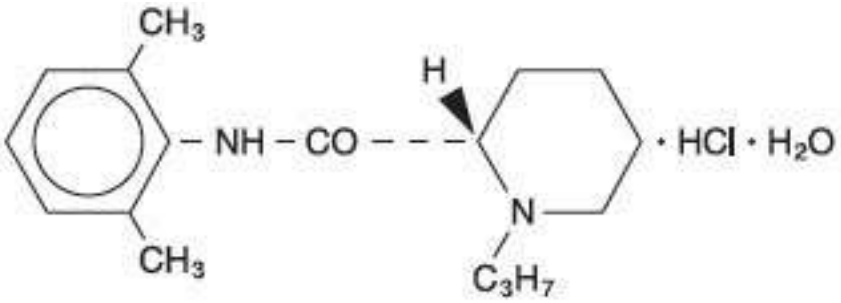


Fig: Structure of Ropivacaine

MECHANISM OF ACTION

Ropivacaine reversibly interferes with the entry of sodium into the nerve cell membranes, leading to decreased membrane permeability to sodium and raises the threshold for electrical excitability. It blocks the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. The order of blockade affecting the nerve fibres is: autonomic, sensory and motor; and the effect disappears in the reverse order. Clinically, the order of loss of sensation

is: pain, temperature, touch, proprioception and skeletal muscle tone.[1] Repeated activation by a train of depolarizing pulses increases the inhibitory effects of ropivacaine and produces a hyperpolarizing shift.

PHYSIOCHEMICAL PROPERTIES

Chemically it is described as S-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate. It is available as a white crystalline powder, with a molecular weight of 328.89. The pKa of ropivacaine is approximately the same as bupivacaine (8.1). But, it has an intermediate degree of lipid solubility compared to bupivacaine and mepivacaine thus making it less liable for central nervous system toxicity and cardiotoxicity. The specific gravity of ropivacaine solution ranges from 1.002 to 1.005 at 25°C.

PHARMACOKINETICS

ABSORPTION

The plasma concentration of ropivacaine is dependent on the route of administration, the vascularity of the administration site, the total dose and concentration of drug administered, and the haemodynamic and circulatory condition of the patient. The absorption of ropivacaine from the epidural space is complete and biphasic. The mean half-life of the initial phase is approximately 14 minutes, followed by a slower phase with a mean absorption half life $t_{1/2}$ of approximately 4.2 hours. The slow absorption is the rate limiting

factor in the elimination of ropivacaine which explains why the terminal half-life is longer after epidural than after intravenous administration. When ropivacaine was administered intravenously in subjects, its pharmacokinetics were linear and dose proportional up to 80 mg.[4]

DISTRIBUTION

After an intravascular infusion, ropivacaine achieves a steady state volume of distribution Vd (52 - 66litres).It is bound to plasma proteins to an extent of 94%, mostly to α1-acid glycoprotein. The total plasma concentration increase during continuous epidural infusion of ropivacaine, which is caused by an increase in the degree of protein binding and subsequent decrease in clearance of ropivacaine, and also most likely because of a postoperative increase of α1-acid glycoprotein. Ropivacaine rapidly crosses the placenta during epidural administration. However, the total plasma concentration of ropivacaine when measured was found to be lower in the foetal circulation than in the maternal circulation. This is because of binding of ropivacaine to α1-acid glycoprotein, which is more concentrated in maternal than in foetal plasma.

METABOLISM

Ropivacaine is metabolized in the liver by aromatic hydroxylation via cytochrome CYP1A2 to 3-hydroxy-ropivacaine which is the major metabolite. 4-hydroxy-ropivacaine, and 4-hydroxy-dealkylated-ropivacaine are

other products. Also it is metabolised by N-dealkylation to 2',6'-pipecoloxylidide by CYP3A4.

Co-administration of a CYP1A2 inhibitor (e.g. fluvoxamine, enoxacin) may reduce plasma clearance of the drug by up to 77% in vitro. The isoenzyme CYP3A4 is also involved in the metabolism of ropivacaine, as administration of a CYP3A4 inhibitor (e.g. fluconazole) reduces the plasma clearance of the drug by 15% in vitro, although this is unlikely to cause a clinically significant effect. Ropivacaine has an intermediate hepatic extraction ratio of approximately 0.4. There is no evidence of in vivo racemization of ropivacaine.[4]

ELIMINATION

The clearance is 0.44-0.82 l/min and the terminal elimination half-life is 59-173 minutes. The kidney is the main excretory organ for most of the metabolites. In total, 86% of the ropivacaine dose is excreted in the urine after intravenous administration of which only 1% relates to unchanged drug. It has a mean ± SD terminal half-life of 1.8 ± 0.7 h and 4.2 ± 1.0 h after intravenous and epidural administration, respectively. It is longer for epidural due to biphasic absorption as described above.[4]

DIFFERENTIAL CONDUCTION BLOCK

With low concentrations of local anaesthetic, selective blockade of pre - ganglionic sympathetic nervous system B fibres occur. Slightly higher concentrations interrupt conduction in small C fibres and small and medium sized Aδ fibres with loss of pain and temperature sensation.

PHARMACODYNAMICS[1,2]

Cardiovascular system

Ropivacaine is less cardiotoxic than bupivacaine. Ropivacaine has a biphasic vascular effect, causing vasoconstriction at low, but not at high, concentrations. In toxic concentrations, the drug decreases the peripheral vascular resistance and myocardial contractility, producing hypotension and possibly cardiovascular collapse.

Central nervous system

The principal effect of ropivacaine is reversible neural blockade. This leads to a characteristically biphasic effect in the CNs. Initially, excitation happen like, light-headedness, dizziness, visual and auditory disturbances, and seizure activity due to inhibition of inhibitory interneurone pathways in the cortex. With increasing doses, depression of both facilitatory and inhibitory pathways occurs, leading to CNS depression like drowsiness, disorientation, and coma. Local anaesthetic agents block neuromuscular transmission when administered

intraneurally. It is thought that a complex of neurotransmitter, receptor, and local anaesthetic is formed, which has negligible conductance.

Genitourinary

Ropivacaine does not compromise uteroplacental circulation.

DOSAGE AND ADMINISTRATION

Ropivacaine may be administered topically, by infiltration, or epidurally; the drug is not currently intended for use in spinal anaesthesia. The maximum recommended dose of ropivacaine is 3 mg/kg.m. Rapid injection of a large volume of ropivacaine solution should be avoided, and fractional incremental doses should always be used. [4]

The dose of ropivacaine to be administered depends on- the anesthetic procedure, the duration of block desired, the local vascularity of the tissues, the area to be anesthetized, the number of neuronal segments to be blocked, the depth of anaesthesia, degree of muscle relaxation required, individual tolerance, and the physical condition of the patient.

Sensory blockade is similar in time course to that produced by bupivacaine. But motor blockade is slower in onset and shorter in duration than that after an equivalent dose of bupivacaine. Alkalinization of 0.75% ropivacaine significantly increases the duration of action of epidural blockade.

To reduce the risk of potentially serious adverse reactions, optimization of the patient's condition before performing major blocks should be done. And dosage should be adjusted accordingly.

SIDE EFFECTS:

Allergic reactions to the amide-type local anaesthetic agents are extremely rare. The side effects are predominantly correlated with excessive plasma concentrations of the drug, as described above.

Hypotension, nausea and vomiting, bradycardia, fever, pain, anemia, paraesthesia, headache, pruritus and back pain constitute more than 5 % of incidences. Urinary retention and urinary tract infection, dizziness, hypokalemia, dyspnea, rigors, hypertension, tachycardia, anxiety, oliguria, hypoesthesia, chest pain and cramps constitute 1 – 5% of incidence.

PRECAUTIONS:

Ropivacaine should be used in patients receiving CYP1A2 (involved in metabolizing Ropivacaine to 3-hydroxy Ropivacaine, a major metabolite) inhibitors like fluvoxamine and enoxacin, since this may lead to an increased plasma concentration of Ropivacaine.

PHAMACOLOGY OF DEXMEDETOMIDINE

DEXMEDETOMIDINE [4,1]

It is animadazole derivative compound. It is an anxiety reducing, sedative and pain medication. Dexmedetomidine has the added advantage to provide sedation without causing respiratory depression unlike other commonly used sedatives such as propofol, fentanyl, and midazolam. It is used to provide cooperative or semi-arousable sedation. It reduces post operative pain and opiod analgesic requirement.

STRUCTURAL FORMULA

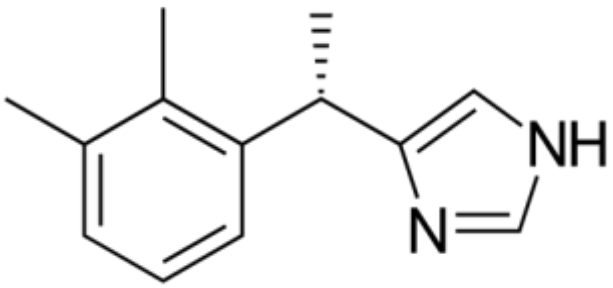


Fig: Structure of Dexmedetomidine

MECHANISM OF ACTION

It is a specific alpha 2 adrenoceptor agonist which acts via post synaptic alpha 2 receptors to increase conductance through potassium ion channels.

PHYSIOCHEMICAL PROPERTIES

Clear colourless, isotonic solution. The solution is preservative free and contains no additives.

PHARMACOKINETICS

DISTRIBUTION

Dexmeditomidine is 94% protein bound in the plasma; the volume of distribution is 1.33 L/kg. The distribution half life is 6 minutes.

METABOLISM

It undergoes extensive hepatic metabolism to methyl and glucuronide conjugates and by cytochrome P450. As such, this drug should be used with caution in people with liver disease.[4]

ELIMINATION

95% metabolites are excreted in the urine. The elimination half life is 2 hours and the clearance is 39L/hour.

PHARMACODYNAMICS [1,2]

Dexmedetomidine is a highly selective α2-adrenergic agonist.. It induces sedation by decreasing activity of noradrenergic neurons in the locus ceruleus in the brain stem, thereby increasing the activity of inhibitory gammaaminobutyric acid neurons in the ventrolateral preopticnucleus. In contrast, other sedatives like propofol and benzodiazepines directly increase activity of gammaaminobutyric acid neurons. Sedation by dexemeditomidine mirrors natural sleep.

As such, dexmedetomidine provides less amnesia than benzodiazepines. Dexmedetomidine also has analgesic effects at the spinal cord level and other supraspinal sites. Thus, unlike other hypnotic agents like propofol, dexmedetomidine can be used as an adjunct medication to help decrease the opioid requirements of people in pain while still providing similar analgesia.

DOSAGE AND ADMINISTRATION

It is administered by intravenous infusion, commencing at 1 micrograms/kg for 10 minutes, then at 0.2 – 0.7 micrograms/kg/hour. The duration of use should not exceed 24 hours. It has also been administered transdermally and intramuscularly. Intravenous infusion of dexmedetomidine is commonly initiated with a loading dose followed by a maintenance infusion. There may be great individual variability in the hemodynamic effects (especially on heart rate

and blood pressure), as well as the sedative effects of this drug. For this reason, the dose must be carefully adjusted to achieve the desired clinical effect.

SIDE EFFECTS

Hypotension, bradycardia, nausea, and a dry mouth are the most commonly reported side effects of the drug.

PHAMACOLOGY OF MAGNESIUM SULPHATE

MAGNESIUM [4,1]

Magnesium is the fourth most plentiful cation in the body. It is also the second most common intracellular cation only after potassium. It serves as a co factor in more than 300 enzymatic reactions involving nucleic acid synthesis and energy metabolism. It is also involved in several processes including: muscle contraction, neuronal activity, cardiac excitability, control of vasomotor tone, hormone receptor binding, gating of calcium channels, transmembrane ion flux and regulation of adenylate cyclise, and neurotransmitter release. In many of its actions it has been likened to a physiological calcium antagonist.

In humans less than 1% of total body magnesium is found in serum and red blood cells. It is distributed principally between bone (53%) and intracellular compartments of muscles (27%) and soft tissues (19%). Serum magnesium comprises only about 0.3% of total body magnesium, where it is present in three states – ionized (62%), protein bound (33%), mainly to albumin, and complexed to anions such as citrate and phosphate (5%). Normal plasma magnesium levels range from 1.5 to 2.5 mEq/L.

MAGNESIUM SULFATE INJECTION

It is a non pyrogenic and sterile concentrated solution of magnesium sulfateheptahydrate which occurs as colorless crystals or white powder freely

soluble in water. Route of administration can be intravenous IV or intramuscular IM. It must be diluted before IV use.

