A STUDY OF EFFICACY OF TRANSDERMAL NITROGLYCERINE PATCH IN ENHANCING ANALGESIA OF INTRATHECAL NEOSTIGMINE FOLLOWING HYSTERECTOMIES UNDER BUPIVACAINE SPINAL ANAESTHESIA

Dissertation submitted to

The Tamil Nadu Dr MGR Medical University, Chennai, Tamil Nadu in partial fulfilment of the degree of

M.D. ANAESTHESIOLOGY [2010-2013]

THANJAVUR MEDICAL COLLEGE

THANJAVUR

TAMIL NADU

ENDORSEMENT BY THE HOD AND DEAN OF THE INSTITUTE

This is to certify that this dissertation entitled A STUDY OF EFFICACY OF TRANSDERMAL NITROGLYCERINE PATCH IN ENHANCING ANALGESIA OF INTRATHECAL NEOSTIGMINE FOLLOWING HYSTERECTOMIES UNDER BUPIVACAINE SPINAL ANAESTHESIA is bonafide research work done by Dr.VINEETH.C.V, Resident in Anaesthesiology, Thanjavur Medical College.

Professor and Head	Dean
Department of Anaesthesiology	Thanjavur Medical College
Thanjavur Medical College	Thanjavur
Thanjavur, Tamil Nadu.	Tamil Nadu.

Date:

Place:Thanjavur

Thanjavur Medical College

THANJAVUR, TAMILNADU, INDIA-613004

(Affiliated to the T.N Dr.MGR Medical University, Chennai)

ETHICAL COMMITTEE CERTIFICATE

Name of the Candidate	: Dr.VINEETH.C.V
Course	: M.D. (ANAESTHESIOLOGY)
Period of Study	: 2010 - 2012
College	: THANJAVUR MEDICAL COLLEGE
Dissertation Topic	: A STUDY OF EFFICACY OF TRANSERMAL NITROGLYCERINE PATCH IN ENHANCING ANALGESIA OF INTRATHECAL NEOSTIGMINE FOLLOWING HYSTERECTOMIES UNDER BUPIVACAINE SPINAL ANAESTHESIA.

The Ethical Committee, Thanjavur Medical College has decided to inform that your Dissertation Topic is accepted and you are permitted to proceed with the above study.

Thanjavur
Date :

Secretary
Ethical Committee

CERTIFICATE BY THE GUIDE

This is to certify that this dissertation entitled A STUDY OF EFFICACY OF TRANSDERMAL NITROGLYCERINE PATCH IN ENHANCING ANALGESIA OF INTRATHECAL NEOSTIGMINE FOLLOWING HYSTERECTOMIES UNDER BUPIVACAINE SPINAL ANAESTHESIA is a bonafide research work done by Dr.VINEETH.C.V, Resident in Anaesthesiology, Thanjavur Medical College, Thanjavur, under my guidance in partial fulfilment of the requirement for the degree of M.D. ANAESTHESIOLOGY [2010-2013].

Date:

Place: Thanjavur

Dr.AL.MEENAKSHI SUNDARAM. **M.D D.A**

Professor

Department of Anaesthesiology

Thanjavur Medical College

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled A STUDY OF EFFICACY OF TRANSDERMAL NITROGLYCERINE PATCH IN ENHANCING ANALGESIA OF INTRATHECAL NEOSTIGMINE FOLLOWING HYSTERECTOMIES UNDER BUPIVACAINE SPINAL ANAESTHESIA is a bonafide and genuine research work carried out by me in the Department of Anaesthesiology, Thanjavur Medical College.

Date:

Place: Thanjavur

Signature of the candidate

[Dr.VINEETH.C.V]

Resident

Department of Anaesthesiology

Thanjavur Medical College.

PLAGIARISM REPORT

ACKNOWLEDGEMENT

It is a sacred duty on my part to pay my debt of gratitude from the depth of my heart and express my endeavouring sincere thanks for all those who have lent a helping hand to make this work come to a completion.

I am extremely thankful **to Dr.GUNASEKARAN.M.D, DCH**, Dean-in-charge, Thanjavur Medical College, for his kind permission to carry out this study.

I wish to express my humble gratitude and profound sense of regard to my respected and learned teacher **Prof.R.MUTHU KUMARAN, M.D D.A**, Professor and HOD, Department of Anaesthesiology, Thanjavur Medical College, for his inspiring guidance, suggestion and support in carrying out this study.

I am deeply indebted to **Prof.R.THENMOZHI, M.D D.A.**, Professor, Department of Anaesthesiology, Thanjavur Medical College, for her guidance, suggestions and encouragement throughout this study.

I fail to find adequate words, with limited vocabulary at my command, to express my deep gratitude to my chief guide and supervisor **Prof.AL.MEENAKSHI SUNDARAM, M.D D.A**, Professor, Department of Anaesthesiology, Thanjavur Medical College without whose inspiring guidance, unstinted cooperation and exceptional attitude, this thesis would not have seen the light of the day. I consider it my proud privilege to work under his superb

supervision, and his cheerful and enchanting personality enabled me to do my work.

I am extremely thankful to the faculty of Department of Obstetrics and Gynaecology for providing me the cases and support during my study period.

I would fail in my duty if I fail to acknowledge the subjects of this study. They have understood the purpose of my study and agreed to participate in it and in the way taught me so much about patients' perception of analgesia and suffering of pain. Without their enthusiasm and cooperation it would not have been possible to complete this study. I am extremely thankful to my statistician for assisting me in analysis of this study. I thank my colleagues and friends for their excellent cooperation during the course of study.

