# PROSPECTIVE RANDOMIZED CONTROL TRIAL TO COMPARE CONTINUOUS THORACIC EPIDURAL VS BUPIVACAINE INTERCOSTAL BLOCK PLUS INTRAVENOUS MORPHINE INFUSION FOR POST OPERATIVE ANALGESIA IN PATIENTS UNDERGOING ELECTIVE THORACOTOMY


A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT OF **THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY, CHENNAI**, FOR THE DEGREE OF **M.D.ANAESTHESIOLOGY (BRANCH X)** TO BE HELD IN APRIL 2013

# CERTIFICATE

This is to certify that the dissertation entitled **"A Prospective Randomized control trail to compare Continuous Thoracic epidural with Bupivacine-Intercostal block plus Intravenous morphine infusion For Post operative Analgesia in patients undergoing elective Thoracotomy"** is the bonafide original work of **Dr.V.SANTHOSH** in partial fulfillment of the requirements for the **M.D. Anaesthesiology** (Branch X) degree examination of The Tamil Nadu Dr. M.G.R Medical University, Chennai, to be held in

**April 2013.**

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# INSTITUTIONAL REVIEW BOARD (IRB)
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December 21, 2011

Dr. V. Santhosh
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Sub: **FLUID Research grant project NEW PROPOSAL:**
A randomized control trial to compare continuous thoracic epidural with bupivacine-intercostal block plus intravenous morphine infusion for post operative analgesia in patients undergoing elective thoracotomy.
Dr. V. Santhosh, PG Registrar. Anaesthesia, Dr. Manickam Ponnaiyah, Anaesthesia, Dr. S. Chitra.

Ref: IRB Min. No. 7695 dated 12.12.2011

Dear Dr. Santhosh,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "A randomized control trial to compare continuous thoracic epidural with bupivacine-intercostal block plus intravenous morphine infusion for post operative analgesia in patients undergoing elective thoracotomy" on December 12, 2011.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Information Sheet and Informed Consent Form (English and Tamil)
3. Protocol Sheet
4. Cv of Dr. V. Santhosh.
5. A CD containing documents 1 – 4

# INSTITUTIONAL REVIEW BOARD (IRB)
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The following Institutional Review Board (Ethics Committee) members were present at the meeting held on December 12, 2011 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore- 632002.

| Name | Qualification | Designation | Other Affiliations |
|---|---|---|---|
| Dr. B.J.Prashantham | MA (Counseling), MA (Theology), Dr Min(Clinical) | Chairperson(IRB)& Director, Christian Counselling Centre | Non-CMC |
| Mr. Harikrishnan | BL | Lawyer | Non-CMC |
| Mrs. S. Pattabiraman | BSc, DSSA | Social Worker, Vellore | Non-CMC |
| Mrs. Ellen Ebenezer Benjamin (on behalf of Dr. Jayarani Premkumar) | M.Sc. (Nursing), Ph.D. | Nursing Superintendent, CMC. | |
| Dr. Gagandeep Kang | MD, PhD, FRCPath. | Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Microbiology & Addl. Vice Principal (Research), CMC. | |

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent and requires a copy of the final report.

A sum of ₹ 31500/- (Rupees Thirty one thousand five hundred only) is sanctioned for 1 year.

Yours sincerely,

Dr. Alfred Job Daniel
Principal& Chairperson (Research Committee)
Institutional Review Board

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# ACKNOWLEDGEMENT

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I am grateful to God for his grace and wisdom.

Last, but not least, I thank all my patients for their cooperation, in this study.

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# ABSTRACT


**TITLE**

A Prospective Randomized control trial to compare Continuous Thoracic Epidural vs Bupivacaine-Intercostal block plus Intravenous Morphine Infusion for Post Operative Analgesia in patients undergoing Elective Thoracotomy.

DEPARTMENT : **ANAESTHESIA**

NAME OF THE CANDIDATE : **DR. V.SANTHOSH**

DEGREE AND SUBJECT : **M.D. ANAESTHESIOLOGY**

NAME OF THE GUIDE : **DR. MANICKAM PONNIAH**

**OBJECTIVES**

Our routine clinical practice has been to use single shot intercostal block (performed by surgeon under vision) with bupivacaine plus continuous intravenous morphine infusion for analgesia following thoracotomy. Thoracic epidural analgesia is usually considered THE GOLD STANDARD method for analgesia after thoracotomy. There are very few studies which compare intercostal block with thoracic epidural, which is the ideal method in terms of analgesia and side effects.

**METHOD**

Patients of both genders, >18yrs of age who underwent unilateral thoracotomy for various lung pathologies were included in this study. Randomization was done with Computer generated randomized numbers using Block randomization. It is an open labeled study, since Masking of intervention allocation is not possible.

Primary Outcome measured was Pain intensity at rest and in doing breathing exercises, during the first post operative day using NUMERICAL RATING SCALE.

Secondary Outcomes measured were post operative sedation, frequencies of rescue analgesia, incidence of postoperative side effects like pruritis, nausea or vomiting.

Sample Size: 50

Primary outcome variables and secondary outcome variables were compared between two study groups using the MANN WHITNEY U TEST.

## RESULTS

Group A- Thoracic Epidural group

Group B- Intercostal block with Bupivacaine plus Intravenous Morphine.

All the demographic variables were almost similar in both groups.

The primary outcome variable- Pain scores were measured using the numerical rating scale during the first post operative day at different time points. Mean pain scores were in the range of 2-2.8 in group A and 2.08-3.2 in group B. Pain scores were significantly less in the epidural group at first (P 0.02)and sixth hours (P 0.05) after surgery, though it is was similar at the end of 24 hours for both at rest and while doing breathing exercises. There was no significant difference in number of times of rescue analgesia or time of first rescue analgesia.

Sedation scores were significantly less in group A throughout the first postoperative day ($P<0.005$)

There was no significant difference in the side effect profile in both groups.

The results of the study shows a slightly better quality of analgesia with thoracic epidural infusion of 0.1% bupivacaine + 2μ/cc fentanyl for post operative pain relief after thoracotomy when compared with single shot intercostals blockade with bupivacaine +continuous morphine infusion. The fact that this difference is probably not clinically significant makes us to believe that an intercostal blockade with morphine infusion can be considered as a valid alternative to thoracic epidural. This method of intercostals blockade plus morphine infusion, which is practiced in our institution can be considered an easier, safe and reliable alternative to thoracic epidural and is a less time consuming method for post thoracotomy analgesia.

# INTRODUCTION

Fear of uncontrolled pain is among the primary concerns of many patients who are about to undergo surgery.

Thoracotomy is widely recognized as being one of the most painful surgical procedures. Respiratory complications like atelectasis, pneumonia are the major cause of post operative complications after lung surgery. Studies have shown that there is a steady decline in the respiratory complications last decade for >10% which is chiefly attributable to improved post operative care especially effective post operative pain management(1).

So, aggressive and well planned pain management is crucial in decreasing morbidity and mortality after thoracic surgery.

Despite an increasing array of techniques and new drugs available for post operative analgesia after thoracic surgery, acute pain management after thoracotomy remains a great challenge for the anesthesiologist. No single method is proven to be sufficient for complete pain relief after thoracotomy with minimal side effects(2).Despite the fact that THORACIC EPIDURAL ANALGESIA is the 'gold standard' of post operative care after thoracotomy(3). Various local and regional techniques especially paravertebral blocks are emerging and seem to be a valid alternative to thoracic epidural(4)

Also in the recent 5 years ,a multimodal approach utilizing combined regional and systemic analgesics with different mechanisms of action is found to be promising and beneficial in terms of treating acute pain and preventing chronic pain after thoracotomy(5).

# AIMS AND OBJECTIVES

## AIMS

The aim of this study is to compare the

- Quality of pain relief
- Incidence of side effects

Of THORACIC EPIDURAL ANALGESIA vs INTERCOSTAL BLOCK PLUS INTRAVENOUS MORPHINE in patients undergoing elective thoracotomy.

## OBJECTIVES

Our routine clinical practices has been to use single shot intercostal block (performed under vision by surgeon) with bupivacaine plus continuous intravenous morphine infusion for analgesia following thoracotomy. This method is easier, reliable, less time consuming and perhaps safer than regional techniques used for analgesia after thoracotomy.

Thoracic epidural analgesia is usually considered THE GOLD STANDARD method for analgesia after thoracotomy. Though side effects are rare with this method, some serious complications can also happen.

Though intercostals block with systemic analgesia is said to provide satisfactory analgesia after thoracic surgery, there are very few studies which compare intercostal block with thoracic epidural, which is the ideal method, In terms of analgesia and side effects.

To determine the true analgesic efficacy of intercostal block plus intravenous morphine for pain management after thoracic surgeries, we designed this prospective randomized study to compare the efficacy of continuous epidural analgesia using bupivacaine and fentanyl with routine single shot intercostals block and intravenous morphine, on post operative pain scores and side effect profile.

## HYPOTHESIS

We hypothesized that a single shot intercostal block plus continuous intravenous morphine might be as effective as Thoracic epidural analgesia with respect to post operative pain control and side effects.

# REVIEW OF LITERATURE

## DEFINITIONS

### PAIN

According to **International Association for the Study of Pain**

Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"

### ACUTE PAIN IN THE PERIOPERATIVE SETTING

**"**Pain that is present in a patient who underwent surgery because of preexisting disease, the surgical procedure or a combination of disease related or procedure related sources" [ASA task force on pain management](6)

It is the normal functional and physiologic reaction to tissue damage by surgery.

### CHRONIC PAIN

Pain that recurs or persists (e.g. along a thoracotomy scar) for at least two months following the surgical procedure.

Pain is always "subjective" varying among different individuals and "unpleasant" and therefore also an "emotional discomfort" for the patients.

**PATHOPHYSIOLOGY OF POSTOPERATIVE PAIN**(7)

It is well recognized that the etiology and treatment of pain produced by surgery is different from other clinical pain conditions (8). Pain is a direct response to mechanical tissue damage caused during surgery.

It is considered as a normal response to tissue injury.

Symptoms vary depending upon the type of tissue injured and extent of injury.

**Acute postoperative pain** is a type of NOCICEPTIVE PAIN and usually it decreases as the tissue injury heals. Nociceptive pain can be divided into visceral, deep somatic and superficial somatic pain. Activity in the nociceptive pathways leads to experience of pain which can be stimulated or modified by endogeneous or exogeneous stress. Endogeneos stress include injury or inflammation within tissues and exogeneous stress include psychosocial factors.

Perception of nociceptive pain involves a complex relationship between three different components:

- Afferent nociceptive stimulation
- Transmission, interpretation and modulation of these signals by central nervous system
- An efferent component (9)

A through knowledge about the neurobiology of pain is essential for pain management, since there is enormous difference between the origin and mechanisms of different types of pain and also for effective treatment with different analgesics.

# **NEUROBIOLOGY OF PAIN**(10)(11)

## 1. PERIPHERAL STIMULUS.

NOCICEPTION

"The evoked response to a specific tissue stimulation from either mechanical, thermal or chemical irritation applied to receptors on the nerve endings, that are potentially capable of damaging nerve tissue"

NEUROGENIC INFLAMMATION

Surgery produces tissue injury with continuous release of histamine and inflammatory mediators. The mediators released include Peptides(eg.bradykinins) ,lipids(eg.prostaglandins), neurotransmitters (eg.serotonins) and neurotrophins (eg.nerve growth factor) which in turn activate the nociceptors(12)

## 2. RECEPTOR (TRANSDUCTION)

NOCICEPTOR

"A sensory receptor that sends signals that cause the perception of pain in response to potentially damaging stimulus"

Nociceptors are usually free nerve endings of two types of small nerve fibres.

a. THIN MYELINATED **Aδ** FIBRES

   Diameter of 2-5mm and a conduction velocity of 6-30m/s

   Conducts "FAST PAIN" – sharp, short lasting, pricking type of pain

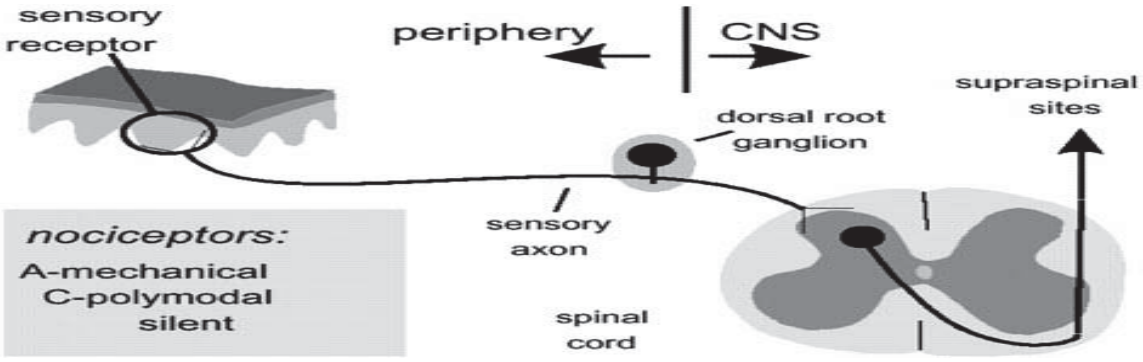
b. UNMYELINATED **C** FIBRES

   Diameter of <2 mm and conduction velocity of less than 2 m/ s.

   Conducts "SLOW PAIN"- dull, poorly localized, burning type of pain

## 3. PERIPHERAL AFFERENT PATHWAYS

The nociceptors in the periphery when activated transmit action potential via afferent nerves to the spinal cord. Primary afferent nociceptors belong to the type of Pseudo- unipolar neurons. Their cell bodies are located in the Dorsal root ganglion. Their central processes project into the Dorsal horn of the spinal cord.




## 4. SPINAL CORD PATHWAYS

The grey matter of the spinal cord is divided into Ten "laminae" by REXED in 1950.

The Laminae that are involved in pain transmission are

Lamina I - marginal nucleus of spinal cord

Lamina II - substantia gelatinosa

Lamina III- nucleus proprius.

Lamina V- neck of dorsal horn.

Laminae VII and VIII - intermedio nucleus of spinal cord.

A δ fibres terminate in laminae I to V

C fibres terminate in lamina II.

Important neurons in this region are :

**Wide dynamic range neurons (WDR)**

Found in Lamina V. These neurons receive impulses from both nociceptive nerve terminals and myenilated A type nerve fibres. These neurons respond to gentle touch, play an important role in pain transmission. They also have the tendency to increase their response if the stimulus increases in intensity.

**Nociceptive specific neurons**

Found in Lamina I. These neurons respond only to noxious stimuli.

The dorsal horn of the spinal cord also contains a wide range of Neurotransmitters like serotonin, Nor epinephrine, substance P, glutamate, glycine and Neuromodulators like opioid peptides like enkephalins, dysnorphins with their respective receptors. These interact in a complex way and play an important role in modulation and transmission of pain.

Mechanism in which Neurotransmission occurs within the dorsal horn of the spinal cord can be summarized as an interaction between:

- Excitatory transmitters released from primary afferent nociceptors
- Excitatory transmission between neurons of the spinal cord
- Inhibitory transmitters released by interneurons within the spinal cord
- Inhibitory transmitters from supra spinal sources

## 5. CENTRAL CONNECTIONS

Following modulation in the dorsal horn, the pain impulses travel along a complex array of spinal cord pathways. Some of the important pathways in which nociceptive information is transmitted include

Spino-thalamic tract

Spino-reticular tract

Spino-mesencephalic tract

These tracts project to a number of nuclei in the thalamus. From the thalamus, the terminal sites of pain appreciation are the Somato sensory cortex (sensoryaspect of pain) and the limbic system(affective component of pain).

The cortex is considered to be the ultimate site of conscious awareness of sensory stimuli.

## 6. DESCENDING INHIBITORY PATHWAYS

Descending modulation of pain sensation originates from three main areas:

Cortex

Thalamus

Brainstem – Peri aqueductal grey matter (PAG)

Fibres pass from Peri aqueductal grey matter to the Reticular formation of the medulla. Axons from there descend via the dorsolateral funiculus of the spinal cord. Finally the neurons

Synapse with the interneurones in the substantia gelatinosa of the spinal cord.

Pain impulses are inhibited by the stimulation of this pathway. Various neuro transmitters like GABA, nor-epinephrine play an important role in the descending inhibition of pain.

**PERIPHERAL AND CENTRAL SENSITIZATION**(13)(14)

Continuous release of inflammatory mediators in the periphery sensitizes functional nociceptors and activates dormant ones. Sensitization of peripheral nociceptors may occur and results in a decreased threshold for activation, increased rate of discharge with activation, and increased rate of basal (spontaneous) discharge.

**Central sensitization** -

"Persistent post injury changes in the CNS that result in pain hypersensitivity"

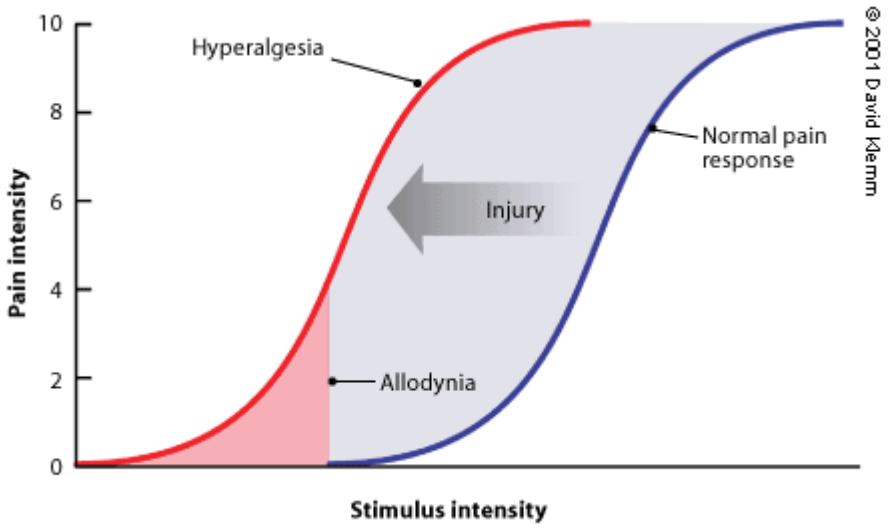
**Hyperexcitability** -

"exaggerated and prolonged responsiveness of neurons to normal afferent input after tissue damage"

This leads to permanent functional changes in the dorsal horn of the spinal cord .

As a result postoperative pain to be perceived as more painful.

**Pain Sensitization**




Despite recent advances and ongoing research our knowledge about the roles of various transmitters and receptors about the neurobiology of pain is still incomplete.

## PHYSIOLOGICAL EFFECTS OF ACUTE POST OPERATIVE PAIN (15)

Acute pain in the postoperative period will cause detrimental effects on the patients recovery following surgery and also lead to increased patients despair and suffering. Optimal perioperative and postoperative analgesia will certainly decrease complications and improve recovery following surgery(15).

Some of the important adverse effects of acute pain in various organ systems are:

### CENTRAL NERVOUS SYSTEM

Continuous transmission of the nociceptive stimulus will lead to activation of the neuroendocrine stress response. Local release of inflammatory mediators (eg-prostaglandins, leukotrienes) unless controlled will sustain this response.

Hypothalamic-pituitary-adrenocortical axis and sympathetic system gets activated and will have adverse effects on the patients outcome. Activation of this system will lead to increase sympathetic tone, decreased secretion of anabolic hormones like insulin and increased catabolic hormone secretion (cortisol ,antidiuretic hormone, glucagon). There will be increased metabolism and as a result oxygen consumption is greatly increased.

A hypermetabolic, catabolic state ensues.

### CARDIVASCULAR SYSTEM

Activation of the sympathetic nervous system will lead to increased myocardial oxygen consumption, coronary vasoconstriction making patients susceptible to myocardial ischemia and infarction. Tachycardia and hypertension will increase cardiac workload.

RESPIRATORY SYSTEM

There will reflex spinal inhibition of phrenic nerve activity which will decrease postoperative pulmonary function especially after thoracic and upper abdominal surgeries(16).

Decreased functional residual capacity, vital capacity, hypoxia, hypercarbia, ventilation perfusion mismatch ensues, which increases post operative morbidty and mortality.

GASTROINTESTINAL SYSTEM

Reflex inhibition of gastrointestinal motility, increased postoperative ileus, and vomiting.

RENAL SYSTEM

Sodium and water retention, oliguria occurs which may have adverse metabolic consequences

COAGULATION SYSTEM

There is increased levels of procogulants, increased platelet activity, decreased fibrinolysis.

The hypercoagulable state which happens may contribute to an increased incidence of deep vein thrombosis, myocardial ischemia and vascular graft failure.

IMMUNOLOGICAL SYSTEM

There is increase cytokine production, acute phase reaction, lymphocyte proliferation, neutrophil leucocytosis due to the stress response. It may also potentiate postoperative immunosupression which lead to poor wound healing and recovery after surgery.

**ACUTE PAIN AS PREDICTOR OF CHRONIC POSTOPERATIVE PAIN**(17)

Experimental and clinical studies suggest that acute pain after surgery can quickly transient into chronic pain which can persist several months after surgery.

Continuous noxious stimuli can lead to the expression of new genes in the dorsal horn of spinalcord within 1 hour, as a result there is alteration in the behavior of pain perception in these areas for a long time(11)

# PAIN MANAGEMENT AFTER THORACIC SURGERY

**RATIONALE**

A posterolateral thoracotomy is one of the most painful surgical incisions(18).

If the acute pain after surgery is not managed appropriately many patients will develop CHRONIC POSTTHORACOTOMY PAIN SYNDROME, incidence of 25-60%(19)(20).

And also it will lead to severe postoperative pulmonary complications, since without adequate analgesia patients will not cooperate for pulmonary physiotherapy and coughing out secretions. As a result atelectasis, pneumonia, respiratory failure can occur. Cardio vascular complications like arrhythmias are also reduced by aggressive acute pain management.

Effective treatment of pain will also help in early mobilization of the patient and shorten length of hospital stay. so the role of well pain management is crucial in reducing morbidity after thoracic surgery.

## PATHOPHYSIOLOGY OF POST THORACOTOMY PAIN

The pathogenesis of post thoracotomy pain transmission and modulation is complex. Nociceptive impulses after thoracic surgery is transmitted by multiple sensory afferents.

These nociceptive receptors are stimulated during surgery by skin incision, spreading of the ribs, division of the intercostals muscles and injury to the intercostals nerves. Sometimes there may be fracture of the ribs, fracture of the costo chondral joints and ligaments.

The parietal pleura which is incised after surgery is continuously irritated by the suture lines, drains and blood from minimal oozing . These lead to prolonged stimulation of the nociceptors which may proliferate at the site of injury(11) and it amplifies the pain transmission .

Peripheral and central sensitization occurs, as a result the perceived pain is much more severe.

