Title of Research Project: Comparing the recovery profiles of opioid based Vs. opioid sparing anaesthesia technique in patients undergoing 1 - 3 levels of lumbar laminectomy with or without discectomy – A double blinded randomized controlled trial.

DISSERTATION SUBMITTED TOWARDS FULFILLMENT OF THE RULES AND REGULATIONS FOR THE MD ANAESTHESIOLOGY EXAMINATION OF THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY TO BE HELD IN MAY 2022

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Comparing the recovery profiles of opioid based Vs. opioid sparing anaesthesia technique in patients undergoing 1 - 3 levels of lumbar laminectomy with or without discectomy – A double blinded randomized controlled trial.

Dr. Shefali William

Postgraduate Registrar

Department of Anaesthesiology

Christian Medical College, Vellore

BONAFIDE CERTIFICATE

I declare that the dissertation entitled " **Comparing the recovery profiles of opioid based Vs. opioid sparing anaesthesia technique in patients undergoing 1 - 3 levels of lumbar laminectomy with or without discectomy – A double blinded randomized controlled trial.**" done towards fulfillment of the requirements of The Tamil Nadu Dr. M.G.R. Medical University, Chennai, for examination of The Tamil Nadu Dr. M.G.R. Medical University, Chennai to be held in May 2022 is a bona fide original work done by Dr. Shefali William.

Dr. Shefali William
Post Graduate student
Registration Number: 201920366
Department of Anaesthesiology
Christian Medical College
Vellore

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Dr Raj Sahajanandan
Head of the Department
Department of Anaesthesiology
Christian Medical College
Vellore

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Dr Anna B Pulimood

The Principal

Christian Medical College

Vellore

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Analysis address	shefali.william.mgrmu@analysis.urkund.com

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Guide

Dr Ramamani Mariappan

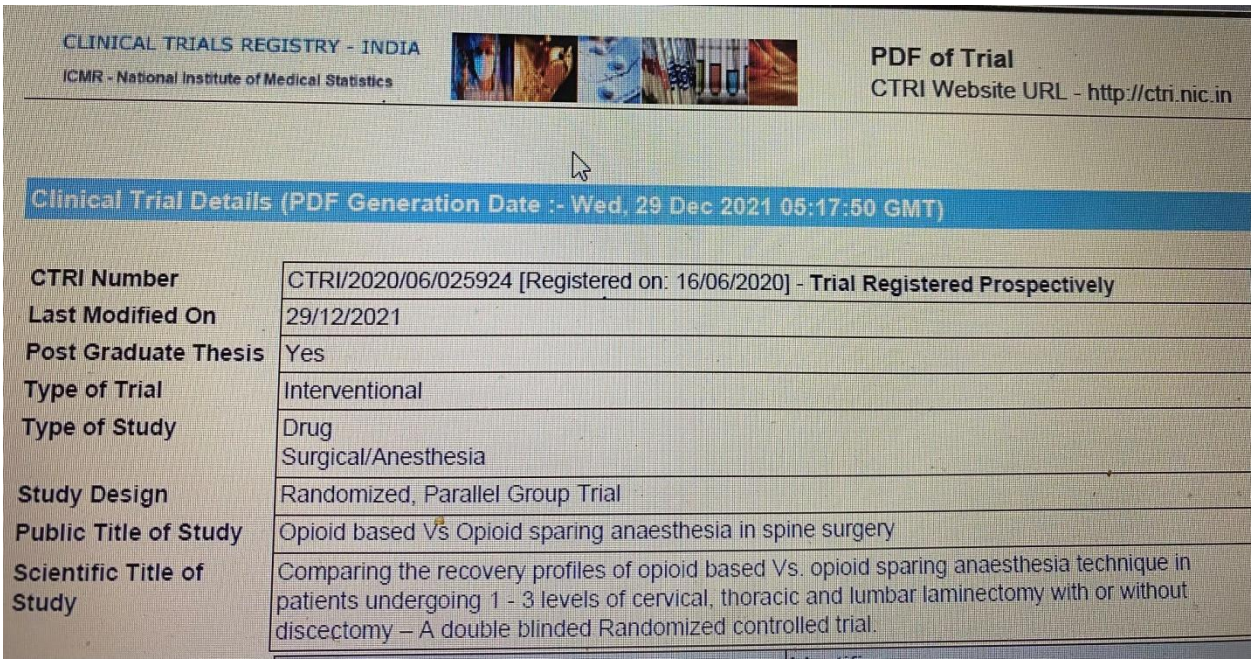
Professor,

Department of Anaesthesiology

Christian Medical College,

vellore

CLINICAL TRIAL REGISTRATION (CTRI)



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CTRI Number	CTRI/2020/06/025924 [Registered on: 16/06/2020] - **Trial Registered Prospectively**
Last Modified On	29/12/2021
Post Graduate Thesis	Yes
Type of Trial	Interventional
Type of Study	Drug Surgical/Anesthesia
Study Design	Randomized, Parallel Group Trial
Public Title of Study	Opioid based Vs Opioid sparing anaesthesia in spine surgery
Scientific Title of Study	Comparing the recovery profiles of opioid based Vs. opioid sparing anaesthesia technique in patients undergoing 1 - 3 levels of cervical, thoracic and lumbar laminectomy with or without discectomy – A double blinded Randomized controlled trial.

The Dissertation work entitled "**Comparing the recovery profiles of opioid based Vs. opioid sparing anaesthesia technique in patients undergoing 1-3 levels of lumbar laminectomy with or without discectomy – A double blinded Randomized controlled trial**" being a double blinded RCT was registered and approved in CTRI and unique CTRI number- CTRI/2020/06/025924 is also obtained.

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CONTENTS

ABBREVIATIONS:

DDS – Degenerative Disease of Spine

LBP – Low Back Pain

NMDA – N Methyl D Aspartate

STT – Spino Thalamic Tract

TENS – Transcutaneous Electrical Nerve Stimulation

ASA – American Society of Anesthesiologists

WHO – World Health Organization

NSAID – Non Steroidal Anti inflammatory Drugs

OFA-Opioid free Anaesthesia

MMA-Multimodal Analgesia

ERAS-Enhanced Recovery from Anaesthesia

COX – Cyclooxygenase

GABA – Gamma Amino Butyric Acid

CSF – Cerebro Spinal Fluid

CNS – Central Nervous System

PONV – Post Operative Nausea and Vomiting

OS – Opioid sparing

OB – Opioid based

5HT3 – Serotonin Receptor

PG – Prostaglandin

CMC – Christian Medical College Hospital

MAC – Minimum Alveolar Concentration

BP – Blood Pressure

NRS – Numeric Rating Scale

VAS – Visual Analog Score

IM – Intramuscular

IV – Intravenous

BMI – Body Mass Index

IVF – Intravenous Fluids

SBP – Systolic Blood Pressure

DBP – Diastolic Blood Pressure

HR – Heart Rate

PACU – Post Anaesthesia Care Unit

RR- respiratory Rate

FIGURES

Tables

INTRODUCTION

Laminectomy and Discectomy are well-recognized; safe surgical procedures improve the quality of life in patients who present with degenerative spine disease.[1] The degenerative spine disease includes spinal canal stenosis or disc prolapse, spondylolisthesis etc. Surgery is offered for whom the medical management fails to improve the symptoms.[2]

In an era of growing health care expenses, along with such dramatic improvement and advances in surgical and anaesthetic techniques over the past four decades in spine surgery along with advancement in modern diagnostic technology and instruments, our health care services demands to balance the clinical needs with cost-effective care of surgical spine patients.[3].

In recent times, lumbar laminectomy and discectomy surgeries are done as a "short stay surgery" that promotes early recovery and ambulation, early discharge from hospital,[4] less health care expenses, and improved quality of life without compromising patient safety. Hence, the anaesthetic techniques are to be tailored to promote faster recovery and early discharge while providing good analgesia.[5]

Avoiding long-acting potent opioids, use of multimodal analgesics with local anaesthetics, non-steroidal anti-inflammatory agents (NSAID), acetaminophen, less potent short-acting opioids, use of regional anaesthesia, and peripheral nerve block are some of the measures for providing good analgesia while preventing opioid addiction,

opioid-induced tolerance, hyperalgesia, postoperative nausea and vomiting (PONV) and cardiorespiratory complications of potent opioid.[6]

Over the last ten years, there has been a renewed interest in providing opioid-sparing/opioid-free Anaesthesia.[7] The technique is practiced more in day surgery and short-stay surgery cases[8]. Now its utilization has extended even for major surgical cases. This technique is practiced even in neurosurgical patients undergoing craniotomy, major spine surgeries. Recent studies and meta-analyses have shown that the opioid-free/sparing technique provide equipotent analgesia while avoiding the complications of opioids, especially postoperative nausea and vomiting[5].

Most patients with degenerative disc disease have back pain, radicular pain of chronic nature. Most of them will be on regular pain medications, including opioids and their adjuvants like dexmedetomidine, clonidine, gabapentin, pregabalin, ketamine, tricyclic antidepressants. [9] Providing opioid-free/sparing anaesthesia is a challenging task in this group of patients. Inadequate pain management can prolong postoperative recovery. Among the 179 surgical procedures, lumbar spinal instrumentation procedures represented three of the top six surgeries with the highest pain scores. Spine surgery is associated with frequent, persistent postsurgical pain. Its incidence varies from 5 to 75 %. Hence providing good analgesia using multimodal analgesia techniques is of paramount importance for reducing medication-induced complications.[10]

Degenerative disc disease (DDS) occurs due to wear and tear of spinal disc most commonly due to ageing. Spinal disc acts as cushion between the two vertebrae, functioning as shock absorbers they help in smooth movements of vertebral column.[11] DDS can lead to 5 % of chronic back pain in adults which reduces the quality of life by interfering with their ability to do daily day to day activities.[12]

Conservative management of DDS includes bed rest, analgesics, physiotherapy and life style modifications. Early surgical intervention improves the quality of life outcome and reduces the neurological deficit which can increase with increasing severity of the disease.[13] Surgical treatment is offered to patients who have unsatisfactory outcomes with conservative management.

Laminectomy and discectomy are the commonly performed surgery for DDS surgical intervention causes 33 percent reduction in back pain score and reduces the disability by 25 percent. Postoperative pain is moderate to severe in intensity following spine surgeries. Opioids have been the mainstay of postoperative pain management, but use of opioids have been is found to have so many side effects which have been listed in various literature. [10]

As the postoperative pain is complex problem, it is difficult to treat this pain with single method. The Combination of local anaesthetic- for Infiltration at surgical site, anti-inflammatory drugs, acetaminophen along with strong or weak opioids (parenteral administration) are often preferred for controlling the postoperative pain. This technique is called “multimodal analgesic approach (MMA).”[14] The purpose of multimodal

approach is to achieve a good quality analgesia with various drugs acts on the different receptors, thereby avoiding large dose of one particular drug leads to complications. The treatment of postoperative pain by combining various drugs which works through different mechanism is preferred to improve analgesia while reducing the side effects of a drug and give effective pain control which will result in early mobilization and discharge from hospital.[4]

Pregabalin is gamma aminobutyric acid analogue that binds alpha 2 subunits decrease the neurons excitability and decrease the pain.[15] Pregabalin use for pain management decreases the opioid usage postoperatively and decreases opioid associated side effects.[9]

Ketamine an NMDA receptor antagonist, it is used for induction and maintenance of anaesthesia.[16] It produces dissociative anaesthesia, ketamine has also been used for pain control in a multimodal pain control regimen.[14]

HYPOTHESIS

Combination of different analgesics which act through different mechanisms will have an "additive analgesic effect" with fewer side effects as compared to using larger doses of a single drug(opioid) used for pain control. Administering opioid sparing anaesthesia technique using multimodal analgesic drugs will reduce opioid induced side effects such as sedation, respiratory depression, PONV and paralytic ileus thereby decreases the time taken for liquid and solid food and improves the ambulation which further enhances the postoperative recovery after decompressive surgery for the degenerative spine disease involving lumbar spine without compromising on the quality of analgesia .

We have hypothesized that, using a multimodal analgesia approach using ketamine, pregabalin and intramuscular local anaesthetic infiltration at the end of surgery will have opioid sparing effect thus reduces the opioid induced side effects such as sedation, respiratory depression, post-operative nausea and vomiting (PONV), paralytic ileus thereby enhances the recovery in terms of DREAM time after lumbar laminectomy for degenerative spine disease and promotes early discharge from the hospital.

AIM

The aim of this study is to see whether the opioid sparing anaesthesia technique decreases the DREAM time (time to drink fluids, eat solid food and time to ambulate) in patients undergoing 1- 3 levels of lumbar laminectomy with or without discectomy when compared to opioid based anaesthesia using long acting potent opioid.(Morphine)

OBJECTIVES:

Primary objective:

The effect of Anaesthesia technique (opioid sparing/opioid based) on DREAM time (Time taken to **Dr**ink, **E**at, **AM**bulate).

Secondary Objectives:

- Numeric Rating Score (NRS) score at 2,6,8,12,18, 24 hours.
- Opioid and ketamine induced side effects – PONV, Post-operative ileus, sedation, Nystagmus, Hallucination.
- Time taken to receive the first dose of rescue analgesia
- Total dose of rescue analgesics received during the first 24 hours
- Duration of hospital stay after surgery
- Post-operative hemodynamics (HR, BP) at 2,6,8,12,18,24 hours
- Patient satisfaction at 24 hours**.**

REVIEW OF LITERATURE:

Laminectomy and Discectomy are well-recognized; safe surgical procedures improve the quality of life in patients who present with degenerative spine disease.[2] The degenerative spine disease includes spinal canal stenosis or disc prolapse, spondylolisthesis etc. Surgery is offered for whom the medical management fails to improve the symptoms.[2]

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Avoiding long-acting potent opioids, use of multimodal analgesics with local anaesthetics, non-steroidal anti-inflammatory agents(NSAID), acetaminophen, less potent short-acting opioids, use of regional anaesthesia, and peripheral nerve block are some of the measures for providing good analgesia while preventing opioid addiction, opioid-

induced tolerance, hyperalgesia, postoperative nausea and vomiting (PONV) and cardiorespiratory complications of potent opioid[7].

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DEGENERATIVE DISEASE OF THE SPINE:

Degenerative spine diseases are the leading cause of chronic pain in the elderly population. Disc prolapse, canal stenosis, osteophyte formation, ossified ligaments, and spondylolisthesis are degenerative diseases involving the lumbar spine.[13] This occurs due to chronic overload, ageing related degeneration, acute trauma on a degenerative spine. Displaced disc tissue lies wholly within an outer perimeter of an uninterrupted outer annulus or capsule.[11] They can be of the following types.

Type 1 – central

Type 2- right – left central

Type 3 – right – left subarticular

Type 4 – right – left foraminal

Type 5 – right – left extra foraminal[13]

Various factors had been studied to determine the cause of degenerative disc disease and its pain generation pathway in an attempt to find an answer to either reverse the pain caused by the prolapsed or degenerated vertebral disc.[18] Understanding the pathophysiology of pain caused by degenerative disc disease of spine is very important to control the pain and improve the quality of recovery. The pain in DDS depends on the degree of the disc prolapse can be due to the release of certain chemical mediators such as nitric oxide[18]. Various stages of disc prolapse and its effect on pain fibers are given in Figure 1. Stimulation of mechanoreceptors by the mechanical compression on the

posterior annulus of the vertebral disc can produce "nociception" leads to the typical back pain which is radiating in nature.

DEFINITION OF PAIN:

Pain is defined as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [11]

TYPES OF PAIN:

Pain can be divided into acute and chronic pain depending on the duration of pain.

1) Acute pain– is usually caused by a nociceptive stimulus resulting from tissue inflammation; it takes 1-2 months for the acute pain to settle [12].
2) Chronic pain – When acute pain persists longer than six months [12]), it is defined as chronic pain. Chronic pain has psychological and social factors contributing to the pain. Chronic pain has continuous nociceptive stimulus. Degenerative disease of the Spine (DDS) can cause chronic pain. Patients with DDS have seen to have a psychological bearing in day to day life due to limitations in doing daily activities. [10]

Pain in DDS is mostly a chronic pain because the disc bears the significant amount of the physical stress before the mobility is limited. The degree and extent of the pain is usually dependent on the degree of the disc prolapse.[13]

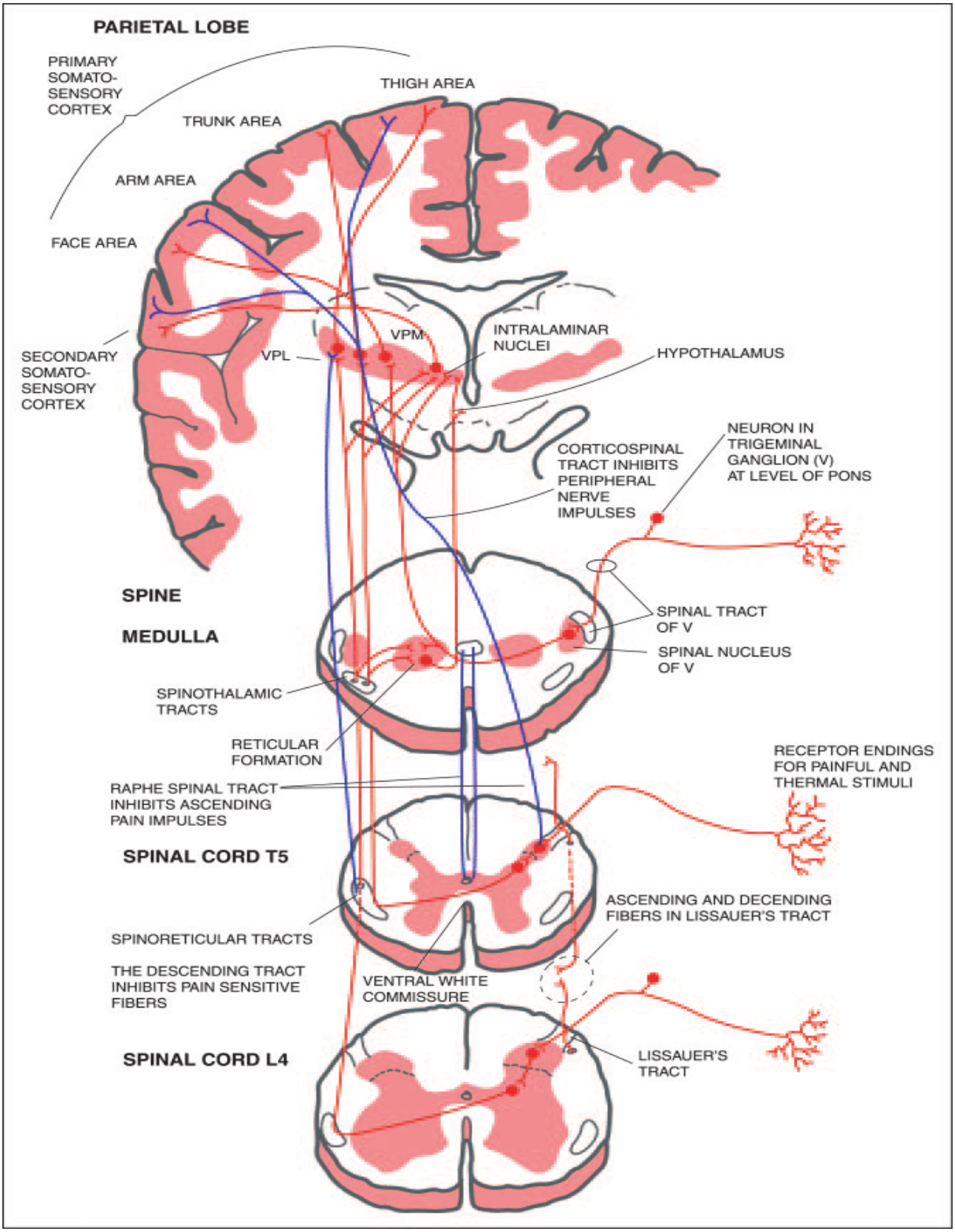

Figure 1 pathway of pain

Mechanism of pain in patients with degenerative disc disease - Sensory nerve fibres innervating discs derive mainly from the sinu vertebral nerve and distribute mainly to the outer third of the disc.[14] The nerve fibers with a small diameter expressing pain-related neuropeptides such as substance-P (SP) and calcitonin gene-related peptide (CGRP) are present in the sensory nerve fibers around discs.[14] These fibers are considered to act as nociceptors transmitting pain sensation.[10]

Management of Pain due to degenerative disc disease:

This can be managed by surgical and by the nonsurgical measures. Nonsurgical measures can be divided into pharmacological and nonpharmacological methods. These methods are usually used to improve the quality of life for the patients[3] Usually a combination of lifestyle modifications and pharmacological methods are used to control the pain, the combination of these methods are made to prolong the duration between the surgery and onset of pain [15]

These steps are commonly followed after the acute onset of pain

1. Bed rest and limitation of the activity after 1-2 days of onset of pain [15]

2. Muscle relaxants and NSAID's are used for 7-10 days till the acute pain is subsidized, however many patients are seen to be dependent on NSAID'S intermittently for long duration. [16]

3. Gentle stretching and aerobic exercise, for at least 3 times a week[15]

4. Physiotherapy is advised if after 3 weeks there is no improvement in pain[15]

5. An epidural steroid injection if after 3 to 6 weeks there is little to no improvement in pain [17]

6. Surgery is recommended if the pain is severe, or patient has limitations in performing in his /her daily activates[2]

Surgery is usually performed 6-12 months after all the above-listed methods are tried, and there is no improvement in pain. Surgery is considered earlier if the patient has a neurological deficit or the mobility of the patient is compromised due to pain caused by DDS [3]

MODALITIES OF PAIN CONTROL

Patients with degenerative disc disease requires combination of drugs to treat the pain during the perioperative period. Mostly these patients are on NSAID's preoperatively for a longer period of time due to chronic pain[19]. Newer drugs like pregabalin have been used in the management of chronic pain in these patients. In combination with NSAID'S, these provide better pain relief without the need to increase the dose of NSAID [7]

Pregabalin: This is a gamma-amino-butyric acid analog shown to be effective in several models of neuropathic pain, incisional injury, and inflammatory injury.[7] Multimodal perioperative analgesia with the use of gabapentins has become common. Based on available evidence from randomized controlled trials and meta-

analysis, the perioperative administration of pregabalin reduces opioid consumption and opioid-related adverse effects in the first 24 h following surgery. [6] It is not only prevents the chronic pain following surgery, also reduces the opioid dependency during the postoperative period.[20]

Adverse effects - visual disturbance, sedation, dizziness, and headache are associated with higher doses[15].

