

**A STUDY ON POSTOPERATIVE ANALGESIC EFFICACY OF EPIDURAL
BUPIVACAINE , BUPIVACAINE WITH FENTANYL AND BUPIVACAINE
WITH NEOSTIGMINE IN ADULTS UNDERGOING ABDOMINAL
SURGERIES UNDER GENERAL ANAESTHESIA**

*Dissertation submitted
in the partial fulfillment of the requirements
for award of the degree*

M.D (ANAESTHESIOLOGY)

BRANCH – X

GOVERNMENT KILPAUK MEDICAL COLLEGE,

CHENNAI -10



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

CHENNAI, TAMIL NADU

APRIL 2017

BONAFIDE CERTIFICATE

This to certify that this dissertation entitled, “**A STUDY ON POSTOPERATIVE ANALGESIC EFFICACY OF EPIDURAL BUPIVACAINE , BUPIVACAINE WITH FENTANYL AND BUPIVACAINE WITH NEOSTIGMINE IN ADULTS UNDERGOING ABDOMINAL SURGERIES UNDER GENERAL ANAESTHESIA**”, is a bonafide original work done by **Dr. B.SRIDHARAN**, in the Department of Anaesthesiology, Government Kilpauk Medical College, Chennai, during his Post Graduate Course from 2014 to 2017. This is submitted as partial fulfillment for the requirement of M.D. Degree examinations – Branch – X (Anaesthesiology) to be held in April 2017 by the Tamil Nadu Dr. M.G.R. Medical University, Chennai.

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CERTIFICATE

This to certify that this dissertation entitled, “**A STUDY ON POSTOPERATIVE ANALGESIC EFFICACY OF EPIDURAL BUPIVACAINE , BUPIVACAINE WITH FENTANYL AND BUPIVACAINE WITH NEOSTIGMINE IN ADULTS UNDERGOING ABDOMINAL SURGERIES UNDER GENERAL ANAESTHESIA**”, is a bonafide original work done by **Dr. B.SRIDHARAN**, in the Department of Anaesthesiology, Government Kilpauk Medical College, Chennai, during his Post Graduate Course from 2014 to 2017. This is submitted as partial fulfillment for the requirement of M.D. Degree examinations – Branch – X (Anaesthesiology) to be held in April 2017 by the Tamil Nadu Dr. M.G.R. Medical University, Chennai.

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DECLARATION

I, **Dr. B.SRIDHARAN**, solemnly declare that the dissertation titled “**A STUDY ON POSTOPERATIVE ANALGESIC EFFICACY OF EPIDURAL BUPIVACAINE , BUPIVACAINE WITH FENTANYL AND BUPIVACAINE WITH NEOSTIGMINE IN ADULTS UNDERGOING ABDOMINAL SURGERIES UNDER GENERAL ANAESTHESIA**”, has been prepared by me, under the guidance and supervision of Professor **Dr. T. MURUGAN, M.D., D.A** Professor and HOD, Department of Anaesthesiology, Government Kilpauk Medical College and Hospital, Chennai - 10. This dissertation is submitted to “The Tamil Nadu Dr. M.G.R. Medical University, Chennai”, Tamilnadu as a partial fulfillment for the requirement of M.D. Degree examinations – Branch – X (Anaesthesiology) to be held in April 2017.

This study was conducted at Government Kilpauk Medical College Hospital and Government Royapettah Hospital , Chennai. I have not submitted this dissertation previously to any university for the award of any degree or diploma

Place: Chennai

Date:

(DR. B. SRIDHARAN)

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INTRODUCTION:

Acute pain in the post operative setting can have adverse physiological and psychological effects due to the stress hormone response induced by anaesthesia and surgery. Thus postoperative pain management plays a vital role in deciding the overall outcome of any surgery.

Postoperative pain is of prime concern following abdominal surgeries. The main objective of providing postoperative analgesia is to make the patient comfortable without pain, promote early ambulation, improve respiratory function and early restoration of his/her routine life. In abdominal surgeries, incidence of postoperative pain is higher causing restriction of the diaphragmatic movements. This could result in basal atelectasis, respiratory tract infections due to decreased effort in coughing out the secretions, deep venous thrombosis due to poor ambulatory effort, all of which lead to increased duration of hospital stay, expenditure, morbidity and mortality.

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Providing epidural block with local anaesthetic drugs in these patients, can efficiently relieve post operative pain. Regional analgesia for abdominal surgeries with epidural is commonly practised nowadays.

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LIST OF ABBREVIATIONS

ASA	American Society of Anaesthesiologists
BP	Blood Pressure
CNS	Central nervous system
CSF	Cerebrospinal fluid
Vd	Volume of Distribution
VAS	Visual Analogue Scale
µg	Microgram
Mg	Milligram
Kg	Kilogram
L	Litre
ml	Millilitre
IV	Intra Venous
IM	Intra muscular
RR	Respiratory rate
MAP	Mean Arterial Blood pressure
IT	Intra-thecal
M1 ,M2	Mucarinic receptors 1 and 2

INTRODUCTION

Acute pain in the post operative setting can have adverse physiological and psychological effects due to the stress hormone response induced by anaesthesia and surgery. Thus postoperative pain management plays a vital role in deciding the overall outcome of any surgery.

Postoperative pain is of prime concern following abdominal surgeries. The main objective of providing postoperative analgesia is to make the patient comfortable without pain, promote early ambulation, improve respiratory function and early restoration of his/her routine life. In abdominal surgeries, incidence of postoperative pain is higher causing restriction of the diaphragmatic movements. This could result in basal atelectasis, respiratory tract infections due to decreased effort in coughing out the secretions, deep venous thrombosis due to poor ambulatory effort, all of which lead to increased duration of hospital stay, expenditure, morbidity and mortality.

Providing epidural block with local anaesthetic drugs in these patients, can efficiently relieve post operative pain. Regional analgesia for abdominal surgeries with epidural is commonly practised nowadays.

Bupivacaine is one of the commonly used drug for post operative analgesia. Bupivacaine belongs to aminoacyl group of local anaesthetics. It has a Pka of about 8.1 with protein binding capacity of 95%. It is highly potent, has a slow onset and longer duration of action. 0.25% and lower

concentrations of Bupivacaine are preferred for use in obstetric patients and out patients for day care procedures.

Fentanyl is 800 times more lipid soluble than Morphine and rapidly is absorbed from the epidural space and CSF. Its onset of action is very rapid which is about 15 – 30 minutes and its duration of action is 2-5 hours. The initial bolus dose of Fentanyl is 5 mcg/kg. Signs and symptoms of respiratory depression are very rare with this dose, although case reports of respiratory depression at these doses are very rare. Pruritus is the most common side effect. Its complementary and synergistic anti-nociceptive interaction results in analgesia with no respiratory depression, decreased incidence of tolerance, dependence and abuse.

Neostigmine, an anticholinesterase drug, which is used to antagonize non-depolarizing muscle relaxants has been tried for post-operative analgesia as an off-label use. Being a quaternary amine, it does not cross blood-brain-barrier . Epidural Neostigmine provides analgesia through M1 and M2 receptors in the spinal cord, inhibiting the breakdown of acetylcholine. It also prolongs and intensifies the analgesia increasing cyclic guanidino-mono phosphate by generating nitric oxide. It prolongs motor block when combined with a local anesthetic. Neostigmine is supposed to prolong the action of Bupivacaine.

Autoradiographic studies have shown muscarinic binding in substantia gelatinosa and to a lesser extent in lamina II and lamina V of dorsal gray matter of spinalcord. Neostigmine also displays peripheral and suprapinal analgesic activity, however the dose necessary to achieve this seems to be higher. However, intrathecal Neostigmine also carries dose dependent nausea and vomiting.

Several studies have demonstrated that the use of epidural Neostigmine is associated with lesser adverse effects and the proposed mechanism of analgesia is by drug spreading into Cerebrospinal Fluid (CSF) at the rate of 1/10th the epidural dose.

AIMS AND OBJECTIVES OF THE STUDY

The aim of the study is to compare “The postoperative analgesic efficacy of epidural Bupivacaine, Bupivacaine plus Fentanyl and Bupivacaine plus Neostigmine in adults undergoing abdominal surgeries under general anesthesia” by assessing :

1. Duration of post operative analgesia, i.e, time interval between epidural drug bolus and time for first rescue analgesia.
2. Ramsay sedation score.
3. Postoperative nausea and vomiting.
4. Pruritus .

ANATOMY AND PHYSIOLOGY OF PAIN

PAIN PATHWAYS

Pain is nothing but any noxious stimulus that is transmitted from the periphery to the cerebral cortex. These noxious stimuli are primarily transmitted by the afferent neurons located in the dorsal root ganglia in the vertebral foramina at each spinal level. These afferent neurons have single axon which bifurcates to reach the peripheral tissues it innervates and other to the dorsal horn of the spinal cord. The majority of the first-order neurons send the proximal end of their axons into the spinal cord via dorsal (sensory) root ganglion located at each spinal level. Once in the dorsal horn, in addition to synapsing with second order neurons, the axons of first-order neurons may synapse with interneurons , sympathetic neurons and ventral horn motor neurons.

The primary afferent neurons located in the dorsal horn of the spinal cord synapses with the second order neurons. The axons from these second order neurons cross the midline and ascend in the contralateral spinothalamic tract to reach the thalamus. Second order neurons in the thalamic nuclei synapse with the third order neurons, which in turn send projections through the internal capsule and corona radiata to the post central gyrus of the cerebral cortex.

Spinal cord gray matter was divided by Rexed into 10 Laminae. The first 6 Laminae, which make up the dorsal horn, receive all afferent neuronal activity, and represent the principal site of modulation of pain by ascending and descending neural pathways.

Second-order neurons are of 2 types :

1. Nociceptive specific neurons.
2. Wide dynamic range neurons.

Wide dynamic range neurons perceive both noxious and non – noxious stimuli. Nociceptive specific neurons are located in lamina I of dorsal horn, and respond only to high threshold noxious stimulation. Wide dynamic range neurons are the most prevalent cell type in the dorsal horn. Although they are found throughout the dorsal horn, wide dynamic range neurons are most abundant in lamina . During repeated stimulation, wide dynamic range neurons characteristically increase their firing rate exponentially in a graded fashion ("wind-up") even with the same stimulus intensity. Most nociceptive C fibers send collaterals or terminate on second order neurons in lamina I, II and to a lesser extent lamina V. In contrast, nociceptive A δ fibers synapse mainly in lamina I, V and to a lesser degree lamina X.

Lamina I responds primarily to noxious (nociceptive) stimulation from cutaneous and deep somatic tissues. Lamina II, also called the substantia gelatinosa, contains many interneurons and is believed to play a major role in

processing and modulating nociceptive input from cutaneous nociceptors. It is also of special interest because it is believed to be a major site of action for opioids. Visceral afferents terminate primarily in lamina V, and to a lesser extent in lamina I. Lamina V responds to both noxious and non-noxious sensory input and receives both visceral and somatic pain afferent. Lamina VIII and IX make up the anterior (motor) horn. Lamina VII is also called the intermediolateral column and contains the cell bodies of preganglionic sympathetic neurons.

The axons of most second-order neurons cross the mid-line close their level of origin i.e the anterior commissure to the contralateral of the spinal cord , before they form the spinothalamic tract and send their fibers to the thalamus, the reticular formation, the nucleus raphe magnus, and the periaqueductal gyrus. Other ascending pain pathways are also important e.g. spinoreticular, spinomesencephalic, spinohypothalamic, and spinothalamic tracts.

PHYSIOLOGY OF PAIN (NOCICEPTION):

CENTRAL MODULATION OF PAIN:

FACILITATION OF PAIN :

Neurochemical mediators of central sensitization include substance P , Vasoactive intestinal peptide, calcitonin gene-related peptide (CGRP), cholecystokinin (CCK) etc. But , the most important of these peptides are substance P and calcitonin gene-related peptide (CGRP), while glutamate is the most important excitatory amino acids. These substances interact with G protein couples receptors on neurons and causes changes in membrane excitability and thereby activating intracellular second messengers. Both these pathways cause an increase in intracellular calcium. The induction and maintenance of central modulation of pain is mainly mediated by these.

INHIBITION OF PAIN:

The inhibitory neurotransmitters (somatostatin, Acetylcholine, β -endorphin, norepinephrine, Gamma amino butyric acid (GABA) and glycine produce a hyperpolarization of the postsynaptic membrane called the inhibitory postsynaptic potential. They modulate nociceptive activity in the dorsal horn. Glycine and Gamma amino butyric acid (GABA) are the most common inhibitory neurotransmitters within the CNS. They play an important role in segmental inhibition of pain in the spinal cord.

SUPRASPINAL INHIBITION:

Supraspinal and descending pathway fibres inhibit pain response in the dorsal horn. The endogenous opioids act presynaptically to hyperpolarize primary afferent neurons and inhibit the release of substance P. Whereas, exogenously supplied opioids have a totally different action. Their action is mostly exhibited postsynaptically, on the second order neurons in substantia gelatinosa of spinal cord. Both opioid and α_2 -adrenergic receptors have been described on or near the terminals of unmyelinated peripheral nerves. Excitatory and inhibitory muscarinic receptors exist on the postsynaptic cell.

Muscarinic receptors are seen in abundance in the following areas :

- Substantia gelatinosa of dorsal horn,
- Motor neuron areas , and
- Lamina 2 and lamina 3 areas of spinal cord have both M1 and M2 receptors.

These are the areas , which are responsible for anti- nociceptive effects.

CLINICAL APPLICATION OF MUSCARINIC STIMULATION:

Exogenously administered acetylcholine has a very short duration of action. This is due to its rapid inactivation by acetylcholinesterase, at synaptic level. Long-acting anticholinesterases can cause prolonged stimulation of the

spinal muscarinic system . This has been proved to have a very high anti-nociceptive property with no neurological side effects. Acetylcholinesterase inhibitors such as Neostigmine when administered intra-theCALLY, acts by inhibiting endogenous breakdown of acetylcholine. Acetylcholine can cause analgesic effects by increasing production of nitric oxide in spinal cord. This has been proven by observing higher levels of spinal cord nitrite following intrathecal administration of acetylcholine.

Both muscarinic and nicotinic receptors take part in anti- nociception. It has also been found that the levels of acetylcholine and noradrenaline are increased in the spinal cord after administration of cholinomimetic substances. This mechanism has been proposed to be involved in producing cholinergic analgesia in acute nociception., such as post operative pain , whereas levels of nitric oxide are increased in spinal cord following chronic pain such as nerve injury.

Antinociception by central muscarinic receptors is mainly dependent on M1 receptor subtype, whereas analgesia can be induced by stimulation of both postsynaptic M1 and presynaptic M2 muscarinic receptors in the brain. Analgesia can also be produced by inhibition of glutamate secretion in the presynaptic muscarinic receptors and activation of muscarinic receptors in the peripheral nerve endings.

Studies have shown that intrathecal (IT) Neostigmine provided analgesia in doses $\geq 10\mu\text{g}$ (surgical patients "as release of Ach is enhanced by pain") to $\geq 50\ \mu\text{g}$ (volunteers).

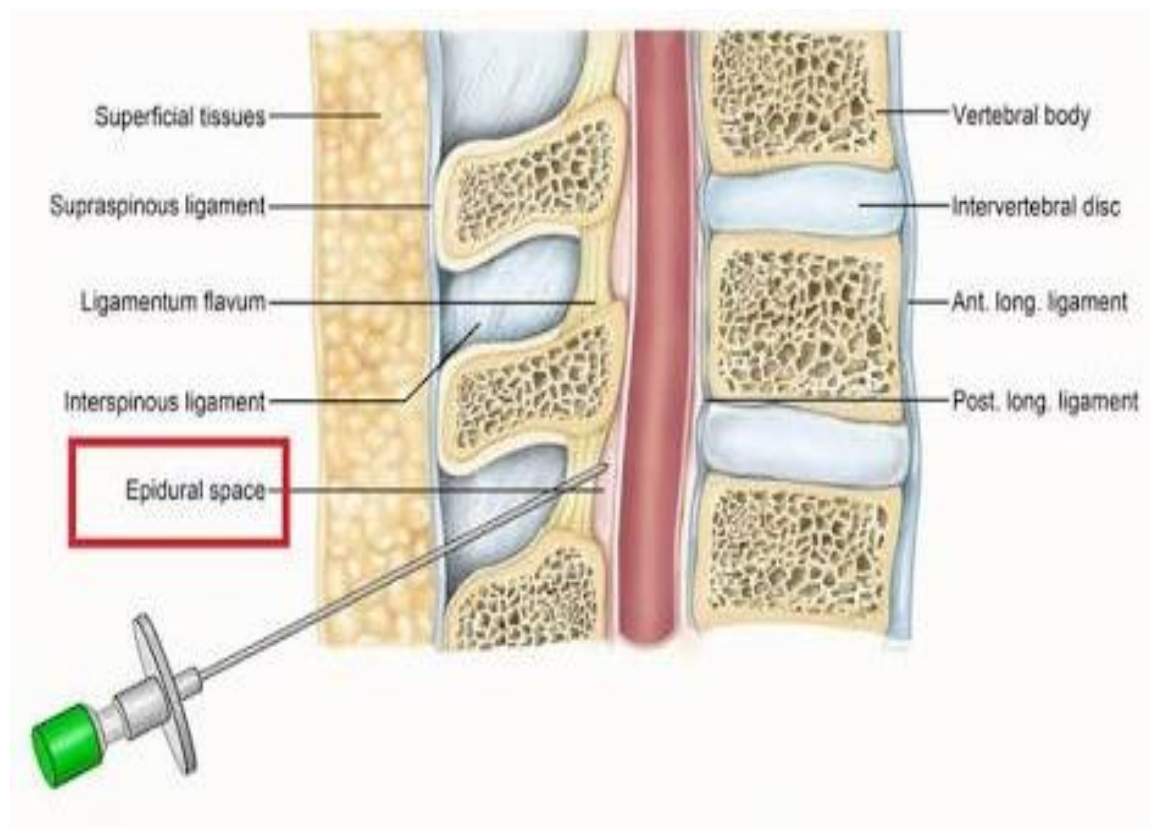
Whereas, Epidural Neostigmine acts on the enzymes acetylcholinesterase and butylcholinesterase expressed in the meninges that cover the spinal cord. Another aspect to be considered is the possible direct action of Neostigmine as a muscarinic agonist, in addition to the indirect stimulation of the release of the second intracellular messenger, nitric oxide.

EPIDURAL SPACE

Is located between the duramater and the periosteum lining the vertebral canal.

It extends from foramen magnum to the sacro-coccygeal ligament. Its contents include:

1. Nerve roots,
2. Fat ,
3. Areolar connective tissue,
4. Lymphatics and ,
5. Blood vessels.



Epidural space also contains Batsons plexus. They are valve-less in nature. These plexuses communicate with pelvic veins through iliac veins and, abdominal and thoracic venous systems through azygous veins.

Epidural fat content is more in case of obese patients. Epidural fat also reduces as the age advances. Hence, reduction in drug dosage is required in elderly patients.

PHARMACOKINETICS OF THE EPIDURAL ANAESTHESIA.

Local anaesthetics when deposited into the epidural space acts by either,

- Acts on the nerve in the intervertebral foramen, or
- On the nerves in the subarachnoid space by diffusing into the space.

LOCATING THE EPIDURAL SPACE :

There are many techniques to identify epidural space like :

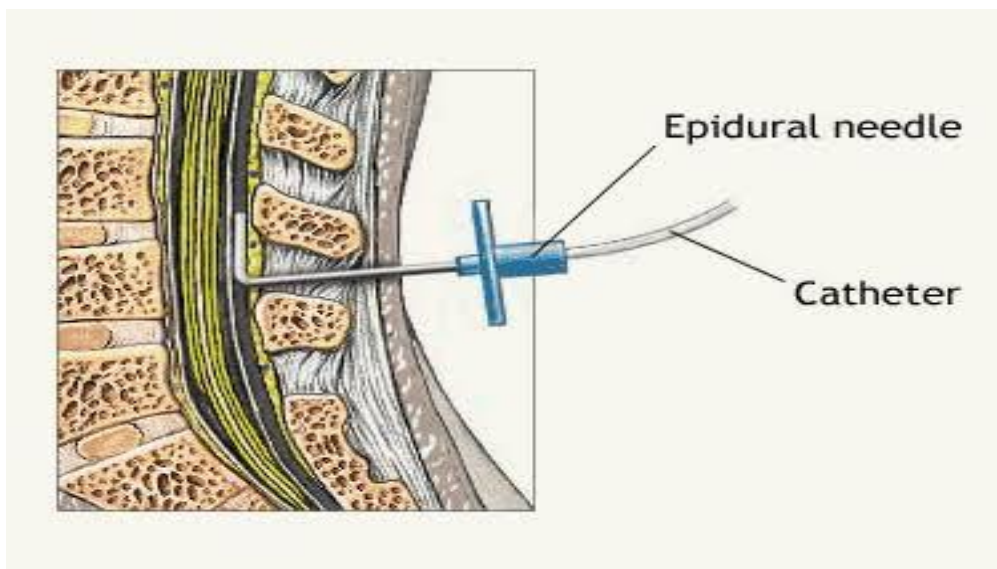
1. Gutierrez sign or Hanging drop technique,
2. Loss of resistance technique,
3. Lund sign : Burning pain is felt by the patient when saline is injected into the epidural space,
4. Bidigital pressure test,
5. Free dripping saline technique,
6. Queckenstedt test : compression of internal jugular vein causes pressure changes in epidural space.

However, the most common is loss of resistance technique. This technique was used in our study.

