"A COMPARATIVE STUDY OF PLACEBO VERSUS OPIOID FREE ANALGESIC MIXTURE FOR MASTECTOMIES PERFORMED UNDER GENERAL ANAESTHESIA ALONG WITH ERECTOR SPINAE PLANE BLOCK"

BY

Dr. B MONISHA

DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA

In partial fulfilment of the requirements for the degree of

DOCTOR OF MEDICINE

IN

ANAESTHESIOLOGY

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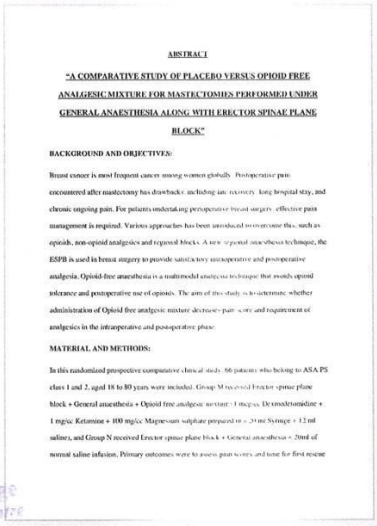

ABSTRACT

"A COMPARATIVE STUDY OF PLACEBO VERSUS OPIOID FREE ANALGESIC MIXTURE FOR MASTECTOMIES PERFORMED UNDER GENERAL ANAESTHESIA ALONG WITH ERECTOR SPINAE PLANE BLOCK"

BACKGROUND AND OBJECTIVES:

Breast cancer is most frequent cancer among women globally. Postoperative pain encountered after mastectomy has drawbacks including late recovery, long hospital stay, and chronic ongoing pain. For patients undertaking perioperative breast surgery, effective pain management is required. Various approaches has been introduced to overcome this, such as opioids, non-opioid analgesics and regional blocks. A new regional anaesthesia technique, the ESPB is used in breast surgery to provide satisfactory intraoperative and postoperative analgesia. Opioid-free anaesthesia is a multimodal analgesic technique that avoids opioid tolerance and postoperative use of opioids. The aim of this study is to determine whether administration of Opioid free analgesic mixture decrease pain score and requirement of analgesics in the intraoperative and postoperative phase.

MATERIAL AND METHODS:

In this randomized prospective comparative clinical study, 86 patients who belong to ASA PS class 1 and 2, aged 18 to 80 years were included. Group M received Erector spinae plane block + General anaesthesia + Opioid free analgesic mixture (1 mg/kg Dexmedetomidine + 1 mg/kg Ketamine + 800 mg/kg Magnesium sulphate prepared in a 20 ml Syringe + 12 ml saline), and Group N received Erector spinae plane block + General anaesthesia + 20ml of normal saline infusion. Primary outcomes were to assess pain scores and time for first rescue

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ABSTRACT

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BACKGROUND AND OBJECTIVES:

Breast cancer is most frequent cancer among women globally. Postoperative pain encountered after mastectomy has drawbacks, including late recovery, long hospital stay, and chronic ongoing pain. For patients undertaking perioperative breast surgery, effective pain management is required. Various approaches has been introduced to overcome this, such as opioids, non-opioid analgesics and regional blocks. A new regional anaesthesia technique, the ESPB is used in breast surgery to provide satisfactory intraoperative and postoperative analgesia. Opioid-free anaesthesia is a multimodal analgesia technique that avoids opioid tolerance and postoperative use of opioids. The aim of this study is to determine whether administration of Opioid free analgesic mixture decreases pain score and requirement of analgesics in the intraoperative and postoperative phase.

MATERIAL AND METHODS:

In this randomized prospective comparative clinical study, 66 patients who belong to ASA PS class 1 and 2, aged 18 to 80 years were included. Group M received Erector spinae plane block + General anaesthesia + Opioid free analgesic mixture (1 mcg/cc Dexmedetomidine + 1 mg/cc Ketamine + 100 mg/cc Magnesium sulphate prepared in a 20 ml Syringe + 12 ml saline), and Group N received Erector spinae plane block + General anaesthesia + 20ml of

normal saline infusion. Primary outcomes were to assess pain scores and time for first rescue analgesia requirement. Secondary outcome was to compare hemodynamics intraoperatively. P <0.05 was measured to be statistically important.

RESULTS:

Group M had a better intraoperative hemodynamic profile, including mean arterial pressure and Heart rate. VAS score is lesser or equal to 3 till 2nd hour postoperatively and provided long duration of analgesia when compared to Group N.

CONCLUSION:

ESPB along with opioid free analgesic mixture is an efficacious approach in patients undergoing mastectomy for both intraoperative and postoperative analgesia and breast conservative surgery under general anaesthesia. OFA mixture has provided better hemodynamic stability, prolonged time for first rescue analgesia requirement, and improved VAS scores postoperatively.

KEYWORDS: Erector spinae plane block, Opioid free anaesthesia, Ketamine, Dexmedetomidine, Magnesium sulfate.

ABBREVIATIONS

HR	Heart Rate
Bpm	Beats Per Minute
MAP	Mean Arterial Pressure
Mm Hg	Millimeters of mercury
ECG	Electrocardiogram
SPO_2	Peripheral capillary oxygen saturation
NIBP	Non-Invasive Blood Pressure
CVS	Cardiovascular system
RS	Respiratory System
CNS	Central Nervous System
NSAIDs	Non-steroidal anti-inflammatory drugs
mg	milligram
dL	deciliter
L	Liter
ml	milliliter
mEq	milliequivalents
mcg	microgram
gm	gram
cc	Cubic centimeter
pH	potential of Hydrogen
pKa	acid dissociation constant
Kg	kilogram

MHz	megahertz
Hz	hertz
G	gauge
USGRA	Ultrasound Guided Regional Anaesthesia
FOV	Field of view
OFA	Opioid Free Anaesthesia
NMDA	N-Methyl-D-Aspartate
GABA	Gamma-aminobutyric acid
Ach	Acetylcholine
ESPB	Erector Spinae Plane Block
PECS	Pectoral Nerve Block
PVB	Paravertebral block
BCS	Breast-Conserving Surgery
MRM	Modified radical mastectomy
LD flap	Latissimus Dorsi flap
MAO	Monoamine oxidase inhibitor
SSRIs	Selective serotonin reuptake inhibitors
COX	Cyclooxygenase
Min	minute
hr	hour
IV	Intravenous
IM	Intramuscular
Vd	Volume of distribution

ASA-PS	American Society of Anaesthesiologists – Physical Status
SA NODE	Sinoatrial node
AV NODE	Atrioventricular node
VAS	Visual Analogue Scale
NRS	Numerical rating scale
PCA	Patient Controlled Analgesia
ACTH	Adrenocorticotropin hormone
QoR	Quality of recovery
SOFA	Sequential Organ Failure Assessment
BMI	Body mass index
HPA axis	Hypothalamic-Pituitary-Adrenal axis
α	Alpha
NMJ	Neuromuscular junction
BBB	Blood-brain barrier
NS	Normal saline
PACU	Post anaesthesia care unit
T1/2	Elimination half life
GA	General anaesthesia
PAE	Pre-anaesthesia evaluation

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INTRODUCTION

"Breast cancer is the most common type of cancer in women worldwide. There will be about million new cases in 2020 which accounts for 11.7% of all cancers, overtaking lung cancer as the leading cause of cancer worldwide."[1]

Surgical treatment for breast carcinoma depends on the lesion's size, hormone receptivity, histological markers, presence or absence of metastases, patient's age, and personal preference. Lumpectomy, Mastectomy, and bilateral mastectomy are possible surgical options.[2]

Breast-conserving therapy refers to a regimen of radiation therapy administered after breast-conserving surgery (BCS, i.e., Lumpectomy) to eliminate any microscopic residual disease. Patients who have breast cancer diagnosed at an early stage have the option of undergoing lumpectomy instead of mastectomy.

Modified radical mastectomy involves removal of entire breast, including the nipple-areola complex, the axillary lymphatic system, and overlying skin near the tumor. A number of variations for this technique have been described by Handley, Auchincloss, and Madden, which represents general technique that preserves the pectoralis major and minor muscles but incompletely removes the axillary lymph nodes at level 3. In this technique, the medial pectoral nerve is more likely to be preserved as it enters pectoralis minor muscle. In Patey's technique, the pectoralis minor is removed, and the axillary lymphnodes are completely removed. Although the lateral and medial pectoral nerves are spared in this technique, preservation of the pectoral nerve will be difficult due to more extensive node removal and excision of the pectoralis minor muscle.[3]

T2-T6 intercostal nerves supply sensory innervation to the breast. Cutaneous branches enter the breast as lateral branches in the anterior axillary line. These branches arise from the intercostal muscles and pass anteriorly to the serratus anterior muscle before entering breast parenchyma. Anterior cutaneous branches of the intercostal nerves emerge more at the parasternal line from the intercostal musculature and produce breast sensation in the midline. The cutaneous branches of the III, IV, and V intercostal nerves innervate the nipple.[4]

Nociceptive axon damage is the most common source of neuropathic pain, while motor nerve damage is associated with less risk of developing chronic pain.[5]

40% of women who undergo breast cancer surgery experience moderate to severe pain in immediate post-operative period, according to reports.[6] Acute postsurgical pain delays functional recovery, impairs functions of pulmonary and immune system, increases the likelihood of thromboembolic events and myocardial infarction, and may extend hospital stay.[7] It also plays an important role in the onset of chronic pain in approximately half of postoperative patients[6,8]. Therefore, appropriate perioperative pain management is essential for patients undergoing breast carcinoma surgery.

Postoperative pain encountered after mastectomy is understood to have several drawbacks such as poor recovery, long hospital stays, and chronic ongoing pain.[9] To overcome this, variety of approaches have been introduced such as opioids, non-opioid analgesics, thoracic PVB, Thoracic epidural block, PECS I and II block, ESPB, Serratus Anterior Plane Block, Transversus thoracic plane block, Intercostal and interpleural nerve blocks. Opioids cause side effects such as postoperative headache, respiratory depression and nausea. Non-opioid analgesics include NSAIDS, Gabapentin and Pregabalin. Wound

infiltration and wound instillation of local anaesthetic through surgical drain are other methods.[10,11]

ESPB is an interfascial plane block which is a safe and simple method to provide sensory block at a multi-dermatomal level.[12]The Erector spinae block is commonly used in breast surgery with aim of providing satisfactory analgesia during and after surgery. ESPB is uncomplicated to perform because of easy identification of anatomical landmarks on ultrasound and it is relatively safe due to absence of vital structures in close vicinity of block. No complications have been recorded so far with this block.[13]

Usually mastectomy is done under general anaesthesia using opioids. Opioid-free general anaesthesia avoids the side effects of opioids while providing less post-operative complications and speedy recovery even in oncological surgeries. Erector spinae nerve block aims to reduce requirement of post-operative analgesia.[14]

Opioid-free anesthesia (OFA) ensures a fast and smooth recovery and avoids acute opioid tolerance after surgery.[15] Mulier did research about opioid free anaesthesia from 2009 and opioid free anaesthesia mixture protocol was reported in 2017.[16]

OFA is multimodal analgesic technique which includes different drugs such as Lidocaine, Ketamine, Magnesium sulphate, alpha 2 agonists such as Dexmedetomidine and Clonidine, Dexamethasone and NSAIDS. These drugs can be used as combination through intravenous route by infusion. Infusion can be titrated according to hemodynamic response. Side effects include bradycardia, hypotension, dyspepsia and elevated blood sugars.[17]

AIMS AND OBJECTIVES:

PRIMARY OBJECTIVES:

The primary objective of this study is to determine whether administration of Opioid free analgesic mixture reduces pain score and requirement of analgesics in the intraoperative and postoperative period.

SECONDARY OBJECTIVES:

To compare intraoperative hemodynamics like heart rate, Mean arterial pressure, SpO2 and postoperative patient satisfaction.

REVIEW OF LITERATURE

PHARMACOLOGY OF KETAMINE:[18]

Ketamine is a derivative of phencyclidine. It provides dissociative anaesthesia, as indicated by the dissociation between the limbic and thalamocortical systems on the EEG. The eyes will remain open with a slow, nystagmic gaze in a cataleptic state corresponding to dissociative anaesthesia.

STRUCTURE:

Ketamine molecule is water-soluble that structurally appears like phencyclidine. It consists of 2 isomers. The R (2)-ketamine is designated as right-handed optical isomer and S (1)-ketamine is designated as left- handed optical isomer.

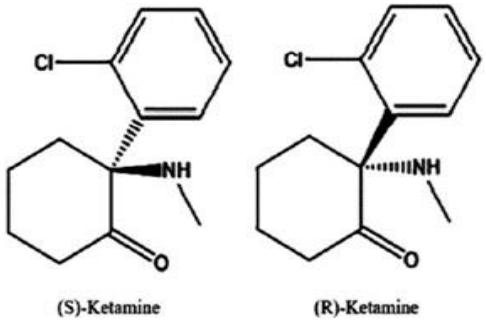

FIGURE 1: CHEMICAL STRUCTURE OF KETAMINE

MECHANISM OF ACTION:

Ketamine acts on NMDA receptors and binds noncompetitively to phencyclidine. Ketamine also exercises results at different sites such as

1. Muscarinic receptor,
2. Monoaminergic receptor,
3. Opioid receptor,
4. L-type calcium channels and voltage-sensitive sodium,

5. Weak actions at GABA receptors,
6. Neuronal nicotinic acetylcholine receptors.

PHARMACOKINETICS:

1. Onset action is rapid
2. Action takes short duration
3. Rapid transfer across BBB is caused by high lipid solubility.
4. Physiologic pH is P Ka of 7.5
5. After IV administration, peak concentrations in plasma occurs in 1 min and after IM injection, in 5 minutes.
6. Hepatic clearance is 1L/min
7. Vd is 3 L/kg
8. T 1/2 is 2 to 3 hours.

METABOLISM:

Ketamine is metabolized primarily in liver. Via the cytochrome p450 it undergoes hepatic transformation to become nor ketamine. Nor ketamine which is an active metabolite is excreted in both bile and urine.

CLINICAL USES:

Ketamine is a distinctive drug. When given in sub anaesthetic doses, it provides analgesia and given at higher doses causes inducing effects.

1. Analgesia: For analgesia, sub anaesthetic dose of ketamine is 0.2 to 0.5 mg/kg IV. For somatic pain rather than for visceral pain Analgesic effect is more. Activity in limbic and thalamic systems causes analgesic effect of ketamine. Ketamine, Magnesium, Dextromethorphan which inhibits spinal NMDA receptors produces analgesia for postoperative pain, decreasing analgesic consumption.

2. Induction of anaesthesia: Induction dose when given through IV is 1 to 2 mg/kg IV or 4 to 8 mg/kg when given as IM. Due to its analgesic effect, it can be used for changing burns dressing, skin grafting procedures and debridement. It is useful for rapid IV induction in asthmatic patients because of its bronchodilator effects.

3. For recovery from effects of opioid tolerance: Sub optimal dose of ketamine given at 0.3 mg/kg/hr will improve analgesia and reduces tolerance to opioids.

SIDE EFFECTS:

Ketamine is potent vasodilator and increases CMRO2 and cerebral blood flow. Administration of Thiopentone or midazolam prior to ketamine can blunt the response of ketamine induced cerebral blood flow.

Ketamine increases heart rate, blood pressure, myocardial oxygen requirement, cardiac output after IV administration. Ketamine-induced drop in blood pressure and cardiac output appears in few patients which can be due to depletion of endogenous catecholamine stores. After IV or IM administration, Ketamine improves tracheobronchial mucus gland and salivary secretions. Patients may have visual, auditory, and proprioceptive illusions which can lead to delirium.

DEXMEDETOMIDINE:

Dexmedetomidine is the most selected alpha 2 agonist. It causes analgesia, sedation, anxiolysis, and sympatholysis. Elevated density of alpha 2 receptors is in pontine locus coeruleus moderating vigilance, sympathetic nervous system function, arousal, analgesia, and memory. The sedative effect made by dexmedetomidine is caused by the inhibition of the nucleus. Dexmedetomidine is an imidazole derivative which is dextro-isomer of the medetomidine.[18]

CHEMICAL FORMULA:

Dexmedetomidine chemical formula (+) 4 - (S)-[-1-(2,3-dimethylphenyl] -1H- imidazole monohydrochloride.

Molecular weight: 236.7.

Molecular formula: C13H16N2.2HCL

Empirical formula: C13 H16 N2 HCl.

STRUCTURAL FORMULA:

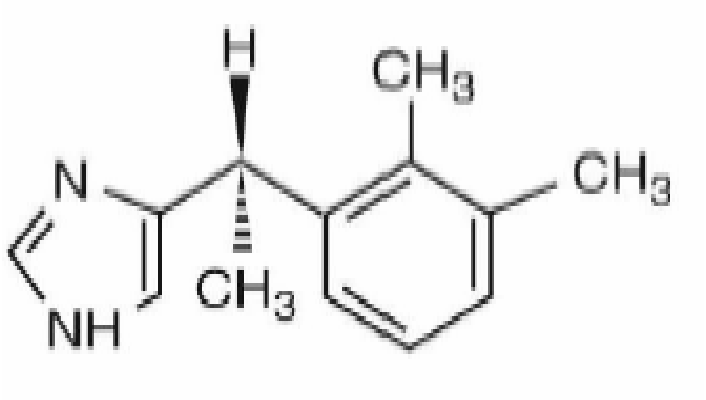

FIGURE 2: CHEMICAL STRUCTURE OF DEXMEDETOMIDINE

MECHANISM OF ACTION:

G-protein transmembrane consists of α-2 receptors that are distributed throughout the body at the post-synaptic, presynaptic, and extra-synaptic sites. Still, most interactions occur with α-2 receptor present in brain and spinal cord.