MULTIMODAL ANALGESIA (MMA):

Major spine surgery with multilevel instrumentation need large amount of opioids after surgery. [5] It is considered one of the top six surgeries that can cause significant pain among 179 surgeries. A multimodal regimen with acetaminophen, NSAIDs, pregabalin, S-ketamine, dexamethasone, ondansetron [9] is used for controlling the postoperative pain . The multimodal approach helps to reduce the post-operative dependency on opioids and helps in early mobilization and early discharge from hospital.

The rationale behind combining opioids and nonopioid adjuvants (MMA) is due to their ability to synergistically act and modulate pain pathways at central and peripheral sites, thereby enhancing analgesic efficacy and decreasing total opioid requirement while providing good quality of analgesia as well as free of opioid-related side effects[19]

Based on MMA evolved a new concept called Opioid Free Anaesthesia (OFA) or Opioid Sparing Anaesthesia (OSA) that aims to avoid the negative impact of intraoperative

opioid on patient's postoperative outcomes and also on the physiology of pathways involved in intraoperative nociception[17].

With MMA , anti-nociception during general Anaesthesia can be obtained by interfering with various neuromodulators not only by interfering with enkephalins with opioids[19]. Based upon the above mentioned concept the various agents used in MMA are listed below as,

1. Acetaminophen:

Acetaminophen is a centrally acting non-opioid analgesic acts on the descending serotonergic pathway. This has additional actions as inhibition of cyclo-oxygenase-3(COX-3) thus inhibits prostaglandin synthesis [23].In the spinal cord level, it blocks the neurotransmission by blocking NMDA, substance P and nitric oxide pathway. Pain reduction with acetaminophen primarily depends on its central mechanism. Paracetamol cannot control moderate and severe postoperative pain however in combination with opioid, it decreases the opioid requirement by 40-50%. Paracetamol is a useful alternative as an adjuvant along with opioids [23] .

2. Non-Steroidal Anti-Inflammatory Drugs (NSAID):

Non-steroidal anti-inflammatory drugs (NSAIDs) are analgesic and anti-inflammatory effects by inhibiting prostaglandin synthesis. NSAIDs block cyclooxygenase and lead to reduction in pain, fever, platelet aggregation and inflammatory responses [24]. NSAID are classified as nonspecific COX-1 and COX-

2 inhibitors and specific COX-2 inhibitor[20]. Examples for non-specific COX-1 inhibitors are diclofenac sodium, ketorolac, ibuprofen, piroxicam[21].

ADVERSE EFFECTS OF COX-1 INHIBITORS: platelet dysfunction, bronchospasm, cardiovascular events, gastric irritation, and renal dysfunction[21].

Specific COX-2inhibitor (celecoxib) acts only on COX-2 inhibition pathway, hence, it does not cause platelet dysfunction and has reduced gastritis and bronchospasm compared to nonspecific COX inhibitors[22].

Combination of NSAID with opioids gives better results than either one alone[19]. Unfortunately, most of these agents increase the risk of bleeding by decreasing platelet adhesiveness, increased bleeding times. Because NSAID induced bleeding may be dangerous after spine surgery, cranial surgeries, and non-selective NSAIDs should be used cautiously in neurosurgical patient[24] .

Due to the opioid-sparing action of NSAIDs, the combination of these two drugs significantly reduces opioid dose and mitigates the incidence of adverse events such as nausea, vomiting, and respiratory depression. For an effective analgesic combination, the selection of the right NSAID and opioid agent at optimal doses is essential.[25]

OPIOIDS-MORPHINE:

Opioids produce effects on neurons by acting on receptors located on neuronal cell membranes. Three major types of opioid receptor, mu, delta and kappa .

Pharmacological studies have shown that the naturally -occurring opioid peptide, beta endorphin, interacts preferentially with mu receptors, the enkephalins with delta receptors and dynorphin with kappa receptors. Morphine has considerably higher affinity for mu receptors than for other opioid receptors. [26]

CLASSIFICATION OF OPIOIDS:

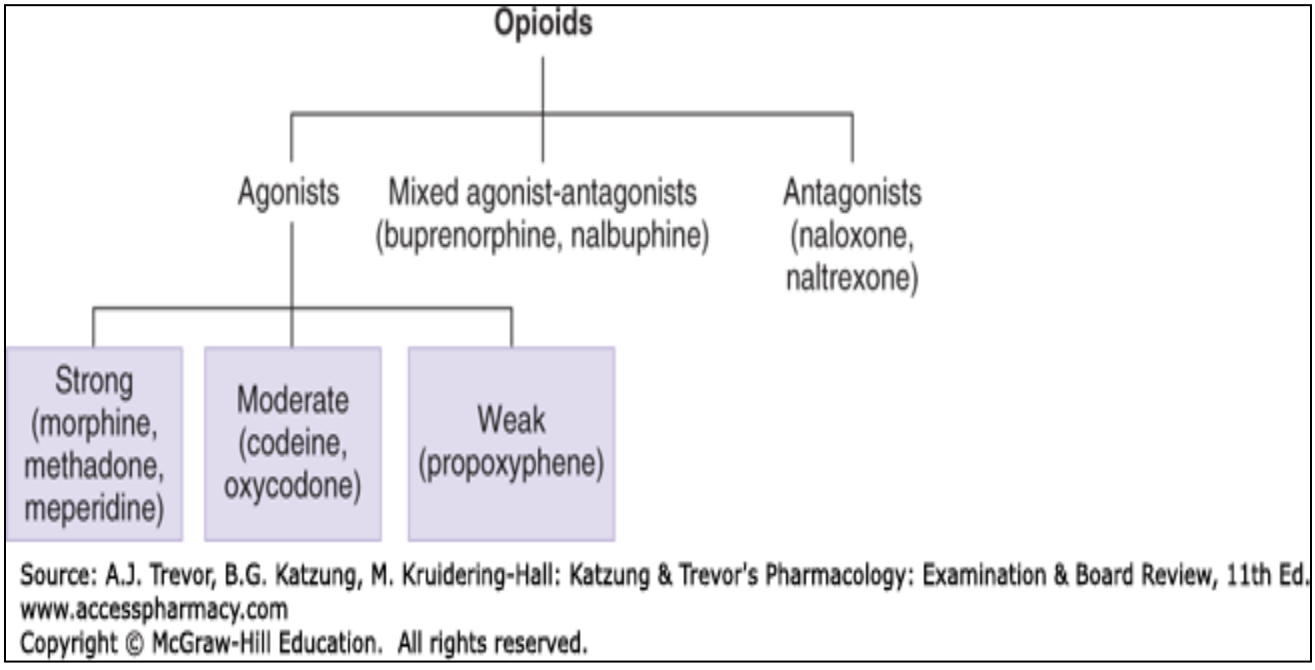

Figure 2- Classification of Opioids

ADVERSE EFFECTS:

The most common side effects of morphine use is constipation - stimulation of mu-opioid receptors on the myenteric plexus, which inhibits gastric emptying and reduces peristalsis[23].

POSTOPERATIVE ILEUS is multifactorial in origin, and studies have identified that the intra-operative use of hydromorphone and postoperative crystalloid fluid administration of $\geq$ 2 liters are the independent risk factors for the development of ileus[23].

RESPIRATORY DEPRESSION is a serious adverse reaction. Patients who are on regular opioid usage during the postoperative period requires a close respiratory function monitoring as it can cause respiratory depression with respiratory acidosis [24]. The pre-Bötzinger complex is a small area in the ventrolateral medulla that generate a 'respiratory' rhythm, it was initially thought to be the pacemaker or 'kernel' for respiratory rhythm. The pre-Bötzinger complex has been shown to form a coupled oscillator with the nearby retro-trapezoid and parafacial respiratory group (RTN/pFRG) [24].

The rhythm generating centers in medulla are strongly modulated by influences from the pons that include the Kölliker-Fuse nucleus, the parabrachial complex, and the locus coeruleus. The most opioid sensitive aspect of respiration is rhythm generation, and changes in the respiratory pattern are even seen at lower opioid doses then change in tidal volume [24].

Higher opioid doses causes reduction in tidal volume due to decreased tonic inputs from opioid sensitive chemoreceptors, which are partly compensated by increases in $PaCO2$[24].. In the ventrolateral medulla, the pre-Bötzinger complex is active during inspiration and is inhibited by opioids, whereas the RTN/pFRG is active during expiration and importantly is insensitive to opioids [24].

CVS SIDE EFFECTS: flushing, bradycardia, hypotension, and syncope[25]

OTHER EFFECTS: lightheadedness, sedation, and dizziness, euphoria, dysphoria, agitation, dry mouth, anorexia. Morphine can also cause urticaria, rash[25]. .

KETAMINE:

Racemic ketamine is a mixture of equal amounts of the two enantiomers (S)-ketamine and (R)-ketamine. The analgesic and anesthetic potency of (S)-ketamine is about threefold superior to (R)-ketamine. Along with faster elimination, improved control of the anesthetic state with reduced drug load is achieved[26].

Pharmacokinetic properties of (S)-ketamine are generally comparable with the racemic mixture[26]. The pharmacological profile of ketamine is characterized by the so-called "dissociative anesthetic state" with profound analgesic and moderate hypnotic properties and by marked sympathomimetic reactions.[8]

ADVERSE EFFECTS - **hallucinations and hypersalivation**[26].

Analgesic, anesthetic and sympathomimetic effects are mediated by different sites of action : N-methyl-D-aspartate (NMDA)-receptor antagonism is the most important

neuropharmacological mechanism for the analgesic effects of ketamine. The same mechanism may be involved in the supposed neuroprotective potency of the substance [16]. Effects on opiate receptors may contribute to the analgesic state as well as to dysphoric reactions.

Sympathomimetic properties are mediated by enhanced central peripheral monoaminergic transmission. Inhibition of central and peripheral cholinergic transmission may contribute to the induction of anaesthetic state and hallucinations[27].

Pentazocine:

It is a benzomorphan derivative, has both opioid receptor agonistic and weak antagonistic action. Acts mainly on delta and kappa opioid receptors. It is a N allyl derivative of the narcotic analgesic pentazocine. It can be administered via oral or intravenous or intramuscular or through neuraxial route [28]. Pentazocine is about 1/3rd as potent as morphine, used as an analgesic to treat the moderate acute postoperative pain and for treating the chronic pain[29].

The recommended oral dose is about 50 mg and for the parenteral administration it is given at the range of 10 to 30 mg. Therapeutic trials comparing pentazocine with other strong analgesics have shown that intramuscular administration produces excellent analgesia for moderate postoperative pain.[5]

In comparison with morphine, the analgesic effect of pentazocine reached a higher initial peak, the plasma level declined more rapidly. It is metabolized by oxidation in liver and excreted in urine and bile and has a half-life of 2 to 3 hours[29].

ADVERSE EFFECTS:

Sedation, dizziness, diaphoresis, tachycardia and increased systemic as well as pulmonary vascular resistance due to sympathetic stimulation, respiratory depression has not proved a significant problem with pentazocine in clinical practice as compared to morphine[30]. Although pentazocine is claimed to be relatively free from the severe respiratory depression, studies have shown that the parenteral doses at 20 mg pentazocine in healthy conscious subjects were shown to cause the same degree of respiratory depression as when it was compared to 10 mg of morphine[31].

Pentazocine causes a slight rise in blood pressure and a slight increase in heart rate following its administration as it is associated with an increase in plasma catecholamine levels, due to the sympathetic stimulation. Pentazocine was shown to cause a delay in gastric emptying and a reduction in propulsive motility of the small intestine [28], but it had no significant effect on renal function or on pupillary constriction.

LOCAL ANAESTHETICS: ROPIVICAINE:

Local Surgical Skin Site infiltration (SSSI) with ropivacaine effectively reduces postoperative pain for 24 hours and reduces the opioid consumption and PONV significantly at 24 hour post operative period. Ropivacaine can be used as a adjuvant to the multimodal pain control model as it reduces opioid consumption in first 24 hours[32]. Different types of local anaesthetics can be used for infiltration post operatively . Bupivacaine and ropivacaine are commonly used for infiltration after surgery, but ropivacaine is reported to have a lower risk of cardiovascular or central nervous system toxicity[33]. Elastomeric pump can be used to infuse 0.5% bupivacaine into the wound for pain control in lumbar spinal fusion and its seen that continuous bupivacaine infusion resulted in lower pain scores and decreased opioid use and lowers the tendency of PONV and helps in early mobilization. Studies have shown that SSI with single dose of ropivacaine improves the postoperative pain for 24 hours, [32] thereby enhances postoperative recovery.

Opioid Free Anaesthesia (OFA) Advantages:

1. **Less PONV :** PONV is an unpleasant side effect feared by many patients during acute postoperative course, which can become a cause for dehydration, electrolyte imbalance, postoperative bleeding, wound dehiscence, and pulmonary aspiration. Using the multimodal pain control approach not only helps to decrease the incidence of these post op complications but also helps in early discharge from hospital[34].

2. Enhanced Recovery from Anaesthesia (ERAS):

Effective pain management is now recognized as one of the three fundamental aspects of ERAS protocol [(4)] Patients who received multimodal approach to pain control have shorter length of postoperative hospital duration thus faster recovery and discharge thus betterment in quality of life[(5).]

3. Reduction in Health care expenses:

OFA was associated with a better recovery, better comfort, early mobilization, less opioid dependence, and opioid induced hyperalgesia[(19)]. OFA also reduces the chance of development of chronic pain. Overall, it promotes early mobilization, early recovery, lesser hospital stay and thus lesser expenses spent on healthcare[(19).]

4. Less opioid related adverse effects:

Reduction in need of postoperative opioids resulted in reduction of opioid induced adverse effects such as respiratory depression, nausea and vomiting, ileus, urinary retention, pruritis[(31).]

5. Beneficial effects in special group of population:

OFA is very beneficial with special group of population such as obese people and elderly population where using excess opioid is associated with adverse effects, prolonged recovery[(35).]

6. Prevents development of chronic pain:

Patients suffering from chronic pain and /consuming opioids before surgery, need more opioids for analgesia, this increase in dose can cause opioid induced hyperalgesia, opioid tolerance and increase PONV[10]. These patients could benefit from OFA.

MMA by ketamine, NSAID and gabapentin acts through various pathways to produce analgesia while reducing the intraoperative opioid dose, thus could reduce the opioid induced side effects while preventing chronic pain[19].

ASSESSMENT OF PAIN:

Pain experience means intensity and affect of the pain [36].

Pain intensity in simple words describe how much pain the patient is having[36].

Pain affect means the 'degree of emotional arousal or changes in action readiness which is caused by the sensory experience of the pain intensity may be perceived by different people differently[36] .

Asking patients about the intensity, (less or more) did not provide correct information about the intensity. Many factors such as social situation, work situation and setting and history of acute or chronic pain or any associated injury with pain modifies the perception of pain and shows big difference in pain perception between patients [36]. Perception of pain also differs with the chronicity of the pain, patients with chronic pain might not perceive pain intensity similar to a patient who has acute pain. To get a quantitative assessment of the pain from patients, different pain assessment scales are

used in which the patients are asked to score the intensity of pain numerically. Based on these numerical assessment scales, acute pain is managed appropriately. [36].

ACUTE PAIN ASSESSMENT SCORES:

During the postoperative period, VAS (visual analogue score), NRS (Numeric Rating Scale) are used commonly for assessing the severity of pain. They are very sensitive score for the assessment of the acute pain. It is used till seven days after surgery[36].

VAS SCORE:

The visual analog scale (VAS) is a pain rating scale ranging from 0-10 cm, which was first used by Hayes and Patterson in 1921. The patient himself defines the pain severity by scoring the VAS score. Patient reports his symptoms that are recorded with a single handwritten mark placed at one point along the length of a 10-cm line that represents a continuum between the two ends of the scale on the left end is (0-cm) which represents "No pain" and on the other hand of the scale is the "worst pain" on the right end of the scale (10 cm) which represents the maximum pain[37].

These values can be used to see the pain progression, can also be used to assess the response to the pain management. In addition to assessing the pain, the scale can also be used to evaluate mood, appetite, asthma, dyspepsia, and ambulation. Though these outcomes are not the primary purpose the score but these conditions can result in unsatisfied patient [37].

The below given scale is VAS scale **(figure3)** ,

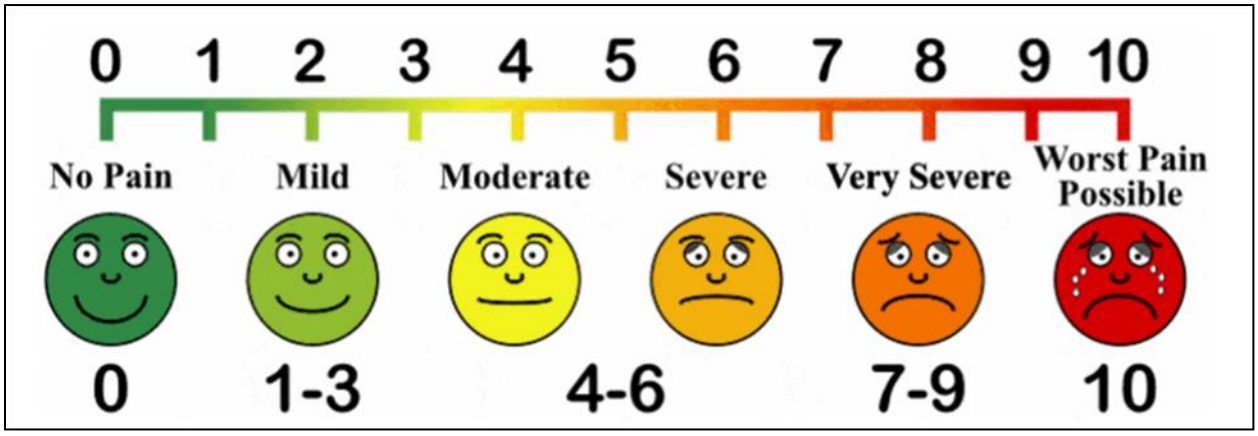

Figure 3- Visual Analogue Scale (VAS)

NRS SCORE:

The NRS scale is one of the most commonly used pain scales in post operative pain assessment The NRS contains numeric version of the VAS score. Most common form of the NRS is a horizontal line with an eleven point numeric range. It is marked from 0 to 10 , with zero being a score for a patient with no pain and ten being the marker of the worst pain possible. This scale can used to assess by asking the patient about his pain or by the showing a scale.[38] The numeric rating scale helps to assess the extent of an individual's pain and also helps in improvement of communication regarding pain with pain team . This scale can help in diagnostic process, track progression of pain.[38]The pictorial representation of NRS scale is given below in figure 4.

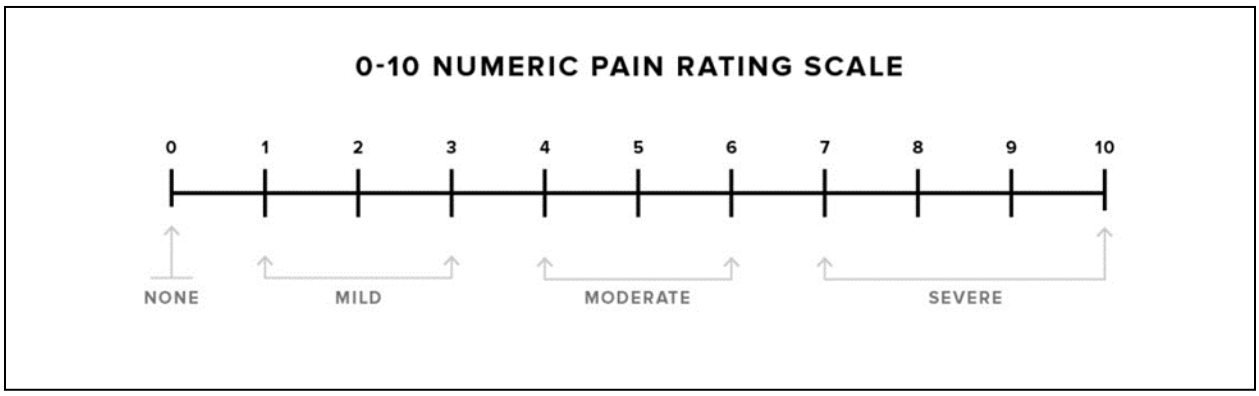

Figure 4- Numeric Rating Scale (NRS)

The advantages and disadvantages of these pain assessment tools

Advantages:[38]

- These takes less time for assessment
- These scales can be used easily without language barriers
- These scales are reliable in measuring the intensity of pain.

Disadvantages: [38]

- Only one aspect of pain is measured that is intensity
- Only acute pain is measured with these scales
- Does not measure the fluctuations in pain.

THE SIGNIFICANCE OF POST OPERATIVE PAIN CONTROL:

Pain is complex in nature and has multiple sites of origin in a surgery with involvement of central and peripheral nervous system. Inadequate pain relief leads to multiple organ injuries and even development of chronic pain. Inadequate pain relief has shown many adverse events including myocardial ischemia, impaired pulmonary function, ileus, thromboembolism, impaired immune function, poor wound healing and anxiety.[21])

Pain delays postoperative mobilization and increases the risk of developing venous thromboembolism. There is also poor patient comfort and satisfaction, overall the postoperative quality of recovery is significantly reduced. It also leads to increase in overall hospital stay .[21]

OFA which breaks this cycle at multiple points combining MMA with SSI provides good quality intraoperative as well as postoperative analgesia without causing any opioid related adverse effects[5] . Thus by studying the multimodal approach of pain management, and studying the outcomes of pregabalin and ketamine - to study the use this multimodal approach cause in opioid consumption and helps early recovery and better mobilization of patients[19].

STUDY DETAILS

STUDY SETTINGS:

This study was conducted in the neurosurgery operating rooms and in neurosurgery postoperative wards at Christian Medical College and Hospital, Vellore. This study was carried out in patients undergoing lumbar laminectomy with or without discectomy.

Inclusion Criteria:

- All ASA I and II, adult patients
- age 18-70 years
- Patients undergoing lumbar laminectomy in prone position for degenerative spine disease.

Exclusion Criteria:

- Hypersensitivity to Pregabalin
- Psychiatric Illness
- ASA 3, 4 patients
- Allergy to local anaesthetic agents
- Morbid obesity BMI > 35
- Obstructive Sleep Apnoea (OSA)
- Serum Creatinine > 1.4 mg%
- Previous surgical procedure at the same level
- Surgeries where intraoperative neuromonitoring is needed

TYPE OF STUDY:

This is double-blinded, randomized controlled clinical study. Patient, and the principal investigator who was doing the postoperative data collection were blinded to the study intervention.

METHOD OF RANDOMISATION:

Patients were allocated equally to two arms. To get the equal allocation, the block randomization technique was done. The randomization schedule was generated using SAS software version 9.4 at the Clinical Data Management Centre, Biostatistics Dept.