## SOURCES OF POST THORACOTOMY PAIN(US SURGERY TOUCH BRIEFINGS 2007)

There are various afferent somatic and visceral sensory nerves which transmit pain impulses to the sensorium after thoracic surgery. The sympathetic system and vagal nerves play an important role in transmitting impulses from the costal and Diaphragmatic pleura.

| SOURCE | AFFERENT SENSORY NERVES |
|---|---|
| | |
| Ribs | Intercostal nerves 4-6 |
| Chest tubes | Intercostal nerves 5-8 |
| Mediastinal pleura | Vagus nerve |
| Diaphragmatic pleura | Phrenic nerve |
| Ipsilateral shoulder pain | Phrenic nerve (21)/brachial plexus |

## PAIN AFTER THORACIC SURGERY – INFLUENCING FACTORS

1. **SEX**(22)

Various studies have shown that there is difference among males and females in perception of pain after surgery. Female patients are generally considered to be more sensitive to nociceptive stimuli than males(23).Menstrual status plays a key role. Reduction in the activation of the endogeneous opoid receptors is seen in low estradiol states. But with advancing age pain perception seems to be similar in both the sexes.

2. **AGE**(24)

Advancing age produces major changes in the perception of pain. Changes in the structure and function of the central and peripheral nervous system affects the signaling and processing of pain. There is also reduction in descending inhibiting modulating systems. Elderly is also more sensitive to the side effects of the various analgesic regimes especially systemic opoids.
Therefore elderly with reduced capacity of pain modulating system in their body are more susceptible to the negative impacts of pain(25)

3. **SURGICAL APPROACH**

There are various surgical approaches utilized for lung surgeries depending on the pathology. These include Sternotomy, Open thoracotomy , Tranverse sternothoracotomy and advanced Video assisted thoracoscopic surgery (VATS) which has the advantage of limited surgical incision and less post operative pain(26).
Open thoracotomy is the most commonly used approach.

The incisions can be Posterolateral incision (classic approach), Anterolateral incision, Muscle sparing incision. Recent evidence shows that in terms of post operative acute pain, no incision has have definite advantage over the other(27),though muscle sparing incisions will reduce the incidence of chronic post thoracotomy pain(28).

### 4. PSYCHOLOGICAL FACTORS

Perception of pain is found to be less among well informed, encouraged and reassured patients(29). Preoperative anxiety and depressed mood is also found to be an important predictor of more severe acute post operative pain(30).

## POSTOPERATIVEANALGESIA AFTER THORACOTOMY

There are various techniques that are currently available for providing analgesia after thoracotomy. Each method has its own merits and demerits. It is a matter of ongoing debate and research about finding out the single ideal technique for managing pain after thoracotomy.

Effective pain control cannot be achieved with a single method as many factors had to be taken into considerations for each individual patient. Analgesic technique should be determined by taking into account

Nature and severity of the disease

Patients - health, preferences, co-morbid illness , contraindications

Type of surgery and incision

Post operative care and monitoring

**Can be broadly divided into analgesia using systemic drugs and analgesia using Regional techniques.**

## SYSTEMIC ANALGESIA

It is method of pain relief which is achieved by administering Analgesic drugs either Intravenously (i.v), intramuscularly (i.m) or subcutaneously (s.c) route and drugs crosses the blood brain barrier to produce central analgesic effects.

Drugs that are commonly used for systemic analgesia after thoracotomy are:

- Opioids – long acting and short acting
- Ketamine
- Paracetamol
- Nonsteroidal Anti inflammatory drugs(NSAIDS)
- Gabapentin.

These drugs with expection of paracetamol and gabapentins can be delivered by intravenous, intramuscular or subcutaneous routes.

With the routine use of PCA(patient controlled analgesia) these drugs can be delivered safely and effectively. These drugs can be used in combinations and is a simpler, economical and probably safer method which is practiced in various institutions.

### OPIOIDS

For many years systemic opioids form the mainstay of treatment of pain after thoracotomy.

Opioids which include Morphine, Fentanyl, Tramadol, Pethidine, buprenorphine are widely used(31)(32).

Opioids suppress pain by their action in the brain, spinal cord and peripheral nervous system. Since 1990s with greater understanding of the molecular pharmacology and isolation of DNA encoding opoid receptors, these drugs now widely used for specific targets and with less side effect profile.

**OPIOD RECEPTORS**

In 1973, based on radioligand binding assays, three types of opoid receptors were postulated, μ-, δ-, and κ-opioid receptors. The three opoid receptor genes DOR, MOR, KOR which encode for μ-, δ-, and κ-opioid receptors were isolated in 1992. Since then various subtypes of the opioid receptors such as μ1,μ2,μ3,δ1,δ2,κ1,κ2,κ3 have been identified. These receptors are found in various regions of the central and peripheral nervous system , spinal cord projections and interneurones, midbrain, cortex and predominantly mediate pain inhibition(33).

The receptors at peripheral, spinal and supra-spinal sites mediate opioid induced analgesic effects. Systemically administered opioids act on the peripheral opioid receptors (34)

**MECHANISM OF ACTION OF OPIOIDS**

The opioid receptors belong to G protein coupled receptor family.

The primary mechanism of action is inhibition of high voltage calcium channels through Gi activation in the primary sensory afferent neurons. opioids also suppress the sodium currents in the sensory nerve endings which result in inhibition of release of pro inflammatory mediators like substance P, calcitonin(35).

There is increase in the number of peripheral opioid receptors in response to tissue injury, Inflammation or damage. In the dorsal root ganglion also there is upregulation of opioid receptors. As a result of breakade of perineural barrier, opioid agonists diffuse to the receptor

sites. Endogeneous opioid peptides like endorphins, enkephalins and dynorphins are released which act synergistically to improve analgesia(36)

**PHARMACOKINETICS OF MORPHINE**(37)

Opioids in general are weak bases.

With a pKa of 8.0 only a small fraction of the drug is unionized at physiological pH. It also has low lipid solubility compared to other opioids. Nearly 20-40% of drug is protein bound in plasma mostly albumin. Principal metabolism is by conjugation in the liver and metabolites are excreted via the kidneys. The metabolites are Morphine-3-glucuronide (90%) and Morphine-6-glucuronide(10%). Since the Hepatic extraction ratio of morphine is very high, bioavailability of morphine when administered orally is very low when compared to intramuscular/subcutaneous routes.

**LIMITATIONS OF SYSTEMIC OPIOIDS**

- Nausea and vomiting (38)

By acting on the δ receptors in the chemo receptor trigger zone in the medulla almost all opiods induce nausea and vomiting. Anti emetic prophylaxis is essential whenever opioids are employed for analgesia.

- Sedation

Most common side effect of systemic opioids. Mechanisms not clearly elicited. Opioid drugs interfere with sleep wake cycle and prolong REM sleep . Monitoring sedation is very important as it is a definite indicator of impending respiratory depression(39)

- Respiratory depression

Most Serious side effect of opioid use. These drugs directly act on the brainstem respiratory centres and decrease the hypoxic ventilatory drive and reduce the stimulatory effect of CO2 on ventilation(40)

- Histamine release – can cause vasodilatation and hypotension
- Bladder dysfunction – inhibit voiding reflex
- Constipation
- Opioid induced hyperalgesia
- Tolerance and physical dependence
- Opioid induced hormonal and immunologic effects.
- Alteration in psychomotor performance

**PATIENT CONTROLLED ANALGESIA(PCA) WITH OPIOIDS**

PCA is now the most popular method for management of postoperative pain with opioids.

With this method treatment options are individualized and also patients play a active role in pain management.

It also have definite advantage of better side effects profile, decreased complications when compared to other methods of administration(41).

Costs, patient education are the definite disadvantages.

Continuous intravenous infusion of opioids is also still popular as it can be used in sedated, mechanically ventilated patients.

It is also effective in controlling breakthrough pain.

**USE OF OPIOIDS IN THORACIC SURGERY**(42)

Systemic opioids cannot be used as a sole treatment option for pain management after thoracic surgery. Though they are effective in controlling background pain, doses required to control acute pain during movement or exercises is associated with sedation and respiratory depression(31).

Although still, opioids play a major role in multimodal analgesic regime after thoracotomy.

Analgesia with opioids is recommended in situations where regional anaesthesia is contraindicated or when failure occurs(43)

## NONSTEROIDAL ANTI INFLAMMTORY DRUGS

For more than 30 yrs NSAIDS have been used as an adjuvant in the manangement of post thoracotomy pain. Prostaglandins, prostacyclins, thromboxanes play an important role in the perception of pain and mediate inflammatory process after tissue injury.

NSAIDS by inhibiting the enzyme cyclo-oxygenase block the synthesis of these inflammatory mediators.Thus these drugs have both peripheral and central analgesic action.

NSAIDS such as diclofenac, ibuprofen, ketorolac, lysine acetyl salicylate, naproxen, Piroxicam have been widely used in pain management after thoracic surgery.

These drugs are mainly used as adjuvants along with systemic opioids.

It is found to reduce opioid consumption by >30%(44) and particularly effective in reducing ipsilateral shoulder pain.

Major adverse effects limiting its use in the postoperative period are

Gastrointestinal bleeding

Increased risk of myocardial infarction and stroke,

Renal impairment (salt and fluid retention) particularly in elderly and hypovolemic patients.

Hyperkalemia

Drug interactions

There can be Systemic bleeding associated with platelet dysfunction irrespective of the route of administration(45)

## KETAMINE

Ketamine is a non competitive antagonist at the phencyclidine site of the NMDA receptor.
It has several unique properties and clinical uses. It produces dissociative anaesthesia, hypnosis and profound analgesia.

It has been successfully used as an adjuvant in treatment of acute pain in thoracic surgery(46) and also particularly useful in patients who are refractory to other modes of therapy.
It is shown that Very low dose ketamine infusion(0.05mg/kg/hr) as an adjuvant to morphine reduced opioid consumption and delayed the development of opioid tolerance(47).

Laboratory data show that *N*-methyl-D-aspartate (NMDA) receptor activation play an important role in postinjury central sensitisation and hyperalgesia (48).

## PARACETAMOL

Forms a integral part of balanced multimodal analgesia after thoracotomy(49)(50).

It is one of the safest analgesic agents. It produces its analgesic and anti inflammatory effects by inhibiting prostaglandin synthesis and via the serotonergic system.

Paracetamol at analgesic doses have fewer side effects and contraindications. So it can be safely used in patients with renal dysfunction and whom NSAIDS are contraindicated.

Recent metaanalysis have shown that addition of paracetamol to IV PCA morphine reduced morphine consumption by 20% following major surgery(51).

It is also very effective in treating ipsilateral shoulder pain following thoracotomy.

### GABAPENTIN (NEURONTIN)

Gabapentin[1( aminomethyl )cyclohexane acetic acid] is an anticonvulsant drug which is successfully used in the treatment of neuropathic pain.

It is also a sedative and anxiolytic.

It acts by distruption of calcium ion channels in the dorsal horn of the spinalcord thus prevents the development of neuropathic pain(52).

A recent study by sihoe et al (53) have shown that use of gabapentin along with morphine reduced post operative pain scores by 50% following thoracotomy.

The main side effects are dizziness, somnolence and diarrhea.

There are no major randomized trails that had proved the role of gabapentin following following thoracic surgery , although it has a definite benefit of preventing chronic post surgical pain(54).

Other drugs that are less commonly used in post thoracotomy analgesia are

**Specific COX-1 and COX-2 inhibitors**

Though the side effects are less than that of NSAIDS, safety of using these drugs in the perioperative period remains controversial, as it is said to increase the risk of cardiovascular events.

**Glucocorticoids**

Has various actions including analgesic, antipyretic, anti inflammatory, anti emetic effects. Can be used as a part of multimodal analgesic. Produces longer acting pain relief associated with dynamic movements.

**NON PHARMACOLOGIC TECHNIQUES**

**TRANS CUTANEOUS ELECTRIVE NERVE STIMULATION(TENS)**

Based on the GATE theory of pain, this technique of analgesia was developed. Earlier a meta-analysis published in 1996 questioned the effectiveness of TENS for analgesia(55).**Current evidence** shows that when TENS is used along with systemic analgesia it is found to be safe and effective in alleviating postoperative pain and in improving patient recovery after thoracic surgery(56).

**CRYOANALGESIA**

Analgesia utilizing a cryo probe(-60$^{o}$C) on the intercostal nerves at the end of surgery is said to provide effective analgesia for long duration up to 6 months after thoracic surgery. It is a technique with conflicting evidence. It is proven that cryoanalgesia increases the incidence of development of CHRONIC POST THORACOTOMY PAIN(57). Recent literature does not recommend the use of cryo analgesia for post thoracotomy pain relief.

# REGIONAL ANALGESIA

Thoracotomy is a major surgical procedure and is associated with exaggerated adrenergic stimulation resulting in various hormonal stress response and systemic inflammation.

So regional anaesthesia play a valuable role in preventing this stress response. This has been extensively studied and proven that without regional technique, analgesia is never complete and regional analgesia has definite advantage over systemic analgesia in reducing morbidity and mortality after major surgery(58)(2)

Common regional analgesic methods that are used for post thoracotomy pain management are:

- Intercostal blocks
- Paravertebral analgesia
- Interpleural blocks
- Thoracic epidural analgesia
- Intra thecal analgesia
- Continuous wound infiltration catheters

**ANATOMY OF REGIONAL ANALGESIA FOR THORACOTOMY**

As mentioned earlier afferent nociceptive pathway following lung surgery occur predominantly through the anterior and posterior rami of the intercostals nerves.

Anterior primary rami — Incisional pain, chest wall and most of the parietal pleura

Posterior primary rami — Retraction pain from posterior spinal muscles and costovertebral Ligaments

Sympathetic nerves — Visceral nocioception from visceral pleura and lungs

So the technique of block determines which nerves are anaesthesized.

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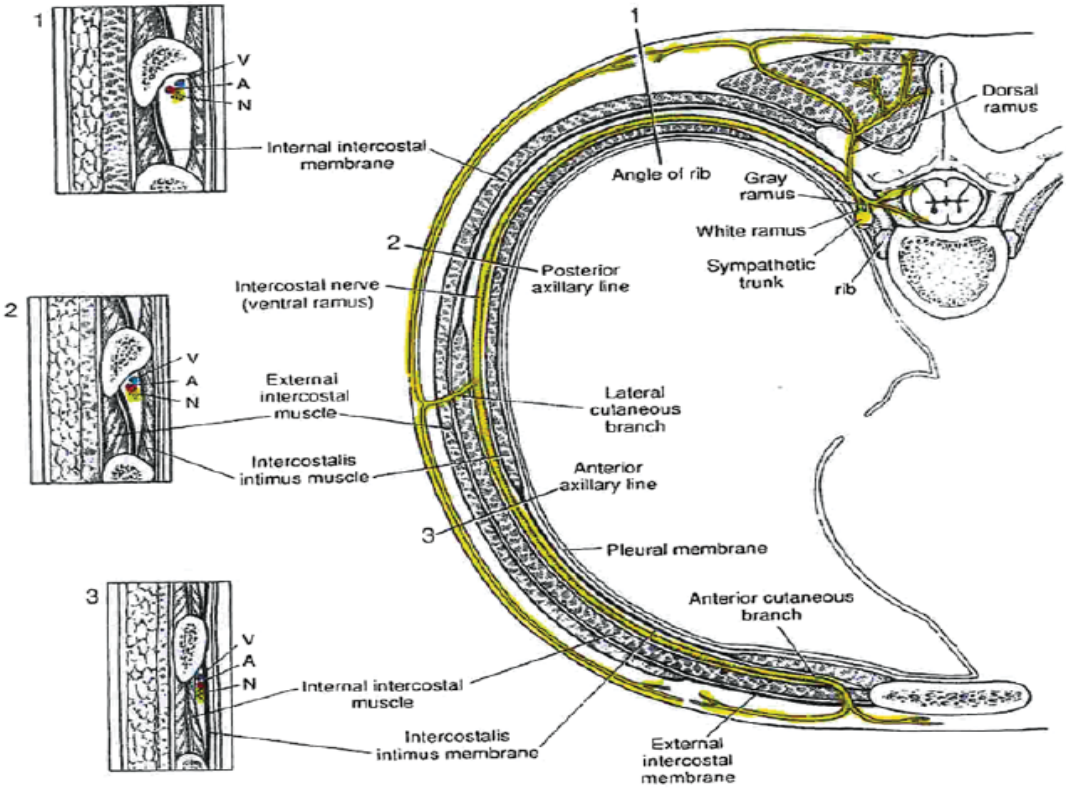



**Anatomy of Intercostal Nerve**

## EFFECT OF DIFFERENT REGIONAL TECHNIQUES ON AFFERENT NOCICEPTIVE PATHWAYS

| Technique | Anterior rami | Posterior rami | Sympathetic N |
|---|---|---|---|
| Intercostal block | Ipsilateral | Not blocked | Not blocked |
| Thoracic epidural analgesia | Bilateral | Bilateral | Bilateral |
| Paravertebral block | Ipsilateral | Ipsilateral | Ipsilateral |

## INTERCOSTAL BLOCK

Blocking of the intercostal nerves at the end of surgery, under vision by the surgeon is one of the safest, reliable methods of analgesia and is practiced worldwide for many years(59).

The block is administered at the lower border of the rib in the region of intercostal bundle along 4-5 spaces. Various techniques for intercostal blockade are Single shot of local anaesthetic before chest closure, as a single percutaneous injection, as multiple percutaneous injections or via an indwelling intercostal catheter.

The site of injection is important for the spread of local anaesthetic solutions and it depends on the angle of the ribs and attachment of the intercostals membranes. Single shot injection of a long acting local anaesthetic like bupivacaine can provide sufficient analgesia for more than six hours(60).To achieve longer durations of analgesia a continuous intercostal catheter is found to be more effective(61).One limitation of continuous infusion method is that Systemic uptake of local anaesthetic solution in the highly vascular intercostal space is very high, so caution with dosage is needed. Though Some studies have shown that even after continuous infusion for more than 5 days, the plasma levels of local anaesthetic is below the toxic levels(62).

Administration of intercostal block have generally provided better pain relief after surgery. There is a reduction in narcotic use(63) and Pulmonary function post surgery is also better preserved(64)(60).

## PARAVERTEBRAL ANALGESIA (PVA)

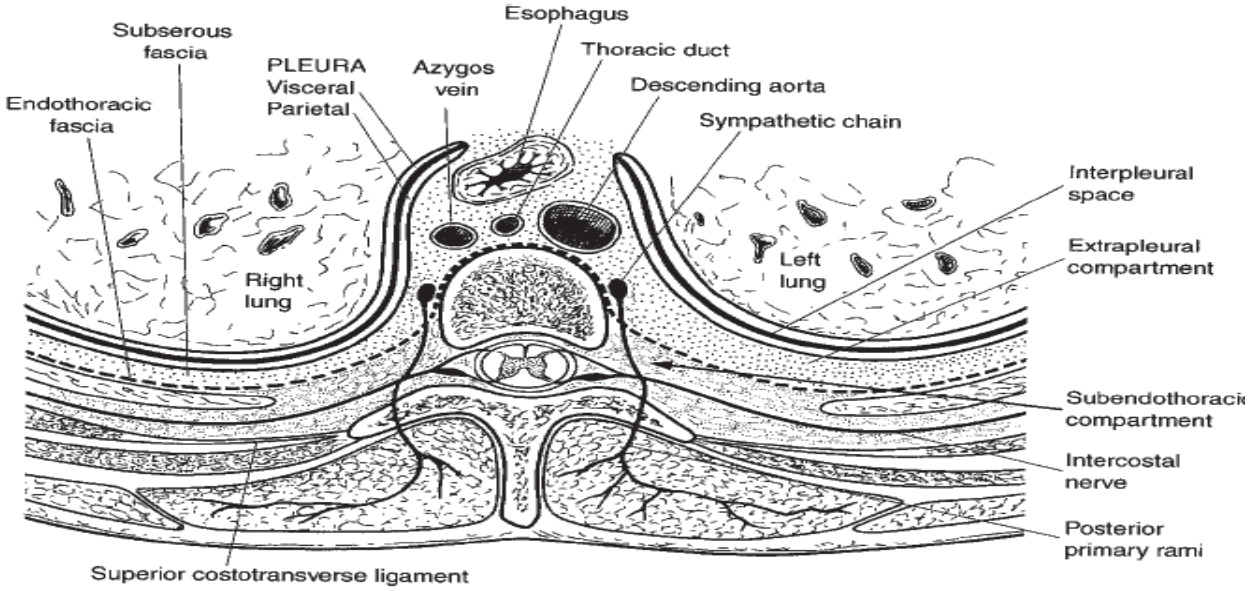
The mechanism of Continuous paravertebral blockade is similar to that of continuous intercostals blockade in which a catheter is placed in the paravertebral space either percutaneously or under direct vision by the surgeon.

In the recent years, PVA have gained popularity and numerous data have established the beneficial effects and safety of PVA(65)

**ADVANTAGES OF PARAVERTEBRAL BLOCK**(66)

- Simpler and technically easier to perform.
- Unilateral blockade – maintains hemodynamic stability
- Better preservation of pulmonary function
- Preserves lower limb motor power
- Promotes early mobilization
- Less incidence of nausea
- Less urinary retention
- Lower failure rate
- Lower serious neurological complications
- Can be used in coagulopathic patients

**Anatomy of paravertebral space**




**LIMITATIONS OF PARAVERTEBRAL BLOCK (60)**

According to the published data the complication rate of paravertebral block is very low. Some rare complications are

- Inadvertent pleural puncture
- Inadvertent dural puncture
- Pulmonary hemorrhage
- Systemic local anaesthetic toxicity – as large volumes are required to fill the highly vascular space
- Neurological sequelae

# THORACIC EPIDURAL ANALGESIA(TEA)

Thoracic epidural analgesia(TEA) is considered the GOLD STANDARD method of analgesia after thoracic surgery(67) and still the widely practiced method of providing analgesia after thoracic and major abdominal surgery(2).

The practice of using thoracic epidural for thoracotomies started in the early 1970's for high risk procedures (68) and incorporated into routine clinical practice in the 80's(69).

The advantages of TEA in providing effective and reliable postoperative analgesia and reduced post thoracotomy pulmonary complications (70) led to the widespread use of TEA

**TECHNIQUE OF THORACIC EPIDURAL ANALGESIA**

Because of the extreme caudad angulation of the thoracic spinous processes, a conventional midline approach to the thoracic epidural space (above T11) can be difficult.

A paramedian approach is required to place the needle.

The thoracic epidural space is identified by two methods LOSS OF RESISTANCE TO SALINE/AIR and HANGING DROP METHOD. Use of saline is associated with a reduced dural puncture rate. 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.

It is recommend that placement of thoracic epidural catheters to be performed only in conscious patients. Two thirds of patients with neurological deficits after epidural had either paresthesia or pain during injection. Though it will not eliminate the risk of cord injuries, it will help to identify them earlier.

## DRUGS USED FOR THORCIC EPIDURAL ANALGESIA

Choice of the drug to be used in thoracic epidural plays a crucial role in reducing the incidence of side effects and providing effective segmental analgesia.

The primary choice of analgesis agents to be infused for TEA are local anaesthetics alone, opioids alone or the combination of local anesthetics and opioids.

When local anaesthetics are used alone, large doses are required to achieve adequate blockade and the incidence of hypotension is also very high(71).

The highly lipid soluble opioids like fentanyl, sufentanyl have faster onset of action ,narrow dorsal spread and less incidence of nausea and pruritis whereas with highly water soluble agents like morphine there is slow onset of action and incidence of nausea and vomiting.