Each mL consists of magnesium sulphate heptahydrate 500 mg. Sulfuric acidor sodium hydroxide may have been added for pH adjustment. pH of a 5% solution is around 5.5 and 7.0. The solution contains no antimicrobial and bacteriostatic agent. It should be discarded after single use. [4]

STRUCTURAL FORMULA

It is chemically designated as MgSO4•7H2O 7H2O with a molecular weight of 246.47

MECHANISM OF ACTION

It has antinociceptive effects in animal and human models of pain. These effects are primarily based on the regulation of calcium influx into the cell, that is natural physiological calcium antagonism and antagonism of *N*-methyl-D-aspartate (NMDA) receptor.

CLINICAL PHARMACOLOGY

Magnesium a divalent cation, is assumed to possess antinociceptive effects. Early symptoms of hypomagnesemia (less than 1.5 mEq/L) are neurological,

e.g., muscle irritability, tremors and clonic twitching. Hypocalcemia and hypokalemia are often associated with low serum levels of magnesium. Large stores of magnesium are present intracellularly and in the bones of adults, but cannot be mobilized sufficiently to maintain normal plasma levels. IV or IM magnesium therapy can repair the plasma deficit and cause the deficiency symptoms and signs to disappear. The effects of hypermagnesaemia are essentially those of a calcium channel blocker combined with a membrane stabiliser.

RDA: [2]

Recommended dietary allowances are as follows

- Females: 310 mg elemental magnesium daily
- Pregnant females: 350 mg elemental magnesium daily.
- Breast-feeding females: 310 mg elemental magnesium daily
- Males: 400 mg elemental magnesium daily

PHARMACOKINETICS

When MgSo4 is administered intravenous, the onset of anticonvulsant action is immediate and duration of action lasts about 30 minutes. While in intramuscular administration, the onset of action occurs in about an hour and persists for three to four hours.

Effective anticonvulsant serum levels range from 2.5 to 7.5mEq/L. Mg is 30% bound in plasma and more than 50% of an exogenous magnesium load is excreted in the urine, even in presence of significant magnesium deficiency.

USES: Magnesium has been used in the management of:

- Hypomagnesemia associated with malabsorption syndromes, diuretics and critical illness.
- Seizures in severe pre-eclampsia and eclampsia.
- Premature labour as a tocolytic.
- Acute myocardial infarction.
- Pediatric acute nephritis.
- Torsade de pointes.
- Various cardiac arrhythmias (VT/VF) caused by hypomagnesemia.
- Barium poisoning.
- Asthma exacerbation (life-threatening), unresponsive to 1 hour intensive conventional treatment.
- Cerebral oedema.
- Laxative for the relief of occasional constipation.

- Magnesium and tracheal intubation: Magnesium sulphate has been shown to obtund the hypertensive response to intubation in patients with pre eclampsia.
- As a component of cardioplegic solutions.

PRECAUTIONS [1]

- If flushing and sweating occurs, it should be administered with caution. Barbiturates, narcotics or other hypnotics (or systemic anesthetics) have additive CNS depressant effects with magnesium. There dosage should be adjusted with caution.
- In Chronic kidney disease patients, magnesium should be used with caution as it is solely excreted through kidneys.
- Urine output should always be maintained at a 100 mL or more, during the four hours preceding each dose.
- Strict monitoring of serum magnesium levels and the patient's clinical status is most important to prevent overdosage in toxemia.

The presence of the patellar kneejerk reflex and absence of respiratory depression are good clinical indications of a safe dosage regimen. When repeated doses of the drug are necessary, knee jerk reflexes should be tested before giving any dose and if they are absent, no additional drug should be given until reflexes return. The toxic effects can be reversed by the

administration of calcium. Intramuscular injection of magnesium sulphate is painful.

SIDE EFFECTS

- Flushing (I.V.; dose related),
- Hypotension (I.V.; rate related),
- Vasodilation (I.V.; rate related)
- Hypermagnesemia: Hypermagnesemia is usually induced due to iatrogenic reasons. Symptoms associated with increased magnesium depend on its blood levels. QRS complex widening, prolonged PR and QT are observed at 2-4 mmol/L levels. Hypoventilation, decreased tendon reflex and muscular weakness are seen at levels of 8-12 mmol/L. Hypotension, bradycardia and vasodilatation are also observed at level of 10-20 mmol/L and coma and apnea at 20-30 mmol/L levels.

REVIEW OF LITERATURE

1. **Tramer MR[1], Schneider J, Marti RA, Rifat K.**(1996) [9]

In a randomized, double-blind study, 42 patients undergoing elective abdominal hysterectomy with general anaesthesia received 20% magnesium sulphate or saline (control) 15 ml intravenously before start of surgery and 2.5 ml/h for the next 20 h. They found magnesium-treated patients consumed less morphine during the first 48h ($P<0.03$), which was most pronounced during the first 6 h ($P<0.004$), and experienced less discomfort during the first and second postoperative days ($P<0.05$-0.005). The magnesium-treated group revealed no change in postoperative sleeping patterns when compared to preoperative patterns. Control patients showed an increase in insomnia during the first and second postoperative nights ($P<0.002$ and $P<0.005$, respectively) compared to preoperative values.

They concluded that the perioperative application of magnesium sulphate is associated with smaller analgesic requirement, less discomfort, and a better quality of sleep in the postoperative period but not with adverse effects. Magnesium could be of interest as an adjuvant to postoperative analgesia.

2. **Buvanendran A1, McCarthy RJ, Kroin JS, Leong W, Perry P, Tuman KJ. 2002** [11]

Intrathecal magnesium prolongs Fentanyl analgesia: a prospective, randomized, controlled trial.

This was the first prospective human study evaluating whether intrathecal magnesium could prolong spinal opioid analgesia. Fifty-two patients requesting analgesia for labor were randomized to receive either intrathecal fentanyl 25 micro g plus saline or fentanyl 25 micro g plus magnesium sulphate 50 mg as part of a combined spinal-epidural technique. The duration of analgesia of the intrathecal drug combination was defined by the time of patient request for additional analgesia. There was significant prolongation in the median duration of analgesia (75 min) in the magnesium plus fentanyl group compared with the fentanyl alone group (60 min). There was no associated increase in adverse events in the group that received intrathecal magnesium. Larger doses of intrathecal magnesium were not studied in this group of patients because of the limitations on cephalad spread when hyperbaric solutions are injected in the sitting position. The data indicated that intrathecal magnesium prolongs spinal opioid analgesia in humans and suggest that the availability of an intrathecal N-methyl-D-aspartate antagonist could be of clinical importance for pain management. They implied that Magnesium occurs naturally in the spinal cord and blocks the NMDA glutamate channel. In animal studies, intrathecal magnesium sulfate improves spinal morphine analgesia. For patients receiving

spinal analgesia for labor, the addition of magnesium sulfate to the opioid fentanyl prolonged analgesia with no increase of side effects.

3. **Ozalevli M, Cetin TO, Unlugenc H, Guler T, Isik G. 2005 Nov. [20]**

The effect of adding intrathecal magnesium sulphate to bupivacaine-fentanyl spinal anaesthesia.

The addition of intrathecal (IT) magnesium to spinal fentanyl prolongs the duration of spinal analgesia for vaginal delivery. In this prospective, randomized, double-blind, controlled study, they investigated the effect of adding IT magnesium sulphate to bupivacaine-fentanyl spinal anaesthesia. One hundred and two ASA I or II adult patients undergoing lower extremity surgery were recruited. They were randomly allocated to receive 1.0 ml of preservative-free 0.9% sodium chloride (group S) or 50 mg of magnesium sulphate 5% (1.0 ml) (group M) following 10 mg of bupivacaine 0.5% plus 25 microg of fentanyl intrathecally. They recorded the following: onset and duration of sensory block, the highest level of sensory block, the time to reach the highest dermatomal level of sensory block and to complete motor block recovery and the duration of spinal anaesthesia. They found that Magnesium caused a delay in the onset of both sensory and motor blockade. The highest level of sensory block was significantly lower in group M than in group S at 5, 10 and 15 min ($P < 0.001$). The median time to reach the highest dermatomal level of sensory block was 17 min in group M and 13 min in group S ($P < 0.05$). The mean degree of motor block was also lower in group M at 5, 10 and 15 min ($P < 0.001$). The median

duration of spinal anaesthesia was longer in group M (P < 0.001). conclusion was made that, in patients undergoing lower extremity surgery, the addition of intrathecal magnesium sulphate (50 mg) to spinal anaesthesia induced by Bupivacaine and Fentanyl significantly delayed the onset of both sensory and motor blockade, but also prolonged the period of anaesthesia without additional side-effects.

4. **Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD 2006.** [22]

   Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block.

In a prospective, double-blind study - 60 patients undergoing transurethral resection of prostate or bladder tumor, under spinal anesthesia were randomly allocated to one of three groups. Group B received 12 mg of hyperbaric bupivacaine, group D received 12 mg of bupivacaine supplemented with 3 mg of dexmedetomidine and group C received 12 mg of bupivacaine supplemented with 30 mg of clonidine. The onset times to reach peak sensory and motor levels, and the sensory and motor regression times, were recorded. Hemodynamic changes and the level of sedation were also recorded.

Patients in groups D and C had a significantly shorter onset time of motor block and significantly longer sensory and motor regression times than patients in group B. The mean time of sensory regression to the S1 segment was 303 +/- 75 min in group D, 272 +/- 38 min in group C and 190 +/- 48 min in group B (B

vs. D and B vs. C, P < 0.001). The regression of motor block to Bromage 0 was 250 +/- 76 min in group D, 216 +/- 35 min in group C and 163 +/- 47 min in group B (B vs. D and B vs. C, P < 0.001). The onset and regression times were not significantly different between groups D and C. The mean arterial pressure, heart rate and level of sedation were similar in the three groups intra-operatively and post-operatively. They concluded that Dexmedetomidineor clonidin, when added to intrathecal bupivacaine, produces a similar prolongation in the duration of the motor and sensory block with preserved hemodynamic stability and lack of sedation.

5. **Lysakowski C, Dumont L, Czarnetzki C, Tramèr MR**.2007 :[31]

Performed a comprehensive search (electronic databases, bibliographies, all languages, to 4.2006) for randomized comparisons of magnesium and placebo in the surgical setting. Information on postoperative pain intensity and analgesic requirements was extracted from the trials and compared qualitatively. Dichotomous data on adverse effects were combined using classic methods of meta-analysis. Fourteen randomized trials (778 patients, 404 received magnesium) tested magnesium laevulinate, gluconate or sulfate. With magnesium, postoperative pain intensity was significantly decreased in four (29%) trials, was no different from placebo in seven (50%), and was increased in one (7%); two trials (14%) did not report on pain intensity. With magnesium, postoperative analgesic requirements were significantly reduced in eight (57%)

trials, were no different from placebo in five (36%), and were increased in one (7%). Magnesium-treated patients had less postoperative shivering (relative risk 0.38, 95% confidence interval 0.17-0.88, number-needed-to-treat 14). These trials do not provide convincing evidence that perioperative magnesium may have favorable effects on postoperative pain intensity and analgesic requirements. They concluded that it may be worthwhile to further study the role of magnesium as a supplement to postoperative analgesia, since this relatively harmless molecule is inexpensive, and the biological basis for its potential anti-nociceptive effect is promising.

6. **A. Bilir S. Gulec A. Erkan A. Ozcelik.** [24]

In April 2007 they conducted study on fifty patients undergoing hip surgery were enrolled to receive either fentanyl (Group F) or fentanyl plus magnesium sulphate (Group FM) for 24 h for epidural analgesia. All patients were equipped with a patient-controlled epidural analgesia device and the initial settings of a demand bolus dose of fentanyl 25 μg. In Group FM, patients received 50 mg magnesium sulphate epidurally as an initial bolus dose followed by a continuous infusion of 100 mg day−1. Ventilatory frequency, heart rate, blood pressure, pain assessment using a visual analogue scale (VAS), sedation scores and fentanyl consumption were recorded in the postoperative period. They found that there was no significant difference between groups in the time to first analgesic requirement. Compared with Group F, patients in Group FM received

smaller doses of epidural fentanyl *(P* < 0.05). The cumulative fentanyl consumption in 24 h was 437 (SD110) µg in Group F and 328 (121) µg in Group FM *(P* < 0.05). Patients in Group F showed a higher VAS score in the first hour of the postoperative period*(P* < 0.05). The groups were similar with respect to haemodynamic and respiratory variables, sedation, pruritis, and nausea. They concluded that co-administration of magnesium for postoperative epidural analgesia results in a reduction in fentanyl consumption without any side-effects.