By modulating nociceptive input and transmission, dexmedetomidine ultimately produces analgesia by acting at spinal and supraspinal sites. Although α-1 receptors are more

prevalent, α-2 receptors in peripheral vascular smooth muscle helps in mediating vasoconstriction.[19]

PHARMACOKINETICS:

Dexmedetomidine undergoes almost complete biotransformation and a small percentage of the drug that does not undergo biotransformation is excreted unchanged in faeces and urine. Biotransformation involves

1. Cytochrome P450 mediated metabolism

2. Direct glucuronidation.

Direct N-glucuronidation to primarily inactive metabolites, N-methylation and hydroxylation are the primary metabolic pathways for dexmedetomidine. 94% of the dexmedetomidine is bound to proteins, and the ratio of dexmedetomidine in plasma to the amount in whole blood is 0.66.

1. Elimination half-life of dexmedetomidine is 2 to 3 hours
2. The context-sensitive half-time is 4 minutes after infusion for 10 minutes and 250 minutes after an infusion for 8 hours.
3. Clearance rate is 10 to 30ml/kg/min
4. The Vd in a steady state is 2 to 3L/kg.[20]

PHARMACODYNAMICS:

CARDIOVASCULAR SYSTEM:

Alpha 2 Agonists can cause either hypertension or hypotension. At a lower dose, the action of α-2 agonists is sympatholysis which is mediated by α-2a receptors. At a higher dose, the hypertensive actions dominate by activation of α-2B receptors which is located on vascular smooth muscle.[21]

It has a biphasic response. If a bolus dose of 1 mcg per kg is given in young adult, it initially increases blood pressure followed by reflex drop in the heart rate. This reaction is going to last for 5 to 10 min. This will be followed by drop in blood pressure which is caused by an inhibition in central sympathetic outflow. With these, presynaptic α-2 receptors also gets stimulated which declines release of norepinephrine and this causes drop in heart rate and blood pressure.[22]

CENTRAL NERVOUS SYSTEM:

SEDATION:

It is due to activation of pre-and postsynaptic α-2-adrenoceptors in locus coeruleus, the main noradrenergic nucleus in the pons.

It provides good sedation and has a very minimal effect on respiration.

ANALGESIA:

It is due to the activation of the central nociceptive receptor, which results in interneuron hyperpolarization and reduced release of nociceptive neurotransmitters such as substance P and glutamate.[23]

Intraoperative infusion of dexmedetomidine is effective for providing analgesia during surgery. It reduces pain and postoperative consumption of opioids. It prolongs the time for first rescue analgesic.[24] It results in opioid sparing effects and is helpful in neuropathic pain.

RESPIRATORY SYSTEM:

Dexmedetomidine at high doses does not suppress respiratory function. It helps in maintaining sedation by eliminating cardiovascular instability or respiratory depression.[25]

RENAL SYSTEM:

1. It improves renal blood flow through vasodilation and diuresis.
2. It reduces accumulation of other analgesic drugs and NSAIDs.
3. It inhibits inflammation, prevents oxidative stress and reduces mitochondrial damage.
4. It relieves hypercoagulability.[26]

ENDOCRINE SYSTEM:

Dexmedetomidine at therapeutic doses has no impact on adrenocorticotropic hormones secretion. The cortisol response to ACTH may be decreased after infusion or a high dose of dexmedetomidine.

CONTRAINDICATIONS OF DEXMEDETOMIDINE:

1. In hypotensive patients.
2. In patients with pre-existing bradycardia and heart blocks
3. Infusion for more than 24 hours.
4. Allergy or known hypersensitivity to dexmedetomidine

SIDE EFFECTS OF DEXMEDETOMIDINE:

Side effects include hypoxia, nausea, hypotension, atrial fibrillation, bradycardia, and first- or second-degree heart block. Most of the adverse effects occur shortly after giving loading dose of the drug.[27]

MAGNESIUM SULPHATE:[28,29,30]

Magnesium is fourth most ample cation in body. It is second in intracellular cation and fourth in plasma. It is a universal anaesthetic drug with high therapeutic index and low cost. Its efficacy in treating and preventing eclampsia, cardiac arrhythmias, and asthma has been proved clinically. It has an enhancing effect on muscle relaxation and perioperative analgesia.

MODE OF ACTION:

At NMJ, it causes a dose-dependent presynaptic inhibition of the release of Ach. No direct analgesic effect is resulted from magnesium. The secondary analgesic effect is due to non-competitive antagonist activity at NMDA receptors, which are voltage-gated ion channels in postsynaptic neuron of dorsal horn of the spinal cord where Calcium inflow will be inhibited which delays central sensitization and attenuates existing pain hypersensitivity.

PHARMACOKINETICS:

ABSORPTION - Oral ingested magnesium is absorbed by 25% to 65%.

DISTRIBUTION - In the plasma, 30% is protein bound

EXCRETION - Exogenous magnesium content excretes more than 50% in the urine, even with considerable magnesium deficiency.

PHARMACODYNAMICS:

CARDIOVASCULAR SYSTEM:

When given high doses, peripheral vasodilation is caused by magnesium, which might cause hypotension. This drug also reduces the speed of impulse formation of the SA node, resulting in bradycardia, as well as prolongation of refractory period of the AV node, sinoatrial conduction, and PR interval.

RESPIRATORY SYSTEM:

Magnesium is a potent bronchodilator that is used as an adjuvant in the treatment of asthmatic patients. It also reduces hypoxic pulmonary vasoconstriction.

THE CENTRAL NERVOUS SYSTEM:

The medication has anticonvulsant and CNS depressant properties. Magnesium in high concentrations inhibits release of catecholamine from adrenal medulla and the adrenergic nerve terminals.

GENITOURINARY SYSTEM:

The drug has diuretic effect and acts as vasodilator. It lowers uterine contractility and tonicity. Perfusion of placenta can get high as the vascular resistance of the uterus gets low. There is increase in risk of neonatal depression and hypotonia when magnesium crosses placenta.

METABOLIC AND OTHER EFFECTS:

The clotting time of whole blood is increased by magnesium, thromboxane B2 synthesis is decreased, and thrombin induced platelets aggregation is inhibited.

SIDE EFFECTS:

Side effects include headache, Nausea, dizziness, and flushing. Magnesium sulfate is very painful when given through intramuscular route.

Dose related side effects include sedation, bradycardia, hypotension, oliguria, areflexia, progressive muscle weakness, AV and intraventricular conduction disorders and cardiac arrest. In patients with renal dysfunction, magnesium toxicity may occur.

SERUM MAGNESIUM LEVELS		CLINICAL EFFECTS
mg/dl	mEq/L	
1.7 to 2.4	1.2 to 2	Normal
4.8 to 9.6	4 to 8	Therapeutic
6 to 12	5 to 10	Prolonged PR interval and widened QRS complex
12	10	Muscle weakness and absence of deep tendon reflexes
18	15	Sinoatrial and Atrioventricular node block, Paralysis of respiratory muscles
24	20	Cardiopulmonary arrest

These harmful consequences can be reversed by administrating loop diuretics and intravenous calcium, which improve renal excretion of magnesium.

USES:

1. In patients with tetanus, it reduces spasms.
2. In myocardial infarction magnesium reduces reoxygenation injury and risk of malignant arrhythmia events.
3. Attenuates intubation response.
4. Used in managing of preeclampsia and eclampsia.
5. Cerebral edema (Attenuates blood-brain barrier defect).
6. To treat ventricular arrhythmias and torsades de pointes.
7. In cases of premature labour, as a tocolytic.
8. For treatment of exacerbation of asthma (resistant or not responsive to other treatments)

Magnesium sulfate not only reduce pain intensity after surgery but also reduce the amounts of opioid intake. Using magnesium during general anaesthesia reduces post-operative pain without increasing the risk on adverse events.

BUPIVACAINE:

Bupivacaine was discovered by Ekenstam in 1957, belongs n-alkyl substituted pipecholyl xylidine family. It is an amino-amide local anaesthetic[31]. Due to a chiral carbon in piperidine ring it exists in 2 stereoisomeric forms that is R (+)-bupivacaine and S (-)-bupivacaine.[32]

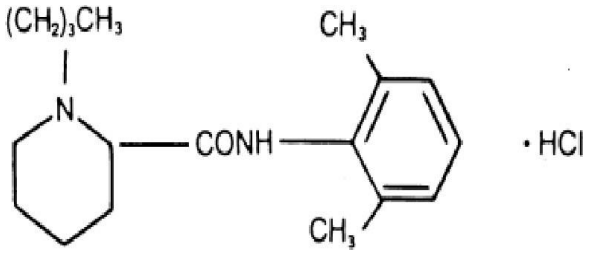

FIGURE 3: CHEMICAL STRUCTURE OF BUPIVACAINE

PHYSICOCHEMICAL PROFILE:

1. Molecular weight is 288.
2. pKa is 8.1.
3. Plasma protein binding: 95%
4. Lipid solubility of bupivacaine is 28.
5. Toxic plasma concentration is 240 to 480min
6. Vd is 71 litres
7. Duration of action is 240 to 480 min
8. Clearance rate is 0.47 litres/min
9. T 1/2 is 210min
10. Onset is Slow

MECHANISM OF ACTION:

In an activated closed state, by selectively binding α subunit of sodium channels, conduction blockade is produced and preventing their transition to activated open and resting closed states, thereby stopping ahead impulse and conduction of action potential. Bupivacaine can also block voltage-dependent potassium channels, resulting in broadening of action potential. L type calcium channels also inhibited by Bupivacaine. Moreover, bupivacaine inhibits both myelinated A – Delta fibers and C fibers. By local anaesthetics Preganglionic-B fibers are easily blocked.[18]

PHARMACOKINETICS:

ABSORPTION:

Absorption depends on the vaso-activity of drug, dosage, rate and site of injection. “After one dose, order for the peak plasma concentration is intrapleural > intercostal > lumbar epidural > brachial plexus > subcutaneous > sciatic > femoral.”

DISTRIBUTION:

Tissue distribution is directly proportional to tissue/blood partition co-efficient and perfusion of tissue and mass.

METABOLISM:

Bupivacaine attaches to α-1-acid glycoprotein. It undergoes amide hydrolysis, conjugation, N-dealkylation, and aromatic hydroxylation. Metabolism produces Pipecolylxylidine. Kinetics of bupivacaine will not be affected by renal disease. In the urine, less than 10 to15% of the drug is released.

USES OF BUPIVACAINE:

1. Anaesthesia infiltration
2. Central neuraxial block (caudal, Spinal and epidural)
3. Nerve block (Peripheral).[33]

SIDE EFFECTS:

Side effects include Angioneurotic edema, Allergy, Accidental intravascular injection, Urticaria and Pruritus

SYSTEMIC TOXICITY:

CNS toxicity:

1. Coma
2. Drowsiness
3. Slurred speech
4. Muscle twitches
5. Tinnitus
6. Vertigo
7. Seizures

Cardiac toxicity:

1. Ventricular fibrillation
2. Ventricular tachycardia
3. Atrioventricular block
4. Arrhythmia
5. Hypotension

Hepatotoxicity[34]

DEXAMETHASONE:[18,20,35]

1. It is a fluorinated derivative of prednisolone.
2. It is an isomer of betamethasone.
3. It belongs to synthetic corticosteroids.
4. It is a long-acting corticosteroid
5. Anti-inflammatory potency is 25
6. Sodium retaining potency is 0
7. Elimination half-life is 3.5 – 5 hours.
8. Duration of action is 36 – 54 hours.

USES:

1. Prolongs regional block duration with minimum side effects
    a) For medium acting local anaesthetics: 2 -3 hours
    b) For long-acting local anaesthetics: 10 hours
2. Provides postoperative analgesia.
3. Less requirement of postoperative opioids.
4. Prolongs duration of 1st rescue analgesia.
5. For postoperative nausea and vomiting (dose 0.5mg/kg)
6. Decreases cerebral edema
7. Decreases airway edema
8. In respiratory distress syndrome

SIDE EFFECTS:

Side effects includes metabolic and electrolyte changes, Suppression of HPA axis, Osteoporosis and Skeletal muscle myopathy.

TRAMADOL:

1. It is a synthetic codeine analogue.
2. Weak Mu opioid receptor agonist.
3. Analgesic effect is by inhibition of uptake of norepinephrine and 5 – Hydroxy tryptamine.
4. Bioavailability is 68%.
5. Vd is 2.3 – 3.9 L/kg
6. Elimination half-life is 4.5 – 7.5 hours
7. Clearance rate is 6 – 12 ml/kg/min
8. Metabolized in liver
9. Excreted in urine.
10. Duration of analgesia is 6hours
11. Peak action is 2.3 hours

USES:

In treatment of mild to moderate pain.

SIDE EFFECTS:

Side effects include dry mouth, headache, vomiting, dizziness, Nausea. It can exacerbate seizures

CONTRAINDICATIONS: Tramadol should be avoided in patients taking MAO inhibitors and SSRI'S.[36]

DICLOFENAC:[36,37]

1. It is phenylacetic acid derivative and COX 2 selective drug.
2. It competes with arachidonic acid derivative and binds to cyclooxygenase, resulting in decreased prostaglandin formation.
3. It has Analgesic, Antipyretic, Anti-inflammatory properties.
4. It is rapidly absorbed and has extensive protein binding.
5. Elimination half-life is 1 – 2 hours (persists in synovial fluid)
6. Peak plasma concentration is 1.5 – 2 hours.
7. It undergoes first-pass metabolism
8. Metabolized in liver.
9. Excreted in urine (65%) and bile (35%).

USES:

1. As analgesic
2. Rheumatoid arthritis, osteoarthritis, Ankylosing spondylitis.
3. Primary dysmenorrhea
4. Acute migraine
5. Reduce cystoid macular edema after cataract surgery.

SIDE EFFECTS:

Side effects include gastrointestinal symptoms such as vomiting, dyspepsia, heartburn, gastrointestinal ulceration, nausea. Other side effects include hypertension, myocardial infarction, severe liver injury and hypersensitivity reactions.

BASICS OF ULTRASOUND[38,39]

DEFINITION OF ULTRASOUND:

Sound propagates as mechanical longitudinal wave, in which the reciprocating motion of the particles is parallel to the direction of wave motion. Diagnosing health issues with ultrasound typically involves frequencies between 2 and 15 MHz

Many things can affect an ultrasound wave as it passes through tissues. Key characteristics include Reflection, Scattering and Absorption.

A-MODE:

The transducer releases a single ultrasound pulse. Ultrasound image which is one-dimensional forms vertical peaks when ultrasound beam hits tissue boundaries. By dividing the tissue's ultrasound speed, elapsed time is reduced by half, the center distance in middle of echoed spikes will be measured, the spatial relationship of imaged structure will not be revealed. For regional anaesthesia A-mode ultrasound is not convenient.

B-MODE:

B-mode scans the area in two dimensions (2D) instead of a single one using a "linear array of 100 to 300 piezoelectric elements." B-mode imaging converts A-scan echo amplitude into dots of other brightness. Tissue distances are represented by horizontal and vertical directions, while grayscale intensity indicates echo strength. Regional anaesthesia's primary mode is B-mode, the area of interest will be shown on a cross-sectional view.

M-MODE:

An ultrasound scan with a single beam can show a structure like heart valve moving in wave-like manner. Regional anaesthesia rarely uses M-mode. It is widely used in cardiac and foetal imaging.

TRANSDUCERS:

Curved and linear transducers are used in regional anaesthesia. A curvilinear transducer produces a curved scan and an arcuate image, whereas linear transducer will produce parallel scan lines and a rectangular image. Presence of very thin layer of air between skin and transducer can hinder clinical scanning which reflects almost all of the ultrasound. To remove the air between the skin and the transducer, a medium called aqueous gel is used.

Although higher transducer frequencies improve spatial resolution, tissues are not well penetrated. Lower transducer frequencies have a lower spatial resolution but can penetrate the tissues more deeply. When selecting the transducer frequency, the balance between beam penetration and spatial resolution must be considered.

SCANNING PLANE:

Both the transverse (axial) and longitudinal planes are accessible for scanning. Transducer should be positioned perpendicular to the target's long axis during a transverse scan, resulting in a cross-sectional image. Transducer is held parallel to long axis of the target (such as a nerve or blood vessel) during a longitudinal (sagittal) scan. Ultrasound scans during USGRA are typically carried out in the transverse plane for optimal visualization of nerves, radial spread of local anaesthetic and surrounding structures.