Recently various studies have shown that there exist a SYNERGY between local anaesthetics and opioids when used in thoracic epidural(72)(73)

RECOMMENDED SOLUTIONS FOR THORACIC EPIDURAL ANLGESIA

Bupivacaine 0.1%+ hydromorphone 5-10µ/cc or fentanyl 2-5µ/cc

Bupivacaine 0.05%+ hydromorphone 5-10µ/cc or fentanyl 2-5µ/cc

Bupivacaine 0.05%+ hydromorphone 20µ/cc or fentanyl 2-5µ/cc

- **The optimal combination with effective analgesia and least side effects is found to be 5µ/cc fentanyl and 0.1% bupivacaine**(74)**.**
- **Studies have shown no substantial long-term benefits to intraoperative epidural catheter activation.**

## BENEFITS OF THORACIC EPIDUAL ANALGESIA IN LUNG SURGERY

- **IMPROVED PAIN RELIEF**

  Thoracic epidural analgesia provides superior postoperative analgesia and is the gold Standard method of pain relief after thoracic surgery.

- **IMPROVED POSTOPERATIVE PULMONARY FUNCTION**(75)

  Prolonged diaphragmatic dysfunction is common after thoracic surgery. If not adequately treated, will lead to atelectasis, intrapulmonary shunting, hypoxemia, retention of secretions, pneumonia and increase pulmonary morbidity and mortality. Diaphragmatic dysfunction occurs secondary to the reflex inhibition of phrenic nerve due to continuous afferent visceral stimulation(76). Diaphragmatic contractility is not impaired.

With TEA it is proven that there is reversal of this diaphragmatic dysfunction.

As a result of this there is,

Increase in functional residual capacity

Improvement of ventilator parameters (77)(78)

With better analgesia, patients are able to cooperate better with physiotherapy which helps in clearing out mucus, and adequate expansion of the lung.

There is also less nausea and vomiting.

There is definite evidence that incidence of pulmonary complications are less with TEA after lung surgery(75) in high risk patients with a FEV1<60%.

- **REDUCED CARDIOVASCULAR COMPLICATIONS**

TEA is shown to improve perioperative cardiovascular morbidity and moratlity(79).

The effects are exerted through reduced pain, reduced stress response and reduction of sympathetic activity. It also dilates the coronary arteries and improve the myocardial demand supply ratio. So there is reduced incidence myocardial ischemia and infarction(79) .

ARRYTHMIAS AFTER THORACIC SURGERY

There is high incidence (20%-30%) of supraventricular arrhythmias atrial fibrillation(65%-85%), atrial flutter, supraventricular tachycardias following thoracic surgery because of right heart strain and sympathetic stimulation(80).Surgical dissection around the pericardium and hilum can damage to the cardiac plexus. Arrhythmias appear within 3 days of surgery with a peak in the second post operative day. Most of the arrhythmias spontaneously resolve.

TEA is shown to be beneficial in reducing the incidence of arrhythmias and improve cardiovascular outcome(81)

- **Reduced thromboembolic events**

By reducing the stress response associated with pain, TEA improves the fibrinolytic function and also attenuates the hypercoagulable state post surgery.

Early mobilization of the patient with adequate pain relief also plays a role.

Others benefits include

- **Reduced intra operative blood loss**
- **Improvement in gastrointestinal function and reduction in post operative ileus.**

- **Decreased post operative protein catabolism**
- **Decreased duration of mechanical ventilation**
- **Reduction in mortality in patients with multiple rib fractures.**

## LIMITATIONS AND ADVERSE EFFECTS OF THORACIC EPIDURAL ANALGESIA IN LUNG SURGERY

- **EPIDURAL FAILURE**

  Insertion of a thoracic epidural catheter is a technically difficult procedure. Depending on the expertise the failure rate can be as high as 15%(65).

- **Epidural hematoma**

  Most serious complication after epidurals with an incidence of 0.02%. Though the overall incidence of central neuraxial block is low 0.007%(82).

- **Hypotension**

  Commonly occur after thoracic epidural because of the blockade of the cardiac sympathetic fibres and also due to decrease in both preload and afterload. Should be treated with vasopressors, since there is limited response to increase in preload or afterload(83).

- **Urinary retention**

  Occurs due to addition of epidural opioids.

- **Delayed gastric emptying**
- **Respiratory depression**
- **Nausea and pruritis.**

## THORACIC EPIDURAL ANALGESIA VS PARAVERTEBRAL ANALGESIA

Over the past decade, there has been much debate about which is the ideal regional technique for post thoracotomy analgesia(84). Numerous studies are being published comparing these two techniques in terms of quality of analgesia and side effects(85)(4)and shown that PVA is as effective as TEA in terms of analgesia and has less side effect profile.

But there are also certain publications which shows less effective pain control with higher opioid requirements with PVA than TEA(86) and the improvement in pulmonary function is better with TEA(87).

Systemic reviews comparing the two methods have shown that neither technique is superior over the other(65)(88).

So it is concluded more randomized controlled trails are required to recommend a definite regional technique for analgesia following thoracotomy(2)

Cochrane Database of Systematic Reviews 2011, Issue 5. Art. No.: CD009121 have submitted a protocol for comparing the two techniques of thoracic epidural vs paravertebral analgesia.

## THORACIC EPIDUAL ANALGESIA VS IV SYSTEMIC ANALGESIA WITH OPOIDS FOR THORACOTOMY

There is definite evidence that continuous TEA is superior to systemic analgesia with opioids for pain relief after major surgeries(abdominal, thoracic)(89)(90) .

With regard to thoracic surgeries also, a meta analysis(91) showed that TEA provided better analgesia and play an important role in reducing postoperative pulmonary complications than systemic analgesia.

Development of long term post thoracotomy pain is also significantly reduced with TEA than IVPCA(92)

## EFFICACY AND OUTCOME WITH THORACIC EPIDURAL ANALGESIA IN THORACIC SURGERY.

Over the past past few decades the morbidity and mortality especially pulmonary complications associated with thoracic surgery is significantly lowered with better post operative analgesia. Thoracic epidural plays an important and definite role in acute pain management after lung surgery. There is strong evidence that TEA produces improvements in key components of outcome in lung surgery like reduced pulmonary complications(75), reduced myocardial ischemia and infarction(79) , reduced length of hospital stay and improved perioperative quality of life(93).

With regard to long term outcomes with TEA, there is no thoracotomy specific Evidence is available. Only transferable evidence which shows there is no benefits of TEA in this aspect(94) .

## LESS COMMONLY USED REGIONAL TECHNIQUES

- **INTRATHECAL OPOIDS** (95)

Admistration of opioids like Morphine, fentanyl, sufentanil in the subarachnoid space for post operative analgesia is less popular method. Mainly used as an adjuvant and alternative to epidural analgesia (96). Major side effects are high incidence of pruritis, nausea and urinary retention. Delayed respiratory depression can also occur.

- **LUMBAR EPIDURAL ANALGESIA**

Though it is easier to perform this technique is not recommended for pain management after thoracic surgery. Since large volumes of local anaesthetics are required to block the desired segment, incidence of side effects like hypotension and pruritis is very high. Now a days it is used only in patients whom multiple attempts of thoracic epidural placement is unsuccessful and in rare instances, where it is appropriate to place a lumbar epidural in an anaesthetised patient.

- **CONTINUOUS WOUND INFILTRATION CATHETERS**

In this method, local anaesthetic is delivered directly into the wound via catheters placed before the closure of skin. This method is shown to reduce postoperative opioid use (97).

It is mainly advocated in situations where local anesthetic infusions with other methods are contraindicated.

- **INTER PLEURAL BLOCKS**

In this method, local anaesthetic is deposited between the parietal and visceral pleura. Administration of local anaesthetic through the basal chest drain is also tried in order to reduce diaphragmatic irritation. The efficacy of these methods is not reliable as there is dilution of drugs can occur by intrapleural blood and air. Moreover chances of systemic toxicity is also very high. Recent literature says for post operative pain management after thoracic surgery, interpleural blocks are not recommended(67)

## IPSILATERAL SHOULDER PAIN AFTER THORACOTOMY

Deep aching shoulder pain is one of the most common problem after thoracic surgery with an incidence of 21%-97%(98). It is mainly seen in patients who received regional technique for post thoracotomy analgesia. The pain is described as intense and may cause severe distress to the patient. Pain is generally described in the deltoid area, posterior aspect of the shoulder and in lateral third of the clavicle. In the first post operative day especially in the first 6 hrs, pain is described very severe. It gradually reduces in intensity and does not persist beyond three days after surgery.

Pain is usually present at rest and independent of movements.

## MECHANISM

Exact clear mechanism for this is still not elucidated. Various theories has been proposed.

Some theories say there is a relationship between shoulder pain and transaction of a major bronchus during surgery. It is also related is positioning of the patient during surgery, due to stretching of the posterior ligaments and brachial plexus.

Irritation of the diaphragm by the pleural drain is also said to contribute.

Recent evidence suggests that PHRENIC NERVE may be involved in the etiology of shoulder pain. The most likely explanation is the irritation of the pleural surfaces of the mediastinum, diaphragm and pericardium and pain is transmitted to shoulder through the phrenic nerve.

It is a REFERRED PAIN rather than pain from actual damage to the shoulder.

## TREATMENT

Various treatment modalities like suprascapular nerve block, brachial plexus block, local anaesthetic infusion, stellate ganglion block had been tried but with little success.

Local infiltration of the peri phrenic pad of fat intra operatively is found to be highly effective in alleviating shoulder and is the treatment of choice(99).

Systemic analgesics like paracetamol, NSAIDS are also effective.

Systemic opioids does not have a role in the treatment of shoulder pain.

## CHRONIC POST THORACOTOMY PAIN

Also called as POST THORACOTOMY PAIN SYNDROME (PTPS).

DEFINITION

“Pain that recurs or persists along a thoracotomy scar at least two months after the surgical procedure”

Along with chronic pain after limb amputation, pain after thoracic surgery is one of the most recognized and prevalent pain syndromes.

INCIDENCE

Incidence is very high (44%-60%) and 30% patients have reported persistent pain even 4-5 yrs after thoracic surgery(100).

The intensity of the pain varies among patients, majority of them describing it as mild pain. 4%-16% of the patients have described pain to be moderate to severe. Sleep disturbances are also seen. The impact of chronic pain in daily quality of life is not very unclear, but serious disabilities have also been reported.

MECHANISM

Chronic pain is not just a prolongation of acute pain.

The exact mechanism for the development of chronic pain is still unclear and is a subject of extensive ongoing research. Neurotransmitter GLUTAMATE is said to play an important role in the development of chronic pain. In chronic pain, there is a continuous release of glutamate which causes major changes in the NMDA receptors in the dorsal horn of the spinal cord. This

results in release of neuro modulators like endorphins, substance P which change the perception of pain and transition from acute to chronic pain.

It is described to be a combination of NEUROPTHIC PAIN and MYOFASCIAL PAIN. Injury to the intercostals nerves and damage to the ribs during surgery is said to play a role.

CHRONIC PAIN ATER THORACIC SURGERY – INFLUENCING FACTORS

PREOPERATIVE FACTORS

Young age, Female sex, chronic opioid use, preoperative pain are said to be independent predictors of development of chronic pain.

Genetic factors and psychosocial factors like anxiety, depression also increases the risk.

INTRAOPERTIVE FACTORS

SURGICAL FACTORS

Technique of the surgical procedure (open thoracotomy/ video assisted thoracic surgery) is an important factor in development of chronic pain.

Though video assisted thoracic surgery utilizes small incisions, trocars for surgery, studies have shown there is no definite advantage over open thoracotomy in incidence of PTPS.

Intercostals nerve irritation and damage while placing trocars, sutures should be avoided.

TIMING OF ANALGESIA

The role of timing and technique of intraoperative analgesia is still unclear. The incidence of PTPS with thoracic epidural analgesia is also very high.

## POST OPERATIVE FACTORS

### ACUTE POSTOPERATIVE PAIN

Transferrable evidence from other procedures have shown that acute pain in the immediate post operative pain is an important predictor of chronic pain(101).

It is proven that if the pain recur after surgery or increases in intensity, it is important to rule out malignancy or relapse of the tumour.

The development of chronic pain after thoracotomy continues to be a major source of morbidity. Despite its prevalence, the understanding of PTPS and the potential means of risk reduction are somewhat deficient. A multimodal analgesic regimen using regional blockade, NSAIDs, and other peripheral and centrally acting analgesics including α2agonists, ketamine, and opioids administered throughout the perioperative period may be the most efficacious strategy in reducing both acute and chronic pain after thoracic surgery.

# PREMPTIVE ANALGESIA IN THORACIC SURGERY

DEFINITION

"Anti- nociceptive treatment that prevents the establishment of altered central processing of afferent input, which amplifies acute post operative pain". By decreasing the altered central processing, preemptive analgesia is thought to decrease the consequent development of hyperalsegia and allodynia after surgery(102).

AIM OF PREMPTIVE ANALGESIA

Though general anaesthesia and systemic opioids administered for analgesia during surgery decreases the noxious impulse transmission from the site of injury to the brain and spinal injury it does not completely block it. Various studies have shown that "**central and peripheral sensitization**" occurs due to this continuous noxious noxious stimulation. As a result of this post operative Hyper sensitivity occurs, "**spinal wind up**" ,which is the reason for development of primary and secondary Hyperalgesia at the site of injury(103).

So Pre emptive analgesia aims at preventing the development of this neuronal sensitization and decreases acute post operative pain and development of chronic pain.

METHODS OF PRE EMPTIVE ANALGESIA

Pre emptive analgesia involves various stratagies for blocking the transmission of pain impulses at various sites along the pain pathways. It involves local infiltration with local anaesthetics before skin incision, peripheral nerve blocks, epidural analgesia. Various drugs like NMDAantagonists, Gabapentin , systemic opioids , dexamethasone , tramadol , celecoxib is also said to play a role.

## EFFICACY OF PRE EMPTIVE ANALGESIA

The concept of pre emptive analgesia is itself have evolved from favourable results from various experiments in animal models. So the effect in clinical scenario is still controversial. Conflictive results had been obtained from various clinical studies (104). But it is generally accepted that pre emptive analgesia is a VALID PHENOMENON (102).

This has led to the development of concept of "PREVENTIVE ANALGESIA" which incorporates the treatment of all the factors involved in the preoperative, intraoperative and the post operative periods(105). So it aims to attenuate the occurrence of sensitization during the entire perioperative period, not only preventing the noxious stimulus during skin incision.

## EVIDENCE IN THORACIC SURGERY

Many studies have reported the benefits of drugs especially NMDA ANTAGONISTS(106), GABAPENTIN(52), CELECOXIB in reducing post operative pain when used as pre emptive analgesia . A meta analysis showed no evidence of benefits with drugs like NSAIDS , KETAMINE, SYSTEMIC ANALGESIA when used for pre emptive analgesia(107).

Recent evidence, meta analysis, shows that pre emptive analgesia with thoracic epidural has definite role in the reduction of acute pain after thoracic surgery but no role in prevention of development of chronic post thoracotomy pain(108).

## MULTIMODAL ANALGESIC APPROACH IN THORACIC SURGERY

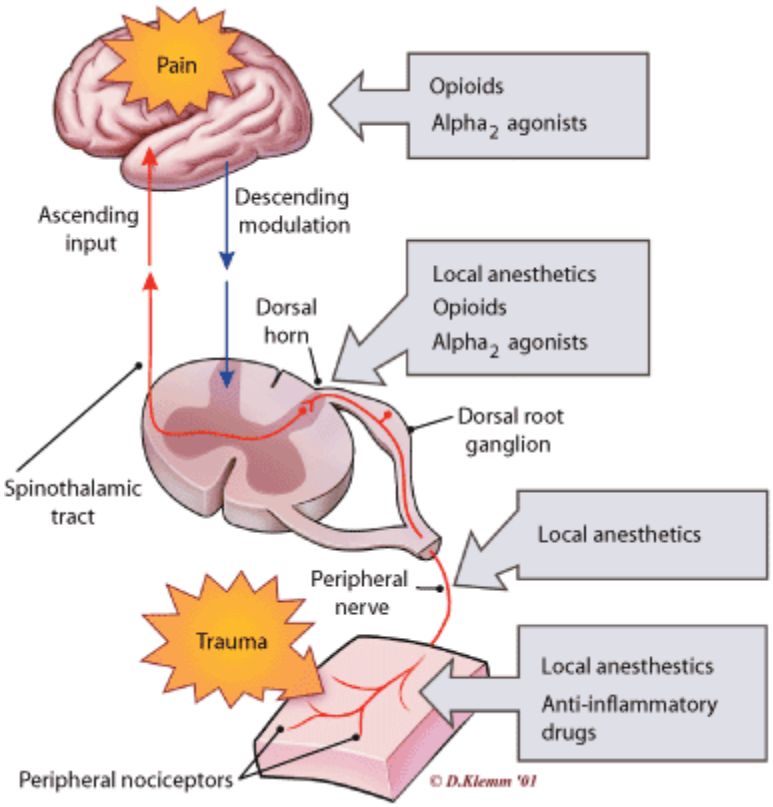
To maximize the beneficial effects of controlling post operative pain a multi modal strategy should be implemented for patient care in the post operative period(109).

Principles of a multimodal strategy include control of postoperative pain to allow early mobilization, early physiotherapy, education, and attenuation of the perioperative stress response through the use of regional anesthetic techniques and a combination of analgesic agents (i.e., multimodal analgesia). A multimodal approach involves the use of more than one analgesic compound or modality of pain control to achieve an opioid-sparing effect by obtaining additive or even synergistic analgesic effects while minimizing adverse events and is currently the gold standard for postoperative pain management.

The use of epidural anesthesia and analgesia is an integral part of the multimodal approach because of the superior analgesia and physiologic benefits conferred by epidural analgesia.

This approach potentially decreases peri operative morbidity by decreasing the hormonal and metabolic stress, reduced pain scores, earlier discharge from ICU, reduces length of hospital stay and improved patient satisfaction.

# PAIN MANAGEMENT ALONG THE PAIN PATHWAY

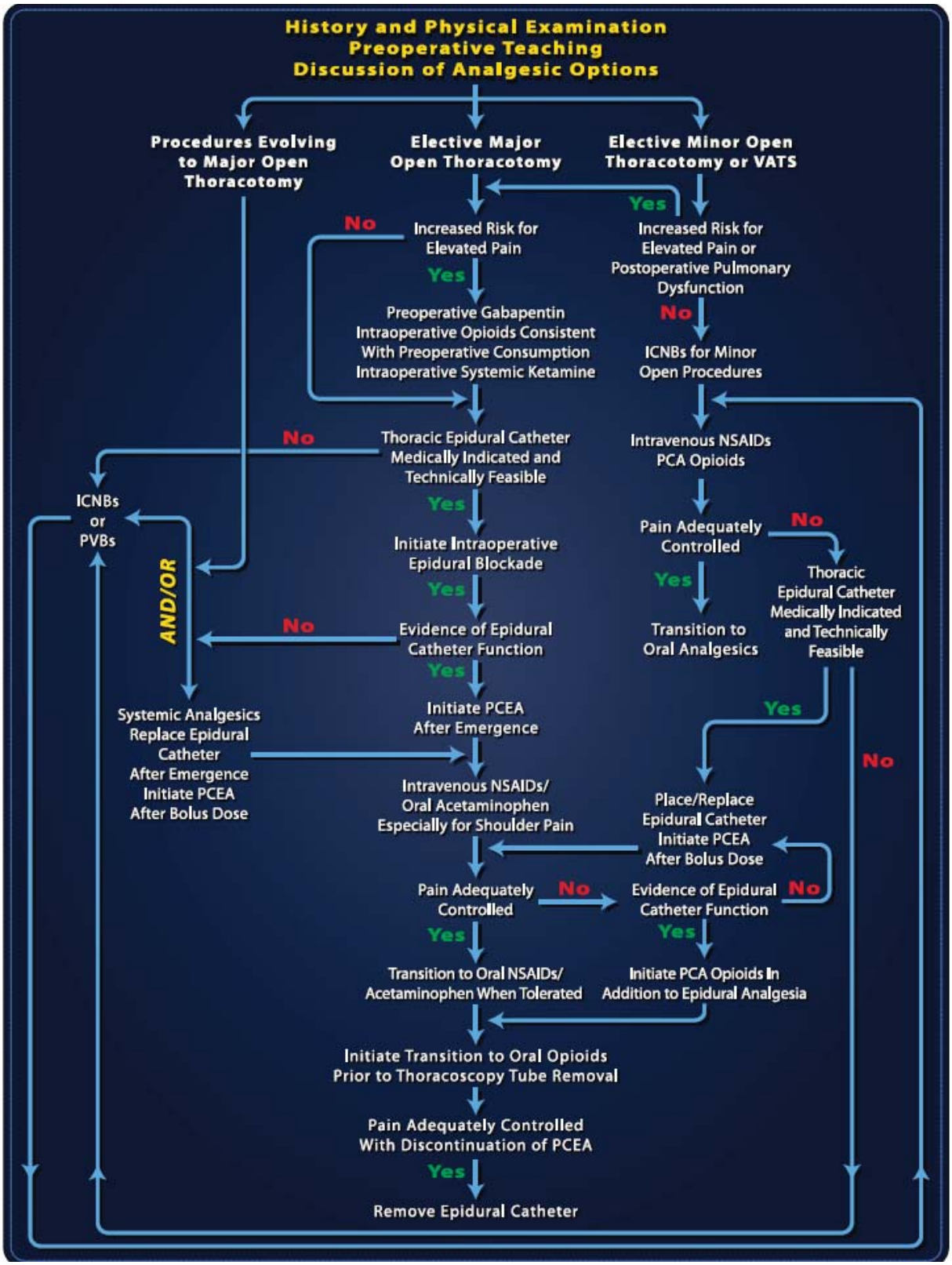



**THE PAIN PATHWAY AND INTERVENTIONS THAT MODULATE PAIN AT DIFFERENT POINTS**

Pain can be attacked at different levels along its path of transmission from the nociceptors to the Somatosensory cortex. Incorporating local anaesthetics in the management of pain is very essential as its effective in blocking at different levels.

So many options are available for the treatment of post operative pain. By careful assessment of individual patients incorporating the risks and benefits of each treatment modality and also considering the patient preferences, post operative analgesic regimen should be optimized for each patient.

FLOW DIAGRAM FOR MANAGEMENT OF ACUTE PAIN AFTER THORACOTOMY(3)



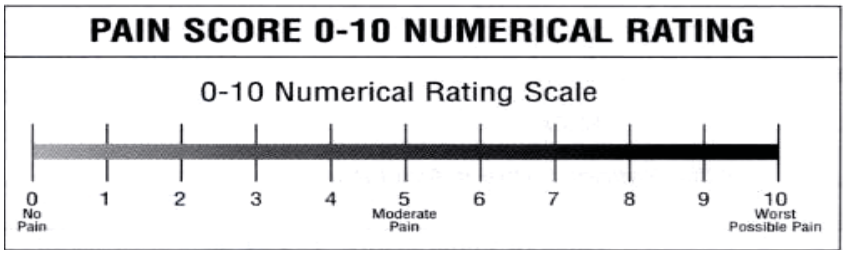
## NUMERICAL RATING SCALE

Pain is a complex, subjective, perceptual phenomenon with a number of dimensions – intensity, quality, time course , impact ,and personal meaning that are uniquely expressed by each individual and can be measured indirectly only.