INDEX

LIST OF ABBREVIATIONS USED

ASA	-American society of Anaesthesiologist
BP	-Blood Pressure
cGMP	- cyclic Guanosine Mono Phosphate
CNS	-Central Nervous System
CSF	- CerebroSpinal Fluid
CVS	-Cardio Vascular System
GMP	-Guanosine Mono Phosphate
IV	- Intra Venous
Kg	-Kilogram
MAP	-Mean Arterial Pressure
mg	-Milligram
min	-Minutes
ml	-Millilitre
µg	- Micrograms

mm	- Millimetres
mm of Hg	- Millimetres of Mercury
NO	-Nitric Oxide
NTG	- Nitroglycerine
PABA	- Para Amino Benzoic Acid
Spo2	- Oxygen saturation
TRI	-Transient Radicular Irritation
VAS	- Visual Analogue Scale

LIST OF TABLES

LIST OF FIGURES

LIST OF GRAPHS

A STUDY OF EFFICACY OF TRANSDERMAL NITROGLYCERINE PATCH IN ENHANCING ANALGESIA OF INTRATHECAL NEOSTIGMINE FOLLOWING HYSTERECTOMIES UNDER BUPIVACAINE SPINAL ANAESTHESIA

Abstract

This study was carried out to assess the effect of transdermal nitroglycerine patch on intrathecal neostigmine with bupivacaine on postoperative analgesia and note the incidence of adverse effects, if any. After taking informed consent, 76 patients of ASA Grade I and II were systematically randomised into three groups of 26 each. Patients were hydrated with Ringer's lactate solution 10ml/kg preoperatively. Group C patients received Intrathecal injection of 15 mg bupivacaine. Group N patients received Intrathecal injection of 15 mg bupivacaine with 25 mcg of neostigmine .Group P patients received Intrathecal injection of 15 mg bupivacaine with 5mcg of neostigmine and transdermal nitroglycerine patch (5 mg/24 hours), applied on a non anaesthetised area after 15 minutes. Groups were demographically similar and did not differ in intraoperative characteristics like duration of surgery, and hemodynamic parameters . The mean duration of analgesia was 150.4 minutes, 211.3 minutes,

316.3 in control group (C), neostigmine group (N), and nitroglycerine patch-neostigmine group (P) respectively ($P<0.01$). There was no significant changes in perioperative hemodynamic parameters, but incidence of nausea and vomiting were increased due to addition of intrathecal neostigmine.To conclude, our results show that transdermal nitroglycerine enhances the analgesic potential of intrathecal neostigmine.

Keywords: Abdominal hysterectomy, neostigmine, nitroglycerine, nitric oxide, postoperative analgesia

INTRODUCTION

Pain is derived from the Latin word “poena”, which means penalty or punishment. Pain is no longer considered a penalty or punishment. The relief of pain is one of the paramount goals of medical science.

Surgery is a severe tissue damage and post-operative pain is a universal phenomenon experienced by millions of patients throughout the world, yet paradoxically after all the efforts taken to make intraoperative period pain and stress free, the patients is left to fend for himself in the postoperative period.

Neuraxial blockade is one of the answers to control post-operative pain. Neostigmine is the universally used neuromuscular block reversal agent whose post-operative pain relief property was first described by Naguib and Yaksh et al in 1994. It inhibits the breakdown of acetylcholine (endogenous neurotransmitter) which has been shown to cause analgesia by stimulating the synthesis of nitric oxide [NO] in the spinal cord. It blocks the activity of both true and pseudocholinesterase and thereby enhancing accumulation and binding of acetylcholine at various cholinergic sites.

But a higher dose of neostigmine shown to produce many untoward side effects such as nausea, vomiting etc. and lower doses of neostigmine doesn’t show much analgesic property. So as to reduce dose of neostigmine and potentiate its analgesic property other adjuvants like clonidine, opioids,

transdermal nitroglycerine patch etc. have been added along with it.

The transdermal nitroglycerine acts as a source for nitric oxide (NO) .NO acts as a second messenger in the CNS and plays an important role in the mediation of pain. Intracellular cGMP levels are increased by NO by activation of enzyme guanyl cyclase. This Nitric Oxide-cyclic GMP cascade in endothelial cells mediates acetylcholine induced vasodilatation as well as acetylcholine induced antinociception.

AIM OF THE STUDY

1) To evaluate and compare the efficacy and safety of combining intrathecal neostigmine with transdermal nitroglycerine patch for pain relief in patients undergoing hysterectomies under bupivacaine spinal anaesthesia.

2) To evaluate the adverse effects of transdermal nitroglycerine patch and intrathecally administered neostigmine in patients undergoing hysterectomies under bupivacaine spinal anaesthesia.

REVIEW OF LITERATURE

Cerebrospinal fluid was discovered by Domenico Cotugno in 1764 and its circulation was described by F.Magendie in 1825 who also named it.

The first neuraxial block was performed 8 months after the demonstration in Heidelberg, Germany, of the local anaesthetic properties of cocaine in 1884. James Leonard Corning (1855-1923) was a neurologist who had learned of the action of cocaine, injected a total of 120 mg of cocaine between the T11 and T12 spinous processes in a 45-year-old man and obtained loss of sensation of the legs and perineum.

Heinrich Iraneus Quincke of Keil in Germany standardized the lumbar puncture as a simple procedure in 1891.In the same year Essex Wynter described lumbar puncture in England.

On 16th of August 1898, in Keil, Germany, August Bier performed the first planned spinal anaesthesia in man. He injected 3ml of 0.5% cocaine into the subarachnoid space of a 34 year old labourer for operation on the lower limb. After using it on 6 patients, he and his assistant injected cocaine into each other's spinal spaces.

Yaksh TL et al. in 1985 studied the antinociceptive effects of intrathecally injected cholinomimetic drugs in rat and cat with carbachol and physostigmine. They found potent antinociceptive effects in rats and cats by injection of carbachol, acetylcholine and physostigmine. Atropine reversed this

antinociceptive effect. This suggests the involvement of muscarinic cholinergic mechanism. There was also absence of changes in general reflex motor function or postural control. They concluded that muscarinic agonists are effective as antinociceptive agents after low dose intrathecal administration.[1]

Hood DD et al. in 1995 studied the cardiorespiratory and spinal cord blood flow effects of intrathecal neostigmine methylsulfate, clonidine and their combination in sheep. They concluded that intrathecal neostigmine alone or in combination with clonidine does not reduce spinal cord blood flow, an important toxicity issue. These results proved additional support for initial clinical trials of intrathecal neostigmine for analgesia.[6]