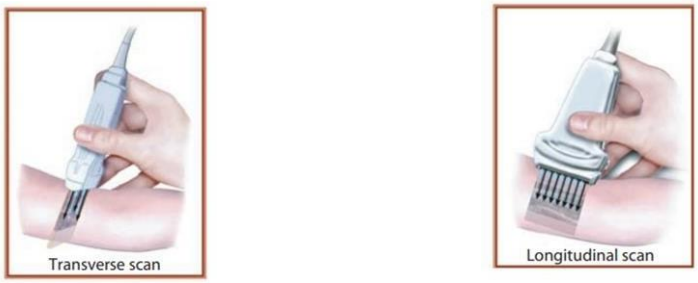

FIGURE 4: AXIS OF SCAN

TRANSDUCER AND IMAGE ORIENTATION:

Orientation dot or marker which is on side of an ultrasound transducer corresponds to marker on the monitor. There are no designated standards for transducer how to orient, although its common to have the transducer's orientation dot directed to right side of the patient when a transverse scan is happening & towards cephalad when a longitudinal scan happens. As a result, "marker" on the monitor should be in the screen towards top-left corner, which represent cephalad end of patient during a longitudinal scan and during a transverse scan it is shown to the right side of the patient. superficial structures are projected to the top of monitor, while deep structures represent the bottom.

AXIS OF INNERVATION:

Block needle can be viewed from its long or short axis. Initially, out of plane approach will hide the needle. The needle appears as echogenic dot on monitor when it crosses the imaging plane. Because it is a short-axis view, this echogenic dot may not be needle tip. The in-plane method inserts the needle through the imaging plane, so both the shaft and tip are visible on the monitor.

FIELD OF VIEW AND NEEDLE VISIBILITY:

While performing Ultrasound guided regional anaesthesia, having a good field of view (FOV) is important because it will let you see not only the "target" but also also the nearby structures such as pleura or blood vessels that you need to avoid injuring. Curved array transducers project a divergent ultrasound beam, which results in a wider FOV, where linear array transducers project a narrow field of view (FOV).

When needles are imaged perpendicular to the ultrasound beam, they are best visible. Linear array transducers may not be able to visualize needles at steep angles required for deep blocks. Linear array transducers are suited for superficial blocks (femoral nerve

block, axillary or interscalene brachial plexus block). Curved array transducers are better suited for deep blocks (for example, central neuraxial blockade, lumbar plexus, and sciatic nerve blocks). Due to the diverging ultrasound beam, curved array transducers have lower lateral resolution at depth. Other factors may also have an impact on needle visibility. Compared to the short axis, needle can be seen better in long axis. As the diameter decreases, visibility decreases linearly.

NERVE: The Peripheral nerves contains of hypoechoic nerve fascicles surrounded by hyperechoic connective tissue. It looks like honeycomb along the transverse axis. Along the longitudinal axis it looks like fibrillar appearance, with fine parallel hyperechoic lines and hypoechoic lines parted by fine hyperechoic lines.

TENDON: On longitudinal scans, tendons appear hyperechoic and fibrillar. The tendon is more hyperechoic than the nerve.

Muscle appears hypoechoic.

Subcutaneous fat lobules looks as round to oval shaped hypoechoic nodules.

Bone surface appears hyperechoic.

Pleurae appear as hyperechoic line deep to the hyperechoic rib.

Blood vessels have anechoic.

ANATOMY OF ERECTOR SPINAE PLANE BLOCK:[40,41]

"The massive erector spinae muscles are located in a groove on both sides of vertebral column, between spinous processes centrally and rib angles laterally." The thoracolumbar fascia, serratus posterior inferior, rhomboid, and splenius muscles cover them in thoracic and lumbar regions.

"The vertebral column's main extensor muscles are erector spinae, bifurcated into three columns. The medial column is formed by the spinalis, the lateral column by iliocostalis, and the intermediate column by the longissimus. Muscle is divided into 3 vertical columns in the upper lumbar region, regionally each is again divided into thoracis, capitis, lumborum and cervicis according to where the muscles are superiorly attached."

Proximal attachments:

It arises from sacral and inferior lumbar spinous process, the dorsal part of iliac crest, from the sacro-iliac ligaments, the supraspinous ligament, as well as posterior surface of sacrum.

Distal attachments:

- "Iliocostalis: Thoracis, cervicis and lumborum; fibers run superiorly to angles of ribs and cervical transverse processes.
- Longissimus: Thoracis, capitis and cervicis. Fibres run superiorly to the ribs between tubercles and angles to transverse processes in the cervical and thoracic regions, and to the mastoid process of the temporal bone.
- Spinalis: capitis, cervicis and thoracis; fibers run superiorly to spinous processes in the upper thoracic region and to cranium."

Nerve supply: Posterior ramus of spinal nerves.

Actions:

1. By acting bilaterally, they make the back straight, helps in returning it from flexed position to an upright posture, and pull the head posteriorly. In addition, they adjust vertebral column flexion through coordinated contraction and relaxation.
2. They bend the vertebral column laterally by acting unilaterally. Besides that, unilateral contraction of muscles that are attached to head will make head turn to the side that is actively contracting.

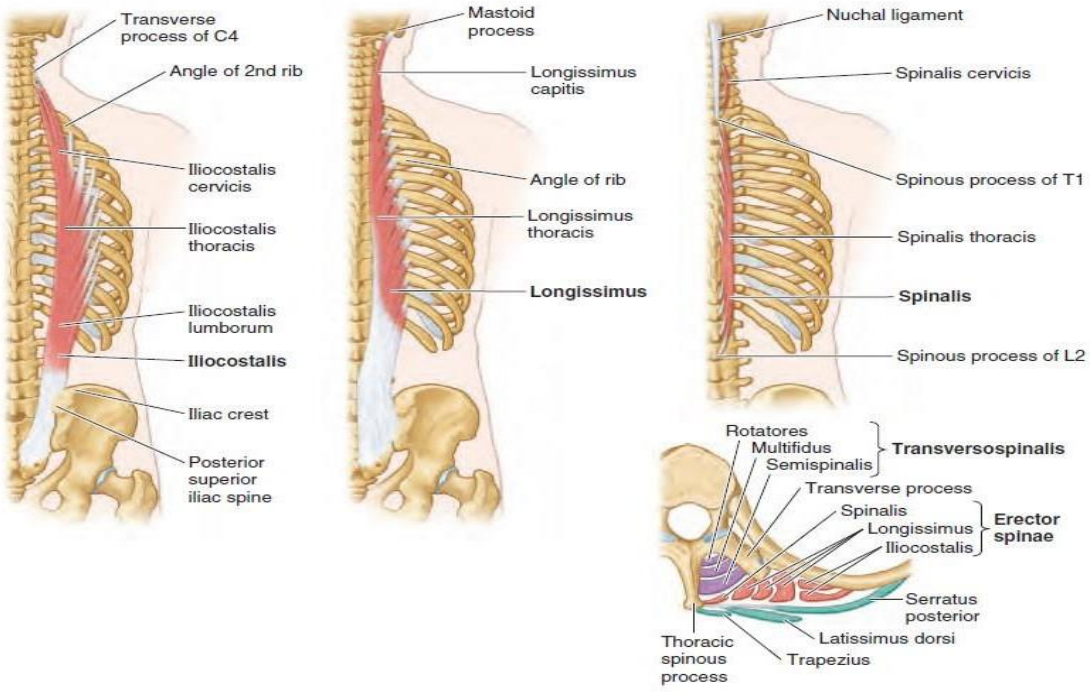

FIGURE NO 5: INTERMEDIATE LAYER OF INTRINSIC MUSCLES OF BACK

ERECTOR SPINAE PLANE BLOCK:

To perform ESPB, the most common technique used is USG guided in plane technique. The needle should be positioned between transverse process of thoracic vertebra and erector spinae muscle. Local anaesthetic will be administered between them, blocking the ventral and dorsal ramus of the thoracic and abdominal spinal nerves.

INDICATIONS:

It provides regional analgesia for various surgical procedures in the anterior, posterior, lateral thoracic, and abdominal walls. It also helps in relieving pain in acute and chronic pain syndromes.

CONTRAINDICATIONS:

Absolute contraindications:

1. Infection at site of injection
2. Patient refusal

Relative contraindications:

1.Coagulopathy

TECHNIQUE:

"Although it can be done lower, the ESPB is typically executed between the T5 and T7 para-spinal levels. The linear ultrasound transducer should be positioned at the desired level cephalocaudal above the midline of back. The transverse process will appear after a slow lateral move of the probe. In comparison to rib, the transverse will be wide and shallow. The transverse process should be confirmed before superficial identification of the erector spinae muscle, rhomboid major muscle, and trapezius. Above the ultrasound probe, Touhy's needle should be inserted through in plane approach from cephalad-to-caudal direction. With ultrasound guidance, the Tuohy's needle should be inserted to hit the transverse process by piercing muscles of the Trapezius, rhomboid major, and Erector spinae muscles. Once the needle tip is below the muscle, little local anaesthetic should be administered. Transverse process should be separated from the muscle to confirm needle position. Inject local

anaesthetic in 5 ml increments, aspirating after each one to prevent intravascular injection. 20 to 30ml of 0.25% of bupivacaine or 0.5% of ropivacaine can be used."[42,43]

COMPLICATIONS:

Local anaesthetic toxicity or allergy, Pleural puncture, Infection at needle insertion site, Vascular puncture, Failed block, Pneumothorax.[44]

PAIN ASSESSMENT SCALES:

Long-term pain and treatment effects are more difficult to assess, both in patients suffering from non-malignant causes and cancer pain. To evaluate qualitative factors of chronic pain and its effect on function, numerous tools have been developed for various chronic pain conditions and subtypes. Pain is a personal and subjective. It is difficult to assess pain in patients we are not able to communicate effectively, particularly those with cognitive impairment and dementia. [45]

An ideal pain assessment tool should possess a high level of internal consistency, inter-observer reliability and construct validity. It should be objective and sensitive. It must be simple to understand and appropriate for all age groups in any clinical setting.[46]

TYPES OF PAIN ASSESSMENT SCALES:

1. VISUAL ANALOGUE SCALE:

This is represented by a 100-mm horizontal line, with left end that denotes no pain and right end that denotes the most excruciating pain. The individual will be asked to mark a point on the line to represent pain intensity. The measurement from the left-hand edge determines a score out of 100 to the mark in mm. "It is determined by no pain and

worst possible pain, in which 0 represents no pain, whereas 1 to 3 is considered mild pain, 4 to 6 is moderate pain and 7 to 10 will be considered severe pain."

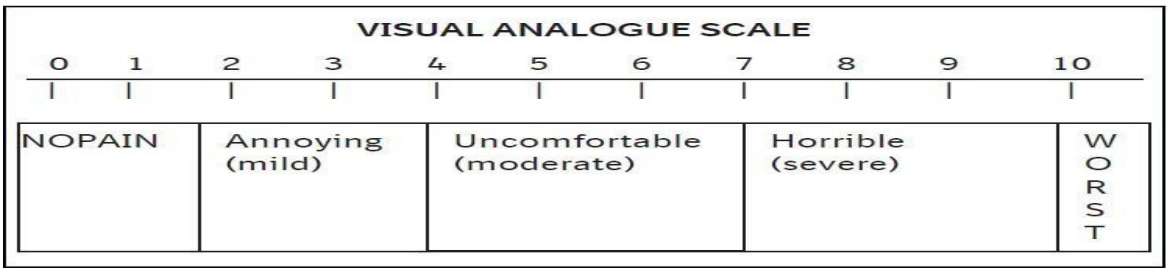

FIGURE 6: VISUAL ANALOGUE SCALE

2. NUMERICAL RATING SCALE:

These typically ask the patient to rate their level of pain on an 11 point integer scale, from 0 representing no pain till 10 that is considered worst pain imaginable. An NRS provides reasonably accurate, repeatable data and is quick and easy to use.

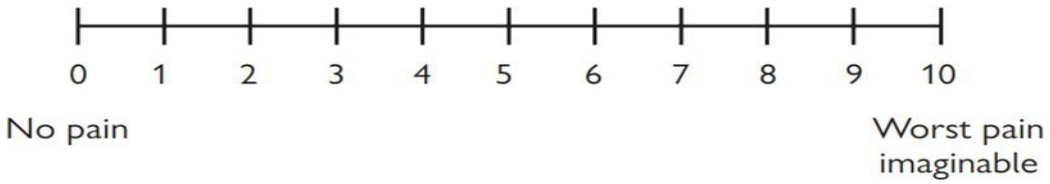

FIGURE 7: NUMERICAL RATING SCALE

3. "WONG BAKER FACES PAIN SCALE:"

For children aged less than 3 years, pain scales with happy and sad faces can be used to represent level of discomfort or pain child is experiencing. The child should be told to indicate face that represents their severity of pain. The child must understand that the face on the left demonstrates no pain or hurt, whereas the face on the right demonstrates severe pain

or hurt, and that you are asking about pain, not how happy or sad the child is or what their face looks like.[47]

FIGURE 8: WONG–BAKER FACES PAIN SCALE

In a study by **Mulier JP et al., in 2018**[48] they stated that opioid free anaesthesia reduced postoperative nausea, vomiting and shivering. This study was done in 50 participants who underwent laparoscopic bariatric surgery. Group opioid anaesthesia received Inj Sufentanil 0.5mcg/kg before induction. Group OFA received 0.5mcg/kg Dexmedetomidine, 1.5mg/kg of Lignocaine and 0.5mg/kg of Ketamine. They have concluded that Opioid free group showed less adverse events in Post anaesthesia care unit and only few analgesics were used and also reduced postoperative need of opioids, hypertension, improved VAS score and QoR.

In a study done by **Altiparmak B et al., in 2019**[49]**,** he included 42 patients and divided them into 2 groups. All patients were induced under general anaesthesia along with ESPB but with different concentrations of Inj Bupivacaine. Group 1 received Inj Bupivacaine 0.375% and Group 2 received Inj Bupivacaine 0.25%. This study concludes that both the concentrations have provided postoperative analgesia effectively, but high concentration required less tramadol than other groups.

According to study done by **Singh S et al., in 2019**[50], they told that Ultrasound guided ESPB along with general anaesthesia have provided effective analgesia postoperatively. This study includes a group of 40 patients of which one group received general anaesthesia alone and other group received ESPB along with general anaesthesia. For ESPB patients received 20ml of 0.5% Bupivacaine on operating side and they have monitored postoperative morphine consumption for 24hours. This study concludes that postoperative morphine consumption was comparatively less in patients who had received ESPB along with general anaesthesia than other group who received general anaesthesia alone.

In a study by **Gad M et al., in 2019**[51] they included 47 patients after exclusion and divided into 2 groups. Group E (Erector Spinae Plane Block) received 20ml of 0.25% Levobupivacaine with 0.5mcg per kg of dexmedetomidine. Group P (pectoral nerve block) received 30ml of 0.25% of Levobupivacaine with 0.5mcg per kg of dexmedetomidine and assessed postoperative Morphine consumption, pain scores and stress levels in both groups. Postoperative morphine requirement and stress levels were less in group P and pain scores were higher in E group.

In the study done by **Malawat A et al., in 2020**[52] 30 participants received ESPB with 20ml of 0.5% Bupivacaine prior to modified radical mastectomy and sensation was assessed from T1 to T8 by pinprick method. Loss of sensation to pinprick within 40 minutes was considered a successful block and patients who did not achieve a loss of sensation were considered block failure. All patients received 1mcg/kg of Inj Fentanyl and infusion of Inj Propofol 25mcg/kg/min to 75mcg/kg/min. Infusion exceeding 75mcg/kg/min was considered

block failure and converted to general anaesthesia. To completely achieve surgical anaesthesia duration required was 31.50 minutes and first rescue analgesic time was 41.73hours. This study concluded that ESP block alone along with moderate sedation can provide adequate postoperative analgesia.

According to study done by **Moustafa MA et al., in 2020**[53] they stated that ESPB is safe and simple alternative to PVB as they have conducted study on 102 female patients undergoing MRM. Both groups received 20ml of 0.25% Bupivacaine and novice anaesthesiologists performed these blocks and they have assessed hemodynamic response during incision of skin and requirement of postoperative analgesia. Time for 1st rescue analgesia requirement was 11.04 ± 1.9 in ESPB group and 11.22±1.95 in PARA group. Total consumption of morphine did not show statistical significance.

In study done by **Luis-Navarro JC et al., in 2020**[54] they stated that combined general and epidural anaesthesia have been used in many cases of Modified Radical Mastectomy. In patients with previous spine surgeries epidural blocks cannot be given and, in such cases, intravenous opioids and regional blocks were given. But in patients with opioid related side effects, opioids cannot be given, and regional blocks do not provide sufficient analgesia for prolonged surgeries. So, opioid free analgesic technique can be used in such patients which showed good intraoperative and postoperative analgesic control.

In the study by **He W et al., in 2020**[55] they conducted a randomised prospective trial in 40 patients. Of these, 20 patients received ESPB along with GA and 20 received GA alone. ESPB group received 20ml 0f 0.5% Ropivacaine for block at T3 level and

Flurbiprofen axetil was given for postoperative analgesia. They have observed that ESPB group had decreased pain score at rest and on movement compared to another group. Time for 1st rescue analgesia request was delayed and there was decreased consumption of analgesic for 48 hours in patients undergoing surgery for breast carcinoma.