PHARMACOLOGY:

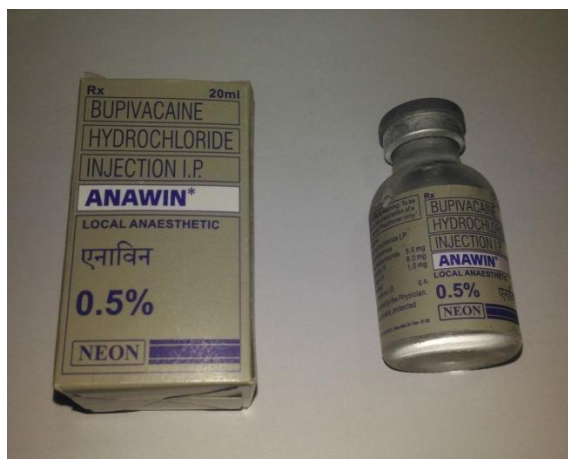
Choice of drug for producing:

1. Surgical anaesthesia: it requires dense sensory blockade and moderate to dense motor blockade. Hence, drugs are used in highest concentration. Like, 2% Lignocaine and 0.5 % Bupivacaine.
2. Labour analgesia : 0.1% - 0.25% Bupivacaine is used, usually in range of 5- 10ml.
3. Post – operative analgesia : weaker concentrations of 0.1 % - 0.166 %.



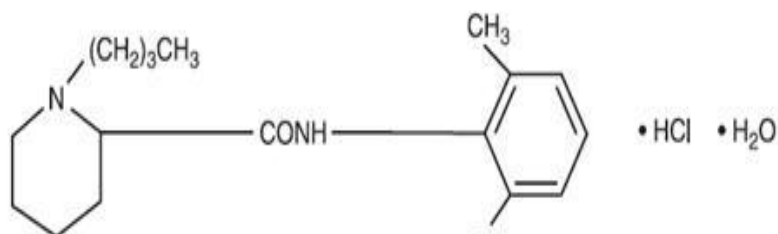
PHARMACOLOGY

BUPIVACAINE



Bupivacaine belongs to the piperidylidide group of local anaesthetics. These are chiral drugs because their molecules possess an asymmetric carbon atom. As a result, Bupivacaine has a left and right handed configuration. It is white, odourless and is soluble in water and 95 % ethanol, and less soluble in chloroform or acetone.

ITS CHEMICAL STRUCTURE:



Solution of Bupivacaine hydrochloride is clear and colorless. It is used for local infiltrations, peripheral nerve blocks, epidural and caudal blocks. Bupivacaine hydrochloride injection solution can be autoclaved.

Bupivacaine belongs to aminoacyl group of local anaesthetics. It is a homologue of Mepivacaine and is chemically related to Lignocaine. All these three local anaesthetics contain an amide linkage between the aromatic nucleus and the amino or piperidine group. These three differ in this respect from the procaine-type local anaesthetics, which have an ester linkage.

Each ml of Bupivacaine hydrochloride injection contains

- 5 mg of anhydrous Bupivacaine hydrochloride
- 8 mg of Sodium chloride
- 1 mg of Methylparaben.

It is also available in 4ml ampoules where each ml contains 5mg hyperbaric Bupivacaine hydrochloride.

BUPIVACAINE - CLINICAL PHARMACOLOGY:

Bupivacaine acts by binding to the intracellular portion of voltage – gated sodium channels and blocks sodium influx into nerve cells, which prevents depolarization.

It blocks the generation and the conduction of nerve impulses by:

1. Increasing the threshold for electrical excitation in the nerve,
2. Slowing the propagation of the nerve impulse,
3. Reducing the rate of rise of the action potential.

Compared to other local anaesthetics, Bupivacaine is markedly cardiotoxic. At low / therapeutic doses, Bupivacaine does not cause major cardiovascular changes or alters cardiac conduction or its contractility. However, toxic blood concentrations of Bupivacaine can cause major abnormalities in cardiac conduction and excitability leading to major ventricular arrhythmias, atrioventricular blocks and bradycardia. Depression of myocardial contractility results in decreased cardiac output and arterial blood pressure, ultimately leading to cardiac arrest and death. But, these changes have been found to be mostly due to inadvertent intravascular injection of Bupivacaine. However, its racemic mixture ie S enantiomer is less cardiotoxic.

Adverse effects on the central nervous system is mainly manifested as circumoral numbness, facial tingling, vertigo, tremors and convulsions.

PHARMACOKINETICS:

Like other local anaesthetics, the rate of absorption of Bupivacaine is mostly dependent on its route of administration, site of administration, total dose and concentration of the drug administered and the presence or absence of epinephrine in the anaesthetic solution. Epinephrine in concentrations of 1:200000 in the anaesthetic solution prolongs the duration of action and permits usage of larger total doses by reducing the rate of absorption and peak plasma concentration of Bupivacaine.

Certain clinical studies have found that its highest peak plasma concentrations, maximum spread of analgesia and motor blockade is found in elderly patients compared to younger subjects.

- The duration of anaesthesia : 240 – 480 minutes,

(Bupivacaine like other liposomal local anaesthetics like lidocaine and tetracaine is incorporated into liposomes to prolong its duration of action and decrease its toxicity),

- Half life: 210 minutes,
- Maximum single dose for infiltration : 175 mg,
- Toxic plasma concentration :> 3 micro g / ml,
- pka : 8.1 (weak base),
- Plasma protein binding : 95% ,
- Fraction non- ionized Bupivacaine at pH 7.4 is 17 % and at pH 7.6 is 24%,
- Volume of Distribution : 73 L,
- Clearance : 0.47 L/ min . The total plasma clearance was decreased in elderly patients.

The rate and degree of diffusion of any local anaesthetics across the placenta depends on the following factors :

- (1) plasma protein binding capacity of the drug,
- (2) the degree of its ionization and
- (3) the lipid solubility of the drug.

The foetal to maternal circulation of local anaesthetics, is inversely related to its plasma protein binding capacity. Thus, only the unbound or free drug in the maternal circulation is available for placental transfer. The plasma protein binding capacity of Bupivacaine is 95 %, hence, the ratio of umbilical vein to maternal arterial concentration of Bupivacaine is only 32%.

Likewise, lipid soluble or water insoluble drugs which occur in nonionized form in the circulation readily crosses maternal circulation to enter the foetal circulation, whereas water soluble or ionized drugs do not readily cross the placental barrier. The lungs are also capable of extracting Bupivacaine from the circulation.

Possible pathways for metabolism of Bupivacaine include aromatic hydroxylation, N – dealkylation, amide hydrolysis and conjugation. Alpha- acid glycoprotein is the most important plasma protein binding site of Bupivacaine. The major metabolite of Bupivacaine is Pipecoloxylidide, which is mainly catalysed by cytochrome p450 3A4. Pipecoloxylidide is then hydroxylated to form glucuronide conjugates.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of Bupivacaine is excreted unchanged in the urine.

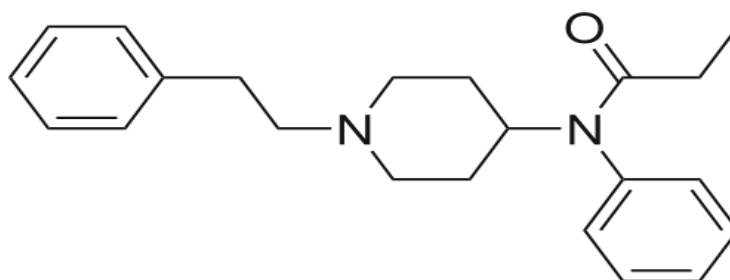
FENTANYL



ITS CHEMICAL STRUCTURE:

Fentanyl citrate is chemically known as N-(1-phenethyl-4-piperidyl) propionanilide citrate. Each ml of its Injection contains 50 µg of Fentanyl citrate. It is a sterile, non-pyrogenic, preservative free aqueous solution for intravenous or intramuscular injection.

The structural formula of Fentanyl citrate is



FENTANYL : ITS CLINICAL PHARMACOLOGY:

Fentanyl is a synthetic opioid belonging to the class of phenylpiperidines. It is a potent opioid agonist acting at mu receptor. Fentanyl has become a very popular anaesthetic agent because of these clinical properties:

- Its relatively short time to peak analgesic effect,
- Its rapid termination of effect after small doses,
- It is cardiac stable.

Fentanyl is 100 times more potent than Morphine.

The principal actions of Fentanyl are analgesia and sedation. It produces its actions at a cellular level by activating opioid receptors. These opioid receptors are mainly located in thalamus, cerebral cortex, substantia gelatinosa of spinal cord and peri – aqueductal grey area.

Opioid receptors are coupled with inhibitory G-proteins. The activation of these inhibitory G-proteins results in:

1. Closure of voltage sensitive channels,
2. Decreased production cyclic adenosine monophosphate,
3. And hyperpolarization (due to stimulation of potassium efflux).

All these effects causes reduction of neuronal cell excitability resulting in reduced transmission of nociceptive impulses. Pure opioid agonists like Fentanyl, Morphine, Pethidine and Diamorphine possess a high intrinsic activity at this opioid receptor.

When given intravenously, Fentanyl has a fast onset of action, but its peak analgesic action is reached within 5 minutes. Fentanyl being more lipid soluble than Morphine, carries very low risk of respiratory depression from rostral spread of intraspinally administered narcotic to respiratory center. However, Fentanyl can cause alterations in alveolar ventilation and very high

decrease in pulmonary gas exchange, which can even last longer than its analgesic effect. This mostly occurs when Fentanyl is used in large doses or in prolonged infusions.

Its peak respiratory depressant effect is mainly seen only after 5 to 15 minutes after a single intravenous dose of Fentanyl citrate. Fentanyl can cause decrease in heart rate and mild decrease in blood pressure. However, it does not cause histamine release and is highly cardiac stable. This property, thus makes Fentanyl the primary anaesthetic agent for patients with poor cardiac function planned for cardiac surgery.

PHARMACOKINETICS:

- Volume of Distribution Fentanyl is 3-5 L/kg ,
- Duration of action : 30 to 60 minutes after iv injection,
- Terminal Half life (hours) : 3.5 hours ,
- pKa : 8.4,
- Amount of drug unionised Fentanyl at pH of 7.4: 9,
- Amount of drug that is plasma bound: 84%,
- Clearance (ml/min/kg): 0.8 – 1,
- Relative Lipid solubility: 580 (very high lipid solubility).

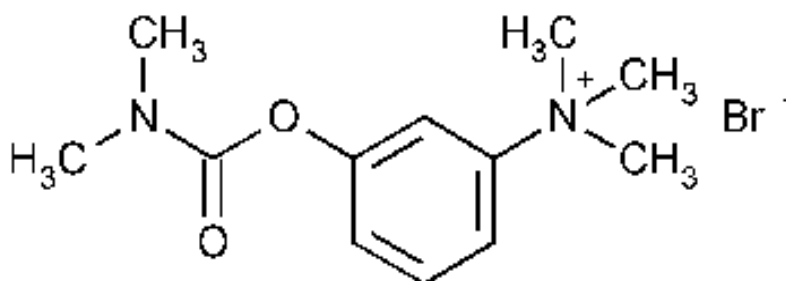
Fentanyl is primarily metabolised in the liver and demonstrates a high first pass clearance. 75% of the intravenous drug is excreted as metabolites in urine, with less than 10% representing the unchanged drug. Approximately 9% of the dose is recovered in the faeces, primarily as metabolites.

NEOSTIGMINE



Neostigmine was introduced in 1931. Neostigmine consists of a carbamate moiety and a quaternary ammonium group. Carbamate moiety provides covalent bonding to acetylcholinesterase. Quaternary ammonium group renders the molecule lipid-insoluble, so that it cannot pass through the Blood Brain Barrier.

ITS CHEMICAL STRUCTURE:

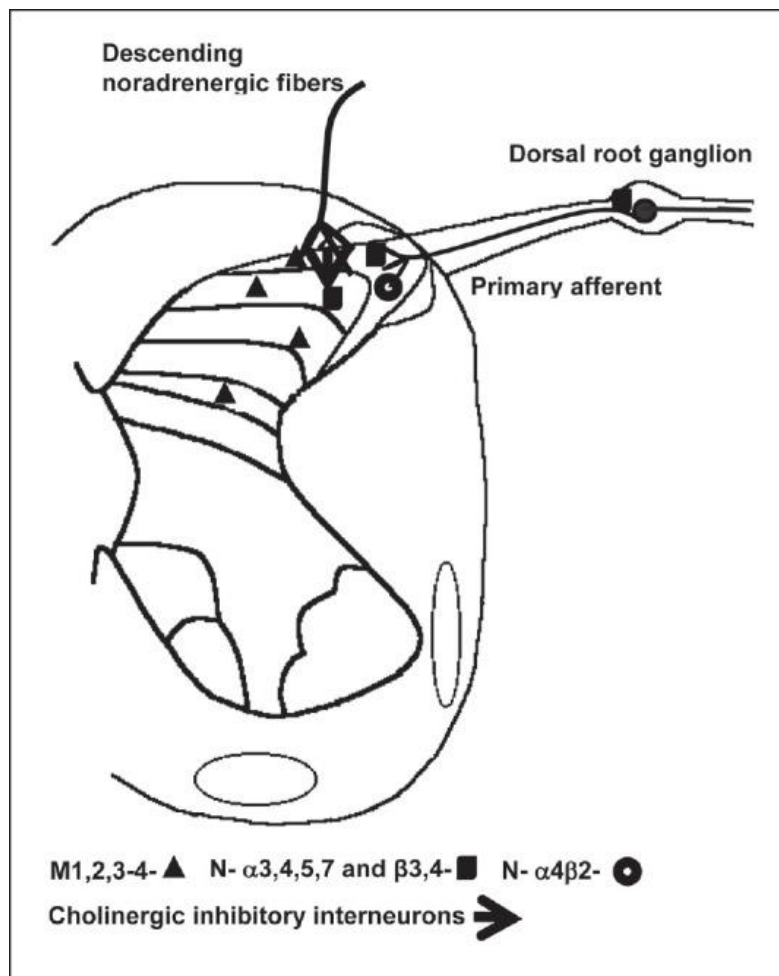


MECHANISM OF ACTION:

Neostigmine is an indirectly acting cholinomimetic drug. It acts primarily by inhibiting the action of acetylcholinesterase, which hydrolyzes acetylcholine to choline and acetic acid. It combines reversibly with

Acetylcholinesterase by the formation of an ester linkage, which lasts about 30 minutes. By inhibiting acetylcholinesterase, it increases the concentration of spinal endogenous acetylcholine.

Muscarinic receptors are located in cholinergic interneurons of the dorsal horn of the spinal cord, in the substantia gelatinosa, in laminae III and V of the spinal cord; while α_3 , α_4 , α_5 , α_7 , β_2 , β_3 and β_4 nicotinic subunits are expressed on primary afferent terminals, inhibitory interneurons, descending noradrenergic fibers in the dorsal root ganglion and in microglias.



It was demonstrated that activation of spinal muscarinic type-2 receptors suppressed spinal gamma-amino butyric acid-B (GABA-B) receptor input and that this dis-inhibiting mechanism ultimately lead to the release of adrenal catecholamines and subsequent reduction in peripheral inflammation. Spinal cord stimulation was also associated with the activation of the cholinergic system in the dorsal horn and mediated via muscarinic receptors, particularly M4, while nicotinic receptors appeared not to be involved. In addition spinal Neostigmine administration resulted in reduction in levels of substance P, and there appears to be unidirectional cross-tolerance between morphine and Neostigmine. In cats, spinal Neostigmine showed antinociceptive effect and this inhibition was only partially mediated by cholinergic mechanism.

Epidural Neostigmine analgesia seems to be a result of central rather than peripheral action. In patients undergoing surgery, epidural Neostigmine resulted in analgesia after the administration of a ten-fold lower dose (1 µg/kg), when compared to intraarticular administration in the knee, suggesting a central effect. Epidural Neostigmine acts on the enzymes acetylcholinesterase and butylcholinesterase expressed in the meninges that cover the spinal cord.

PHARMACOKINETICS:

The pharmacokinetics of Neostigmine administered by bolus injection is linear with respect to bolus injection. The time of the peak concentration ranged from 5-30 minutes. The absorption phase is followed by a

bi- exponential distribution and elimination phase. Diffusion in CSF plays a major role in drug distribution. There is a sustained plateau of increased Acetylcholine concentration in CSF after intrathecal Neostigmine administration. It has been found that CSF Neostigmine concentration even in the lowest of doses can significantly inhibit cholinesterase in CSF.

Dosage of intrathecal administration:

From controlled clinical studies it has been found that the effective dose of intrathecal Neostigmine to produce good analgesic effect is about 10-100 µg.

Side effects:

Neostigmine when given intrathecally can cause lower limb weakness and hypertension due to its local spinal cord action. It also produces sedation and gastrointestinal side effects, which are mainly due to its central action. The incidence and severity of these adverse effects mainly depends on :

- the dose of Neostigmine used,
- method and route of administration and,
- the baricity of the solution.

The incidence of nausea and vomiting is about 30% following intrathecal administration of Neostigmine. Small dose of about 6.25µg of intrathecal Neostigmine can cause nausea and vomiting which is severe , prolonged and

quite resistant to anti-emetic and prokinetic drugs. Nausea and vomiting is reduced by injecting it in a hyperbaric solution. Currently available formulations contain the preservatives methyl and propyl-paraben and are usually mixed with glucose to yield hyperbaric solutions.

Administration of Neostigmine by the epidural route would be mainly characterized by the action of enzymes located in the meninges, with low participation at spinal sites. Gastrointestinal symptoms like nausea and vomiting are rare with epidurally administered Neostigmine. Until date, epidural doses exceeding 30 $\mu\text{g}/\text{kg}$ were associated with a higher incidence of nausea and vomiting and post-operative sedation was increased after 300 μg epidural Neostigmine following caesarean delivery.

REVIEW OF LITERATURE

In one prospective randomized double-blind study evaluating low-dose Dexmedetomidine and Neostigmine with Bupivacaine for postoperative analgesia in orthopedic surgeries done by Sharma. A et al. (1) showed that epidurally administered Dexmedetomidine and Neostigmine exhibit synergism in analgesic action. The incidence of drug-related side-effects was also low. In their study 60 patients belonging to ASA class 1 and 2 who required lower limb surgeries of ≤ 3 hours duration were subjected to combined spinal - epidural anaesthesia. The patients were randomized into three groups. The epidural drug was administered at the end of surgery, with the patients in Group I, II and III receiving 6 ml of 0.25% Bupivacaine alone, with 1 $\mu\text{g}/\text{kg}$ of Neostigmine and with 0.5 $\mu\text{g}/\text{kg}$ of Dexmedetomidine + 5 $\mu\text{g}/\text{kg}$ of Neostigmine, respectively. Post op rescue analgesia was given with intravenous Tramadol 50 mg. The patients were assessed for hemodynamic changes, visual analogue pain scores, duration of analgesia, rescue analgesic requirements and the incidence of side-effects over the next 10 hours. Data was analyzed and $P < 0.05$ was considered as statistically significant. The study revealed that the patients in Group III had significantly longer mean duration of analgesia (273.5 min) compared to Group II (176.25 min) and Group I (144 min). There was also increased requirement of fluids to maintain blood pressures in Group III. Neostigmine did not cause any significant gastrointestinal side effects.

In a randomized, double-blinded study, conducted by Mohamed Abdulatif et al (2) to examine the post operative analgesic efficacy of caudal Neostigmine, Bupivacaine, or Bupivacaine with Neostigmine in 60 children undergoing hypospadias surgery revealed that the patients receiving Bupivacaine or a Bupivacaine and Neostigmine mixture required less inhalation anesthetics. The children in the Bupivacaine/ Neostigmine group also experienced better analgesia. These children also had prolonged duration of analgesia.

Roelants et al. (3) studied the use of the use of neuraxial adjuvant drugs like Neostigmine and Clonidine for labour analgesia in obstetric patient. They found that small doses of intrathecal Clonidine (30 µg), combined with local anaesthetics and opioids, prolong labour analgesia. Hypotension is a common problem and must be promptly treated with Ephedrine to avoid fetal side effects, but epidural Clonidine in doses of 60 to 75µg produces prolonged analgesia when combined with local anaesthetics . Intrathecal Neostigmine has analgesic properties, but its gastro-intestinal side effects contraindicate its clinical use. Epidural Neostigmine, combined with Sufentanil or Clonidine, initiates labour analgesia when used in doses of minimum 6 to 7 µg/kg or 500 µg without any such side effects, and allows for a walking epidural.

Kumar. P et al. (4) did a study in paediatric patients posted for inguinal herniotomy. They used Midazolam, Ketamine, and Neostigmine were used as additives to caudal Bupivacaine. They found out there was no significant

hemodynamic changes in neither of the 3 groups. The duration of post operative analgesia was significantly higher in Group Bupivacaine + Neostigmine ,Group Bupivacaine + Midazolam and Group Bupivacaine + Ketamine , compared with Group Bupivacaine . ($P < 0.05$). Group Bupivacaine + Neostigmine and Group Bupivacaine + Midazolam a longer time to first rescue analgesia when compared with Group Bupivacaine + Ketamine. The incidence of vomiting was not significantly different among groups. However, two patients in Group Bupivacaine +Ketamine experienced hallucinations.

Another study by Kaya FN et al. (5) in patients posted for caesarean also confirmed that epidural Neostigmine did increase the duration of post operative analgesia. In their study , the randomly selected eighty patients underwent elective caesarean section under combined spinal –epidural anaesthesia. These patients were divided into 2 groups. Both the groups received 8 mg hyperbaric Bupivacaine plus 10 μ g Fentanyl intrathecally , but the Neostigmine Group received 300 μ g Neostigmine (n= 40 per group) in 10 ml saline after clamping of the umbilical cord, whereas the Saline Group received only saline. Post op pain relief was monitored using visual analogue score and sedation using Ramsay sedation score for the first 24 hours. The study found that the global pain satisfaction was significantly reduced in the Neostigmine group. They also found that the Neostigmine group also experienced dose dependant increase in sedation scores ($P < 0.05$).