Method of allocation concealment:

Allocation concealment was done by an opaque envelope method

Blinding and masking:

This study is a double blinded study. The principal investigator and the patient and the nurse who are assessing the postoperative recovery were blinded to the study intervention. The principal investigator was involved only in following up the patients in ward, not involved in managing the patient in the operating room**.**

METHODOLOGY:

All patients undergoing decompression for lumbar degenerative spine was randomized into two groups, opioid sparing (OS) and opioid based (OB). All patients received standard anaesthesia protocol according the groups they belonged to. Postoperatively they are encouraged to drink, eat and ambulate with support as early as possible. Haemodynamics, sedation, respiration was monitored at regular interval in PACU and in the ward during the first 24 hours. The side effect of opioids like PONV, pruritis, ileus all were noted at regular intervals. Pain was assessed in the PACU and in the ward at regular intervals during the first 24 hours after surgery using NRS scale. The duration of hospital stay after surgery and patient satisfaction was noted and compared between the two groups. Time taken to receive the first dose of Pentazocine and the total dose of Pentazocine received as rescue analgesics in the first 24 hours was noted. All the above-mentioned parameters were compared between the two groups.

All patients who are admitted for lumbar laminectomy surgeries with or without discectomy who met the inclusion criteria was recruited after obtaining the informed patient consent. All patients who were recruited into the study was randomized into one of the two groups, Opioid sparing or Opioid based. A computer generated randomization was done to randomize these patients. Allocation concealment was done by using opaque envelopes

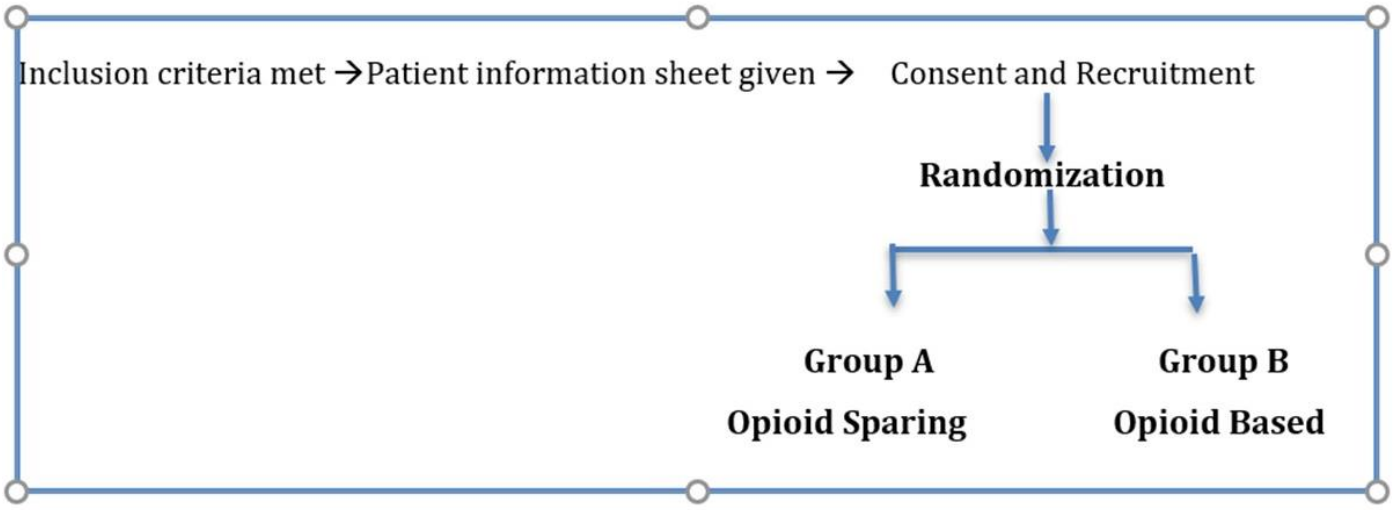

Figure 5 : Diagrammatic Algorithm of Study Methodology

GROUP PROTOCOLS

Group A- Opioid Sparing Protocol: Patients were kept nil per oral for solids, 6 hours prior to surgery; and given water till 2 hours prior to surgery; T. Pregabalin 75 mg the night before surgery and 75 mg on the morning of surgery along with T. Pantoprazole 40 mg was given. On the day of surgery, after reassessing the patient at holding bay, patient was taken to the anaesthesia room and an 18 or 16 G cannula was placed and 500 ml of 0.9% Saline or RL preloading was done. 1 gm paracetamol was given prior to the start of surgery. Depending on the patient's profile, the decision to monitor the BP non invasively or invasively was decided. (NiBP or ABP) In the operating room after placing the standard anaesthesia monitors (ECG, NIBP, SPO2, ETCO2), patients were induced with Inj. Ketamine 0.5 mg/kg, Inj. Fentanyl 1mcg/kg and Inj. Propofol 1.5 mg/kg titrated to keep the BIS between 40-50 and patients were paralysed with Inj. Vecuronium (0.1mg/kg). Phenylephrine 50 to 100 µg or ephedrine 5 mg was given to

combat the anaesthetic induced hypotension if needed. Inj Lignocaine (preservative free) 1.5 mg/kg was given 30 sec prior to intubation. Propofol 0.5 mg/kg and fentanyl 0.5 µg/kg was given during intubation to obtund the intubation response. Anaesthesia was maintained using Air+ Oxygen+ Sevoflurane 0.8-0.9 MAC (age corrected). Depth of anaesthesia was monitored using Bispectral Index monitor. BIS was maintained between 40-60, this number range is considered as adequate depth of anaesthesia. Antibiotics was given before turning the patient prone. After ensuring the patients' haemodynamic stability, patients were turned to prone position. Inj.Dexamethasone 4 mg was given for prevention of postoperative nausea and vomiting (PONV) as prophylaxis. 20 ml of 0.2% ropivacaine with 1 in 2 lakh adrenaline was given for skin infiltration. Low dose of Ketamine 0.1mg/kg/hr was administered from the time of turning prone till the beginning of skin closure. Intraoperatively pain response was treated with 0.5 µg/kg of i.v fentanyl. Inj. Ondensetron 0.1 mg/kg was given for the prevention of postoperative nausea and vomiting 30 mins before the end of surgery. At the end of laminectomy muscle and skin was infiltrated with 10-30 ml of 0.2 % ropivacaine calculating the toxic dose based on the weight and the length of the skin wound and the duration of surgery. Sevoflurane was discontinued and Inj. Lignocaine (Preservative free- Xylocard)1.5mg/kg was given 30 sec before turning the patient to supine position when the surgeon applied the skin dressing. Patients was turned to supine position and fresh gas flow was increased to 6 l/min. The neuromuscular relaxant effect was reversed with 0.05 mg/kg of Neostigmine and 0.01 mg/kg of Glycopyrrolate. The ETT was removed once the extubation criteria is met. Intraoperatively, the haemodynamics were maintained within 20% of baseline. Hypotension was treated either with phenylephrine boluses or ephedrine boluses. If needed Inj. Noradrenaline was started for maintaining

haemodynamics within 20% of baseline. Fluid was administered according to the discretion of attending anaesthesiologist. Time time of extubation, time of getting oriented to time, place, person, duration of anaesthesia and surgery will be noted in the data sheet. Once the patients are fully awake, they were allowed to take clear fluids, if there is no vomiting, they are encouraged to take oral fluids as tolerated. Catheter was taken off as early as possible. Patient was encouraged to sit and ambulate with support after 6 hours. Inj.Paracetamol 1 gm was given Q6h. T. Pregabalin 75mg was given 6 hours after extubation or after 18 hours after the first dose. If they had moderate to severe pain (NRS> 4), Inj. Pentazocine was given 30 mg I.M as rescue analgesic. Pain score, and haemodynamics were monitored at regular intervals. Incidence of PONV, delirium, hallucination, nystagmus, sedation, respiratory depression all were noted. Time of ambulation and time of receiving the first rescue analgesia, days of hospital stay after surgery, incidence of any other complications such as paralytic ileus and wound infection was noted. Patient satisfaction was assessed at 24 hours after surgery. Time taken to drink, eat and ambulation (DREAM TIME), and time of receiving the first rescue analgesia, days of hospital stay post-surgery, incidence of any other complications such as PONV, pruritis, hallucination, nystagmus and paralytic ileus was noted. In case the patient had vomiting after the intake of liquids, they were kept NPO for 2 hrs and then oral fluids were restarted. The time of tolerating oral fluids were taken as drinking time.

Group B (Opioid based) protocol: No sedative premedication will be given. On the day of surgery, after reassessing the patient at holding bay, patient was taken to anaesthesia room and an 18 or 16 G cannula were placed and 500 ml of saline or RL preloading was done. Depending

on the patient's profile, NiBP or ABP monitoring was selected. In the operating room after placing the standard anaesthesia monitors (ECG, NiBP, SPO2, ETCO2), patients were induced with Inj. Fentanyl 2 mcg/kg and Inj. Propofol 2 mg/kg and paralysed with Inj. Vecuronium (0.1mg/kg). Phenylephrine 50 to 100 μg or ephedrine 5 mg was given to combat the anaesthetic induced hypotension if needed. Propofol 0.5 mg/kg and fentanyl 0.5 μg/kg was given during intubation. Anaesthesia was maintained using Air+ Oxygen+ Sevoflurane 0.8-0.9 MAC (age corrected). Depth of anaesthesia was monitored using Bispectral Index monitor. BIS was maintained between 40-60, this number range is considered as adequate depth. Antibiotics was given before turning the patient prone. After ensuring the patients' haemodynamic stability, patients was turned to prone position. Inj.Dexamethasone 4 mg was given for prevention of postoperative nausea and vomiting (PONV) as prophylaxis. 20 ml of 0.2% Ropivacaine with 1 in 2 lakh adrenaline was given for skin infiltration. Inj. Morphine 0.1 mg/kg morphine was administered in a titrating doses after turning the patient prone over 30 mins. Intraoperatively pain response was treated with 0.5 μg/kg of i.v fentanyl. Inj. Ondensetron 0.1 mg/kg was given for prevention of postoperative nausea and vomiting 30 mins before the end of surgery. Sevoflurane was discontinued and Inj. Lignocaine (Preservative free- Xylocard)1.5mg/kg was given 30 sec before turning the patient to supine position when the surgeon applied the skin dressing. Patients was turned supine and neuromuscular relaxant effect was reversed with 0.05 mg/kg of Neostigmine and 0.01 mg/kg of Glycopyrrolate. The ETT was removed once the extubation criteria is met. Intraoperatively, the haemodynamics was maintained within 20% of baseline. Hypotension was treated either with phenylephrine boluses or ephedrine boluses. If needed Inj. Noradrenaline was started for maintaining haemodynamics within 20% of baseline.

Fluid was administered according to the discretion of attending anaesthesiologist. Time of stopping sevoflurane, time of extubation, time of getting oriented to time, place, person, duration of anaesthesia and surgery was noted in the data sheet. Postoperatively, Inj.Paracetamol 1 gm was given Q6h for pain. If they have severe pain (NRS> 4) Inj. Pentazocine 30 mg I.M was given as rescue analgesia. Pain score, and haemodynamics was monitored at regular intervals. Incidence of PONV, postoperative delirium, sedation, and respiratory depression was noted. Time taken to drink, eat and ambulation (DREAM TIME), and time of receiving the first rescue analgesia, days of hospital stay post-surgery, incidence of any other complications such as PONV, pruritis, hallucination, Nystagmus, paralytic ileus and wound infection were noted.

Table 1: Showing the difference between the Group A and Group B protocol

Parameters/ Group	**Group A Opioid Sparing**	**Group B Opioid Based**
Premedication	T. Pregabalin 75 mg at night and on the day of surgery	No Premedications**No table of figures entries found.**
Pre induction	**Paracetamol 1gm i.v over 15 mins. 500 ml of NS/RL preloading**	**500 ml of 0.9% NS /RL Preloading**
Induction	**Inj. Ketamine 0.5 mg/kg Inj. Fentanyl 1 µg/kg Inj. Propofol 1.5 mg /kg**	**Inj. Fentanyl 2 µg/kg, Inj. Propofol 2 mg/kg**

Intubation	Inj. Fentanyl 0.5 µg/kg, Propofol 0.5 mg/kg **Inj. Xylocard 1.5 mg/kg**	Inj. Fentanyl 0.5 µg/kg, Propofol 0.5 mg/kg
Maintenance	**1.Skin infiltration at the beginning of the case 20 ml of 0.2% Ropivacaine + 1in 2 Lakh adrenaline and 10-30 ml at the end of laminectomy into the muscle and skin and subcutaneous tissue.** 2.Air+O2+ Sevo – Mac 0.8-0.9 3. **0.1 mg/kg/ hr of ketamine as an infusion from proning till time of skin closure** 4. 0.5µg/kg Fentanyl bolus fentanyl for response 5. Inj. Xylocard 1.5 mg/kg 30 sec before supining the patient.	1. Skin infiltration 20 ml of 0.2% Ropivacaine with 1 in 2 lakh adrenalin the beginning of surgery. 2.Air+O2+Sevo – Mac 0.8-0.9; 3. Paracetamol 1 gm i.v after proning, before skin incision **4. 0.1 mg/kg of Morphine for analges** **5.No ketamine infusion or bolus** 4.0.5µg/kg Fentanyl bolus fentanyl for pain response. 5. Inj. Xylocard 1.5 mg/kg 30 sec befo supining the patient.
In PACU	Inj. Fentanyl 20 µg/bolus for every 10 Mins if NRS > 4 till it reduces to < 4.	Inj. Morphine 2 mg /bolus for every 10 mins if NRS > 4 till it reduces to < 4
Post-opearative Period	Inj. Paracetamol 1gm I.V Q6 h **T. Pregabalin 75 mg at 6 hrs after surgery and 18 hrs after surgery** Inj. Pentazocine 30 mg IM if the NRS score > 4.	Inj. Paracetamol 1 gm i.v Q6 h No pregabalin Inj. Pentazocine 30 mg IM if the NRS score > 4

SAMPLE SIZE CALCULATIONS:

Initially the sample size was calculated keeping both the DREAM time and the QoR-15 Score as primary outcomes (composite outcome). Based on our pilot trial, we have estimated that 100 patients were needed to show the difference of 2 hours in Dream time between the groups. To study the difference in recovery, (using QoR-15), 200 patients were needed. The details of the sample size calculation was mentioned below.

To study the primary outcomes, that is, the difference in total score in quality of recovery 15 between the two groups (Group A- Opioid sparing group (OS), Group B- Opioid based group (OB), a similar study was taken (Hakim et al). The reference article is "Hakim KYK, Wahba WZB. Opioid-Free Total Intravenous Anaesthesia Improves post-operative Quality of Recovery after Ambulatory Gynecologic Laparoscopy. ***Anesth Essays Res***. 2019;13(2):199–203. doi:10.4103." Since the study was reported in Median with IQR, the mean was calculated, and it was found to be 184 ± 23.7 and 170 ±25.9 in OS group and OB group respectively. The mean difference was 14 in their study using a QoR -40 questionnaire. The QoR-40 ranges from 40-200. Since there were no studies available looking at the quality of recovery using the QoR -15 score. We had used the above-mentioned study to calculate the sample size. In our study, we had calculated the sample size keeping the difference of 10 between the two groups. QoR -15 score ranges from 0-150. Assuming the mean difference of 10 in QoR score between the groups with 80% power and 5% alpha error, the number needed to study is around 100 in each group.

STATISTICAL ANALYSIS:

For continuous data such as age, the descriptive statistics n, Mean, SD and for non-normally distributed interval data and ordinal data, median (interquartile range [IQR]) will be presented. Number of patients and percentage will be presented for categorical data. Based on the normality of data, the parametric t test or non-parametric Mann Whitney test will be applied to compare the following outcomes "Time taken to receive first rescue analgesia (Inj. Pentazocine), Pain score (NRS 0-10) at rest and movement at specified postoperative intervals, Time of ambulation, Length of hospital stay after surgery, Cumulative opioid consumption in the first 24 hours". The Shapiro–Wilk or Kolmogorov–Smirnov tests or histogram with summary values will be used to test the hypothesis of normal distribution. The Chi-square or Fisher's exact test will be applied to find association between categorical variables. Repeated measures ANOVA will be used to compare the two group for the following variables-postoperative hemodynamics (BP& pulse), respiration, sedation during the first 24 hours, at specified intervals. All tests will be two-sided at α=0.05 level of significance. Other statistical test will be carried out if it is deemed. All analyses will be done using Statistical Package for Social Services (SPSS) software Version 21.0 (Armonk, NY: IBM Corp).

RESULTS:

The study was conducted after the institutional research board (IRB) approval (IRB - 12636) and after registering into the clinical trial registry of India (CTRI/2020/06/025924). A total of 74 patients were screened for this study, out of which, 67 patients met the inclusion criteria and they were recruited into the study after an informed patient consent. There were randomly allocated into opioid sparing group or opioid based group. Out of 67, 35 patients who received opioid sparing technique and the rest 32 received Opioid based technique. All the patient's data were taken for analysis. The data were divided into three variables -i) preoperative ii) intraoperative iii) postoperative variable. Figure 6- is depicting the Consort Diagram

Figure 6 - CONSORT DIAGRAM

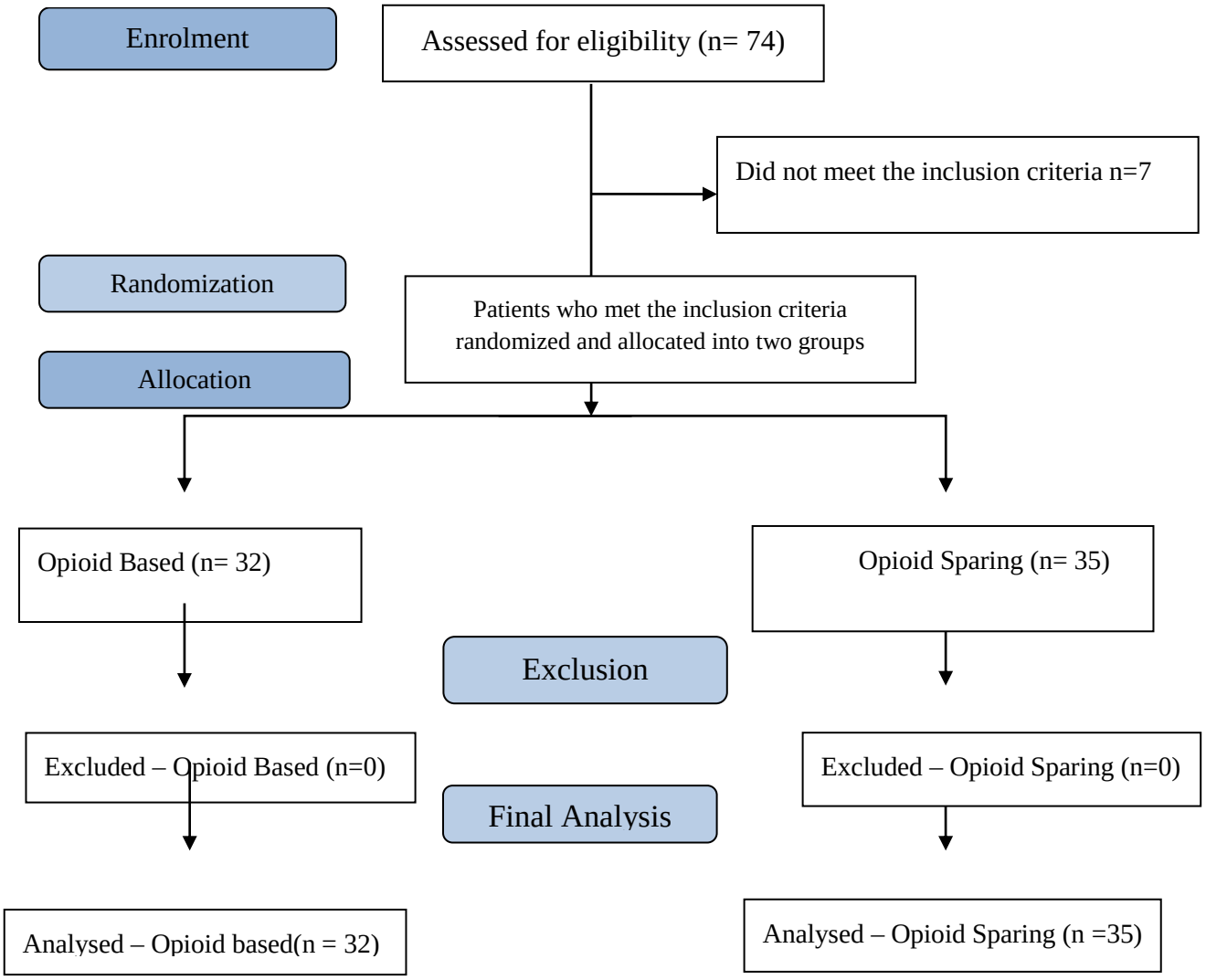

Figure 5- consort diagram

I- PREOPERATIVE VARIABLES:

Demographics:

The demographic variables such as age, sex, ASA status, height, weight, and BMI were compared between the groups. They were equally distributed among the two groups. Table (1) showing the mean (SD) of each variable between the groups and its statistical significance.

Table 2: Baseline Demographics

Parameters/ Groups	Opioid Based (N=32)	Opioid Sparing (N=35)	p-value
Age in Years (Mean ± SD)	43.62 ± 11.21	41.83 ± 14.08	0.564[1]
Gender (Number (%)			
Male	22 (68.8%)	21 (60.0%)	0.456[2]
Female	10 (31.2%)	14 (40.0%)	
ASA Status			
I	18 (56.2%)	18 (51.4%)	0.693[2]
II	14 (43.8%)	17 (48.6%)	
Weight in Kg (Mean ± SD)	67.75 ± 11.44	67.77 ± 9.99	0.994[1]
Height in Cm (Mean ± SD)	160.84 ± 29.86	164.66 ± 10.81	0.836[3]
BMI in Kg/m² (Mean ± SD)	24.95 ± 3.86	25.15 ± 3.01	0.816[1]

1: t-test, 2: Chi-Squared Test, 3: Wilcoxon-Mann-Whitney U Test, 4: Fisher's Exact Test; ASA- American Society of Anaesthesiologist; BMI-Body Mass Index.

Co-Morbidities

Comorbidities such as diabetes, hypertension, asthma, COPD, IHD were compared between the groups and they were comparable between the groups. Patients with history of motion sickness/PONV and previous surgery were comparable between the groups.

Table 3 : Co-Morbidities between the groups

Parameters/ Groups	Opioid Based (N=32) Number (%)	Opioid Sparing (N=35) Number (%)	p-value
Previous Surgery	9 (28.1%)	15 (42.9%)	0.209[2]
History of PONV	1 (3.1%)	0 (0.0%)	0.478[4]
Motion Sickness	0 (0.0%)	0 (0.0%)	1.000[2]
Diabetes	4 (12.5%)	6 (17.1%)	0.736[4]
Hypertension	4 (12.5%)	10 (28.6%)	0.106[2]
Asthma/ COPD	1 (3.1%)	2 (5.7%)	1.000[4]
IHD	1 (3.1%)	0 (0.0%)	0.478[4]

1: t-test, 2: Chi-Squared Test, 3: Wilcoxon-Mann-Whitney U Test, 4: Fisher's Exact Test; PONV- postoperative Nausea and Vomiting; COPD- Chronic Obstructive Pulmonary Disease; IHD- Ischaemic Heart Disease.