7. **Ghatak T, Chandra G, Malik A, Singh D, Bhatia VK (2010)** [32]

They did prospective randomised double-blind study to establish the effect of addition of magnesium or clonidine, as adjuvant, to epidural bupivacaine in lower abdominal and lower limb surgeries. A total of 90 ASA grade I and II patients undergoing lower abdominal and lower limb surgeries were enrolled to receive either magnesium sulphate (Group B) or clonidine (Group C) along with epidural bupivacaine for surgical anaesthesia. All patients received 19 ml of epidural bupivacaine 0.5% along with 50 mg magnesium in group B, 150 mcg clonidine in Group C, whereas in control group (Group A), patients received same volume of normal saline. Onset time, heart rate, blood pressure, duration of analgesia, pain assessment by visual analogue score (VAS) and adverse effects were recorded. They found onset of anaesthesia was rapid in magnesium group (Group B). In group C there was prolongation of duration of anaesthesia

and sedation with lower VAS score, but the incidence of shivering was higher. The groups were similar with respect to haemodynamic variables, nausea and vomiting. They concluded that magnesium sulphate is a predictable and safe adjunct to epidural bupivacaine for rapid onset of anaesthesia and clonidine for prolonged duration of anaesthesia with sedation.

8. **Sukhminder Jit Singh Bajwa1, Sukhwinder Kaur Bajwa2, Jasbir Kaur (2011)**[33]

Dexmedetomidine and clonidine in epidural anaesthesia: A comparative evaluation.

A prospectiverandomized study was carried out which included 50 adult female patients between the ages of 44 and 65 years of (American Society of Anaesthesiologists) ASAI/II grade who underwent vaginal hysterectomies. The patients were randomly allocated into two groups; ropivacaine + dexmedetomidine (RD) and ropivacaine + clonidine (RC), comprising of 25 patients each. Group RD was administered 17 ml of 0.75% epidural ropivacaine and 1.5 μg/kg of dexmedetomidine, while group RC received admixture of 17 ml of 0.75% ropivacaine and 2 μg/kg of clonidine. Onset of analgesia, sensory and motor block levels, sedation, duration of analgesia and side effects were observed. The data obtained was subjected to statistical computation with analysis of variance and chi-square test using statistical package for social science (SPSS) version 10.0 for windows and value of $P< 0.05$ was considered significant and $P< 0.0001$ as highly significant. The demographic profile, initial and post-operative block characteristics and cardio-respiratory parameters were

comparable and statistically non-significant in both the groups. However, sedation scores with dexmedetomidine were better than clonidine and turned out to be statistically significant (P< 0.05). The side effect profile was also comparable with a little higher incidence of nausea and dry mouth in both the groups which was again a non-significant entity (P> 0.05). Dexmedetomidine is a better neuraxial adjuvant compared to clonidine for providing early onset of sensory analgesia, adequate sedation and a prolonged post-operative analgesia.

9. **Mohammad W, Mir SA, Mohammad K, Sofi K.**(2015) [34]

Compared postoperative pain relief in patients undergoing an elective thoracotomy with thoracic epidural analgesia using single shot magnesium and clonidine as adjuvants to bupivacaine. In a randomized prospective study, 60 patients of American Society of Anesthesiologists physical status I-III of either sex, between 20 and 60 years undergoing elective unilateral thoracotomy, were allocated to three equal groups of 20 patients. Each patient received thoracic epidural analgesia using bupivacaine alone (Group A) or with magnesium (Group B) or clonidine (Group C) at the end of surgery during skin closure. Postoperatively, pain was measured using a visual analogue scale (VAS). Rescue analgesia (50 mg tramadol intravenous) was given at a VAS score of ≥4. Duration of analgesia and total dose of rescue analgesic during 24 h was calculated. Postoperative sedation and other side effects if any were recorded. The duration of analgesia was prolonged in Group C (165 ± 49.15 min),

followed by Group B (138 ± 24.6 min), and Group A (118.5 ± 52.8 min). The duration of analgesia was significantly prolonged in the clonidine group as compared to the control group (P = 0.001). The number of rescue analgesia doses were more in Group A (3.3 ± 1.65) followed by Group B (2.35 ± 0.98) and Group C (1.75 ± 0.71). The sedation scores were significantly higher in Group C. However, shivering was seen in Group A (40%) and Group C (20%) and absent in Group B (P = 0.003). They concluded that thoracic epidural analgesia using bupivacaine with clonidine is an efficient therapeutic modality for post-thoracotomy pain. Magnesium as an adjuvant provided quality postoperative analgesia decreasing the need for postoperative rescue analgesia and incidence of postoperative shivering without causing sedation.

MATERIALS AND METHODS

METHODS

DESIGN OF THE STUDY

The study isa prospective, controlled, double blind randomized study "Comparing Epidural Dexmedetomidine Vs Magnesium Sulphate used as an adjuvant to Ropivacaine for post operative analgesia in patients undergoing Thoracotomy" was duly submitted before the ethical committee of our Institution and the ethical committee approval was obtained. The study was done in 60 patients who underwent thoracotomy under general anaesthesia.

INCLUSION CRITERIA

- Age : 18 - 60 years
- Sex : Both Male and Female
- Weight : BMI < 35 kg/m2
- ASA: status 1, 2 & 3
- Surgery : Elective
- Who have given valid informed consent

EXCLUSION CRITERIA

- Patient's refusal to participate in the study
- Allergy to local anaesthetics

- Coagulopathy
- Patients on anti coagulants
- Systemic or local sepsis
- Patients with severe cardiovascular, endocrine, renal, hepatic and psychiatric diseases
- H/O seizure or any neurological deficit
- Vertebral abnormalities like kyphoscoliosis
- Pregnant female
- Emergency procedures

STUDY DURATION

6 months

STUDY GROUPS

60 patients who need to be operated by elective thoracotomy will be randomly assigned into two groups

Group D: 30 patients given thoracic epidural analgesia using Inj. Ropivacaine 0.375% 8ml and Dexmedetomidine 1µ/kg

Group B:30 patients given thoracic epidural analgesia using Inj. Ropivacaine 0.375% 8ml and Magnesium sulphate 75mg

The patients who satisfied the inclusion criteria were explained about the nature of procedure, tests, advantages and side effects in an elaborate manner in his/her own language. A written informed consent was then obtained from the patients. Then they were assessed and investigated. Age, height, weight, and body mass index of the patients were noted down. Various other vital parameters like blood pressure, heart rate, respiratory rate, oxygen saturation were also noted. Explanation about the visual analogue score (VAS) was given to all patients. They were told that 0 represents “no pain” and 10 represents “worst possible pain” on the grading scale.

MATERIALS

18G Venflon IV Catheter

Epidural set

Fibreoptic Bronchoscope

Drugs–

Inj.Ropivacaine, Inj Dexmedetomidine, Inj Magnesium Sulphate, Inj.Glycopyrrolate,Inj. Fentanyl, Inj.Thiopentone Sodium,Inj Neostigmine, Sevoflurane, Emergency drugs, Ringer lactate and Normal saline

• Monitors – ECG, NIBP, SPO2, EtCO2.

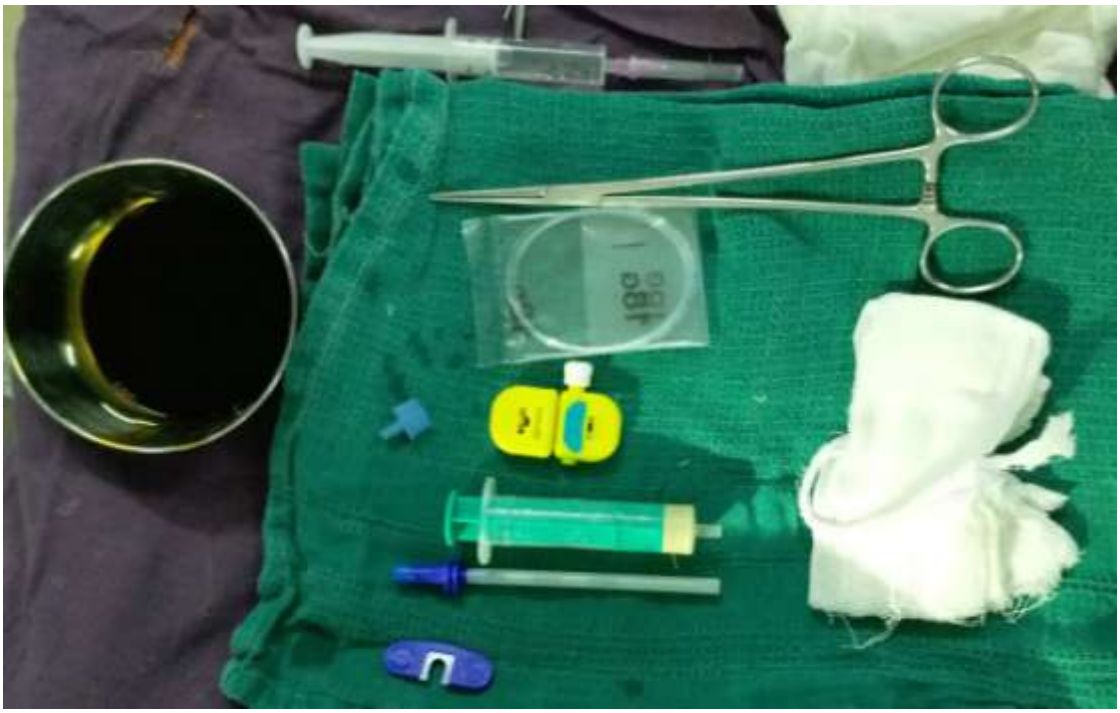
METHODOLOGY OF STUDY

After approval from institutional ethical committee, 60 patients, ASA physical status II–III, scheduled for elective pulmonary surgery, gave their written informed consent to participate in this prospective, controlled, double blind randomized study. All patients required thoracotomies for various surgeries like decortication, lobectomy, excision of hydatid cyst in the lateral decubitus position and one-lung ventilation. Total pneumonectomy were excluded from this study.

Preoperative history, clinical examination, pulmonary function tests, laboratory results, electrocardiogram, chest radiograph, were noted. Before induction of anesthesia hemodynamic monitoring was established with a radial artery catheter contralateral to the operated side for invasive blood pressure monitoring, arterial blood gas sampling and hemoglobin determinations. Heart rate, arterial blood pressure, arterial oxygen saturation (Spo2) by pulseoximetry, electrocardiogram, oropharyngeal temperature, inspired oxygen fraction and end-tidal isoflurane concentration as well as end-tidal CO2 monitored continuously. All patients received 0.5 mg alprazolam orally 2 h before their arrival in the operatingroom. Anesthesia was induced in both groups with IV doses of Propofol (2–3 mg/kg), Fentanyl (2-3 μg/kg), and Vecuronium (0.1 mg/kg) and maintained with an end-tidal concentration of 1- 2 vol % isoflurane or desflurane. After induction of anesthesia, a left sided double-lumen tube was inserted. The correct position of the tube was determined by auscultation and

confirmed by fiberoptic bronchoscopy before and after the patient was in the lateral decubitus position. After induction and loss of resistance technique epidural catheter was placed at the T6-7 orT7-8 interspace with 18G epidural needle using the paramedian approach.

The patients' lungs were ventilated with intermittent positive pressure. Ventilation was controlled with Fio2 0.5-1.0 % and a tidal volume of 7- 10 mL/kg a to maintain Etco2 in the range of 35 to 45 mm Hg. Erythrocyte transfusions were administered to maintain a hemoglobin level of 10 g/dL. Volume treatment was controlled in both groups with crystalloids and colloids to keep the patient in stable fluid balance.



After closing and dressing of the surgical wound, patient made supine from lateral surgical position and extubated after adequate reversal. Patients were shifted to post-operative room and monitored. Once the patient in the post-operative room was noted to have pain (visual analogue scale (VAS) of >3), the study was started. A test dose of 3 ml Lignocaine with adrenaline (1:200,000) was injected and the patients were randomly allocated to one of the following two groups randomly. Group D (N=30): Receivedropivacaine0.375% 8ml (1.5ml/segment) plus dexmedetomidine 1mcg/kg and Group M (N=30): Received ropivacaine 0.375% 8ml plus magnesium sulphate 75mg. After administering the drug, the following parameters were noted :

The pain score, by using VAS until the need for next epidural top.