Numerical rating scale have been used in the social and behavioral sciences for measuring a number of subjective phenomena. Pain doesn't take a discreet jump to be described as none, mild,moderate,severe.. etc. to bring out the idea that pain increases or decreases in continuum, the numerical rating scale is an useful tool. Thus numerical rating scale is a simple reporting instrument that can help to quantify a patients subjective pain.

Various studies have validated the accuracy of numerical rating scale for description of pain in different study populations and proved to be efficient in acute postoperative pain(110)

### Numerical rating scale (NRS)




The numerical rating scale is administered by asking the patient to verbally estimate her pain from a scale of 1-10.can also be used as a written instrument by asking the patient to point out the current perception of pain from the scale.

Usually NRS is 1-3 (mild pain) , 4-6 (moderate pain) ,7-10(severe pain).

As such is clearly highly subjective ,these scales are of most value when looking at change within individuals, and are of less value for comparing across a group of individuals at one time point.

Many researchers prefer to use a method of analysis that is based on the rank ordering of scores rather than their exact values, to avoid reading too much into the precise NRS SCORE.

## RAMSAY SEDATION SCALE

The Ramsay Sedation Scale (RSS, Table), was the first scale to be defined and was designed as a test of reusability.

It was described by Michael A. E. Ramsay.

The scale, from 1 to 6, describes a patient as follows:

1. anxious and agitated or restless, or both
2. co-operative, oriented, and calm
3. responsive to commands only
4. exhibiting brisk response to light glabellar tap or loud auditory stimulus
5. exhibiting a sluggish response to light glabellar tap or loud auditory stimulus
6. unresponsive

# MATERIALS AND METHODS

## STUDY SETTING

The study was conducted in conducted in Christian Medical College Hospital, Vellore , a 2500 Bedded tertiary academic medical center in south india.

## STUDY DESIGN

Prospective randomized control trail

## SUBJECTS

In this study we recruited all sequentially encountered patients older than 18 years of age who underwent lung surgery (unilateral thoracotomy) secondary to various lung pathologies.

We recruited a total of 50 patients over a period of 7 months.

## INCLUSION CRITERIA

1. Age: 18 yrs and older
2. Genders: Both
3. Patients undergoing unilateral thoracotomy

## EXCLUSION CRITERIA

1. Contraindications for use of Regional anaesthesia
2. Infection around puncture site
3. Coagulation disorder
4. h/o Drug abuse
5. Emergency and redo surgeries
6. Pregnancy
7. Critically ill patient
8. Decision of surgeon or anaesthetist or patient

## INTERVENTION AND COMPARATOR AGENT

Patients who underwent elective unilateral thoracotomies were randomly assigned to one of the two groups for post operative analgesia.

Group A – THORACIC EPIDURAL ANALGESIA

Group B – INTERCOSTAL BLOCK WITH BUPIVACINE AND CONTINUOUS INTRAVENOUS INFUSION OF MORPHINE.

Pain scores using NUMERICAL RATING SCALE were compared between the two groups in the first post operative day.

## METHOD OF RANDOMIZATION AND BLINDING

This was a prospective randomized control trail. The patients were randomized to one of the two groups for post operative analgesia by Computer generated randomized numbers using BLOCK RANDOMIZATION technique with blocks of ten.

Allocation concealment was done using opaque envelopes containing the method of post operative analgesia and the serial number was written on top of the envelope. The envelopes were opened sequentially after finding a patient who met the inclusion criteria and consented for taking part in this study.

The envelope was opened by the anaesthetist performing the case and the instructions to be followed in each group were given to them.

This is a OPEN LABELLED STUDY since blinding was not possible because of the obvious difference between the two methods.

## TARGET SAMPLE SIZE AND RATIONALE

The sample size was calculated based on a primary outcome variable – post operative pain assessed by Numerical Rating Scale (NRS) from a previous metaanalysis in ANAESTHESIOLOGY 2005(86).

We found that the difference in pain scores between the two study groups was 1.2(SD1.5)

Mean NRS score in epidural group = 2.4 +/- 1.3

Mean NRS score in morphine group= 3.6+/- 1.5

Sample size was calculated using the formula $n=2(Z1-\alpha/2 +Z1-\beta)^2\sigma^2/\delta^2$

Based on this sample size was calculated as 25 in each group

Sample size calculated is 50 for significance level ($\alpha$) of 5 with power of 80.

## METHODOLOGY

All the patients were seen by the investigator on the day prior to the surgery. The procedure and study was explained to the patients. A written informed consent was taken from patient prior to enrollment. The Numerical rating pain scale (NRS) was explained to all the patients.

The Anaesthetist posted for the particular patient opened the envelope on the day of surgery and will know which technique of Post operative analgesia to follow. Patients were explained which method they belong to. The envelope and allocation sheet were destroyed after this.

In the Thoracic epidural group, Before the induction of general anaesthesia, A epidural catheter was placed in any of the intervertebral spaces between T5-T8 and a test dose of 3ml of

0.5%bupivacaine was given. Response to cold stimulation was used to ensure the adequacy of the block.

Standard anaesthesia protocols for induction and maintenance of anaesthesia in thoracic surgery were followed for all these patients. They were preoxygenated with 100% oxygen for 3 minutes. Induction was done with propofol 2-2.5 mg/kg. Intra operative analgesia provided with fentanyl upto 5µg/kg and morphine 0.1mg/kg for all patients. Any adverse hemodynamic events like hypotension, tachycardia were appropriately treated. Trachea intubated with appropriate size and side doublelumen endotracheal tube(DLT) and position confirmed with fibre optic bronchoscopy. Anaesthesia maintained with 1 MAC isoflurane.

All the vital parameters, drugs administered, any adverse hemodynamic events, total amount of intravenous fluids given were noted in the data collection sheet.

In epidural group, at the end of surgery, before chest closure, epidural was activated using 5-10ml bolus of 0.2%bupivacaine was given over a period of 20 min and standard infusion of 0.1%bupivacine with 2µ/cc fentanyl was started at a rate of 5-8ml/hour via infusion pump.

In intravenous morphine group, at the end of surgery, before chest closure, Intercostal block of 5 levels (intercostals spaces 3-8) was performed using 20ml of 0.25%bupivacine under direct vision by the surgeon. Then continuous morphine infusion of 0.015-0.02mg/kg/hour was started using a elastometric device(DOSIFUSER) for 48 hours.

After completion of surgery, trachea was extubated in all patients and shifted to THORACIC High dependency unit( HDU). Standard Post operative care and monitoring was done for all patients in thoracic HDU for 48 hours.

During the first post operative day, as per thoracic HDU protocol,

All patients received oxygen via Hudson mask.

Vital parameters like Heart rate, blood pressure, respiratory rate were noted every hour.

Pain was assessed using the Numerical rating scale (NRS) every 2 hours by the concerned ICU personnel.

Sedation Scale was noted according to RAMSAY SEDATION SCALE.

Pain scores and Sedation score at 1,6,12,18, 24 hours were also noted in the data collection sheet.

In both groups,

Anytime during the first post operative day if patient complained of pain (nrs>6), Rescue analgesia was given with inj.tramadol 50mg or inj.morphine 2mg depending on the HDU protocol . Dose, time (hours after surgery) and number of times of rescue analgesia were noted.

Side effects like Nausea, Vomiting, Pruritis, Hypotension requiring treatment, respiratory depression were noted and treated accordingly. Time and number of episodes also noted.

In the epidural group, Brommage motor blockade scale was also noted.

Physiotherapy and incentive spirometry were given to all patients and pain scores were noted while performing breathing exercises.

Patients were ambulated in morning of the second postoperative day.

The patients were followed up for 48 hours.

## STATISTICAL ANALYSIS

The data collected from the patients were entered in EPIDATA.

Pain scores at different time points 1,6,12,18,24 hours during the first post operative day between the two groups were compared using MANN- WHITNEY U TEST.

Results were considered statistically significant if p value is $<0.05$

The statistical software used was STATA 11(Stata corp, college station, Texas, USA).

The study design and methods were approved by the Institutional Review Board, Christian Medical College, Vellore

# RESULTS

Group A- Thoracic epidural group

Group B- Intercostal block with 0.25%bupivacaine plus continuous intravenous morphine.

Fifty patients, 25 in each group were included in this study during the period of 7 months from May 2012 to November 2012. The baseline characteristics are shown in table1. The baseline data between the two groups were compared. The data were comparable; there were no significant differences as shown by **p** values in the table.

**TABLE 1:BASELINE CHARACTERISTICS**

| **PATIENT CHARACTERISTICS** | | **THORACIC EPIDURAL GROUP** | **INTRAVENOUS MORPHINE GROUP** | **p VALUE** |
|---|---|---|---|---|
| **MEAN AGE (years)** | | **37.72** | **39** | **0.7510** |
| **SEX (Male: Female)** | | **16:9** | **16:9** | **1.000** |
| **MEAN WEIGHT(kg)** | | **58.96** | **56.4** | **0.4469** |
| **MEAN HEIGHT(cm)** | | **158.72** | **157.52** | **0.5763** |
| **BODY MASS INDEX** | | **23.204** | **22.784** | **0.7441** |
| **ASA GRADING** | **I** | **11** | **9** | **0.842** |
| | **II** | **13** | **15** | |
| | **III** | **1** | **1** | |

**FIGURE 1: SEX RATIO**

**Figure 1** shows the number of males and females separately in the Thoracic epidural and intravenous morphine group. Overall the male patients who took part in the study were more than the female patients (M:F=32:18)

Both the Groups had equal distribution of male and female patients (M:F=16:9)

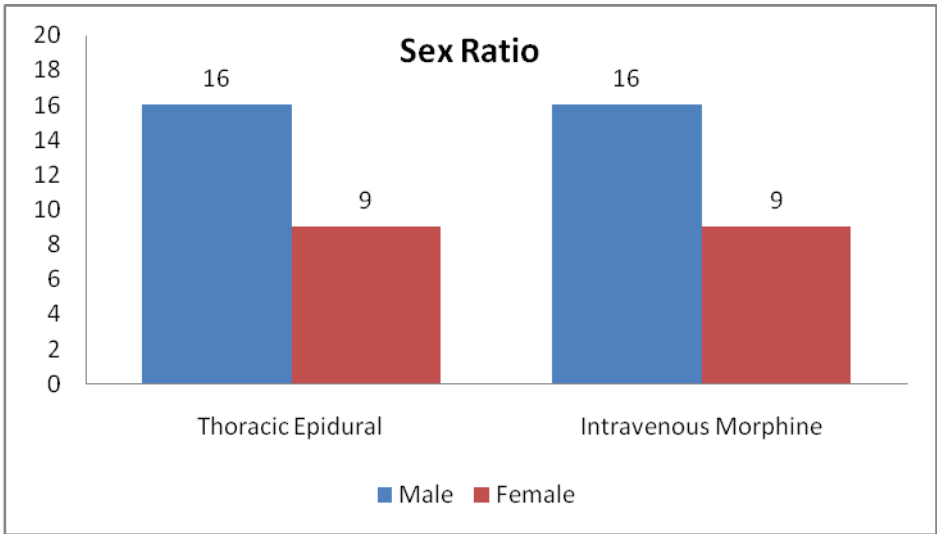



**FIGURE 2: AGE DISTRIBUTION**

Figure 2 shows the distribution of age between both the groups.

Intravenous morphine group had more number of patients <40 yrs of age(morphine 15pat)

Only 5 patients were more than 60 yrs of age in both groups.

However mean age for both thoracic epidural and morphine groups were similar (37.72 and 39) respectively.

| AGE IN YEARS | <40 | 40-60 | >60 |
|---|---|---|---|
| EPIDURAL GROUP n = 25 | 13 | 10 | 2 |
| MORPHINE GROUP n = 25 | 15 | 7 | 3 |

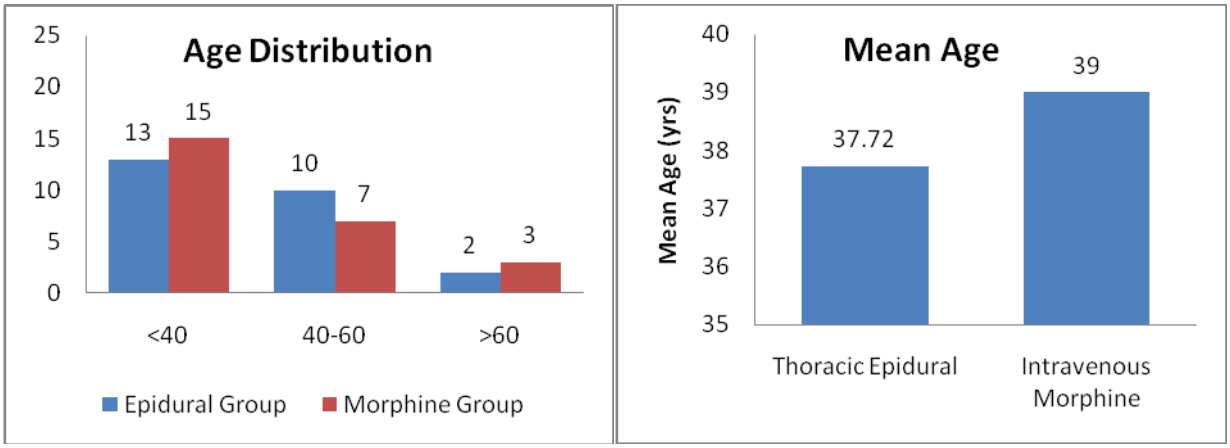



**FIGURE 3: WEIGHT**

Figure 3 shows distribution of weight between thoracic epidural and intravenous morphine groups. The weight was classified into 3 categories.

Both the groups in the maximum number of patients were in the weight range 50-70. Epidural 16/25 and Morphine 11/25 patients.

Mean weight showed no difference between the two groups (epidural 58.96, morphine 56.4) difference was also not statistically significant (p = 0.4469)

| WEIGHT | <50 | 50-70 | >70 |
|---|---|---|---|
| EPIDURAL GROUP | 5 | 16 | 4 |
| MORPHINE GROUP | 10 | 11 | 4 |

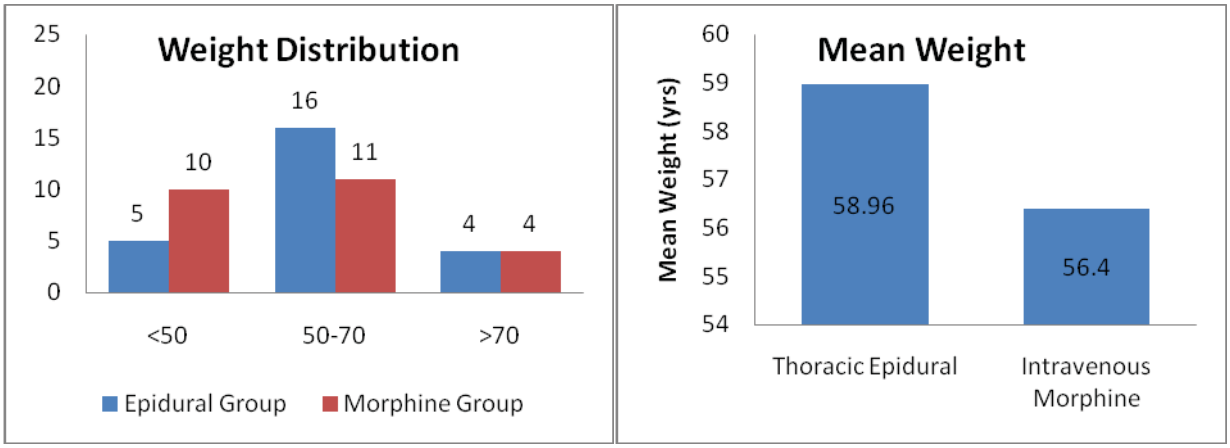



**FIGURE 4: HEIGHT OF THE PATIENT**

Figure 4 shows distribution of height between the two groups of patients. Mean height showed not much difference between the two groups (epidural-158.72 morphine-157.52) and

The difference wasn't statistically significant (p= 0.5763).

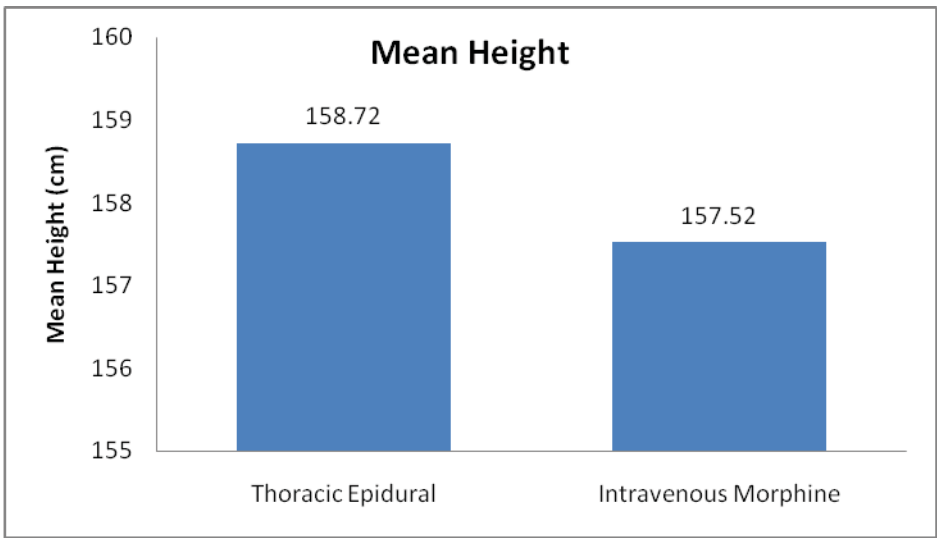



**FIGURE 5: BODY MASS INDEX (BMI)**

Figure 5 shows the distribution of Body mass index between the two groups of patients.

The mean BMI wasn't significantly different in two groups (p=0.7441) and was in the lower range in both the groups (morphine 22.784 and epidural 23.204).

This shows that most of the patients who participated in this study were underweight.

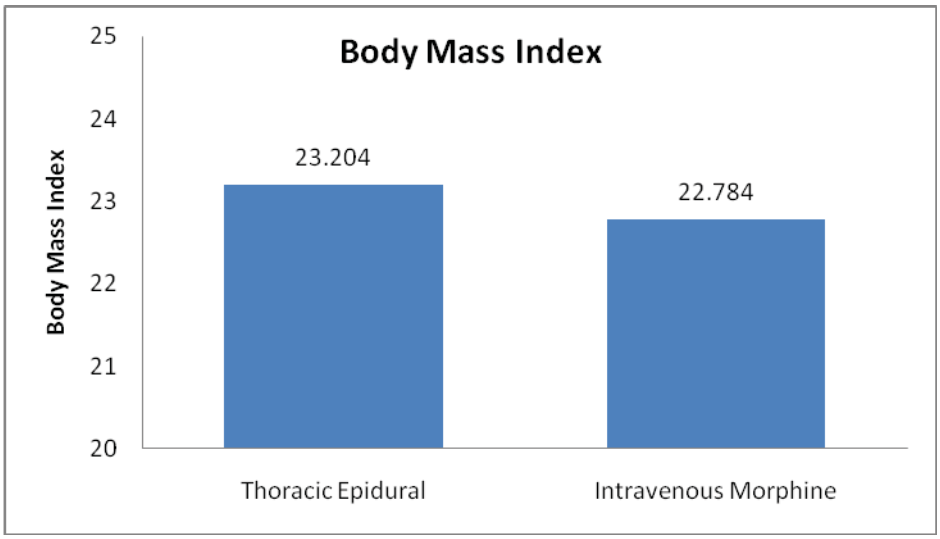
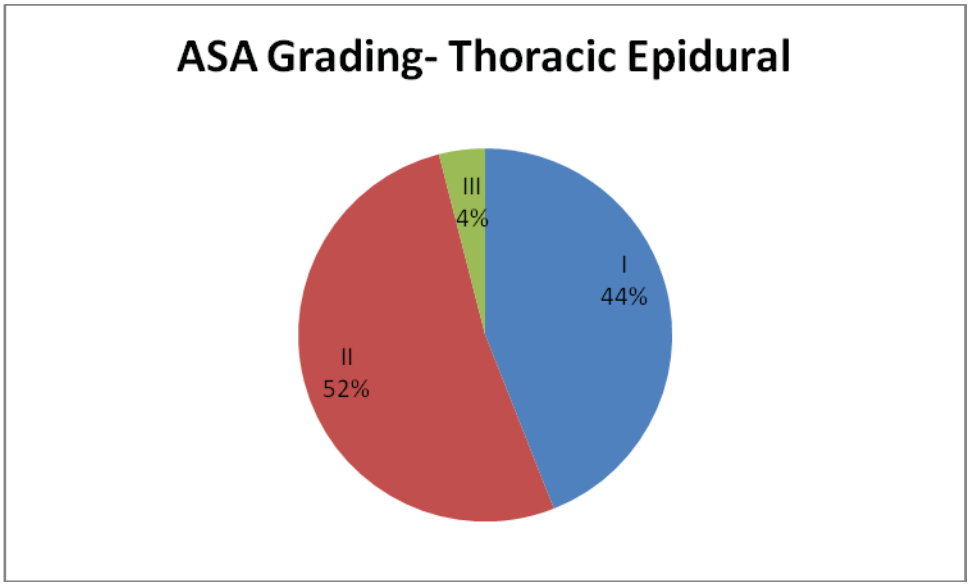


**FIGURE 6: AMERICAN SOCIETY OF ANAESTHESIOLOGISTS (ASA)**

Maximum number of patients (56%) in both groups belonged to ASA grade 2, with co-morbid illness (epidural 13, morphine 15). Only 1 patient in each group was in ASA 3 category.



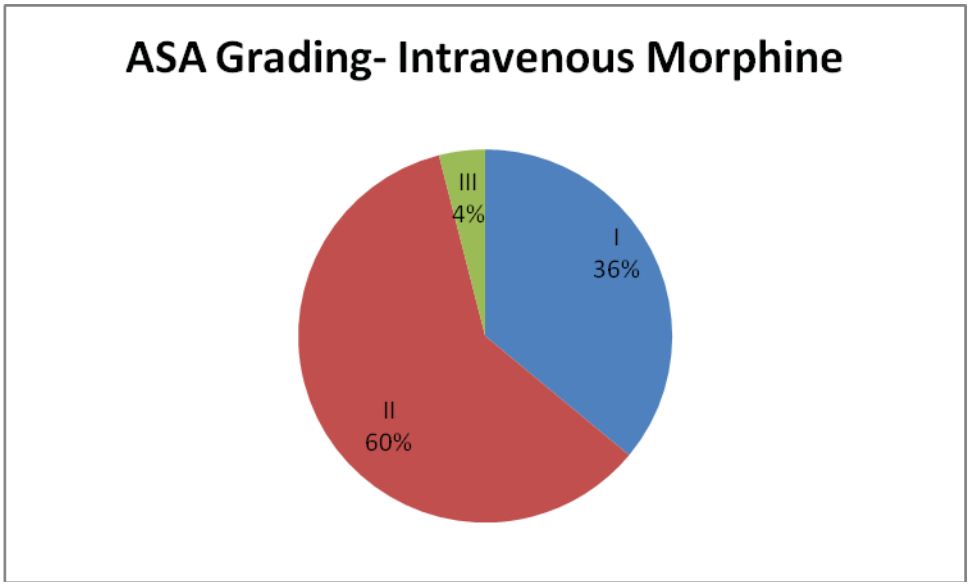



**TABLE 2 : TYPE AND DURATION OF SURGERY AND ANAESTHETIC REQUIREMENTS**

| CHARACTERISTICS | EPIDURALGROUP n=25 | MORPHINEGROUP n=25 | p value |
|---|---|---|---|
| TYPE OF SURGERY | | | |
| Pnemonectomy | 5 | 2 | |
| Lobectomy | 8 | 7 | |
| Tumour/cyst excision | 10 | 5 | |
| Decortication | 2 | 11 | |
| DURATION OF SURGERY(hrs) | 3.8(3-4) SD 0.0816 | 3.23(3-4) SD 0.0613 | 0.0195 |
| TOTAL DOSE OF FENTANYL(µG) | 168.6(100-200) SD 67.2 | 188.6(150-200) SD 65.7 | 0.1961 |
| TOTAL DOSE OF MORPHINE(mg) | 6.84(6-8) SD 2.35 | 7.68(6-10) SD 2.41 | 0.2546 |
| TOTAL AMOUNT OF FLUIDS USE(LIT) | 1.364 SD 0.309 | 1.312 SD 0.57 | 0.382 |

**FIGURE 7: DURATION OF SURGERY**

Figure 7 shows the duration of surgery between the two groups. Mean duration in morphine group (3.23) is less than the epidural group (3.8) and is statistically significant(p=0.0195).