A comparative study was done by Fyneface-Ogan S et al.(7) between caudal Bupivacaine and Bupivacaine co-administered with Neostigmine for postoperative analgesia in children in which 66 children aged between 1-6 years, of ASA class I or II posted for elective unilateral herniotomy under general anaesthesia without premedication were studied. The Mean duration of post operative analgesia in patients who received mixture of Bupivacaine with Neostigmine was significantly longer, 460 ± 60.2 min. compared to the group which received only plain Bupivacaine, 286.4 ± 47.8 mins, ($p < 0.001$). The analgesic requirement within the first 24 hours postoperatively was also significantly reduced in that group, $p < 0.001$.

A comparative study on the post operative analgesic efficacy of Neostigmine and Fentanyl as adjuvants to Bupivacaine was done by Tekin S et al. (9) in patients undergoing abdominal hysterectomy under general anaesthesia. The study was conducted in Seventy-five adult females between the age group 18- 65 years belonging to the American Society of Anesthesiologists physical status I-II. These patients were subjected to epidural insertion before undergoing surgery under general anaesthesia. After completion of the surgery , these patients were randomly chosen and divided into 3 groups. The patients in Group B received 0.125% Bupivacaine, Group N received 0.125% Bupivacaine plus Neostigmine 4 ug/ kg and Group F with 0.125% Bupivacaine plus 1 ug/ kg Fentanyl solutions . They found that the total analgesic consumption in Group F and Group N was considerably lesser when compared to the patients in Group B($p < 0.05$).

And in one study, Chia YY et al (12) evaluated the efficacy of thoracic epidural infusion of Neostigmine after thoracotomy. In this study, ninety patients were randomized into 3 groups i.e pre – neo , post – neo and control group . All these patients were subjected to epidural catheterization at T5 – T8 levels. They underwent thoracotomy under general anaesthesia. The patients in pre-neo group were given 500 µg Neostigmine epidurally before induction of anaesthesia and 125 µg / hour through epidural infusion till the completion of the surgical procedure. The patients in Post-neo group were given only saline epidurally before anaesthesia induction , but 500 µg epidural Neostigmine bolus at the end of the surgery. While the patients in the control group were given only saline as placebo. The patients in the pre – neo and post – neo groups were subjected to receive a mixture of Morphine , Neostigmine and Bupivacaine through continuous patient controlled epidural analgesia in the post operative period for the next 6 days. The patients in the control group received only mixture of Morphine and Bupivacaine through continuous patient controlled epidural infusion. These patients were followed up for the next 6 days. From the study they found out that the daily requirement of patient-controlled epidural analgesia in mL for the patients in the Pre-neo group was remarkably less when compared to the requirement levels of patients in post-neo and control groups. (P < 0.05). They also found that the intensity and severity of pain was also considerably low in patients of pre- neo group, particularly in the first 3 days. (P < 0.05).

Lauretti GR et al. (14) studied the postoperative analgesic property of intra-articular and epidural Neostigmine in 58 ASA physical status I and II patients undergoing knee surgery under combined Spinal – epidural anaesthesia. All the patients in the study were subjected to epidural catheterization at L2-3 space and spinal blockade was performed at L3-4 space. The dose of spinal anaesthesia in all these patients was 20mg of hyperbaric Bupivacaine. After this, the patients were randomly divided into three groups. The Group EG received 500µg epidural Neostigmine and intra-articular saline, the patients in group AG received epidural saline and 500 µg intra-articular Neostigmine, whereas the patients in group CG received saline both epidurally and intra-articularly. Dose of 10 ml was selected for both epidural and intra-articular injection. The study revealed that duration of post operative analgesia was significantly higher in the patients in Groups EG and AG when compared to the patients in Group CG ($P < 0.05$). The total analgesic consumption was also significantly higher in the control group CG ($P < 0.05$). They also found that when the dose of Neostigmine was only 1 µg / kg, the post operative analgesia when given intra – articularly was of not much significance. However, when the similar 1 µg /kg dose of Neostigmine was given epidurally, it provided significant post operative analgesia for about 5 hours.

In one study Ross VH et al. (16) did a randomized controlled study on a group of obstetric patients using Bupivacaine and Neostigmine as patient controlled epidural analgesia in 40 healthy patients posted for elective caesarean

section. In these patients Bupivacaine 1.25 mg/mL alone or with Neostigmine 4 ug /mL by patient-controlled epidural analgesia. The primary outcome measured by them was hourly Bupivacaine use. The result of this study proved that Epidural Neostigmine bolus did not alter baseline Foetal heart rate, induce uterine contractions, or produced gastro-intestinal side effects.. Epidural Neostigmine infusion reduced Bupivacaine requirement by 19% in all patients and 25% in those with >4 h of treatment ($P < 0.05$ for both). It was also found that these patients also experienced mild sedation.

Zhang N et al. (18) did a study using epidural Clonidine and Neostigmine, and their effects when used for labour analgesia. The patients were randomly selected into two groups by double blinding technique. They found out that when Epidural Clonidine and Neostigmine were used adjuvants to epidural Bupivacaine for labour analgesia , there was a significant analgesic effect (monitored through vas scores) ($P < 0.05$). There was also a significant reduction in the dose of Bupivacaine and opioids used for rescue analgesia. ($P < 0.05$).

In a study by Heba I.A. et al. (20) where the effect of addition of Neostigmine to epidural Levobupivacaine/Fentanyl mixture on return of intestinal motility in cases posted for abdominal hysterectomy. There were a total of 40 patients who were divided into group N (Neostigmine group) and group C (control group). In group N, Neostigmine 1 $\mu\text{g}/\text{kg}$ was added to the epidural infusion of Levobupivacaine and Fentanyl. They found that Group N

had significantly lower visual analogue scale ($P < 0.05$). In addition, time to first analgesic request was significantly longer in group N (9.5 ± 1.3 vs. 8.1 ± 0.9 in group C). The number of patients requiring analgesia in group N was two (10%), whereas in group C the number was nine (45%), which was statistically significant. Total narcotic consumption was significantly less in group N (104 ± 21.6 vs. 218 ± 35.2 mg in group C) and return of intestinal sounds was significantly faster in group N (8.1 ± 0.7 vs. 10.5 ± 1.8 h in group C). Group N had less nausea and vomiting.

In November 2014 Mohamed AmrAbusabaa et al. (22) evaluated the efficacy of epidural Dexmedetomidine, Tramadol, or Neostigmine for postoperative pain after major breast surgeries. In this study Eighty female patients scheduled for major breast surgery were divided into four equal groups (20 patients each) in a randomized double-blinded manner. Thoracic epidural anesthesia was given at T6-7 level and the surgery was carried out under general anaesthesia. In group C 15 ml of 0.5% Bupivacaine (control group), in group D 15 ml of 0.5% Bupivacaine +75 μ g of Dexmedetomidine, in group T 15 ml of 0.5% Bupivacaine +75 mg of Tramadol, and in group N 15 ml of 0.5% Bupivacaine +75 μ g of Neostigmine were given. Perioperative cortisol levels, postoperative analgesia, time to ambulation, and complications were assessed as the major outcome following surgery. Patients in groups D and T experienced lower pain scores compared with patients in groups C and N. Hence, patients in groups D and T consumed a lower dose of Bupivacaine in the postoperative period compared with patients in groups C and N.

Gabriela Rocha Lauretti et al. (24) in 2014, did a double-blinded prospective study in 60 boys of ASA physical status I or II undergoing unilateral orchidopexy under general anaesthesia combined with caudal block. They compared the efficacy of intravenous and caudal routes of Sufentanyl and addition of caudal Adrenaline and Neostigmine as an adjuvant to Sufentanyl in children undergoing unilateral orchidopexy under general anaesthesia combined with caudal block. Sixty patients scheduled for orchidopexy were divided into the following four groups: 1) Group IVSu received IV 0.5 µg/kg Sufentanyl and caudal saline; 2) Group CSu received caudal 0.5 µg/kg Sufentanyl and IV saline; 3) Group CSuAdr received caudal Sufentanyl plus Adrenaline 5 µg/ml (1:200,000) and IV saline; 4) Group CSuNeo received caudal Sufentanyl plus Neostigmine, and IV saline; and 5) Group CSuNeoAdr received caudal Sufentanyl plus Neostigmine plus Adrenaline, and IV saline. Consumption of Isoflurane, side effects, quality of sleep, time to first administration of rescue analgesia, and number of doses of 24-h rescue analgesia were recorded. Heart rate and mean blood pressure >15% was treated with increasing Isoflurane concentration. They found out that the total Isoflurane consumption was higher and similar in Groups IVSu, CSuNeo and CSuNeoAdr, and lesser in Groups CSu and CSuAdr ($P < 0.02$). Visual Analogue score for sedation on reversal of anesthesia revealed that the sedation scores in Groups CSuNeo and CSuNeoAdr was less when compared to Groups CSu, CSuAdr and IVSu ($P < 0.005$). The time to the first administration of rescue analgesia showed that the groups IVSu, CSu and CSuAdr required rescue analgesia very early in the post operative period which was around (3-4 h), and that was significantly higher in

Groups CSuNeo and CSuNeoAdr (10-11 h) ($P < 0.05$). Number of doses of rescue analgesia showed the following association like GroupIVSu = Group CSu = Group CSuAdr > Group CSuNeo = Group CSuNeoAdr ($P < 0.005$). They concluded that caudal Sufentanyl alone was no better when administered in the IV route, and would just be justified by the association of Neostigmine, but not Adrenaline. Neostigmine as an adjuvant to Sufentanyl resulted in better perioperative analgesia.

In 2012, Amit Jain et al. (26) did a study in patients posted for total knee replacement surgery. They “ compared the post operative analgesic efficacy of low dose intra- thecal Neostigmine as an adjuvant to Fentanyl and Bupivacaine for total knee replacement surgery” . In this study forty-five patients were selected and divided into three groups. All patients received intrathecal Bupivacaine 15 mg with group 1 patients receiving Bupivacaine with normal saline (0.1 ml), group 2 patients receiving intrathecal Bupivacaine with Fentanyl 20 ug (0.4 ml) and group 3 patients receiving intrathecal Bupivacaine with Neostigmine 1 ug (0.1 ml). From this study, they concluded that the analgesia produced by the Fentanyl group was better when compared to the Group which received intra-thecal Neostigmine. ($P < 0.05$). However, the total duration of post op analgesia was significantly high in group 2 and group 3. . ($P < 0.001$). The total number of rescue analgesia required was significantly higher in group 1 ($P < 0.05$). They also found that epidural Neostigmine did not cause any adverse gastrointestinal side effects like nausea and vomiting.

Medge D. Owen et al. (27) in 2000 did a study using “Low-dose Clonidine and Neostigmine as an adjuvant to local anaesthetics and observed that they can prolong the duration of labour analgesia when combined with spinal hyperbaric Bupivacaine and Fentanyl”. In their study, 45 healthy patients in active stage of labour were divided into 3 groups. All these patients were subjected to combined spinal- epidural technique. Each patient in group 1 received 2.5 mg of hyperbaric Bupivacaine and 25 µg Fentanyl. The patients in group 2 received a mixture of hyperbaric Bupivacaine 2.5 mg , Fentanyl 25 µg and Clonidine 30 µg , whereas the patients in group 3 received a mixture of 2.5 mg hyperbaric Bupivacaine , Fentanyl 25 µg , Clonidine 30 µg and Neostigmine 100 µg . The total intra-thecal dose was 2ml in all the 3 groups. They found that the total duration of labour analgesia was very high in group 3 where mixture of Bupivacaine, Fentanyl, Clonidine and Neostigmine was used . They also found out that this group also had a very high incidence of gastrointestinal side effects like nausea and vomiting.

In one study conducted by Cossu AP et al. (29), Neostigmine was used as an adjuvant to local anaesthetics for neuraxial blockade in obstetric patients to find out its efficacy in producing post operative analgesia. From this study , they found that the epidural addition of Neostigmine to local anaesthetic like Bupivacaine or Ropivacaine resulted in greater analgesic response and greater patient tolerance when compared to the intra-thecal administration of Neostigmine. Post op requirement of subsequent doses of local anaesthetics was

also significantly reduced. ($P < 0.05$). Intra-thecal administration of Neostigmine was associated with vomiting in nearly half of the patients, but not with the patients who received epidural Neostigmine. They also found that epidural Neostigmine administration can cause mild to moderate sedation.

In 2012 ,Hany A. Shehab and Samar A. Salman (32) conducted a study in 90 women belonging to ASA class 1 and 2 who were subjected to undergo open abdominal hysterectomy for dysfunctional uterine bleeding under epidural combined with general anaesthesia. The purpose of the study was to compare the therapeutic efficacy of a preoperative epidural single shot of Dexamethasone/ Levobupivacaine and Neostigmine/ Levobupivacaine for postoperative analgesia. The patients were randomly divided into three equal groups on the basis of the use of epidural adjuvant as only one preemptive shot epidural injection: group L included patients assigned to receive 12 ml of plain Levobupivacaine 0.1% (1 mg/ml), group L/D included patients assigned to receive a total volume of 12 ml of both Levobupivacaine 0.1% (1 mg/ml) and Dexamethasone 8 mg, and group L/N included patients assigned to receive a total volume of 12 ml of both Levobupivacaine 0.1% (1 mg/ml) and neostigmine 500 ug. They found out that the preemptive epidural therapy provided PO analgesia without significant difference until 2 hours postoperatively. Until 8 hours postoperatively, pain VAS scores were significantly lower in groups L/D and L/N compared with group L; at 10 hours postoperatively, pain VAS scores were significantly lower in the L/D group

compared with the other groups. The total pain VAS score at the end of 24 h was significantly lower in the L/D group compared with the L/N and L groups, with significantly lower scores in the L/N group compared with group L. The mean duration of PO analgesia was significantly longer in the L/D group compared with groups L/N and L, with significantly longer duration in the L/N group compared with group L.

In one other study by Rajesh Mahajan et al. (35), different doses of caudal Neostigmine in was used as an adjuvant to Bupivacaine to analyse its analgesic property in children undergoing repair of hypospadias. These children were randomly allocated into 4 groups. The children in group 1 received caudal Bupivacaine with saline being the control group. The children in group 2 received caudal Bupivacaine with caudal Neostigmine in doses of 2 $\mu\text{g}/\text{kg}$, group 3 with caudal Bupivacaine and 3 $\mu\text{g}/\text{kg}$ caudal Neostigmine and children in group 4 received caudal Bupivacaine with 4 $\mu\text{g}/\text{kg}$ caudal Neostigmine. From the study , they inferred that the duration of post operative analgesia was considerably higher in groups 2, 3 and 4 when compared to the group 1. Among the three caudal Neostigmine groups, the 4 $\mu\text{g}/\text{kg}$ caudal Neostigmine group showed a significant increase in duration of post op analgesia whrn compared to the 2 $\mu\text{g}/\text{kg}$ and 3 $\mu\text{g}/\text{kg}$ caudal Neostigmine group. In this study intravenous Paracetamol was used as the rescue analgesic in all the 4 groups. From this they conclude that the amount of rescue analgesia consumption (in ml) was also significantly higher in the group 1 compared to the groups 2, 3 and 4.

In 2012, SayedKaoudAbd-Elshafy et al. (36) did a study using Neostigmine as an adjuvant to Bupivacaine in caudal block for children undergoing open heart surgery under general anaesthesia. These children randomly allocated into 2 groups in a double blinded manner. After performing orotracheal intubation in these children, the patients in group 1 received a caudal block using Bupivacaine and 2 µg/kg dose of caudal Neostigmine. Whereas, the children in group 2 were given intravenous Fentanyl infusion throughout the post operative period. From this study, they concluded that weaning from mechanical ventilation in the post op period was early in the children in group 1 than group 2. The children in group 1 also experienced longer post op duration of analgesia. Thus, they concluded that caudal Neostigmine as an adjuvant to Bupivacaine facilitated early extubation and provided longer duration of postoperative analgesia in children undergoing open heart surgery under general anaesthesia.

MamtaHarjai et al (37) in 2010 did a randomized double blind study on ninety adult females who underwent lower intra abdominal surgeries comparing two different doses of epidural Neostigmine administered with Lignocaine for post operative analgesia and sedation. They divided the patients into three groups of 30 each. Group I received Lignocaine 1% (9ml) with normal saline (1ml), group II Lignocaine 1% (9ml) with Neostigmine 100µg in saline (1ml) and group III received Lignocaine 1% (9ml) with Neostigmine 200µg in NS (1ml). After putting epidural catheter, all these patients underwent surgery under

general anesthesia using Propofol (2mg kg⁻¹), Succinylcholine (2mg kg⁻¹) and maintained with O₂, N₂O, relaxant technique. At the end of surgery, patients were reversed and extubated. Epidural analgesic medication was administered to after proper recovery from anesthesia. Intensity of pain relief on VAS, duration of analgesia, level of sensory block, motor blockade, sedation by sedation score and complications were assessed. From these findings they found out that the addition of Neostigmine resulted in significant longer duration of analgesia (dose independent) and sedation (dose dependent). Sensory and motor blockade were identical in all three groups. There was no incidence of respiratory depression, pruritus, bradycardia or hypotension in any group.

One other study on the analgesic efficacy of epidural Neostigmine as an additive to Bupivacaine was done by Nakayama. M et al. (40). Forty five ASA 1 patients posted for elective abdominal hysterectomy were enrolled in this study. These patients were randomly divided into 3 groups. All these patients were subjected to epidural catheterization at T12- L1 space in the pre op period and underwent abdominal hysterectomy under general anaesthesia. At the end of the surgery, the patients in group 1 were given epidural Bupivacaine alone with saline, the patients in group 2 with epidural Bupivacaine mixed with Neostigmine in dose of 5 µg/kg and the patients in group 3 received epidural Bupivacaine mixed with Neostigmine in dose of 10 µg/kg. They found that the time to first rescue analgesia was longer in the 5 µg/kg and 10 µg/kg Neostigmine groups.

A study on labour analgesia using mixture of epidural Clonidine and Neostigmine with Ropivacaine was done by Boogmans et al, (41). In this study, parturients in their active stage of labour were subjected to labour analgesia by combined spinal epidural technique. From this study, they found out that the group of patients who were subjected to undergo labour analgesia using the mixture of epidural Neostigmine and Clonidine to spinal Ropivacaine showed that the total use of local anaesthetics i.e Ropivacaine used in this group was very less. ($P < 0.05$) The quality of analgesia and the duration of analgesia was also higher in this group.

Getu Ataro et al. (43) did a comparative study between caudal Neostigmine added to Bupivacaine and caudal Bupivacaine alone on paediatric patients undergoing elective orthopaedic surgery under general anaesthesia. The children who are posted for elective orthopaedic surgery of the lower limbs were randomized into 2 groups. The children in group 1 received only caudal Bupivacaine (0.125%), whereas the children in group 2 received caudal Bupivacaine (0.125%) with Neostigmine in dose of 2 $\mu\text{g}/\text{kg}$ at the end of the procedure. They concluded that the duration of analgesia and time to first rescue analgesia was longer in group 2. The values were also highly significant ($p < 0.003$).

Mayank Mohan Agarwal et al. (44) did a study in adult patients of 40 – 60 years of age. These patients were devoid of any urinary tract infections or voiding problems. The purpose of this study was to monitor the urinary tract

function in these adult patients after epidural administration of Neostigmine. After insertion of an epidural catheter at lumbar levels, these patients underwent rigid cystoscopy under local anaesthesia. They underwent multichannel urodynamics (filling cystometry and pressure-flow study) before and 30 min after lumbar epidural administration of Neostigmine (2 µg/kg). They found that these patients had very low maximum cystometric capacity with no alterations in end filling pressure. These patients also experienced very good analgesic effects in the post operative period.

Yet another study to evaluate the effects of epidural Neostigmine on post operative ileus in patients posted for elective abdominal aortic aneurysm surgery was conducted by Caliskan et al (46) in 2003. The patients posted for abdominal aortic surgery were allocated into 2 groups. Thoracic epidural catheter was inserted pre-operatively in all these patients. These patients were allowed to undergo abdominal aortic aneurysm under general anaesthesia. At the end of the surgery, the patients in the group 1 received a 5-mL bolus of Neostigmine in dose of 1 µg/kg diluted with normal saline, whereas the patients in Group 2 received only 5 mL normal saline. The patients in both the groups received 0.125% Bupivacaine continuously via epidural infusion pumps for the next 48 hours. They observed that the patients in group 1 experienced early return of bowel activity, compared to the patients in group 2. These patients also passed flatus early in the post operative period. ($P < 0.05$).

Eiji Masaki et al. (48) studied the postoperative analgesic effects of epidural Neostigmine and the responses of plasma cortisol and Interleukin-6. The study was done in 20 patients undergoing lower abdominal surgery. The 20 patients were allocated into 2 groups. Neostigmine group (n=10) received epidural 10 ml of 1% Mepivacaine with 0.1 mg Neostigmine before the induction of general anaesthesia, while control group (n=10) received Mepivacaine alone. The general anaesthesia was induced with Propofol (2 mg/kg) and Vecuronium (0.1 mg/kg), and maintained with Sevoflurane / O₂ / N₂O. Blood was collected at various time intervals , before and after induction of anaesthesia and in the post operative period to assess the effects of Neostigmine on the plasma cortisol and interleukin-6 levels. From this study , they concluded that patients who received epidural Neostigmine before skin incision showed low cortisol levels even in the intra – operative period , whereas the patients in the control group showed high cortisol levels. (P < 0.05). There was no change in the interleukin – 6 levels in both the group of patients. (P > 0.05).