In a study done by **Seelam S et al., in 2020**[56] 100 patients who underwent mastectomy were included out of which one group received ESPB with 30ml of 0.25% Bupivacaine and other group had received general anaesthesia alone. In both groups VAS scores were compared. Total requirement of analgesia was calculated in first 24 hours. Their study concluded that morphine requirement was less in ESPB group that is 0.12 mg ± 0.59 mg when compared to other group that is 1.70 ± 2.29 mg. Only 3 patients required Inj Morphine in ESPB group, and 22 patients required analgesic in other group.

According to study by **Sharma S et al., in 2020**[57] they have compared efficacy of ESPB against general anaesthesia alone in 60 patients who underwent mastectomy with axillary clearance. Block group received 0.4ml/kg of 0.5% Ropivacaine, while others received general anaesthesia alone. Both groups were compared for total analgesic requirement, time for 1st rescue analgesia request and VAS score. Analgesic requirement was 42% lower in block group and even VAS scores were less. Only 14 patients in block group required analgesic in the 1st hour of surgery whereas 26 patients in other group required analgesia.

In the study done by **Leger M et al., in 2021**[58] efficacy of OFA using magnesium sulfate, clonidine, ketamine and lignocaine was compared to standard anaesthesia protocol in

which opioids were used. They included 140 patients and divided them into 2 groups and assessed quality of recovery in both groups. The primary outcome was assessing QoR – 15 values at 24, 48,72 hours and at 3months after surgery. SOFA trial was done which will assess beneficial effect of OFA on QoR and chronic pain postoperatively.

In the study done by **Jambodkar TC et al., in 2021**[59], efficacy of ultrasound guided ESPB with 0.25% Bupivacaine in thoracotomies was assessed in 30 children aged between 1 – 12years. This study concluded that ultrasound guided ESPB provided effectual analgesia intraoperatively and postoperatively for six hours in almost half of the children and other half required minimal rescue analgesia.

In the study done by **Wang X et al., in 2021**[60] ESPB was given in 2 groups with 30 ml of 0.33 % inj Ropivacaine to one group and 30 ml 0.33% inj Ropivacaine along with 1mcg/kg Dexmedetomidine to the other group and postoperative pain scores were assessed for the first 48hours . It was concluded that dexmedetomidine as an adjunct relieves pain effectively and reduces need for opioids.

According to study done by **Parks et al., in 2021**[61] included 58 patients and investigated Analgesic efficacy of ESPB in breast reconstruction along with tissue expander. They were divided into group P (PCA) and group E (ESPB + PCA). Group E received 30ml of 0.375% Ropivacaine and Inj Fentanyl 10mcg hourly was used for PCA in both groups. This study concluded that requirement of fentanyl was less intraoperatively and postoperatively in E group and there was increased patient satisfaction.

According to the study done by **Sinha C et al in 2021**[62] they have compared deep vs superficial ESPB to evaluate Analgesia and sensory blockade in patients who underwent MRM. They included 44 patients and divided them into two groups where one group was given block deep to Erector spinae muscle that is between the muscle and transverse process and other group received superficial to Erector spinae muscle. Both groups received 20ml of 0.2% Ropivacaine and concluded that injecting drug deep to the Erector spinae muscle provide craniocaudal blockade of lateral and posterior chest wall and injecting drug superficial to the muscle provides inferior analgesia.

In a study done by **Agarwal S et al in 2021**[63] compared efficacy of USG guided PVB versus ESPB for providing analgesia postoperatively in patients undergoing MRM using 20ml of 0.5% Ropivacaine in both groups. This group included 80 female patients aged 18 to 70 years. In this study they have measured time taken for first rescue analgesia request and total doses of rescue analgesia requirement for 24hours postoperatively. They came to conclusion that ESPB can be a better alternative to provide analgesia over PVB in patients undergoing MRM.

In the study done by **Elshafie MA et al in 2022**[64] opioid free anaesthesia with ESPB was compared with conventional balanced anaesthesia with opioids in 40 cirrhotic patients posted for hepatic resection. OFA included drugs such as dexmedetomidine, magnesium sulfate, Lignocaine, and Paracetamol. Bilateral ESPB was given with 20ml of 0.25% bupivacaine along with 0.5mcg per kg of Dexmedetomidine and anaesthesia was provided with Propofol of 1.5 to 2 mg per kg, Rocuronium of 0.9 mg per kg and Lignocaine 60 mg. Magnesium sulfate of 1000mg was given as infusion during induction and Dexmedetomidine

infusion (0.7 mcg per kg per hour) was started after tracheal intubation. For maintenance, Dexmedetomidine infusion was used to obtain hemodynamic stability in one group and other group received conventional balanced anaesthesia. The request for first rescue analgesia was more in ESPB group compared to other group. This study concluded that bilateral ESPB is effective for intraoperative and postoperative analgesia.

MATERIALS AND METHODS:

SOURCE OF DATA:

"This study was conducted on 66 Patients undergoing Modified Radical Mastectomy at R. L. Jalappa Hospital and Research center, Tamaka, Kolar, during the study period January 2021 to May 2022 after obtaining permission from Institutional Ethical Committee."

Study Design: Randomized prospective comparative clinical study.

Sample Size: 2 Groups of 33 subjects each.

Study duration: January 2021 to May 2022.

Sampling Method: Computer generated random sampling.

METHOD OF COLLECTION OF DATA:

1. Patients who underwent MRM under GA were randomly selected.
2. Informed consent was taken prior to surgery.
3. Results were recorded using a Proforma.

INCLUSION CRITERIA

1. Female patients posted for elective MRM surgery.
2. Age: 18 -80years.
3. ASA PS 1 and 2.

EXCLUSION CRITERIA

1. Respiratory and cardiac disorders, hepatic or renal disorders, coagulopathy.
2. Local infection at site of injection.

3. Allergy to any of the study drug (After test dose).
4. Structural abnormalities of spine.
5. Pregnancy or breast feeding.
6. Severe obesity (BMI > 35kg/m2) and psychiatric illness.

SAMPLING PROCEDURE

PAE was done for all patients on day before surgery. Informed consent was taken from the patient. All patients were kept NPO for solids 8 hours and clear fluids 2 hours. All routine investigations were checked. On day of surgery an 18G IV cannula was secured on non- operating hand and IV fluids started. After shifting patient to operation theatre monitors were attached and basal vitals documented. SpO2, 5 – lead ECG, HR and NIBP were monitored throughout the surgery. By computerized randomized sampling, the patients were allotted to one of the study groups (Group M or Group N).

GROUP M – Patients allotted to this group receive Opioid free analgesic mixture (1 mcg/cc Dexmedetomidine + 1 mg/cc Ketamine + 100 mg/cc Magnesium sulfate prepared in a 20 ml Syringe + 12 ml saline) as an infusion started immediately after intubation @ 1ml/10Kg/hr till 30 minutes prior to extubation.

GROUP N – Patients allotted to this group receive 20 ml of NS loaded in a 20 ml syringe as an infusion started @ 1 ml/10Kg/hr till 30 minutes prior to extubation

The principle investigator and the patient were blinded to the group to which patient belongs. Allocation of the group and drug preparation will be done by a resident doctor not involved in intraoperative and postoperative monitoring of the patient.

ESPB was performed in patients of both groups under strict aseptic precautions on the operative side by placing patient in a sitting position. Linear probe of 5-10 Hz was placed in the paramedian longitudinal plane over T4 transverse process. 23 Gauge Quincke needle was used to perform the ultrasound guided block using in-plane approach from cephalad to caudal direction. 25 ml of 0.25% Bupivacaine combined with 8 mg dexamethasone was deposited posterior to the tip of T4 transverse processes under Erector spinae muscle.

Patients were given 100% oxygen for three minutes and premedicated with iv Glycopyrrolate 0.2mg. Induction was done with 2-2.5 mg /kg of propofol following which check ventilation was performed and 0.08-0.1mg /kg of iv vecuronium was given for muscle relaxation. Patient was ventilated for 3 mins with isoflurane 1%, following which intubation was performed with an appropriate size endotracheal tube. Following confirmation of endotracheal tube placement anaesthesia was maintained with O2, N2O, isoflurane and boluses of vecuronium.

All patients were monitored intraoperatively for hemodynamic changes and documented every 15minutes and if any change in blood pressure and heart rate above 20% of the baseline was documented and rescue analgesic given with iv tramadol 1mg/kg or iv Diclofenac 75mg, IV fentanyl(1-2mcg/kg) was supplemented if the patient did not respond to the above analgesics. All patients were kept under observation in the PACU for 6 hours before shifting to ward.

Postoperatively the patient was assessed for pain in the surgical site at rest and on movement using VAS score. Patient was assessed at 0,1,2,4,6,12 and 24 hrs of postoperative period. Any score of more than 3 was considered as presence of pain and rescue analgesic was given depending on the severity of pain with iv tramadol 50 mg with or without iv

Diclofenac 75mg . Patient was assessed for postoperative pain and overall satisfaction regarding post operative analgesia for 24 hrs.

SAMPLE SIZE

Based on study done by Singh et al., to detect difference of 15% reduction in analgesic requirement in a 24hr postoperative period with ȧ - error of 1%, power of 80%, sample size was calculated to be 33 in each group.[50]

FORMULA:

$$n = \frac{2[z_{\dot{\alpha}}+z_{1-ß}]^2\ \sigma^2}{d^2}$$

$$S2P = \frac{S_1^2 + S_2^2}{2}$$

Where,

S_1^2 = Standard deviation in 1st group

S_2^2 = Standard deviation in 2nd group

σ = standard deviation

d =precision

ȧ = Significance level

1-ß = Power

STATISTICAL ANALYSIS

1. Collected data were coded and was entered into an excel database.
2. All quantitative measures were presented as (Mean+/-SD), Confidence interval, qualitative measures like gender, ASA Physical status etc., by proportions and CI.
3. Independent sample t test, chi square test,Fisher's exact test and Mann-Whitney U-test was considered appropriate to interpret results.
4. P value <0.05 was considered statistically significant.

PARAMETERS OBSERVED:

1. Intraoperative hemodynamics (Heart Rate and mean arterial pressure).
2. Intraoperative analgesic requirement.
3. Postoperative VAS score at 0,1^{st},2^{nd},6^{th},12^{th}, and 24^{th} hours from the time of extubation.
4. Postoperative 1^{st} rescue analgesic time.
5. Total analgesic requirement for first 24hrs of post operative period.

RESEARCH QUESTION:

Does opioid free analgesic mixture provide better intraoperative and postoperative analgesic profile in patients undergoing Modified Radical Mastectomy.

RESEARCH HYPOTHESIS:

Opioid free analgesic mixture along with Erector spinae block will provide better intraoperative and postoperative analgesia compared to Erector spinae block alone.

NULL HYPOTHESIS:

Opioid free analgesic mixture along with Erector spinae block will not provide better intraoperative and postoperative analgesia compared to Erector spinae block alone.

RESULTS

This was a Prospective randomized comparative clinical study conducted on 66 patients and Data was collected. All 66 participants have been included in data analysis in the current study.

GROUPING:

In the current study, two groups are named Group M and Group N.

Group M: Will receive- Opioid Free Analgesic Mixture

Group N: Will receive - Normal saline.

TABLE 1: DESCRIPTION OF TWO GROUPS IN THE STUDY (GROUP M AND GROUP N)

Group	Group Description	Number of cases	% of cases
Group 1	Opioid-Free Analgesic Mixture	33	50.0%
Group 2	Normal saline	33	50.0%
Total		**66**	100%

AGE DISTRIBUTION:

TABLE 2: INTERGROUP COMPARISON OF AGE AMONG THE GROUPS

Age (years)	Group M (n=33)		Group N (n=33)		P value
	frequency	%	frequency	%	
31-40	8	24.2%	5	15.2%	0.228
41-50	8	24.2%	11	33.3%	
51-60	7	21.2%	13	39.4%	
61-70	6	18.2%	2	6.1%	
71-80	4	12.1%	2	6.1%	

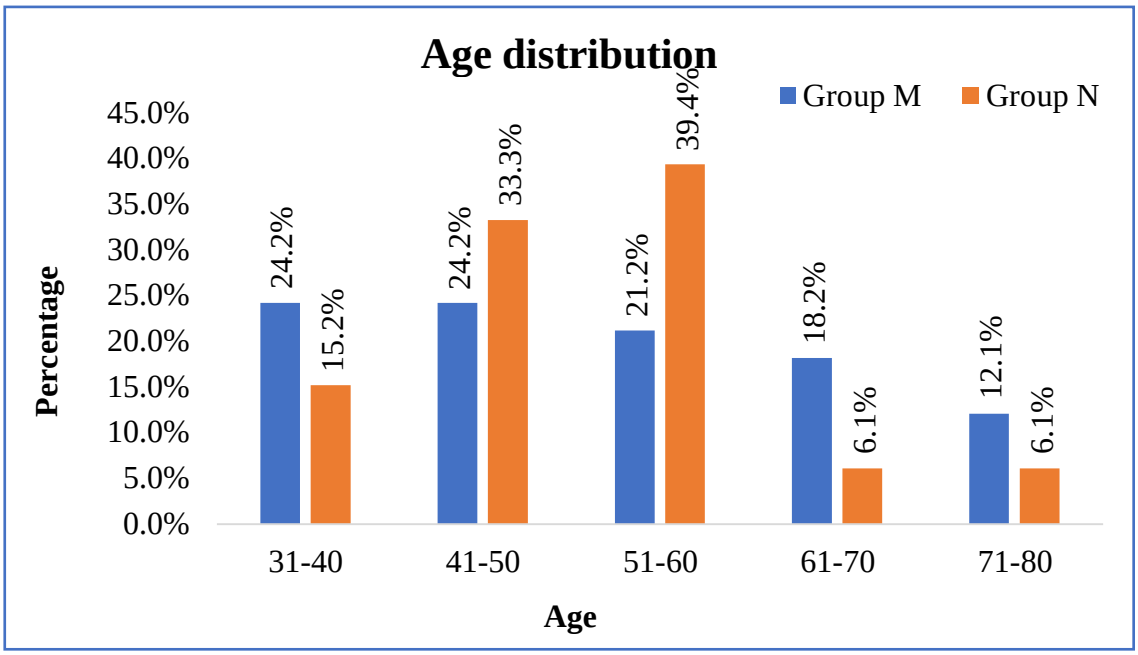

FIGURE 9: COMPARISON OF MEAN AGE AMONG THE GROUPS

The current study sample size was 66, and data has been collected. The age group ranges from 30 to 80 years.

In group M, most participants lie in the age group of 31-40 years (24.2%), 41-50 years (24.2%) and the least in 71-80 years (12.1%).

In group N, most participants lie in the age group of 51-60 years (39.4%) and the least in 71-80 years (6.1%).

INTERGROUP COMPARISON OF BMI:

TABLE 3: INTERGROUP COMPARISON OF MEAN BMI AMONG THE GROUPS

	group M (n=33)		group N (n=33)		P value
	Mean	**SD**	**Mean**	**SD**	
BMI	22.958	4.1188	24.015	3.3513	0.257

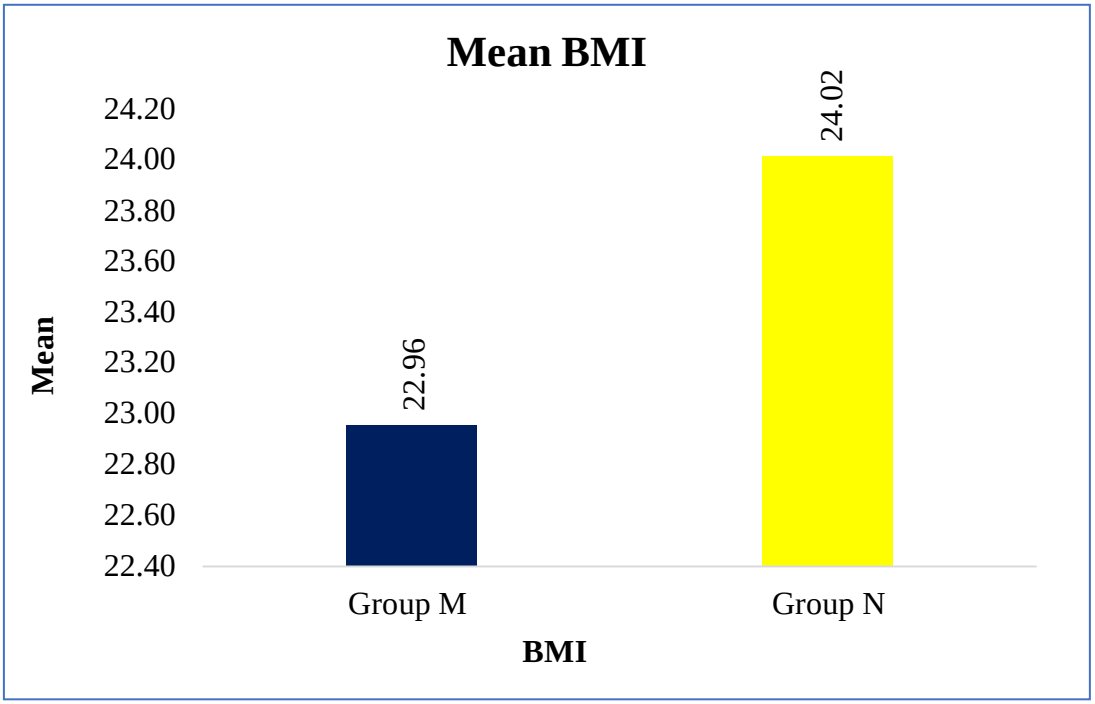

FIGURE NO 10: INTERGROUP COMPARISON OF MEAN BMI AMONG THE GROUPS

In group M, BMI ranges from 14 to 32, with a mean of 22.95±4.11. Similarly, in group N, BMI ranges from 16.7 to 30.6, with a mean of 24.015 ±3.3513.