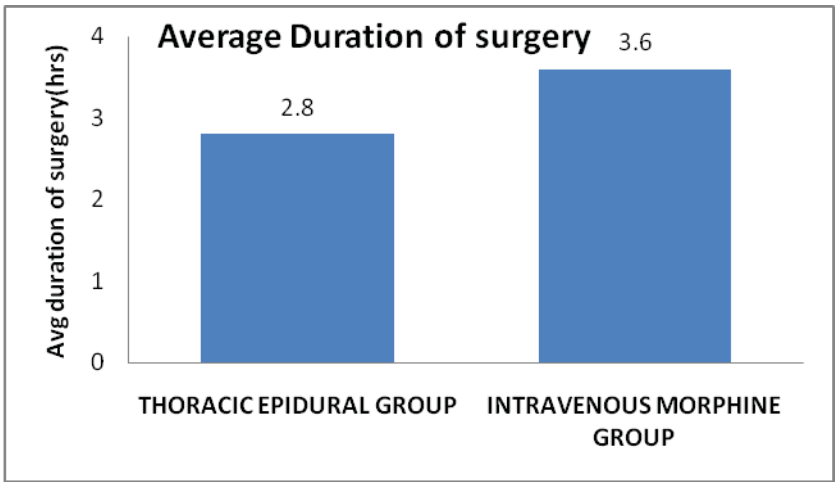



**FIGURE 8: TOTAL AMOUNT OF FENTANYL**

Total amount of fentanyl used in two groups is shown in figure 8.

The mean amount of fentanyl used in both groups (epidural 168.6µg, morphine188.6) does not vary significantly (0.1961).

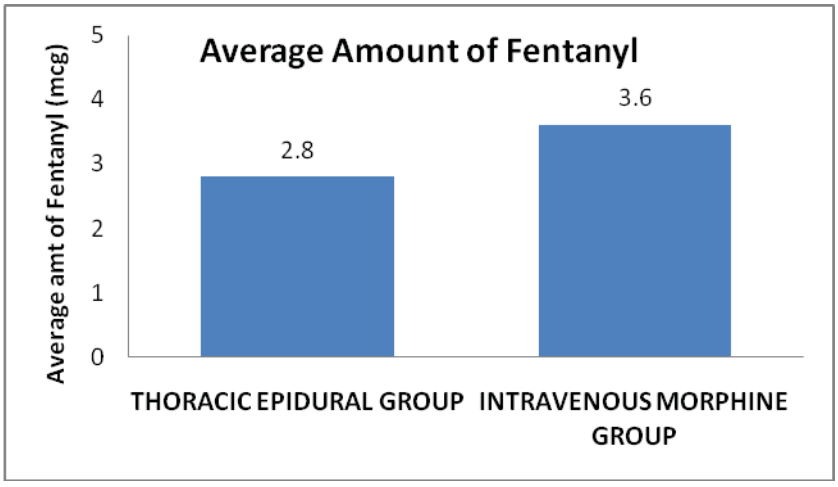


**FIGURE 9: AMOUNT OF MORPHINE**

Figure 9 shows the distribution of amount of morphine used in two groups.

Mean dose of morphine used for intraoperative for analgesia does not vary between the two groups (epidural 6.84, morphine7.68) and wasn't statistically significant (p=0.2546).

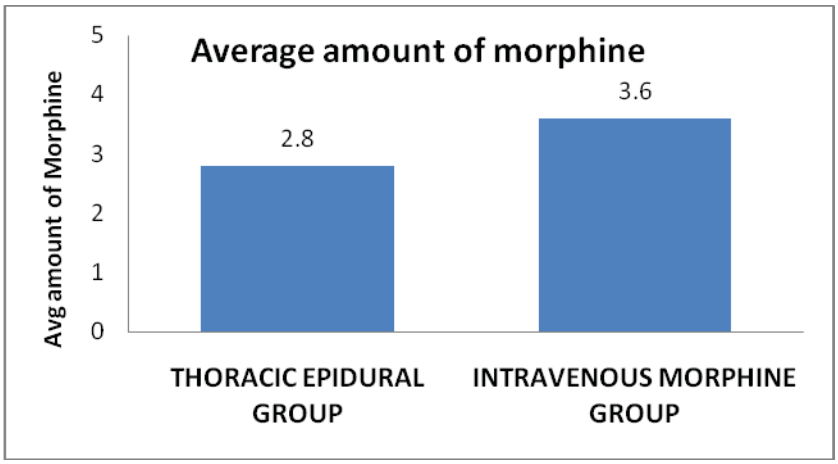



**Figure10: TOTAL INTRAVENOUS FLUID USE**

Figure 10 shows the total amount of intravenous fluids used in both the groups.

There is not much difference among the mean amount of fluids used in both groups (epidural 1.364L, morphine 1.312L) and wasn't statistically significant.

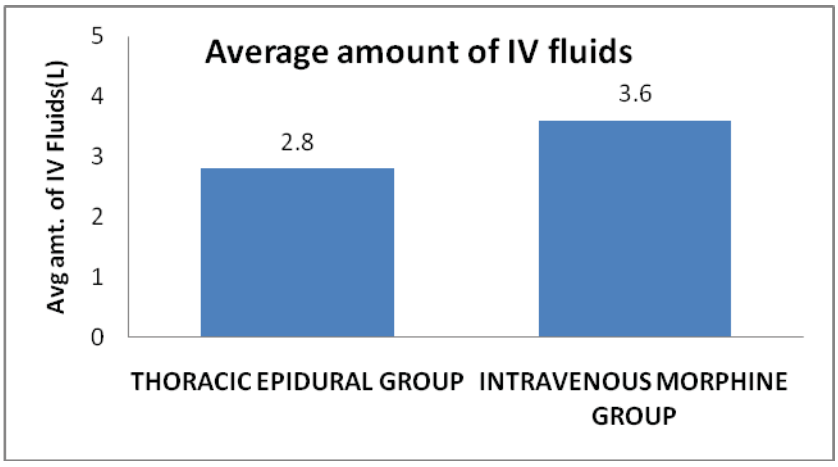


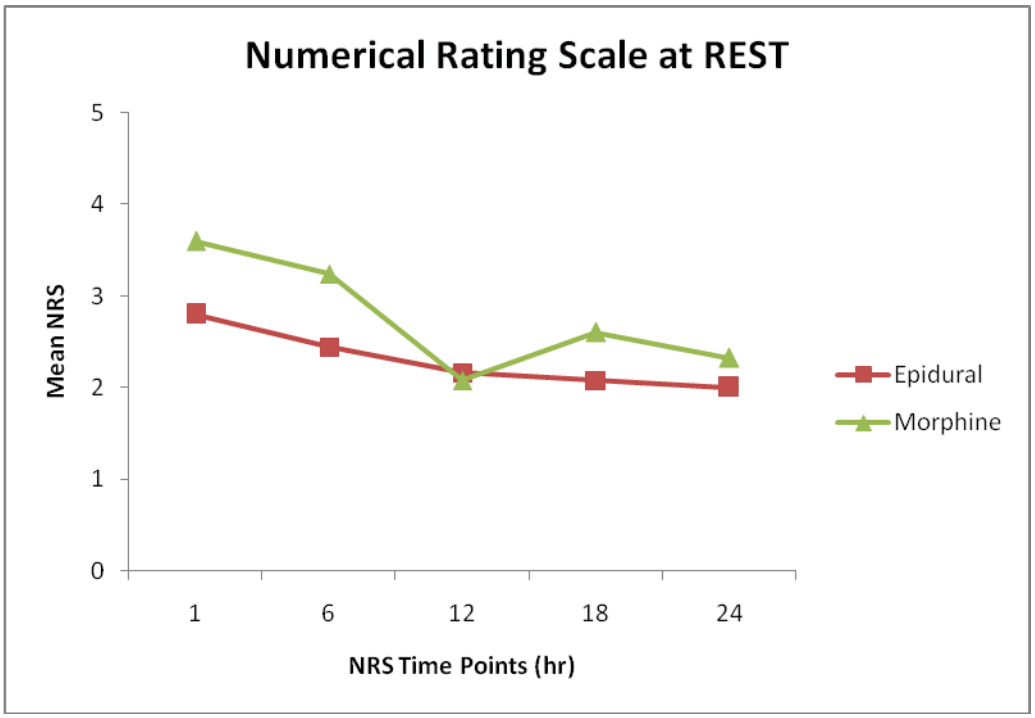
**TABLE 3: NUMERICAL RATING SCALE (NRS) [PAIN SCORE] AT REST DURING FIRST POSTOPERATIVE DAY.**

**AT REST**

| NRS TIME POINTS | GROUP | N | MEAN | STANDARD DEVIATION | p value |
|---|---|---|---|---|---|
| 1ST HOUR | EPIDURAL | 25 | 2.8 | 1.55 | 0.0278 |
| | MORPHINE | 25 | 3.6 | 0.91 | |
| 6TH HOUR | EPIDURAL | 25 | 2.44 | 1.26 | 0.0505 |
| | MORPHINE | 25 | 3.24 | 1.45 | |
| 12TH HOUR | EPIDURAL | 25 | 2.16 | 1.21 | 0.9918 |
| | MORPHINE | 25 | 2.08 | 0.95 | |
| 18TH HOUR | EPIDURAL | 25 | 2.08 | 0.75 | 0.0330 |
| | MORPHINE | 25 | 2.6 | 1.08 | |
| 24TH HOUR | EPIDURAL | 25 | 2 | 1 | 0.1090 |
| | MORPHINE | 25 | 2.32 | 0.74 | |

Table 3 shows the comparison of the numerical rating scale at different time periods following surgery between epidural and morphine group at rest. Though not statistically significant at end of 24 hrs, there is a significant difference in pain scores for the first 12 hours.

**FIGURE 11: NUMERICAL RATING SCALE (NRS)[PAIN SCORE] AT REST DURING FIRST POSTOPERATIVE DAY**




As shown in the fig.11 during rest, the NRS (PAIN SCORES) were less in the epidural group than morphine group. The difference in the pain scores were statistically significant for the first 12 hours (p=0.0505). Though the pain scores were less in epidural group at the end of 24 hours, the difference weren't statistically significant.

The graph shows the trend of pain relief in both groups. In epidural group it is a plateau with steady pain relief. In morphine group there is a decrease in first 12 hours, then there is a plateau.

Important to note that is pain scores were never severe in both groups. In the morphine group even though the pain scores were higher than epidural, it was mild at the end of 24hrs.The highest pain score was recorded in morphine group, at 1$^{st}$ hour after surgery mean3.6(sd0.91)

**TABLE 4: NUMERICAL RATING SCALE (NRS) [PAIN SCORE] WHILE DOING EXERCISE DURING FIRST POSTOPERATIVE DAY**

**WHILE DOING BREATHING EXERCISE**

| NRS TIME POINTS | GROUP | N | MEAN | STANDARD DEVIATION | pVALUE |
|---|---|---|---|---|---|
| 1ST HOUR | EPIDURAL | 25 | 2.96 | 1.485 | 0.0105 |
| | MORPHINE | 25 | 3.96 | 1.019 | |
| 6TH HOUR | EPIDURAL | 25 | 3.16 | 1.462 | 0.0327 |
| | MORPHINE | 25 | 4.12 | 1.763 | |
| 12TH HOUR | EPIDURAL | 25 | 2.68 | 1.573 | 0.5129 |
| | MORPHINE | 25 | 2.72 | 1.1 | |
| 18TH HOUR | EPIDURAL | 25 | 3 | 1.322 | 0.1029 |
| | MORPHINE | 25 | 3.4 | 1.190 | |
| 24TH HOUR | EPIDURAL | 25 | 2.6 | 0.866 | 0.1642 |
| | MORPHINE | 25 | 2.92 | 0.909 | |

Table 4 shows the NRS SCORES while doing breathing exercises (ie) DYNAMIC PAIN RELIEF. As during rest, the scores weren't statistically significant at the end of 24 hrs(p=0.1642) and results were comparable. The pain scores were significantly higher in morphine group in first 12 hours.

**FIGURE 12: NUMERICAL RATING SCALE (NRS)[PAIN SCORE] WHILE DOING BREATHING DURING FIRST POSTOPERATIVE DAY**

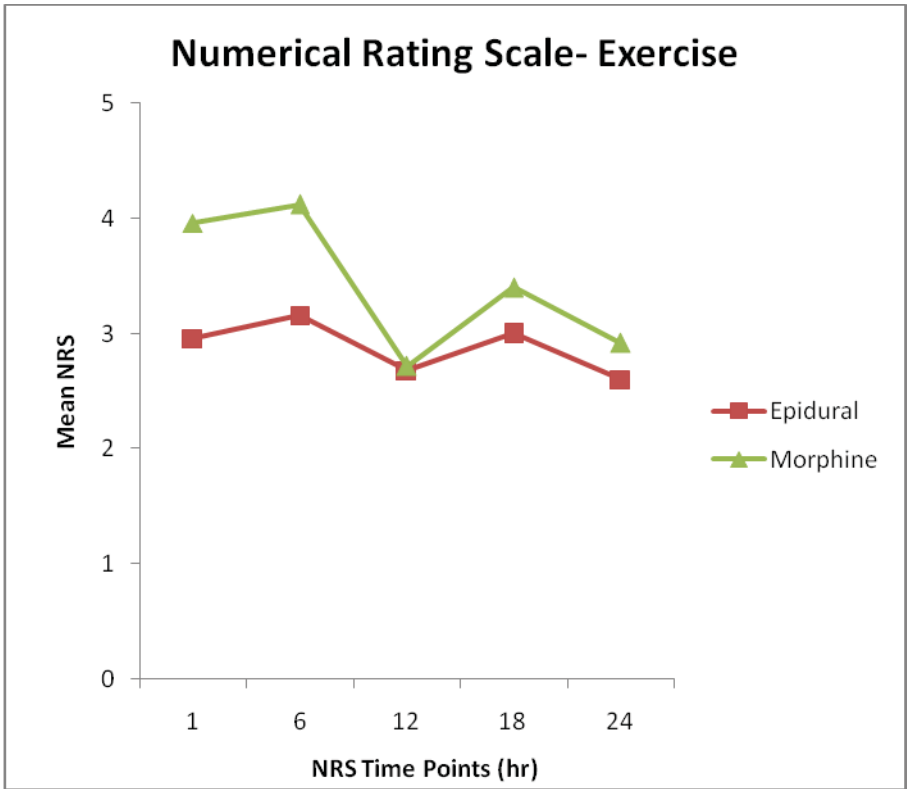



Figure 12 shows the pain scores while doing breathing exercise during the first post operative day. As in the figure the mean were significantly higher in the morphine group in the first 12 hours after surgery. The highest pain score recorded is at 6$^{th}$ hour in the morphine group mean 4.12(sd1.673) .

The pain scores seem to be steady and low in the epidural group, whereas in the morphine group the pain scores shows a declining trend in the first 12 hrs and it reaches a pleateau. Beyond 12 hours there is no significant difference in pain scores between the two groups.

**TABLE 5: RAMSAY SEDATION SCALE DURING FIRST POSTOPERATIVE DAY**

**SEDATION SCALE**

| SEDATION SCALE TIME POINTS | GROUP | N | MEAN | STANDARD DEVIATION | pVALUE |
|---|---|---|---|---|---|
| 1ST HOUR | EPIDURAL | 25 | 3.28 | 0.737 | 0.0005 |
| | MORPHINE | 25 | 4.04 | 0.888 | |
| 6TH HOUR | EPIDURAL | 25 | 2.88 | 0.725 | 0.0830 |
| | MORPHINE | 25 | 3.24 | 0.969 | |
| 12TH HOUR | EPIDURAL | 25 | 2.64 | 0.568 | 0.0007 |
| | MORPHINE | 25 | 2.72 | 0.918 | |
| 18TH HOUR | EPIDURAL | 25 | 3.48 | 0.2 | 0.0000 |
| | MORPHINE | 25 | 3.4 | 0.489 | |
| 24TH HOUR | EPIDURAL | 25 | 2.64 | 0.2 | 0.0423 |
| | MORPHINE | 25 | 2.28 | 0.541 | |

Table 5 shows the sedation scale between the two groups. There is a significant difference in the level of sedation, patients in the morphine group were more sedated than in epidural group. The highest sedation score noted in morphine group was in the first 6 hrs. In the first hr mean score in morphine group is 4(0.088) ie patients exhibited a brisk response to light glabellar tap or loud auditory stimulus.

**FIGURE 13 : RAMSAY SEDATION SCALE DURING FIRST POSTOPERATIVE DAY**

**SEDATION SCALE**

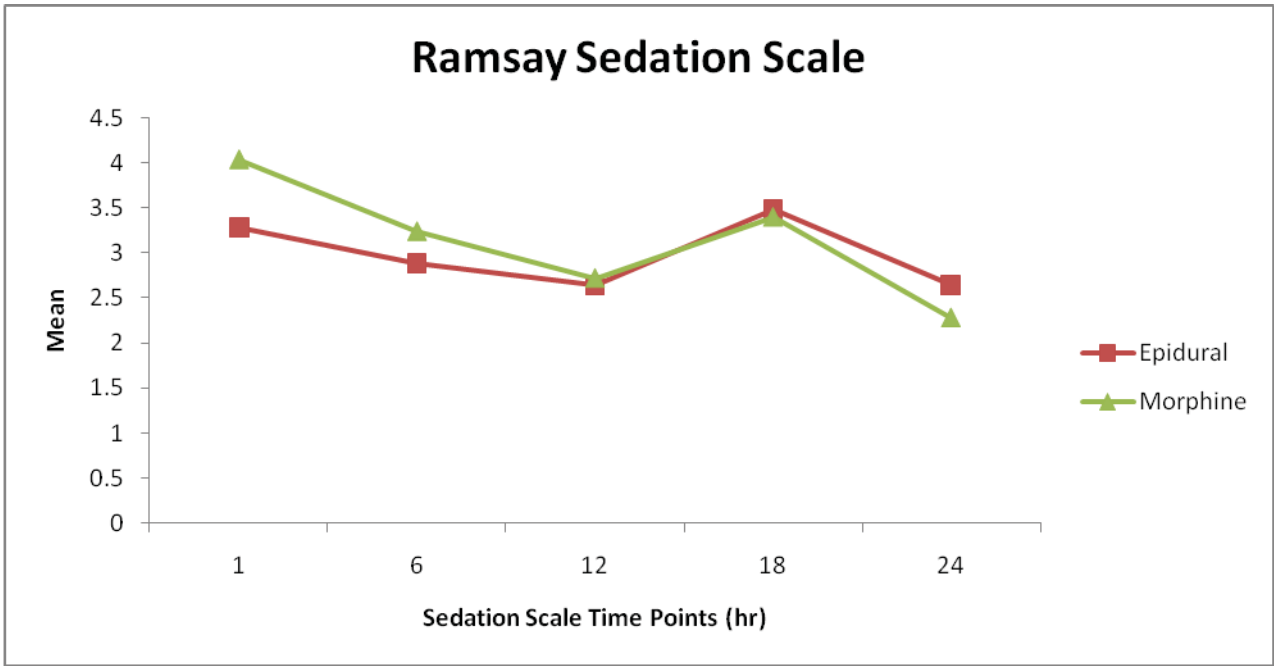



Figure 13 shows ramsay sedation scale between the two groups.

In the epidural group, the graph shows a linear trend and the mean were low and were around 2 (ie) pt were cooperative, calm and oriented.

In the morphine group there is a declining trend for the first 12 hrs. During the 1st hour, sedation score were mean4, which can be interpreted due to the residual effects of narcotics used intraoperatively.

By the end of first postoperative day, sedation scores were more or less similar in both groups.

**RESCUE ANALGESIA**

**TABLE 6: NUMBER OF PATIENTS REQUIRING RESCUE ANALGESIA**

| RESCUE ANALGESIA | EPIDURAL GROUP n=25 | MORPHINEGROUP n=25 | p VALUE |
|---|---|---|---|
| YES | 11 | 12 | 0.777 |
| NO | 14 | 13 | |

**TABLE 7: NUMBER OF TIMES OF RESCUE ANALGESIA**

| NUMBER OF TIMES OF RESCUE ANALGESIA | EPIDURAL GROUP n = 11 | MORPHINE GROUP n = 12 | p VALUE |
|---|---|---|---|
| ONCE | 8 | 7 | O.494 |
| TWICE | 3 | 5 | |
| THRICE | 0 | 1 | |

**TABLE 8: TIME FOR FIRST RESCUE ANALGESIA**

| GROUP | n | MEAN(hrs) | STANDARD DEVIATION | p VALUE |
|---|---|---|---|---|
| EPIDURAL | 11 | 5.272 | 3.663 | 0.2340 |
| MORPHINE | 12 | 3.909 | 3.700 | |

**FIGURE 14: NUMBER OF PATIENTS REQUIRING RESCUE ANALGESIA**

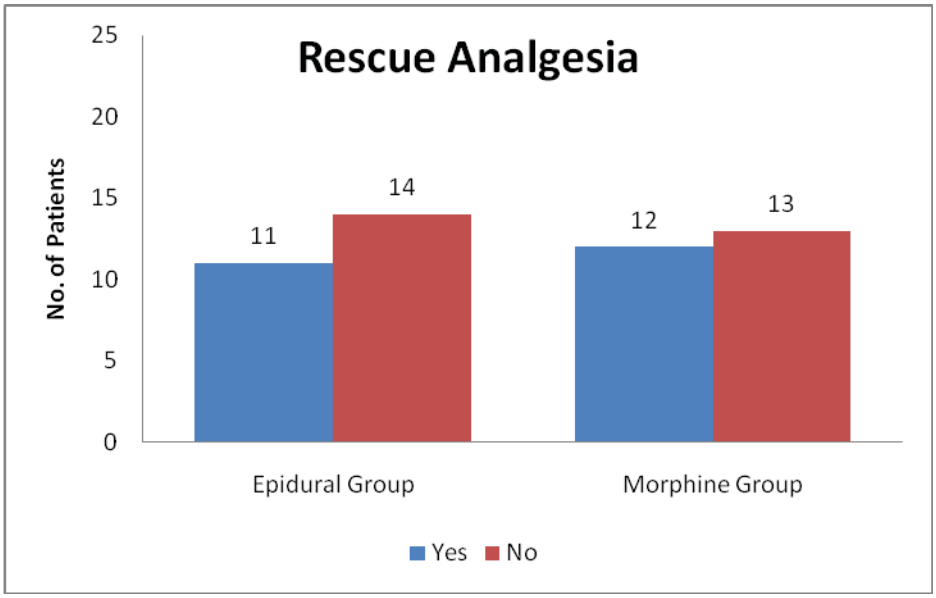



Table 6 and figure14 shows the number of patients who required rescue analgesia in the study. There was no significant difference between both groups(p=0.777).so rescue analgesia was administered to both group patients equally.