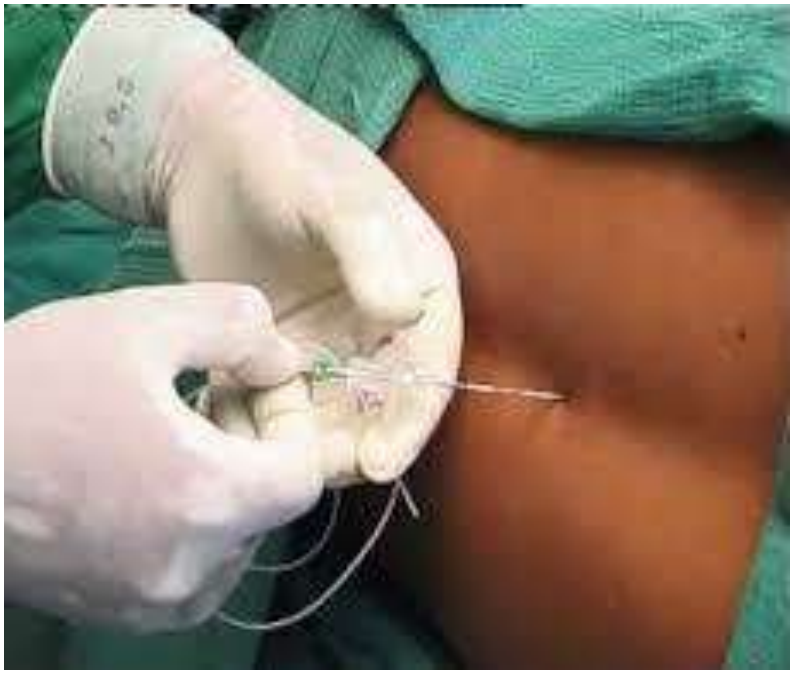
(1) The level of anesthesia was determined by loss of pinprick sensation

(2) Peak level of analgesia (achieving VAS score 0).

(3) First Epidural top up/duration of analgesia (epidural drug administration to once the patient asks for additional epidural analgesia with VAS>3).

(4) Observation of vital parameters such as IBP, pulse rate

(5) Side-effects such as hypertension/ hypotension, respiratory depression, nausea- vomiting, pruritis and dry mouth.



Once the patient asked for additional epidural analgesia (VAS>3) for pain relief during the observation period, the study was terminated and the above mentioned parameters were noted. Hypotension was treated with injection ephedrine 5mg IV bolus and heart rate<50 beats/min was treated with 0.01 mg/kg of injection atropine. Post-operative maintenance IV fluids were given as per body weight. Nausea and vomiting were treated with 0.1 mg/kg of IV Ondansetron.

METHODOLOGY

ETHICAL COMMITTEE APPROVAL

⇩

PATIENT SATISFYING INCLUSION CRITERIA

⇩

INFORMED CONSENT OBTAINED

⇩

RANDOMIZATION BY CLOSED ENVELOPE METHOD

⇩

HR, BP, MAP, sPO_2, RR MEASUREMENT

⇩

PLACING OF EPIDURAL CATHETER AT THE T6-7 OR T7-8 INTERSPACE WITH 18G EPIDURAL NEEDLE USING THE PARAMEDIAN APPROACH

⇩

HR,BP,MAP, SPO_2, RR MEASUREMENT

⇩

PREOXYGENATION

⇩

INDUCTION

⇩

INTUBATION WITH DOUBLE

LUMEN ENDOTRACHEAL TUBE

SURGERY PROCEEDED WITH MAINTENANCE OF ANAESTHESIA

END OF SURGERY

EXTUBATION

GROUP D Patients

(Received Ropivacaine 0.375% 8ml plus
plus Dexmedetomidine 1mcg/kg)

GROUP M Patients

(Received Ropivacaine 0.375%

75mg Magnesium Sulphate)

MEASUREMENT OF STUDY OUTCOMES

DATA COMPILATION

STATISTICAL ANALYSIS

CONCLUSION

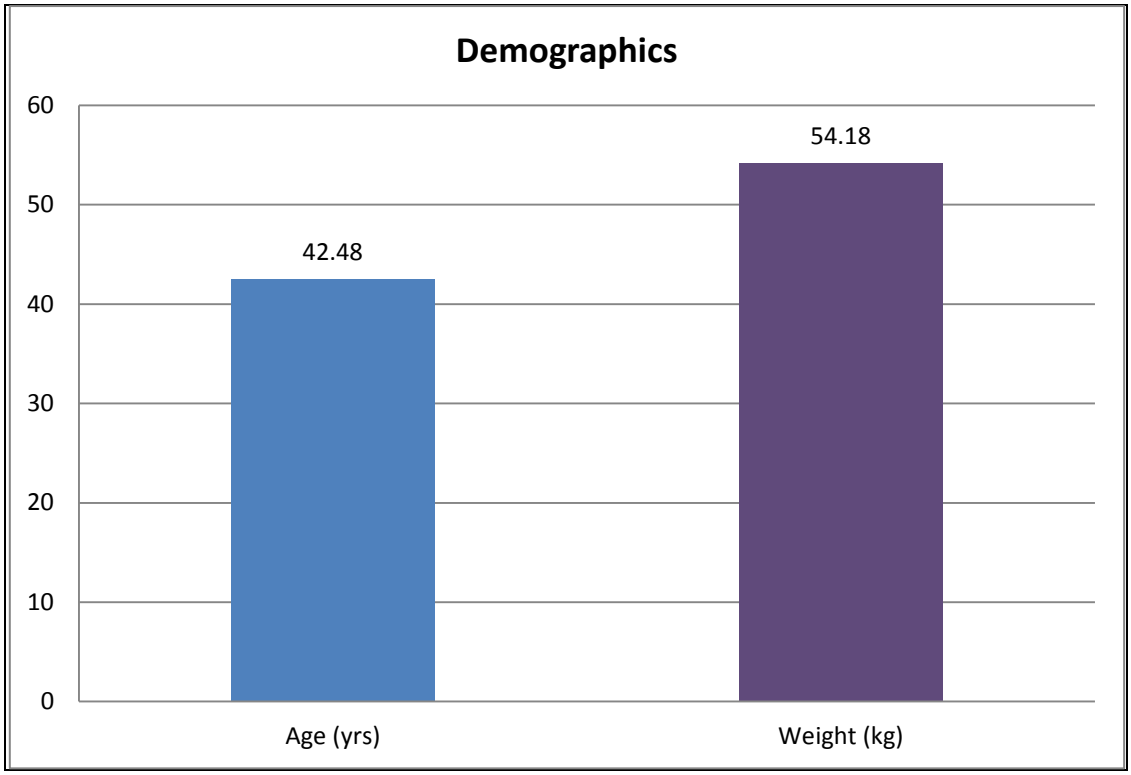
OBSERVATION RESULTS AND ANALYSIS

DATA ANALYSIS

Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired t test. Categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using SPSS version 16 and Microsoft Excel 2007

DEMOGRAPHIC PROFILE

Demographics	Mean ± SD
Age (yrs)	42.48 ± 7.84
Weight (kg)	54.18 ± 6.97

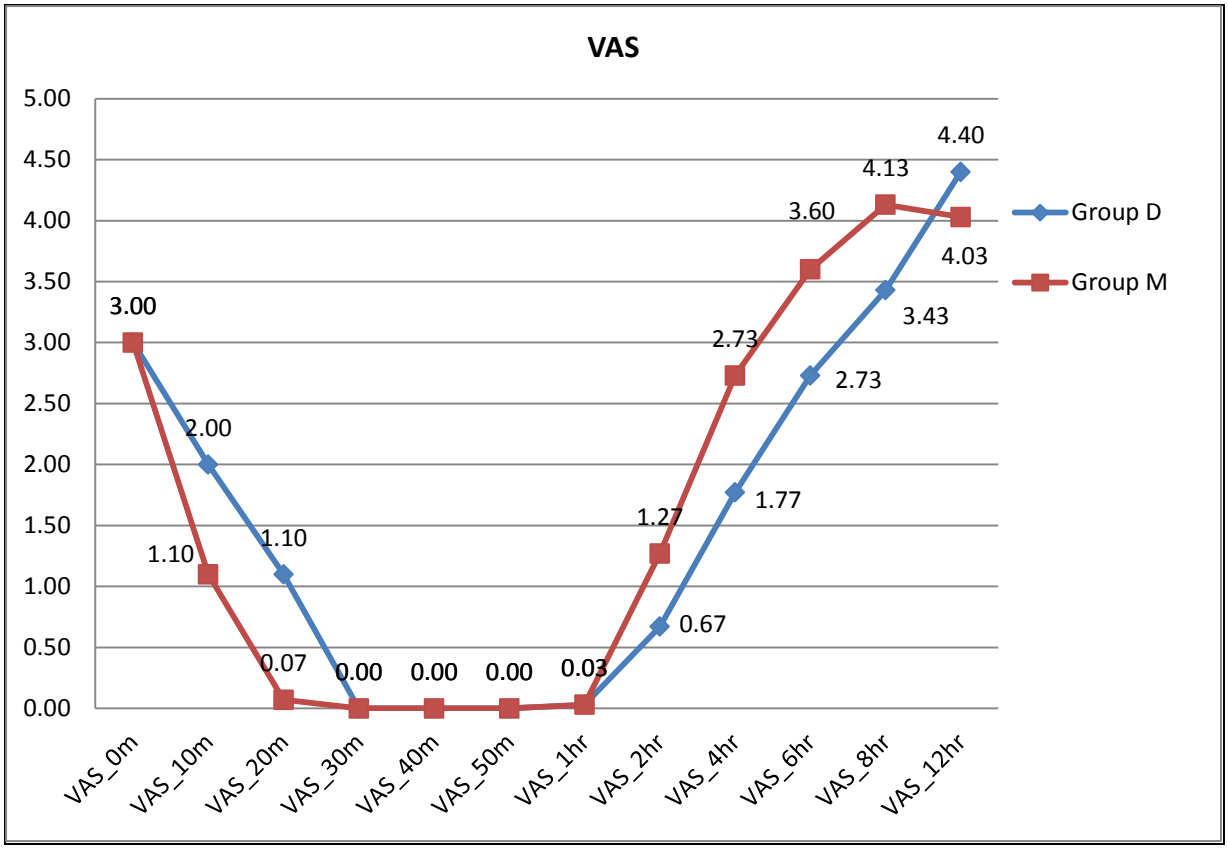


S.No	Demographic Characteristics	D Group	M Group	p-value
1	Age in years	42.93 (±7.57)	42.03 (± 8.21)	0.661
2	Weight in Kgs	56.30 (±7.38)	52.07 (± 5.92)	0.06
3	Male/Female	14/16	20/10	0.118
4	ASA 2 & 3	25/5	26/4	0.718

By conventional criteria the age distribution, weight, gender and ASA PS Classification status between the D group and M group among study subjects is considered to be not statistically significant since $p > 0.05$.

MEAN VAS SCORE

Mean VAS Scores	Group D	Group M	Mean diff	S.E Mean diff	95% Confidence Interval		p value
					Lower	Upper	
VAS 0 min	3.00 ± 0.00	3.00 ± 0.00	-	-	-	-	-
VAS 10 min	2.00 ± 0.00	1.10 ± 0.48	0.900	0.088	0.724	1.076	<0.01*
VAS 20 min	1.10 ± 0.30	0.07 ± 0.25	1.033	0.072	0.888	1.178	<0.01*
VAS 30 min	0.00 ± 0.00	0.00 ± 0.00	-	-	-	-	-
VAS 40 min	0.00 ± 0.00	0.00 ± 0.00	-	-	-	-	-
VAS 50 min	0.00 ± 0.00	0.00 ± 0.00	-	-	-	-	-
VAS 1 hr	0.03 ± 0.18	0.03 ± 0.18	0.000	0.047	-0.094	0.094	1.000
VAS 2 hrs	0.67 ± 0.47	1.27 ± 0.45	-0.600	0.120	-0.840	-0.360	<0.01*
VAS 4 hrs	1.77 ± 0.50	2.73 ± 0.45	-0.967	0.123	-1.214	-0.720	<0.01*
VAS 6 hrs	2.73 ± 0.45	3.60 ± 0.62	-0.867	0.140	-1.147	-0.586	<0.01*
VAS 8 hrs	3.43 ± 0.50	4.13 ± 0.34	-0.700	0.112	-0.923	-0.477	<0.01*
VAS 12 Hrs	4.40 ± 0.49	4.03 ± 0.32	0.367	0.108	0.150	0.583	0.001*



VAS 0, 30, 40, 50 have same values in both groups. So, mean diff etc are not applicable.