Presenting Symptoms:

Most patients with degenerative spine disease can present with various types of pain including chronic pain. For which they will be on chronic medications. The presence of chronic pain and the complications of chronic compression such as limb weakness, radiculopathy and the bowel and the bladder involvement all can influence the results of the study. Hence, they were compared between the groups, and they were equally distributed among the groups. **Table 4** depicting the presenting symptoms between the groups.

Table 4: Presenting symptoms between the groups

Parameters/ Groups	**Opioid Based (N=32) Number (%)**	**Opioid Sparing (N=35) Number (%)**	**p-value**
Chronic Pain	0 (0.0%)	1 (2.9%)	1.000[4]
Back Pain	31 (96.9%)	34 (97.1%)	1.000[4]
Radicular Pain	15 (46.9%)	18 (51.4%)	0.710[2]
Bladder or Bowel Involvement	2 (6.2%)	1 (2.9%)	0.603[4]
Weakness of Limbs	2 (6.2%)	1 (2.9%)	0.603[4]
Back Pain at Rest (NRS)	4.22 ± 1.56	3.74 ± 1.63	0.085[3]
Back Pain at Movement (NRS)	7.06 ± 1.24	6.57 ± 1.52	0.178[3]

1: t-test, 2: Chi-Squared Test, 3: Wilcoxon-Mann-Whitney U Test, 4: Fisher's Exact Test; NRS – Numerical Rating Scale

II- **INTRAOPERATIVE VARIABLES**

Intraoperative Sedative, Analgesics, Vasopressor requirements:

The total dose of fentanyl, propofol and the vasopressor requirement during surgery were compared between the two groups. (Table 5) All were comparable between the groups. The propofol and the fentanyl used soon after extubation and in the PACU were included with this intraoperative requirement. We have observed that, the patients in the opioid sparing group received fentanyl at and soon after extubation. Also, we have observed that the patient in opioid sparing group woke-up with mild coughing which needed small dose of propofol (20-30 mg) or fentanyl (20 µg) to suppress the cough. This may be reason for the almost similar requirement of fentanyl and propofol between the groups.

Table 5 : Intraoperative Sedative, Analgesics, Vasopressors requirements between the groups

Parameters/ Group	**Opioid Based (N=32) Mean (SD)**	**Opioid Sparing (N=35) Mean (SD)**	**p value**
Total dose of Fentanyl (µg)	217.81 (50.72)	206.71 (68.46)	0.283[3]
Total dose of Propofol (mg)	174.06 (40.23)	164.29 (42.52)	0.213[3]
Total dose of Ephedrine (mg)	6.88 (7.29)	8.20 (9.87)	0.879[3]
Total dose of Phenylephrine (µg)	171.09 (173.10)	229.14 (256.30)	0.497[3]

3: Wilcoxon-Mann-Whitney U Test

The requirement of ephedrine and phenylephrine were very minimal, and it was similar between the groups indicate that both the technique provide stable haemodynamics.

Intravenous fluid (IVF) administration and the intraoperative blood loss

IVF administrations were left with the attending anaesthesiologist who anaesthetized the patients for surgery. But the volume of IVF administration was comparable between the groups. Patients who lost > 500 ml of blood during surgery were given 500 ml of colloid (tetra starch) to replace the intravascular volume. The blood loss was slightly more in opioid based group compared to opioid sparing group, which came as statistically significant (295.94±133.73 Vs 224.29±114) ($p< 0.05$). (Table5) There were 6 patients in the opioid based group received starch compared to 4 in opioid sparing group, this could be due to increased blood loss in the opioid based group.

Table 6: Blood loss and the volume of crystalloids given between the groups

Parameters/ Group	**Opioid Based (N=32) Mean (SD)**	**Opioid Sparing (N-35) Mean (SD)**	**p value**
Blood loss in ml	295.94 (133.73)	224.29 (114.00)	0.028[3]
Total amount of fluids given in ml	1876.56 (623.59)	1911.43 (494.54)	0.469[3]

3: Wilcoxon-Mann-Whitney U Test

Extubation time, Duration of anaesthesia and Surgery between the groups

The time of stopping sevoflurane to time of ETT removal is considered as extubation time. The time from induction to time of extubation was taken as duration of anaesthesia. Duration of surgery is defined as the time taken from the skin incision to application of skin dressing. All were comparable between the groups. The administration of pregabalin and the administration of small dose of propofol or fentanyl for controlling the cough at extubation could be the reasons for similar extubation time between the two groups. The duration of anaesthesia and surgery were similar between the two groups. Both the techniques were comparable in terms of waking up from anaesthesia.

Table 7 : Extubation time, Duration of Anaesthesia and Surgery between the groups.

Parameters / Group	**Opioid Based (N=32) Mean (SD)**	**Opioid Sparing (N=35) Mean (SD)**	**p value**
Extubation Time (mins)	16.25 (2.99)	15.66 (4.26)	0.624[3]
Duration of Surgery (mins)	164.38 (42.36)	172.71 (72.16)	0.850[3]
Duration of Anaesthesia (mins)	217.03 (44.32)	221.94 (74.61)	0.660[3]

3: Wilcoxon-Mann-Whitney U Test

III- POSTOPERATIVE VARIABLES

Patients were given rescue analgesic if the pain score exceeded NRS > 4. Inj Pentazocine 30 mg I.M was given for rescue analgesia. Number of patients who received rescue analgesic were significantly less for the Opioid sparing group 27 Vs 77 (P< 0.001). Also, the time to receive first rescue analgesic was longer and statistically significant in opioid sparing group compared to opioid based group. (P= 0.03). Most patients in opioid sparing group received only one dose of recue analgesia while patients in opioid based group received two doses of rescue analgesia. The results indicates that opioid sparing technique using ketamine and pregabalin provide longer duration of analgesia while reducing the opioid use during the postoperative period.

Table 8: Details of rescue analgesics between the groups

Parameters/ Groups	**Opioid Based (N=32) Number (%)**		**Opioid Sparing (N=35) Number (%)**		**p-value**
No of patients who received rescue analgesia [Number (%)]	27 (84.4%)		11 (31.4%)		<0.001[2] ⁂
Time to First Rescue Analgesia in minutes [Mean ± SD]	**Mean (SD)**	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	0.036[3] ⁂
	169.63 (160)	120 (75-187.5)	286.36 (190.26)	300 (187.5-330)	
Number of doses of rescue analgesic received during the first 24 hours	1.85 ± 0.46		1.55 ± 0.69		0.085[3]

1: t-test, 2: Chi-Squared Test, 3: Wilcoxon-Mann-Whitney U Test, 4: Fisher's Exact Test; ⁂- P < 0.05

DREAM TIME

The time taken to **dr**ink oral fluids, **e**at solid food and **am**bulation is called as **DREAM** time. All these were compared between the groups. The time taken for starting oral fluids were comparable between the groups. But the time taken to start solid food was significantly less (p-0.003) in opioid based group.

Table 9: Showing the "DREAM TIME"- between the group

Parameter/ Group	Group		Wilcoxon-Mann-Whitney U Test	
	Opioid Based	Opioid Sparing	W	p value
Time of Drinking Oral Fluids				
Mean (SD)	14.16 (8.63)	16.86 (7.03)	491.500	0.504
Median (IQR)	18 (5.75-22.16)	18.8 (14.48-22.08)		
Range	1 – 24	1.15 - 24.3		
Time of eating solid food				
Mean (SD)	10.47 (5.37)	16.19 (7.40)	326.000	0.003
Median (IQR)	8.3 (7.75-10)	19.45 (8.8-23)		
Range	5 - 22.4	1 - 24.3		
Time of Ambulation				
Mean (SD)	11.00 (3.43)	9.41 (4.11)	677.500	0.045
Median (IQR)	10 (9-13)	8.45 (7.25-10)		
Range	6 – 18	2.3 - 24.3		

1: t-test, 2: Chi-Squared Test, 3: Wilcoxon-Mann-Whitney U Test, 4: Fisher's Exact Test; ⁂- P < 0.05

Despite encouraging the patients to take fluid as early as possible, they were not actively encouraged by the nurses in ward. Also, most cases were done as a last case on the list, and the time of shifting to ward after the PACU stay became very late (after 9 p.m). High patient/nurses ratio during the night shift could have led to longer time for initiating oral fluids and solids after surgery. The time for ambulation was significantly less in opioid sparing group (p=0.045), which indicate that the analgesia provided by the opioid sparing technique is superior to opioid based group.

Time of passing Flatus and Stool

Positioning the patient prone and doing a spine decompressive surgery itself can cause ileus and abdominal distention which can gets worsened using potent opioids. Hence, we have compared these parameters between the groups. The time of passing flatus and stool was comparable between the groups.

Table 10 : Time of passing flatus and stool between the groups

Parameter/ Group	Group		Wilcoxon-Mann-Whitney U Test	
	Opioid Based	Opioid Sparing	W	p value
Time of passing Flatus				
Mean (SD)	13.34 (5.50)	12.05 (5.17)	506.000	0.241
Median (IQR)	14 (9.25-17.5)	11 (9-13)		
Range	5 – 23	5 – 24		
Time of passing Stool				
Mean (SD)	16.57 (5.83)	16.50 (3.85)	0.030	0.976
Median (IQR)	15 (13-22)	16 (14-20)		
Range	8 – 23	9 – 22		

Duration of hospital stay and the patient Satisfaction score:

The duration of hospital stay was less ($p = 0.006$)and the patient satisfaction score was more which was statistically significant for opioid sparing group ($P< 0.001$) (Table11)

Table 11: Duration of Hospital stay and the Patient satisfaction between the groups

Duration of Hospital Stay After Surgery	Group		Wilcoxon-Mann-Whitney U Test	
	Opioid Based	Opioid Sparing	W	p value
Mean (SD)	2.53 (0.88)	2.11 (0.40)	721.000	0.006
Median (IQR)	2 (2-3)	2 (2-2)		
Range	2 – 6	2 - 4		

Patient Satisfaction	Group			Chi-Squared Test	
	Opioid Based	Opioid Sparing	Total	$\chi 2$	P Value
Excellent	3 (9.4%)	21 (60.0%)	24 (35.8%)	22.745	<0.001
Very Good	15 (46.9%)	12 (34.3%)	27 (40.3%)		
Good	14 (43.8%)	2 (5.7%)	16 (23.9%)		

IV -PACU AND POSTOPERATIVE VITAL PARAMETERS

Hemodynamics: Were compared between the groups and they were comparable.

Table 12: Pulse rate over time in PACU and in the ward between the groups:

Time interval/Group (Pulse Rate/min)	Group		P value
	Opioid Based	Opioid Sparing	
	Mean (SD)	Mean (SD)	
PACU at 5 Minutes	96.62 (15.36)	92.40 (14.05)	0.246
PACU at 30 Minutes	93.06 (14.82)	88.46 (14.74)	0.207
PACU at 1 Hour	90.34 (13.26)	86.58 (14.92)	0.286
PACU at 1.5 Hour	89.50 (11.45)	86.27 (13.45)	0.320
PACU at 2 Hours	90.17 (12.40)	85.08 (13.57)	0.176
PACU - At Discharge	90.03 (11.59)	88.26 (11.76)	0.537
In the ward at arrival	95.53 (12.53)	90.17 (16.34)	0.135
In the ward at 2 Hours	96.03 (11.49)	90.63 (13.62)	0.083
In the ward at 6 Hours	96.44 (12.15)	87.71 (13.06)	0.006
In the ward at 12 Hours	91.38 (13.49)	86.14 (11.24)	0.091
In the ward at 18 Hours	89.88 (12.38)	87.09 (12.27)	0.358
In the ward at 24 Hours	89.44 (12.28)	86.00 (9.99)	0.216
p value for change in pulse rate over time within each group ⁂	0.823	0.927	
p value comparison in pulse rate over time between the two groups*	0.665		

⁂ Repeated measures of ANOVA; *Generalized Estimating Equations)

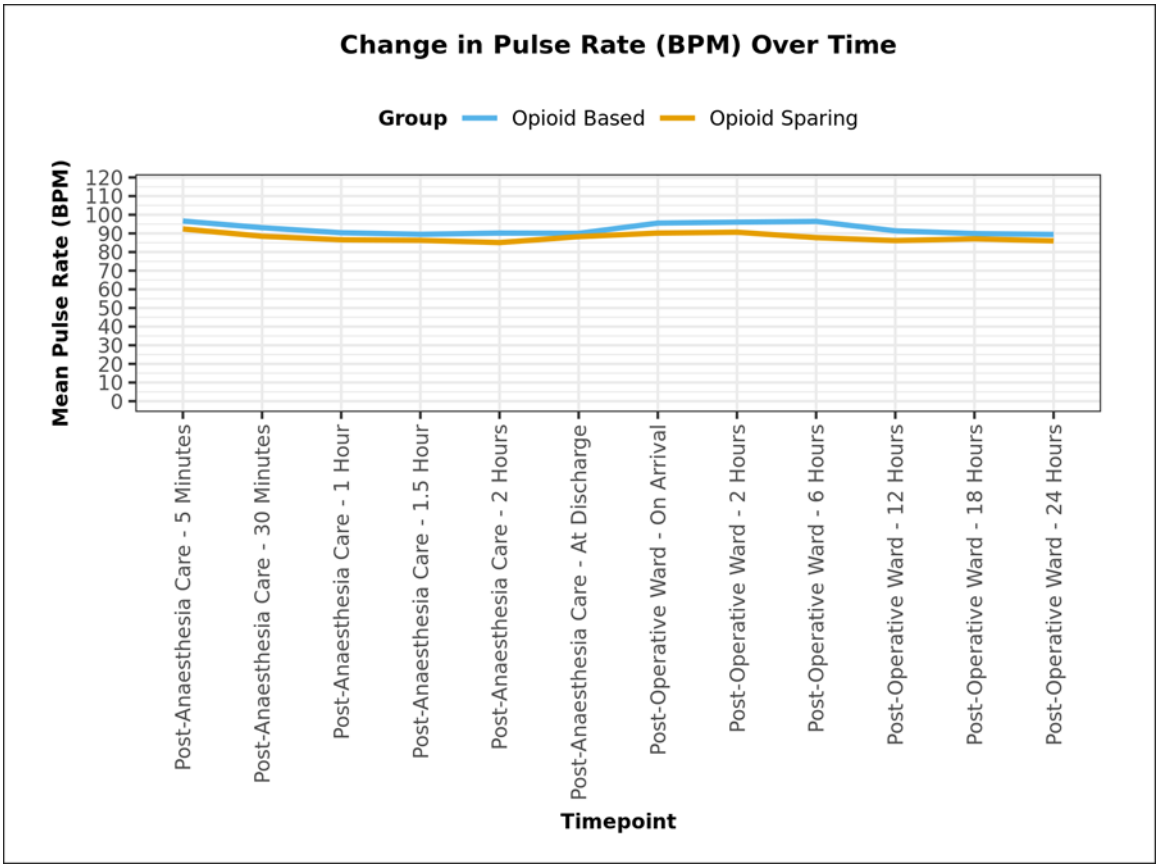

Figure 6- Pulse rate trend

The change in pulse rate/min over time was compared within the group and between the two groups using repeated measures of ANOVA the Generalized Estimating Equations method respectively. There were no significant difference within the groups (Opioid based; p=0.823, Opioid sparing p=0.927) and between the two groups over a varied time period (p = 0.665).

Table 13: Systolic BP trends in PACU and ward over time between the groups

Time interval/Group	Group		p value †
Systolic BP (SBP) in mmHg	Opioid Based	Opioid Sparing	
	Mean (SD)	Mean (SD)	
PACU at 5 Minutes	122.84 (14.38)	132.40 (15.99)	0.027
PACU at 30 Minutes	124.59 (11.71)	132.66 (13.72)	0.011
PACU at 1 Hour	120.47 (20.72)	129.27 (15.47)	0.085
PACU at 1.5 Hour	122.67 (8.60)	129.03 (15.07)	0.083
PACU at 2 Hours	125.43 (8.68)	125.12 (14.52)	0.864
PACU - At Discharge	124.38 (7.57)	127.06 (14.16)	0.437
In the ward at arrival	125.34 (11.78)	124.20 (11.05)	0.673
In the ward at 2 Hours	119.94 (12.65)	120.60 (9.54)	0.738
In the ward at 6 Hours	115.84 (14.87)	119.26 (11.78)	0.392
In the ward at 12 Hours	116.06 (13.50)	118.71 (13.80)	0.408
In the ward at 18 Hours	121.34 (14.57)	119.97 (17.03)	0.724
In the ward at 24 Hours	119.16 (13.73)	119.37 (12.88)	0.950
p value for change in SBP over time within each group ⁂	0.028	<0.001	
p value comparison in pulse rate over time between the two groups*	0.275		

Figure 8: Showing the SBP in PACU and in the ward for the two groups over time.

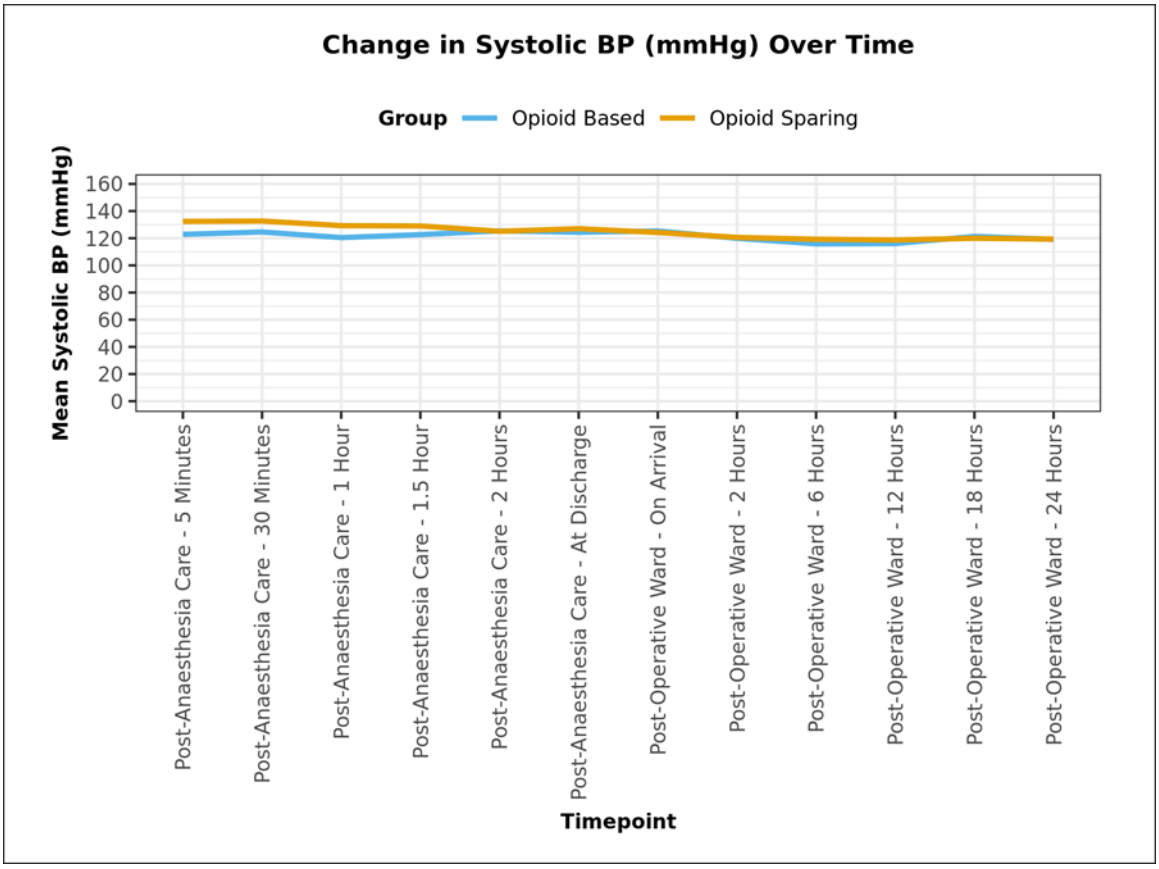

Figure 7- SBP Trend

The change in Systolic BP (SBP) in mmHg over time was compared within the groups and between the two groups using repeated measures of ANOVA the Generalized Estimating Equations method respectively. There was a statistically significant difference noted within the groups over a period. (Opioid Sparing $p < 0.001$; Opioid Based $P= 0.028$). But there was no significant difference between the two groups over a varied time period ($p = 0.275$).