Lauretti GR et al. in 1996 conducted a study designed to examine post operative analgesia with intrathecal neostigmine in a randomized blinded trial with morphine as the active control in patients undergoing anterior and posterior vaginoplasty. They concluded that spinal neostigmine produces analgesia similar in duration to spinal morphine and that the combination of morphine and neostigmine may allow a reduction in the dose of each component for post operative analgesia.[7]

Lauretti GR et al. in 1996 conducted a double blind study on 27 female patients posted for both tubal ligation and vaginoplasty at the same surgical time. They concluded that 100μg of intrathecal neostigmine was more effective in the treatment of vaginal somatic pain, compared with tubal ligation visceral

pain. The addition of a peripheral anticholinergic substantially improved the intrathecal neostigmine analgesic effect on visceral pain.**[8]**

Krukowski JA et al. in 1997 conducted a dose response study of intrathecal neostigmine for post caesarean section analgesia and suggested that neostigmine is associated with reduced post operative morphine requirement, and effect that lasts approximately 10 hours. **[10]**

Klamt JG et al. in 1997 conducted a study on post operative analgesic effect of intrathecal neostigmine. They concluded that in patients undergoing anterior and posterior vaginoplasty under spinal anaesthesia, provided analgesia lasting for about 12hours. **[11]**

Lauretti GR et al. 1998 conducted a multicenter study of intrathecal neostigmine for analgesia on 92 patients undergoing vaginal hysterectomy under spinal anaesthesia with doses of 25μg, 50μg and 75μg of neostigmine and concluded that analgesia from intrathecal neostigmine may occur at doses less than 50μg. In these doses, neostigmine does not reduce spinal-bupivacaine induced hypotension but may increase the need for treatment of nausea. **[18]**

ChoSS et al. **in 1998** conducted a study on effect of intrathecal neostigmine on post-cesarean section analgesia. This study was designed to evaluate the efficacy and safety of intrathecal neostigmine for post-caesarean section analgesia. Forty-five women undergoing cesarean section under spinal

anaesthesia were randomly assigned into 3 groups to receive normal saline 0.2 ml, or neostigmine 12.5 microgram, or neostigmine 25 microgram intrathecally along with 0.5% hyperbaric bupivacaine 12 mg. Degrees of sensory and motor blocks, maternal hemodynamic changes, and side effects were recorded. Apgar scores and umbilical vein blood gas analysis (UVBGA) were checked for evaluation of fetal status. There were no significant differences among the three groups in characteristics of spinal anaesthesia, maternal blood pressure and heart rate, Apgar scores, and UVBGA data. Compared to saline group, intrathecal neostigmine significantly prolonged time for first PCA use and decreased 24 hr and 48 hr PCA consumptions ($P<0.05$). Pain scores in neostigmine groups were significantly lower than those in saline group for first 4 hours after which there were no differences among the three groups. There were significantly higher incidence of nausea and vomiting in neostigmine groups than in saline group. Their study data indicate that intrathecal neostigmine can be an alternative postoperative analgesic without adverse fetal effects for cesarean section. However, high incidence of nausea and vomiting seem to limit its clinical usefulness. [19]

Liu SS et al. in 1999 studied the effects of spinal neostigmine added to bupivacaine spinal anaesthesia in volunteers in a varying dose of 6.25μg, 12.5μg or 50μg. The addition of 50μg significantly increased the duration of sensory and motor blockade, but with higher incidence of side effects such as nausea and vomiting and may limit the clinical use of these doses for spinal

anaesthesia.[20]

Dwivedi A et al. in 2000 did a study on intrathecal neostigmine for post operative pain relief and concluded that intrathecal neostigmine significantly reduces pain and analgesic requirements in the post operative period, but the severity of adverse effects like nausea and vomiting might restrict the usefulness of intrathecal neostigmine as sole post operative analgesic. [21]

Saini S et al. (2006) undertook a study to evaluate the efficacy and safety of intrathecal neostigmine in two different doses for the relief of post operative pain in patients undergoing elective lower abdominal surgery under spinal anaesthesia. The two study groups used intrathecal neostigmine in doses of 50μg and 150μg with bupivacaine 12.5mg (0.5%) and compared the results with that of control group which used bupivacaine 12.5mg (0.5%) alone. They concluded that duration of analgesia (time for requirement of first rescue analgesic) was significantly prolonged in 150μg neostigmine group and average 24 hour VAS score was lower in both the neostigmine groups. The incidence of vomiting was higher in both the neostigmine groups when compared to control group and was dose independent. [23]

Lauretti, Gabriela R. et al. in 2000 conducted a study to determine whether association of transdermal nitroglycerine would enhance analgesia from a low dose of intrathecal neostigmine in patients undergoing gynaecologic surgery during spinal anaesthesia. Their study concluded that neither intrathecal 5 μg neostigmine alone nor transdermal nitroglycerine alone (5 mg/day) showed

analgesic potential but their combination provided an average of 14 hours of postoperative analgesia after vaginoplasty. [22]

Gurvinder Kaur, Narjeet Osahan, Lalita Afzal in 2007 conducted a study to examine the effect of transdermal NTG patch (5mg/24hours) on intrathecally administered neostigmine (5μg) and incidence of untoward effects. They found that average duration of analgesia in intrathecal neostigmine alone group (Group I) was 6.50 hours and in neostigmine with transdermal nitroglycerine patch group (Group II) was 9.10 hours. Duration of analgesia was significantly higher in Group II patients as compared to Group I. Patients in Group II required fewer rescue analgesia in first 24 hours than in Group I patients. The incidence of adverse effects was higher in Group I than in Group II. [24]

Fareed Ahmed.et. al. 2010 conducted a study to determine the effects of transdermal nitroglycerine patch on intrathecal neostigmine. Patients were allocated into four groups with Group I received 15 mg bupivacaine intrathecally, Group II received 15mg of bupivacaine with 5μg neostigmine intrathecally, patients in Group III received 15mg of bupivacaine with 1ml of normal saline intrathecally and transdermal NTG patch (5 mg/24 hours). Patients in Group IV received 15 mg bupivacaine with 5μg of neostigmine intrathecally and transdermal NTG patch [5 mg/24 hours]. The mean duration of analgesia was 202.2min, 407.6min, 207.8 min and 581.6 min in Group-1 , Group -II, Group-III, Group-IV respectively. [25]

ANATOMICAL CONSIDERATIONS OF SPINAL ANAESTHESIA

Knowledge of the anatomy of vertebral column and of the lumbar vertebrae in particular is essential for anaesthesiologists.