**FIGURE 15: NUMBER OF TIMES OF RESCUE ANALGESIA**

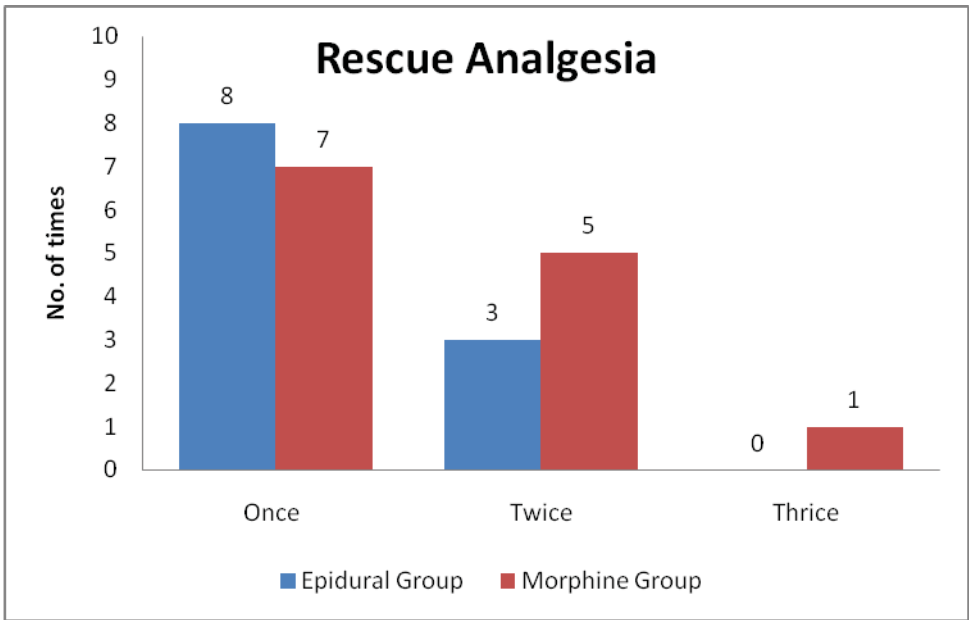


Table 7 and figure 15 shows the number of times rescue analgesia was administered to both group patients in the first post operative day. In the morphine group, among the patients who required rescue analgesia, it was administerd twice in 5 patients and thrice in one patient. The results weren't significant between the two groups.(p=0.494)

**FIGURE 16: TIME FOR FIRST RESCUE ANALGESIA**

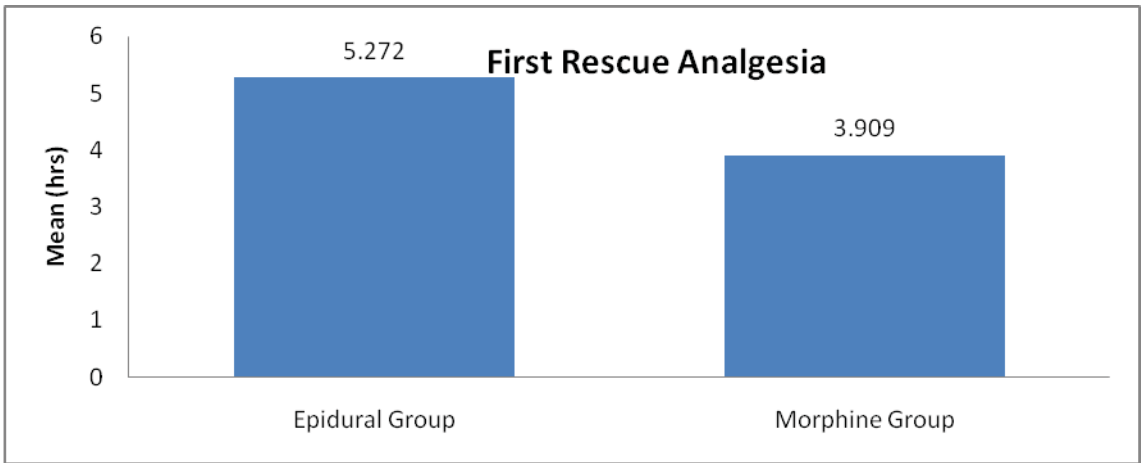



Table 8 and figure 16 shows the duration after surgery when the rescue analgesia was administered. In the epidural group it was around a mean of 5.2 hrs after surgery and in the morphine group it was 3.9hrs after surgery. The results weren't statistically significant(p=0.234).

**TABLE 9: INCIDENCE OF SIDE EFFECTS LIKE NAUSEA, VOMITING, PRURITIS, HYPOTENSION REQUIRING TREATMENT**

| SIDE EFFECTS | EPIDURAL GROUP n = 25 | MORPHINE GROUP n = 25 | P VALUE |
|---|---|---|---|
| YES | 7 | 7 | |
| NO | 18 | 18 | 1.000 |

**FIGURE 17**

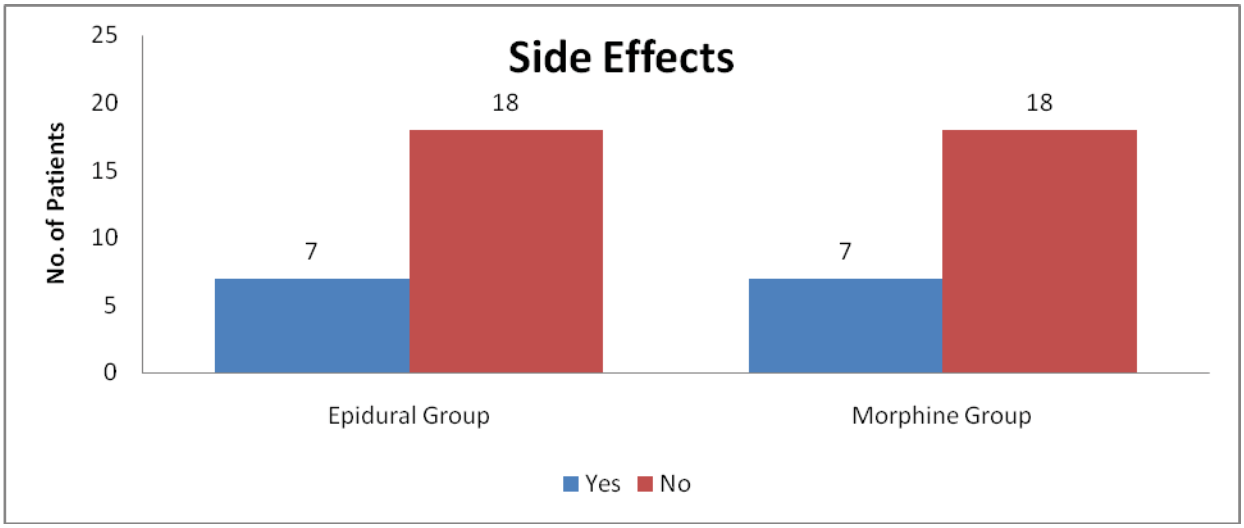



Table 9 and figure 17 shows the incidence of side effects between the two groups. The incidence of side effects were less in both groups, only 7 out 25 patients had any one side effects and the incidence was equal among both the groups. Thus the results weren't statistically significant(p=1.000)

**TABLE 10: NAUSEA**

| NAUSEA | EPIDURAL GROUP n = 25 | MORPHINE GROUP n = 25 | P VALUE |
|---|---|---|---|
| | 1 | 4 | 0.157 |

**FIGURE 18**

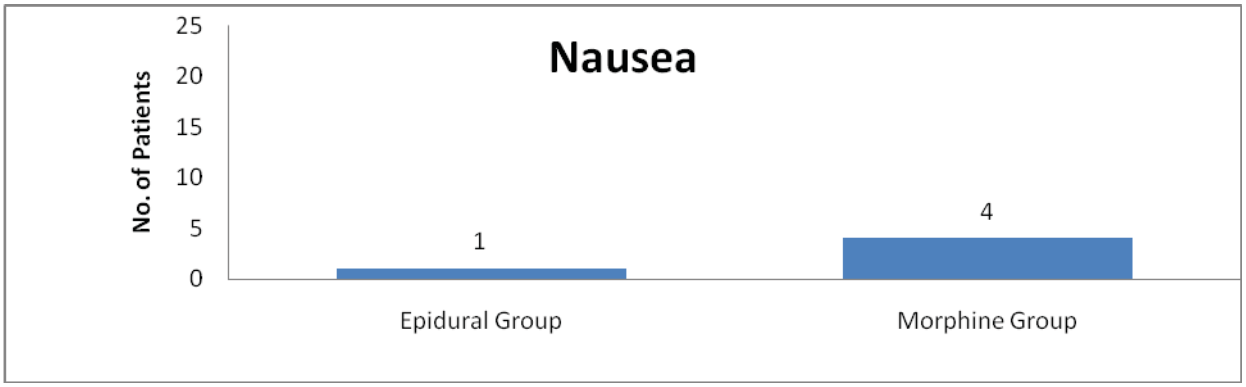



Table 10 and figure 18 shows the incidence of nausea. It was high in the morphine group mean 4.

There was no statistically significant difference between two groups.

**TABLE 11: VOMITING**

| VOMITING | EPIDURAL GROUP n = 25 | MORPHINE GROUP n = 25 | P VALUE |
|---|---|---|---|
| | 5 | 6 | 0.733 |

**FIGURE 19**

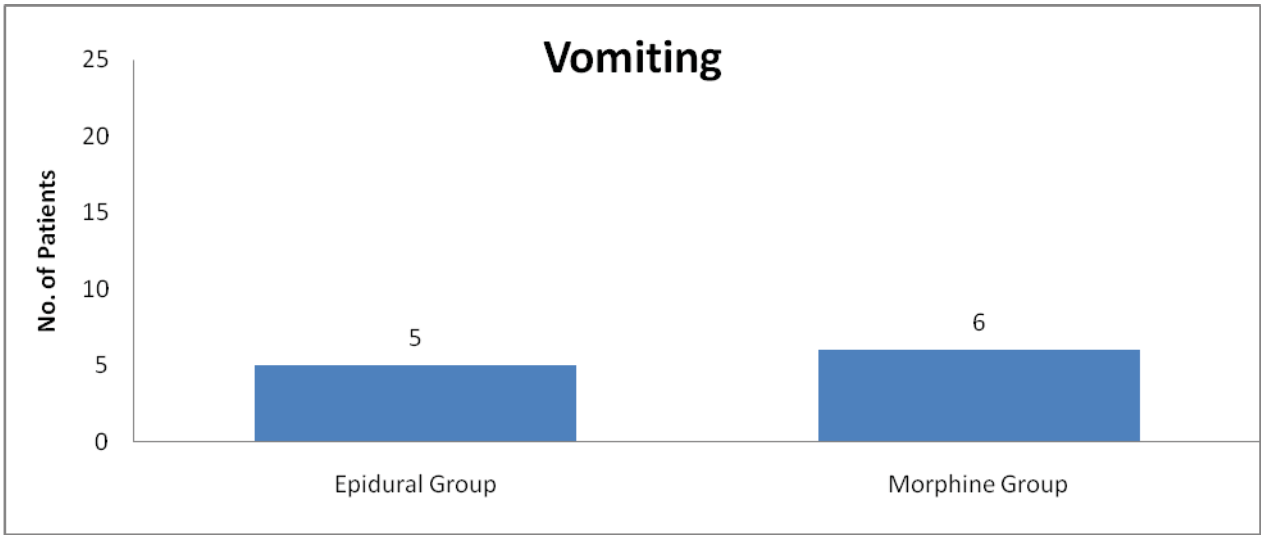



Table 11 and figure 19 shows the incidence of vomiting among epidural and morphine groups. No significant difference was found between the two groups.

In general the incidence of nausea and vomiting was less between two groups and difference was not significant.

None of the patients in the study group had pruritis.

**TABLE 12: HYPOTENSION REQUIRING TREATMENT**

| HYPOTENSION REQUIRING TREATMENT | EPIDURAL GROUP n = 25 | MORPHINE GROUP n = 25 | P VALUE |
|---|---|---|---|
| | 4 | 1 | 0.157 |

**FIGURE 20**

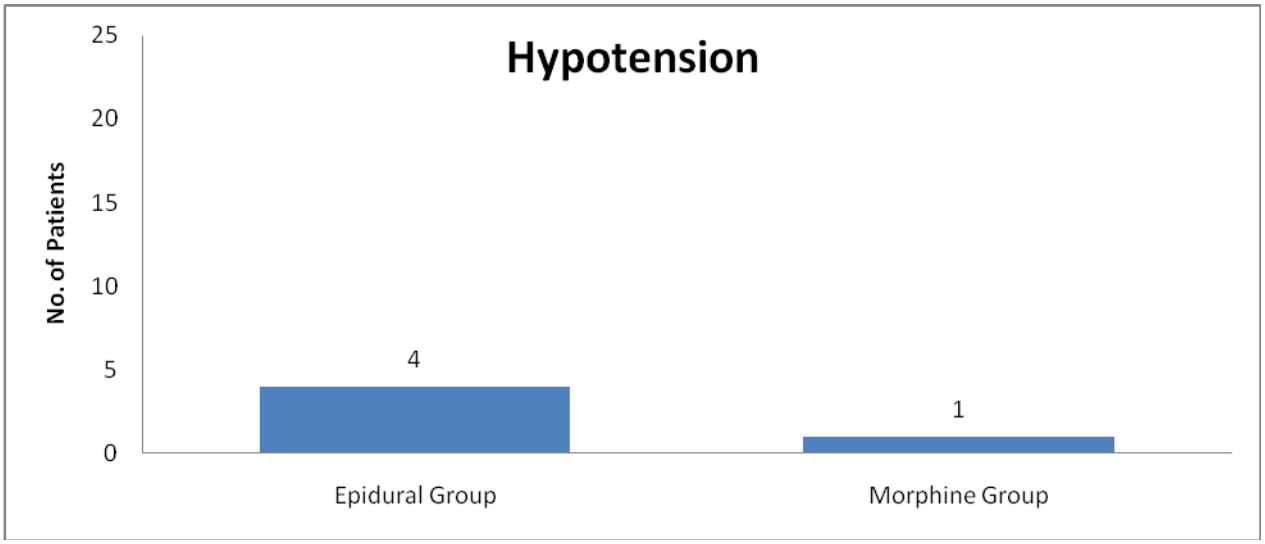



Table 12 and figure 20 shows the number of patients who had significant hypotension requiring treatment in the post operative period. Four patients in epidural group and one patient in the morphine group had hypotension. There was no statistically significant difference in the incidence of hypotension between the two groups(p=0.157).

The incidence of respiratory depression was nil among both the groups. None of the patients had desaturation requiring re intubation in this study.

MODIFIED BROMMAGE SCALE was used to assess the motor blockade in the epidural group. No patients in the study had significant motor blockade.

# DISCUSSION

This study was done in the Cardiothoracic unit in Christian Medical College Vellore, collaborating with the Cardiothoracic and Anaesthesia departments of this institution. This study was designed as a randomized controlled trial and aimed at studying the quality of analgesia and incidence of side effects between two different methods of post operative analgesia (thoracic epidural and intercostals block plus intravenous morphine) in thoracotomies. We also aimed at looking at the timing and number of rescue analgesic requirement between the two groups. The sample size calculated was 50, of which 25 patients are randomized to thoracic epidural group and 25 patients in intercostals block plus intravenous morphine group.

Thoracotomy is a frequently performed surgical procedure for various lung pathologies. Pain following thoracic surgery is described very severe and management of post operative analgesia is particularly challenging. Adequate and effective pain management is pivotal in decreasing post operative mortality and morbidity after thoracic surgery. Effective post operative analgesia relieves suffering for the patient, promotes early recovery, leads to early mobilization, shortens hospital stay and increase patient satisfaction apart from playing an important role in reducing complications related to lung surgeries.

It is well known fact that pain control regimens should not be standardized; it should be tailored to individual needs of the patient taking into account various factors. But the general goal in all post operative patients is to minimize the exposure to side effects of various drugs, while providing adequate analgesia.

This study was proposed after going through literature search using Pubmed and Cochrane database.

Pain management after thoracotomies has undergone extensive modifications over several years. Various analgesic modalities had been proposed, and extensively reviewed for their merits and demerits. Still no analgesic regime is found to be the best with definite advantages over the others. Recently paravertebral blocks are gaining popularity as an ideal technique for post thoracotomy analgesia.

Single shot intercostal block with local anaesthetic is one of the earliest and effective technique for post operative analgesia for thoracotomy, which is a still popular method practiced in various centres including our institution.

With regard to thoracotomy, Thoracic epidural analgesia is considered the benchmark with distinct benefits in improving post operative outcome. However it has its own disadvantages. Placement of an epidural catheter can be technically difficult. Failure rates and potentially serious complications limit the routine use of thoracic epidural in all surgeries.

There are only a few studies in literature which compare single shot intercostal block plus systemic analgesia with morphine versus thoracic epidural analgesia, the results of these studies have been inconsistent and are not entirely reliable.

In order to find out the true analgesic efficacy of intercostal block plus systemic morphine, we designed this study to compare this method with thoracic epidural in terms of post operative analgesia and incidence of side effects. The aim of this study is not demonstrate the superiority of one analgesic regime over the other, but to find out whether Intercostal block plus systemic morphine can be used as an alternative to thoracic epidural analgesia.

This study is designed as a Non- inferiority clinical trial.

## COMPARISON OF BASELINE CHARACTERISTICS

Demographic characteristics were well matched in both the groups. We compared the following variables: age, sex, height, weight, BMI, ASA grading for comorbid illness.

Though these patients underwent thoracotomies for different lung pathologies there was no statistically significant difference in baseline variables and both groups were comparable.

This study was designed in such a way that, the intra operative management of anaesthesia was standardized and similar in both the groups.

In the epidural group, the catheter was placed preoperatively, 3 ml of test dose with 0.5% bupivacaine given. Adequacy of block was checked before induction of anaesthesia. Epidural wasn't activated during the surgery.

Moiniche et al in a systemic review concluded that there is no substantial benefit with intra operative epidural catheter activation(107) and also there is no definite guidelines on the management of epidural catheter analgesia along with general anaesthesia in thoracic surgery.

### INTRAOPERATIVE CHARACTERISTICS

As with study design, there was no statistically significant difference in intraoperative characteristics between the two groups.

There was a significant difference in duration of surgery between both groups. Mean duration in morphine is less than epidural group.

The total dose of fentanyl and morphine used intraoperatively was also similar and comparable.

There was not much difference in the intraoperative fluid use between the two groups.

## POST OPERATIVE ANALGESIA

### COMPARISON OF PAIN SCORES BETWEEN THORACIC EPIDURAL AND INTERCOSTAL BLOCK PLUS INTRAVENOUS MORPHINE

We used NUMERICAL RATING SCALE (NRS) for assessing pain intensity, which is rated by the patient themselves so that we can slightly reduce the observer bias, still the patient bias existed.

We analysed pain scores at different time durations (1,6,12,18,24 hours ) during 1st post operative day, since pain during the first postoperative day is considered very severe and aggressive treatment of acute pain have long term outcome in thoracic surgery(111)

This study failed to demonstrate clinically significant difference in pain scores between the two groups at the end of the first post operative day. Though the pain scores were significantly less in the first 12 hours after surgery in the thoracic epidural group, by the end of 24 hours pain scores were similar both during rest($p=0.109$) and dynamic exercise($p=0.164$) in both groups.

The quality of analgesia was better in epidural group in first 12 hours both during rest and while doing breathing exercises, as the epidural group showed lesser mean pain scores (2-4) and there was a steady pain relief with no breakthrough pain. The Mean pain scores in the morphine group in the first 12 hours were also less (3-4), but higher than epidural.

These results were similar to the study done by Concha and colleagues (112) which showed that intercostals nerve block plus intraveneous PCA morphine is a good alternative for post thoracotomy pain management. Grant et al (113) also shown that satisfactory analgesia can be achieved with lumbar epidural and intravenous PCA fentanyl. Pertunnan et al(114)

demonstrated no significant difference between intercostals, epidural and paravertebral infusions and in this study all patients received background iv PCA morphine infusions. Wurning et al(115) also showed that pain relief with intercostal block was comparable to thoracic epidural analgesia. This study also showed pain management with intercostal block was superior in the first 24 hrs after surgery.

Toledo-pereyra et al had demonstrated that single shot intercostals block can provide good analgesia up to 6 hrs after surgery(57). Our study also had a similar result.

A systemic review of randomized trials evaluating regional techniques for post thoracotomy analgesia by Joshi et al(65) in 2008 showed that thoracic epidural analgesia and continuous paravertebral blocks provided better quality of analgesia than other regional techniques like intrathecal and intercostals methods for pain relief after thoracic surgery. They recommended thoracic epidural analgesia with LA plus opioid or continuous paravertebral blocks for post operative analgesia after thoracic surgery. They also opined that where these techniques are not possible, or are contraindicated, intrathecal opioid or intercostal blocks are recommended despite insufficient duration of analgesia, which requires the use of supplementary systemic analgesia.

CONTINUOUS INTRAVENOUS MORPHINE INFUSION

A meta analysis by Wu et al (91) compared thoracic epidural with Patient controlled analgesia with opioids and confirmed the efficacy and safety of epidural analgesia . The Meta analysis also concluded that continuous epidural infusion is better than patient controlled epidural analgesia.

After through search of literature, there was only one recent study by Della Rossa et al which compared thoracic epidural with continuous morphine infusion(116) which showed that epidural is much effective and the incidence of side effects is less. Problems with continuous infusion of

morphine is the danger of respiratory depression and other side effects of opioids. It also results in drug accumulation.

Still there are studies that have demonstrated the safety and efficacy of continuous morphine infusion. It is widely used in treatment of uncontrolled cancer pain (117) and also after scoliosis surgery(118).

With regard to thoracotomy, there is only a very few studies which compared continuous thoracic epidural with continuous intravenous morphine. No definite conclusion can be obtained from these studies as there was a lot of heterogenicity in the study design and subject numbers were small(91).

So for continuous infusion, in the morphine group, we used morphine at 0.015-0.02 mg/kg/hr. The drug was delivered using a secure elastrometric device (DOSIFUSER) for 48 hrs to avoid accidental overdosage. Low dose of morphine infusion used helped to reduce the incidence of side effects. All patients were carefully monitored for respiratory depression, desaturation and other side effects in thoracic HDU.

Our study showed pain relief was adequate, mean NRS 3-4 in the morphine group.

The incidence of side effects was also less in the morphine group.