The mean VAS scores of both the groups are compared using independent samples t test. The mean VAS scores of Group D were significantly lesser than in group M. The difference was statistically significant since $p > 0.05$.

COMPARISON OF ANALGESICS

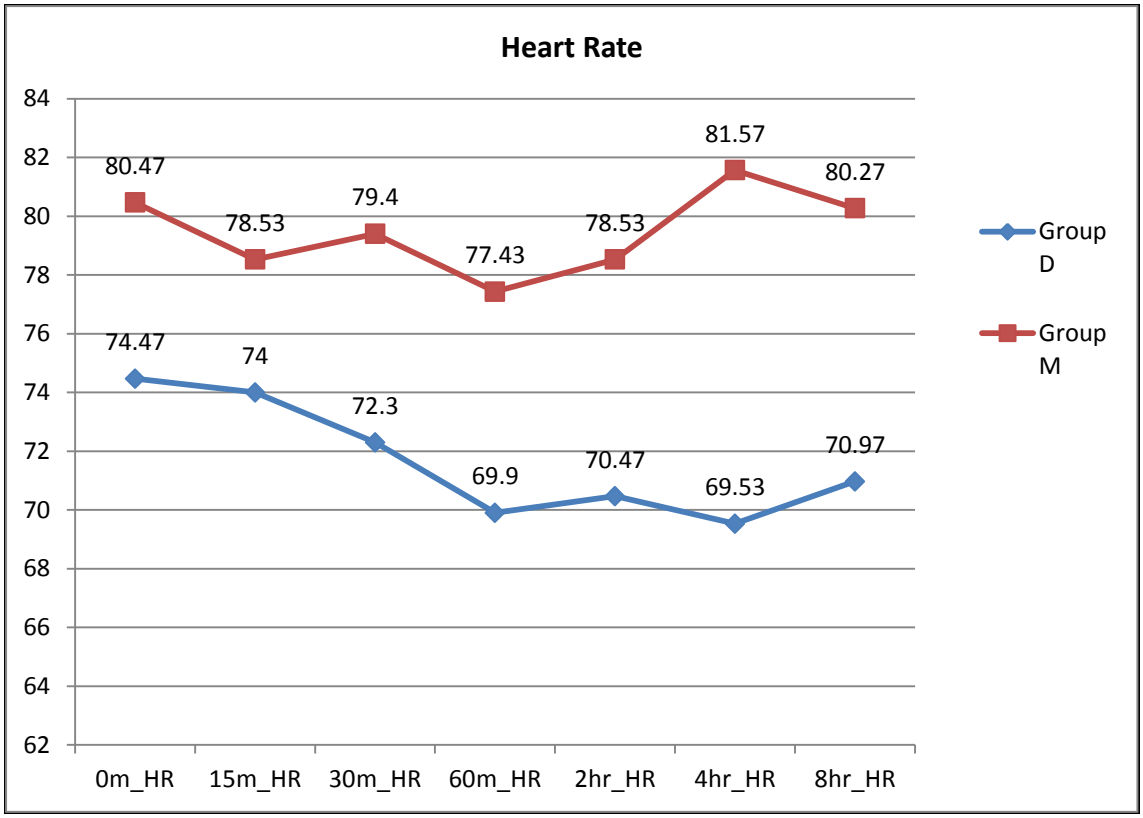
Characteristic of Block	Group D	Group M	p-value
Time to reach maximum sensory block level(min)	21.03 (± 3.23)	14.93 (±2.57)	<0.0001
Sensory block level	T3 – T4	T3 – T5	
First epidural top up in Hrs.(after VAS>3)	6.47 (± 1.0)	4.53 (± 0.90)	<0.0001

The time to reach maximum sensory block level for group D is 21.03 (± 3.23) minutes and for group M is 14.93 (±2.57) minutes. The p value is less than 0.0001. By conventional criteria, this difference is considered to be extremely statistically significant.

Duration of analgesia i.e the time to first epidural top up (after VAS>3) in group D is 6.47 (± 1.0) hours whereas for group M it is 4.53 (± 0.90) hours. The p value is less than 0.0001. By conventional criteria, this difference is considered to be extremely statistically significant.

MEAN POSTOPERATIVE HEART RATE

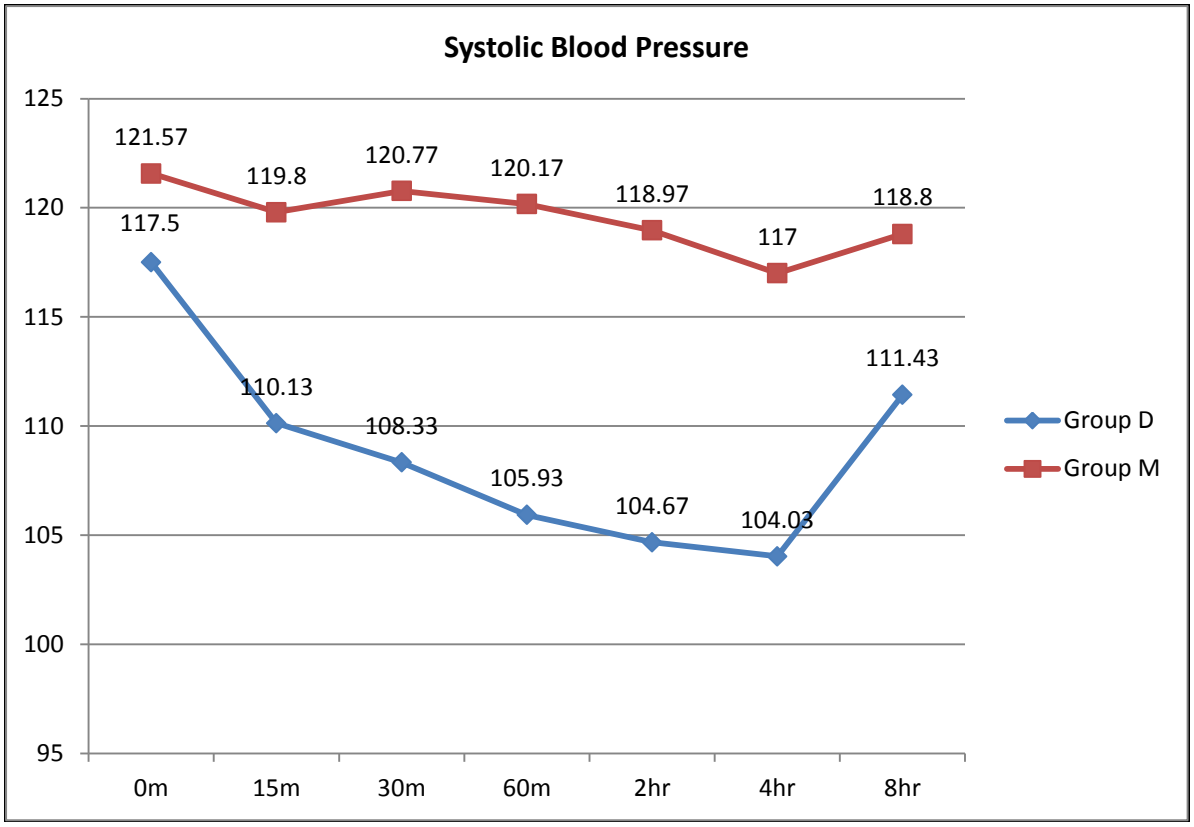
Mean heart Rate	Group A	Group B	Mean diff	S.E Mean diff	95% Confidence Interval		p value
					Lower	Upper	
Heart Rate 0 min	74.47 ± 5.07	80.47 ± 5.84	-6.000	1.412	-8.827	-3.173	<0.01*
Heart Rate 15 min	74.00 ± 5.59	78.53 ± 5.77	-4.533	1.468	-0.747	-1.594	0.003
Heart Rate 30 min	72.30 ± 5.60	79.40 ± 6.03	-7.100	1.505	-10.112	-4.088	<0.01*
Heart Rate 60 min	69.90 ± 7.43	77.43 ± 6.00	-7.533	1.745	-11.026	-4.041	<0.01*
Heart Rate 2 hr	70.47 ± 7.91	78.53 ± 6.04	-8.067	1.818	-11.707	-4.427	<0.01*
Heart Rate 4 hr	69.53 ± 7.67	81.57 ± 5.78	-12.033	1.755	-15.546	-8.521	<0.01*
Heart Rate 8 hr	70.97 ± 6.49	80.27 ± 5.23	-9.300	1.523	-12.348	-6.252	<0.01*



The mean post operative heart rates of both the groups were compared using independent samples t test. The mean heart rates of group D were significantly lower than in Group M. The difference was statistically significant.

MEAN SYSTOLIC BLOOD PRESSURE

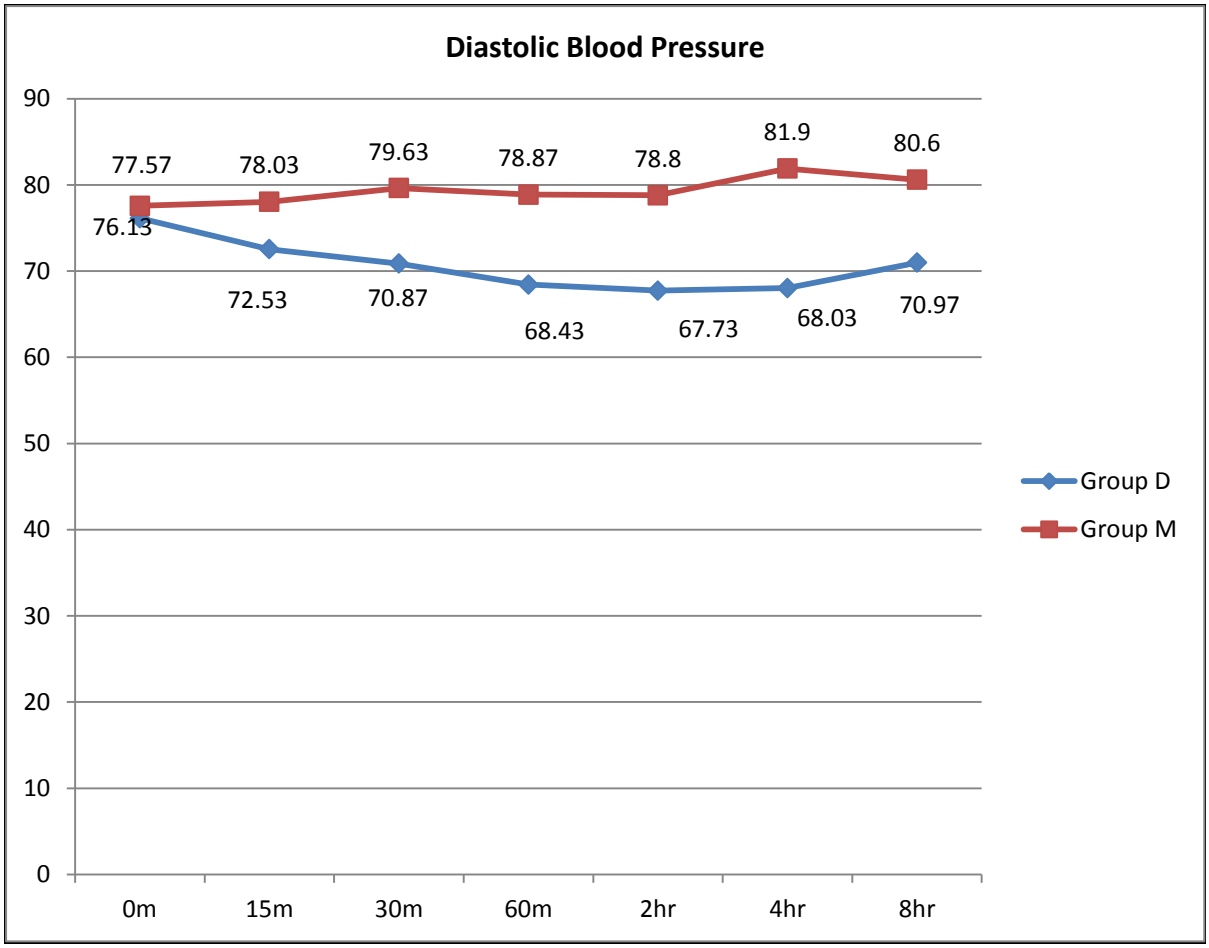
Mean SBP	Group A	Group B	Mean diff	S.E Mean diff	95% Confidence Interval		p value
					Lower	Upper	
SBP 0 min	117.50 ± 8.68	121.57 ± 5.90	-4.067	1.916	-7.903	-0.231	0.039*
SBP 15 min	110.13 ± 6.31	119.80 ± 5.37	-9.667	1.514	-12.697	-6.636	<0.01*
SBP 30 min	108.33 ± 5.80	120.77 ± 5.38	-12.433	1.446	-15.327	-9.540	<0.01*
SBP 60 min	105.93 ± 5.15	120.17 ± 6.51	-14.233	1.516	-17.268	-11.198	<0.01*
SBP 2 hr	104.67 ± 4.31	118.97 ± 6.08	-14.300	1.362	-17.026	-11.574	<0.01*
SBP 4 hr	104.03 ± 3.41	117.00 ± 6.12	-12.967	1.281	-15.530	-10.403	<0.01*
SBP 8 hr	111.43 ± 8.31	118.80 ± 6.21	-7.367	1.895	-11.160	-3.573	<0.01*



The mean post operative systolic BP between both the groups were compared using independent samples t test. The mean systolic blood pressure of group D were significantly lower than in Group M. The difference was statistically significant.