Alparslan Turan et al. (52) evaluated the effect of caudal Ropivacaine and Neostigmine in paediatric patients posted for elective surgery of inguinal hernia or hypospadias. They divided them into Group I (n = 22), who received 0.2% Ropivacaine 0.5 ml/kg, and Group II (n = 22), who received 0.2% Ropivacaine 0.5 ml/kg with 2 µg/kg Neostigmine via the caudal route. From this study they found that the patients in group 2 showed very low VAS scores

when compared the patients in group 1. The values were also highly significant. ($P < 0.001$). But, the post operative sedation scores in both the group of patients were similar and not significant.

In 2003, Y.K. Batra et al. (58) did a study in 120 ASA class 1 children posted for elective hypospadias correction surgery . They used Neostigmine as adjuvant to Bupivacaine to find the its efficacy in providing post op analgesia in these children. Adequate dose of caudal Neostigmine when added to caudal Bupivacaine did increase the duration of analgesia in these patients. However, they found that higher doses of Neostigmine caused vomiting in some patients.

I. Saadawy at al. (63) in 2008 did a study to evaluate the effects of Dexmedetomidine on paediatric patients when used as an additive to Bupivacaine in caudal block. The children included in the study were allocated into 2 groups. They found that the end-tidal Sevoflurane concentration and the incidence of agitation were significantly lower in the Group where Dexmedetomidine was used as additive to caudal Bupivacaine ($P < 0.05$). The children in this group also experienced longer duration of analgesia and therefore lesser amount of rescue analgesia consumed. Quality of sleep and the overall physical activity of the children in the Dexmedetomidine group was very encouraging. Caudally administered Dexmedetomidine ($1 \mu\text{g}/\text{kg}$), combined with Bupivacaine, was associated with an extended duration of post-operative pain relief.

MATERIALS AND METHOD

SOURCE OF DATA:

Patients undergoing abdominal surgeries done under general anesthesia at Govt. Kilpauk Medical College Hospital and Govt. Royapettah Hospital , Chennai between February 2016 and July 2016 were assessed for inclusion and exclusion criteria and were included in the study only after obtaining written informed consent.

SAMPLE SIZE: 60

Sample size was determined based on the study “ Postoperative analgesic efficacy of epidural Fentanyl and Neostigmine as adjuvant to Bupivacaine in adults undergoing abdominal surgeries”, authored by Selcen Tekin et al. published in Saudi Med J 2006 ; Vol. 27(8): 1199- 1203. In this study the total analgesic consumption was significantly higher in Group B 147.7 ± 7.2 ml, when compared to Group N 123.4 ± 6.2 ml and in Group F 106 ± 8.3 ml, with a Standard Deviation of about 7.2 ml.

DESCRIPTION:

The formula for determining sample size is given as:

Where

n = Sample size

σ = Population standard deviation

e = Margin of error

Z = The value for the given confidence interval

- The confidence level is estimated at 95%
- Standard deviation 58
- With a z value of 1.96
- The confidence interval or margin of error is estimated at +/-15
- Assuming that 80 percent as power of the study, minimum sample size required for the study was calculated to be 58.

In our study 60 subjects were chosen

(n=20 in Group B arm, n= 20 in Group F and n=20 in Group N arm)

STUDY DESIGN:

A prospective, Non –Randomized, Triple Arm, Single- Blind, Controlled study.

INCLUSION CRITERIA:

- 1) Patients undergoing elective abdominal surgeries under general anaesthesia.
- 2) Age between 20 to 60 years.
- 3) Males and females.
- 4) ASA class I and II.
- 5) Patients who have given valid informed consent.

EXCLUSION CRITERIA:

- 1) Patients not satisfying inclusion criteria.
- 2) Patients with an allergy or sensitivity to opioid group of drugs and local anesthetics.
- 3) Patients with spinal deformities.
- 4) Any contraindication to epidural anesthesia.
- 5) Patients with neurological disorders.
- 6) Impaired ability to communicate (e.g., confusion, poor hearing or language barrier).
- 7) Patients who are unconscious or severely ill.
- 8) Pregnant patients.
- 9) Patients with Coagulation disorders.

MATERIALS:

- 1) Boyles' apparatus
- 2) Laryngoscope with different blade sizes
- 3) Other airway gadgets used in case of difficult intubation
- 4) Endotracheal tubes
- 5) Drugs for administering general anesthesia
- 6) Epidural needle and catheter set
- 7) Glass syringe
- 8) Inj. Fentanyl , available as ampoules(one ampoule contains 2ml, each ml contains 50 mcg of Fentanyl)

- 9) Inj. Neostigmine , available as ampoules (one ampoule contains 1 ml , each ml contains 500 mcg of Neostigmine)
- 10) Inj. Bupivacaine, available as vials in concentration of 0.5% (each vial contains 20 ml, each ml contains 5 mg of Bupivacaine)

METHODOLOGY:

Patients in the above mentioned inclusion criteria selected were counselled about the risks and benefits involved in the study. After getting consent, patients who were willing to be included in the study were enrolled and analyzed. A total of 60 patients were included in the study. Patients were divided into three groups of 20 in each based on computerized random number into group B, group F and group N . The patients in Group B received 0.125% Bupivacaine ,the patients in Group F received solution containing 0.125% Bupivacaine with Fentanyl (1mcg/kg) and patients in Group N received 0.125% Bupivacaine with Neostigmine (10 mcg/kg) epidurally at the end of the procedure (which was around 200 mins in all the cases). The total volume of drug in either group was 10ml.

This study was designed as a prospective, comparative study. Patients were preoperatively evaluated, clinically examined and proper investigations were done prior to the assessment. Procedures were explained in detail and written consent was obtained. Routine monitoring included ECG, Pulse Oximetry, NIBP. Intravenous cannulation was done with 18 G venflon.

Patient was premedicated with Inj. Glycopyrrolate 6mcg/kg IV, Inj. Midazolam 0.01mg/kg IV, Inj. Fentanyl 2 mcg/kg IV. Under sterile aseptic precautions, with patient in right lateral position, at the level of T12-L1 intervertebral space, after subcutaneous infiltration of 2ml of 2% Lignocaine, using 18G Tuohy epidural needle, epidural space was identified by loss of resistance technique, and 20 G catheter was threaded in via the needle. After ensuring that blood or cerebrospinal fluid was not aspirated via catheter, 3ml of 2% Lignocaine with Adrenaline (1:2,00,000) dilution was administered via it.

Patient was then made to lie in supine position. Preoxygenated with 100% oxygen for at least 3 minutes under closed circuit. Then induced with Injection Propofol 2mg/kg and Atracurium 0.5mg/kg was administered. Intubated with endotracheal tube of appropriate size for the patient and secured in a proper manner. Maintenance was done with Nitrous oxide and Oxygen in the ratio of 2:1 and Sevoflurane.

The epidural drug administration was given at the start of incisional wound closure according to the group the patient belongs to. The total volume of drug in either group was 10ml. At the end of surgery, patient was extubated after reversal of neuromuscular blockade by injecting Neostigmine (50mcg/kg) and Glycopyrrolate (10mcg/kg) and shifted to postoperative care unit.

ASSESSMENT CRITERIA	GROUP B	GROUP F	GROUP N
Visual analogue pain scale			
Time for first rescue analgesia/ Duration of analgesia			
Ramsay sedation score			
Postoperative nausea and vomiting			
Heart rate			
Blood pressure			
Respiratory rate			
Oxygen saturation			
Pruritus			

METHOD OF COLLECTION OF DATA

60 patients enrolled in the study who underwent elective abdominal surgeries under general anesthesia were assessed post-operatively. The parameters mentioned above in the table were recorded at every 15 minutes for the first two hours and then hourly upto 12 hours in the postoperative ward. The epidural bolus dose at the end of the procedure was 10ml of 0.125% Bupivacaine in group B with normal saline, 10ml of 0.125% Bupivacaine with Fentanyl 1mcg/kg in group F and 10 ml of 0.125% Bupivacaine with

Neostigmine 10 mcg/ kg in group N. Duration of analgesia was calculated from the time of epidural bolus to the time when first top up dose is required. Also the number of episodes of vomiting and number of patients complaining of pruritus was recorded.

STATISTICAL ANALYSIS:

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

OBSERVATIONS AND RESULTS

The study population consisted of 60 patients posted for elective abdominal surgery under general anaesthesia with epidural block . They were divided into three groups of 20 each. All these patients received epidural bolus doses at the end of the procedure. The patients in Group B received 0.125% Bupivacaine with normal saline ,the patients in Group F received solution containing 0.125% Bupivacaine with Fentanyl (1mcg/kg) and patients in Group N received 0.125% Bupivacaine with Neostigmine (10mcg/kg) epidurally at the end of the procedure. The total volume of drug in either group will be 10ml.

Patient characteristics involved were age, gender, weight and ASA grade. The pre -operative heart rate, respiratory rate, mean arterial blood pressure and oxygen saturation were recorded prior to administering epidural block. After that patient is allowed to undergo surgery under general anaesthesia. Patients' vitals including heart rate, respiratory rate, mean arterial blood pressure and oxygen saturation are measured at the following time intervals 15, 30, 45, 60, 90, 120, 180 mins and hourly till 12 hours in the post operative period. Most of the surgeries were completed by around 180 – 210 mins. Time for first rescue analgesia, post -operative nausea and vomiting, pruritus, visual analogue scale and Ramsay sedation score were observed hourly till 12 hours into the post operative period.

The following observations were made during the course of the study.

Table 1 and Figure 1 shows the sex difference among the patients in the three groups. The association between gender status and intervention groups is considered to be insignificant since p value is > 0.05 .

Table 1: Shows the sex difference among the patients in the three groups.

Group	GENDER STATUS		Chi square	P value
	Male	Female		
Bupivacaine	6	14	0.16	0.921
Bupivacaine with Fentanyl	5	15		
Bupivacaine with Neostigmine	6	14		

Figure 1: Shows the sex difference among the patients in the three groups.

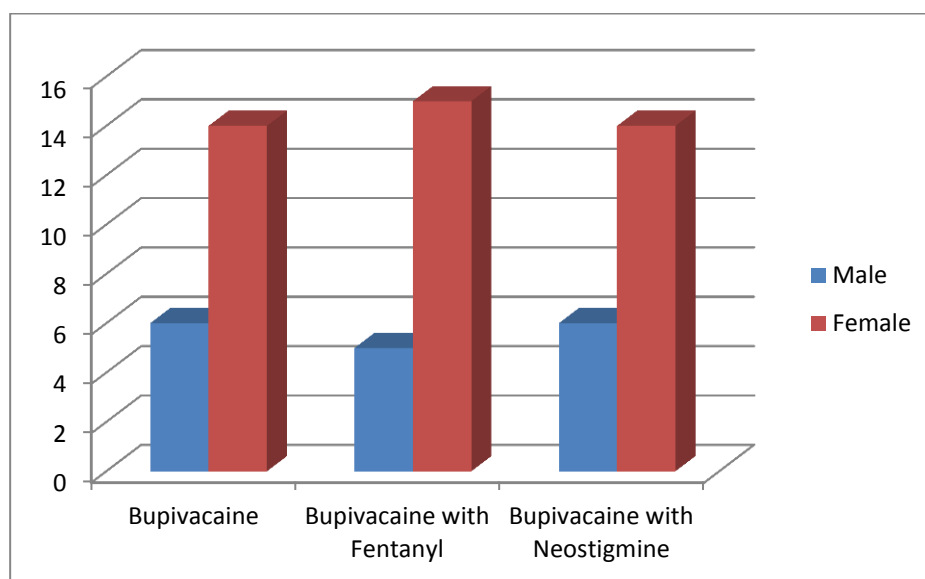


Table 2 and Figure 2 shows the age distribution among the patients in the three groups. The mean weight in Group B was 36.65 ± 2.04 , Group F 35.55 ± 1.79 was and Group N was 35.45 ± 1.80 . The association between age distribution and intervention groups is considered to be non significant since p value is > 0.05 .

Table 2 : Shows Age distribution among the patients in the three groups.

Parameter	Bupivacaine	Bupivacaine with Fentanyl	Bupivacaine with Neostigmine	F value	P value
Age	36.65 ± 2.04	35.55 ± 1.79	35.45 ± 1.80	0.125	0.883

Figure 2 : Shows Age distribution among the patients in the three groups.

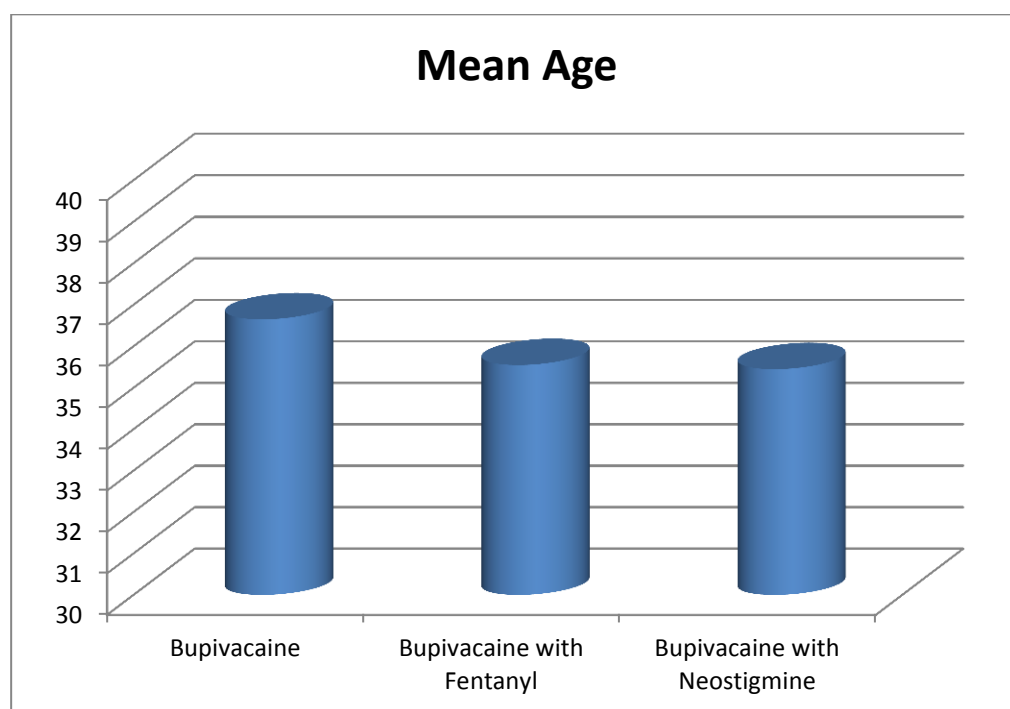


Table 3 and Figure 3 shows the Weight distribution among the patients in the three groups. The mean weight in Group B was 61.35 ± 1.60 , Group F was 58.85 ± 1.57 and Group N was 61.35 ± 1.39 . The association between weight distribution and intervention groups is considered to be non significant since p value is > 0.05 as per unpaired t test.

Table 3 : Shows Weight distribution among the patients in the three groups.

Parameters	Bupivacaine	Bupivacaine with Fentanyl	Bupivacaine with Neostigmine	F value	P value
Weight	61.35 ± 1.60	58.85 ± 1.57	61.35 ± 1.39	0.900	0.412

Figure 3 : Shows Weight distribution among the patients in the three groups.

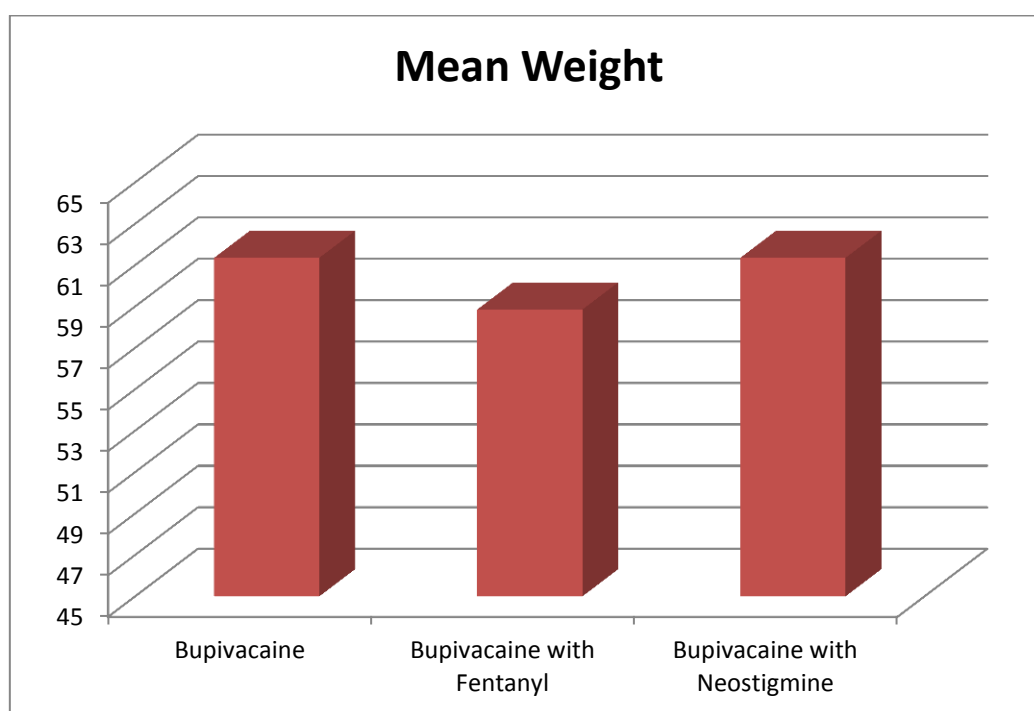


Table 4 and Figure 4 shows that the Mean time for first rescue analgesia in Group B was 104.75 ± 1.60 , Group F was 289.25 ± 3.23 and Group N was 261.00 ± 4.13 . The three groups were comparable with respect to the time for first rescue analgesia. Analysis of variants in table 1 and Figure 1 showed they were highly statistically significant. ($p < 0.05$).

Table 4 : Comparison of average time for first rescue analgesia in Group B, Group F and Group N .

TIME FOR FIRST RESCUE ANALGESIA

Heart rate	Bupivacaine	Bupivacaine with Fentanyl	Bupivacaine with Neostigmine	F value	P value
Time for first rescue Analgesia	104.75 ± 1.60	289.25 ± 3.23	261.00 ± 4.13	986.026	0.0001

Figure 4 : Comparison of average time for first rescue analgesia in Group B, Group F and Group N .

TIME FOR FIRST RESCUE ANALGESIA

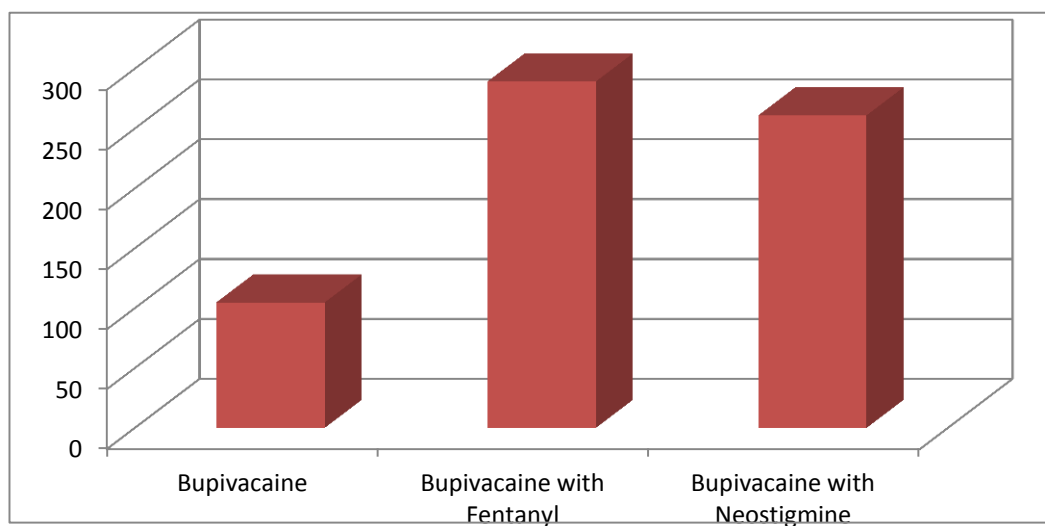


Table 5 and figure 5 shows the heart rate variation in the three groups. The three groups were comparable with respect to heart rate changes. There was no statistically significant difference in heart rate at 15, 30, 45, 60, 90, 120 and 180 mins till the end of surgery (which was around 200 mins in all the three groups). But, there was a statistically significant difference in heart rate ($p < 0.05$) at 360 , 480 and 540 mins in the post operative period.