SURGERY:

TABLE 4: INTERGROUP COMPARISON OF SURGERY AMONG THE GROUPS

Surgery	group M (n=33)		group N (n=33)		p value
	frequency	%	frequency	%	
Modified radical mastectomy	18	54.5%	19	57.5%	0.8
Breast conservative surgery + axillary sampling + ld flap	15	45.5%	14	42.5%	

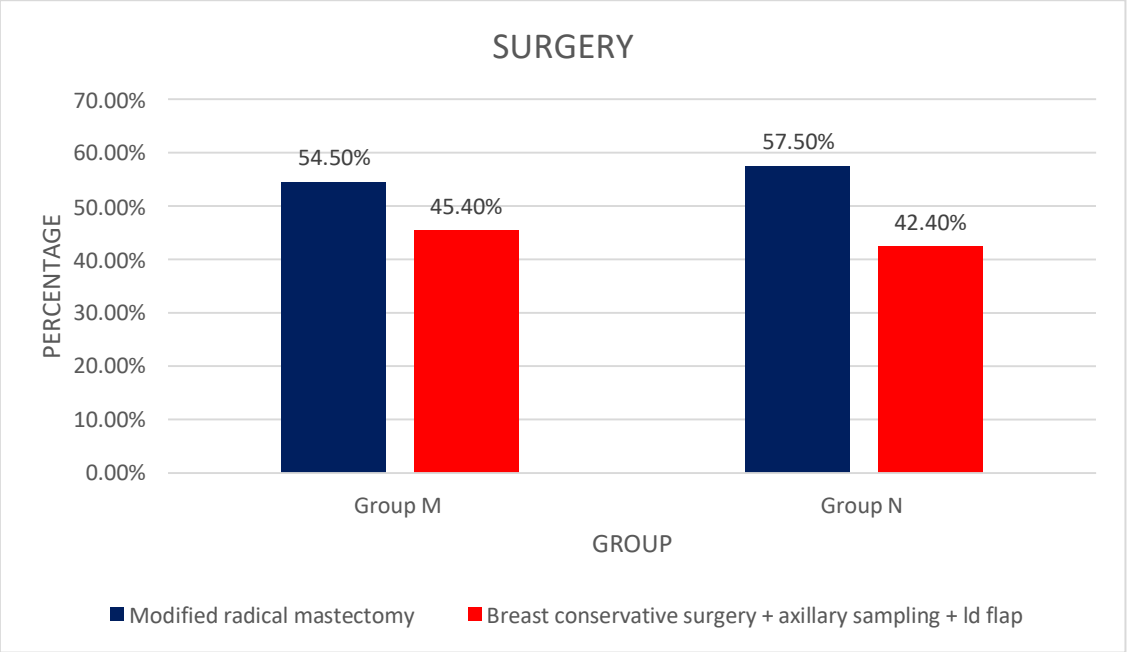

FIGURE 11: INTERGROUP COMPARISON OF SURGERY AMONG THE GROUPS

In group M, most participants underwent Modified radical mastectomy (54.5%), and the rest had undergone Breast conservative surgery + axillary sampling + Ld flap (45.4%).

In group N, most participants underwent Modified radical mastectomy (57.5%), and the rest had undergone Breast conservative surgery + axillary sampling + Ld flap (42.4%).

INTERGROUP COMPARISON OF HEART RATE:

TABLE 5: INTERGROUP COMPARISON OF MEAN HEART RATE

Heart Rate	group M (n=33)		group N (n=33)		*Mean Difference*	*t value*	*P value*
	Mean	**SD**	**Mean**	**SD**			
HR 0min	82.52	13.60	86.94	8.14	-4.424	-1.604	0.114
HR 5	81.91	12.89	87.18	11.84	-5.273	-1.731	0.088
HR 10	84.42	11.87	86.85	12.03	-2.424	-.824	0.413
HR 15	82.79	12.10	86.52	11.77	-3.727	-1.268	0.209
HR 30	82.73	10.55	85.09	11.77	-2.364	-.859	0.394
HR 45	80.15	11.19	85.91	12.37	-5.758	-1.983	0.052
HR 60	80.55	11.15	86.97	9.80	-6.424	-2.486	0.016*
HR 75	77.94	10.32	83.24	11.11	-5.303	-2.008	0.049*
HR 90	76.30	9.69	81.64	11.43	-5.333	-2.044	0.045*
HR 105	75.06	9.78	82.42	11.23	-7.364	-2.841	0.006*
HR 120	75.36	8.36	81.24	10.10	-5.879	-2.576	0.012*
HR 135	73.67	9.84	80.53	11.12	-6.865	-2.638	0.010*
HR 150	73.09	9.48	80.90	11.55	-7.809	-2.936	0.005*
HR 165	71.48	8.66	82.61	10.73	-11.123	-4.400	<0.001*
HR 180	71.21	8.16	81.64	9.71	-10.436	-4.399	<0.001*
HR 195	69.21	8.37	81.36	10.72	-12.155	-4.306	<0.001*
HR 210	69.25	7.60	79.41	11.29	-10.162	-3.254	0.003*
HR 225	70.00	8.91	77.54	10.24	-7.538	-2.184	0.037*
HR 240	68.42	9.87	77.86	14.45	-9.440	-1.698	0.108
HR 255	69.56	9.49	66.00	9.17	3.556	.566	0.584
HR 270	69.17	9.02	68.00	.00	1.167	.174	0.868
HR 285	72.40	8.29	67.00	.	5.400	.594	0.584
HR 300	74.50	9.19	68.00	.	6.500	.577	0.667
HR 315	77.00	14.14	.	.			
HR 330	76.00	.	.	.			
HR 345	78.00	.	.	.			

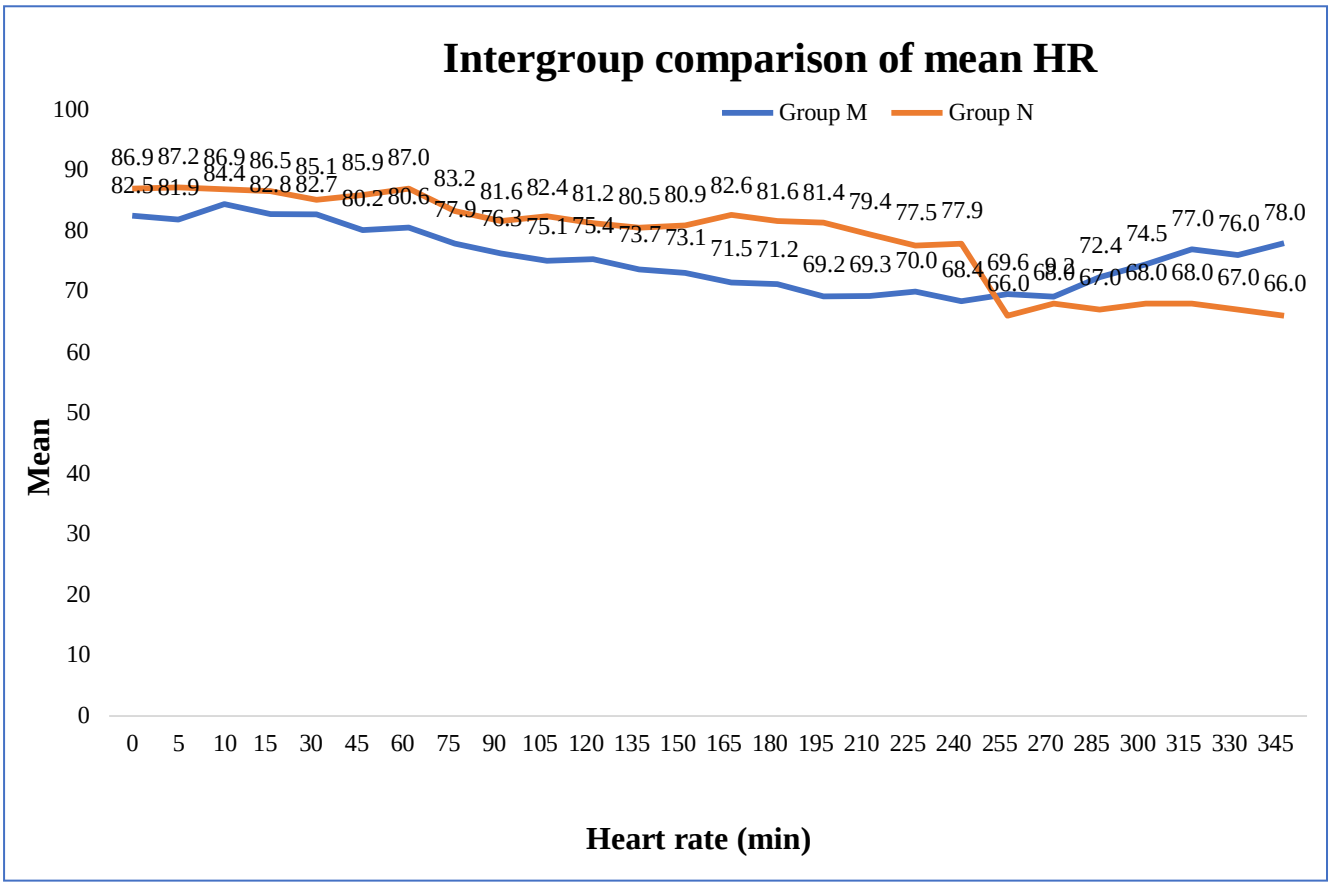

FIGURE 12: INTERGROUP COMPARISON OF HEART RATE IN BOTH GROUPS

The two study groups have a significant difference in mean heart rates at each interval. Heart Rate at 0 min in both the groups has a mean difference of 4.424 with a t value of 1.604 and a p value of 0.114, which is not statistically significant.

Heart rate at 60 min in both the groups has a mean difference of 6.424 with a p value of 0.016, which was statistically significant

Heart Rate at 105 min in both the groups has a mean difference of 7.364 with a t value of 2.841 and a p value of 0.006, which shows statistical significance.

Heart Rate at 225 min in both the groups has a mean difference of 7.538 with a t value of 2.184 and a p value of 0.037, which shows statistically significant.

INTERGROUP COMPARISON OF MAP:

TABLE 6: INTERGROUP COMPARISON OF MEAN MAP

MAP (in Minutes)	Group M (n=33)		Group N (n=33)		*Mean Difference*	*t value*	*P value*
	Mean	**SD**	**Mean**	**SD**			
0	86.45	11.82	94.48	10.74	-8.030	-2.888	0.005*
5	86.18	11.38	96.33	10.86	-10.152	-3.707	<0.001*
10	83.33	10.01	96.12	9.43	-12.788	-5.341	<0.001*
15	83.45	8.81	97.39	12.92	-13.939	-5.120	<0.001*
30	82.82	9.97	93.48	9.87	-10.667	-4.367	<0.001*
45	84.61	11.37	94.79	7.36	-10.182	-4.319	<0.001*
60	85.21	11.87	94.09	10.25	-8.879	-3.252	0.002*
75	85.15	10.26	94.67	8.52	-9.515	-4.100	<0.001*
90	85.85	10.95	93.55	9.60	-7.697	-3.037	0.003*
105	83.61	10.30	92.12	11.66	-8.515	-3.145	0.003*
120	83.64	11.06	94.18	9.41	-10.545	-4.172	<0.001*
135	82.82	10.61	94.06	9.21	-11.244	-4.557	<0.001*
150	82.38	9.97	95.52	9.42	-13.141	-5.373	<0.001*
165	83.13	8.44	95.43	10.71	-12.300	-4.924	<0.001*
180	82.00	9.32	93.82	11.60	-11.821	-4.249	<0.001*
195	82.25	10.33	92.14	10.50	-9.886	-3.217	0.002*
210	81.65	8.90	91.24	5.66	-9.585	-3.827	0.001*
225	83.78	7.80	91.46	8.19	-7.684	-2.651	0.013*
240	84.75	11.03	98.86	8.90	-14.107	-2.872	0.011*
255	85.50	9.90	101.00	10.00	-15.500	-2.308	0.046*
270	84.33	11.04	101.50	4.95	-17.167	-2.046	0.087
285	80.80	10.69	103.00	.	-22.200	-1.896	0.131
300	80.50	4.95	105.00	.	-24.500	-4.041	0.154
315	85.00	21.21					
330	65.00	.					
345	70.00	.					

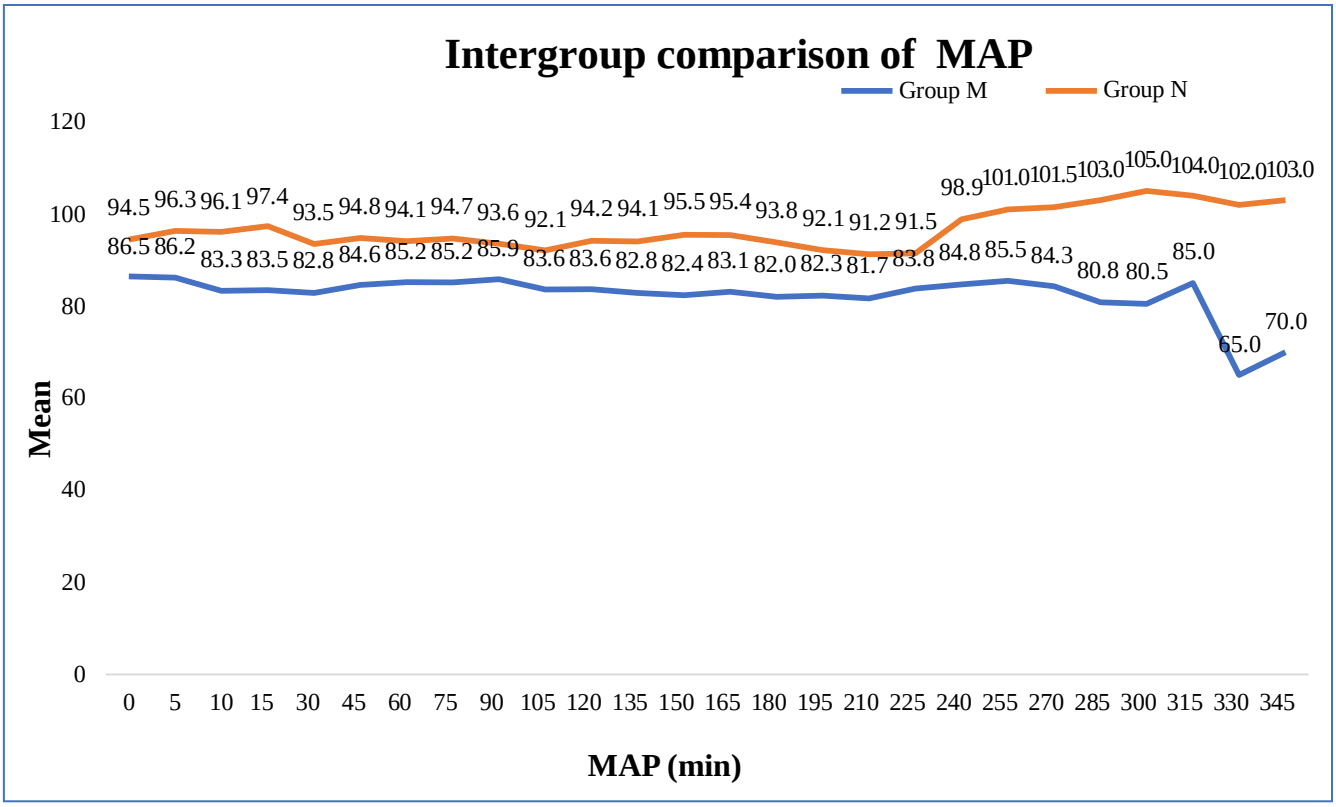

FIGURE 13: INTERGROUP COMPARISON OF MAP IN BOTH GROUPS

The two study groups have shown significant mean MAP differences at each interval.

MAP at 0 min in group M was 86.45±11.8 mm Hg, and in group N, it was 94.48±10.74 mm Hg with a mean difference of 8.030, a t value of 2.89 and a p value of 0.005, which is statistically significant.

MAP at 150 min in group M was 82.38 ± 9.97mm Hg, and in group N, it was 95.52 ± 9.42 mm Hg with a mean difference of 13.141, a t value of 5.373 and a p value of < 0.001, which showed statistical significance.

MAP at 255 min in group M was 85.50±9.90 mm Hg, and in group N, it was 101.10±10.00mm Hg with a mean difference of 15.50 and p value of 0.046, which was significant statistically.