TIME TO FIRST RESCUE ANALGESIC

The rescue analgesic was given to patients when they requested for pain relief. We analysed the time to first analgesic in hours. The mean hour at which patients required rescue analgesia were similar in both the groups. There was no significant difference between the groups

(p=0.2340).We also categorized the patients for number of times rescue analgesia for calculating the breakthrough pain. There was no significant difference.

SEDATION SCALE

Post operative sedation is an important and common side effect of morphine infusion with an incidence of 60%. Young McCaughan et al validated that sedation scale is also an important important indicator of impending respiratory depression (35).

In our study, there was statistically significant difference in sedation score between the two groups throughout the first post operative day.

There is a common assumption that, adequate pain relief induces sleep. Paqueron et al found that morphine induced sedation is not an appropriate indicator of adequate analgesia(119). These findings, clinically induced sedation with opioids does not assure adequate pain relief were also confirmed by a case controlled study done by Lentschener et al(120). Recent literature in 2012 by auburn et al also emphasized the titration of intravenous morphine(121).

But in our study we demonstrated that though the sedation scores were significantly different between the two groups (epidural group were less sedated). In the morphine group, mean scores were only between 2-3 during first post operative day that is most of the patients were cooperative, calm and oriented .

Only during the 1$^{st}$ hour after surgery patients in morphine group had highest mean sedation score of 4 (sd 0.88), in the epidural group also sedation scores were mean of 3.2 (sd 0.737). We interpreted that this difference may be due to the effects of general anaesthesia and drugs used intraoperatively.

At the end of first day, mean sedation scores and pain scores were similar in both the groups. This could be due to the accumulation of morphine after continuous infusion and achieving its effective therapeutic concentration.

SIDE EFFECTS

Bray et al said that one of the main side effect of using morphine infusion for postoperative analgesia is respiratory depression(40). In our study none of the patients had respiratory depression, since we used low dose morphine infusion. The incidence of side effects like nausea and vomiting were also less and there was no statistically significant difference between the two groups.

Kam p et al(122) studied the incidence and mechanisms of opioid induced pruritis and found that there is a very high incidence of 20-93% with epidural opioids and 13% after i.v administration. In our study, the incidence was zero and none of the patients had pruritis in both groups. We assumed that this could be due to the low dose of fentantyl 2µ/cc we used in epidural infusions as against the recommended 5µ/cc fentanyl in epidural infusions(74).

Since all patients were catheterized intraoperatively during the surgery as per surgical protocol, the incidence of urinary retention could not be studied.

Hypotension is said to be the main drawback of thoracic epidural(83). There was no significant difference in the incidence of hypotension between the two groups.

Since we used a low concentration of bupivacaine 0.1% in epidural, the incidence of hypotension was low and none of the patients had motor blockade. As showed in our study the quality of analgesia was also good with this concentration of local anaesthetic.

# LIMITATIONS OF THE STUDY

- Results fail to demonstrate a clear advantage of one group over the other in all aspects.
- No blinding was possible.

  This is a open labeled study, there is a high potential for patient and observer bias.

  We considered that sham epidural catheter placement in morphine group is unethical.
- Spirometric measurements weren't measured during the first post operative day due technical difficulties; though no major respiratory complications happened during the study period.
- We did not specifically look for shoulder pain
- We have not followed up patients until their discharge from hospital
- No data was collected regarding the patient satisfication regarding the quality of analgesia in both groups.

# CONCLUSION

**This randomized trial comparing post operative analgesia with CONTINUOUS THORACIC EPIDURAL VS BUPIVACAINE INTERCOSTAL BLOCK PLUS INTRAVENOUS MORPHINE INFUSION among patients undergoing elective lung surgery** showed that

- Pain scores were less in the epidural group during first 12hrs after surgery and the difference was statistically significant (p0.0505) both during rest and while doing breathing exercises.
- There was no statistically significant difference in pain scores between the two groups at the end of first post operative day both during rest (p=0.1090) and while doing breathing exercises (p=0.1642).
- There was no statistically significant difference in time for first rescue analgesia (p=0.2340) and incidence of side effects like nausea, vomiting, pruritis, respiratory depression and hypotension (p=1.000) between the two groups.
- There was significant difference in sedation scale between the two groups (p=0.0007). Patients in the thoracic epidural group were less sedated.

The study results show a slightly better quality of analgesia with thoracic epidural infusion of 0.1%bupivacine +2µ/cc fentanyl for post operative pain relief after thoracotomy when compared with single shot intercostals blockade with bupivacine +continuous morphine infusion.

The fact that this difference is probably not clinically significant makes us to believe that an intercostal blockade with morphine infusion can be considered as a valid alternative to thoracic epidural. This method of intercostals blockade plus morphine infusion, which is practiced in our

institution can be considered an easier, safe and reliable alternative to thoracic epidural and is a less time consuming method for post thoracotomy analgesia.

This study can be used as a pilot study for further extensive studies. A larger case series and a longer follow up plan should be done which will probably give a much more accurate estimation of pain relief. Future trials should take much more detailed consideration of the pulmonary morbidity and mortality and outcome with respect to better post operative analgesia.

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# APPENDIX 1

## PATIENT DATA COLLECTION SHEET

RANDOMIZED CONTROL TRIAL TO COMPARE CONTINOUS THORACIC EPIDURAL WITH BUPIVACINE- INTERCOSTAL BLOCK PLUS INTRAVENOUS MORPHINE FOR POST OPERATIVE ANALGESIA IN PATIENTS UNDERGOING ELECTIVE THORACOTOMY.

Number on study envelope:

Treatment Group:

**PATIENT DETAILS**

DATE:

NAME: AGE: SEX:

HOSPITAL NO:

WEIGHT: HEIGHT: BMI:

DIAGNOSIS:

SURGERY:

ASA:

COMORBIDITIES:

MEDICATIONS:

Standard Monitoring: ECG, ABP, $SPO_2$, $ETCO_2$

Induction with Propofol 2-3 mg/kg

Fentanyl upto 4 µg/kg

Morphine 0.1 mg/kg (max upto 0.15 mg/kg) and

Paracetamol 1 gm immediately after induction

Muscle Relaxant – Vecuronium / Atracurium

Please Note:

Significant rise in heart rate: > 10 beats rise during the event compared to just before the event.

Significant rise in BP: > 10 mm Hg rise in mean blood pressure compared to just before the event.

| EVENT | TIME | HEART RATE | BLOOD PRESSURE | INTERVENTION |
|---|---|---|---|---|
| **PRE INDUCTION** | | | | |
| **SKIN INCISION** | | Before / During | Before / During | |
| **OTHER EVENTS INTRA OP** | | | | |
| **CLOSING CHEST WALL** | | Before / During | Before / During | |
| **SKIN CLOSURE** | | Before / During | Before / During | |
| **AFTER EXTUBATION** | | | | |
| **15 MINUTES AFTER EXTUBATION BEFORE TRANSFER** | | | | |

Duration of $S_x$:

Total dose of Propofol:

Total dose of Fentanyl:

Total dose of Morphine:

Volume of administered blood, crystalloids, colloids:

Any other drug used to treat significant rise in HR/BP, dose:

| TIME | Drug Conc | Infusion Rate | Pain Score | Sedation Score | RR | BP | HR | Rescue Analgesia | Side Effect |
|---|---|---|---|---|---|---|---|---|---|
| **1st hour**<br><br>At Rest | | | | | | | | | |
| On coughing/position change | | | | | | | | | |
| **6th hour**<br><br>At Rest | | | | | | | | | |
| On Coughing/ Position Change | | | | | | | | | |
| **12th hour**<br><br>At Rest | | | | | | | | | |
| On Coughing/ Position Change | | | | | | | | | |
| **18th hour**<br><br>At Rest | | | | | | | | | |
| On Coughing/ Position Change | | | | | | | | | |
| **24th hour**<br><br>At Rest | | | | | | | | | |
| On Coughing/ Position Change | | | | | | | | | |

Time at first Rescue Analgesia:

NRS at time of rescue analgesia:

In epidural group please note motor blockade

Note:

Side effect like: Decrease in saturation, Hypotension requiring treatment, Respiratory depression, Nausea, Vomiting, Itching

# APPENDIX 2

## INFORMATION SHEET

## Christian Medical College, Vellore

## Department of Anaesthesia

***A Randomized Control Trail to Compare continuous Thoracic Epidural with Bupivacine Intercostal Block plus Intravenous Morphine for Post operative Analgesia in patients Undergoing Elective Thoracotomy.***

## Information sheet

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You are being requested to participate in a study to see if a technique called Thoracic Epidural can help give you better pain relief after lung surgery.

**Routine pain management after lung surgery**

Post operative pain after lung surgery is treated with intravenous/oral pain killers usually opoids(like morphine) and NSAIDS(voveran).Sometimes these drugs can cause nausea, vomitting,drowsiness. Ocassionally pain relief may not be complete.

Hence we are doing this study to Identify the best possible method with minimal side effects for post operative pain relief after lung surgery.

We hope to include about 50 patients in this study.

**What is Thoracic Epidural?**

The Spinal cord, in our back, is the main pathway connecting the brain and rest of our body. It is a long thin bundle of nervous tissue. The Cord is protected by three layers of nervous tissue and also by the surrounding bones. Epidural space is the space lying between the outermost layer of spinalcord and the surrounding thick muscles attached to bones. It contains nerve roots which carry pain sensation from particular area of the body. Thoracic Epidural anaesthesia is a technique where pain killing drugs are passed into your back via small tube in the epidural space. It is a regional anaesthetic, which means the drugs is injected around the nerves that carry signal from the part of your body. The result will be you feel numb at that operated site,giving you effective pain relief.

**What are the potential problems with this technique?**

Thoracic epidural technique is being routinely practised for various major abdominal surgery and proven to be very beneficial.It is a technically challenging procedure. There is a very small risk of nerve damage leaving you a numb patch on leg or foot, this rarely happens.The risk is about 4 in 10000(0.04%).some time you may also experience headache,itching. I can assure you that placement of the cathetar will be done only experienced anaesthesia doctors and you will be carefully monitored for any complications.

**If you take part in this study what will you have to do?**

If you agree to participate in this study, you will be alloted by computer to receive either thoracic epidural or usual intravenous morphine for pain relief after surgery.

After operation all patients will be transferred to thoracic ICU/HDU and careful monitoring and nursing will be done.

In the postoperative period you will be asked to grade your pain on a scale of 1 to 10.[1 =no pain,10=extreme pain].In case pain relief is inadequate ,you will be given other pain killers.

**Can you withdraw from this study after it starts?**

Your participation in this study is entirely voluntary and you are also free to decide, to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way. In addition,

if you experience any serious side effects or your condition worsens, the study will be stopped and you may be given additional treatment

**What will happen if you develop any study related injury?**

We do not expect any injury to happen to you but if you do develop any side effects or problems due to the study, these will be treated at no cost to you. We are unable to provide any monetary compensation, however.

**Will you have to pay for drugs/participating in this study?**

Both epidural kit and the drugs for epidural infusion will be given free.

All other protocols for post operative patients will be followed strictly, only method of pain relief will vary.

**What happens after the study is over?**

You may or may not benefit from the study drug that you are given. Once the study is over, if the technique shows benefit in treatment of post operative pain relief, then the this method will be used in future in all patients undergoing elective thoracotomy.

**Will your personal details be kept confidential?**

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

**If you have any further questions, please ask the thoracic surgery doctor or anaesthetist.**

# APPENDIX 3

# INFORMED CONSENT

**CONSENT TO TAKE PART IN A CLINICAL TRIAL**

**Study Title:** *A randomized control trail to compare continous thoracic epidural with bupivacine intercostal block plus intravenous morphine for post operative analgesia in patients undergoing elective Thoracotomy.*

**Study Number:**

**Participant's name:**

**Date of Birth / Age (in years)**:

I_____

_____, son/daughter of _____

(Please tick boxes)

Declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had. [ ]

I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]

I also understand that neither I, nor my doctors, will have any choice or knowledge of whether I will get intravenous morphine or epidural for analgesia[ ]

I also understand that, bupivacaine and epidural will be provided free()

I understand that I will receive free treatment for any study related injury or adverse event but I will not receive and other financial compensation [ ]

I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]

I understand that my identity will not be revealed in any information released to third parties or published [ ]

I voluntarily agree to take part in this study [ ]

| | |
|---|---|
| Name: | Name of witness: |
| Signature: | Relation to participant |
| Date: | Date: |

# APPENDIX 4

## MASTER SHEET

| Relation to p | grouprand | sexsex | ageage | wtweight | htheight | bmibodym | diagdiagno | sursurgery | typetypesu | anaesthesi | comorbidc | hr1heartra | sbp1systol |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 2 | 31 | 60 | 153 | 25.6 | bronchicta | L pnemone | 1 | 1 | | 107 | 125 |
| 2 | 1 | 1 | 19 | 65 | 171 | 22.2 | r main bror | r pnemone | 1 | 2 | | 92 | 120 |
| 3 | 2 | 2 | 43 | 46 | 157 | 18.7 | l lower lob | l lower lob | 2 | 2 | 6 hypothyr | 82 | 102 |
| 4 | 1 | 1 | 62 | 72 | 168 | 25.5 | l ul nsclc | l upper lob | 2 | 2 | 2 | 68 | 170 |
| 5 | 2 | 2 | 44 | 65 | 145 | 30.9 | hydatid cys | l pl thoracc | 3 | 2 | 2 | 112 | 170 |
| 6 | 1 | 1 | 43 | 54 | 165 | 19.8 | r ll hydatid | r pl thoracc | 3 | 1 | | 90 | 100 |
| 7 | 2 | 2 | 53 | 51 | 152 | 22.1 | b/l hydatid | r pl thoracc | 3 | 1 | | 102 | 140 |
| 8 | 1 | 1 | 19 | 68 | 165 | 25 | r ll hydatid | r pl thoracc | 3 | 1 | | 92 | 107 |
| 9 | 2 | 1 | 31 | 35 | 150 | 15.6 | l loculated | l pl thoracc | 4 | 2 | 6 restrictiv | 98 | |
| 10 | 2 | 2 | 22 | 53 | 156 | 21.8 | r pyothora | r pl thoracc | 4 | 2 | 6 pulm tb | 110 | 125 |
| 11 | 1 | 1 | 22 | 68 | 155 | 28.3 | l lung multi | l pl thoracc | 3 | 1 | | 130 | 130 |
| 12 | 2 | 2 | 48 | 62 | 148 | 28.3 | r middle lo | r pl thoracc | 2 | 1 | | 98 | 148 |
| 13 | 1 | 1 | 65 | 83 | 164 | 30.9 | postr medi | r pl thoracc | 5 | 2 | 2 | 97 | 197 |
| 14 | 1 | 2 | 43 | 59 | 145 | 28.1 | bronchiect | l pnemone | 1 | 3 | 6 | 122 | 158 |
| 15 | 2 | 1 | 76 | 70 | 157 | 28.4 | carcinoma | r pl thoracc | 3 | 2 | 2 | 57 | 122 |
| 16 | 1 | 2 | 26 | 53 | 157 | 21.5 | cystic mass | l pl thoracc | 3 | 1 | | 150 | 136 |
| 17 | 1 | 2 | 21 | 32 | 148 | 14.6 | l destroyed | l pnemone | 1 | 2 | 6 | 120 | 105 |
| 18 | 2 | 1 | 42 | 63 | 173 | 21 | r loculated | r pl thoracc | 4 | 2 | 6 | 72 | 133 |
| 19 | 1 | 1 | 56 | 48 | 154 | 20.2 | r ll hydatid | r lower lob | 2 | 2 | 3 | 100 | 140 |
| 20 | 2 | 1 | 39 | 64 | 155 | 26.6 | postr medi | r pl thoracc | 3 | 1 | | 92 | 118 |
| 21 | 1 | 1 | 30 | 66 | 160 | 25.6 | r intermedi | r pl thoracc | 2 | 1 | | 106 | 107 |
| 22 | 2 | 1 | 38 | 85 | 160 | 33.2 | l loculated | l pl thoracc | 4 | 1 | | 83 | 124 |
| 23 | 2 | 1 | 38 | 59 | 170 | 20.3 | r ul aspergi | r pl thoracc | 2 | 1 | | 94 | 136 |
| 24 | 1 | 2 | 45 | 57 | 158 | 22.6 | r ll bronchi | r pl thoracc | 2 | 2 | 3 | 90 | 163 |
| 25 | 2 | 2 | 24 | 39 | 155 | 16.2 | r side bullo | r thoracotc | 4 | 1 | | 92 | 108 |
| 26 | 1 | 1 | 41 | 72 | 160 | 24.2 | r ul aspergi | r pl thoracc | 2 | 1 | | 104 | 140 |
| 27 | 2 | 2 | 38 | 48 | 145 | 22.8 | r pleural ef | r pl thoracc | 4 | 2 | 6 jaundice | 144 | 133 |
| 28 | 1 | 2 | 55 | 60 | 150 | 26.7 | l ul bronchi | l pl thoracc | 2 | 2 | 6 | 88 | 155 |
| 29 | 2 | 1 | 60 | 70 | 166 | 25.3 | spindle cell | r pl thoracc | 3 | 2 | 6 rld | 115 | 152 |
| 30 | 1 | 2 | 36 | 54 | 154 | 22.6 | l ll endolun | l pl thoracc | 1 | 2 | 6 bronchie | 122 | 138 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 31 | 1 | 2 | 26 | 50 | 154 | 21.1 | r ml bronch | r mid lobec | 2 | 2 | 6 bronchie | 92 | 100 |
| 32 | 2 | 1 | 41 | 49 | 160 | 18.9 | r ul,ml bror | r pl thoracc | 2 | 2 | | 75 | 104 |
| 33 | 2 | 1 | 36 | 63 | 150 | 28 | l lung bron | l pl thoracc | 1 | 3 | 6 restrictiv | 86 | 130 |
| 34 | 1 | 1 | 18 | 42 | 160 | 16.4 | hydatidosis | r pl thoracc | 3 | 1 | | 92 | 89 |
| 35 | 2 | 1 | 30 | 61 | 156 | 25.1 | l lung bron | l pl thoracc | 2 | 2 | 6 bronchie | 98 | 147 |
| 36 | 1 | 1 | 40 | 57 | 161 | 22 | sub carinal | r pl thoracc | 5 | 1 | | 81 | 145 |
| 37 | 1 | 1 | 46 | 44 | 152 | 19 | r lung rupt | r pl thoracc | 3 | 2 | 6 obst lung | 94 | 163 |
| 38 | 2 | 1 | 17 | 48 | 156 | 19.7 | l ll hydatid | l pl thoracc | 3 | 1 | | 60 | 90 |
| 39 | 1 | 2 | 31 | 72 | 160 | 29.7 | l ll ul bronc | l pl thoracc | 1 | 2 | 6 pulm tb | 94 | 124 |
| 40 | 2 | 1 | 62 | 61 | 161 | 23.5 | l loculated | l pl thoracc | 4 | 2 | 1,2 | 110 | 124 |
| 41 | 1 | 1 | 30 | 46 | 154 | 19.4 | r hydatid cy | r pl thoracc | 3 | 1 | | 103 | 110 |
| 42 | 2 | 1 | 17 | 46 | 165 | 16.9 | l loculated | l pl mthora | 4 | 1 | | 114 | 125 |
| 43 | 1 | 2 | 30 | 66 | 154 | 27.8 | l bronchial | l pl thoracc | 2 | 2 | obst lung d | 103 | 138 |
| 44 | 2 | 1 | 31 | 43 | 165 | 15.8 | l hemothor | l pl thoracc | 4 | 2 | 6 seizure d | 107 | 145 |
| 45 | 1 | 1 | 52 | 55 | 165 | 20.2 | l ll hydatid | l pl thoracc | 3 | 1 | | 76 | 149 |
| 46 | 2 | 2 | 29 | 41 | 148 | 18.7 | ant med tu | l pl thoracc | 2 | 2 | 6 hypothyr | 102 | 130 |
| 47 | 1 | 1 | 43 | 75 | 172 | 25.4 | l lingular ha | l pl thoracc | 3 | 2 | 2 | 86 | 175 |
| 48 | 2 | 1 | 59 | 70 | 160 | 27.3 | r loculated | r pl thoracc | 4 | 2 | 1 | 77 | 121 |
| 49 | 2 | 1 | 26 | 58 | 175 | 18.9 | r loculated | r pl thoracc | 4 | 2 | 6 pulm tb | 90 | 130 |
| 50 | 1 | 1 | 44 | 56 | 162 | 21.3 | adenocarci | r pl thoracc | 2 | 1 | | 115 | 116 |