Table 5 : Comparison of heart rate changes in Group B, Group F and Group N

Heart rate	Bupivacaine	Bupivacaine with Fentanyl	Bupivacaine with Neostigmine	F value	P value
Baseline	81.55 ± 2.41	80.30 ± 2.07	82.25 ± 2.06	0.204	0.816
15 min	94.60 ± 2.89	94.00 ± 2.81	95.75 ± 2.27	0.111	0.895
30 min	91.60 ± 2.92	85.30 ± 2.61	89.35 ± 2.65	1.369	0.263
45 min	82.80 ± 2.04	80.80 ± 2.12	83.15 ± 2.24	0.353	0.704
60 min	83.00 ± 2.32	78.05 ± 2.28	79.65 ± 2.21	1.240	0.297
75 min	79.70 ± 2.11	77.95 ± 1.94	80.25 ± 2.07	0.347	0.709
90 min	80.65 ± 1.71	77.20 ± 1.68	79.40 ± 1.75	1.039	0.360
120 min	81.70 ± 2.40	77.00 ± 2.20	79.25 ± 2.18	1.078	0.347
180 min	84.60 ± 2.16	80.30 ± 2.83	83.00 ± 2.14	0.823	0.444
240 min	83.05 ± 2.30	77.45 ± 2.66	78.80 ± 1.94	1.591	0.213
300 min	82.40 ± 2.36	73.30 ± 2.33	77.80 ± 1.87	4.290	0.018
360 min	83.30 ± 2.32	70.85 ± 1.88	77.70 ± 2.06	8.888	0.0001
420 min	83.45 ± 2.13	70.80 ± 1.91	77.05 ± 2.08	9.596	0.0001
480 min	82.05 ± 2.20	71.40 ± 1.71	77.65 ± 2.05	7.166	0.002
540 min	80.40 ± 2.35	75.00 ± 2.33	82.80 ± 2.11	3.114	0.052
600 min	80.50 ± 2.05	78.40 ± 2.35	82.65 ± 2.16	0.944	0.395
660 min	79.55 ± 1.86	77.90 ± 2.40	81.15 ± 1.93	0.613	0.545
720 min	80.25 ± 1.99	78.20 ± 2.21	81.70 ± 2.04	0.714	0.494

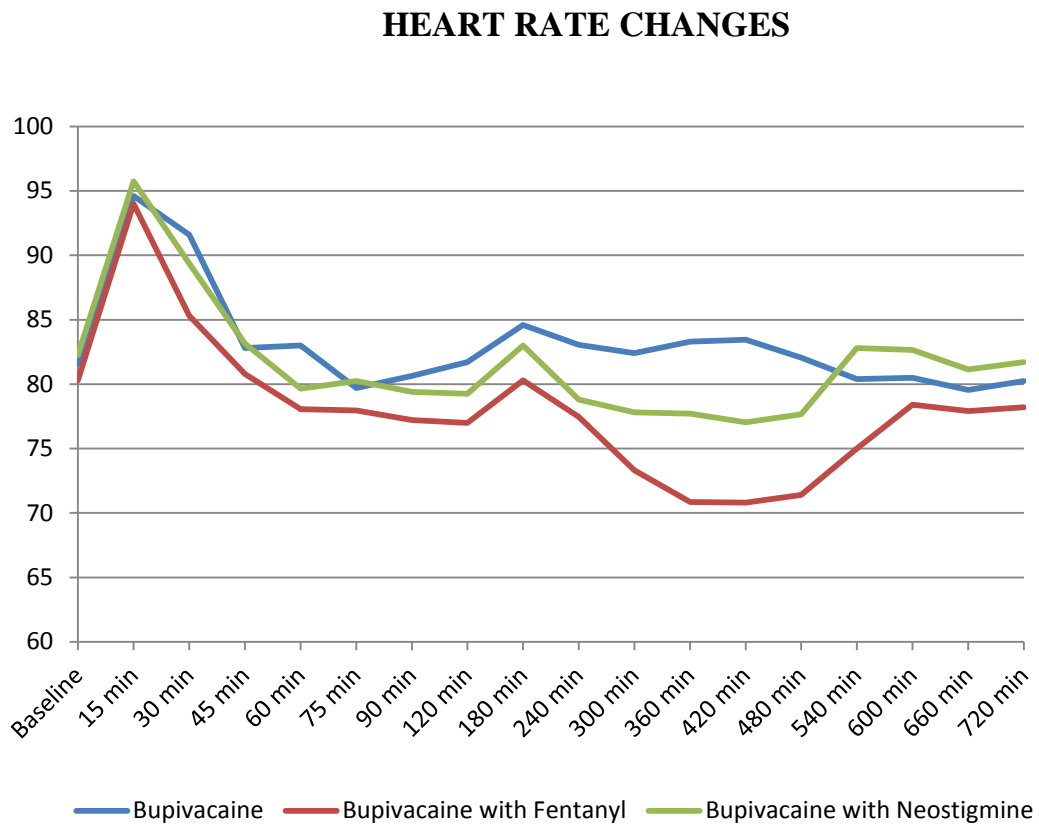
Figure 5: Comparison of heart rate changes in Group B, Group F and Group N

Table 6 and figure 6 shows the Mean arterial blood pressure variation in the three groups. The three groups were comparable with respect to arterial blood pressure changes. There was no statistically significant difference in mean arterial blood pressure either at 15, 30, 45, 60 , 90, 120, 180 mins till the end of surgery (which was around 200 mins in all the three groups) or hourly into the post – operative period till 12 hours.

Table 6 : Comparison of MAP changes in Group B, Group F and Group N.

Mean arterial BP	Bupivacaine	Bupivacaine with Fentanyl	Bupivacaine with Neostigmine	F value	P value
Baseline	90.45 ± 2.34	90.95 ± 2.06	91.55 ± 2.09	0.065	0.937
15 min	80.50 ± 1.85	83.05 ± 1.81	83.35 ± 1.70	0.768	0.468
30 min	84.15 ± 1.58	84.60 ± 1.67	84.90 ± 1.75	0.051	0.950
45 min	84.30 ± 1.34	86.60 ± 1.62	86.55 ± 1.71	0.702	0.500
60 min	84.95 ± 1.46	86.30 ± 1.61	86.15 ± 1.77	0.209	0.812
75 min	84.80 ± 1.34	86.70 ± 1.77	86.75 ± 1.90	0.434	0.650
90 min	84.90 ± 1.42	86.15 ± 1.76	86.35 ± 1.87	0.215	0.807
120 min	84.65 ± 1.45	86.20 ± 1.67	86.80 ± 1.87	0.441	0.646
180 min	87.35 ± 1.93	86.75 ± 1.65	86.80 ± 1.87	0.034	0.967
240 min	87.60 ± 2.41	87.15 ± 1.70	87.30 ± 1.97	0.013	0.988
300 min	83.85 ± 1.65	86.45 ± 1.74	86.60 ± 1.91	0.764	0.471
360 min	85.95 ± 1.86	86.50 ± 1.72	86.60 ± 1.91	0.037	0.964
420 min	86.25 ± 1.84	86.95 ± 1.68	86.60 ± 1.93	0.037	0.964
480 min	86.35 ± 1.84	87.15 ± 1.75	87.40 ± 1.94	0.088	0.916
540 min	86.65 ± 1.87	87.35 ± 1.69	87.85 ± 1.96	0.107	0.899
600 min	86.40 ± 1.67	87.55 ± 1.91	88.15 ± 2.12	0.216	0.806
660 min	86.55 ± 1.91	87.40 ± 1.82	87.00 ± 1.90	0.051	0.950
720 min	86.45 ± 1.81	87.65 ± 1.87	87.15 ± 1.99	0.102	0.903

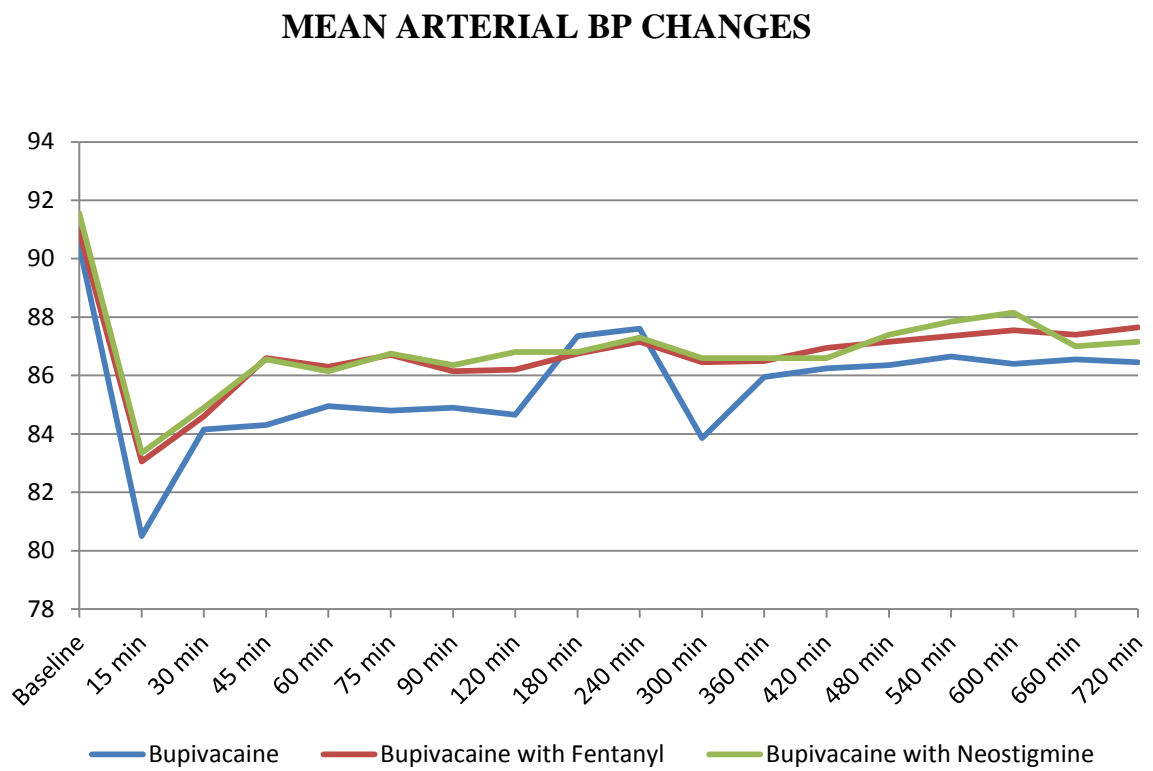
Figure 6: Comparison of MAP changes in Group B, Group F and Group N.

Table 7 and figure 7 shows the respiratory rate variation in the three groups. The three groups were comparable with respect to respiratory rate changes. There was no statistically significant difference in heart rate at 15, 30, 45, 60 , 90, 120 and 180 mins till the end of surgery (which was around 200 mins in all the three groups). But, there was a statistically significant difference in respiratory rate ($p < 0.05$) at 360 mins in the post operative period.

Table 7: Comparison of respiratory rate changes in Group B, Group F and Group N

Respiratory Rate	Bupivacaine	Bupivacaine with Fentanyl	Bupivacaine with Neostigmine	F value	P value
Baseline	12.55 ± 0.33	12.50 ± 0.28	12.10 ± 0.37	0.570	0.569
15 min	12.70 ± 0.27	12.70 ± 0.27	12.60 ± 0.22	0.051	0.951
30 min	12.00 ± 0.07	12.00 ± 0.07	12.00 ± 0.07	0.00	1.00
45 min	12.00 ± 0.00	12.00 ± 0.00	12.00 ± 0.00	0.00	1.00
60 min	12.00 ± 0.00	12.00 ± 0.00	11.95 ± 0.05	1.000	0.374
75 min	12.00 ± 0.00	12.00 ± 0.00	12.00 ± 0.00	0.00	1.00
90 min	12.05 ± 0.90	12.05 ± 0.09	12.05 ± 0.09	0.00	1.00
120 min	12.45 ± 0.28	12.45 ± 0.28	12.45 ± 0.28	0.00	1.00
180 min	13.20 ± 0.36	13.15 ± 0.36	13.30 ± 0.44	0.039	0.962
240 min	10.95 ± 0.17	11.05 ± 0.17	11.00 ± 0.19	0.079	0.924
300 min	11.15 ± 0.25	11.10 ± 0.26	11.15 ± 0.27	0.012	0.988
360 min	12.70 ± 0.53	11.35 ± 0.18	11.85 ± 0.20	3.984	0.024
420 min	13.25 ± 0.41	12.25 ± 0.25	12.70 ± 0.32	2.275	0.112
480 min	12.85 ± 0.30	12.80 ± 0.30	13.50 ± 0.48	1.095	0.341
540 min	13.10 ± 0.28	13.90 ± 0.34	13.30 ± 0.27	1.941	0.153
600 min	12.90 ± 0.24	13.00 ± 0.24	13.05 ± 0.26	0.097	0.908
660 min	12.95 ± 0.28	13.00 ± 0.29	13.00 ± 0.27	0.011	0.989
720 min	12.80 ± 0.24	12.85 ± 0.22	12.70 ± 0.23	0.111	0.895

Figure 7: Comparison of respiratory rate changes in Group B, Group F and Group N.

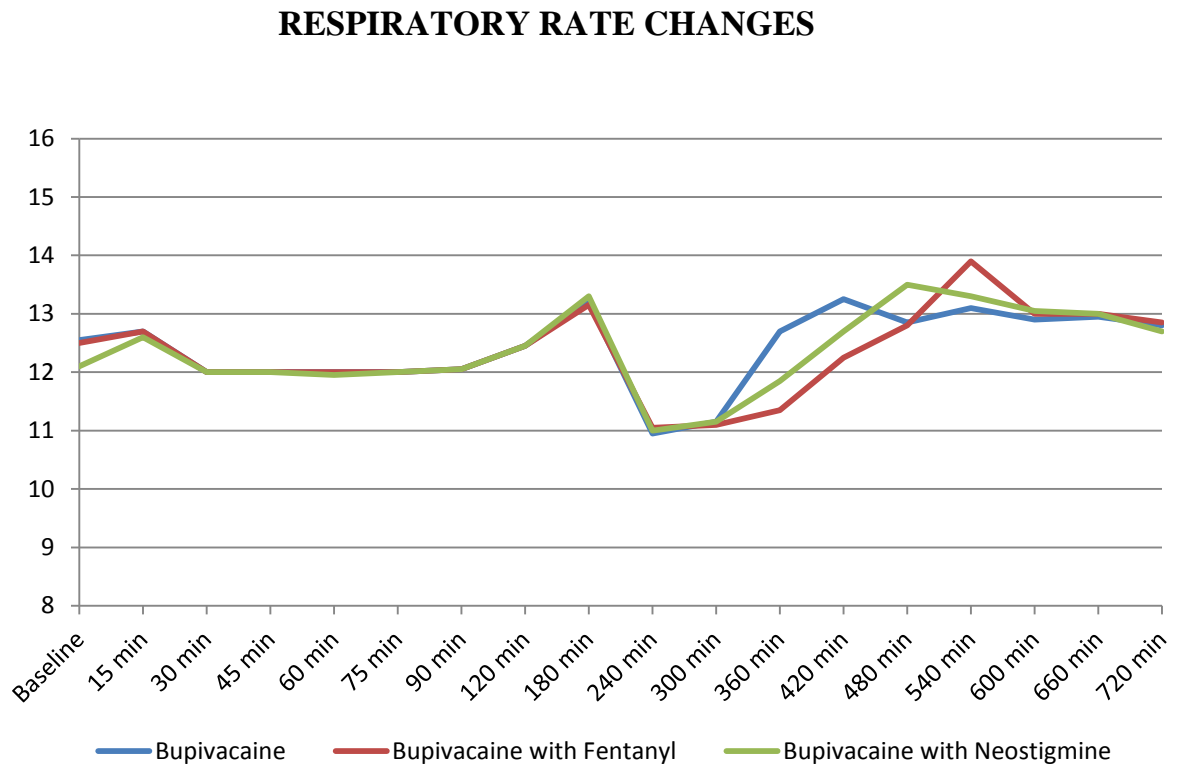


Table 8 and figure 8 shows the oxygen saturation variation in the three groups. The three groups were comparable with respect to oxygen saturation changes. There was no statistically significant difference in oxygen saturation at 15, 30, 45, 60, 90, 120 and 180 mins till the end of surgery (which was around 200 mins in all the three groups). But, there was a statistically significant difference in oxygen saturation ($p < 0.05$) at 360 mins in the post operative period.

Table 8: Comparison of oxygen saturation changes in Group B, Group F and Group N.

Oxygen saturation	Bupivacaine	Bupivacaine with Fentanyl	Bupivacaine with Neostigmine	F value	P value
Baseline	99.65 ± 0.13	99.75 ± 0.10	99.90 ± 0.07	1.492	0.234
15 min	100.00 ± 0.00	100.00 ± 0.00	100.00 ± 0.00	0.00	1.00
30 min	99.95 ± 0.05	99.90 ± 0.07	99.95 ± 0.05	0.257	0.774
45 min	99.95 ± 0.05	100.00 ± 0.00	100.00 ± 0.00	1.000	0.374
60 min	99.90 ± 0.07	99.85 ± 0.08	99.95 ± 0.05	0.538	0.587
75 min	100.00 ± 0.00	99.90 ± 0.07	99.95 ± 0.05	1.036	0.361
90 min	100.00 ± 0.00	100.00 ± 0.00	100.00 ± 0.00	0.00	1.00
120 min	99.90 ± 0.07	99.95 ± 0.05	100.00 ± 0.00	1.036	0.361
180 min	100.00 ± 0.00	99.95 ± 0.05	99.85 ± 0.08	1.900	0.159
240 min	100.00 ± 0.00	100.00 ± 0.00	99.90 ± 0.07	2.111	0.130
300 min	100.00 ± 0.00	100.00 ± 0.00	100.00 ± 0.00	0.00	1.00
360 min	99.10 ± 0.22	99.90 ± 0.07	100.00 ± 0.00	14.153	0.0001
420 min	99.65 ± 0.13	99.85 ± 0.08	99.75 ± 0.12	0.768	0.469
480 min	99.75 ± 0.10	99.75 ± 0.12	99.85 ± 0.08	0.315	0.731
540 min	99.95 ± 0.05	99.95 ± 0.05	99.95 ± 0.05	0.00	1.00
600 min	99.95 ± 0.05	99.95 ± 0.05	99.95 ± 0.05	0.00	1.00
660 min	100.00 ± 0.00	99.85 ± 0.08	100.00 ± 0.00	2.353	0.142
720 min	99.95 ± 0.05	99.85 ± 0.08	99.90 ± 0.07	0.538	0.587

**Figure 8: Comparison of oxygen saturation changes in Group B,
Group F and Group N.**

O₂ SATURATION CHANGES

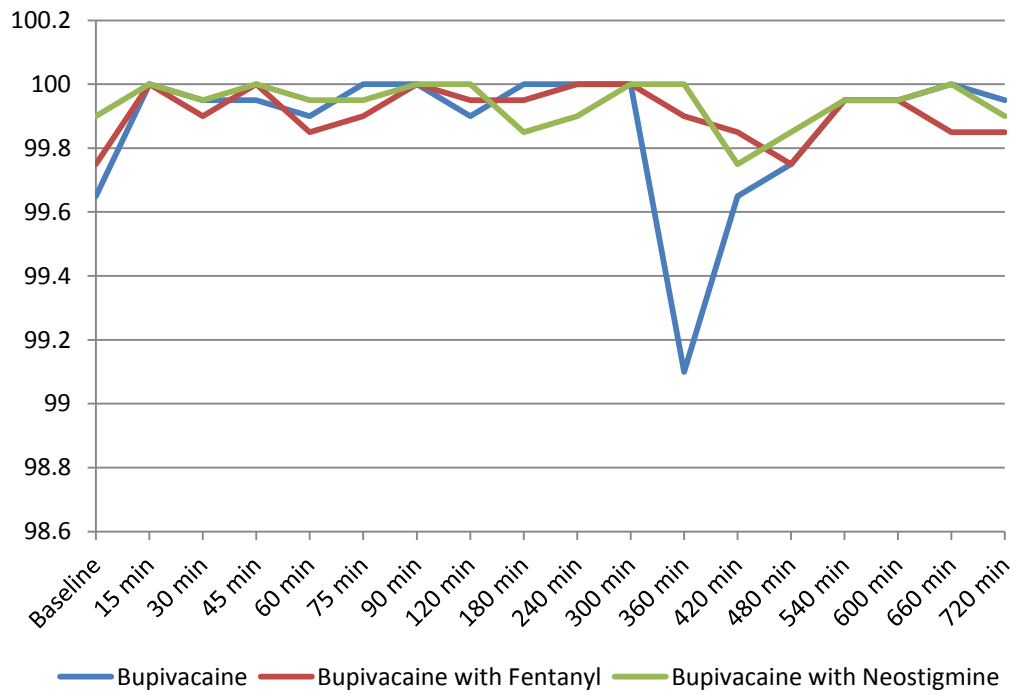


Table 9 and figure 9 shows visual analogue scale variation in the three groups. The three groups were comparable with respect to visual analogue scale changes. Analysis of variants in table 6 and Figure 6 showed they were highly statistically significant. ($p < 0.05$)

**Table 9: Comparison of visual analogue scale in Group B,
Group F and Group N.**

VISUAL ANALOGUE SCALE CHANGES

VAS	Bupivacaine	Bupivacaine with Fentanyl	Bupivacaine with Neostigmine	F value	P value
300 min	3.55 ± 0.95	0.25 ± 0.12	0.45 ± 0.14	10.912	0.0001
360 min	7.85 ± 0.41	0.60 ± 0.18	1.15 ± 0.17	211.302	0.0001
420 min	5.50 ± 0.36	0.75 ± 0.16	1.25 ± 0.18	110.160	0.0001
480 min	4.75 ± 0.23	1.55 ± 0.44	3.75 ± 0.68	11.297	0.0001
540 min	4.80 ± 0.26	6.30 ± 0.65	6.55 ± 0.47	3.806	0.028
600 min	4.60 ± 0.26	4.80 ± 0.42	4.70 ± 0.29	0.092	0.912
660 min	4.80 ± 0.24	3.90 ± 0.24	3.90 ± 0.22	5.062	0.009
720 min	4.55 ± 0.24	3.60 ± 0.29	4.05 ± 0.22	3.541	0.036

**Figure 9: Comparison of visual analogue scale in Group B,
Group F and Group N.**

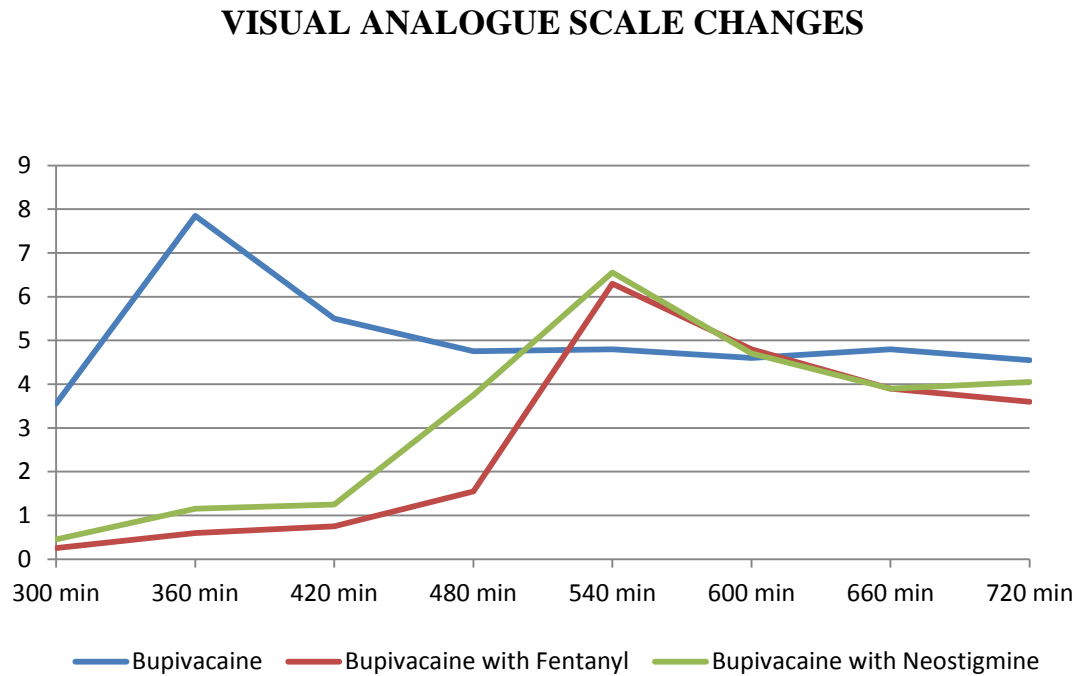


Table 10 and figure 10 shows Ramsay sedation score variation in the three groups. The three groups were comparable with respect to Ramsay sedation score changes. Analysis of variants in table 7 and Figure 7 showed they were highly statistically significant. ($p < 0.05$).