MEAN DIASTOLIC BLOOD PRESSURE

Mean DBP	Group A	Group B	Mean diff	S.E Mean diff	95% Confidence Interval		p value
					Lower	Upper	
DBP 0 min	76.13 ± 5.88	77.57 ± 4.72	-1.433	1.378	-4.191	1.324	0.302
DBP 15 min	72.53 ± 4.18	78.03 ± 2.37	-5.500	0.878	-7.257	-3.743	<0.01*
DBP 30 min	70.87 ± 4.25	79.63 ± 2.91	-8.767	0.942	-10.653	-6.881	<0.01*
DBP 60 min	68.43 ± 4.18	78.87 ± 4.94	-10.433	1.183	-12.801	-8.066	<0.01*
DBP 2 hr	67.73 ± 3.14	78.80 ± 4.66	-11.067	1.026	-13.121	-9.012	<0.01*
DBP 4 hr	68.03 ± 2.42	81.90 ± 4.73	-13.867	0.971	-15.810	-11.924	<0.01*
DBP 8 hr	70.97 ± 2.87	80.60 ± 4.97	-9.633	1.048	-11.732	-7.535	<0.01*



The mean post operative diastolic BP between both the groups were compared using independent samples t test. The mean diastolic blood pressure of Group D were significantly lower than in Group M. The difference was statistically significant.

THE COMPARISON OF SIDE EFFECTS IN BOTH GROUPS

Side Effects	Group D (N=30)	Group M (N=30)
PONV	03	01
Hypotension	17	0
Bradycardia	05	0
Respiratory depression	0	0
Dry mouth	7	0
Pruritis	2	0

Almost all the tolerable side effects were most commonly found in Group D. Post operative nausea and vomiting occur in three patients in Group D and in one patient in group M. Minimal side-effects like pruritis, dry mouth occur in group D. Respiratory depression was not observed in either group.

DISCUSSION

Thoracotomies are painful operations, and well-planned pain management is crucial in decreasing morbidity after major thoracic surgery for lung resection. The main aim of postoperative analgesia is to provide patients comfort, in addition to inhibiting nociceptive impulse caused by surgical trauma and to blunt somatic as well as autonomic reflexes in response to pain. Multiple literature reported that when epidural local anesthetic dose is combined with an adjuvant as compared to local anesthesia alone provide superior pain relief, early mobilization, early chest physiotherapy and avoid pneumonia. Dexmedetomidine is highly lipid soluble and appears rapidly in CSF and has high binding affinity to a α 2 receptors in the spinal cord used as adjuvant to regional anaesthetic drug provide analgesia, sedative properties and causes minimal respiratory depression. The synergistic effects between epidural dexmedetomidineand local anesthetics is well established but evidence regarding combination of ropivacaine with magnesium through epidural route is very scarce in literature.

In both the group demographic profile were comparable. My study was started when patient complained of minimal pain (VAS >3). Time to reach peak effect of analgesia was significantly earlier in M group (14.93±2.57) minutes as compare to Dexmedetomidine group (21.03± 3.23) minutes. However, mean VAS scores were higher in group M in comparison to group D at different time intervals hence first epidural top was earlier in group M as compare to group D

(4.53± 0.90 vs6.47± 1.0). In present study, epidurally magnesium 75 mg and dexmedetomidine 1mcg/kg was added with ropivacaine, the mean duration of analgesia was significantly prolonged with dexmedetomidine as compared with magnesium. Possible mechanism may be that magnesium analgesic effect occurred at the supra-spinal level and might be related to its systemic absorption and epidural usage may be related to the diffusion of magnesium from the duramater. There are many studies the role of magnesium for postoperative analgesia. But most of these studies shown that systemic administration of magnesium is associated with smaller analgesic requirement and less discomfort in the postoperative period. Implying that, it is an effective analgesic when magnesium is added to opioid either epidurally or intrathecal. The side-effect profiles of both groups of are quite favourable as none of the patient had profound deep sedation (ramsay sedation score>3) or respiratory depression.

Postoperatively, heart rates and systolic and diastolic blood pressures remained on the lower side but remained stable throughout the study period in group Dexmedetomidine. But none of them require atropine or vasopressors, while in group magnesium there was no change in blood pressure and heart rate. None of groups of the patients in the present study developed motor blockade/ hemodynamic instability. Dry mouth is a known side effect of α-2 agonists and the incidence in the present study was found in about 30% of dexmedetomidine group which is almost similar to other studies. Goodman et al reported two case, larger doses (8.7 g, 9.6 g) of magnesium inadvertently administered into the

epidural space did not cause any neurologic injury.[23] Also another report described an inadvertent intrathecal injection of 1000 mg of magnesium producing a transient motor block followed by a complete resolution and no neurological deficit at long-term follow-up. So, when compared with these doses, our epidural dose is too low for the systemic effect.

My study has the limitation of only single dose response evaluation. Epidural dose of magnesium used was very small and this is among the very few study which has directly compared the effects of epidurally administered Dexmedetomidine and Magnesium in thoracotomy.

SUMMARY

This study was conducted to compare the post operative analgesia duration using Inj. Ropivacaine with Dexmedetomidine and Inj. Ropivacaine with Magnesium Sulphate for patients undergoing open thoracotomy surgery under general anaesthesia.

The following observations were made

- The mean VAS scores of Group Dexmedetomidine were significantly lesser than in Group Magnesium sulphate, which also has statistical significance
- The mean duration of analgesia i.e the time to first epidural top up (after VAS>3) was longer in Group Dexmedetomidine (6.47 ± 1.0) hours whereas for Group Magnesium sulphate group it was (4.53 ± 0.90) hours.
- The time to reach maximum sensory block level was faster in Group M 14.93 (±2.57) minutes & for Group D it was 21.03 (± 3.23) minutes which was statistically significant.
- Both the group were maintained well with good post operative hemodynamics when mean HR, SBP, DBP are monitored. In patients receiving Dexmedetomidine heart rates and systolic and diastolic blood pressures remained on the lower side.

Hence, thoracic epidural analgesia plays a very important role in providing post operative analgesia. In addition side effects of opiod usage like, PONV, sedation, respiratory depression can be minimized.

CONCLUSION

From my study, I conclude that Epidural Dexmedetomidine is a better neuraxial adjuvant to Ropivacaine when compared to Magnesium sulphate regarding post-operative analgesia. Also it provides stable cardiorespiratory parameters. But epidural magnesium can be added as an adjuvant for better pain relief & VAS score without any side effects with the concentrations used in my study.

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INFORMATION TO PARTICIPENTS

Investigator: Dr.MILANJYOTI PATAR

Name of the Participant:

Title.
"Comparison of Epidural DexmedetomidineVs Magnesium Sulphate used as Adjuvant to Ropivacaine for Analgesia in Post Thoracotomy patients"

You are invited to take part in this research study. We have got approval from the IEC. You are asked to participate because you satisfy the eligibility criteria. We want to compare and study the safety and post operative analgesia of Epidural Dexmedetomidine and Magnesium Sulphate used as Adjuvant to Ropivacaine for Post-Operative Analgesia in patients undergoing Thoracotomy surgery under general anesthesia.

What is the Purpose of the Research: It measures

- Post-operative Visual Analogue Scale for pain score.
- Duration of analgesia.
- Sensory block level.
- Post operative Hemodynamics .
- Complications if any.

The Study Design:

All the patients in the study will be divided into two groups:

Group D (N=30): Received Ropivacaine 0.375% 8ml (1.5ml/segment) plus Dexmedetomidine 1mcg/kg

GROUP M (N=30): Received ropivacaine 0.375% 8 ml plus magnesium sulphate 75mg.

Benefits Thoracic Epidural block improves intra operative hemodynamic, reduces opioid requirement, causespost operative pain relief.

Discomforts and risks

Intravascular local anaesthetic injection

Damage to neuro vascular structure

This intervention has been shown to be well tolerated as shown by previous studies.And if you do not want to participate you will have alternative of setting the standard treatment and your safety is our prime concern.

Time :
Date :
Place :

Signature / Thumb Impression of Patient
Patient Name:

Signature of the Investigator : _____

Name of the Investigator : _____

PATIENT CONSENT FORM

Study title "Comparison of Epidural Dexmedetomidine Vs Magnesium Sulphate used as Adjuvant to Ropivacaine for Analgesia in Post Thoracotomy patients"

Study Center : INSTITUTE OF ANAESTHESIOLOGY AND CRITICAL CARE,

RAJIV GANDHI GOVT. GENERAL HOSPITAL,

MADRAS MEDICAL COLLEGE,

CHENNAI- 03.

Participant name: Age: Sex: I.P.No:

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the pitfall in the procedure. I have been explained about the safety, advantage and disadvantage of the technique.

I understand that my participation in the study is voluntary and that I am free to withdraw at anytime without giving any reason.

I understand that investigator, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from the study.

Time:

Date: Signature / thumb impression of patient

Place: Patient name:

Signature of the investigator:

Name of the investigator:

PROFORMA

DATE: ROLL NO:

NAME:

AGE: SEX: IP NO:

DIAGNOSIS:

SURGICAL PROCEDURE DONE:

Ht: CVS: HB:

Wt: RS:

AIRWAY: MMS - IID - DENTITION -

PRE OP ASSESSMENT:

HISTORY: Any Co-morbid illness

H/O Documented Difficult Airway

H/O previous surgeries

MEASURES OF STUDY OUTCOME

TIME (min)	HEART RATE	SYSTOLIC BP	DIASTOLIC BP	SITE OF INJECTION	HIGHEST SENSORY LEVEL	Time to max sensory level (min)
BASELINE						
POST OPERATIVE						
O min						
15 min						
30 min						
60 min						
2 hrs						
4 hrs						
8 hrs						

TIME	0	10 min	20 min	30 min	40 min	50 min	1 hr	2hr	4 hr	6 hr	8hr	12hr
VAS												

COMPLICATIONS / SIDE EFFECTS IN POST OPERATIVE PERIOD

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சி தலைப்பு

மார்புகூட்டு அறுவை சிகிச்சையின்போது எபிடியூரல் முறையில் ரோபிவாகைன் மருந்து செலத்தும்போது சிறந்த வலி நிவாரணத்திற்கு துணை மருந்தாக டெக்ஸ்மெடிடோமிடினையும் மெக்னீசியம் சல்பைட்டையும் ஒப்பீடு செய்தல்.

ஆராய்ச்சியாளர் பெயர் : மருத்துவர்.மிலன் ஜோதி படார்

பங்கேற்பாளர் பெயர் :

ஆராய்ச்சியின் நோக்கம்

மார்புகூட்டு அறுவை சிகிச்சையின்போது எபிடியூரல் முறையில் ரோபிவாகைன் மருந்து செலத்தும்போது சிறந்த வலி நிவாரணத்திற்கு துணை மருந்தாக டெக்ஸ்மெடிடோமிடினையும் மெக்னீசியம் சல்பைட்டையும் ஒப்பீடு செய்தல்.

1. அறுவை சிகிச்சைக்குப்பின் வலி நிவாரண நேரம்.
2. அறுவை சிகிச்சையின்போதும், அதன் பின்பும், நாடித்துடிப்பு, இரத்த அழுத்தம்.
3. அறுவை சிகிச்சைக்கு பின்னான விசுவல் அனலாக் அளவுகோலின் படி வலியின் அளவு.
4. பக்க விளைவுகள்
5. அறுவை சிகிச்சையின்போது இதர வலி நிவாரணிகளின் தேவை

ஆய்வு முறை

ஆய்வில் பங்குபெறும் நோயாளிகள் இரண்டு குழுக்களாகப் பிரிக்கப்படுவர்.