CERVICAL VERTEBRA- 7

THORACIC VERTEBRA- 12

LUMBAR VERTEBRA- 5

SACRAL VERTEBRA- 5 (fused)

COCCYX- 4 (fused)

A typical vertebra is composed of following parts:

1. BODY or the base anteriorly, which bears the weight.
2. THE ARCH, which surrounds the cord laterally and posteriorly consisting of lamina and pedicles.
3. There are seven processes or projections
    a. Three muscular process – two transverse and one spinous.
    b .Four articular processes – two upper and two lower.

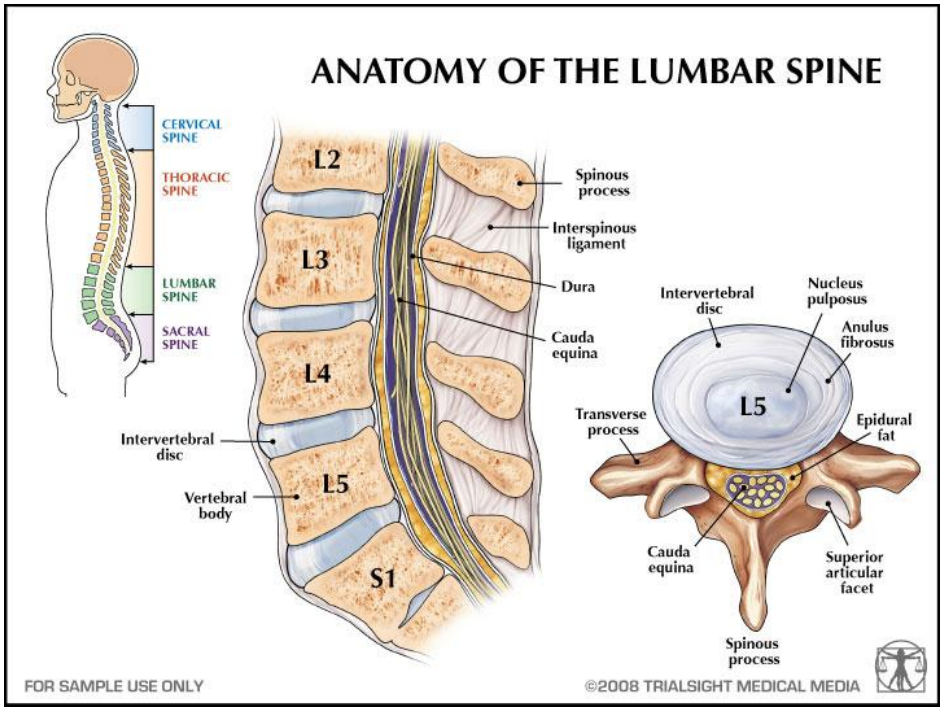
Vertebra differs in shape and size at the various levels. The first cervical vertebra, the atlas, lacks a body and has unique articulations with the base of the skull and the second vertebra. The second vertebra, also called the axis, consequently has atypical articulating surfaces. All 12 thoracic vertebrae

articulate with their corresponding rib. Lumbar vertebrae have a large anterior cylindrical vertebral body. The spinal canal is defined anteriorly by the vertebral body, laterally by the pedicles and transverse processes, and posteriorly by the lamina and spinous processes. The laminae extend between the transverse processes and the spinous processes and the pedicle extends between the vertebral body and the transverse processes.

The individual vertebral bodies are connected by the intervertebral disks. There are four small synovial joints at each vertebra, two articulating with the vertebra above it and two with the vertebra below. These are the facet joints, which are adjacent to the transverse processes. The pedicles are notched superiorly and inferiorly, these notches forming the intervertebral foramina, from which the spinal nerves exit. Sacral vertebrae normally fuse into one large bone, the sacrum, but each one retains discrete anterior and posterior intervertebral foramina. The laminae of S5 and all or part of S4 normally do not fuse, leaving a caudal opening to the spinal canal, the sacral hiatus.

Identifying individual vertebrae is important for correctly locating the desired interspace for epidural and spinal blockade. The spine of C7 is the first prominent spinous process encountered while running the hand down the back of the neck. The spine of T1 is the most prominent spinous process and immediately follows C7. The 12th thoracic vertebra can be identified by

palpating the 12th rib and tracing it back to its attachment to T12. A line drawn between the iliac crests crosses the body of L5 or the L4-L5 interspaces.



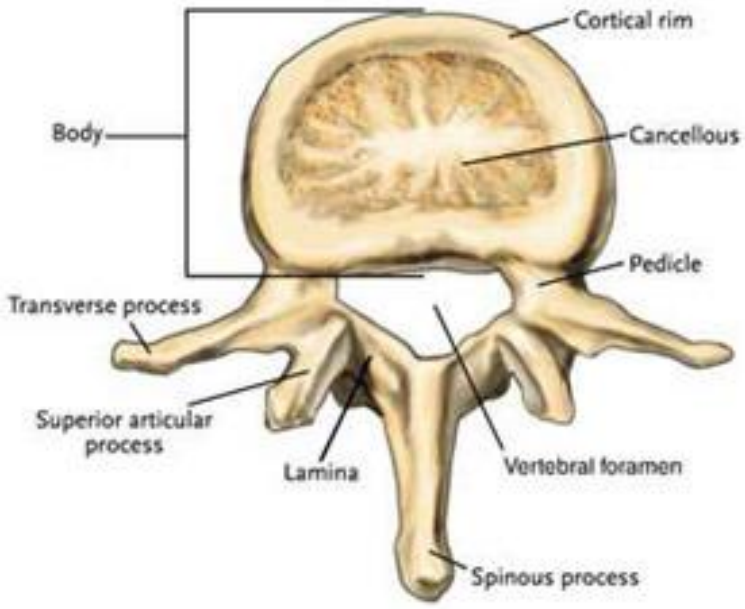


Fig-1: Anatomy of lumbar spine

CONTENTS OF VERTEBRAL CANAL: -

1. Spinal cord and meninges.
2. Cerebrospinal fluid.
3. Spinal nerve roots.
4. Blood vessels and areolar tissue.

SPINAL CORD: -

Medulla oblongata continues as spinal cord below the level of foramen magnum and it tapers off into conical extremity known as *Conus Medullaris*. Due to differential growth of vertebral column and spinal cord the lumbosacral nerve roots are considerably elongated to reach their respective intervertebral foramen which forms the *Cauda Equina.* From the apex of conus medullaris, delicate fibrous filaments descend towards first segment of coccyx, which is called *Filum Terminale.*