| dbp1diasto | hrb2heartr | hra2heartr | sbpb2systo | sbpa2systo | dbpb2diast | dbpa2diast | hrb3heartr | hra3heartr | sbpb3systo | sbpa3systo | dbpb3diast | dbpb3dias1 | otherevent |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 70 | 106 | 115 | 98 | 142 | 60 | 83 | 90 | 92 | 79 | 79 | 45 | 57 | 1 |
| 70 | 92 | 94 | 92 | 90 | 56 | 60 | 97 | 97 | 92 | 90 | 60 | 60 | 2 |
| 60 | 59 | 77 | 97 | 101 | 63 | 50 | 70 | 72 | 80 | 73 | 42 | 43 | 2 |
| 84 | 68 | 70 | 110 | 120 | 60 | 66 | 66 | 72 | 106 | 110 | 70 | 70 | 2 |
| 80 | 108 | 104 | 82 | 136 | 55 | 85 | 82 | 82 | 96 | 96 | 58 | 58 | 2 |
| 61 | 90 | 90 | 86 | 120 | 56 | 63 | 75 | 89 | 83 | 94 | 44 | 50 | 2 |
| 83 | 78 | 84 | 100 | 89 | 50 | 47 | 76 | 77 | 71 | 83 | 38 | 44 | 1 |
| 60 | 85 | 91 | 107 | 115 | 73 | 75 | 96 | 93 | 115 | 106 | 81 | 73 | 1 |
| 54 | 100 | 104 | 97 | 99 | 60 | 62 | 103 | 106 | 89 | 93 | 54 | 54 | 1 |
| 68 | 89 | 84 | 95 | 108 | 54 | 64 | 69 | 85 | 96 | 102 | 44 | 53 | 2 |
| 90 | 69 | 69 | 93 | 98 | 58 | 62 | 88 | 92 | 80 | 85 | 50 | 50 | 2 |
| 68 | 77 | 95 | 90 | 151 | 50 | 79 | 82 | 84 | 112 | 118 | 62 | 66 | 2 |
| 977 | 87 | 81 | 97 | 112 | 51 | 56 | 76 | 76 | 100 | 110 | 50 | 53 | 1 |
| 102 | 114 | 116 | 100 | 90 | 70 | 50 | 96 | 98 | 90 | 90 | 50 | 50 | 2 |
| 59 | 52 | 52 | 105 | 81 | 47 | 39 | 53 | 53 | 109 | 114 | 52 | 54 | 2 |
| 82 | 107 | 110 | 90 | 112 | 57 | 73 | 122 | 133 | 123 | 109 | 75 | 72 | 2 |
| 65 | 89 | 76 | 84 | 103 | 40 | 60 | 109 | 87 | 100 | 96 | 62 | 54 | 2 |
| 74 | 57 | 64 | 101 | 121 | 56 | 67 | 67 | 70 | 102 | 101 | 53 | 56 | 2 |
| 77 | 88 | 77 | 74 | 73 | 47 | 44 | 100 | 89 | 96 | 98 | 57 | 59 | 2 |
| 76 | 72 | 79 | 85 | 106 | 50 | 69 | 65 | 67 | 98 | 100 | 51 | 58 | 2 |
| 66 | 92 | 110 | 100 | 108 | 62 | 74 | 64 | 66 | 94 | 96 | 53 | 54 | 2 |
| 74 | 67 | 68 | 87 | 93 | 53 | 57 | 74 | 78 | 105 | 89 | 60 | 50 | 1 |
| 71 | 78 | 101 | 80 | 92 | 43 | 56 | 80 | 83 | 78 | 86 | 45 | 49 | 2 |
| 86 | 88 | 94 | 111 | 124 | 68 | 75 | 103 | 98 | 73 | 90 | 51 | 58 | 2 |
| 66 | 81 | 84 | 88 | 92 | 36 | 41 | 68 | 68 | 92 | 94 | 43 | 51 | 2 |
| 74 | 95 | 98 | 88 | 96 | 59 | 64 | 78 | 77 | 80 | 95 | 54 | 61 | 1 |
| 73 | 129 | 130 | 108 | 110 | 57 | 55 | 119 | 120 | 92 | 91 | 41 | 40 | 2 |
| 75 | 61 | 58 | 129 | 132 | 57 | 68 | 92 | 94 | 84 | 86 | 50 | 58 | 2 |
| 81 | 103 | 102 | 121 | 114 | 71 | 68 | 90 | 91 | 80 | 83 | 47 | 53 | 2 |
| 73 | 72 | 72 | 94 | 96 | 58 | 60 | 72 | 74 | 111 | 109 | 61 | 60 | 2 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 72 | 88 | 91 | 98 | 99 | 60 | 62 | 81 | 86 | 92 | 90 | 50 | 47 | 2 |
| 55 | 84 | 88 | 119 | 120 | 62 | 64 | 76 | 82 | 96 | 90 | 60 | 58 | 2 |
| 70 | 100 | 126 | 110 | 125 | 70 | 65 | 84 | 86 | 95 | 94 | 60 | 62 | 2 |
| 54 | 109 | 113 | 98 | 113 | 56 | 73 | 120 | 113 | 86 | 103 | 53 | 60 | 2 |
| 90 | 100 | 102 | 112 | 114 | 70 | 70 | 101 | 100 | 108 | 109 | 74 | 75 | 2 |
| 73 | 77 | 76 | 94 | 90 | 61 | 60 | 87 | 80 | 101 | 103 | 53 | 54 | 2 |
| 89 | 75 | 73 | 86 | 87 | 55 | 55 | 73 | 72 | 93 | 95 | 43 | 45 | 2 |
| 60 | 64 | 84 | 80 | 110 | 50 | 70 | 80 | 80 | 84 | 90 | 60 | 50 | 2 |
| 65 | 68 | 65 | 81 | 128 | 45 | 73 | 66 | 65 | 105 | 82 | 69 | 52 | 2 |
| 62 | 62 | 64 | 92 | 98 | 60 | 56 | 72 | 70 | 90 | 92 | 50 | 54 | 2 |
| 72 | 97 | 101 | 82 | 83 | 48 | 51 | 105 | 108 | 109 | 93 | 48 | 37 | 2 |
| 77 | 75 | 85 | 102 | 108 | 52 | 61 | 106 | 108 | 90 | 96 | 50 | 56 | 2 |
| 84 | 85 | 81 | 89 | 88 | 50 | 47 | 94 | 94 | 84 | 84 | 48 | 47 | 2 |
| 90 | 109 | 105 | 112 | 108 | 69 | 64 | 109 | 106 | 114 | 117 | 74 | 74 | 2 |
| 68 | 69 | 64 | 100 | 104 | 59 | 56 | 73 | 74 | 93 | 94 | 53 | 53 | 2 |
| 80 | 104 | 102 | 106 | 110 | 64 | 72 | 92 | 94 | 100 | 104 | 60 | 62 | 2 |
| 109 | 67 | 68 | 95 | 99 | 54 | 53 | 78 | 72 | 118 | 102 | 70 | 63 | 2 |
| 71 | 68 | 72 | 117 | 132 | 53 | 62 | 81 | 86 | 102 | 114 | 58 | 61 | 2 |
| 80 | 102 | 110 | 98 | 116 | 56 | 80 | 92 | 96 | 98 | 110 | 60 | 70 | |
| 65 | 95 | 91 | 97 | 106 | 57 | 62 | 78 | 77 | 102 | 102 | 62 | 60 | 2 |

| hrb4heartr | hra4heartr | sbpb4systo | sbpa4systo | dbpb4diast | dbpb4dias1 | hr5heartra | sbp5systol | dbp5diasto | durationdu | prodosetot | fendosetot | mordoseto | fluidsintr |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 90 | 90 | 85 | 90 | 52 | 60 | 84 | 124 | 74 | 3 | 200 | 200 | 10 | 0.5 |
| 98 | 97 | 94 | 90 | 58 | 60 | 88 | 130 | 84 | 4 | 500 | 150 | 7 | 1 |
| 73 | 70 | 74 | 72 | 42 | 42 | 77 | 94 | 52 | 4 | 100 | 150 | 6 | 1.5 |
| 64 | 62 | 110 | 114 | 60 | 64 | 80 | 122 | 62 | 3 | 170 | 300 | 0 | 1 |
| 85 | 83 | 95 | 95 | 62 | 62 | 95 | 98 | 62 | 3 | 120 | 100 | 8 | 1 |
| 73 | 72 | 93 | 94 | 46 | 48 | 86 | 130 | 55 | 3 | 100 | 180 | 6 | 1 |
| 84 | 94 | 95 | 82 | 51 | 43 | 103 | 91 | 52 | 3 | 250 | 160 | 6 | 0.6 |
| 90 | 87 | 108 | 110 | 80 | 82 | 90 | 147 | 77 | 4 | 180 | 270 | 10 | 1 |
| 99 | 104 | 100 | 97 | 63 | 53 | 98 | 96 | 40 | 4 | 150 | 140 | 4 | 1 |
| 78 | 73 | 111 | 93 | 58 | 45 | 110 | 120 | 75 | 3 | 100 | 225 | 4 | 0.5 |
| 92 | 95 | 84 | 85 | 49 | 50 | 120 | 120 | 90 | 4 | 130 | 200 | 10 | 1.5 |
| 77 | 76 | 95 | 102 | 53 | 55 | 85 | 142 | 68 | 3 | 100 | 200 | 8 | 1 |
| 71 | 73 | 115 | 119 | 56 | 58 | 89 | 143 | 65 | 3 | 130 | 275 | 6 | 1 |
| 98 | 98 | 96 | 98 | 60 | 60 | 104 | 110 | 60 | 4 | 160 | 250 | 6 | 1.5 |
| 50 | 50 | 109 | 109 | 52 | 52 | 52 | 131 | 84 | 2 | 110 | 150 | 6 | 0.7 |
| 110 | 101 | 91 | 86 | 64 | 60 | 99 | 110 | 54 | 3 | 150 | 200 | 5 | 1 |
| 80 | 85 | 110 | 100 | 60 | 70 | 74 | 100 | 70 | 4 | 80 | 140 | 4 | 1.5 |
| 76 | 78 | 110 | 108 | 60 | 78 | 78 | 130 | 70 | 3 | 100 | 200 | 10 | 1 |
| 98 | 96 | 92 | 90 | 53 | 52 | 92 | 100 | 60 | 4 | 150 | 100 | 5 | 1.5 |
| 60 | 62 | 93 | 94 | 53 | 52 | 64 | 100 | 60 | 4 | 100 | 200 | 10 | 1.5 |
| 68 | 68 | 93 | 95 | 49 | 61 | 91 | 108 | 67 | 5 | 100 | 200 | 6 | 1.5 |
| 79 | 78 | 93 | 92 | 53 | 51 | 78 | 100 | 60 | 3 | 200 | 200 | 8 | 1.5 |
| 89 | 83 | 81 | 89 | 51 | -49 | 85 | 115 | 71 | 4 | 130 | 200 | 10 | 1 |
| 85 | 80 | 74 | 80 | 43 | -43 | 88 | 98 | 58 | 4 | 100 | 200 | 10 | 0.5 |
| 71 | 67 | 92 | 90 | 42 | 40 | 90 | 124 | 60 | 4 | 80 | 100 | 4 | 1 |
| 75 | 76 | 85 | 88 | 55 | 57 | 95 | 110 | 60 | 5 | 100 | 100 | 6 | 0.5 |
| 122 | 123 | 107 | 108 | 54 | 55 | 112 | 113 | 71 | 3 | 70 | 140 | 6 | 0.5 |
| 99 | 92 | 87 | 82 | 55 | 52 | 94 | 107 | 68 | 4 | 100 | 150 | 6 | 1 |
| 85 | 84 | 95 | 99 | 50 | 57 | 101 | 110 | 60 | 4 | 100 | 200 | 10 | 1 |
| 80 | 87 | 101 | 105 | 59 | 60 | 110 | 95 | 37 | 5 | 100 | 100 | 6 | 0.5 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 80 | 81 | 89 | 87 | 50 | 50 | 82 | 90 | 50 | 3 | 100 | 300 | 10 | 1 |
| 83 | 81 | 90 | 94 | 57 | 61 | 113 | 134 | 75 | 3 | 260 | 300 | 4 | 1 |
| 90 | 92 | 100 | 100 | 70 | 60 | 92 | 110 | 70 | 4 | 200 | 300 | 10 | 3 |
| 120 | 114 | 103 | 110 | 60 | 70 | 108 | 114 | 70 | 4 | 250 | 150 | 5 | 1 |
| 96 | 97 | 108 | 116 | 73 | 80 | 111 | 132 | 85 | 3 | 350 | 350 | 10 | 1 |
| 82 | 84 | 90 | 89 | 51 | 51 | 113 | 107 | 65 | 3 | 100 | 100 | 7 | 1 |
| 74 | 70 | 102 | 101 | 44 | 43 | 110 | 111 | 54 | 3 | 100 | 100 | 8 | 1 |
| 80 | 82 | 84 | 85 | 50 | 52 | 92 | 120 | 60 | 4 | 100 | 200 | 7 | 2 |
| 68 | 68 | 98 | 94 | 60 | 57 | 76 | 113 | 72 | 5 | 100 | 125 | 10 | 0.5 |
| 76 | 78 | 86 | 90 | 50 | 50 | 92 | 100 | 68 | 3 | 100 | 150 | 10 | 0.5 |
| 102 | 103 | 98 | 98 | 40 | 40 | 108 | 106 | 43 | 4 | 100 | 100 | 6 | 1 |
| 110 | 113 | 82 | 104 | 56 | 37 | 63 | 105 | 57 | 2 | 100 | 100 | 7 | 0.5 |
| 84 | 83 | 93 | 92 | 50 | 50 | 126 | 124 | 53 | 5 | 100 | 150 | 7 | 1 |
| 101 | 100 | 117 | 118 | 75 | 76 | 104 | 127 | 82 | 3 | 100 | 150 | 10 | 0.5 |
| 74 | 73 | 99 | 110 | 60 | 60 | 92 | 131 | 74 | 3 | 100 | 100 | 7 | 1 |
| 94 | 90 | 110 | 112 | 64 | 64 | 106 | 114 | 72 | 4 | 80 | 150 | 4 | 0.5 |
| 64 | 66 | 102 | 101 | 57 | 56 | 77 | 104 | 48 | 2 | 100 | 100 | 8 | 1 |
| 85 | 87 | 116 | 138 | 62 | 62 | 110 | 132 | 74 | 3 | 200 | 300 | 10 | 1 |
| 90 | 92 | 94 | 90 | 58 | 60 | 96 | 124 | 74 | 3 | 250 | 150 | 10 | 1 |
| 82 | 77 | 105 | 95 | 59 | 53 | 102 | 101 | 59 | 4 | 100 | 175 | 10 | 1 |

| fluidsint1 | vaspressan | painscr1nu | painscr12n | painscr6nu | painscr62n | painscr121 | painscr122 | painscr181 | painscr182 | painscr241 | painscr242 | ranalgresc | ranalgnonu |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.5 | 1 | 2 | 2 | 7 | 8 | 1 | 1 | 3 | 5 | 2 | 2 | 1 | 1 |
| 0.5 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 2 | 8 | 1 | 3 | 2 | |
| | 2 | 3 | 6 | 2 | 4 | 3 | 4 | 2 | 4 | 3 | 5 | 2 | |
| | 2 | 2 | 2 | 1 | 3 | 1 | 1 | 1 | 4 | 1 | 2 | 2 | |
| | 2 | 4 | 5 | 7 | 8 | 1 | 5 | 4 | 5 | 2 | 3 | 2 | |
| | 2 | 5 | 5 | 5 | 5 | 4 | 5 | 3 | 3 | 2 | 2 | 1 | 1 |
| | 1 | 3 | 2 | 4 | 8 | 2 | 2 | 3 | 2 | 2 | 2 | 1 | 1 |
| | 2 | 2 | 3 | 2 | 3 | 3 | 4 | 2 | 3 | 4 | 4 | 1 | 1 |
| 0.5 | 2 | 5 | 5 | 3 | 3 | 1 | 1 | 2 | 3 | 2 | 3 | 1 | 1 |
| 0.5 | 2 | 2 | 3 | 2 | 2 | 1 | 1 | 5 | 4 | 3 | 4 | 2 | |
| | 2 | 3 | 4 | 3 | 4 | 3 | 3 | 2 | 3 | 3 | 2 | 1 | 2 |
| | 2 | 4 | 4 | 3 | 4 | 2 | 2 | 2 | 3 | 4 | 3 | 1 | 2 |
| 0.5 | 2 | 5 | 5 | 3 | 4 | 3 | 4 | 2 | 3 | 2 | 2 | 1 | 2 |
| | 2 | 5 | 5 | 3 | 4 | 2 | 3 | 2 | 3 | 4 | 4 | 2 | |
| | 2 | 4 | 4 | 2 | 3 | 2 | 2 | 3 | 3 | 1 | 2 | 1 | 1 |
| | 1 | 5 | 5 | 5 | 8 | 1 | 1 | 3 | 4 | 3 | 3 | 1 | 2 |
| 0.5 | 2 | 2 | 3 | 4 | 4 | 2 | 2 | 2 | 4 | 3 | 4 | 2 | |
| | 2 | 5 | 5 | 3 | 3 | 4 | 4 | 2 | 3 | 2 | 2 | 2 | 1 |
| | | 3 | 3 | 4 | 5 | 4 | 4 | 2 | 3 | 2 | 2 | 2 | |
| | 2 | 2 | 3 | 5 | 7 | 2 | 4 | 5 | 7 | 2 | 3 | 1 | 2 |
| | 2 | 1 | 1 | 2 | 3 | 1 | 2 | 2 | 2 | 1 | 2 | 1 | 1 |
| | 1 | 3 | 3 | 2 | 3 | 2 | 2 | 3 | 3 | 1 | 2 | 2 | |
| 0.5 | 2 | 4 | 4 | 3 | 4 | 4 | 4 | 2 | 2 | 3 | 4 | 2 | |
| 0.5 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 2 | 3 | 2 | 3 | 1 | 1 |
| | 2 | 4 | 5 | 2 | 3 | 1 | 2 | 3 | 3 | 2 | 2 | 1 | 2 |
| 0.5 | 1 | 5 | 3 | 4 | 4 | 1 | 2 | 5 | 5 | 2 | 2 | 1 | 1 |
| 0.5 | 2 | 4 | 4 | 3 | 4 | 2 | 3 | 2 | 3 | 2 | 2 | 2 | |
| 0.5 | 1 | 2 | 2 | 3 | 3 | 6 | 7 | 2 | 2 | 1 | 2 | 1 | 1 |
| 0.5 | 2 | 4 | 4 | 2 | 3 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | |
| 1 | 2 | 2 | 3 | 1 | 2 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | |

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| | 2 | 4 | 5 | 2 | 2 | 3 | 6 | 2 | 3 | 2 | 3 | 2 | |
| | 2 | 2 | 2 | 2 | 3 | 2 | 3 | 3 | 4 | 3 | 4 | 1 | 1 |
| 0.5 | 2 | 4 | 4 | 5 | 5 | 3 | 4 | 2 | 3 | 3 | 4 | 2 | |
| 1 | 2 | 6 | 6 | 3 | 3 | 2 | 3 | 2 | 2 | 2 | 2 | 1 | 1 |
| | 2 | 4 | 4 | 2 | 3 | 3 | 3 | 3 | 4 | 2 | 3 | 2 | |
| 0.5 | 2 | 3 | 3 | 2 | 3 | 2 | 2 | 2 | 2 | 4 | 5 | 2 | |
| 0.5 | 2 | 3 | 3 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| | 2 | 5 | 5 | 4 | 4 | 4 | 4 | 2 | 3 | 2 | 2 | 2 | |
| 0.5 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 1 | 2 | 2 | |
| 0.5 | 2 | 4 | 4 | 3 | 4 | 2 | 3 | 1 | 2 | 2 | 3 | 2 | |
| 0.5 | 2 | 1 | 1 | 1 | 2 | 1 | 1 | 2 | 3 | 2 | 3 | 2 | |
| 0.5 | 2 | 4 | 4 | 3 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| 0.5 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 3 | 2 | |
| 0.5 | 2 | 3 | 4 | 3 | 4 | 1 | 2 | 1 | 2 | 2 | 3 | 1 | 3 |
| 0.5 | 2 | 1 | 1 | 2 | 3 | 1 | 1 | 1 | 2 | 1 | 2 | 2 | |
| 0.5 | 2 | 4 | 4 | 3 | 4 | 2 | 3 | 4 | 5 | 3 | 4 | 1 | 2 |
| 0.5 | 2 | 2 | 2 | 3 | 3 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | |
| 0.5 | 2 | 3 | 4 | 2 | 2 | 1 | 2 | 1 | 3 | 4 | 4 | 1 | 2 |
| 0.5 | 2 | 4 | 5 | 4 | 4 | 2 | 3 | 3 | 4 | 2 | 3 | 1 | 1 |
| 0.5 | 2 | 1 | 2 | 1 | 2 | 2 | 2 | 2 | 3 | 1 | 2 | 1 | 1 |

| hoursafter | hoursafte1 | painscrran | sedscr1sed | sedscr6sed | sedscr12se | sedscr18se | sedscr24se | sesideeffe | naunausea | nnaunoepi: | vomvomitt | nvomnoep |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 15 | 7 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | | 2 | 1 |
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| | | | 5 | 4 | 5 | 3 | 2 | 2 | 2 | | 2 | |
| | | | 3 | 2 | 2 | 2 | 2 | 2 | 2 | | 2 | |
| | | | 4 | 2 | 3 | 2 | 3 | 2 | 2 | | 2 | |
| 1 | | 5 | 3 | 3 | 2 | 2 | 2 | 2 | 2 | | 2 | |
| 7 | | 8 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | | 2 | |
| 8 | | 4 | 3 | 2 | 2 | 2 | 2 | 1 | 2 | | 1 | 1 |
| 1 | 20 | 8 | 1 | 2 | 4 | 3 | 2 | 1 | 1 | 1 | 2 | |
| | | | 3 | 2 | 4 | 2 | 2 | 2 | 2 | | 2 | |
| 9 | | 8 | 3 | 3 | 2 | 2 | 2 | 2 | 2 | | 2 | |
| 0 | 30 | 8 | 4 | 3 | 2 | 3 | 2 | 1 | 1 | 1 | 1 | 1 |
| 1 | | 5 | 3 | 3 | 3 | 2 | 2 | 1 | 2 | | 1 | 1 |
| | | | 5 | 3 | 2 | 3 | 2 | 2 | 2 | | 2 | |
| 1 | | 9 | 4 | 3 | 2 | 2 | 2 | 2 | 2 | | 2 | |
| 3 | | 8 | 3 | 3 | 3 | 2 | 2 | 2 | 2 | | 2 | |
| | | | 4 | 2 | 2 | 2 | 2 | 2 | 2 | | 2 | |
| | | | 5 | 4 | 4 | 3 | 3 | 2 | 2 | | 2 | |
| | | | 4 | 4 | 3 | 2 | 2 | 2 | 2 | | 2 | |
| 5 | | 5 | 4 | 1 | 4 | 3 | 2 | 1 | 2 | | 1 | 1 |
| 9 | | 7 | 4 | 3 | 3 | 2 | 3 | 1 | 2 | | 1 | 1 |
| | | | 4 | 3 | 4 | 2 | 2 | 2 | 2 | | 2 | |
| | | | 4 | 3 | 4 | 3 | 4 | 1 | 1 | 2 | 1 | 1 |
| 9 | | 6 | 4 | 4 | 3 | 2 | 2 | 2 | 2 | | 2 | |
| 1 | | 8 | 5 | 4 | 4 | 3 | 2 | 1 | 2 | | 1 | 2 |
| 1 | 30 | 6 | 3 | 2 | 3 | 2 | 2 | 2 | 2 | | 2 | |
| | | | 4 | 3 | 4 | 3 | 2 | 2 | 2 | | 2 | |
| 6 | | 6 | 4 | 5 | 3 | 2 | 2 | 2 | 2 | | 2 | |
| | | | 4 | 3 | 2 | 2 | 2 | 2 | 2 | | 2 | |
| | | | 3 | 3 | 3 | 2 | 2 | 2 | 2 | | 2 | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 3 | 3 | 3 | 2 | 2 | 1 | 2 | | 2 | |
| 8 | | 8 | 5 | 5 | 5 | 3 | 3 | 1 | 2 | | 1 | 2 |
| | | | 4 | 4 | 4 | 3 | 3 | 2 | 2 | | 2 | |
| 2 | | 7 | 3 | 3 | 3 | 2 | 2 | 1 | 2 | | 1 | 1 |
| | | | 5 | 4 | 4 | 3 | 2 | 2 | 2 | | 2 | |
| | | | 3 | 3 | 2 | 2 | 2 | 2 | 2 | | 2 | |
| | | | 3 | 2 | 2 | 2 | 2 | 2 | 2 | | 2 | |
| | | | 4 | 4 | 4 | 3 | 3 | 1 | 2 | | 1 | 1 |
| | | | 2 | 3 | 2 | 2 | 2 | 2 | 2 | | 2 | |
| | | | 4 | 4 | 3 | 2 | 2 | 2 | 2 | | 2 | |
| | | | 3 | 3 | 3 | 2 | 2 | 1 | 1 | 1 | 2 | |
| | | | 4 | 3 | 3 | 2 | 2 | 2 | 2 | | 2 | |
| | | | 4 | 3 | 3 | 2 | 2 | 2 | 2 | | 2 | |
| | 45 | 7 | 4 | 4 | 3 | 3 | 2 | 2 | 2 | | 2 | |
| | | 3 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | | 2 | |
| 9 | | 7 | 4 | 4 | 3 | 3 | 2 | 2 | 2 | | 2 | |
| | | | 4 | 3 | 4 | 2 | 2 | 2 | 2 | | 2 | |
| 9 | 45 | 7 | 5 | 4 | 4 | 3 | 2 | 2 | 2 | | 2 | |
| 1 | 30 | 6 | 5 | 4 | 4 | 3 | 2 | 2 | 1 | 1 | 2 | |
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