Table 10: Comparison of Ramsay sedation score in Group B, Group F and Group N.

RAMSAY SEDATION SCORE CHANGES

Ramsay Sedation score	Bupivacaine	Bupivacaine with Fentanyl	Bupivacaine with Neostigmine	F value	P value
Baseline	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00	0.00	1.00
240 min	1.85 ± 0.08	2.60 ± 0.15	2.10 ± 0.07	12.643	0.0001
300 min	2.00 ± 0.00	3.15 ± 0.15	2.00 ± 0.00	58.778	0.0001
360 min	2.00 ± 0.00	3.45 ± 0.11	2.00 ± 0.00	161.404	0.0001
420 min	2.00 ± 0.00	3.10 ± 0.07	2.00 ± 0.00	255.444	0.0001
480 min	2.00 ± 0.00	2.60 ± 0.11	2.00 ± 0.00	28.500	0.0001
540 min	2.00 ± 0.00	2.35 ± 0.11	2.00 ± 0.00	10.231	0.0001
600 min	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00	0.00	1.00
660 min	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00	0.00	1.00
720 min	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00	0.00	1.00

Figure 10: Comparison of Ramsay sedation score in Group B, Group F and Group N.

RAMSAY SEDATION SCORE CHANGES

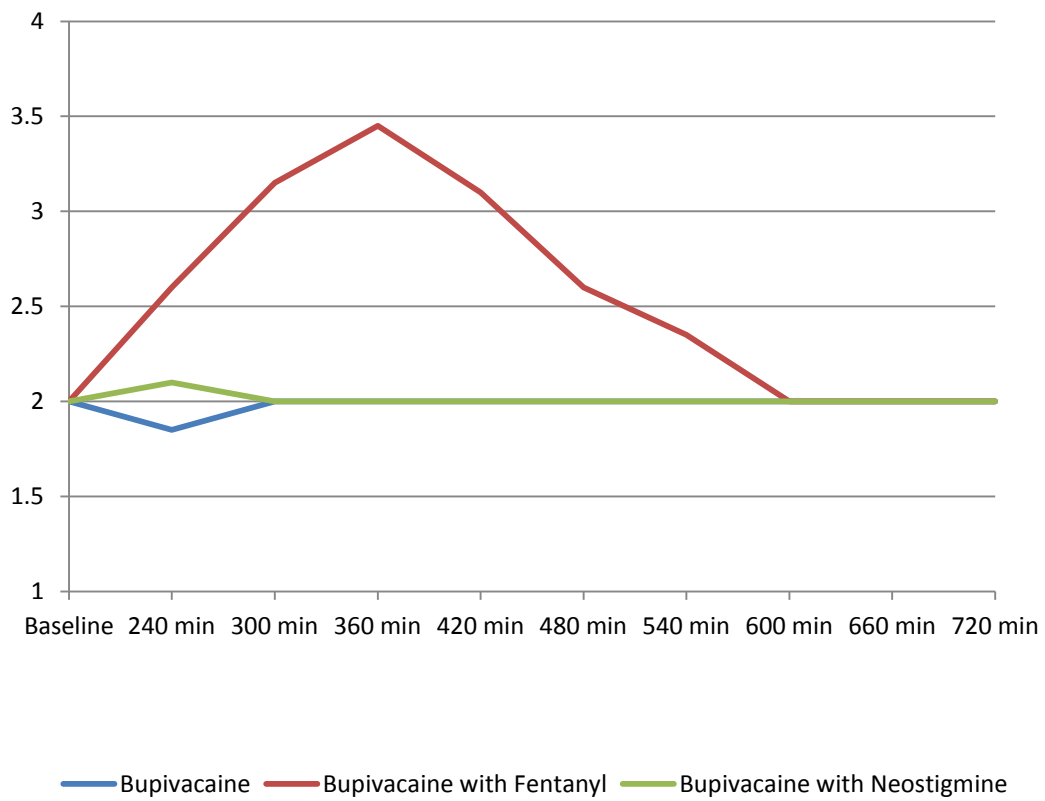


Table 11 and Figure 11 shows that the number of patients who had post operative nausea and vomiting was 13 in Group F, 1 in Group N and none in Group B . The three groups were comparable with respect to patients who had post operative nausea and vomiting . Analysis of variants in table 8 and Figure 8 showed they were highly statistically significant. ($p < 0.05$)

Table 11: Comparison of number of patients with post operative nausea and vomiting in Group B, Group F and Group N.

Group	Nausea / vomiting		Chi square	P value
	Present	Absent		
Bupivacaine	0	20	29.25	0.0001
Bupivacaine with Fentanyl	13	7		
Bupivacaine with Neostigmine	1	19		

Figure 11: Comparison of number of patients with post operative nausea and vomiting in Group B, Group F and Group N.

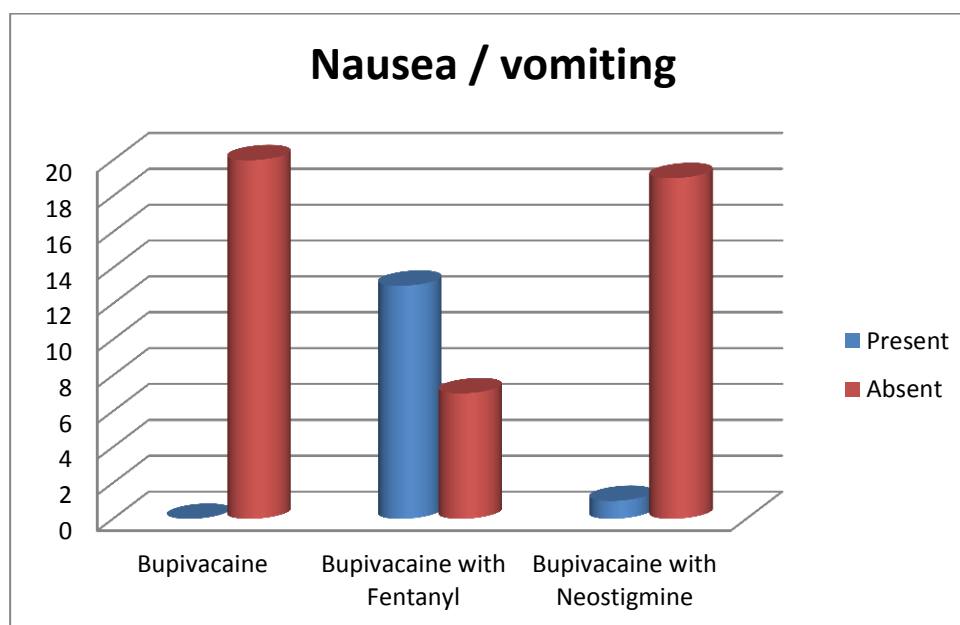


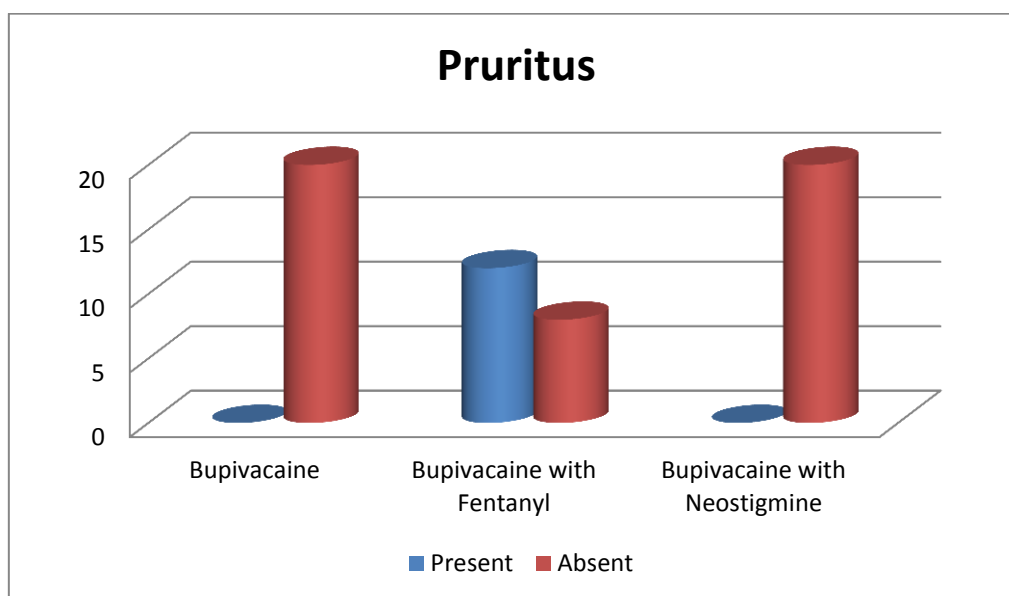
Table 12 and Figure 12 shows that the number of patients who had pruritus was 12 in Group F and none in Group B and Group N. The three groups were comparable with respect to patients who had pruritus . Analysis of variants in table 8 and Figure 8 showed they were highly statistically significant. ($p < 0.05$).

Table 12: Comparison of number of patients with pruritus in Group B, Group F and Group N.

PRURITUS

Group	Pruritus		Chi square	P value
	Present	Absent		
Bupivacaine	0	20	30.00	0.0001
Bupivacaine with Fentanyl	12	8		
Bupivacaine with Neostigmine	0	20		

Figure 12: Comparison of number of patients with post operative nausea and vomiting in Group B, Group F and Group N.



DISCUSSION

The results of our study showed there was no significant difference in age distribution, weight distribution and gender status among the three groups in our study (p value > 0.05).

The time for first rescue analgesia in Group B is 104.75 ± 1.60 , Group F is 289.25 ± 3.23 and Group N was 261.00 ± 4.13 . Based on this evaluation, the duration of post operative analgesia in Group F and Group N was found to be much higher when compared to Group B.

The study done by Tekin S et al. (9) comparing the post operative analgesic activity of the Neostigmine and Fentanyl when used as an additive to Bupivacaine in patients undergoing abdominal hysterectomy under general anaesthesia was similar to our study and substantiating to our results.

One another similar study which was consistent with our results was done by Fyneface-Ogan S et al. (7), who compared Neostigmine as an adjuvant to caudal Bupivacaine and caudal Bupivacaine alone for postoperative analgesia in children. They found that the patients in Bupivacaine – Neostigmine group required only very low doses of analgesia in the post operative period. ($p < 0.001$).

In a similar study by Ross VH et al. (16) where they did a randomized controlled study on a group of obstetric patients using Bupivacaine and Neostigmine for elective caesarean section. It was found that epidural

Neostigmine infusion reduced Bupivacaine requirement by 19% in all patients and 25% in those with >4 h of treatment ($P < 0.05$ for both), which was similar and consistent with our findings. It was also found that these patients also experienced mild sedation similar to our study.

Similarly, another study done by Nakayama. M et al.(40) to evaluate the analgesic effects of epidural Neostigmine in adult patients undergoing abdominal hysterectomy also validated our results. Here the duration of post op analgesia was higher in the 10 μg group than 5 μg group.

Another study which was consistent with our results was done by Lauretti GR et al. (14) to compare the postoperative analgesic property of intra-articular and epidural Neostigmine in patients undergoing knee surgery under combined Spinal – epidural anaesthesia. The time (min) for first rescue analgesia was much longer in both the 1 μg /kg epidural Neostigmine (EG)Group and 500 μg intra – arterial Neostigmine (AG) Groups. ($p < 0.05$).

In our study, the number of patients who had pruritus was 12 in Group F and none in Group B and Group N. Analysis showed that they were highly statistically significant. ($p < 0.05$). It was substantiated by a study conducted by Cossu AP et al. (29) where Neostigmine was added as an adjuvant to local anaesthetics for neuraxial blockade in obstetric patients. Pruritus was also very rare in patients who received epidural Neostigmine.

Hany A. Shehab and Samar A. Salman (32) conducted a study in women who underwent open abdominal hysterectomy for dysfunctional uterine bleeding under epidural combined with general anaesthesia. The results were similar to our study where the mean duration of post operative analgesia was significantly longer in the Dexamethasone/Levobupivacaine group compared with groups Neostigmine/ Levobupivacaine and Levobupivacaine, with significantly longer duration in the Neostigmine/ Levobupivacaine group compared with group Levobupivacaine.

In our study , the number of patients who had post operative nausea and vomiting was 13 in Group F, 1 in Group N and none in Group B. Analysis showed that they were highly statistically significant. ($p < 0.05$). This was consistent with one prospective randomized double-blind study evaluating low-dose Dexmedetomidine and Neostigmine with Bupivacaine for postoperative analgesia in orthopedic surgeries done by Sharma. A et al. (1). It showed that epidurally administered Dexmedetomidine and Neostigmine exhibit synergism in analgesic action. Neostigmine did not cause any significant gastrointestinal side effects like nausea and vomiting.

Getu Ataro et al. (43) conducted a comparative study between caudal Neostigmine added to Bupivacaine and caudal Bupivacaine alone on paediatric patients undergoing elective orthopaedic surgery under general anaesthesia. They concluded that the duration of analgesia and time to first rescue analgesia was longer in group where Neostigmine was added to caudal Bupivacaine. The values were also highly significant ($p < 0.003$). Thus validating our results.

SUMMARY

Out of 60 patients included with 20 each in three groups in this study, Group B received 10 ml of 0.125% Bupivacaine with normal saline, the patients in Group F received 10 ml of 0.125% Bupivacaine with Fentanyl (1mcg/kg) and patients in Group N received 10 ml of 0.125% Bupivacaine with Neostigmine (10mcg/kg) for elective abdominal surgeries under general anaesthesia at the end of the procedure.

The pre operative hemodynamic parameters were comparable between the three groups. There was minimal intra – operative variations in heart rate, mean arterial blood pressure, respiratory rate and oxygen saturation in all the cases.

The duration of analgesia i.e, time interval between epidural drug bolus and time for first rescue analgesia was higher in Bupivacaine +Fentanyl group and Bupivacaine +Neostigmine Group when compared to the Group which received only Bupivacaine. The post operative variations in heart rate, mean arterial blood pressure, respiratory rate and oxygen saturation were also comparable between the three groups. The parameters were also statistically significant when compared to the baseline values.

Post operative sedation and visual analogue scores were also significantly higher in Group F and Group N when compared to the Group B.

Adverse effects like pruritus and gastrointestinal side effects like nausea and vomiting were significantly less in Group N and Group B , but increased in Group F where Fentanyl was used.

CONCLUSION

The duration of post operative epidural analgesia was higher when either Fentanyl or Neostigmine was used as an adjuvant to epidural Bupivacaine than with Bupivacaine alone. However, because of adverse effects like pruritus and gastrointestinal side effects like nausea and vomiting with Fentanyl, epidural Neostigmine can be preferred to epidural Fentanyl as an adjuvant to Bupivacaine since the duration of post operative analgesia was comparatively similar in both these Groups (Group F and Group N).

LIMITATIONS

1. Further studies are required to study the efficacy of epidural Neostigmine for post operative analgesia using different doses of Neostigmine.
2. The efficacy of Epidural Neostigmine when used with other local anaesthetics like Ropivacaine must be studied.
3. In our study epidural Neostigmine was used only postoperatively. We must also study the intra-operative hemodynamic changes produced when epidural Neostigmine is coadministered with local anaesthetics before the start of the surgery.

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INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Protocol ID. No. 15/2016 Dt: 23.01.2016
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A study on postoperative analgesic efficacy of epidural bupivacaine, bupivacaine plus fentanyl and bupivacaine plus neotigmine in adults undergoing abdominal surgeries under general anaesthesia" - For Project Work submitted by Dr.B.Sridharan, PG Student of MD (Anaesthesia), Govt. Kilpauk Medical College, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.


DEAN, 17/2/16

Govt.Kilpauk Medical College,
Chennai - 10.

PROFORMA

“A STUDY ON POSTOPERATIVE ANALGESIC EFFICACY OF EPIDURAL BUPIVACAINE, BUPIVACAINE WITH FENTANYL AND BUPIVACAINE WITH NEOSTIGMINE IN ADULTS UNDERGOING ABDOMINAL SURGERIES UNDER GENERAL ANAESTHESIA”

Name: Age/ Gender: IP.Number:

Weight: Diagnosis: Plan of surgery:

Date of surgery: ASA Physical status:

Comorbidities: Drug history:

Group (Tick any one):

Group B : 10 ml of 0.125% Bupivacaine.

Group F : 10ml of 0.125% Bupivacaine with Fentanyl($1\mu\text{g}/\text{kg}$).

Group N: 10 ml of 0.125% Bupivacaine with
Neostigmine($101\mu\text{g}/\text{kg}$).

Medications:

Inj. Ondansetron 8 mg IV if patient develops nausea and vomiting.

OBSERVATION :**Duration of surgery:**

Time (from induction of anaesthesia to 12 hours in the postoperative period)	Heart rate	MAP	Respiratory rate	Oxygen saturation
Before start of surgery / baseline				
15 mins				
30 mins				
45 mins				
60 mins				
90 mins				
120 mins				
180 mins				
240 mins				
300 mins				
360 mins				
420 mins				
480 mins				
540 mins				
600 mins				
660 mins				
720 mins				

VISUAL ANALOGUE SCALE AND RAMSAY SEDATION SCORE

DURATION OF SURGERY:

Time (from end of surgery to 12 hours in the postoperative period)	Visual Analogue Scale	Ramsay Sedation Score	Pruritus (present /+ or absent /-)	Nausea and vomiting (present /+ or absent-)
At the end of surgery				
180 mins				
240 mins				
300 mins				
360 mins				
420 mins				
480 mins				
540 mins				
600 mins				
660 mins				
720 mins				

The time for first rescue analgesia / total duration of post operative analgesia :

PATIENT CONSENT FORM

STUDY: ” A STUDY ON POSTOPERATIVE ANALGESIC EFFICACY OF EPIDURAL BUPIVACAINE , BUPIVACAINE WITH FENTANYL AND BUPIVACAINE WITH NEOSTIGMINE IN ADULTS UNDERGOING ABDOMINAL SURGERIES UNDER GENERAL ANAESTHESIA”.

STUDY CENTRE: GOVT. KILPAUK MEDICAL COLLEGE & GOVT ROYAPETTAH HOSPITAL, CHENNAI

PATIENT’S NAME:

PATIENT’S AGE:

I.P NO :

Patient may check (\checkmark) these boxes

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

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.

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

I agree not to restrict the use of any data or results that arise from the study. I agree to take part in the above study and to comply with the instructions given during the study and faithfully co operate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms.

I hereby consent to participate in this study.

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests.

Signature / thumb impression:

Patient's name and address:

place:

date:

Signature of the investigator:

Study investigator's name:

place:

date:

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு

கீழ்ப்பாக்கம் அரசு மருத்துவமனை மற்றும் ராயபேட்டை அரசு மருத்துவமனையில் வயிறு அறுவை சிகிச்சைக்கு பின் முதுகுத்தண்டுவட மேல்சவ்வில் பொருத்தப்பட்டிருக்கும் வடிகுழாய் வழியாக செலுத்தப்படும் புபிவகைன், பென்டநைல் சேர்க்கப்பட்ட புபிவகைன் மற்றும் நியோஸ்டிக்மின் சேர்க்கப்பட்ட புபிவகைன் ஆகியவற்றின் வலி நிவாரணி பண்புகளை ஒப்பிட்டு ஆய்வு.

ஆராய்ச்சி நிலையம்: மயக்கவியல் மருத்துவத் துறை, கீழ்ப்பாக்கம் மற்றும் ராயபேட்டை மருத்துவக்கல்லூரி அரசு மருத்துவமனை, சென்னை

பங்கு பெறுபவரின் பெயர்: உறவு முறை:

பங்கு பெறுபவரின் எண்:

பங்கு பெறுபவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களைக் கேட்கவும், அதற்கான தகுந்த விளக்கங்களைப் பெறவும் வாய்ப்பளிக்கப்பட்டது.