Table 14: Diastolic BP trends in PACU and ward over time between the groups

Time interval/Group	Group		P value (Wilcoxon-Mann-Whitney Test)
Diastolic BP (DBP) in mmHg	Opioid Based	Opioid Sparing	
	Mean (SD)	Mean (SD)	
PACU at 5 Minutes	75.53 (12.01)	76.77 (11.49)	0.821
PACU at 30 Minutes	77.28 (13.71)	76.31 (11.21)	0.725
PACU at 1 Hour	76.28 (16.13)	78.00 (11.63)	0.299
PACU at 1.5 Hour	74.40 (9.18)	77.77 (8.87)	0.166
PACU at 2 Hours	82.61 (11.06)	75.38 (10.21)	0.017
PACU - At Discharge	78.47 (11.79)	100.97 (135.93)	0.995
In the ward at arrival	80.31 (9.66)	75.43 (11.09)	0.134
Comparison in DBP over time between the groups*(p-value)	0.002		

⁂-Repeated measures of ANOVA; *-Generalized estimated equation

Figure 9: Diastolic BP trends in PACU and in the ward over time

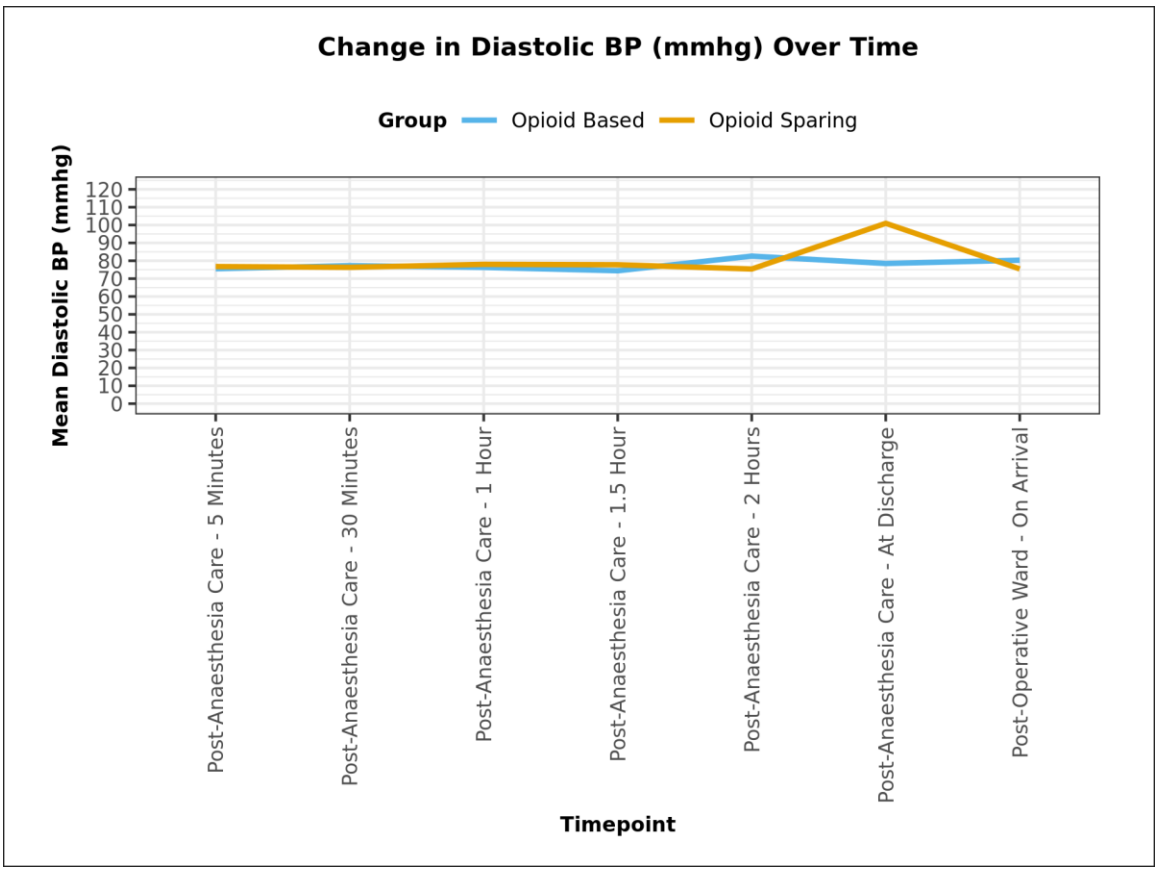

Figure 8-DBP trend

The overall change in Diastolic BP (DBP) in mmHg over time was compared between the groups using the Generalized Estimating Equations method. There was a significant difference in the trend of DBP over time between the two groups ($p = 0.002$).

Table 15: Mean BP trends in PACU and in the ward over time

Time interval/Group	Group		p value (Wilcoxon-Mann-Whitney Test)
Mean BP (MBP) in mmHg	**Opioid Based**	**Opioid Sparing**	
	Mean (SD)	**Mean (SD)**	
PACU at 5 Minutes	84.91 (13.77)	89.63 (10.14)	0.106
PACU at 30 Minutes	86.09 (12.79)	89.66 (9.22)	0.180
PACU at 1 Hour	84.41 (10.56)	88.24 (10.77)	0.130
PACU at 1.5 Hour	83.40 (7.67)	84.93 (16.59)	0.321
PACU at 2 Hours	87.91 (9.19)	83.81 (17.68)	0.346
PACU - At Discharge	85.81 (7.90)	88.54 (9.25)	0.160
In the ward at arrival	86.16 (9.75)	85.54 (10.99)	0.801
In the ward at 2 hours	82.50 (9.78)	82.34 (9.27)	0.890
In the ward at 6 hours	80.78 (9.08)	80.11 (8.59)	0.777
In the ward at 12 hours	80.75 (8.64)	81.46 (10.36)	0.915
In the ward at 18 hours	85.09 (10.91)	80.97 (9.43)	0.157
In the ward at 24 hours	81.19 (13.85)	81.20 (10.80)	0.365
Comparison in MBP over time within the groups ⁂ (p-value)	0.014	<0.001	
Comparison in MBP over time between the groups*(p-value)	0.083		

Figure10: Mean BP trends in PACU and in the ward over time between the groups.

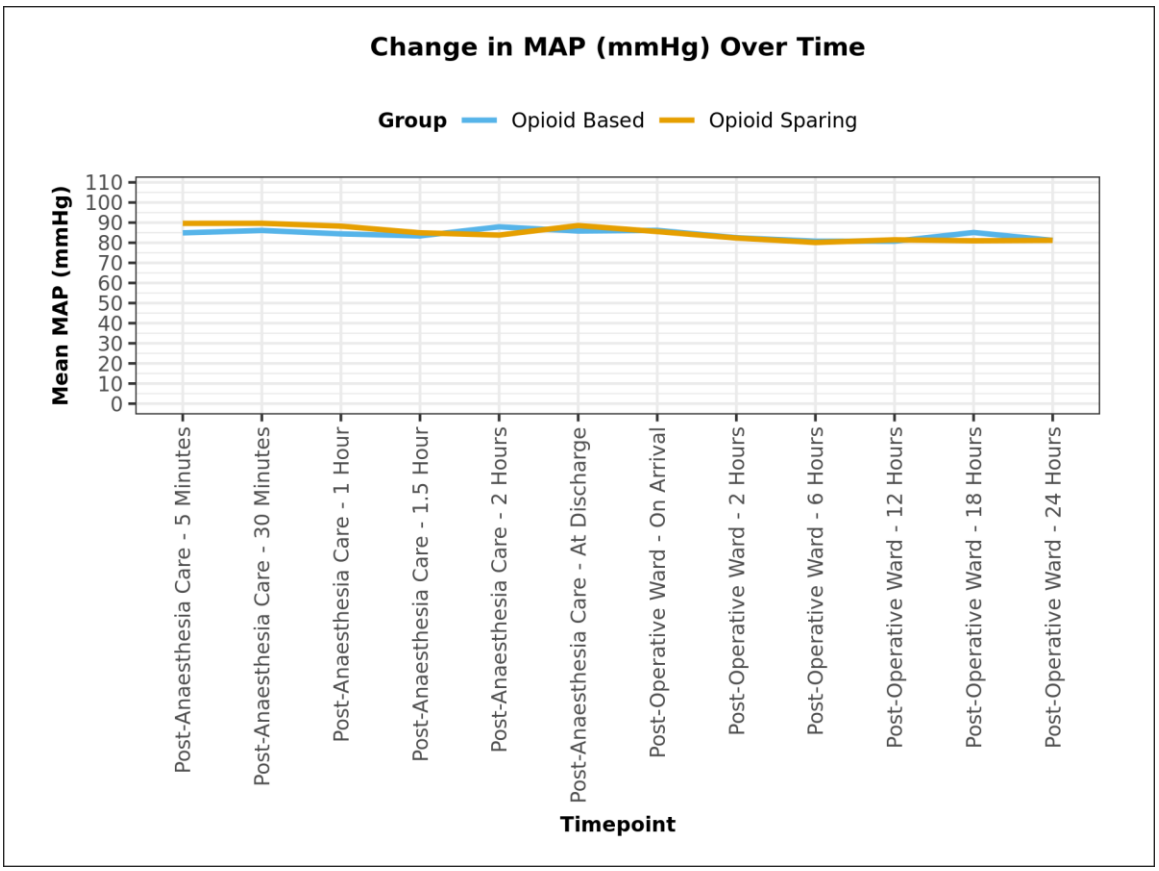

Figure 9-MAP Trends

The overall change in mean blood pressure (MBP) in mmHg over time was compared within the groups using repeated measures of ANOVA. There was a significant difference noted within the groups (Opioid based p=0.014; Opioid sparing p< 0.001). The overall change in mean blood pressure (MBP) in mmHg over time was compared between the groups using the Generalized Estimating Equations method. There was no significant difference in the trend of MBP (mmHg) over time between the two groups (p = 0.083).

Table 16: Sedation Score between the groups in PACU and in the ward over time

Sedation Score	Group		P value (Wilcoxon-Mann-Whitney Test)
	Opioid Based	Opioid Sparing	
	Mean (SD)	Mean (SD)	
PACU at 5 Minutes	2.56 (0.91)	2.09 (0.70)	0.010
PACU at 30 Minutes	3.16 (3.52)	2.00 (0.64)	<0.001
PACU at 1 Hour	2.41 (0.80)	2.64 (3.53)	0.017
PACU at 1.5 Hour	2.03 (0.72)	2.07 (0.58)	0.852
PACU at 2 Hours	1.87 (0.46)	2.85 (3.96)	0.139
PACU - At Discharge	1.84 (0.51)	2.03 (0.57)	0.184
In the ward at arrival	2.53 (3.58)	2.54 (3.39)	0.484
In the ward at 2 hours	1.91 (0.39)	1.97 (0.17)	0.355
In the ward at 6 hours	2.59 (3.55)	2.00 (0.00)	1.000
In the ward at 12 hours	1.97 (0.31)	2.57 (3.38)	0.320
In the ward at 18 hours	2.00 (0.00)	2.00 (0.00)	-
In the ward at 24 hours	2.00 (0.00)	2.00 (0.00)	-
Sedation score comparison over time within the groups ⁑ (p-value)	<0.001	0.994	
Sedation score comparison over time between the groups* (p-value)	-		

⁑-Repeated measures of ANOVA; *-Generalized Estimated Equations

Figure 11Sedation score between the groups at various time points in PACU and in ward.

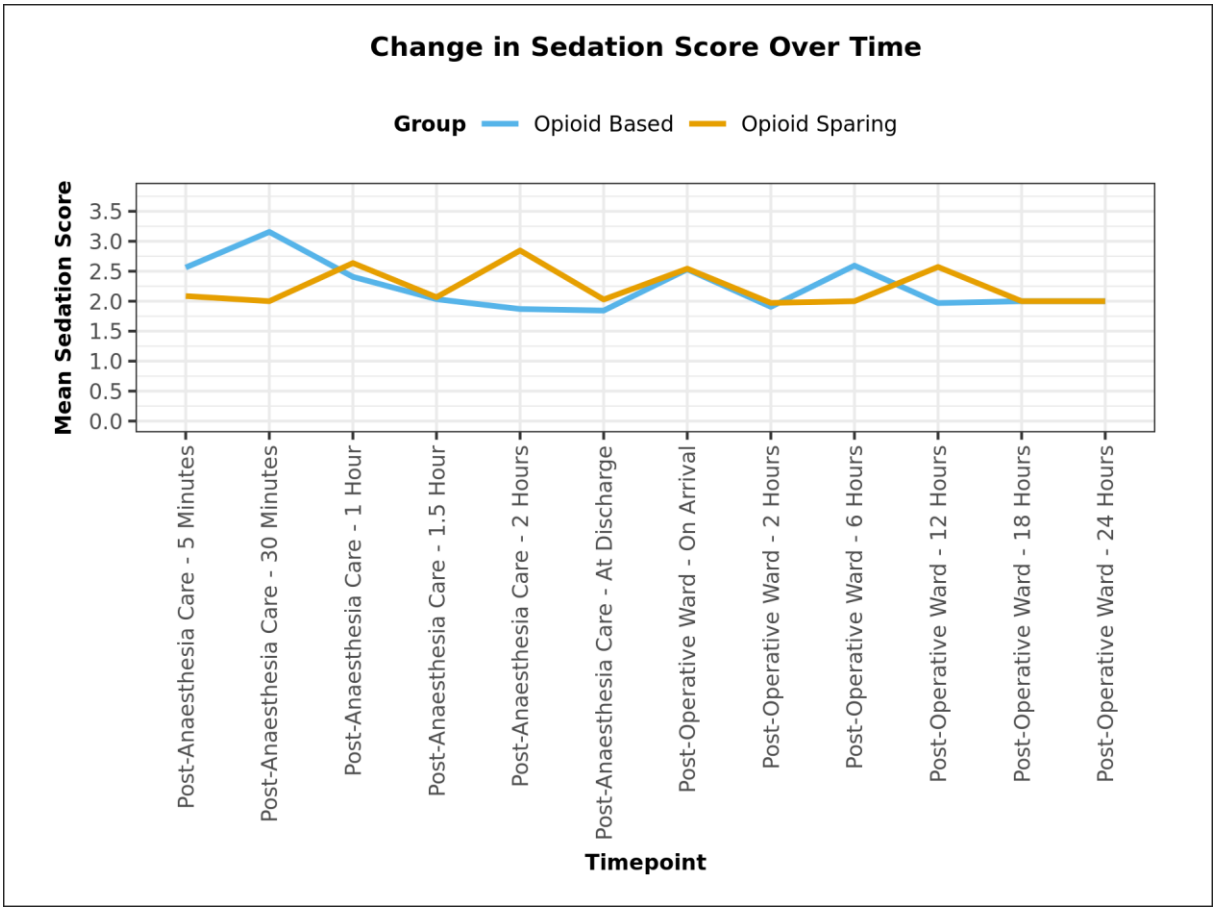

Figure 10-Sedation score trend

There was significant difference Sedation Score at the following time points: PACU at 5, 30 minutes, at 1 hour. In the opioid based group, the mean Sedation Score was 2.56 at the PACU-5 min, which had increased to 3.16 at 30 min at PACU, and then decreased to 2.00 at the Post-Operative Ward at 24 Hours' time point. This change was statistically significant (Friedman Test: $\chi 2 = 54.4$, $p = <0.001$).

In the Opioid Sparing group, the mean Sedation Score increased from 2.09 at the Post-Anaesthesia Care - 5 Minutes time point to a maximum of 2.85 at the Post-Anaesthesia Care - 2 Hours' time point, and then decreased to 2.00 at the Post-Operative Ward - 24 Hours' time point. This change was not statistically significant (Friedman Test: $\chi 2 = 2.7$, $p = 0.994$).

The overall change in Sedation Score over time was compared in the two groups using the Generalized Estimating Equations method. There was no significant difference in the trend of Sedation Score over time between the two groups ($p = 0.994$).

Table 17: Respiratory Rate comparison between the groups in PACU and in the ward over time

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Time Intervals/Group Respiratory Rate/min	Group		P value (Wilcoxon-Mann-Whitney Test)
	Opioid Based	Opioid Sparing	
	Mean (SD)	Mean (SD)	
PACU at 5 Minutes	17.91 (3.83)	17.26 (3.17)	0.770
PACU at 30 Minutes	18.38 (3.07)	18.20 (2.67)	0.934
PACU at 1 Hour	22.97 (17.07)	18.55 (3.06)	0.371
PACU at 1.5 Hour	19.07 (2.15)	18.80 (3.00)	0.784
PACU at 2 Hours	21.13 (11.31)	19.38 (3.14)	0.547
PACU - At Discharge	21.22 (11.70)	19.77 (2.65)	0.372
In the ward at arrival	21.03 (4.26)	21.89 (3.97)	0.367
In the ward at 2 hours	21.44 (2.45)	22.40 (2.46)	0.144
In the ward at 6 hours	21.88 (2.64)	21.37 (4.11)	0.724
In the ward at 12 hours	20.81 (2.16)	21.71 (2.12)	0.103
In the ward at 18 hours	20.16 (2.76)	22.83 (9.31)	0.046
In the ward at 24 hours	20.91 (1.75)	21.54 (2.28)	0.318
Respiratory rate comparison over time within the groups ⁂ (p-value) (Friedman Test)	<0.001	<0.001	
Respiratory rate comparison over time between the groups⁑(p-value) (GEE method)	0.153		

Figure12 : Respiratory rate comparison between the groups in PACU and in the ward over time

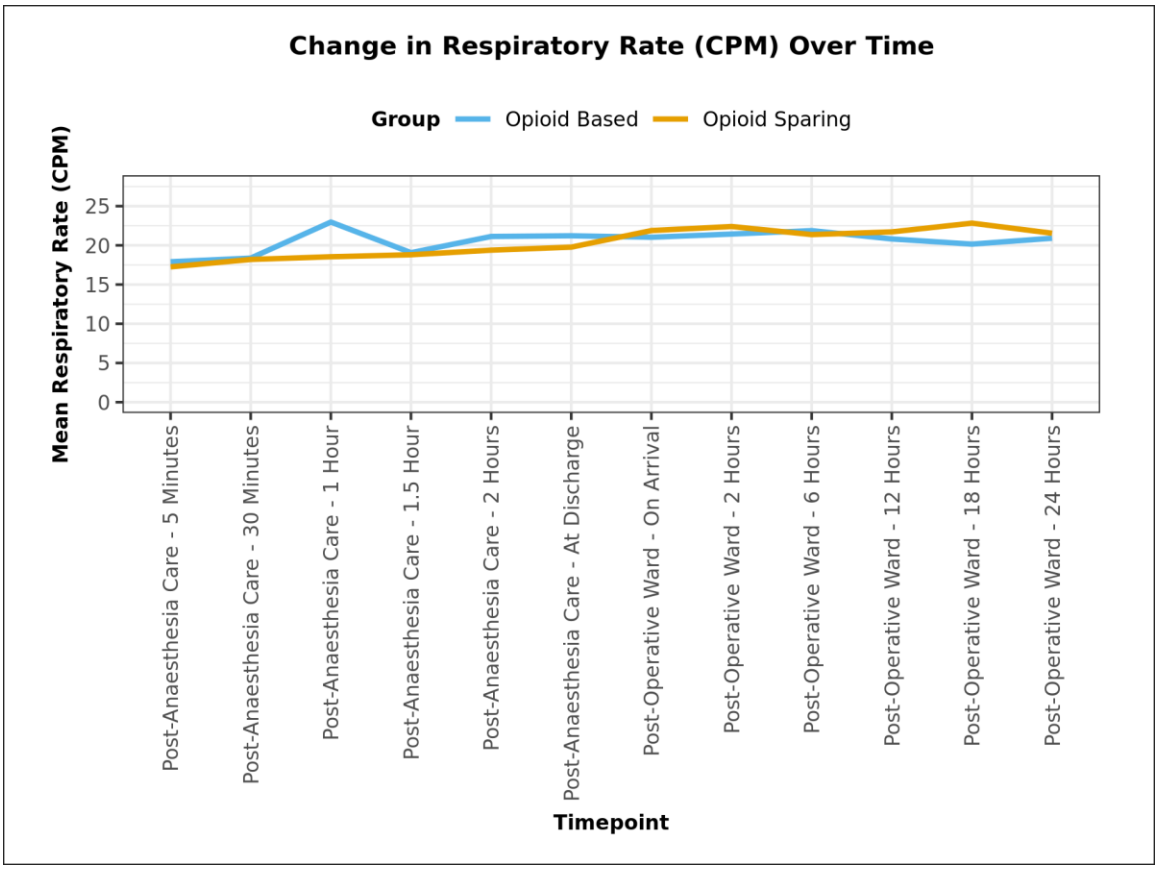


Figure 11-respiratory rate trend

The overall change in Respiratory Rate over time was compared between the groups using the Generalized Estimating Equations method. There was no significant difference in the trend of Respiratory Rate over time between the two groups ($p = 0.153$).

Table 18: Comparison of pain score (NRS) at rest over time between the groups

NRS Score at Rest	Group		p-value (Wilcoxon-Mann-Whitney Test)
	Opioid Based	Opioid Sparing	
	Mean (SD)	Mean (SD)	
In the ward - on arrival	2.91 (1.57)	1.97 (1.50)	0.022
In the ward at 2 hours	2.81 (1.40)	1.89 (1.30)	0.010
In the ward at 6 hours	2.59 (1.34)	2.29 (1.81)	0.247
In the ward at 12 Hours	3.03 (1.47)	1.80 (1.64)	<0.001
In the ward at 18 Hours	2.94 (1.46)	2.00 (1.73)	0.009
In the ward at 24 Hours	2.50 (1.19)	1.69 (1.21)	0.014
Change in NRS Score at rest over time within each group (Friedman Test) (p-value)	0.393	0.196	
Comparison of change in NRS Score at Rest over time between the two groups (GEE)(p value**)**	0.072		

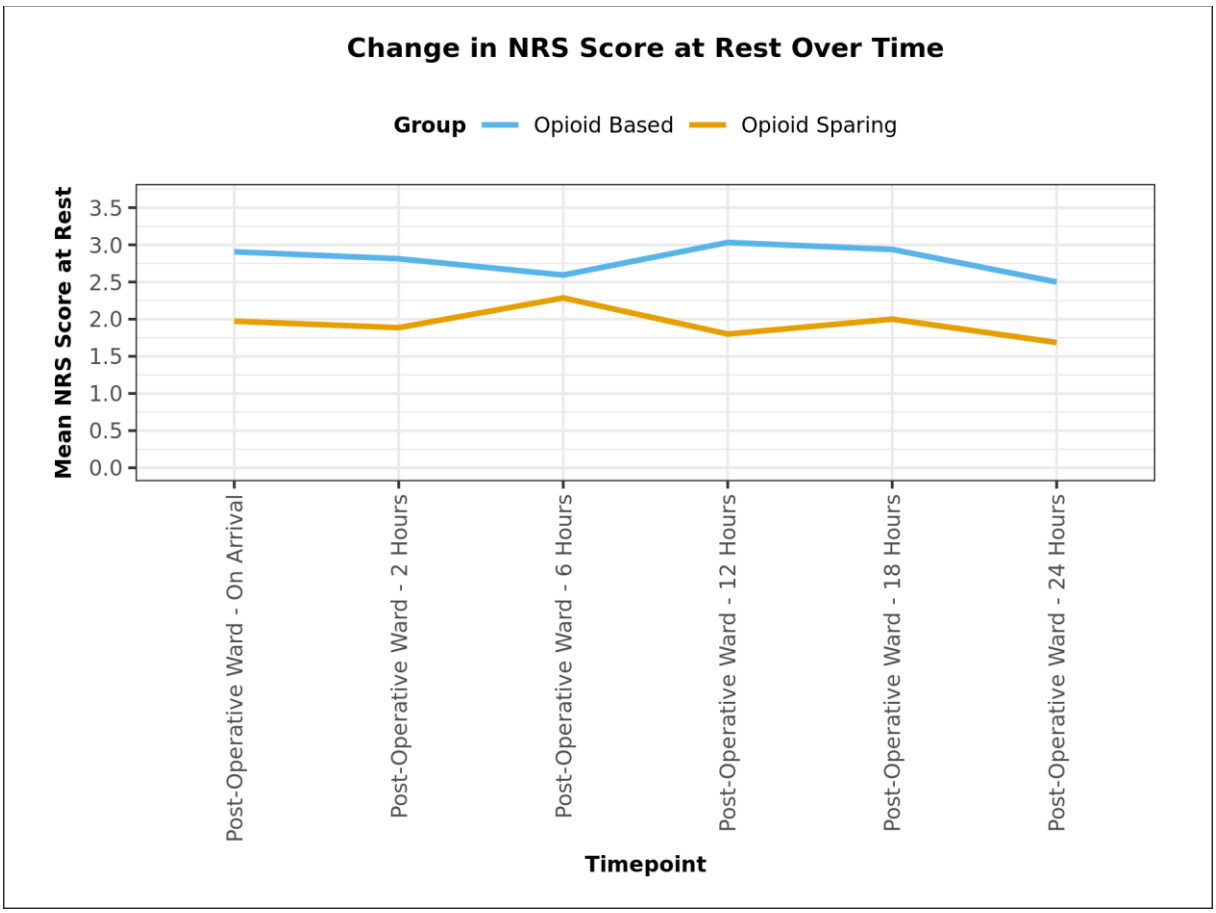


Figure 12-NRS Score at rest

Figure 13 depict **t**he overall change in NRS Score at Rest over time was compared in the two groups using the Generalized Estimating Equations method. There was no significant difference in the trend of NRS Score at Rest over time between the two groups (p = 0.072).