குழு-1 துணை மருந்தாக டெக்ஸ்மெடிடோமிடின் செலுத்தப்பட்டவர்கள்

குழு-2 துணை மருந்தாக மெக்னீசியம் சல்பேட் செலுத்தப்பட்டவர்கள்

நன்மைகள்

1. அறுவை சிகிச்சையின்போது நாடித்துடிப்பு மற்றும் இரத்த அழுத்தம் சீராக செயல்பட உதவுகின்றன.
2. இதர வலி நிவாரணிகளின் தேவை வெகுவாக குறைக்கப்படுகின்றன.

3. அறுவை சிகிச்சைக்குப் பின்னர் வலி நிவாரணத்தின் தன்மை நீட்டிக்கப்படுகின்றது.

பக்கவிளைவுகள்

ஊசி போடும்போது அசௌகரியம் ஏற்படலாம். மரத்துப்போகும் ஊசியின் மூலம் இது தவிர்க்கப்படும். குறைந்த இரத்த அழுத்தம், குறைந்த நாடித்துடிப்பு ஏற்படலாம். அதற்கு மாற்று மருந்துகள் உடனடியாக கொடுக்கப்படும்.

இந்த முறையான ஆய்வு ஏற்கனவே பல இடங்களில் நடத்தப்பட்டுள்ளது. மேலும் இதன் பாதுகாப்பு உறுதிசெய்யப்பட்டுள்ளது. நீங்கள் இந்த ஆய்வில் பங்குகொள்ள விரும்பவில்லை என்றால் எப்போதும் உபயோகிக்கப்படும் மருந்தே கொடுக்கப்படும். உங்கள் பாதுகாப்பே எங்களின் முக்கிய நோக்கம்.

இந்த ஆய்வு சம்பந்தமான எல்லா புள்ளி விவரங்கள் மற்றும் நோயாளிகளின் விவரங்கள் ரகசியமாக வைக்கப்படும். இந்த ஆய்வு சம்பந்தப்பட்ட எல்லா பரிசோதனைகள், மருந்துகள் மற்றும் மருத்துவ சேவைகள் அனைத்தும் நோயாளிகளுக்கு இலவசமாக வழங்கப்படும்.

ஆய்வாளரின் பெயர் **பங்குபெறுபவரின் பெயர்**

ஆய்வாளரின் கையொப்பம் **பங்குபெறுபவரின் கையொப்பம்**

<u>ஆராய்ச்சி ஒப்புதல் படிவம்</u>

ஆராயச்சியின் தலைப்பு

மார்புகூட்டு அறுவை சிகிச்சையின்போது எபிடியூரல் முறையில் ரோபிவாகைன் மருந்து செலத்தும்போது சிறந்த வலி நிவாரணத்திற்கு துணை மருந்தாக டெக்ஸ்மெடிடோமிடினையும் மெக்னீசியம் சல்பைட்டையும் ஒப்பீடு செய்தல்.

ஆய்வு நிலையம் : மயக்கவியல் துறை, சென்னை மருத்துவக் கல்லூரி சென்னை – 3.

பங்கு பெறுவரின் பெயர் :

பங்குபெறுபவரின் எண் :

பங்குபெறுபவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கின்றேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் ‘இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிகிறேன். ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம்..... தேதி.....

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம்..... தேதி.....

ஆய்வாளரின் பெயர் .....

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.Milanjyoti Patar
Post Graduate in M.D. Anaesthesiology
Institute of Anaesthesiology & Critical Care
Madras Medical College
Chennai 600 003

Dear Dr.Milanjyoti Patar,

The Institutional Ethics Committee has considered your request and approved your study titled **"COMPARISON OF EPIDURAL DEXMEDETOMIDINE VS MAGNESIUM SULPHATE USED AS ADJUVANT TO ROPIVACAINE FOR ANALGESIA IN POST THORACOTOMY PATIENTS " - NO.07012017 (III).**

The following members of Ethics Committee were present in the meeting hold on **24.01.2017** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD., Prof.of Pharmacology.,MMC,Ch-3	: Member
5.Prof.A.Rajendran,MS, Prof. of Surgery,MMC,Ch-3	: Member
6.Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
7.Prof.Baby Vasumathi,MD.,Director, Inst. of O & G	: Member
8.Prof.K.Ramadevi,MD.,Director,Inst.of Bio-Che,MMC,Ch-3	: Member
9.Prof.R.Padmavathy, MD, Director,Inst.of Pathology,MMC,Ch-3	: Member
10.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
11.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
12.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
13.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
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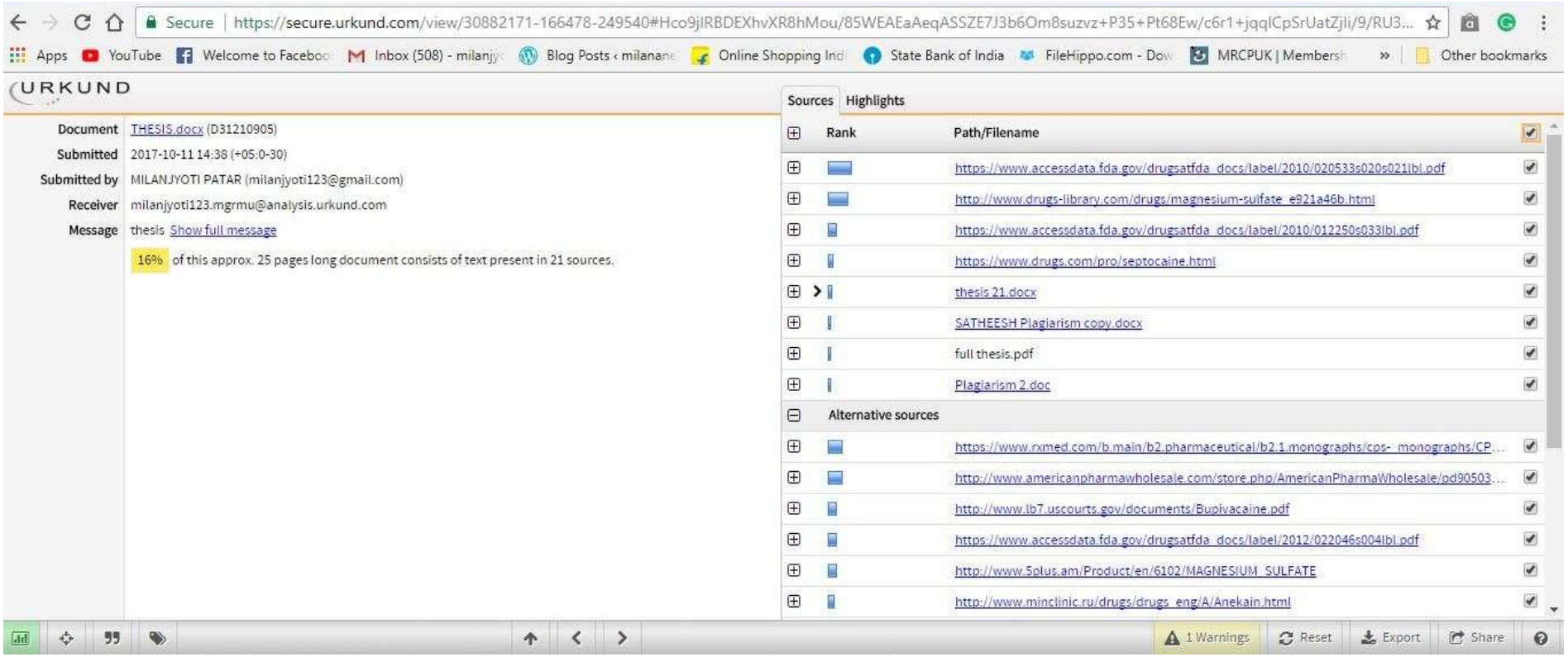
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PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled "COMPARISON OF EPIDURAL DEXMEDETOMIDINE Vs MAGNESIUM SULPHATE USED AS ADJUVANT TO ROPIVACAINE FOR ANALGESIA IN POST THORACOTOMY PATIENTS" of the candidate Dr.MILANJYOTI PATAR with Registration Number 201520017 for the award of M.D ANAESTHESIOLOGY. I personally verified the urkund.com website for plagiarism check. I found that the uploaded file containing from introduction to conclusion pages shows a result of 16% plagiarism in this dissertation.

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GROUP D

	Patient details					Pre operative			Site of	Highest	Time to	VAS											
Sl. No	IP no	Age	weight	ASA PS	Sex	PR	SBP	DBP	injection	sensory	max sensory	0 min	10 min	20 min	30 min	40 min	50 min	1 hour	2 hour	4 hour	6 hour	8 hour	12 hour
										level T	level (min)												
1	37130	45	60	2	M	60	130	88	T6-7	T3	20	3	2	1	0	0	0	0	0	1	3	3	4
2	29258	37	45	2	F	65	130	90	T6-7	T3	17	3	2	1	0	0	0	0	1	2	2	3	5
3	23185	29	50	3	F	76	126	72	T6-7	T3	22	3	2	1	0	0	0	0	0	2	3	4	4
4	29724	47	55	2	M	85	139	90	T6-7	T4	20	3	2	1	0	0	0	0	0	1	2	3	5
5	36718	45	58	2	M	64	124	85	T6-7	T4	25	3	2	1	0	0	0	1	1	2	3	3	4
6	38131	58	68	2	M	66	120	87	T6-7	T3	15	3	2	2	0	0	0	0	0	2	3	4	5
7	39053	47	50	2	F	78	122	84	T6-7	T3	18	3	2	1	0	0	0	0	0	1	2	3	4
8	33498	34	40	3	F	72	118	78	T6-7	T3	19	3	2	1	0	0	0	0	0	1	3	3	5
9	31576	39	48	2	F	75	132	82	T6-7	T4	20	3	2	1	0	0	0	0	1	2	3	4	4
10	34567	45	60	2	M	59	134	88	T6-7	T3	25	3	2	1	0	0	0	0	1	3	3	3	4
11	41234	42	55	2	F	62	117	80	T6-7	T3	24	3	2	1	0	0	0	0	1	2	3	4	4
12	42367	30	46	2	F	68	119	82	T6-7	T4	26	3	2	1	0	0	0	0	1	2	2	3	4
13	36421	36	67	2	M	80	125	77	T6-7	T3	25	3	2	1	0	0	0	0	0	1	3	3	4
14	29870	32	59	2	M	74	110	72	T6-7	T4	22	3	2	1	0	0	0	0	1	2	3	4	5
15	46624	44	50	2	F	84	116	78	T6-7	T3	20	3	2	1	0	0	0	0	0	1	3	3	4
16	35469	56	48	3	F	62	140	89	T6-7	T3	24	3	2	1	0	0	0	0	0	1	3	3	5
17	26071	50	62	3	M	68	134	95	T6-7	T3	16	3	2	1	0	0	0	0	0	1	2	3	4
18	44355	53	56	2	M	64	111	70	T6-7	T3	18	3	2	2	0	0	0	0	1	2	2	3	5
19	39867	43	65	2	M	70	128	77	T6-7	T3	20	3	2	1	0	0	0	0	1	2	3	4	4
20	51087	42	62	2	F	60	129	79	T6-7	T4	25	3	2	1	0	0	0	0	1	2	3	4	4
21	40112	57	66	2	F	66	130	82	T6-7	T3	25	3	2	1	0	0	0	0	1	2	3	3	5
22	47788	45	68	2	M	64	134	86	T6-7	T3	20	3	2	1	0	0	0	0	1	2	3	4	5
23	32436	44	48	2	F	66	116	78	T6-7	T3	22	3	2	1	0	0	0	0	1	2	3	3	5
24	42861	43	52	2	M	70	120	78	T6-7	T3	18	3	2	2	0	0	0	0	1	2	3	4	4
25	39426	47	60	3	F	65	122	82	T6-7	T4	16	3	2	1	0	0	0	0	1	2	2	3	4
26	38754	46	57	2	F	62	131	81	T6-7	T3	20	3	2	1	0	0	0	0	1	2	3	4	4
27	47523	36	56	2	F	65	128	82	T6-7	T4	25	3	2	1	0	0	0	0	1	2	3	4	4
28	56063	33	60	2	M	70	128	85	T6-7	T3	20	3	2	1	0	0	0	0	1	2	3	4	5
29	39168	38	55	2	F	72	129	72	T6-7	T3	25	3	2	1	0	0	0	0	1	2	3	4	4
30	61234	45	63	2	M	74	116	70	T6-7	T3	19	3	2	1	0	0	0	0	1	2	2	3	5