நான் இவ்வாய்வில் தன்னிச்சையாகத்தான் பங்கேற்கிறேன். எந்தக் காரணத்தினாலோ எந்தக் கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல்

நான் இவ்வாய்வில் இருந்து விலகிக் கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்மந்தமாகவும், மேலும் இது சார்ந்தஆய்வு மேற்கொள்ளும்போதும், இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளைப் பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்துகொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன்.

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக் கொள்ளவும், அதைப் பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன்.

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்குக் கொடுக்கப்பட்ட அறிவுரைகளின் படி நடந்துகொள்வதுடன், இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறாக நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன்.

இந்த ஆய்வில் எனக்கு மருத்துவப் பரிசோதனை, வயிறு அறுவை சிகிச்சைக்கு பின் முதுகுத்தண்டுவட மேல்சவ்வில்

பொருத்தப்பட்டிருக்கும் வடிகுழாய் வழியாக
 செலுத்தப்படும் புவிவகைன், பென்டரைல்
 சேர்க்கப்பட்ட புவிவகைன் மற்றும் நியோஸ்டிக்மின்
 சேர்க்கப்பட்ட புவிவகைன் ஆகியவற்றின் வலி
 நிவாரணி பண்புகளின் ஒப்பிட்டு ஆய்வு குறித்து
 ஆராய்ச்சி செய்து கொள்ள நான் முழு மனதுடன்
 சம்மதிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம்

.....

இடம்

தேதி

கட்டைவிரல் ரேகை:

பங்கேற்பவரின் பெயர் மற்றும் விலாசம்

.....

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ஆய்வாளரின் கையொப்பம்

.....

இடம்

தேதி

ஆய்வாளரின் பெயர்

.....

PARTICIPANTS' INFORMATION SHEET

Investigator : - Dr.B. SRIDHARAN

Name of the participant : -

Title: ” **A STUDY ON POSTOPERATIVE ANALGESIC EFFICACY OF EPIDURAL BUPIVACAINE , BUPIVACAINE WITH FENTANYL AND BUPIVACAINE WITH NEOSTIGMINE IN ADULTS UNDERGOING ABDOMINAL SURGERIES UNDER GENERAL ANAESTHESIA**”.

You are invited to take part in this research study. We have got approval from the IEC. You are asked to participate because you satisfy the eligibility criteria.

What is the purpose of this research?

In this study, efficacy of epidural Fentanyl and Neostigmine as adjuvant to Bupivacaine in postoperative analgesia will be evaluated so that the patient will have increased duration of analgesia, improved respiratory function, reduced requirement of epidural Bupivacaine and reduced postoperative NSAID and opioid requirements.

BENEFITS:

This study will help us in determining how Neostigmine when given through epidural route prolongs the post operative pain free duration, its role in reducing pain scores. It helps in reducing the number of epidural top up doses get reduced. Hence it decreases the amount of epidural Bupivacaine required to be given for analgesia in the postoperative period. It also helps in reducing the requirements of other

opioid analgesic drugs and NSAIDS given via systemic route in the postoperative period which causes many side effects like nausea, vomiting, itching, respiratory depression.

DISCOMFORTS AND RISKS:

Epidural Fentanyl may also cause nausea, vomiting, pruritus and dizziness in some patients.

CONFIDENTIALITY:

Patients who participated in the study and their details will be maintained confidentially and at any cost, those details will not be let out

RIGHT TO WITHDRAW :

Patients will not be forced to complete the study. At any cost, in such circumstances the treatment will not be compromised.

Date :

Signature of the investigator:

Place :

Signature/Thumb impression of
the participant

பங்கேற்பாளர் தகவல் தாள்

கீழ்ப்பாக்கம் அரசு மருத்துவமனை மற்றும் ராயபேட்டை அரசு மருத்துவமனையில் வயிறு அறுவை சிகிச்சைக்கு பின் முதுகுத்தண்டுவட மேல்சவ்வில் பொருத்தப்பட்டிருக்கும் வடிகுழாய் வழியாக செலுத்தப்படும் புபிவகைன், பென்டநைல் சேர்க்கப்பட்ட புபிவகைன் மற்றும் நியோஸ்டிக்மின் சேர்க்கப்பட்ட புபிவகைன் ஆகியவற்றின் வலி நிவாரணி பண்புகளின் ஒப்பிட்டு ஆய்வு செய்ய உள்ளோம்.

நீங்கள் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் பங்கேற்பதால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிக்கப்படாது என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியின் முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது

அடையாளங்களையோ வெளியிடமாட்டோம்
என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய
விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள்
எந்நேரமும் இந்த ஆராய்ச்சியில் இருந்து பின்வாங்கலாம்
என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்புப் பரிசோதனைகளின் முடிவுகளை
ஆராய்ச்சியின் போதோ அல்லது ஆராய்ச்சியின்
முடிவின் போதோ தங்களுக்கு அறிவிப்போம்
என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியாளர்

பங்கேற்பாளர்

கையொப்பம்

கையொப்பம்

தேதி:

KEY TO MASTER CHART

NAUSEA AND VOMITING

- 0- ABSENT
1- PRESENT

PRURITUS

- 0- ABSENT
1- PRESENT

RAMSAY SEDATION SCORE

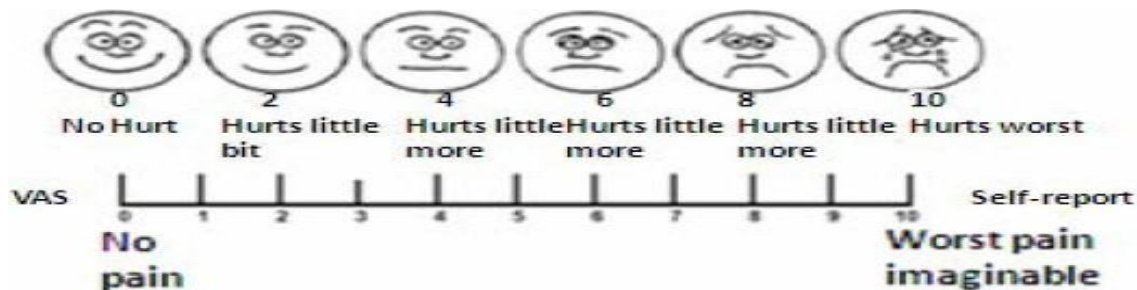
IF AWAKE:

- Ramsay 1 - Anxious, agitated, restless,
Ramsay 2 - Cooperative, oriented, tranquil,
Ramsay 3 - Responsive to commands only,

IF ASLEEP:

- Ramsay 4 - Brisk response to light glabellar tap or loud auditory stimulus,
Ramsay 5 - Sluggish response to light glabellar tap or loud auditory stimulus,
Ramsay 6 - No response to light glabellar tap or loud auditory stimulus

VISUAL ANALOGUE SCALE



BUPIVACAINE																									
SL. NO	NAME	AGE	SEX	WEIGHT	ASA	IP NO.	SURGERY	HEART RATE																	
								BASELINE	15MIN	30 MIN	45 MIN	60 MIN	75 MIN	90 MIN	120 MIN	180 MIN	240 MIN	300 MIN	360 MIN	420 MIN	480 MIN	540 MIN	600 MIN	660 MIN	720 MIN
1	NAGAMMAL	45	F	56	2	46543	TAH WITH BSO	86	91	82	86	81	80	84	88	84	94	96	98	82	84	78	86	80	84
2	DEVARAJ	34	M	62	1	41245	LAPOROTOMY AND WIDE LOCAL EXCISION	67	73	74	78	76	78	86	82	92	87	78	74	71	67	64	68	71	74
3	RANGANATHAN	46	M	66	2	46457	OPEN CHOLECYSTECTOMY	62	74	70	68	64	66	70	62	66	68	78	72	70	70	68	68	66	64
4	PACHYAMMAL	41	F	59	1	39991	LAPOROTOMY AND WIDE LOCAL EXCISION	98	103	108	98	96	99	91	95	92	86	90	92	92	90	90	88	92	90
5	RAJESHWARI	46	F	47	1	40012	TAH WITH BSO	84	92	98	89	91	80	83	89	86	87	84	86	83	88	88	86	82	82
6	PONGOTHAI	52	F	58	2	39994	TAH WITH BSO	68	79	76	70	74	66	66	62	70	66	62	72	68	68	68	69	70	68
7	KAVERY	34	F	62	1	45671	TOTAL ABDOMINAL HYSTERECTOMY	84	92	98	89	91	80	83	89	86	87	84	86	83	88	92	86	82	86
8	MALLIKA	37	F	60	1	38343	TOTAL ABDOMINAL HYSTERECTOMY	82	96	82	80	82	88	84	84	90	92	94	82	82	84	80	84	82	84
9	SENTHAMARAI	21	F	65	1	46101	DESMOID TUMOR EXCISION IN ANTERIOR ABDOMINAL WALL	90	114	102	89	94	88	84	89	80	85	99	95	88	87	86	86	90	84
10	PAZHANI	29	M	68	1	39800	CHOLECYSTECTOMY WITH CBD EXPLORATION	71	83	80	75	70	66	68	70	64	80	72	76	72	74	70	70	71	72
11	VICTORIA	41	F	57	2	46742	TAH WITH BSO	88	98	101	87	91	80	83	89	96	82	80	93	83	88	86	86	82	86
12	DHANDAPANI	32	M	61	1	43901	ANATOMICAL MESH REPAIR	64	85	80	64	64	65	68	60	73	60	62	61	72	65	59	60	62	60
13	VIMALA	49	F	72	2	40906	TAH WITH BSO	85	92	98	89	91	80	83	89	86	87	84	90	83	88	85	86	82	86
14	VEERAPANDI	24	M	63	1	41990	LEFT HEMICOLECTOMY	83	96	92	80	81	80	82	79	91	80	79	80	91	82	82	82	81	83
15	GOWRI	39	F	68	1	43567	TAH WITH BSO	94	109	105	89	91	90	87	89	86	87	84	86	96	88	92	92	86	88
16	KALAISELVI	41	F	54	1	38691	TAH WITH BSO	90	118	114	92	88	86	90	89	99	88	90	90	104	102	90	88	90	90
17	MUNUSAMY	36	M	58	1	37927	LAPOROTOMY AND WIDE LOCAL EXCISION	70	92	75	72	68	68	71	72	82	70	68	82	70	68	70	72	72	72
18	GANGAMMAL	39	F	66	1	41091	TAH WITH BSO	85	95	94	82	84	86	80	79	91	84	84	80	92	80	82	84	80	78
19	GANGA	28	F	76	1	37402	TOTAL ABDOMINAL HYSTERECTOMY	84	92	98	89	91	80	83	89	86	87	84	86	83	88	92	86	82	86
20	SARANYA	29	F	49	1	49904	TOTAL ABDOMINAL HYSTERECTOMY	96	118	105	90	92	88	87	89	92	104	96	99	92	90	88	85	88	88
BUPIVACAINE WITH FENTANYL																									
SL. NO	NAME	AGE	SEX	WEIGHT	ASA	IP NO.	SURGERY	HEART RATE																	
								BASELINE	15MIN	30 MIN	45 MIN	60 MIN	75 MIN	90 MIN	120 MIN	180 MIN	240 MIN	300 MIN	360 MIN	420 MIN	480 MIN	540 MIN	600 MIN	660 MIN	720 MIN
21	ILAMATHI	28	F	43	1	31389	TOTAL ABDOMINAL HYSTERECTOMY	89	112	106	84	85	91	90	94	98	90	86	82	81	83	96	88	86	86
22	VANMATHY	41	F	58	1	32671	TAH WITH BSO	80	92	84	78	78	81	72	79	84	74	72	69	66	70	78	89	78	82
23	LAKSHMI	49	F	51	2	38768	TAH WITH BSO	68	78	72	69	62	65	68	62	63	57	58	60	60	66	68	67	64	65
24	AFRIN BANU	29	F	49	1	26391	TOTAL ABDOMINAL HYSTERECTOMY	90	105	94	94	92	90	85	84	95	98	90	84	82	83	80	86	88	86
25	THAMARAI	33	F	57	1	30092	LAPOROTOMY AND CYTOREDUCTION	88	96	90	85	80	82	84	80	84	85	84	76	75	75	87	90	84	85
26	SULOCHANA	41	F	65	2	28729	TOTAL ABDOMINAL HYSTERECTOMY	84	100	95	90	86	82	76	78	90	80	76	74	75	74	78	80	82	82
27	SENGOTAVAN	29	M	59	1	33791	OPEN CHOLECYSTECTOMY	68	74	72	69	64	68	72	62	63	60	60	58	60	62	68	62	64	64
28	BABU	36	M	63	1	29172	LAPOROTOMY AND WIDE LOCAL EXCISION	65	84	62	62	60	62	64	70	62	60	60	59	56	55	56	64	60	61
29	KALPANA	28	F	55	1	42980	LAPOROTOMY AND CYTOREDUCTION	84	99	88	89	91	80	83	89	86	80	77	73	75	74	82	85	82	84
30	ABDUL RAHEEM	39	M	71	1	30952	OPEN CHOLECYSTECTOMY	78	89	80	76	75	72	71	70	70	85	70	64	65	66	69	75	72	72
31	VINODHINI	44	F	61	2	28539	TAH WITH BSO	88	103	92	85	85	86	82	81	91	80	78	76	77	73	74	80	104	96
32	NIROSHA	49	F	54	1	47296	TAH WITH BSO	91	108	94	94	88	89	85	84	95	98	90	79	80	80	80	85	80	85
33	RAJA	24	M	64	1	39275	ANATOMICAL MESH REPAIR OF INCISIONAL HERNIA	68	74	72	69	64	68	72	62	63	60	60	62	64	66	68	62	64	64
34	JAMUL RASHI	36	F	59	1	40761	LAPOROTOMY AND EXCISION OF OVARIAN CYST	76	90	73	76	72	71	72	70	76	70	66	68	66	65	64	70	75	74
35	SAFEENA BEGUM	24	F	58	1	25735	TOTAL ABDOMINAL HYSTERECTOMY	79	101	98	84	81	80	82	88	86	76	70	72	72	74	72	86	82	86
36	RAMANI	46	F	61	2	26819	TAH WITH BSO	80	84	86	78	78	76	72	79	84	74	71	69	68	70	70	80	78	82
37	SELVI	35	F	51	1	23751	OPEN CHOLECYSTECTOMY	88	104	92	86	80	82	80	78	78	84	78	76	77	76	76	88	84	82
38	JAFFER ALI	35	M	70	1	49425	ANATOMICAL MESH REPAIR OF INCISIONAL HERNIA	64	74	70	69	66	68	66	62	60	72	59	58	58	60	58	59	64	64
39	SHAJITHA	39	F	62	1	49692	TAH WITH BSO	90	111	96	90	88	84	85	86	94	84	81	82	84	80	92	86	85	84
40	NITHYA	31	F	66	1	39016	TOTAL ABDOMINAL HYSTERECTOMY	88	102	90	89	86	82	83	82	84	82	80	76	75	76	84	86	82	80
BUPIVACAINE WITH NEOSTIGMINE																									
SL. NO	NAME	AGE	SEX	WEIGHT	ASA	IP NO.	SURGERY	HEART RATE																	
								BASELINE	15MIN	30 MIN	45 MIN	60 MIN	75 MIN	90 MIN	120 MIN	180 MIN	240 MIN	300 MIN	360 MIN	420 MIN	480 MIN	540 MIN	600 MIN	660 MIN	720 MIN
41	JOTHI	34	F	56	1	33292	TOTAL ABDOMINAL HYSTERECTOMY	81	94	85	80	78	80	78	76	78	84	78	78	76	77	91	85	80	81
42	THAHIRA BEGUM	38	F	62	1	38724	TOTAL ABDOMINAL HYSTERECTOMY	75	92	84	74	72	73	70	68	80	70	72	72	70	71	72	80	75	72
43	ANNAPURNI	42	F	66	2	36428	TAH WITH BSO	82	96	90	80	78	76	76	75	76	84	78	77	78	76	78	84	80	80
44	PUSHPALATHA	22	F	59	1	31649	LAPOROTOMY AND EXCISION OF OVARIAN CYST	98	103	108	98	96	99	91	95	92	86	90	92	92	90	90	88	94	96
45	CHINRASU	26	M	47	1	42989	ANATOMICAL MESH REPAIR OF INCISIONAL HERNIA	74	86	80	78	70	72	70	72	76	70	72	70	68	70	76	74	75	76
46	JAYASURYA	23	F	58	2	40957	MYOMECTOMY	82	92	90	83	80	78	78	80	86	80	80	78	76	78	90	84	80	82
47	THAMEEM	36	F	62	1	29534	TOTAL ABDOMINAL HYSTERECTOMY	83	96	84	80	81	80	80	79	81	80	78	78	80	82	86	83	80	84
48	INDHIRA	41	F	60	1	38572	LAPOROTOMY AND CYTOREDUCTIVE SURGERY	94	107	105	89	91	86	87	86	86	82	84	85	86	88	92	102	96	94
49	LOGANATHAN	37	M	65	1	46301	LAPOROTOMY AND WIDE LOCAL EXCISION	70	84	78	68	68	67	70	68	80	72	68	67	68	70	72	68	76	78
50	AMBIKAI	29	F	68	1	39968	TOTAL ABDOMINAL HYSTERECTOMY	92	106	86	88	84	90	88	86	96	88	86	85	84	86	90	92	86	88
51	SAFASUL	46	F	57	2	47892	TAH WITH BSO	84	96	88	82	82	80	84	85	90	80	82	82	83	84	92	86	80	86
52	SHEIK DAMOOD	38	M	61	1	31090	LEFT HEMICOLECTOMY	91	108	94	94	88	89	85	84	90	88	86	90	88	85	90	90	89	92
53	KUPPAM	30	M	72	2	40828	CHOLECYSTECTOMY WITH CBD EXPLORATION	65	74	72	69	64	68	72	62	63	64	63	62	60	60	68	63	66	64
54	MARY	46	F	63	1	43967	TAH WITH BSO	76	90	73	76	69	71	72	72	76	70	72	68	66	65	64	70	75	74
55	SHANKAR	48	M	68	1	39686	OPEN CHOLECYSTECTOMY	79	101	98	84	81	80	82	88	86	80	80	80	79	82	88	86	82	84
56	JAYAPREETHIKA	29	F	54	1	20005	OPEN OOPHORECTOMY	92	112	110	101	85	91	92	94	98	90	88	90	88	88	90	86	87	86
57	GOMATHI	35	F	71	1	29002	TAH WITH BSO	79	92	88	78	78	81	72	79	84	74	72	78	76	74	78	89	76	76
58	MEENAKSHI	41	F	65	2	43680	TAH WITH BSO	68	78	72	69	62	65	68	62	63	60	59	58	59	60	70	67	64	65
59	SAJIK AHMED	28	M	54	1	49739	LAPOROTOMY AND WIDE LOCAL EXCISION	88</																	