Table 19 Comparison of pain score (NRS) at Movement among the two groups

NRS Score at Movement	Group		P value (Wilcoxon-Mann-Whitney Test)
	Opioid Based	Opioid Sparing	
	Mean (SD)	Mean (SD)	
In the ward - on arrival	2.84 (2.52)	2.51 (1.98)	0.831
In the ward at 2 hours	3.97 (2.19)	2.74 (1.85)	0.023
In the ward at 6 hours	4.19 (1.99)	3.69 (1.75)	0.310
In the ward at 12 hours	4.47 (1.76)	3.29 (1.78)	0.004
In the ward at 18 hours	4.44 (1.72)	3.46 (1.82)	0.014
In the ward at 24 hours	3.56 (1.66)	2.97 (1.36)	0.181
Change in NRS Score at rest over time within each group (Friedman Test) (p-value)	0.026	0.323	
Comparison of change in NRS Score at Rest over time between the two groups (GEE) (p value)	0.056		

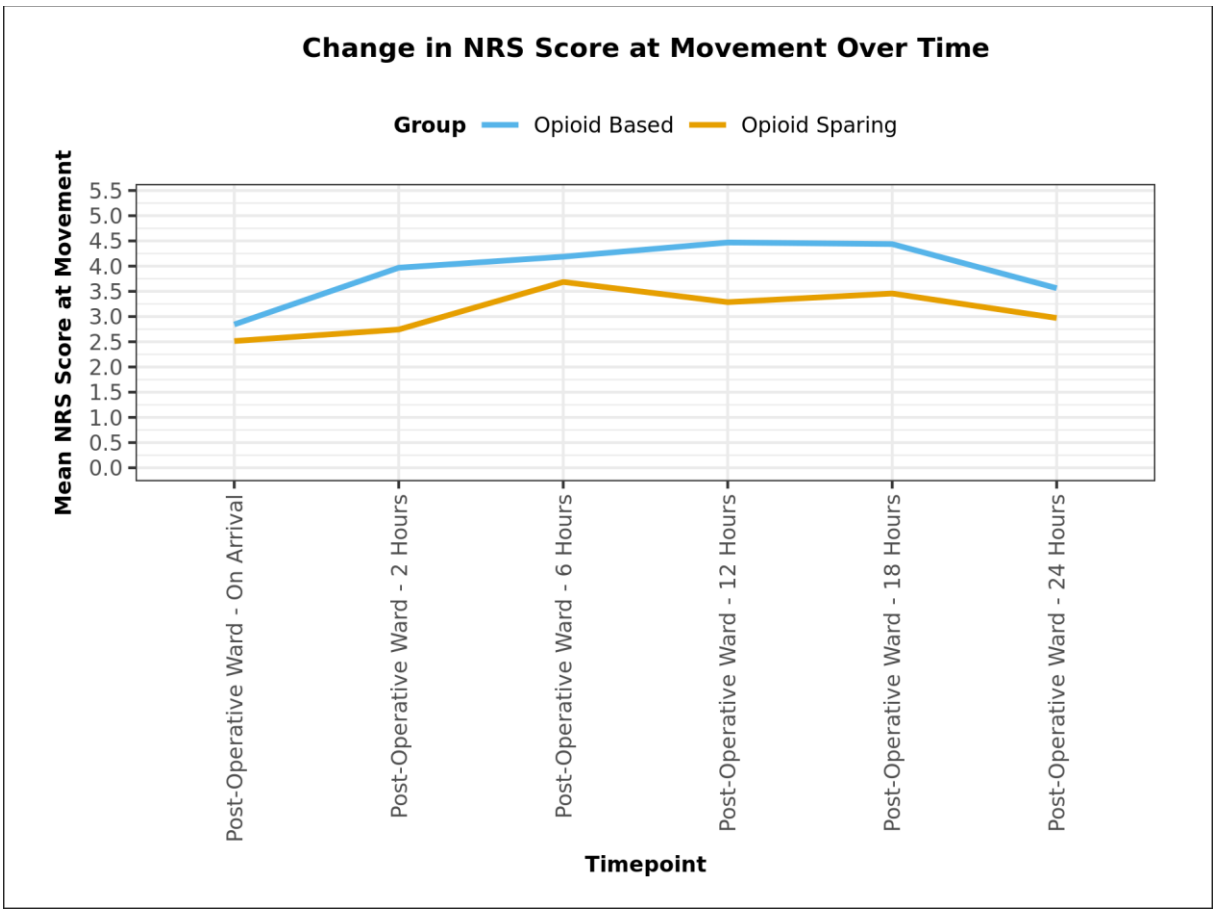


Figure 13- NRS Score at Movement

Figure 14 above depicts the overall change in NRS Score at Movement over time was compared in the two groups using the Generalized Estimating Equations method. There was no significant difference in the trend of NRS Score at Movement over time between the two groups ($p = 0.056$).

Incidence of complications:

The incidence of complications was compared between the groups. The incidence of PONV and the abdominal distention was more in opioid based group which has reached the statistical significance. There are no patients who received low dose ketamine in opioid sparing group has hallucination or nystagmus, which signifies that the low dose ketamine potentiates analgesia without causing side effects.

Table 20 : The incidence of complications between the groups.

Complications	Groups		**p-value**
	Opioid based (N=32)	**Opioid sparing (N=35)**	
Nausea	9 (28 %)	2 (6.1 %)	0.018
Vomiting	4 (12.5 %)	0	0.04
Abdominal distention	11 (34.4 %)	0	<0.001
Hallucination	1 (3.1%)	0	0.478
Nystagmus	1 (3.1 %)	0	0.492
Pruritis	1 (3.1 %)	0	0.492

DISCUSSION

This research was undertaken to study the effect of two Anaesthesia techniques -opioid-sparing Vs. opioid-based Anaesthesia technique on DREAM time. Dream time is defined as the time taken to drink oral fluids, eat solid food and the time taken to ambulate. We have found that the time taken to drink oral fluids was comparable between the groups. But the intake of solid food was earlier in the opioid-based group, which is statistically significant. (P=0.003) The time taken for ambulation was faster in an opioid-sparing group with statistical significance. (P=0.04)

Opioid-based techniques can increase the incidence of PONV and bowel dysfunction leading to PONV, abdominal distention (Kurz et al.- 1, Weitzman et al-2), which can further delay the time to eat or drink. Hence one should expect a delay in time taken to drink or eat in an opioid-based group[39]. In contrary to this, our study has shown that the time to eat solid food was delayed in the opioid-sparing group despite achieving early ambulation (P=0.04). Also, the time to drink was prolonged in both groups (14-16 hours) compared to the patients who undergo decompressive spine surgery, where patients are started on oral fluids at 6-8 hours after surgery .When we analyzed the reason, we found that most of these cases were done in the evening as a last case of the list, and the surgery had been completed late (after 7 p.m.). The patients got shifted to the ward very late after the PACU stay. (after 9 p.m.). Late-night shifting and the high patient/nurses ratio during the night shift failed the nurses to motivate the patient to drink or eat as early as possible. Most patients started to drink orally only the next day morning. This could be the reason

for the delay in starting oral fluids and solids after surgery. The study results will be communicated to the staff in the postoperative neurosurgical ward of our institution, and the necessary measures will be taken to reduce the time delay for starting oral fluids and solid food to enhance the recovery.

In our study, the time to ambulate was significantly less in the opioid-sparing group (9 Vs 11hrs) (p=0.045), which indicate that the analgesia provided by the opioid-sparing technique is equivalent or superior to the opioid-based approach. Also, the patients in opioid-sparing groups were awake enough to get ambulated early compared to the opioid-based group. Similar to our study, Hakim K et al. [(40)] have shown that opioid-sparing/opioid-free Anaesthesia enhances the quality of recovery after laparoscopic gynecological surgery.

In this study, a highly potent long-acting opioid, morphine was replaced with ketamine, pregabalin and local anesthetic infiltration (0.2% ropivacaine) in opioid sparing group. Ketamine, an NMDA receptor blocker, purportedly results in decreased nociceptive and inflammatory pain transmission.[(41)] Recent evidence shows that ketamine exerts its analgesic effect by interacting with mu and delta opioid receptors. [(42)], Studies have shown that utilizing low-dose intravenous ketamine for postoperative analgesia after a variety of surgical interventions and concluded that ketamine provides a 40% opioid-sparing effect.[(41)] Similar to these studies, our study also has proved the opioid-sparing effect. In our study, the time for the administration of the first rescue analgesia was

longer, and the number of total rescue analgesia given was lower in the opioid-sparing group compared to the opioid-based group proving the opioid sparing effect of ketamine.

The effect of pregabalin for treating acute and chronic pain has been studied and proven extensively. Recently a study by Freedman et al.[43] in their study has shown that perioperative pregabalin administration reduced postoperative narcotic use by 70% in patients undergoing breast surgery. This study also reported that there is a reduction in nausea about (46%) in the pregabalin-treated group, with very few side effects and no drug interactions. They have recommended that pregabalin can be considered safe in an analgesic regime for treating acute pain. Similar to this study, our study also has proven the opioid-sparing effect of pregabalin with no side effects. None of our patients were over sedated or complained of dizziness, nausea or visual disturbances. This could be due to the small dose of pregabalin used in our study and none of our study patients were more than 60 years old. The similar extubation time, the duration of Anaesthesia and surgery, and the early ambulation signify that oral pregabalin administration does not cause over sedation, thereby helps in enhanced recovery.

In our study, patients in the opioid-sparing group received the local anesthetic (10-20 ml of 0.2% Ropivacaine), which was infiltrated into the intramuscular as well as in the subcutaneous plane during the closure of the surgical wound. This could have helped in prolonging analgesia. Hence, the time to receive the first dose of rescue analgesia was significantly prolonged in this group compared to the opioid-based group. Similar to our

study result, the systematic review and meta-analysis by Perara et al.[44] have reported the effectiveness of intramuscular administration of local anesthetic on the postoperative analgesic requirement and the time to receive the first analgesic and proven that the requirement of analgesic had significantly reduced and the time to receive the first dose of analgesic was prolonged.

Both techniques provided comparable pain scores (NRS) at rest and during movement, which signifies that both technique provides satisfactory analgesia for lumbar laminectomy with or without discectomy. The incidence of PONV and abdominal distention was higher in the opioid-based group than the opioid-sparing group, which has been proven in many studies reported in the literature. [44]

Reduction in side effects could be one of the reasons for the improved patient satisfaction in the opioid-sparing group. Also, low dose ketamine has its antidepressant effect.[45] Surgical stress can cause perioperative depression. Administration of low dose ketamine could have helped reduce the perioperative depression, thereby improving patient satisfaction in the opioid-sparing group.

None of the patients in either group had hemodynamic instability during the postoperative period signifies that both techniques are safe for patients who are risk for hemodynamic stability.

Limitations:

1. As it was technically difficult for making placebo capsules similar to pregabalin, it was difficult to blind the nursing staff who were involved with the perioperative management. This could have created observer bias.
2. Because of the COVID pandemic, we could not complete the sample size within the study period. We are planning to re randomize and continue the study till we finish the estimated sample size.
3. The use of patient-controlled analgesia with morphine or fentanyl could have predicted the exact dose of opioid consumption during the perioperative period. The administration of Inj. Pentazocine i.m 30 mg is the routine practice in our neurosurgical wards for providing postoperative analgesia for this surgery. Hence we wanted to continue the standard practice and see whether opioid-sparing technique helps in enhanced recovery.

CONCLUSION:

1. Administration of opioid-sparing anaesthesia using pregabalin, low dose ketamine and intramuscular administration of ropivacaine helps in early ambulation in patients undergoing 1-3 levels of lumbar laminectomy with or without discectomy.
2. Administration of opioid-sparing anaesthesia prolongs the time to receive the first rescue analgesia. It also reduces the number of patients receiving rescue analgesia.
3. Opioid sparing Anaesthesia helps in reducing opioid-induced postoperative complications such as PONV and abdominal distention without increasing the incidence of over sedation, nystagmus and hallucination.
4. Providing Anaesthesia using opioid-sparing techniques improves the patients' satisfaction significantly.
5. Analgesia produced by the opioid-sparing technique is non-inferior to opioid-based technique.

REFERENCES

1. Lee YC, Zotti MGT, Osti OL. Operative Management of Lumbar Degenerative Disc Disease. Asian Spine J. 2016 Aug;10(4):801–19.

2. MD BM. Surgical Treatments for Degenerative Disc Disease [Internet]. Spine-health. [cited 2021 Dec 4]. Available from: https://www.spine-health.com/conditions/degenerative-disc-disease/surgical-treatments-degenerative-disc-disease

3. Miletic J, Gart A. Land Based Rehabilitation and the Aging Spine. In: The Comprehensive Treatment of the Aging Spine [Internet]. Elsevier; 2011 [cited 2021 Dec 1]. p. 99–102. Available from: https://linkinghub.elsevier.com/retrieve/pii/B978143770373310017X

4. Soffin EM, Beckman JD, Tseng A, Zhong H, Huang RC, Urban M, et al. Enhanced Recovery after Lumbar Spine Fusion. Anaesthesiology. 2020 Aug 1;133(2):350–63.

5. Feng C, Zhang Y, Chong F, Yang M, Liu C, Liu L, et al. Establishment and Implementation of an Enhanced Recovery After Surgery (ERAS) Pathway Tailored for Minimally Invasive Transforaminal Lumbar Interbody Fusion Surgery. World Neurosurg. 2019 Sep;129:e317–23.

6. Kumar K, Kirksey MA, Duong S, Wu CL. A Review of Opioid-Sparing Modalities in Perioperative Pain Management: Methods to Decrease Opioid Use Postoperatively. Anesth Analg. 2017 Nov;125(5):1749–60.

7. Soffin EM, Wetmore DS, Beckman JD, Sheha ED, Vaishnav AS, Albert TJ, et al. Opioid-free Anaesthesia within an enhanced recovery after surgery pathway for minimally invasive lumbar spine surgery: a retrospective matched cohort study. Neurosurg Focus. 2019 Apr 1;46(4):E8.

8. Rawal N. Analgesia for day-case surgery†. British Journal of Anaesthesia. 2001 Jul 1;87(1):73–87.

9. Verma V, Singh N, Singh Jaggi A. Pregabalin in Neuropathic Pain: Evidences and Possible Mechanisms. Curr Neuropharmacol. 2014 Jan;12(1):44–56.

10. Anderson JT, Haas AR, Percy R, Woods ST, Ahn UM, Ahn NU. Chronic Opioid Therapy After Lumbar Fusion Surgery for Degenerative Disc Disease in a Workers' Compensation Setting. Spine (Phila Pa 1976). 2015 Nov;40(22):1775–84.

11. Intervertebral disc as a source of pain | BJA Education | Oxford Academic [Internet]. [cited 2021 Dec 4]. Available from: https://academic.oup.com/bjaed/article/12/6/279/279726

12. Acute Pain vs. Chronic Pain: Differences & Causes [Internet]. [cited 2021 Dec 4]. Available from: https://my.clevelandclinic.org/health/articles/12051-acute-vs-chronic-pain

13. Kim HS, Wu PH, Jang I-T. Lumbar Degenerative Disease Part 1: Anatomy and Pathophysiology of Intervertebral Discogenic Pain and Radiofrequency Ablation of Basivertebral and Sinuvertebral Nerve Treatment for Chronic Discogenic Back Pain: A Prospective Case Series and Review of Literature. Int J Mol Sci. 2020 Feb 21;21(4):E1483.

14. Multimodal Analgesia for Acute Postoperative and Trauma-Rela... : AJN The American Journal of Nursing [Internet]. [cited 2021 Dec 4]. Available from: https://journals.lww.com/ajnonline/fulltext/2017/03001/Multimodal_Analgesia_for_Acute_Postoperative_and.3.aspx

15. Khademi S, Jouybar R, Emami S, Kamalipour H. Effects of Pregabalin on Postoperative Pain and Agitation following Coronary Artery Bypass Grafting: Randomized Clinical Trial. 2017 Jan 1;55–61.

16. Singh H, Kundra S, Singh RM, Grewal A, Kaul TK, Sood D. Preemptive analgesia with Ketamine for Laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol. 2013;29(4):478–84.

17. Frauenknecht J, Kirkham KR, Jacot-Guillarmod A, Albrecht E. Analgesic impact of intra-operative opioids vs. opioid-free anaesthesia: a systematic review and meta-analysis. Anaesthesia. 2019 May;74(5):651–62.

18. Section 2, Chapter 4: Pain Generators and Pathways of Degenerative Disc Disease [Internet]. Wheeless' Textbook of Orthopaedics. 2018 [cited 2021 Dec 1]. Available from: https://www.wheelessonline.com/issls/section-2-chapter-4-pain-generators-and-pathways-of-degenerative-disc-disease/

19. Helander EM, Menard BL, Harmon CM, Homra BK, Allain AV, Bordelon GJ, et al. Multimodal Analgesia, Current Concepts, and Acute Pain Considerations. Curr Pain Headache Rep. 2017 Jan;21(1):3.

20. Shah DD, Sorathia ZH. Tramadol/Diclofenac Fixed-Dose Combination: A Review of Its Use in Severe Acute Pain. Pain Ther. 2020 Jun;9(1):113–28.

21. Qureshi O, Dua A. COX Inhibitors. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [cited 2021 Dec 28]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK549795/

22. Hawkey CJ. COX-1 and COX-2 inhibitors. Best Pract Res Clin Gastroenterol. 2001 Oct;15(5):801–20.

23. Goettsch WG, Sukel MPP, van der Peet DL, van Riemsdijk MM, Herings RMC. In-hospital use of opioids increases rate of coded postoperative paralytic ileus. Pharmacoepidemiol Drug Saf. 2007 Jun;16(6):668–74.

24. Pattinson KTS. Opioids and the control of respiration. BJA: British Journal of Anaesthesia. 2008 Jun 1;100(6):747–58.

25. Murphy P, Bechmann S, Barrett M. Morphine. StatPearls [Internet]. 2021 May 30 [cited 2021 Dec 3]; Available from: https://www.statpearls.com/ArticleLibrary/viewarticle/25271

26. Rosenbaum SB, Gupta V, Palacios JL. Ketamine. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [cited 2021 Dec 4]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK470357/

27. Jain R, Kochhar N. Influence of difference in timing of perioperative administration of low-dose ketamine on postoperative analgesia. Anaesthesia: Essays and Researches. 2017 Apr 1;11(2):406.

28. Pentazocine - an overview | ScienceDirect Topics [Internet]. [cited 2021 Dec 4]. Available from: https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/pentazocine

29. Magrini M, Rivolta G, Bolis C, Furiosi D. Analgesic activity of tramadol and pentazocine in postoperative pain. Int J Clin Pharmacol Res. 1998;18(2):87–92.

30. Harmer M, Slattery PJ, Rosen M, Vickers MD. COMPARISON BETWEEN BUPRENORPHINE AND PENTAZOCINE GIVEN I.V. ON DEMAND IN THE

CONTROL OF POSTOPERATIVE PAIN. British Journal of Anaesthesia. 1983 Jan;55(1):21–5.

31. Paddock R, Beer EG, Bellville JW, Ciliberti BJ, Forrest Jr. WH, Miller EV. Analgesic and side effects of pentazocine and morphine in a large population of postoperative patients. Clinical Pharmacology & Therapeutics. 1969;10(3):355–65.

32. Swennen C, Bredin S, Eap C, Mensa C, Ohl X, Girard V. Local infiltration analgesia with ropivacaine in acute fracture of thoracolumbar junction surgery. Orthopaedics & Traumatology: Surgery & Research. 2017 Apr 1;103(2):291–4.

33. Li K, Ji C, Luo D, Feng H, Yang K, Xu H. Wound infiltration with ropivacaine as an adjuvant to patient controlled analgesia for transforaminal lumbar interbody fusion: a retrospective study. BMC Anaesthesiology. 2020 Nov 18;20(1):288.

34. Ziemann-Gimmel P, Goldfarb AA, Koppman J, Marema RT. Opioid-free total intravenous anaesthesia reduces postoperative nausea and vomiting in bariatric surgery beyond triple prophylaxis. Br J Anaesth. 2014 May;112(5):906–11.

35. Basha I. A Systematic Analysis On Opioid-Free General Anaesthesia Versus Opioid-Based General Anaesthesia For Bariatric Surgery. :22.

36. Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Breivik Hals EK, et al. Assessment of pain. BJA: British Journal of Anaesthesia. 2008 Jul 1;101(1):17–24.

37. Delgado DA, Lambert BS, Boutris N, McCulloch PC, Robbins AB, Moreno MR, et al. Validation of Digital Visual Analog Scale Pain Scoring With a Traditional Paper-based Visual Analog Scale in Adults. J Am Acad Orthop Surg Glob Res Rev. 2018 Mar 23;2(3):e088.

38. Numeric Pain Rating Scale [Internet]. Physiopedia. [cited 2021 Dec 4]. Available from: https://www.physio-pedia.com/Numeric_Pain_Rating_Scale

39. Kurz A, Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. Drugs. 2003;63(7):649–71.

40. Hakim KYK, Wahba WZB. Opioid-Free Total Intravenous Anaesthesia Improves Postoperative Quality of Recovery after Ambulatory Gynecologic Laparoscopy. Anesth Essays Res. 2019;13(2):199–203.

41. Jouguelet-Lacoste J, La Colla L, Schilling D, Chelly JE. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. Pain Med. 2015 Feb;16(2):383–403.

42. Smith DJ, Bouchal RL, deSanctis CA, Monroe PJ, Amedro JB, Perrotti JM, et al. Properties of the interaction between ketamine and opiate binding sites in vivo and in vitro. Neuropharmacology. 1987 Sep;26(9):1253–60.