At birth, the tip of the spinal cord lies at the level of lower border of third lumbar vertebra. In adults spinal cord ends at lower border of L1.Anterior and posterior nerve root arises from the spinal cord, joins together to form spinal nerve and exit through the corresponding intervertebral foramen. The portion of the spinal cord that gives rise to all of the rootlets of a single spinal nerve is called a cord segment. The skin area innervated by a given spinal nerve and its corresponding cord segment is called a *dermatome.* The sympathetic neurons

run with the corresponding spinal nerve to a point just beyond the intervertebral foramen where they exit to join the sympathetic chain ganglia.

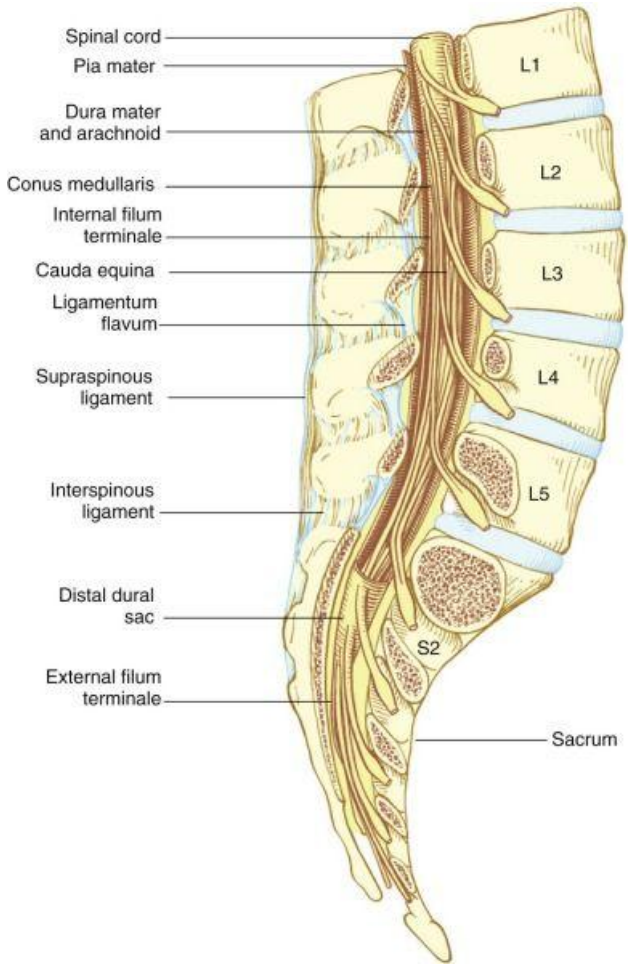


Fig:2-Termination of spinal cord..

THE MENINGES: -

Surrounding the spinal cord in the bony vertebral column are three membranes (from within to the periphery), the piamater, arachnoid mater and duramater.

The piamater is a highly vascular membrane that closely invests the spinal cord. *Linea splendens is* formed by pia which is thickened anteriorly and it runs along the anterior median fissure. The extension of piamater on either side

forms the *Ligamentum denticulatum* . The *posterior subarachnoid septum* is an extension of piamater from posterior median sulcus towards the dura. Pia mater continues down as the *filum terminale*, which extends into the coccyx piercing the lower end of duramater and carries with it a covering of dura.

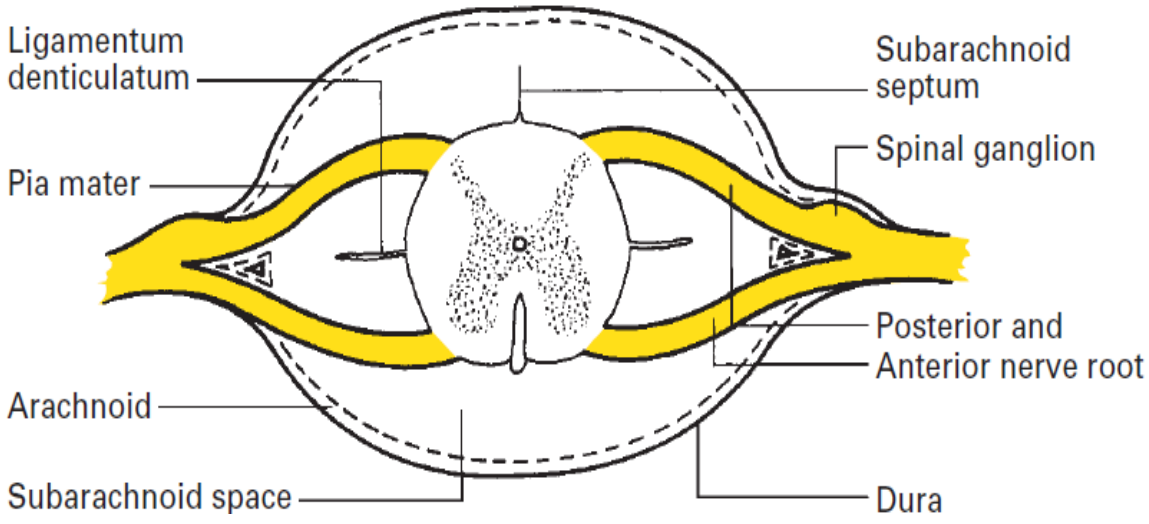


Fig-3: Cross section of spinal cord

The arachnoid mater is the inner most layer, a thin membrane which sends projection along with each spinal nerve root. Superiorly it is continuous with arachnoid of brain. Between the two innermost membranes is the subarachnoid space. In this space are the cerebrospinal fluid, spinal nerve roots, blood vessels that supply the spinal cord and the denticulate ligaments. Although at the lower border of L1 spinal cord ends, subarachnoid space continues upto S2.