INTERGROUP COMPARISON OF MEAN VAS SCORE AT REST:

VAS at rest (in hours)	Group M (n=33)		Group N (n=33)		*Mean Difference*	*p value*
	Mean	**SD**	**Mean**	**SD**		
0	1.33	1.53	2.15	1.18	-.818	0.018*
1	1.39	1.50	2.42	1.00	-1.030	0.002*
2	1.58	1.28	2.79	1.11	-1.212	<0.001*
4	2.48	1.44	2.94	1.12	-.455	0.156
6	2.82	1.36	3.15	.97	-.333	0.256
12	2.94	1.00	2.76	.97	.182	0.456
24	3.09	1.16	2.97	1.05	.121	0.656
Values are mean and SD; P value by Man-Whitney-U-test. P value <0.05 is considered to be statistically significant						

TABLE 7: INTERGROUP COMPARISON OF VAS SCORE AT REST

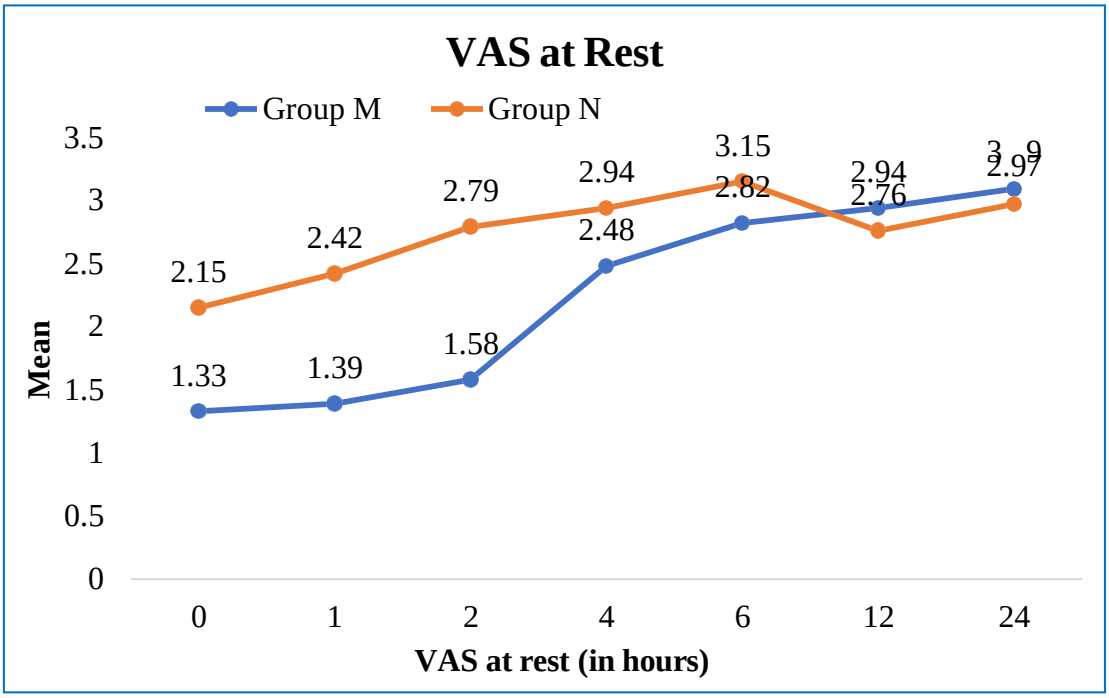

FIGURE 14: INTERGROUP COMPARISON OF MEAN VAS SCORE AT REST

The mean resting VAS score at 0 hours in group M is 1.33±1.53, and in group N is 2.15±1.18, with a mean difference of 0.818 and a p value of 0.018, which shows statistical significance.

Similarly, at the 24th hour, the mean VAS score in group M is 3.09±1.16, and in the group, N is 2.97±1.05 with a mean difference of 0.121 and a p value of 0.656, which is not statistically significant.

INTERGROUP COMPARISON OF MEAN VAS AT ABDUCTION:

TABLE 8: INTERGROUP COMPARISON OF VAS SCORE AT ABDUCTION

VAS at abduction (in hours)	**Group M (n=33)**		**Group N (n=33)**		***Mean Difference***	***p value***
	Mean	**SD**	**Mean**	**SD**		
0	2.00	1.75	2.82	1.33	-2.136	0.036*
1	2.03	1.70	3.27	1.01	-3.604	0.001*
2	2.27	1.26	3.52	1.03	-4.385	<0.001 *
4	3.30	1.61	3.79	1.14	-1.412	0.163
6	3.58	1.56	3.88	1.14	-.901	0.371
12	3.76	1.17	3.73	1.07	.110	0.913
24	3.85	1.35	3.73	1.15	.392	0.696

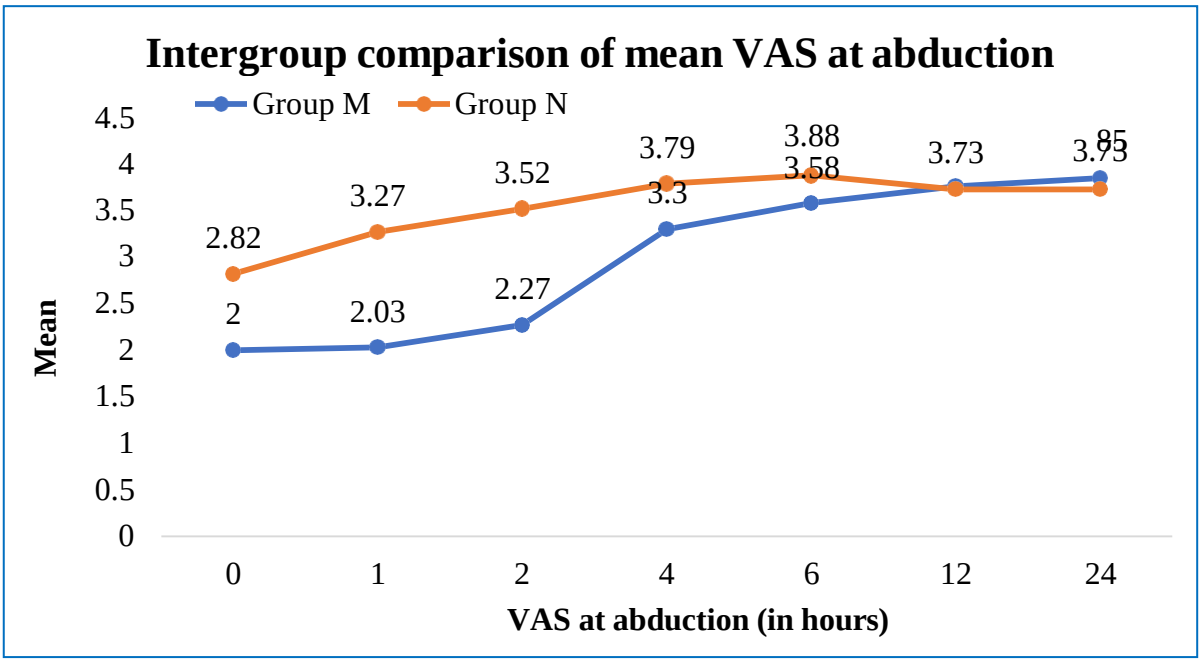

FIGURE 15: INTERGROUP COMPARISON OF MEAN VAS SCORE AT ABDUCTION

The mean VAS score on abduction at 0 hours is 2.0 ± 1.75 in group M, and 2.82 ± 1.33 in group M with a mean difference of 2.136 and a p value of 0.036, which showed statistical significance.

Similarly, at the 24th hour, the mean VAS score is 3.85±1.35 in group M and 3.73±1.15 in group N with a mean difference of 0.392 and a p value of 0.696, which is not statistically significant.

INTERGROUP COMPARISON OF TIME FOR RESCUE ANALGESIA:

TABLE 9: INTERGROUP COMPARISON OF MEAN TIME FOR RESCUE ANALGESIA

Time for Rescue analgesia	Group M (n=33)		Group N (n=33)		*Mean Difference*	*p value*
	Mean	**SD**	**Mean**	**SD**		
	726.67	390.99	468.18	278.79	3.092	0.003*

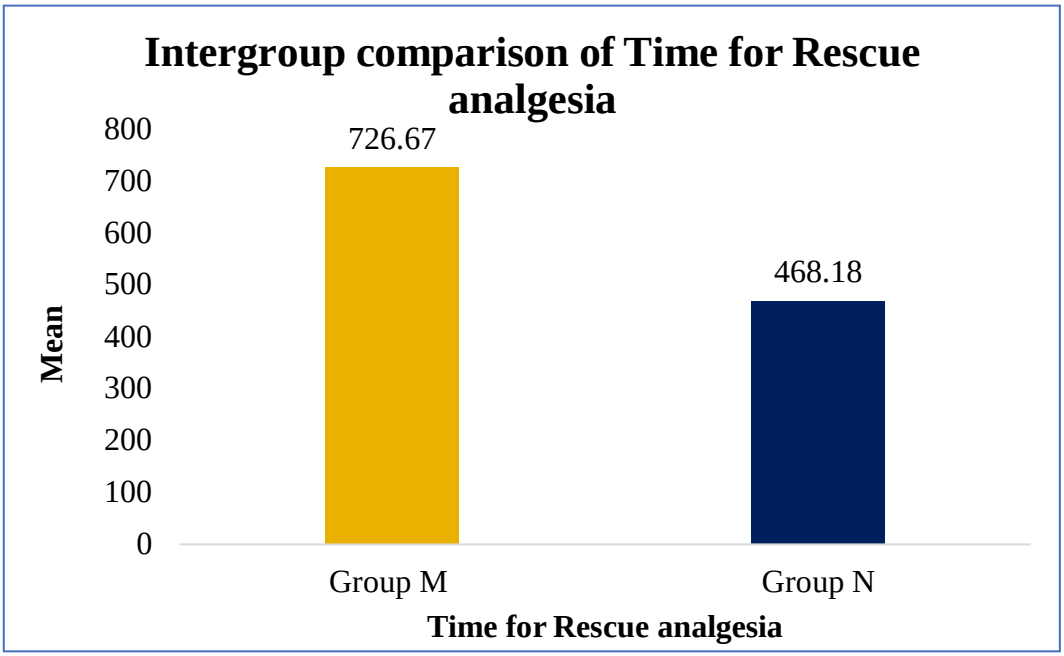

FIGURE 16: INTERGROUP COMPARISON OF MEAN TIME FOR RESCUE ANALGESIA

In the current study, the time for the requirement of 1st rescue analgesia in group M was 726.67±390.99 minutes. In group N, it was 468.18±278.79 with a mean difference of 3.092 minutes and a p value of 0.003, which showed statistical significance. In group M, the time for requirement of 1st rescue analgesia is more compared to group N.

TOTAL INJECTIONS:

TABLE 10: INTERGROUP COMPARISON OF INJ. DICLOFENAC REQUIREMENT

INJ DICLOFENAC MG 24hrs	Group M		Group N		P value
	Frequency	%	Frequency	%	
Not given	8	24.2%	5	15.2%	0.168
50 mg	0	0.0%	1	3.0%	
75 mg	19	57.6%	14	42.4%	
150 mg	6	18.2%	10	30.3%	
225 mg	0	0.0%	3	9.1%	

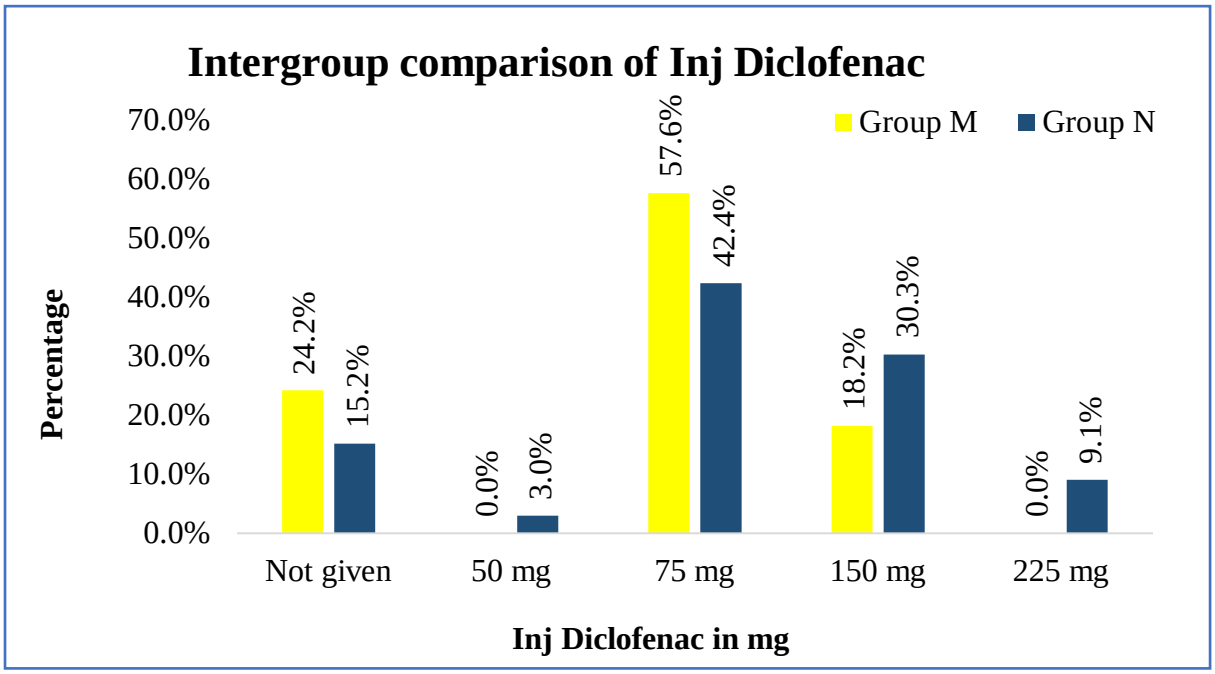

FIGURE 17: INTERGROUP COMPARISON OF INJ. DICLOFENAC REQUIREMENT

In group M, 57.6% (18) required 75 mg of diclofenac, 18.2% (6) of them required 150 mg and 24.2%(8) did not require. In group N, 42.4%(14) required 75mg of diclofenac, followed by 150 mg in 30.3%(10) and 225 mg in 9.1%(3) and not given in 15.2%(5). This is not statistically significant.

TABLE 11: INTERGROUP COMPARISON OF INJ. TRAMADOL REQUIREMENT

Inj Tramadol MG 24hrs	Group M		Group N		P Value
	Frequency	%	Frequency	%	
Not given	12	36.4%	3	9.1%	0.012*
25 mg	0	0.0%	1	3.0%	
50 mg	17	51.5%	17	51.5%	
100 mg	3	9.1%	12	36.4%	
150 mg	1	3.0%	0	0.0%	

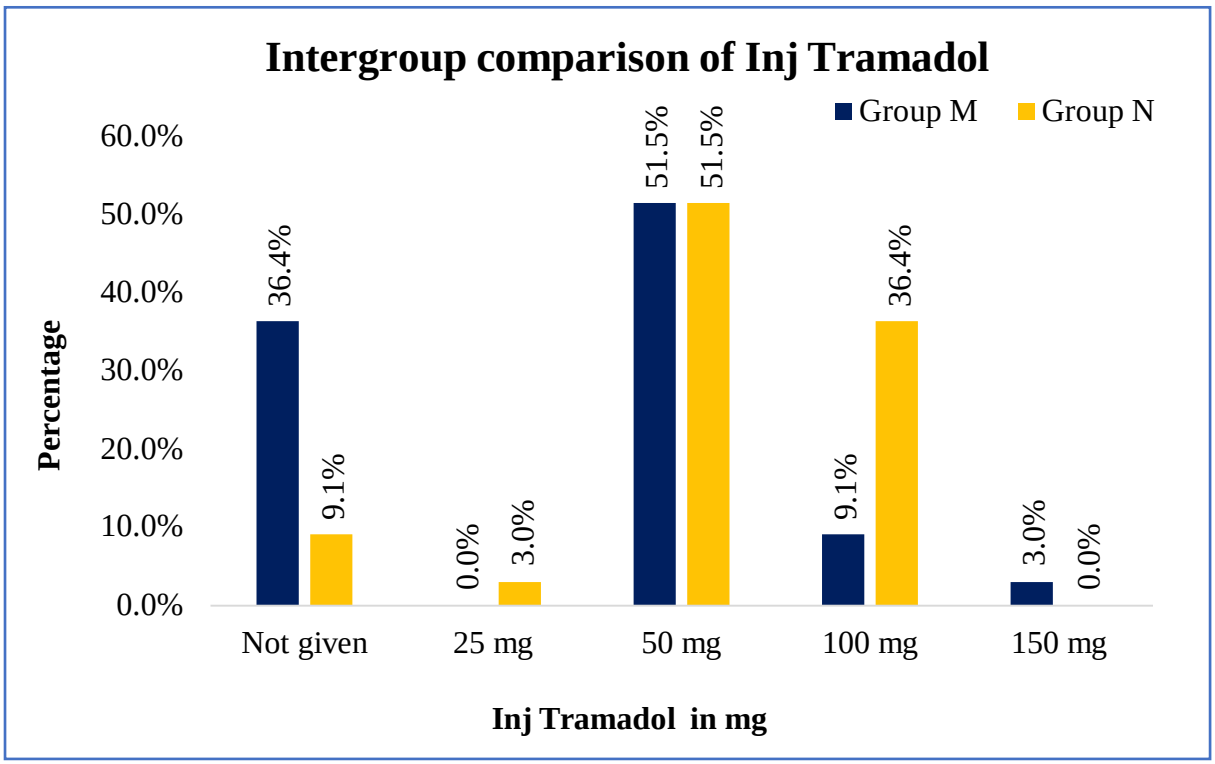

FIGURE 18: INTERGROUP COMPARISON OF INJ. TRAMADOL REQUIREMENT

In group M, 51.5%(17) were given 50 mg of tramadol, followed by 100 mg in 9.1%(3) and 150 mg in 3%(1) and not given in 36.4%(12). In group N, 51.5%(17) were given 50 mg of tramadol, followed by 100 mg in 36.4%(12) and not given in 9.1%(3).