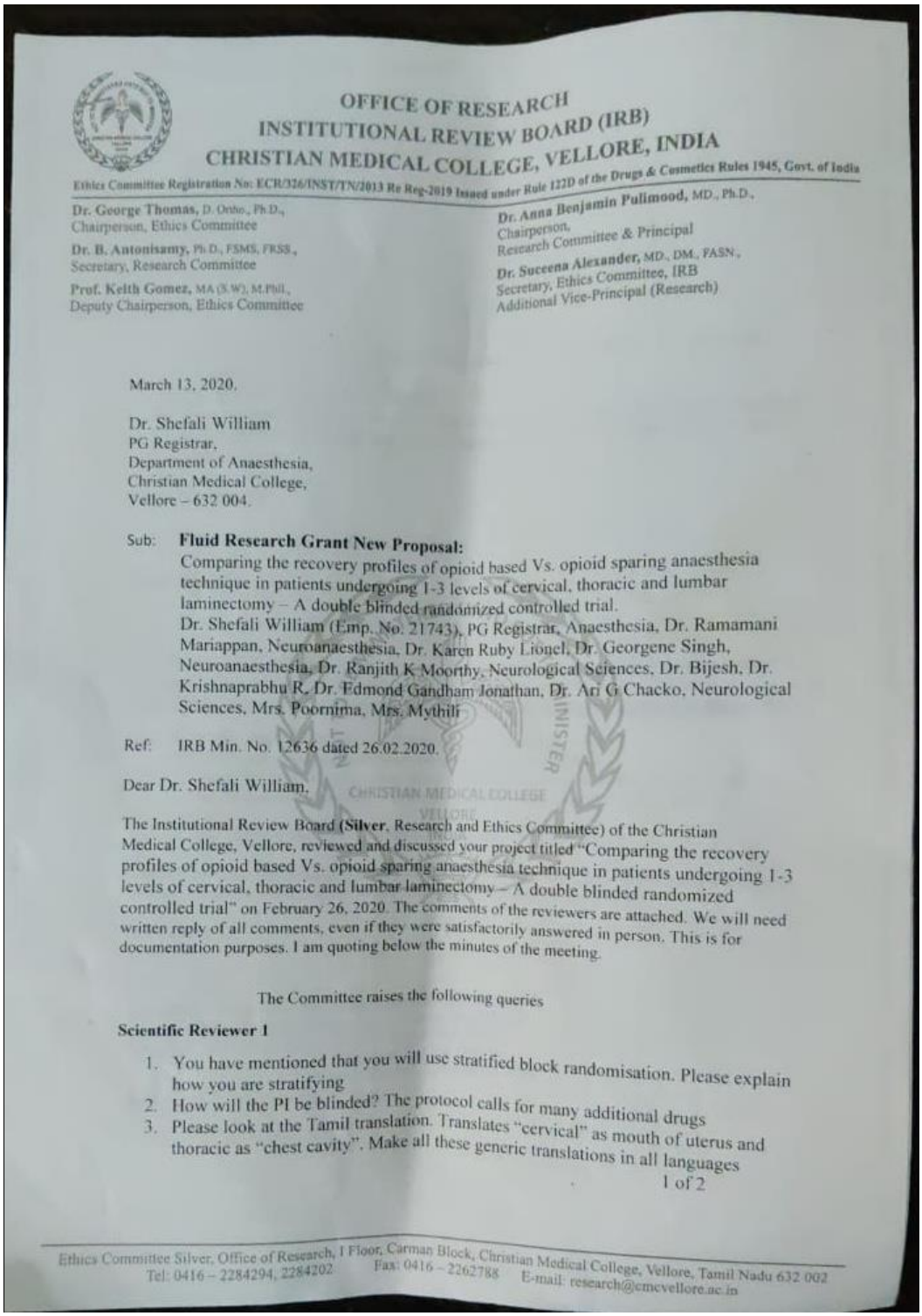
43. Freedman BM, O'Hara E. Pregabalin has opioid-sparing effects following augmentation mammaplasty. Aesthet Surg J. 2008 Aug;28(4):421–4.

44. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Opioid complications and side effects. Pain Physician. 2008 Mar;11(2 Suppl):S105-120.

45. Xu Y, Hackett M, Carter G, Loo C, Gálvez V, Glozier N, et al. Effects of Low-Dose and Very Low-Dose Ketamine among Patients with Major Depression: a Systematic Review and Meta-Analysis. Int J Neuropsychopharmacol. 2016 Apr;19(4):pyv124.

ANNEXURES:

IRB FORM:



OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Ethics Committee Registration No: ECR/326/INST/TN/2013 Re Reg-2019 Issued under Rule 122D of the Drugs & Cosmetics Rules 1945, Govt. of India

Dr. George Thomas, D. Ortho., Ph.D., Chairperson, Ethics Committee
Dr. B. Antonisamy, Ph.D., FSMS, FRSS., Secretary, Research Committee
Prof. Keith Gomez, MA (S.W), M.Phil., Deputy Chairperson, Ethics Committee
Dr. Anna Benjamin Pulimood, MD., Ph.D., Chairperson, Research Committee & Principal
Dr. Suceena Alexander, MD., DM., FASN., Secretary, Ethics Committee, IRB Additional Vice-Principal (Research)

March 13, 2020.

Dr. Shefali William
PG Registrar,
Department of Anaesthesia,
Christian Medical College,
Vellore – 632 004.

Sub: **Fluid Research Grant New Proposal:**
Comparing the recovery profiles of opioid based Vs. opioid sparing anaesthesia technique in patients undergoing 1-3 levels of cervical, thoracic and lumbar laminectomy – A double blinded randomized controlled trial.
Dr. Shefali William (Emp. No. 21743), PG Registrar, Anaesthesia, Dr. Ramamani Mariappan, Neuroanaesthesia, Dr. Karen Ruby Lionel, Dr. Georgene Singh, Neuroanaesthesia, Dr. Ranjith K Moorthy, Neurological Sciences, Dr. Bijesh, Dr. Krishnaprabhu R, Dr. Edmond Gandham Jonathan, Dr. Ari G Chacko, Neurological Sciences, Mrs. Poornima, Mrs. Mythili

Ref: IRB Min. No. 12636 dated 26.02.2020.

Dear Dr. Shefali William,

The Institutional Review Board **(Silver**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Comparing the recovery profiles of opioid based Vs. opioid sparing anaesthesia technique in patients undergoing 1-3 levels of cervical, thoracic and lumbar laminectomy – A double blinded randomized controlled trial" on February 26, 2020. The comments of the reviewers are attached. We will need written reply of all comments, even if they were satisfactorily answered in person. This is for documentation purposes. I am quoting below the minutes of the meeting.

The Committee raises the following queries

Scientific Reviewer 1

1. You have mentioned that you will use stratified block randomisation. Please explain how you are stratifying
2. How will the PI be blinded? The protocol calls for many additional drugs
3. Please look at the Tamil translation. Translates "cervical" as mouth of uterus and thoracic as "chest cavity". Make all these generic translations in all languages

1 of 2

Ethics Committee Silver, Office of Research, I Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788 E-mail: research@cmcvellore.ac.in

4. What is BIS electrode used for in THIS study? It is budgeted but no explanation in methodology
5. Please mention protocol variations
6. Please mention the study based on which the sample size was calculated. Is that based on a different scale since that score is based on 200 points and QoR-15 scores till 150?

Ethics Reviewer 1

1. Who will pay for pregabalin, ketamine?

Ethics Reviewer 2

1. Recalculate sample size to be sure of the assumptions for 'd'?

Drs. Shefali William and Ramamani were present during the presentation of the proposal and satisfactorily responded to the queries raised by the Members. After discussion, it was resolved to **ACCEPT the proposal after receiving the suggested modifications and answers to the queries.**

Note: 1. Kindly HIGHLIGHT the modifications in the revised proposal.
2. Keep a covering letter and point out the answer to the queries.
3. Reply to the queries should be submitted within 3 months duration the time of the thesis/ protocol presentation, if not the thesis/protocol has to be resubmitted to the IRB.
4. The checklist has to be sent along with the answers to queries.

Email the details to research@cmcvellore.ac.in and send a hard copy through internal dispatch to Dr. Suceena Alexander, Addl. Vice-Principal (Research), Principal's Office, CMC.

Yours sincerely,

Suceena

Dr. Suceena Alexander
Secretary (Ethics Committee)
Institutional Review Board

Dr. Suceena Alexander, MD.,DM.,FASN.
Secretary - (Ethics Committee)
Institutional Review Board
Christian Medical College,
Vellore - 632 002, Tamil Nadu, India.

IRB Min. No. 12636 dated 26.02.2020

Ethics Committee Silver, Office of Research, I Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788 E-mail: research@cmcvellore.ac.in

PATIENT INFORMATION SHEET

Title of Research Project: Comparing the recovery profiles of opioid based Vs. opioid sparing Anaesthesia technique in patients undergoing 1 to 3 levels of cervical, thoracic and lumbar laminectomy – A single blinded Randomized controlled trial.

Introduction

You are being asked to take part in a research study. Please read this explanation about the study and its risks and benefits before you decide if you would like to take part in this study. You should take as much time as you need to make your decision. You should ask the study doctor or study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish. Participation in this study is voluntary.

Background

You have been asked to participate in this study because you are having surgery for the back problem which is causing spinal cord or nerve compression. For this surgery, we need to make you fully unconscious, for which full body anaesthesia is necessary. During surgery your blood pressure, heart rate, sleep status will be monitored continuously and kept within normal range by your anaesthesiologist. Routinely, we administer strong pain medications such as morphine for controlling the pain. Since this pain medication acts for several hours, it takes care of pain during and few hours after operation. In some patients, these strong pain medicines can cause excessive sleepiness, vomiting, fullness of stomach which can affect the general wellbeing and recovery after anaesthesia. So we wanted to do a study in which we are planning to give two other medications instead of one strong pain medication for controlling the pain which are considered to be less strong thereby avoiding the long acting strong pain medication (morphine) and its related side effects such as excessive sleepiness, nausea and vomiting. We feel, avoiding the long acting strong pain medication will make you recover better and faster. Your pain status will be monitored during surgery and after surgery (at regular intervals), if you have moderate to severe pain, appropriate pain killers will be given immediately.

Study Design: Standard anaesthesia drugs will be given and monitoring techniques will be done during your surgery. If you are willing to participate in this study, you will be randomly assigned to one of the two groups. One group will receive strong pain medications during surgery (Group A) while the other group will receive two other medications for reliving pain(Group B).You and the primary investigator may not know which group you belong to, you may belong to Group A or Group B. During surgery, pain will be monitored and will be treated according to our study protocol by the anaesthesiologist who will take care of you during surgery. After the operation, you will be monitored for 2 hours in the operating room recovery area and then will be sent to ward or monitory area (HDU) where your blood pressure, heart rate and breathing and your sleep status and the other well beings will be assessed at regular interval. You will be asked to score your pain severity and the pain medication will be given if necessary. You will be assessed periodically by the pain nurse, pain doctor and by the primary investigator during the first 24 hours after surgery. The time, that you are starting your liquid food or water, eat solid food and able to walk with support all will be noted. At the end of 24hours we will give a set of 15 questions to assess your well-being over the last 24 hours.

Benefits: You may or may not receive any direct benefit from being in this study. Information learned from this study may help other people with your condition in the future.

Risks: Administration of pain medication (morphine) which we give routinely for all surgeries can cause sedation and nausea and vomiting and slow your breathing rate. The drug ketamine can cause vivid dreams and Pregabalin can cause sedation and dizziness. But you will be monitored continuously in the ward. The blood pressure, heart rate, breathing rate all, will be monitored regularly and you will be given appropriate treatment for the side effects.

Voluntary Participation:

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now and then changing your mind later. You may leave the study at any time without affecting your care. You may refuse to answer any question you do not want to answer. You will not have to pay extra money for participating in this study. Also, you will not receive any reimbursement for participating in this study.

From: Dr. Shefali William, PG- Registrar,

Department of Anaesthesia, CMC, Vellore.

Contact Number: 8146268468

INFORMED CONSENT FORM

Title of Research Project: Comparing the recovery profiles of opioid based Vs. opioid sparing anaesthesia technique in patients undergoing 1 to 3 levels of cervical, thoracic and lumbar laminectomy – A single blinded Randomized controlled trial.

Study Number: _____

Subject's Initials: _____ Subject's Name_____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

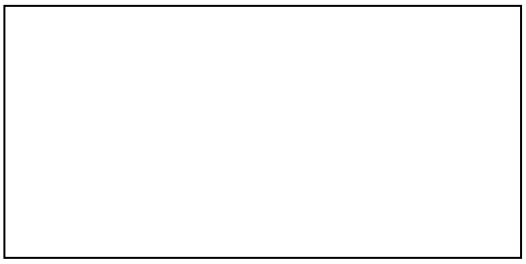
(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Or



Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

DATA COLLECTION SHEET

Title of Research Project: Comparing the recovery profiles of opioid based Vs. opioid sparing anaesthesia technique in patients undergoing 1 or 2 levels of cervical, thoracic and lumbar laminectomy – Double blind Randomized controlled trial.

Case Number: _____ Hospital Number: _____

Section 1: Preoperative details:

Demographic Data

Age (years): _____ Gender: M / F _____

ASA Status: I/II Weight (kg):_____ Height (cm): _____ BMI:

History:

Previous surgery: Y / N Allergies: Y / N
History of PONV: Y / N H/o Motion sickness: Y / N

Co- morbidities:

Co-Morbidity	**Yes/No**	**Medication**
1.Diabetes	**Yes/No**	
2. Hypertension	**Yes/No**	
3. Asthma/ COPD	**Yes/No**	
4. IHD	**Yes/No**	
5. Chronic Pain	**Yes/No**	

Diagnosis: **Level of spine surgery: Cervical/Thoracic/Lumbar**

Complaints: Back pain / Radicular pain / Bladder or Bowel involvement/ Weakness of limbs

Back pain at rest (NRS 0-10): **Back pain at Movement (NRS 0-10)**:

Section II - Intraoperative details:

Case Number _____ Hospital Number: _____

1. **Anaesthesia (total dose)**

Drugs	Dose
Inj. Fentanyl (µg)	
Inj. Propofol (mg)	
Inj. Ephedrine (mg)	
Inj. Phenylephrine (µg)	
Inj. Noradrenaline (µg)	

2. Intraoperative blood loss:

3. Total amount of fluids given:

Type of IVF	Amount in ml
Crystalloids	
Colloid	
Type of colloid	Starch/ Gelatin/Albumin
Blood/ Blood Products	

4. Time of stopping Sevoflurane:

5. Time of Extubation:

6. Duration of Surgery (skin incision to skin closure):

7. Duration of Anaesthesia (induction to extubation):

DATA COLLECTION SHEET

Section III – Post anaesthesia care unit Details

Case Number: _____ Hospital Number: _____

Time	5 min	30min	1hr	1.5 hr	2hr	At discharge
Pulse						
BP (Sys/Dias/Mean)						
Respiratory rate						
Pain score (NRS 1-10)						
Sedation Score (1-6)						
Nausea Y/N						
Vomiting Y/N						
Pruritus Y/N						
Nystagmus Y/N						
Hallucination Y/N						
Analgesia given (Time, drug, dose)						
Antiemetic given (Y/N)						

Pain scores will be reported according to a 10 point scale (0 = no pain, 10 = worse pain)
Sedation scores will be reported according to the six point Ramsey score
(1-3 for the awake patient: 1 = anxious and agitated, 2 = co-operative and orientated, 3 = responds to commands only.
Levels 4-6 for response to loud auditory stimulus in asleep patients: 4 = brisk response, 5 = sluggish response, 6 = no response)

Section IV: Postoperative Ward –Details

Case Number: _____ Hospital Number: _____

Time	On arrival	2 hrs	6hrs	12 hrs	18 hrs	24 hrs
Pulse						
BP (Sys, Dias, MAP)						
Resp.Rate						
Sedation (1-6)						
Nausea Y/N						
Vomiting Y/N						
Pruritis Y/N						
Nystagmus Y/N						
Hallucination Y/N						
Abdominal distention Y/N						
NRS score (0-10) At rest						
NRS (0-10) At movement						

Time of receiving 1st dose of rescue analgesia (Inj.Pentazocine 30 mg I.M):

Total dose of Pentazocine received over first 24 hours:

Time of **Dr**inking oral fluids –

Time of intake of Solid food (**e**at) -

Time of **Am**bulation:

Time of passing Flatus -

Time of Passing Stools -

Duration of Hospital stay after surgery:

Patient Satisfaction (1-10): 1-2 – poor; 3-4 – fair; 5-6- good; 7-8-very good; 9-10- Excellent.

Quality of Recovery -15 Score:

QoR-15 Patient Survey

Date: _ _ / _ _ / _ _ Study #: _____

Preoperative ☐ Postoperative ☐

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1. Able to breathe easily	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
2. Been able to enjoy food	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
3. Feeling rested	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
4. Have had a good sleep	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
5. Able to look after personal toilet and hygiene unaided	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
6. Able to communicate with family or friends	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
7. Getting support from hospital doctors and nurses	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
8. Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
9. Feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
10. Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11. Moderate pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
12. Severe pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
13. Nausea or vomiting	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
14. Feeling worried or anxious	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
15. Feeling sad or depressed	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time

Data Sheet

slno	caseno	hospno	age	gend	asa	weigh	heigh	bmi	prevs	allerg	histpc	motsi	dm	dmmed	htn	htnmed	asthc	copde	ihd	ihdm	chron	chron	diagn	backp	radip
1	s2-1	899931h	42	1	2	72	174	23	1	2	2	2	1	metformin 5(	2		2		2		1	not o	3	1	1
2	s2-2	953645h	31	1	2	85	168	30.1	2	2	2	2	2	nil	2		2		2		2		3	1	2
3	s2-3	957631h	44	2	1	60	180	18.5	1	2	2	2	2		2		2		2		2		3	1	1
4	s2-4	954600h	40	2	1	53	163	19.9	1	2	2	2	2		2		2		2		2		3	1	1
5	s2-5	959878h	59	2	2	60	154	25.3	1	2	2	2	2		1		2		2		2		3	1	1
6	s2-6	952674h	59	1	1	60	170	20.8	2	2	2	2	2		2		2		2		2		3	1	2
7	s2-7	952674h	58	1	1	60	170	20.8	2	2	1	2	2		2		2		2		2		3	1	1
8	s2-8	878057h	53	1	1	63	160	24.6	2	2	2	2	2		2		2		2		2		3	1	1
9	s2-9	963260h	28	2	1	68	152	29.5	2	1	2	2	2		2		2		2		2		3	1	1
10	s2-10	847474h	32	1	1	72	164	26.8	1	2	2	2	2		2		2		2		2		3	1	2
11	s2-11	860581h	60	1	2	67	164	24.9	1	2	2	2	2		1	T.Telmisartan+c	2		2		2		3	1	1
12	s2-12	965318h	30	1	1	73	170	25.3	2	2	2	2	2		2		2		2		2		3	1	1
13	s2-13	946354h	56	2	1	53	143	25.9	2	2	2	2	2		2		2		2		2		3	2	1
14	s2-14	959409h	46	1	2	88	168	30.8	2	2	2	2	1	T.Metformin	2		2		2		2		3	1	2
15	s2-15	008847p	52	1	2	63	157	25.6	2	2	2	2	1	T.Metformin	1	T.Telmisartan 4(	2		2		2		3	1	2
16	s2-16	807209h	60	2	2	65	151	28.6	2	2	2	2	2		1	T.Telmisartan 4(	2		2		2		3	1	2
17	s2-17	963054h	75	1	1	75	184	22.2	2	2	2	2	2		2		2		2		2		3	1	1
18	s2-18	014361p	52	2	2	79	156	32.5	2	2	2	2	2		1	T.Telmisartan 4(	2		2		2		3	1	2
19	s2-19	010703p	60	1	2	76	172	25.7	2	2	2	2	1	T.Metformin	1	T.Telmisartan ,	2		2		2		3	1	2
20	s2-20	552624h	20	2	2	60	152	26	2	2	2	2	1	T.Metformin	2		2		2		2		3	1	2
21	s2-21	017556p	41	1	2	63	158	26.6	2	2	2	2	2		1	T.Amlodipine5m	2		2		2		3	1	1
22	s2-22	024358p	39	2	1	66	165	27.2	1	2	2	2	2		2		2		2		2		3	1	2
23	s2-23	849694g	46	2	1	72	160	28.1	2	2	2	2	2		2		2		2		2		3	1	2
24	s2-24	797911h	51	2	2	72	154	30.2	2	2	2	2	2		2		2		2		2		3	1	2
25	s2-25	052097p	51	2	1	46	151	20.2	1	2	2	2	2		2		2		2		2		3	1	1
26	s2-26	051331p	44	2	1	55	156	22.7	1	2	2	2	2		2		2		2		2		3	1	2
27	s2-27	016731p	22	1	1	62	171	21.2	2	2	2	2	2		2		2		2		2		3	1	2
28	s2-28	085819p	24	1	2	90	167	32.3	1	2	2	2	2		2		2		2		2		3	1	2
29	s2-29	600838g	59	1	1	74	160	29	2	2	2	2	2		2		2		2		2		3	1	1
30	s2-30	072900p	30	1	1	63	169	26.7	2	2	2	2	2		2		2		2		2		3	1	2
31	s2-31	020731p	31	1	2	80	176	24.8	2	1	2	2	2		2		1	inhale	2		2		3	1	2
32	s2-32	079080p	52	1	2	70	168	24.8	1	2	2	2	1	T.metformin	2		2		2		2		3	1	2
33	s2-33	083208p	42	1	1	66	169	23.2	2	2	2	2	2		2		2		2		2		3	1	1
34	s2-34	055779p	19	1	1	60	160	23.4	2	2	2	2	2		2		2		2		2		3	1	1
35	s2-35	253904p	35	1	1	50	2	18.4	1	2	2	2	2		2		2		2		2		3	1	2
36	s2-36	243666p	56	2	2	67	168	23.9	1	2	2	2	1	T.metformin	1	T.temisartan	2		2		2		3	1	1
37	s2-37	236415p	41	1	2	72	170	24.8	2	2	2	2	2		2		2		2		2		3	1	1
38	s2-38	844082h	32	1	1	65	165	24.1	2	2	2	2	2		2		2		2		2		3	1	1
39	s2-39	266805p	58	1	1	64	181	19.7	1	2	2	2	2		2		2		2		2		3	1	2
40	s2-40	256169p	34	1	1	88	165	32.3	2	2	2	2	2		2		2		2		2		3	1	1
41	s2-41	954086b	45	2	2	65	165	24.8	2	2	2	2	2		2		1	MDI f	2		2		3	1	2
42	s2-42	961436h	41	1	1	74	175	24.2	1	2	2	2	2		2		2		2		2		3	1	1
43	s2-43	278257p	31	2	1	85	175	27.7	1	2	2	2	2		2		2		2		2		3	1	2
44	s2-44	040444p	26	1	1	61	169	21.5	1	2	2	2	2		2		2		2		2		3	1	2
45	s2-45	772145h	52	1	2	60	165	22	2	2	2	2	2		1	T.amlodipine	2		2		2		3	1	1
46	s2-46	272569p	26	2	1	58	160	22.7	1	2	2	2	2		2		2		2		2		3	1	1
47	s2-47	242836p	56	2	2	60	154	25.3	1	2	2	2	1	T.glimepride	1	T.Telmisartan	2		2		2		3	1	1
48	s2-48	096271f	37	2	2	48	157	19.6	2	2	2	2	2		2		2		2		2		3	1	1
49	s2-49	385188f	53	1	1	66	147	28.7	2	2	2	2	2		2		2		2		2		3	1	1
50	s2-50	018827p	40	2	1	65	165	24.1	2	2	2	2	2		2		2		2		2		3	1	1
51	s2-51	079913p	42	1	2	82	176	26.6	2	2	2	2	1	T.Metformin	1	T.telmisartan+a	2		2		2		3	1	1
52	s2-52	544346p	62	1	2	70	168	25.9	2	2	2	2	1	T.metformin	2		2		2		2		3	1	2
53	s2-53	019599p	22	1	1	81	174	26.9	2	2	2	2	2		2		2		2		2		3	1	2
54	s2-54	744792h	31	1	1	65	168	23.2	2	2	2	2	2		2		2		2		2		3	1	2
55	s1-1	749936	43	1	2	90	175	29	1	2	2	2	2		1	T.Amlodipine	2		2		2		3	1	2
56	s1-2	524125p	26	1	2	57	170	20	1	1	2	2	2		2		2		1	know	2		3	1	2
57	s1-3	285320p	36	1	2	76	179	23.8	2	2	2	2	2		1	T.Amlong	2		2		2		3	1	1
58	s1-4	433425h	55	1	1	88	180	27.2	2	2	2	2	2		2		2		2		2		3	1	1
59	s1-5	248637p	34	1	2	79	168	28.3	2	2	2	2	2		2		2		2		2		3	1	2
60	s1-6	288153p	40	2	2	61	145	29	1	1	2	2	2		1	T.Telmisartan+a	2		2		2		3	1	2
61	s1-7	864697h	42	2	2	51	156	21.2	2	2	2	2	2		2		1	MDI S	2		2		3	2	1
62	s1-8	225043p	37	2	1	76	168	27.2	1	2	2	2	2		2		2		2		2		3	1	1
63	s1-9	253077p	54	1	1	59	183	22.2	2	2	2	2	2		2		2		2		2		3	1	2
64	s1-10	298777p	63	1	2	78	170	27.1	2	2	2	2	2		2		2		2		2		3	1	2
65	s1-11	227200p	36	2	2	55	156	22.6	2	2	2	2	2		2		2		2		2		3	1	2
66	s1-14	874693g	25	1	1	63	169	22.1	2	2	2	2	2		2		2		2		2		3	1	1
67	s1-17	521251p	41	1	1	70	166	25.5	1	2	2	2	2		2		2		2		2		3	1	2