The outermost membrane in the spinal canal is the longitudinally organized fibro elastic membrane, the duramater. This layer is the direct

extension of the cranial duramater and extends as the spinal duramater from the foramen magnum to S2, where the filum terminale attaches it to the coccyx.

Surrounding the duramater is the epidural space which extends from the foramen magnum to the sacral hiatus. Posterior to the epidural space is the ligamentum flavum (the so-called yellow ligament), which also extends from the foramen magnum to the sacral hiatus. Although classically portrayed as a single ligament, it is really composed of two ligamenta flava, the right and the left, which join in the middle and form an acute angle with a ventral opening.

Immediately posterior to the ligamentum flavum is the interspinous ligament. Supraspinous ligament which extends from the external occipital protuberance to the coccyx lies posterior to these structures. Lumbar puncture is routinely done below the L2 vertebrae down to the L5-S1 interspace to avoid damaging the spinal cord which ends at the lower border of LI in adults.

TABLE:1- **Ligamentum Flavum at Different Vertebral Levels**

Site	Thickness of Ligament
Cervical	1.5-3mm
Thoracic	3-5mm
Lumbar	5-6mm
Caudal	2-6mm

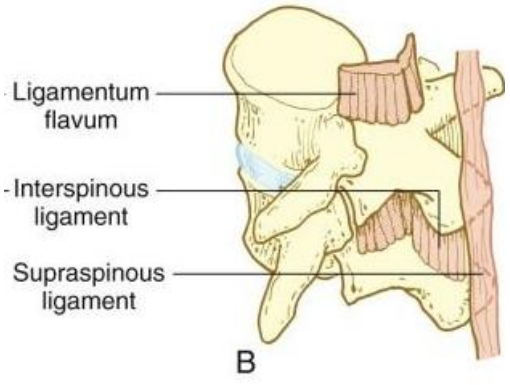


Fig:4—Ligaments of vertebral column

CEREBROSPINAL FLUID: -

It is normally clear and colourless and fills all the cavities and spaces around the central nervous system. It is isotonic with plasma. It is secreted mainly by choroid plexus of Lateral ventricle and is reabsorbed by arachnoid villi and granulations. In normal adults cerebrospinal fluid is formed at 25ml/hr or 500ml/day. There is replacement of total spinal fluid under normal physiological conditions every 6hrs.

Table:2- Physical characteristics of cerebrospinal fluid

pH	**7.4**
Specific gravity at body temperature	1.007
Density	1.0003g/ml
Baricity	1.000
Pressure in supine position	8-12mm Hg
Cells	3-5/cu.mm
Proteins	20 mg/dl
Glucose	45-80 mg/dl

BLOOD SUPPLY OF SPINAL CORD: -

The blood supply to the spinal cord and nerve roots is derived from a single anterior spinal artery and paired posterior spinal arteries. The anterior spinal artery is formed from the vertebral artery at the base of the skull and courses down along the anterior surface of the cord. The anterior spinal artery supplies the anterior two-thirds of the cord, whereas the two posterior spinal arteries supply the posterior one-third. The posterior spinal arteries arise from the posterior inferior cerebellar arteries and course down along the dorsal surface of the cord medial to the dorsal nerve roots.

The anterior and posterior spinal arteries receive additional blood flow from the intercostal arteries in the thorax and the lumbar arteries in the abdomen. One of these radicular arteries is typically large; the artery of Adamkiewicz, or arteria radicularis magna, arising from the aorta .It is typically unilateral and nearly always arises on the left side, providing the major blood supply to the anterior, lower two-thirds of the spinal cord. Injury to this artery can result in the anterior spinal artery syndrome.

It results in impaired motor function on ipsilateral side with bowel and bladder incontinence. Sensory impairment occurs occasionally with impairment of pain and temperature on contralateral side.