PATIENT SATISFACTION SCORE:

TABLE 12: INTERGROUP COMPARISON OF PATIENT SATISFACTION SCORE

PATIENT SATISFACTION SCORE	Group M		Group N		p value
	Frequency	%	Frequency	%	
Good	11	33.3%	15	45.5%	0.004*
Satisfactory	3	9.1%	12	36.4%	
Poor	1	3.0%	1	3.0%	
Very Good	18	54.5%	5	15.2%	

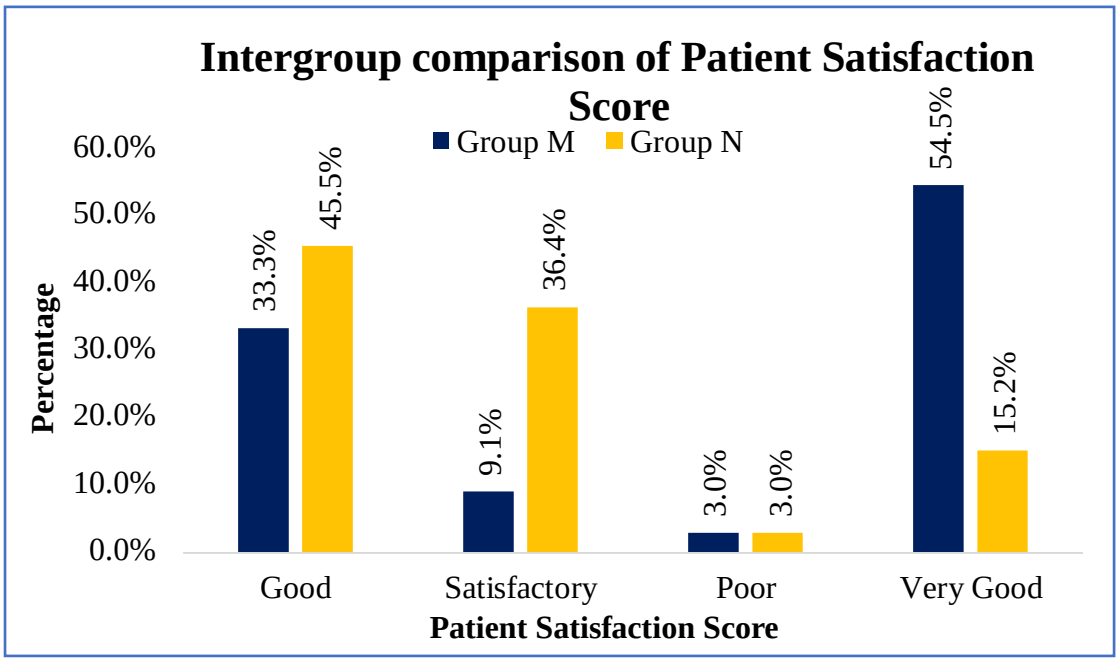

FIGURE 19: INTERGROUP COMPARISON OF PATIENT SATISFACTION SCORE

In group M, most of the patients had a satisfaction score of very good (54.5%), followed by good (33.3%) and satisfactory (9.1%). 3% of the participants expressed a satisfaction score of poor.

Similarly, in group N, most of the patients had a satisfaction score of good (45.5%), followed by satisfactory (36.4%), very good (15.2%), and 3% of them mentioned poor satisfaction.

SURGEON SATISFACTION SCORE:

TABLE 13: INTERGROUP COMPARISON OF SURGEON SATISFACTION SCORE

SURGEON SATISFACTION SCORE	Group M		Group N		p value
	Frequency	%	Frequency	%	
Very good	17	51.5%	7	21.2%	
Good	14	42.4%	16	48.5%	0.008*
Satisfactory	2	6.1%	10	30.3%	
Poor	0	0.0%	0	0.0%	

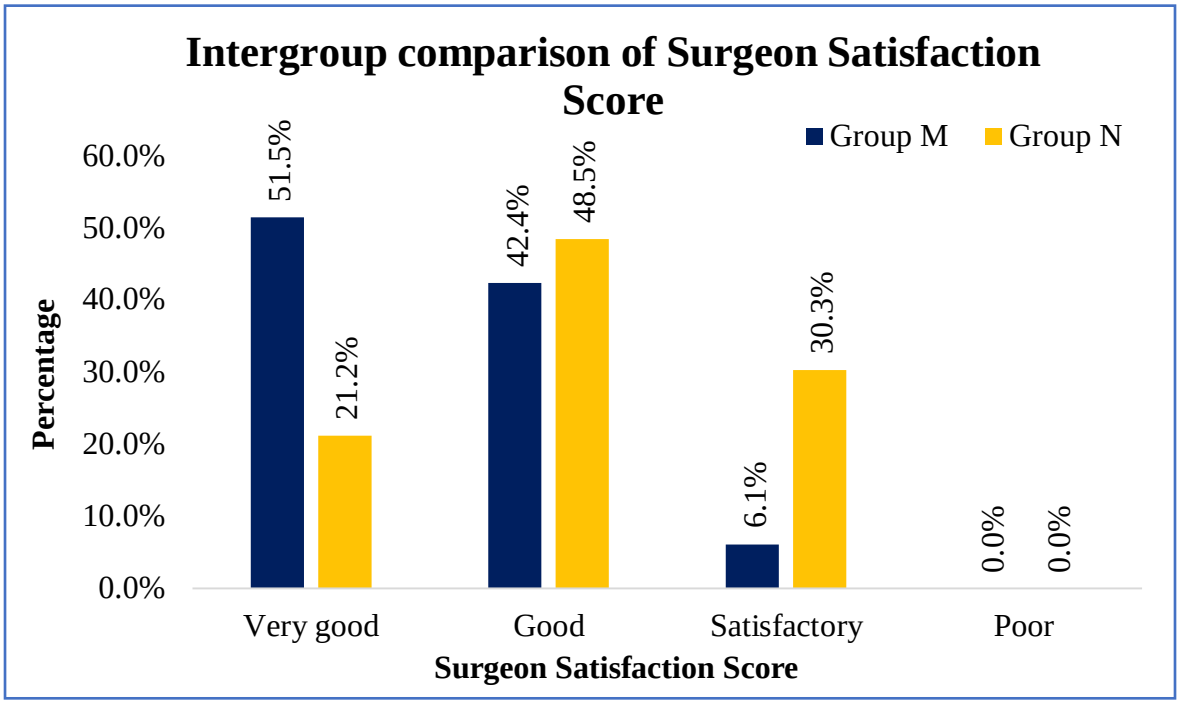

FIGURE 20: INTERGROUP COMPARISON OF SURGEON SATISFACTION SCORE

In group M, the majority of the surgeons have a satisfaction score of very good (51.5%), followed by good (42.2%) and satisfactory (6.1%).

Similarly, in group N, most of the surgeons had a satisfaction score of good (48.5%), followed by satisfactory (30.3%) and very good (21.2%).

INTERGROUP COMPARISON OF DICLOFENAC REQUIREMENT:

TABLE 14: INTERGROUP COMPARISON OF DICLOFENAC REQUIREMENT:

Inj. Diclofenac mg 24 hrs	**Group M (n=33)**		**Group N (n=33)**		***Mean Difference***	***p value***
	Mean	**SD**	**Mean**	**SD**		
	93.00	32.692	116.96	52.728	-23.964	0.055

In group M Mean requirement of Inj Diclofenac in 24 hrs was 93 ± 32.692mg and in Group N, it was 116.96 ± 52.728mg. This is not statistically significant.

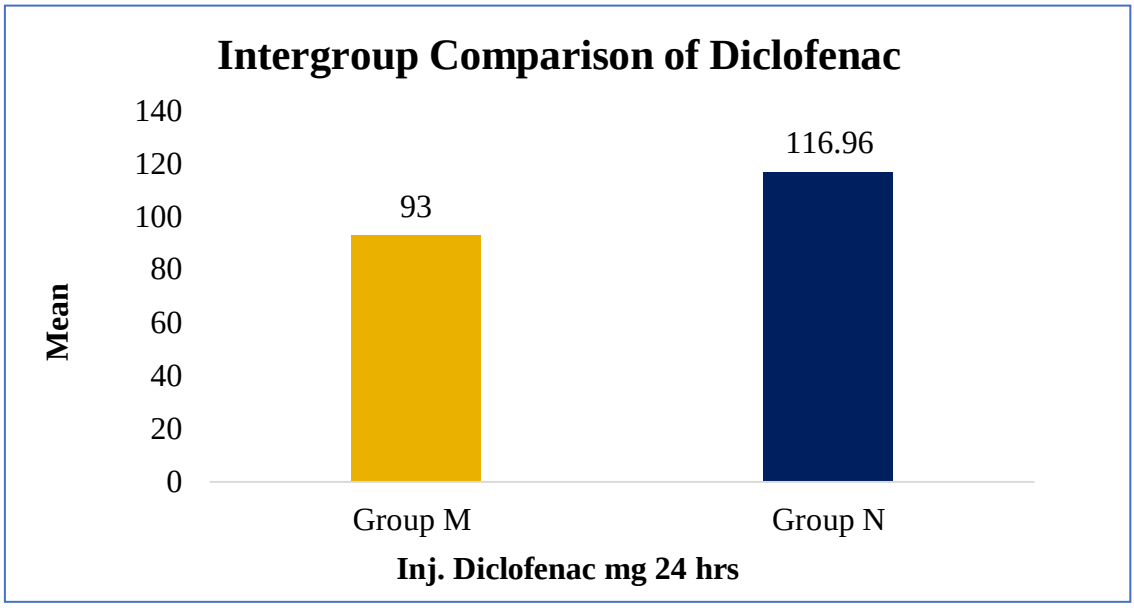

FIGURE 21: INTERGROUP COMPARISON OF DICLOFENAC

INTERGROUP COMPARISON OF TRAMADOL REQUIREMENT:

TABLE 15: INTERGROUP COMPARISON OF TRAMADOL REQUIREMENT

INJ TRAMADOL MG 24 hrs	Group M (n=33)		Group N (n=33)		*Mean Difference*	*p value*
	Mean	**SD**	**Mean**	**SD**		
	61.90	26.948	69.17	26.000	-7.262	0.338

In group M, Mean Tramadol requirement in 24 hrs was 61.9 ± 26.948mg and in Group N was 69.17 ± 26.000mg. This is not statistically significant.

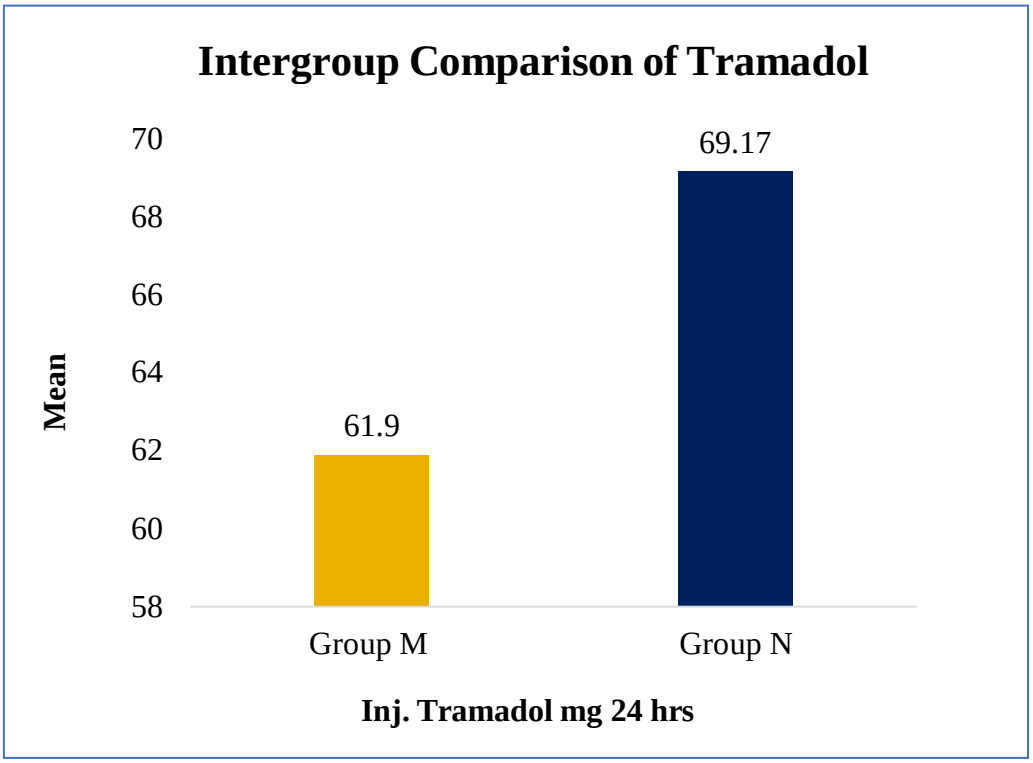

FIGURE 22: INTERGROUP COMPARISON OF TRAMADOL

DISCUSSION

Patients undergoing breast cancer surgery experience severe pain, which affects quality of life. To reduce postoperative pain, various techniques can be used which are multimodal analgesia, opioids and regional anaesthesia. Opioids when used cause adverse effects such as constipation, sedation, vomiting, nausea, and respiratory depression. Regional anaesthetic techniques such as Intercostal nerve block, Thoracic epidural, Pectoral nerve block, Interpleural block, PVB, and new techniques such as ESPB and Transversus thoracic plane block are used in providing intraoperative and post-operative analgesia.[11]

With the use of ultrasound, regional anaesthetic techniques have become more popular because of better visualization of anatomical structures which helps in administration of local anaesthetics under vision and reduces risk of block failure.

Much research has been done to improve analgesia in patients receiving modified radical mastectomy.[65] General anaesthesia alone cannot provide postoperative analgesia so regional anaesthesia has gained popularity in recent years which reduces postoperative pain and improves patient comfort. In our study we have used Ketamine, Magnesium sulfate and Dexmedetomidine mixture to provide OFA.

We have preferred ESPB over other regional anaesthetic techniques in our study because of its ease of administration and it is associated with less complications. OFA was preferred because opioids are related with postoperative adverse effects.

This study was Randomized prospective comparative clinical study done from period of January 2021 to May 2022. 66 patients aged 18 years to 80 years with ASA PS 1 and 2 undergoing Modified Radical Mastectomy and Breast Conservative Surgery for breast carcinoma were included. These patients are bifurcated into 2 groups.

GROUP M – General anaesthesia + ESPB + Opioid Free Analgesic mixture infusion

GROUP N – General anaesthesia + ESPB + Normal saline infusion

ESPB was given with 25ml of 0.25% Bupivacaine with 8mg of dexamethasone. Opioid free analgesic mixture was prepared with 1mcg/cc Dexmedetomidine + 1 mg/cc Ketamine + 100 mg/cc Magnesium sulphate in a 20 ml Syringe with 12 ml NS and started as an infusion immediately after intubation @ 1ml/10Kg/hr till 30 minutes prior to extubation. 20ml of NS infusion is received by another group. As per the protocol mentioned in our study, general anaesthesia was given to all patients.

DEMOGRAPHIC DATA:

The demographic parameters of age and BMI were compared between groups and there was no statistical significance between these parameters.

TYPE OF SURGERY:

In group M, 54.5% of patients has undergone Modified radical mastectomy and 45.5% of patients has undergone Breast conservative surgery + axillary sampling + Ld flap. In group N, 57.5% of patients has undergone Modified radical mastectomy and 42.5% has undergone Breast conservative surgery + axillary sampling + Ld flap.

HAEMODYNAMIC PARAMETERS:

Both groups have shown different mean heart rates at each interval. The baseline Heart Rate for both groups at 0 min has a mean difference of 4.424 with p value of 0.114, and statistically which is not significant.

Heart rate at 60 min in both the groups has a mean difference of 6.424 with a p value of 0.016, which was significant statistically. Heart Rate at 105 min in both the groups has a mean difference of 7.364 with p value of 0.006, which was significant statistically. Heart

Rate at 225 min in both the groups has a mean difference of 2.184 with a p value of 0.037, which was significant statistically.

Heart rate didnot show a statistical difference between the 2 groups till 45 minutes after giving block but there was significant statistical difference from 60 minutes till 225 minutes. But the heart rate in both the groups from 60 min onwards was within the normal physiological range so clinically not significant.

In group M, mean MAP at 0 min was 86.45±11.82, and in group N, it was 94.48±10.74 with a mean difference of 8.030 and p value of 0.005, statistically which is significant. In group M mean MAP at 150 min was 82.38±9.97, and in group N, it was 95.52±9.42 with a mean difference of 13.141 and p value of <0.001, statistically which is significant. In group M mean MAP at 255 min was 85.50±9.90, and in group N, it was 101.10±10.00 with a mean difference of 15.50 and p value of 0.046, statistically which is significant.