1ST Epi Top up time (hrs)	Post operative																					PONV	Hypotension	Bradycardia
	0 min			15 min			30 min			60 min			2 hr			4 hr			8hr					
	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP			
6	75	120	80	72	120	78	79	117	76	65	100	64	60	102	65	62	100	62	64	104	70	NO	NO	NO
8	80	130	85	77	122	78	70	120	76	66	111	71	65	108	70	64	100	64	66	102	68	NO	YES	NO
6	70	116	76	74	114	72	70	110	77	72	108	75	66	106	73	65	104	71	67	105	72	YES	YES	NO
8	75	108	75	89	100	76	84	102	74	80	100	72	76	102	70	75	101	68	76	102	70	NO	NO	NO
6	70	124	80	84	109	70	80	108	68	78	106	66	77	104	64	71	102	65	72	103	67	NO	NO	NO
6	80	122	76	80	111	69	72	109	67	70	107	65	75	105	64	70	103	67	77	104	69	NO	NO	NO
8	77	120	82	77	110	78	70	108	76	68	106	74	66	104	72	59	102	70	68	103	72	NO	YES	YES
6	78	126	77	68	107	79	69	105	77	70	103	75	70	101	73	73	105	71	74	110	72	NO	NO	NO
6	80	122	75	75	104	71	74	103	69	70	101	69	76	102	67	74	100	72	72	104	75	NO	NO	NO
4	88	126	89	79	100	70	77	101	68	76	102	66	78	99	64	80	105	68	73	109	75	NO	YES	NO
6	80	109	67	75	110	66	75	108	64	74	106	62	74	104	66	72	102	69	75	118	71	NO	NO	NO
8	72	110	68	77	113	70	80	111	68	82	109	66	84	107	65	81	105	66	78	108	69	YES	YES	NO
6	70	117	70	70	118	79	68	116	77	69	115	75	66	113	73	58	109	71	62	116	73	NO	YES	NO
6	69	104	72	69	122	73	60	120	72	56	118	70	58	116	68	65	114	66	77	110	68	NO	NO	YES
6	65	130	83	60	108	76	66	106	74	64	104	72	68	102	70	69	100	68	66	104	70	NO	YES	NO
6	70	128	85	77	102	69	75	100	69	78	104	67	75	102	65	77	104	69	75	110	80	NO	YES	NO
8	75	119	77	75	99	65	78	101	64	74	99	62	72	101	65	75	105	67	80	115	69	NO	NO	NO
8	80	115	74	76	109	70	74	108	68	71	106	64	78	104	64	70	103	66	69	110	68	NO	YES	NO
6	75	109	72	75	107	78	74	100	76	78	98	74	79	100	72	77	104	70	72	104	72	YES	YES	NO
6	70	100	80	69	104	73	73	102	71	74	100	69	75	99	67	70	105	65	75	106	67	NO	NO	NO
6	72	128	66	75	105	70	74	103	68	55	100	66	60	102	65	58	106	68	76	107	70	NO	YES	YES
6	70	124	75	74	112	70	65	110	68	57	108	66	55	106	67	58	104	69	62	129	72	NO	YES	YES
6	80	122	71	75	112	68	77	110	66	74	108	64	73	106	66	68	103	65	66	128	67	NO	NO	NO
6	76	128	74	76	117	67	71	115	65	64	113	63	62	111	65	67	109	68	68	118	70	NO	YES	NO
8	78	120	78	75	110	73	68	108	71	66	106	69	68	104	67	76	102	68	72	124	70	NO	YES	NO
6	74	117	85	72	106	73	71	104	71	73	102	69	75	100	67	76	104	68	69	120	72	NO	NO	NO
6	66	113	80	64	114	70	60	112	68	55	110	66	56	108	68	54	106	70	58	118	74	NO	NO	YES
6	70	103	70	67	119	72	68	117	69	70	116	67	75	114	69	70	112	68	69	129	70	NO	YES	NO
6	74	105	70	70	109	73	70	107	71	68	105	69	67	103	67	66	100	70	62	110	73	NO	YES	NO
8	75	110	72	74	111	80	77	109	78	80	107	76	85	105	74	86	102	72	89	113	74	NO	YES	NO

GROUP M

Sl. No	Patient details					Pre operative			Site of injection	Highest sensory level T	Time to max sensory level (min)	VAS											
	IP no	Age	weight	ASA PS	Sex	PR	SBP	DBP				0 min	10 min	20 min	30 min	40 min	50 min	1 hour	2 hour	4 hour	6 hour	8 hour	12 hour
1	23133	51	57	2	M	78	125	78	T6-7	T3	13	3	1	0	0	0	0	0	2	3	4	4	4
2	21378	45	60	2	F	79	112	76	T6-7	T4	13	3	2	0	0	0	0	0	1	2	3	4	4
3	24216	46	62	2	M	82	119	73	T6-7	T3	15	3	2	0	0	0	0	0	1	3	4	4	4
4	38907	48	56	3	M	91	134	71	T6-7	T3	16	3	1	0	0	0	0	0	1	3	5	4	4
5	34245	50	58	2	F	78	125	80	T6-7	T5	11	3	1	0	0	0	0	0	1	2	3	4	4
6	28654	52	54	2	M	60	112	83	T6-7	T3	18	3	0	0	0	0	0	0	1	2	3	4	4
7	26734	45	50	2	M	69	106	76	T6-7	T3	15	3	1	0	0	0	0	0	2	3	5	4	4
8	31356	48	48	2	F	77	119	76	T6-7	T4	19	3	0	0	0	0	0	0	1	3	4	4	4
9	24578	40	50	3	M	79	135	90	T6-7	T3	20	3	1	1	0	0	0	0	1	2	3	4	4
10	32566	35	48	2	M	83	126	73	T6-7	T4	13	3	1	0	0	0	0	0	1	3	4	4	3
11	26743	35	44	2	M	85	114	77	T6-7	T5	13	3	1	0	0	0	0	0	1	3	4	5	4
12	21345	28	40	2	F	85	119	75	T6-7	T3	15	3	1	0	0	0	0	0	1	3	4	4	4
13	25777	29	47	2	F	64	121	79	T6-7	T3	12	3	1	0	0	0	0	0	2	3	4	4	4
14	30975	30	46	2	M	75	140	90	T6-7	T4	17	3	1	0	0	0	0	0	1	3	4	4	4
15	30321	32	40	2	M	78	127	78	T6-7	T3	16	3	1	0	0	0	0	0	1	2	3	4	4
16	55553	45	48	2	M	74	116	70	T6-7	T4	18	3	2	0	0	0	0	1	1	3	4	4	5
17	47567	50	50	2	F	73	112	72	T6-7	T5	15	3	1	0	0	0	0	0	1	2	3	5	4
18	45245	55	48	2	M	80	124	74	T6-7	T3	17	3	1	0	0	0	0	0	1	3	4	4	4
19	34563	46	60	2	F	90	120	76	T6-7	T3	18	3	1	1	0	0	0	0	2	3	3	4	4
20	52298	47	58	2	M	84	119	78	T6-7	T5	19	3	1	0	0	0	0	0	2	3	3	4	4
21	38542	35	55	3	F	89	114	70	T6-7	T4	12	3	1	0	0	0	0	0	2	3	4	4	4
22	68732	31	56	2	M	93	111	69	T6-7	T3	12	3	1	0	0	0	0	0	1	2	3	4	5
23	41173	30	50	2	F	84	130	92	T6-7	T4	11	3	2	0	0	0	0	0	1	3	3	4	4
24	68211	45	62	2	M	85	121	78	T6-7	T5	15	3	1	0	0	0	0	0	2	3	3	4	4
25	35105	44	57	2	M	90	112	77	T6-7	T3	14	3	2	0	0	0	0	0	2	3	3	4	4
26	41297	51	55	2	M	92	109	80	T6-7	T3	15	3	1	0	0	0	0	0	1	3	3	5	4
27	32873	43	48	2	F	82	112	79	T6-7	T5	14	3	1	0	0	0	0	0	1	2	3	5	4
28	46003	47	52	3	M	69	115	83	T6-7	T3	11	3	1	0	0	0	0	0	1	3	4	4	4
29	41433	48	53	2	M	66	118	84	T6-7	T4	17	3	1	0	0	0	0	0	1	3	4	4	4
30	60480	30	50	2	M	78	120	76	T6-7	T4	14	3	1	0	0	0	0	0	1	3	4	4	4

1ST Epi Top up time (hrs)	Post operative																					PONV	Hypotension	Bradycardia
	0 min			15 min			30 min			60 min			2 hr			4 hr			8hr					
	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP			
4	78	128	83	76	126	81	75	127	82	73	125	76	74	124	75	77	122	79	76	123	80	NO	NO	NO
6	72	124	78	70	122	77	71	123	78	69	121	72	70	120	71	73	118	74	76	119	75	NO	NO	NO
4	71	117	79	69	115	77	67	116	78	65	114	77	66	113	76	69	111	70	68	110	72	NO	NO	NO
4	78	118	76	76	116	77	77	117	79	75	114	78	76	115	77	79	112	80	78	113	82	NO	NO	NO
6	78	125	75	76	123	78	77	124	79	75	121	80	76	120	79	79	118	81	78	119	83	NO	NO	NO
6	83	125	78	81	123	76	82	125	77	80	120	81	82	119	79	85	117	84	84	115	85	NO	NO	NO
4	90	121	79	88	119	77	89	120	78	87	127	83	88	126	82	90	124	92	88	125	90	NO	NO	NO
4	85	117	83	83	115	82	85	116	83	83	110	82	84	111	81	87	109	89	86	111	87	NO	NO	NO
6	78	126	79	76	123	80	77	124	81	75	120	75	76	118	74	79	116	80	78	117	83	NO	NO	NO
4	74	129	76	74	125	77	75	126	78	73	124	79	74	123	78	77	121	79	76	125	80	NO	NO	NO
4	82	130	83	80	128	81	81	127	83	79	118	84	80	117	83	83	115	81	81	116	83	NO	NO	NO
4	73	110	73	71	112	75	72	113	76	70	113	83	71	112	81	73	111	74	72	112	75	YES	NO	NO
4	79	123	73	77	121	74	78	122	78	76	115	72	77	114	71	79	112	74	78	113	76	NO	NO	NO
4	89	118	84	87	116	82	88	117	89	86	117	84	87	116	86	89	114	86	88	114	84	NO	NO	NO
6	84	132	72	82	130	76	83	132	84	81	110	79	82	109	81	85	107	83	83	115	85	NO	NO	NO
4	83	119	70	81	117	78	82	118	79	80	126	74	81	125	80	84	123	82	84	125	77	NO	NO	NO
6	84	125	78	82	122	80	83	124	81	81	134	73	82	133	81	85	131	83	84	134	84	NO	NO	NO
4	83	130	75	81	130	78	82	132	79	80	122	74	82	121	81	86	119	84	85	124	85	NO	NO	NO
4	82	127	78	80	125	78	81	126	79	79	121	89	80	120	87	83	118	86	81	120	88	NO	NO	NO
4	81	126	85	79	124	82	80	122	83	78	120	84	80	118	83	84	116	87	82	118	83	NO	NO	NO
4	77	112	72	75	110	78	76	112	79	74	112	74	75	111	73	79	110	81	78	113	80	NO	NO	NO
6	73	117	74	71	115	75	72	115	76	70	116	77	71	115	76	74	112	79	72	114	87	NO	NO	NO
4	79	115	73	77	113	78	78	114	79	76	116	83	77	115	81	78	113	82	76	112	84	NO	NO	NO
4	89	119	74	87	117	76	88	118	77	86	121	90	87	118	89	90	116	84	87	117	75	NO	NO	NO
4	73	120	78	71	118	80	72	119	81	70	135	79	71	131	78	75	130	80	74	132	74	NO	NO	NO
4	77	125	90	75	123	79	76	124	80	74	116	72	75	115	71	79	113	81	78	116	73	NO	NO	NO
6	89	121	73	87	119	76	88	120	77	86	130	74	87	128	73	89	126	85	85	126	76	NO	NO	NO
4	92	110	84	90	113	82	91	114	83	89	128	84	90	126	83	89	124	86	87	123	74	NO	NO	NO
4	84	122	74	82	120	76	83	121	77	81	115	76	82	113	77	89	111	86	85	117	79	NO	NO	NO
4	74	116	78	72	114	75	73	115	76	72	124	78	73	123	77	79	121	85	80	126	79	NO	NO	NO