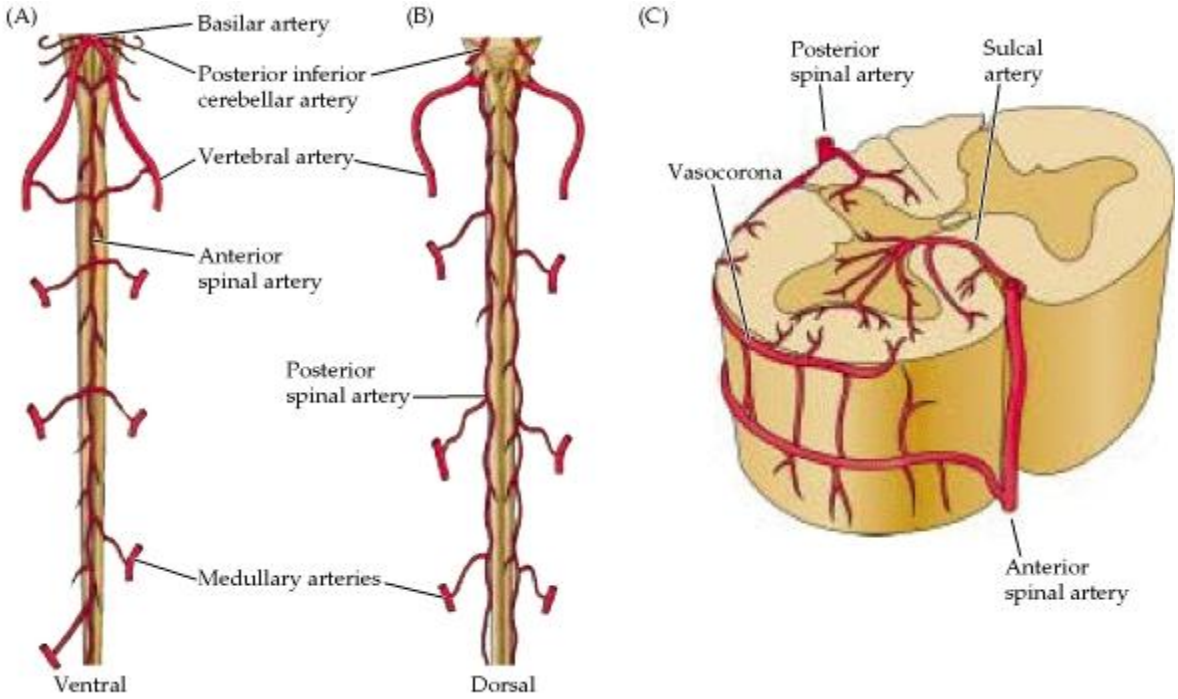
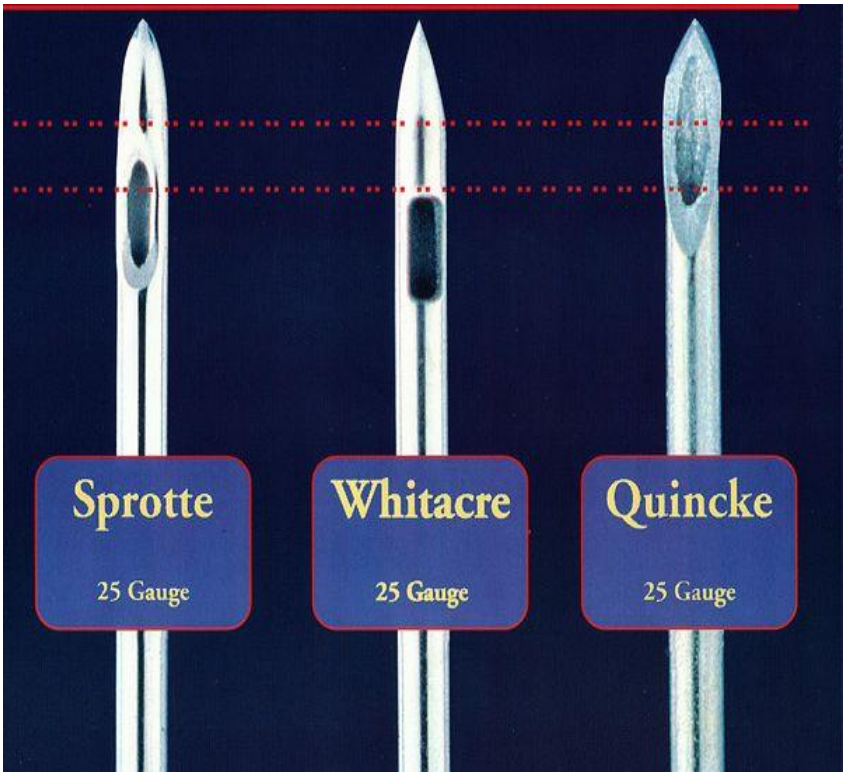


Fig: 6- Blood supply of spinal cord.

PHYSIOLOGY OF SUBARACHNOID BLOCK

The average CSF volume in the adult ranges from 120-150 ml of which 35 ml is in the ventricles, 25 ml is in the cerebral subarachnoid space and 75 ml is in the spinal subarachnoid space. The cerebrospinal fluid plays an important role in spinal anaesthesia as media for dispersion of the local anaesthetic drug to the spinal nerves.

Spinal needles fall into two main categories: those that cut the duramater and those with a conical tip. The former include the Quincke-Babcock needle, and the latter Whitacre and Sprotte.The pencil point needles requires more force to insert and give better "feel" of the tissues penetrated and they do not deviate much from intended pathway.



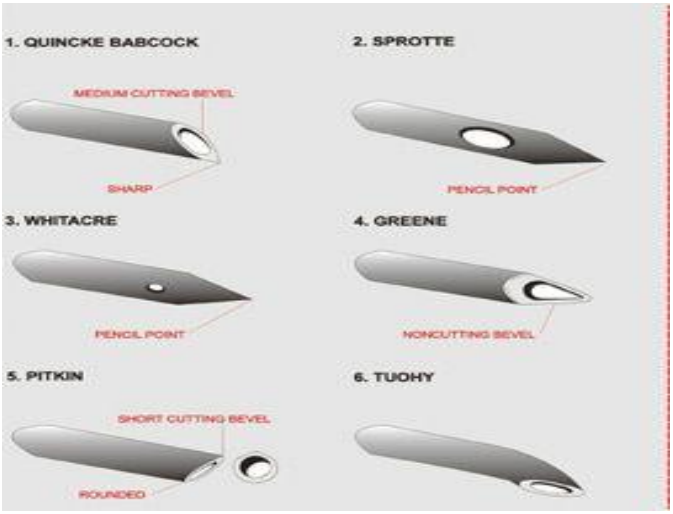


Fig: 7- Types of spinal needles

Three sites of action of local anaesthetics placed in the subarachnoid space are identified in order of importance:

1. Primary – on the nerve roots of spinal cord.
2. Secondary – on dorsal root ganglia and posterior – anterior horn synapses.
3. Limited and incomplete – in spinal cord parenchyma on ascending and descending tracts.

Injection of local anaesthetic solution into the spinal CSF allows access to sites of action, both within the spinal cord and the peripheral nerve roots. The nerve roots leaving the spinal canal are not covered by epithelium and are readily exposed to the local anaesthetic within the CSF. Therefore afferent impulses leaving via the nerve roots are blocked during spinal anaesthesia. Local anaesthetics block sodium channels and propagation of action potential in spinal nerve roots. There are also multiple potential actions of local anaesthetics within the spinal cord at different sites. Local anaesthetics can exert sodium channel block within the dorsal and ventral horns, inhibiting generation and propagation of electrical activity.

Zone of Differential Blockade:

Sensory: In subarachnoid block sensory fibers are blocked two to three segments below sympathetic fibers.

Motor: Level of motor anaesthesia averages two segments below sensory anaesthesia.

Order of blocking nerve fibers:

1. Autonomic preganglionic B fibers.
2. Temperature fibers- cold before warmth.
3. Pinprick fibers.
4. Fibers conveying pain greater than pin prick.
5. Touch fibers.
6. Deep pressure fibers.
7. Somatic motor fibers.
8. Fibers conveying vibratory sense and proprioceptic impulses.