Mean arterial pressure showed statistical difference till 255 minutes in both groups. Patients in group M showed a lower mean arterial pressure compared to group N up to 255 minutes which suggests that ESPB along with opioid free analgesic mixture, provides better blood pressure intraoperatively. Mean arterial pressure in group N was also maintained within the normal range.

Overall, there was not much difference in mean arterial pressures and heart rate clinically in the intraoperative period though there was significant difference statistically. In both groups MAP and HR were within normal physiological range. Patients in group M who received OFA showed mean arterial pressure and heart rate in lower range of normal values and patients in group N showed slightly higher values.

VAS SCORE AT REST AND ON ABDUCTION:

VAS Scores were assessed postoperatively at 0,1 ,2, 4, 6, 12 and 24 hours. The mean VAS score during rest at 0 hours in group M was 1.33±1.53, and in the group N is 2.15±1.18, with a p value of 0.018, which was statistically significant but clinically not significant as scores were less than 3 in both groups. VAS scores showed significant statistical differences at 1st and 2nd hour which was not clinically significant. Similarly, at the 24th hour, the mean VAS score in group M is 3.09±1.1, and in the group, N is 2.9±1.0 with a p value of 0.5, which is statistically not significant. Overall, VAS scores showed no clinical difference in pain except at 6th hour in group N and 24th hour in group M which showed mild pain.

Pain on movement showed mean VAS score of 2.00±1.75 in group M and 2.82±1.33 in group N at 0 hours with p value of 0.036, which was statistically significant but clinically not significant as VAS scores in both the groups was less than 3. At 1st and 2nd hours VAS scores showed significance statistically and clinically as group N had moderate pain with a score of more than 3 at both hours. From 4th to 24th hours both groups had moderate pain as VAS score was more than 3 and it was not statistically significant.

In both groups patients showed VAS score < 3 till 2 hours postoperatively both at rest and on movement. After 2 hrs, VAS scores were less than 3 at all time intervals except at 6th hour in group N and 24th hour in group M where the VAS score was just above 3. Few patients underwent axillary dissection and LD flap in which a Lateral cutaneous branch of T2 innervates the axilla that forms an Intercostobrachial nerve. The Thoracodorsal nerve which arises from C6 to C8 innervates LD muscle which helps in abduction of shoulder. ESPB was given at T4 in our study which would not have blocked thoracodorsal nerve with the volume of drug used in our study. This might be the reason for pain on movement.

Overall MAP and Heart rate showed statistical significance at almost all-time intervals but there was no significance clinically in both groups. Postoperative pain was significantly less in both groups at rest. Pain on movement was also less till 2 hrs. After 2 hrs pain was moderate in both the groups.

Kim W J et al.[66] conducted a study and assessed efficacy of ESPB along with opioid sparing analgesia in patients undergoing BCS. 20ml of 0.375% Ropivacaine was given for block at T4 level. Median pain scores were noted at 2,4,12,24 and 48hours and pain was assessed at breast and axilla region. Median pain scores were less in ESPB group compared to control group who did not receive block but pain at axilla was more at all time intervals. This study stated that axilla has T2 innervation which will be spared when block is given at T4 but in our study we have used 25ml of 0.25% Bupivacaine along with 8mg dexamethasone which has shown reduced pain scores that is VAS score was less than 4 at all time intervals both on rest and abduction even on patients who underwent breast conservative surgery + axillary sampling + LD flap reconstruction.

PATIENT SATISFACTION SCORE:

In group M, most of the patients had satisfaction score of very good that is 54.5%, followed by good in 33.3% and satisfactory in 9.1% of patients. 3% of the participants expressed a satisfaction score of poor. Similarly, in group N, most of the patients had a satisfaction score of good that is 45.5%, followed by satisfactory in 36.4%, very good in 15.2% and 3.0% of them mentioned poor satisfaction. This was statistically significant.

SURGEON SATISFACTION SCORE:

In group M, most of the surgeons have a satisfaction score of very good, that is 54.5%, followed by good in 33.3% and satisfactory in 9.1%. Similarly, in group N, most of

the surgeons had a satisfaction score of good that is 48.5%, followed by very good in 21.2%% and satisfactory in 30.3% which was statistically significant.

This shows both surgeons and patients had better satisfaction in group M. Intraoperative hemodynamic stability also decreases blood loss in the surgical field which in turn reduces the time taken for surgery.

TIME FOR FIRST RESCUE ANALGESIA:

In group M the time for rescue analgesia is 726.67±390.99 minutes and In group N, it was 468±278.79 minutes with a p value of 0.003, which statistically showed significance. Out of which 1 patient from group N and 4 patients from group M did not require analgesia for more than 24 hours.

For first rescue analgesia, the mean time was 20.40 ± 4.98 hours in a study done by **Elsabeeny W Y et al.,**[67] in which patients received 25ml of 0.25% Bupivacaine and Inj Morphine was given as rescue analgesic.

Mean tine for first rescue analgesia requirement was 468.2 ± 80 minutes in study conducted by **Elfadel I A et al.,**[68] in which one group received ESPB with 0.25% Bupivacaine along with general anaesthesia and other group had received general anaesthesia with intravenous analgesia.

The mean time for first rescue analgesia requirement was 871.30± 589.51 minutes in ESPB group and 460.00± 507.40 minutes in PECS group in study conducted by **Majumdar U et al.,**[69] in which a comparison was made between ESPB and PECS block.

In study conducted by **Maustafa et al.,**[53] Time for first rescue analgesia request time was 11.22±1.95 hrs in PVB group and 11.04±1.9 hours in ESPB group

Time for first rescue analgesia requirement was 48 ± 38.75 hours in ESPB group (20ml of 0.5% Ropivacaine) and 4.5 ± 7.5 hours in general anaesthesia alone group in study conducted by **He W et al.,**[55]

In our study 8mg of dexamethasone was added to Inj Bupivacaine which prolongs the duration of action of block. Patients who also received an Opioid Free Analgesic mixture had a longer duration of analgesia and time taken for the first rescue analgesia request was longer than Group N in patients who received only block.

Total Analgesic requirement:

In group M, 57.6% (18) required 75 mg of diclofenac, and 18.2%(6) of them required 150 mg and 24.2%(8) did not require . In group N, 42.4%(14) required 75mg of diclofenac, followed by 150 mg in 30.3%(10) and 225 mg in 9.1%(3) and not given in 15.2%(5). This is not statistically significant.

In group M, 51.5% (17) were given 50 mg of tramadol, followed by 100 mg in 9.1% (3) and 150 mg in 3% (1) and not given in 36.4% (12). In group N, 51.5% (17) were given 50 mg of tramadol, followed by 100 mg in 36.4% (12) and not given in 9.1% (3).

Intergroup comparison of total analgesic requirement:

In group N, mean amount of diclofenac requirement was 116.96mg whereas in group M, mean requirement was 93.00mg with p value of 0.055 which is statistically not significant.

In group N, mean amount of Tramadol requirement was 69.17mg whereas in group M, mean requirement was 61.90mg with p value of 0.338 which is statistically not significant.

Our study shows that in M group total analgesic requirement for 24 hrs was less when compared to group N. In a study done by **Altiparmak B et al.**[49]**(**ESPB with 20ml of Inj Bupivacaine with different concentrations that is 0.25% and 0.375%**)** where rescue analgesic given was Inj Tramadol through PCA pump, patients who received 0.375% required 149.52 ± 25.39 mg and 0.25% received 199.52 ± 32.78 mg of Inj Tramadol and none of the patient's required opioids. This when compared to our study we used 25ml of 0.25% Bupivacaine with 8mg of dexamethasone because with higher concentrations we would reach toxic dose and dexamethasone will increase the analgesic effect of Bupivacaine. **Singh S et al.**[50] in their study compared efficacy of ESPB by giving 20ml of 0.5% Bupivacaine where out of 40 patients only 3 patients required Inj Morphine for 24 hours postoperatively compared to patients who underwent surgery under general anaesthesia.

When compared to study done by **Gurkan et al.**[70] they have used 25ml of 0.25% Bupivacaine at T4 which is similar to our study but we have added adjuvant for better analgesia and to extend the duration of block and they have used Inj Morphine for postoperative analgesia. Their mean consumption of Morphine was 5.76 ± 3.8 mg in ESPB group and it was 16.6 ± 6.92 mg in control group. In our study we have used Inj Tramadol and Inj Diclofenac as analgesics in first 24hours.

In our study in Group M opioid free analgesic mixture was used which decreased total analgesic requirement intraoperatively and hemodynamics were stable compared to other group which when compared to case report done by **Sarma R et al**[71] where 5 patients received ESPB with 2% Ropivacaine along with opioid free analgesia which included Inj Dexmedetomidine 0.5mcg/kg initiated 10min before induction and 40mg/kg Magnesium sulphate infusion over 10min after induction. If hemodynamics are unstable they have increased Inj Dexmedetomidine infusion and gave Inj Ketamine 10mg to reduce response. Similar drugs were given in our study along with block but Dexmedetomidine, Ketamine and

Magnesium sulfate was given as a mixture in same syringe which provided better hemodynamic stability.

In our study we have given ESPB at T4 level with 25ml of Inj Bupivacaine 0.25% which can block dermatomes from T2 to T6 whereas other group received opioid free analgesic mixture along with ESPB. Adding Inj Dexamethasone as an adjunct to Inj Bupivacaine 0.25% have prolonged the duration of block. When compared to the other group, OFA group had a longer duration of analgesia. This could have been due to the additive action of the drugs used in OFA. Group M showed better hemodynamic profile intraoperatively compared to other group especially in terms of HR and MAP which was due to Opioid free analgesic mixture infusion given intraoperatively. VAS scores in both groups were less than or equal to 3 till 2nd hour postoperatively both on movement and at rest. First rescue analgesia request time was more in group M patients than in group N. 1 patient from group N and 4 patients from group M did not require analgesia for more than 24 hours. Patients did not have any side effects like vomiting, nausea and bradycardia.

LIMITATIONS

Our study has few limitations. The block was performed when patients were awake and general anesthesia was given as soon as block was performed. In our study we had not assessed the effect of block and detect block failures.

Another limitation was due to covid we could not get adequate number of modified radical mastectomy cases, so we have included breast conservative surgery + axillary sampling + Latissimus Dorsi flap cases. ESPB was given at T4 in our study which would not have blocked thoracodorsal nerve with volume of local anaesthetic used in our study. This could be the reason for increased VAS scores on movement.

CONCLUSION

ESPB along with opioid free analgesic mixture is an efficacious approach for both intraoperative and postoperative analgesia in patients undergoing mastectomy and breast conservative surgery under general anaesthesia. OFA mixture has provided better hemodynamic stability, prolonged time for first rescue analgesic requirement and improved VAS scores postoperatively.

SUMMARY

This was a randomized prospective comparative clinical study conducted on 66 Patients undergoing MRM from study period January 2021 to May 2022 after obtaining permission from Institutional Ethical Committee. 66 patients were divided into 33 in each group.

GROUP M – General anaesthesia + ESPB + Opioid Free Analgesic mixture infusion

GROUP N – General anaesthesia + ESPB + Normal saline infusion

ESPB was given with 25ml of 0.25% Bupivacaine with 8mg of dexamethasone. Opioid free analgesic mixture was prepared with 1 mg/cc Ketamine +1mcg/cc Dexmedetomidine + 100 mg/cc Magnesium sulfate in a 20 ml Syringe with 12 ml normal saline and infusion was started immediately after intubation @ 1ml/10Kg/hr till 30 minutes before extubation. The other group received 20 ml of NS infusion. GA was given to all patients as per the protocol mentioned in our study.

The demographic parameters of age and BMI were comparable between the two groups. HR and MAP showed significance statistically at almost all time intervals but there was no significance clinically in both groups. Postoperative pain was significantly less in both groups at rest. Pain on movement was also less till 2 hrs postoperatively. After 2 hrs pain was moderate in both the groups. Both patients and surgeons had better satisfaction score in Opioid free analgesia group. Opioid Free Analgesic mixture had a longer duration of analgesia and time for the first rescue analgesic request was longer than Group N patients who received only block. Total analgesic requirement was less in group M than in group N. None of the patients reported any side effects.

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ANNEXURE - I

PROFORMA

TITLE: "A COMPARATIVE STUDY OF PLACEBO VERSUS OPIOID FREE ANALGESIC MIXTURE FOR MASTECTOMIES PERFORMED UNDER GENERAL ANAESTHESIA ALONG WITH ERECTOR SPINAE PLANE BLOCK"

Investigators: Dr B Monisha / Dr Sujatha M P / Dr P N Sreeramulu

UHID: **SEX:** **AGE:**

Height: **Weight:** **BMI:**

Group:

Block given: **Surgery:**

Surgery started: **Duration of surgery:**

TIME	Heart Rate	Mean Arterial Pressure	SPO2
0 min			
5min			
10min			
15min			
30min			
45min			
60min			
75min			
90min			
105min			
120min			
135min			
150min			
165min			
180min			
195min			
210min			
225min			
240min			

1. **VAS score immediately after surgery –**

Time (after surgery)	VAS Score (at rest)	VAS Score (on Abduction)	PONV Score
0 hrs			
1hr			
2hr			
4hr			
6hr			
12hr			
24hr			

1. **Time for first rescue analgesic –**

   (From block given time)

2. **Total amount of Tramadol or Diclofenac -**

   given in first 24hrs

3. **Patient Satisfaction score –**

   Very Good/Good/Satisfactory/Poor

4. **Surgeon Satisfaction Score-**

   Very Good/Good/Satisfactory/Poor

5. **Complications -** Hypotension / Bradycardia / Delirium / Residual Neuromuscular Blockade

ANNEXURE - II

PATIENT INFORMATION SHEET

TITLE: "A COMPARATIVE STUDY OF PLACEBO VERSUS OPIOID FREE ANALGESIC MIXTURE FOR MASTECTOMIES PERFORMED UNDER GENERAL ANAESTHESIA ALONG WITH ERECTOR SPINAE PLANE BLOCK"

Investigators: Dr B Monisha / Dr Sujatha M P / Dr P N Sreeramulu

Study Location: R L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

Details - All Patients posted for Modified Radical Mastectomy under general anaesthesia will be included in this study. Patients with co morbid conditions will be excluded from the study.

This study aims to reduce the incidence of intraoperative and postoperative pain in patients undergoing Modified Radical Mastectomy under general anaesthesia. Patient and the attenders will be completely explained about the procedure being done i.e., Erector Spinae Block will be given under ultrasound guidance. One group will be given general anaesthesia with Opioid free analgesic mixture (20mg Ketamine + 20mcg Dexmedetomidine + 2g Magnesium sulphate) and other group will be given general anaesthesia without Opioid free analgesic mixture. Opioid free analgesic mixture causes very minimal side effects such as hypotension, nausea and allergic drug reactions. Selection of group will be arbitrary. Patient will not be charged for the drugs given. Patient will not get any monetary benefits for participating in the study.

Please read the information and discuss with your family members. You can ask any question regarding the study. If you agree to participate in the study we will collect information.

Relevant history will be taken. This information collected will be used only for dissertation and publication.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

For any further clarification you are free to contact,

DR. SUJATHA M P

(PROFESSOR IN ANAESTHESIOLOGY)

MOBILE NO:9448854349.

ANNEXURE - III

INFORMED CONSENT FORM

"A COMPARATIVE STUDY OF PLACEBO VERSUS OPIOID FREE ANALGESIC MIXTURE FOR MASTECTOMIES PERFORMED UNDER GENERAL ANAESTHESIA WITH ERECTOR SPINAE PLANE BLOCK"

DATE:

I,_____aged_____ ,after being explained in my own vernacular language about the purpose of the study and the risks and complications of the procedure, hereby give my valid written informed consent without any force or prejudice for performing Erector Spinae Block. The nature and risks involved have been explained to me to my satisfaction. I have been explained in detail about the study being conducted. I have read the patient information sheet and I have had the opportunity to ask any question. Any question that I have asked, have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research. I hereby give consent to provide my history, undergo physical examination, undergo the procedure, undergo investigations, and provide its results and documents etc., to the doctor / institute etc., For academic and scientific purpose the operation / procedure etc., may be video graphed or photographed. All the data may be published or used for any academic purpose. I will not hold the doctors / institute etc., responsible for any untoward consequences during the procedure / study.

A copy of this Informed Consent Form and Patient Information Sheet has been provided to the participant.

_____ _____

(Signature & Name of Pt. Attendant) (Signature/Thumb impression & Name of Patient or Guardian)

(Relation with patient)

Witness 1:

Witness 2:

_____

(Signature & Name of Research person /doctor)

KEYS TO MASTER CHART

Sl.No	Serial Number
UHID	Unique Health Identification Number
F	Female
BMI	Body Mass Index
Kg	Kilogram
M^2	Square meters
Bpm	Beats per minute
mm hg	Millimeter of Mercury
SpO2	Peripheral capillary Oxygen saturation
LD flap	Latissimus Dorsi flap
VAS	Visual Analogue Scale
mg	milligram
hr	hour
min	minutes