bladd	weak	backr	backr	fenta	propd	ephed	phen	norad	iopbl	fluids	cryst	colloi	collty	sevot	extutim	surgd	anaes	puls5	sys5n	dias5	mean	rr5m	ps5m	seds5	naus5	vomi5	prur5	nyst5
2	2	2	3	220	150	0	150	0	200	1500	1	2		11.1	11.4	165	179	98	180	104	102	19	5	2	1	2	2	2
2	2	6	8	240	200	6	350	0	300	2500	1	2		12.1	12.2	210	300	112	115	74	74	16	0	4	2	2	2	2
2	2	2	8	320	120	15	0	0	400	1500	1	2		12.3	12.4	195	300	64	133	77	93	22	0	2	2	2	2	2
2	2	5	8	200	140	0	0	0	300	2000	1	2		15.3	15.4	120	175	60	123	86	96	14	2	2	2	2	2	2
2	2	3	5	180	120	18	400	0	100	1500	2	2		9.5	10.2	105	170	81	144	70	89	14	5	2	2	2	2	1
2	2	4	5	280	220	0	200	0	450	2000	1	1	1	16.1	16.35	260	285	100	136	88	96	16	8	5	2	2	2	2
2	2	1	5	140	120	18	400	0	100	1500	1	2		15.4	15.5	120	180	80	120	68	80	14	1	2	2	2	2	2
2	2	6	8	160	100	0	0	0	100	1200	1	2		17.1	17.2	90	170	71	111	65	70	22	2	2	2	2	2	2
2	2	5	8	140	120	0	250	0	200	1800	1	2		16.4	16.45	120	210	110	103	65	76	12	4	1	2	2	2	2
2	2	2	6	100	140	0	200	0	150	2500	1	2		18.4	19	195	250	94	137	93	89	14	4	4	2	2	2	2
2	2	1	6	160	170	0	75	0	150	2500	1	2		17.1	17.3	150	210	84	124	70	85	16	2	2	2	2	2	2
2	2	5	8	230	240	6	150	0	200	1500	1	2		13.3	13.45	135	200	78	140	88	102	14	6	3	1	1	2	2
2	2	0	5	180	180	18	400	0	400	2500	1	1	1	17.1	17.15	170	240	86	145	82	96	24	7	2	2	2	2	2
2	2	2	6	240	150	6	150	0	550	2000	1	1	1	18.2	18.35	130	215	86	134	80	88	14	7	2	2	2	2	2
2	2	3	7	250	150	24	450	4	250	4000	1	2		11.1	11.29	190	240	103	108	72	85	16	0	2	2	2	2	2
2	2	1	4	140	120	12	0	0	250	1200	1	2		17.3	17.55	100	130	64	116	60	73	18	0	2	2	2	2	2
2	2	3	7	170	100	0	400	0	100	2000	1	2		9.45	10	90	150	76	135	88	100	16	1	2	2	2	2	2
2	2	5	7	200	210	18	300	0	120	1250	1	2		16.1	16.2	135	180	77	142	81	102	16	3	3	2	2	2	2
2	2	3	5	150	150	0	75	0	50	1500	1	2		10.2	10.25	130	175	80	138	84	98	14	0	2	2	2	2	2
2	2	4	7	200	170	20	450	0	200	1500	1	2		16.3	16.36	150	180	98	125	70	87	18	7	1	2	2	2	2
2	2	3	6	200	200	0	750	8	600	1500	1	1	1	17.5	17.55	150	240	93	105	68	63	20	0	3	2	2	2	2
2	2	6	9	350	230	18	250	0	400	1600	1	2		15.2	15.3	180	220	100	140	94	111	16	4	2	2	2	2	2
2	2	4	6	200	170	6	350	0	350	2000	1	2		11.5	12.2	195	260	98	145	82	99	14	0	2	2	2	2	2
2	2	3	6	240	200	6	150	0	200	1500	1	2		16.2	16.45	150	195	114	152	78	114	20	7	3	1	2	2	2
2	2	3	5	100	90	30	250	120	150	2000	1	2		17.2	17.35	200	235	120	113	73	85	10	4	2	2	2	2	2
2	2	4	6	200	120	18	175	0	200	2000	1	2		18.4	18.45	150	195	88	110	61	78	16	0	2	2	2	2	2
2	2	4	9	300	180	6	0	0	100	2500	1	2		16.3	16.4	165	240	100	155	80	95	14	0	4	2	2	2	2
2	2	3	6	260	180	0	50	0	250	1600	1	2		17.4	17.45	210	240	102	134	87	92	20	0	1	2	2	2	2
2	2	7	8	200	200	0	50	0	300	1500	1	2		16.4	17	155	240	101	114	61	79	13	0	2	2	2	2	2
2	2	4	5	250	150	0	0	0	150	3000	1	2		12.1	12.2	210	270	94	128	96	88	13	1	2	2	2	2	2
2	2	4	6	250	180	6	0	0	200	2000	1	2		17.3	17.35	130	160	93	134	68	100	24	2	2	2	2	2	2
2	2	4	7	280	220	0	0	0	400	2000	1	2	1	12.1	12.25	240	265	88	125	70	87	15	6	4	2	2	2	2
2	2	4	9	200	170	12	150	0	100	1500	1	2		17.5	18.03	130	220	84	121	69	82	18	0	3	2	2	2	2
2	2	5	7	170	200	0	0	0	200	1500	1	2		3.25	3.4	140	180	99	125	59	74	16	0	2	2	2	2	2
1	2	5	9	290	150	12	500	0	450	2500	1	1	1	18.2	18.42	135	190	108	128	74	88	14	6	3	1	2	2	2
2	2	3	8	200	140	18	300	160	150	2000	1	2		10.2	10.3	150	180	92	134	97	98	18	0	2	2	2	2	2
2	2	5	8	250	140	0	0	0	300	1500	1	2		16.5	17.1	210	280	120	132	89	98	22	0	3	2	2	2	2
2	2	8	9	160	150	0	0	0	400	1500	1	2		22	22.05	100	140	84	135	73	102	16	3	2	2	2	2	2
2	2	3	6	270	230	18	250	0	350	2500	1	2		21.5	22.15	200	280	112	140	90	101	16	7	1	1	2	2	2
2	1	4	7	100	160	0	0	0	200	3000	1	2		19.2	17.45	150	165	108	130	90	94	14	5	1	1	2	2	2
2	2	8	9	200	200	12	100	0	100	2000	1	2		15.4	16.05	100	155	102	130	70	84	22	7	1	2	2	2	2
2	2	5	6	220	140	6	0	0	150	1500	1	2		11	11.2	150	200	108	177	93	108	16	0	3	2	2	2	2
2	2	2	8	250	200	12	0	0	150	1500	1	2		11.3	11.45	170	195	85	105	62	72	22	4	2	1	2	2	2
2	2	3	5	200	230	12	200	160	150	1500	1	2		22.3	22.45	105	125	75	120	70	82	18	10	1	2	2	2	2
2	2	5	8	200	140	12	500	60	200	1500	1	1	1	12.4	12.55	150	180	88	117	72	85	14	4	2	2	2	2	2
2	2	5	9	200	100	12	100	0	400	2000	1	2		17.5	18.1	165	225	98	118	56	70	20	0	3	2	2	2	2
2	2	5	8	200	140	0	950	14	100	1600	1	2		17.1	17.2	140	220	102	125	62	76	19	1	3	2	2	2	2
2	2	0	6	160	170	0	200	0	250	1000	1	2		17.3	17.42	105	120	112	103	61	70	18	0	3	2	2	2	2
2	2	4	9	240	180	6	70	0	300	2500	1	2		19.3	19.55	180	210	72	113	72	84	18	0	2	2	2	2	2
2	2	5	6	200	180	6	100	0	200	1500	1	2		10.2	10.3	105	150	96	134	81	86	16	0	3	2	2	2	2
2	2	4	8	240	150	24	950	160	500	3000	1	1	1	21.5	21.5	370	410	104	130	90	100	20	0	2	2	2	2	2
2	2	4	6	230	200	10	200	0	300	1800	1	1	1	19.2	19.3	195	225	116	140	80	92	24	2	3	2	1	2	2
2	2	4	6	200	170	0	200	0	200	2000	1	2		18.1	18.3	155	200	76	111	53	63	16	0	3	2	2	2	2
1	1	6	8	170	180	0	50	0	400	2000	1	2		17.2	17.35	180	210	108	127	87	84	22	2	3	2	2	2	2
1	1	4	6	460	200	0	800	160	400	3000	1	2		18.1	18.34	280	334	110	135	85	94	16	0	2	2	2	2	2
2	2	3	6	270	230	6	0	0	300	1500	1	2		18.1	18.25	130	180	118	106	46	62	16	6	3	1	1	2	2
2	2	5	8	180	200	6	200	0	350	2000	1	2		20.3	20.45	250	300	78	100	72	68	24	0	1	2	2	2	2
2	2	6	8	160	130	0	150	0	500	2000	1	1	1	19.2	19.5	180	220	112	116	76	77	26	0	3	2	1	2	2
2	2	5	8	200	200	0	0	0	300	2000	1	2		19.5	20	240	270	109	144	76	100	20	2	3	2	2	2	2
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2	2	5	7	200	150	0	150	0	400	1500	1	2		11.1	11.2	165	195	108	96	72	65	24	1	1	1	2	2	2
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2	2	5	8	260	180	30	250	0	350	2500	1	1	1	19.6	20	415	480	105	130	78	89	20	6	2	2	2	2	2
2	2	4	6	260	250	0	250	0	200	2000	1	2		16.5	17.05	170	210	100	140	80	96	18	0	2	2	2	2	2

hall5r	anal5mpa	anad5	anti5(	puls3	sys30	dias3(	mean	rr30p	ps30p	seds3	naus3	vomi3	prur3	nyst3	hall3(	anal3	anad3	anti3(	puls1	sys1h	dias1	mean	rr1hp	ps1hp	seds1	naus1	vomi1
2	inj . fetanyl	20	2	71	138	83	82	20	1	2	1	2	2	2	2	nil	0	2	74	141	87	87	18	0	2	2	2
2	nil	0	2	102	126	81	82	18	0	4	2	2	2	2	2	nil	0	2	114	128	77	84	18	0	3	2	2
2	nil	0	2	62	134	81	94	20	2	2	2	2	2	2	2	nil	0	2	66	122	78	90	22	1	2	2	2
2	nil	0	2	64	124	88	96	18	0	2	2	2	2	2	2	nil	0	2	66	118	71	88	20	0	2	2	2
2	inj fentanyl	20	2	77	121	59	87	16	3	2	2	2	2	1	2	nil	0	2	76	102	69	76	20	2	2	2	2
2	fentanyl	20	2	115	141	90	102	14	7	4	2	2	2	2	2	fenta	20	2	102	128	82	90	18	4	3	2	2
2	nil	0	2	71	140	80	89	18	0	1	2	2	2	2	2	nil	0	2	68	128	74	78	18	0	2	2	2
2	nil	0	2	83	101	62	68	20	0	2	2	2	2	2	2	nil	0	2	84	116	64	66	20	0	2	2	2
2	inj fentanyl	20	2	102	105	66	80	16	2	1	1	2	2	2	2	nil	0	2	100	100	63	76	16	0	2	2	2
2	nil	0	2	92	135	89	87	16	5	2	2	2	2	2	2	nil	0	2	80	121	82	79	16	6	2	2	2
2	nil	0	2	98	140	84	88	18	0	2	2	2	2	2	2	nil	0	2	78	123	77	78	28	0	2	2	2
2	inj.fentanyl	20	1	98	130	92	100	18	6	3	1	2	2	2	2	inj.fer	20	2	102	120	80	88	18	4	4	1	2
2	inj.fentanyl	20	2	82	143	80	96	22	8	2	2	2	2	2	2	nil	0	2	80	123	94	84	22	9	2	2	2
2	nil	0	2	84	123	78	72	16	8	2	2	2	2	2	2	inj.pa	1000	2	86	120	77	76	16	8	2	2	2
2	nil	0	2	101	108	76	84	16	0	3	2	2	2	2	2	nil	0	2	101	108	76	84	18	0	3	2	2
2	nil	0	2	60	127	67	78	20	0	2	2	2	2	2	2	nil	0	2	60	127	70	78	20	0	2	2	2
2	nil	0	2	54	129	83	98	16	1	2	2	2	2	2	2	nil	0	2	54	124	83	94	14	1	22	2	2
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2	inj.fentanyl	20	2	94	150	89	100	18	8	1	2	2	2	2	2	inj.fer	20	2	108	160	100	112	18	6	1	1	1
2	nil	0	2	88	111	70	67	20	0	3	2	2	2	2	2	nil	0	2	88	113	69	72	20	0	3	2	2
1	inj fentanyl	40	1	81	143	89	112	14	2	22	2	2	2	2	1	inj ke	10	2	79	119	69	79	16	2	3	1	1
2	nil	0	2	113	149	86	101	14	0	2	2	2	2	2	2	nil	0	2	108	152	92	112	16	0	2	2	2
2	inj.Fentanyl	20	1	98	140	90	108	20	8	3	1	2	2	2	2	inj.fer	20	2	96	137	72	99	18	6	3	1	2
2	inj.fentanyl	15	2	109	119	75	84	12	3	2	2	2	2	2	2	nil	0	2	101	112	62	84	13	3	2	2	2
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2	nil	0	2	96	150	78	92	14	0	5	2	2	2	2	2	nil	0	2	76	126	80	90	16	0	5	1	1
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2	nil	0	2	93	125	63	83	14	0	2	2	2	2	2	2	nil	0	2	82	114	63	78	14	0	2	2	2
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2	inj.fentanyl	20	2	92	124	70	87	14	5	3	2	2	2	2	2	inj.fer	20	2	90	115	74	84	86	4	1	2	2
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2	inj.fentanyl	20	2	114	130	90	92	14	6	3	1	2	2	2	2	inj . fe	20	2	102	150	90	109	16	4	3	2	1
2	nil	0	2	90	168	79	115	20	0	2	2	2	2	2	2	nil	0	2	93	140	90	104	18	0	2	2	2
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2	inj.paracetan	1000	2	114	140	102	104	16	8	1	1	2	2	2	2	inj.fer	20	2	108	130	90	97	18	3	1	1	2
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2	inj.fentanyl	20	2	99	132	71	82	22	3	1	2	2	2	2	2	nil	0	2	73	115	69	78	20	4	1	2	2
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2	nil	0	1	81	115	62	82	20	0	3	2	2	2	2	2	nil	0	2	79	108	64	76	20	0	3	2	2
2	inj.fentanyl	30	2	74	132	74	86	16	10	2	2	2	2	2	2	nil	0	2	80	147	90	88	16	10	2	2	2
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2	nil	0	2	90	118	56	70	18	0	3	2	2	2	2	2	nil	0	2	102	120	56	72	18	3	1	1	2
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2	nil	0	2	108	120	70	88	20	0	2	2	2	2	2	2	nil	0	2									
2	nil	0	1	108	130	70	88	22	2	2	2	2	2	2	2	nil	0	2	98	126	76	80	22	2	2	2	2
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2	nil	0	2	102	110	90	80	22	2	3	2	2	2	2	2	nil	0	2	97	120	90	84	22	2	3	2	2
2	nil	0	2	114	143	88	96	18	0	2	2	2	2	2	2	nil	0	2	112	154	94	100	18	0	2	2	2
2	inj.fentanyl	20	1	108	112	52	60	16	4	3	1	2	2	2	2	nil	0	2	88	120	70	76	16	3	3	2	2
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2	inj.fentanyl	20	2	109	138	83	94	22	4	2	2	2	2	2	2	nil	0	2	102	136	80	93	22	2	2	2	2
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prur1	nyst1	hall1	anal1	anad1	anti1	puls1	sys15	dias1	mean	rr15p	ps15p	seds1	naus1	vomi1	prur1	nyst1	hall1	anal1	anad1	anti1	puls2	sys2h	dias2	mean	rr2hp	ps2hp	seds2	naus2	vomi2
2	2	2	nil	0	2	78	130	80	81	20	0	2	2	2	2	2	2	nil	0	2	74	120	89	77	20	0	2	2	2
2	2	2	nil	0	2	101	127	72	82	20	0	3	2	2	2	2	2	nil	0	2	108	127	72	82	20	0	3	2	2
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2	2	2	nil	0	2																								
2	2	2	nil	0	2	80	110	79	76	20	6	2	2	2	2	2	2	inj fer	20	2	88	110	70	73	22	5	2	1	2
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prur2	nyst2	hall2	anal2	anad2	anti2	pulsa	sysad	diasa	mean	rradp	psadp	sedsa	nausa	vomi2	prura	nysta	halla	anala	anad2	antia	pulso	sysoa	diaso	mapd	rroap	sedso	nauso	vomi2	pruro
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nysto	hallo	abdo	resto	move	puls2	sys2h	dias2	map2	rr2hp	seds2	naus2	vomi2	prur2	nyst2	hall2	abd2	rest2	move	puls6	sys6h	dias6	map6	rr6hp	seds6	naus6	vomi6	prur6	nyst6	hall6
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abd6	rest6	move	puls1	sys12	dias1	map1	rr12p	seds1	naus1	vomi1	prur1	nyst1	hall12	abd1	rest1	move	puls1	sys18	dias1	map1	rr18p	seds1	naus1	vomi1	prur1	nyst1	hall18
2	0	0	76	98	60	60	18	2	2	2	2	2	2	2	1	1	72	116	60	63	16	2	2	2	2	2	2
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abd1	rest1	move	puls2	sys24	dias2	map2	rr24p	seds2	naus2	vomi1	prur2	nyst2	hall2	abd2	rest2	move	rescti	penta	fluitir	solidt	ambu	flattir	stoolt	hosps	patisa
2	0	1	70	120	54	68	18	2	2	2	2	2	2	2	0	1	0	0	18.3	19	8	8.45	0	2	5
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2	3	4	100	110	70	70	22	2	2	2	2	2	2	2	3	5	135	1	22	8.3	10	8	0	2	3
1	5	4	92	120	76	84	22	2	2	2	2	2	2	1	4	6	75	2	4	7	16	9	0	2	4
2	0	4	98	100	70	78	26	2	2	2	2	2	2	2	0	4	0	0	22	23.3	10	24	16	2	5
2	2	3	95	130	70	84	22	2	2	2	2	2	2	2	2	3	195	2	5	8.45	17	6	0	2	4
2	5	7	74	120	87	88	22	2	2	2	2	2	2	2	3	4	60	2	8	11	16	0	0	3	3
1	2	3	120	100	74	70	22	2	2	2	2	2	2	1	2	0	45	2	7	9	0	0	0	6	3
2	2	3	84	124	80	80	20	2	2	2	2	2	2	2	2	3	0	0	23	24.3	10	7.15	20	2	5
2	2	3	81	110	70	80	20	2	2	2	2	2	2	2	2	3	0	0	19.4	20.2	7	5	20.2	2	5
1	2	5	74	130	70	82	20	2	2	2	2	2	2	1	2	3	120	2	4	5	9	16	0	2	3
2	6	7	82	134	84	84	22	2	2	2	2	2	2	2	3	4	300	2	20	21	10	21	0	2	4
2	2	3	84	115	60	65	24	2	2	2	2	2	2	2	2	3	0	0	23.2	24	18	10	20	2	5
1	5	5	83	140	82	100	22	2	2	2	2	2	2	1	4	6	195	2	18	20.5	10	0	0	2	3
2	2	2	72	120	74	82	24	2	2	2	2	2	2	2	2	2	0	0	14.3	15	7.2	20	11	2	5
2	3	4	92	116	80	76	18	2	2	2	2	2	2	2	3	2	0	0	23.3	24.2	8.45	13	20	2	5
2	5	8	94	130	80	86	20	2	2	2	2	2	2	2	3	4	0	0	19.3	20	7	12	18	2	5