BUPIVACAINE																			
MEAN ARTERIAL BLOOD PRESSURE																			
SL. NO	NAME	BASELINE	15MIN	30 MIN	45 MIN	60 MIN	75 MIN	90 MIN	120 MIN	180 MIN	240 MIN	300 MIN	360 MIN	420 MIN	480 MIN	540 MIN	600 MIN	660 MIN	720 MIN
1	NAGAMMAL	102	81	88	87	87	86	87	81	87	111	86	91	93	93	94	95	96	95
2	DEVARAJ	88	71	80	82	81	82	82	82	82	85	81	79	80	80	81	83	84	82
3	RANGANATHAN	95	84	85	86	85	85	85	84	90	84	81	82	81	87	88	89	90	90
4	PACHYAMMAL	80	75	81	80	81	81	80	80	88	76	77	80	80	81	79	80	80	80
5	RAJESHWARI	81	69	75	77	78	78	78	78	77	78	76	79	80	78	79	80	76	79
6	PONGOTHAI	115	80	96	96	99	95	96	98	98	113	100	109	108	107	107	103	106	106
7	KAVERY	97	82	87	88	87	87	86	88	99	89	86	85	86	93	92	89	91	90
8	MALLIKA	87	79	80	82	81	82	82	80	81	77	76	79	80	81	80	81	83	83
9	SENTHAMARAI	85	84	84	83	86	89	88	84	90	83	84	88	88	87	89	88	86	86
10	PAZHANI	97	92	93	90	91	91	90	92	108	91	90	96	92	92	91	90	91	90
11	VICTORIA	108	99	100	96	99	99	100	98	98	102	96	99	100	102	102	101	101	101
12	DHANDAPANI	93	91	88	88	89	87	88	88	90	89	90	88	88	88	90	90	91	90
13	VIMALA	83	76	75	77	78	78	78	78	78	78	77	80	80	80	80	80	76	78
14	VEERAPANDI	91	86	87	88	90	88	88	89	90	98	87	88	90	91	92	89	91	91
15	GOWRI	81	69	82	80	80	81	80	81	80	84	80	80	79	79	80	79	80	80
16	KALAISELVI	86	80	85	86	86	87	87	87	88	82	81	88	89	84	85	85	86	84
17	MUNUSAMY	102	90	87	88	87	86	90	91	89	91	96	91	94	89	90	92	91	91
18	GANGAMMAL	82	78	80	80	80	81	80	80	80	81	80	84	83	80	81	80	80	80
19	GANGA	77	70	72	76	78	77	77	77	78	80	77	77	78	77	76	77	76	76
20	SARANYA	79	74	78	76	76	76	76	77	76	80	76	76	76	78	77	77	76	77
BUPIVACAINE WITH FENTANYL																			
MEAN ARTERIAL BLOOD PRESSURE																			
SL. NO	NAME	BASELINE	15MIN	30 MIN	45 MIN	60 MIN	75 MIN	90 MIN	120 MIN	180 MIN	240 MIN	300 MIN	360 MIN	420 MIN	480 MIN	540 MIN	600 MIN	660 MIN	720 MIN
21	ILAMATHI	79	72	78	80	77	78	79	80	80	78	76	76	77	77	82	78	78	80
22	VANMATHY	92	85	88	88	89	87	86	88	87	88	87	88	89	93	89	90	88	87
23	LAKSHMI	108	86	90	98	89	100	99	100	98	99	98	100	99	99	99	106	98	100
24	AFRIN BANU	95	82	88	88	88	87	86	88	88	89	87	89	90	92	88	89	91	90
25	THAMARAI	88	80	80	82	81	81	79	80	80	82	80	79	80	81	80	81	83	84
26	SULOCHANA	94	92	88	88	89	88	88	88	90	89	90	88	88	89	91	96	97	96
27	SENGOTAVAN	85	79	75	77	80	78	78	78	78	78	77	80	80	80	80	80	76	78
28	BABU	94	86	87	88	90	88	88	89	90	88	90	88	90	90	90	89	91	91
29	KALPANA	78	70	71	78	80	78	77	77	78	80	77	77	78	77	76	77	76	76
30	ABDUL RAHEEM	87	80	83	84	85	84	87	87	88	86	88	88	89	84	85	85	86	84
31	VINODHINI	102	98	99	100	106	106	105	101	102	102	100	100	99	103	100	102	100	102
32	NIROSHA	98	90	92	93	90	90	87	81	87	95	96	92	93	93	94	95	96	95
33	RAJA	89	78	80	82	81	82	82	82	82	80	81	79	80	81	81	83	85	82
34	JAMUL RASHI	95	87	88	90	88	90	90	90	92	91	91	92	91	91	90	89	90	90
35	SAFEENA BEGUM	82	77	80	80	81	81	80	80	79	78	77	80	80	81	79	80	80	80
36	RAMANI	105	90	88	92	92	90	90	91	89	91	90	91	90	89	96	90	91	91
37	SELVI	86	80	85	88	87	87	87	87	88	88	87	88	89	88	87	85	86	89
38	JAFFER ALI	103	99	98	99	97	100	99	99	100	100	98	98	100	98	99	99	100	102
39	SHAJITHA	82	78	80	81	80	81	80	81	81	81	81	80	79	80	84	80	80	80
40	NITHYA	77	72	74	76	76	78	76	77	78	80	78	77	78	77	77	77	76	76
BUPIVACAINE WITH NEOSTIGMINE																			
MEAN ARTERIAL BLOOD PRESSURE																			
SL. NO	NAME	BASELINE	15MIN	30 MIN	45 MIN	60 MIN	75 MIN	90 MIN	120 MIN	180 MIN	240 MIN	300 MIN	360 MIN	420 MIN	480 MIN	540 MIN	600 MIN	660 MIN	720 MIN
41	JOTHI	88	82	81	82	81	81	79	80	80	82	80	80	80	81	80	81	83	82
42	THAHIRA BEGUM	92	85	89	90	89	88	86	89	90	88	90	88	89	93	89	90	88	88
43	ANNAPURNI	103	94	95	96	95	101	100	100	100	101	99	100	99	102	100	106	100	100
44	PUSHPALATHA	82	75	80	81	83	81	80	81	81	81	81	80	79	80	81	80	80	80
45	CHINRASU	108	92	97	99	99	100	99	100	98	99	98	100	99	99	100	106	102	102
46	JAYASURYA	79	72	78	80	77	78	79	80	80	78	76	76	77	77	82	78	78	80
47	THAMEEM	96	90	88	90	88	90	90	89	89	90	91	92	92	91	90	89	90	90
48	INDHIRA	83	77	78	79	79	80	80	80	80	80	78	80	80	81	84	81	80	80
49	LOGANATHAN	105	93	91	97	98	98	99	98	98	100	99	99	99	98	100	98	99	100
50	AMBIKAI	86	79	76	78	77	77	78	77	78	80	79	79	78	79	80	80	80	80
51	SAFASUL	99	91	98	99	99	100	99	99	100	100	99	98	101	103	102	102	100	102
52	SHEIK DAMOOD	94	84	89	89	91	90	88	91	90	89	90	90	90	90	93	90	89	89
53	KUPPAM	84	76	75	81	80	80	80	79	79	80	80	81	81	80	81	85	80	80
54	MARY	98	92	92	92	91	93	93	93	93	94	94	92	91	90	92	94	91	90
55	SHANKAR	100	90	92	93	91	92	90	92	91	91	90	91	90	90	96	92	91	92
56	JAYAPREETHIKA	84	76	80	82	84	83	84	83	83	83	84	83	84	83	86	86	82	80
57	GOMATHI	82	77	79	78	79	80	80	80	80	79	79	80	80	84	80	80	80	80
58	MENAKSHI	78	71	72	75	72	73	72	73	72	70	73	72	71	73	70	72	73	72
59	SAJIK AHMED	102	89	87	88	87	88	90	90	92	95	92	90	90	92	90	91	92	94
60	SUNDARI	88	82	81	82	83	82	81	82	82	86	80	81	82	82	81	82	82	82

BUPIVACAINE																			
		RESPIRATORY RATE																	
SL. NO	NAME	BASELINE	15MIN	30 MIN	45 MIN	60 MIN	75 MIN	90 MIN	120 MIN	180 MIN	240 MIN	300 MIN	360 MIN	420 MIN	480 MIN	540 MIN	600 MIN	660 MIN	720 MIN
1	NAGAMMAL	14	16	12	12	12	12	13	12	15	12	12	20	18	15	13	14	16	14
2	DEVARAJ	12	14	13	12	12	12	13	11	12	10	12	12	14	14	13	14	14	14
3	RANGANATHAN	12	13	12	12	12	12	12	12	12	11	10	12	15	15	12	12	12	12
4	PACHYAMMAL	14	12	12	12	12	12	12	15	12	12	12	18	16	14	12	13	12	12
5	RAJESHWARI	12	15	12	12	12	12	12	12	12	10	10	12	12	14	15	14	12	12
6	PONGOTHAI	13	14	12	12	12	12	12	12	18	12	10	12	14	12	12	12	12	12
7	KAVERY	10	12	12	12	12	12	12	12	14	10	10	11	12	12	14	12	12	12
8	MALLIKA	14	12	12	12	12	12	12	12	12	12	10	11	12	10	14	15	13	14
9	SENTHAMARAI	12	12	12	12	12	12	12	12	12	11	14	10	12	15	16	14	14	14
10	PAZHANI	12	11	12	12	12	12	12	12	12	11	10	11	10	12	12	12	14	12
11	VICTORIA	14	12	12	12	12	12	12	12	14	10	12	14	13	12	14	14	14	12
12	DHANDAPANI	12	12	11	12	12	12	12	12	11	10	12	12	12	13	14	12	12	13
13	VIMALA	15	12	12	12	12	12	12	15	12	12	12	12	12	12	13	14	14	15
14	VEERAPANDI	10	12	12	12	12	12	11	12	14	10	11	12	12	12	12	12	13	14
15	GOWRI	13	13	12	12	12	12	12	15	14	11	10	12	15	12	12	12	12	12
16	KALAISELVI	14	12	12	12	12	12	12	12	14	11	10	14	14	12	12	14	12	14
17	MUNUSAMY	10	12	12	12	12	12	12	12	14	11	11	12	14	12	12	12	12	12
18	GANGAMMAL	12	12	12	12	12	12	12	12	14	11	12	12	12	14	15	12	12	12
19	GANGA	12	13	12	12	12	12	12	14	14	11	12	12	12	12	12	12	15	12
20	SARANYA	14	13	12	12	12	12	12	11	12	11	11	13	14	13	13	12	12	12
BUPIVACAINE WITH FENTANYL																			
		RESPIRATORY RATE																	
SL. NO	NAME	BASELINE	15MIN	30 MIN	45 MIN	60 MIN	75 MIN	90 MIN	120 MIN	180 MIN	240 MIN	300 MIN	360 MIN	420 MIN	480 MIN	540 MIN	600 MIN	660 MIN	720 MIN
21	ILAMATHI	12	12	12	12	12	12	12	12	14	10	12	10	10	12	14	12	14	12
22	VANMATHY	12	12	11	12	12	12	12	12	11	10	12	12	12	12	14	12	12	13
23	LAKSHMI	12	12	12	12	12	12	12	15	13	12	12	10	12	12	13	14	12	13
24	AFRIN BANU	14	12	12	12	12	12	11	12	14	10	12	11	12	12	15	14	13	14
25	THAMARAI	13	13	12	12	12	12	12	15	14	11	10	12	12	12	14	14	15	14
26	SULOCHANA	14	12	12	12	12	12	12	12	14	11	10	12	14	12	12	14	12	14
27	SENGOTAVAN	10	12	12	12	12	12	12	12	12	11	11	12	12	12	12	12	12	12
28	BABU	12	12	12	12	12	12	12	12	14	11	10	10	12	12	15	12	12	12
29	KALPANA	12	13	12	12	12	12	12	14	14	11	12	12	12	14	14	12	15	14
30	ABDUL RAHEEM	14	13	12	12	12	12	12	11	12	11	11	12	14	13	13	12	12	14
31	VINODHINI	14	16	12	12	12	12	13	12	15	12	12	12	13	15	18	14	16	14
32	NIROSHA	12	14	13	12	12	12	13	11	12	10	12	12	14	14	13	14	14	14
33	RAJA	12	13	12	12	12	12	12	12	12	11	10	12	12	15	13	12	12	12
34	JAMUL RASHI	14	12	12	12	12	12	12	15	12	12	12	12	14	14	15	13	12	12
35	SAFEENA BEGUM	12	15	12	12	12	12	12	12	10	10	11	12	14	15	14	12	12	12
36	RAMANI	13	14	12	12	12	12	12	12	18	12	10	12	12	12	12	12	12	13
37	SELVI	10	12	12	12	12	12	12	12	14	12	10	11	12	12	14	12	12	12
38	JAFFER ALI	14	12	12	12	12	12	12	12	12	12	10	11	12	10	14	15	13	12
39	SHAJITHA	12	12	12	12	12	12	12	12	12	11	14	10	12	15	16	14	14	13
40	NITHYA	12	11	12	12	12	12	12	12	12	11	10	11	10	12	12	12	14	11
BUPIVACAINE WITH NEOSTIGMINE																			
		RESPIRATORY RATE																	
SL. NO	NAME	BASELINE	15MIN	30 MIN	45 MIN	60 MIN	75 MIN	90 MIN	120 MIN	180 MIN	240 MIN	300 MIN	360 MIN	420 MIN	480 MIN	540 MIN	600 MIN	660 MIN	720 MIN
41	JOTHI	12	13	12	12	12	12	12	14	14	11	12	12	12	18	12	12	15	12
42	THAHIRA BEGUM	13	13	12	12	11	12	12	11	12	11	11	13	14	13	13	12	12	12
43	ANNAPURNI	14	12	12	12	12	12	13	12	15	12	12	13	14	19	13	14	16	14
44	PUSHPALATHA	12	14	13	12	12	12	13	11	12	10	12	12	14	14	13	14	14	14
45	CHINRASU	10	13	12	12	12	12	12	12	12	11	10	12	12	15	12	12	12	12
46	JAYASURYA	13	14	12	12	12	12	12	12	18	12	10	12	13	12	12	12	12	13
47	THAMEEM	10	12	12	12	12	12	12	12	14	10	10	11	12	15	14	12	12	14
48	INDHIRA	14	12	12	12	12	12	12	12	12	12	10	11	11	14	14	15	13	12
49	LOGANATHAN	10	12	12	12	12	12	12	12	12	11	14	10	12	15	16	14	14	13
50	AMBIKAI	12	11	12	12	12	12	12	12	12	11	13	11	10	12	15	14	14	11
51	SAFASUL	14	12	12	12	12	12	12	12	14	10	12	14	13	12	14	14	14	12
52	SHEIK DAMOOD	12	12	11	12	12	12	12	12	11	10	12	12	12	13	14	12	12	13
53	KUPPAM	15	12	12	12	12	12	12	15	12	12	12	12	12	12	13	14	14	15
54	MARY	10	12	12	12	12	12	11	12	14	10	11	12	12	12	12	12	13	14
55	SHANKAR	10	13	12	12	12	12	12	15	14	11	10	12	15	12	12	12	12	12
56	JAYAPREETHIKA	12	12	12	12	12	12	12	15	12	12	12	12	16	14	12	13	12	12
57	GOMATHI	12	15	12	12	12	12	12	12	12	10	10	12	12	14	15	14	12	12
58	MEENAKSHI	13	14	12	12	12	12	12	12	18	12	10	12	14	12	12	12	12	13
59	SAJK AHMED	10	12	12	12	12	12	12	12	14	10	10	11	12	12	14	12	12	12
60	SUNDARI	14	12	12	12	12	12	12	12	12	12	10	11	12	10	14	15	13	12

BUPIVACAINE																				
VISUAL ANALOGUE SCALE																				
SL. NO	NAME	BASELINE	15MIN	30 MIN	45 MIN	60 MIN	75 MIN	90 MIN	120 MIN	180 MIN	240 MIN	300 MIN	360 MIN	420 MIN	480 MIN	540 MIN	600 MIN	660 MIN	720 MIN	TIME FOR FIRST RESCUE ANALGESIA
1	NAGAMMAL	-	-	-	-	-	-	-	-	0	1	9	5	4	3	5	5	5	4	104 MINS
2	DEVARAJ	-	-	-	-	-	-	-	-	0	1	2	8	4	4	5	4	5	5	115 MINS
3	RANGANATHAN	-	-	-	-	-	-	-	-	0	0	10	6	5	5	5	6	5	6	91 MINS
4	PACHYAMMAL	-	-	-	-	-	-	-	-	0	1	9	6	5	4	5	4	5	4	101 MINS
5	RAJESHWARI	-	-	-	-	-	-	-	-	-	0	1	9	8	6	6	6	5	5	104 MINS
6	PONGOTHAI	-	-	-	-	-	-	-	-	-	1	0	9	8	6	6	5	6	5	110 MINS
7	KAVERY	-	-	-	-	-	-	-	-	-	1	0	10	7	5	6	5	6	5	107 MINS
8	MALLIKA	-	-	-	-	-	-	-	-	-	0	0	8	5	4	4	3	4	4	100 MINS
9	SENTHAMARAI	-	-	-	-	-	-	-	-	0	0	9	5	4	4	4	5	4	4	113 MINS
10	PAZHANI	-	-	-	-	-	-	-	-	-	1	0	10	8	7	6	5	6	5	103 MINS
11	VICTORIA	-	-	-	-	-	-	-	-	-	0	1	9	5	4	3	3	3	3	109 MINS
12	DHANDAPANI	-	-	-	-	-	-	-	-	-	1	0	9	3	3	4	3	3	3	114 MINS
13	VIMALA	-	-	-	-	-	-	-	-	-	1	0	10	7	5	6	5	6	5	102 MINS
14	VEERAPANDI	-	-	-	-	-	-	-	-	-	0	0	8	5	4	4	3	3	3	114 MINS
15	GOWRI	-	-	-	-	-	-	-	-	-	0	9	5	4	4	4	5	4	4	105 MINS
16	KALAISELVI	-	-	-	-	-	-	-	-	-	1	0	9	8	6	7	6	6	6	107 MINS
17	MUNUSAMY	-	-	-	-	-	-	-	-	0	0	9	4	4	5	3	3	4	3	104 MINS
18	GANGAMMAL	-	-	-	-	-	-	-	-	-	1	2	8	4	4	5	4	5	5	111 MINS
19	GANGA	-	-	-	-	-	-	-	-	-	0	9	6	5	5	5	6	5	6	98 MINS
20	SARANYA	-	-	-	-	-	-	-	-	-	1	9	9	6	6	5	6	6	6	104 MINS
BUPIVACAINE WITH FENTANYL																				
VISUAL ANALOGUE SCALE																				
SL. NO	NAME	BASELINE	15MIN	30 MIN	45 MIN	60 MIN	75 MIN	90 MIN	120 MIN	180 MIN	240 MIN	300 MIN	360 MIN	420 MIN	480 MIN	540 MIN	600 MIN	660 MIN	720 MIN	TIME FOR FIRST RESCUE ANALGESIA
21	ILAMATHI	-	-	-	-	-	-	-	-	-	0	1	0	0	0	9	5	4	4	277 MINS
22	VANMATHY	-	-	-	-	-	-	-	-	0	0	0	1	1	1	8	4	4	4	301 MINS
23	LAKSHMI	-	-	-	-	-	-	-	-	-	0	0	1	1	1	3	9	5	4	285 MINS
24	AFRIN BANU	-	-	-	-	-	-	-	-	0	0	0	0	0	1	8	3	3	3	297 MINS
25	THAMARAI	-	-	-	-	-	-	-	-	-	0	0	1	1	2	2	9	4	3	271 MINS
26	SULOCHANA	-	-	-	-	-	-	-	-	-	0	0	0	1	1	2	6	3	2	287 MINS
27	SENGOTAVAN	-	-	-	-	-	-	-	-	-	1	0	0	0	3	9	6	6	5	281 MINS
28	BABU	-	-	-	-	-	-	-	-	0	0	0	0	0	1	8	3	3	2	299 MINS
29	KALPANA	-	-	-	-	-	-	-	-	-	-	0	1	2	2	2	1	6	7	278 MINS
30	ABDUL RAHEEM	-	-	-	-	-	-	-	-	-	1	0	0	0	0	6	5	4	4	297 MINS
31	VINODHINI	-	-	-	-	-	-	-	-	-	0	0	0	1	2	8	5	3	5	261 MINS
32	NIROSHA	-	-	-	-	-	-	-	-	-	1	0	2	1	0	10	4	4	3	289 MINS
33	RAJA	-	-	-	-	-	-	-	-	-	0	0	0	0	0	0	5	3	2	312 MINS
34	JAMUL RASHI	-	-	-	-	-	-	-	-	0	0	0	0	0	1	6	4	3	2	306 MINS
35	SAFEENA BEGUM	-	-	-	-	-	-	-	-	-	0	1	0	1	1	9	4	3	4	286 MINS
36	RAMANI	-	-	-	-	-	-	-	-	-	0	1	1	1	1	7	5	4	4	276 MINS
37	SELVI	-	-	-	-	-	-	-	-	1	2	2	3	2	9	7	6	5	5	303 MINS
38	JAFFER ALI	-	-	-	-	-	-	-	-	0	0	0	0	0	1	7	3	2	2	300 MINS
39	SHAJITHA	-	-	-	-	-	-	-	-	-	0	0	1	2	1	8	5	4	3	293 MINS
40	NITHYA	-	-	-	-	-	-	-	-	-	0	0	1	1	3	7	4	5	4	288 MINS
BUPIVACAINE WITH NEOSTIGMINE																				
VISUAL ANALOGUE SCALE																				
SL. NO	NAME	BASELINE	15MIN	30 MIN	45 MIN	60 MIN	75 MIN	90 MIN	120 MIN	180 MIN	240 MIN	300 MIN	360 MIN	420 MIN	480 MIN	540 MIN	600 MIN	660 MIN	720 MIN	TIME FOR FIRST RESCUE ANALGESIA
41	JOTHI	-	-	-	-	-	-	-	-	-	0	1	2	2	1	5	6	3	5	257 MINS
42	THAHIRA BEGUM	-	-	-	-	-	-	-	-	-	1	0	0	1	1	9	4	3	3	276 MINS
43	ANNAPURNI	-	-	-	-	-	-	-	-	-	0	0	1	2	1	8	4	3	3	251 MINS
44	PUSHPALATHA	-	-	-	-	-	-	-	-	0	0	0	1	0	6	3	3	4	2	256 MINS
45	CHINRASU	-	-	-	-	-	-	-	-	0	0	1	1	0	7	4	4	3	4	251 MINS
46	JAYASURYA	-	-	-	-	-	-	-	-	0	1	0	0	1	2	6	5	4	5	283MINS
47	THAMEEM	-	-	-	-	-	-	-	-	-	1	0	2	1	0	9	7	5	5	249 MINS
48	INDHIRA	-	-	-	-	-	-	-	-	-	-	1	1	2	2	10	7	5	6	236 MINS
49	LOGANATHAN	-	-	-	-	-	-	-	-	0	0	0	1	0	7	4	3	3	3	264 MINS
50	AMBIKAI	-	-	-	-	-	-	-	-	-	0	1	1	2	8	4	5	4	3	267 MINS
51	SAFASUL	-	-	-	-	-	-	-	-	-	0	0	1	1	7	6	5	3	4	247 MINS
52	SHEIK DAMOOD	-	-	-	-	-	-	-	-	0	0	0	1	1	1	7	4	3	4	275 MINS
53	KUPPAM	-	-	-	-	-	-	-	-	-	0	1	1	2	2	9	6	5	4	281 MINS
54	MARY	-	-	-	-	-	-	-	-	-	0	0	1	1	1	7	5	4	5	266 MINS
55	SHANKAR	-	-	-	-	-	-	-	-	-	2	2	3	2	9	7	6	5	5	241 MINS
56	JAYAPREETHIKA	-	-	-	-	-	-	-	-	0	1	1	2	2	3	9	6	5	5	247 MINS
57	GOMATHI	-	-	-	-	-	-	-	-	-	0	0	1	0	1	8	4	5	4	281 MINS
58	MEENAKSHI	-	-	-	-	-	-	-	-	-	0	0	2	1	2	7	3	2	3	283 MINS
59	SAJIK AHMED	-	-	-	-	-	-	-	-	0	0	0	1	2	8	4	3	4	4	269 MINS
60	SUNDARI	-	-	-	-	-	-	-	-	-	0	1	1	2	6	5	4	5	4	255MINS