During recovery, sensations return in the reverse order, but it has been suggested that sympathetic activity returns before sensation.

SPREAD OF LOCAL ANAESTHETICS IN SUBARACHNOID SPACE

The local anaesthetic solution is diluted by CSF. Spread is also determined by the baricity of the injected solution. Baricity is a ratio comparing the density of a local anaesthetic solution at a specified temperature to the density of CSF at the same temperature. A hypobaric solution has a baricity less than 1.000. A hyperbaric solution has a baricity greater than 1.000. Hypobaric and Hyperbaric solutions are prepared from isobaric solutions by the addition of various amounts of sterile distilled water and dextrose respectively. Isobaric solutions do not move under the influence of gravity in the CSF. Hyperbaric solutions, being heavier than CSF, settle to the most dependent aspect of the

subarachnoid space, which is determined by the position of the patient. Hypobaric solution floats up against the gravity.

TABLE – 3: Baricity of Solutions Commonly Used for Spinal Anaesthesia

▪**HYPERBARIC SOLUTIONS**	**BARICITY**
Tetracaine: 0.5% in 5% dextrose	1.0133
Bupivacaine: 0.75% in 8.25% dextrose	1.0227
Lidocaine: 5% in 7.5% dextrose	1.0265
Procaine: 10% in water	1.0104
▪**ISOBARIC**	
Tetracaine: 0.5% in normal saline	0.9997
Bupivacaine: 0.75% in normal saline	0.9988
▪**HYPOBARIC**	
Tetracaine: 0.2% in water	0 .9922
Bupivacaine: 0.3% in water	0.9946
Lidocaine: 0.5% in water	0.9985

Baricity is important in determining local anaesthetic spread and thus block height because gravity causes hyperbaric solutions to flow downward in CSF to the most dependent regions of the spinal column, whereas hypobaric solutions tend to rise in CSF. In contrast, gravity has no effect on the distribution of truly isobaric solutions. Thus, the anaesthesiologist can exert

considerable influence on block height by choice of anaesthetic solution and proper patient positioning.

Spinal block can be restricted to the sacral and low lumbar dermatomes (“saddle block”) by administering a hyperbaric local anaesthetic solution with the patient in the sitting position or by administering a hypobaric solution with the patient in the prone jackknife position. Similarly, high thoracic to midcervical levels of anaesthesia can be reached by administering hyperbaric solutions with the patient in the horizontal and Trendelenburg positions or by administering hypobaric solutions with the patient in a semisitting position. However, this use of hypobaric solutions is not recommended because the high block achieved and the diminished venous return associated with the upright posture can lead to significant cardiovascular compromise.

The sitting, Trendelenberg and jackknife positions have marked influences on the distribution of hypobaric and hyperbaric solutions because these positions accentuate the effect of gravity. However, most spinal anaesthetics are administered as hyperbaric solutions injected while patients are in the horizontal lateral position after which they are turned to the horizontal supine position. In this situation the influence of gravity is more subtle because the dependent areas of the spinal column do not deviate as much from the horizontal. While the patient is turned laterally, gravity has a small but measurable effect on local anaesthetic distribution in that the hyperbaric solutions will produce a denser, longer lasting block on the dependent side,

while hypobaric solutions will have the opposite effect. This makes hypobaric solutions ideal for unilateral procedures performed in the lateral position (e.g., hip surgery). Hyperbaric solutions can be used for unilateral procedures performed in the supine position if the operative side is dependent during drug injection and the patient is left in the lateral position for at least 6 minutes.

Despite differences in block density and duration, peak block height will be comparable between the dependent and nondependent sides. When the patient is turned supine following hyperbaric drug injection in the lateral position, the normal spinal curvature will influence subsequent movement of the injected solution.

Hyperbaric solutions injected at the height of the lumbar lordosis will tend to flow cephalad to pool in the thoracic kyphosis and caudad to pool in the sacrum. Pooling of hyperbaric local anaesthetic solutions in the thoracic kyphosis has been evoked to explain the clinical observation that hyperbaric solutions tend to produce blocks with an average height in the midthoracic region .In addition, hyperbaric solutions have also been observed to produce blocks with a bimodal distribution, that is, one group of patients with blocks centered in the low thoracic region and a second group of patients with blocks centered in the high thoracic region. The presumed explanation for this observation is that the lumbar lordosis produces “splitting” of the local anaesthetic solution with some portion flowing caudad towards the sacrum and the remainder flowing cephalad into the thoracic kyphosis. The cephalad extent

of the block then depends on what fraction of the injected drug flows cephalad. Consistent with this hypothesis is the fact that eliminating the lumbar lordosis by maintaining the hips flexed has been shown to significantly reduce or eliminate the bimodal distribution of blocks without affecting maximal block height.

FATE OF LOCAL ANAESTHETICS IN SUBARACHNOID SPACE

Following injection of local anaesthetic solution into subarachnoid space, its concentration falls rapidly. The initial steep fall is due to mixing with CSF and subsequent absorption into nerve roots and spinal cord. The regress of local anaesthetic solution following subarachnoid injection is primarily by vascular absorption. Depending on the type of the drug used, it is metabolized in plasma by cholinesterase [ester local anaesthetics] or in the liver [amide local anaesthetic]. As duration of anaesthesia is in part, result of the rate of absorption of local anaesthetic from the subarachnoid space, the addition of a vasoconstrictor will retard absorption of the drug and thus increase the duration of anaesthesia.

Physiologic Effects

The physiologic effects of neuraxial blocks are often misinterpreted as complications, which is highlighted by observers listing hypotension under complications of the techniques. Clear distinction should be made between the physiologic effects of an anaesthetic technique and complications, which imply

some harm to the patient. This distinction is important to determine the risk-benefit equation of the technique in question.

Cardiovascular Effects

The sympathectomy that accompanies the spinal anaesthesia depends on the height of the block, with the sympathectomy typically described as extending for two to six dermatomes above the sensory level in spinal anaesthesia and at the same level with epidural anaesthesia. This sympathectomy causes venous and arterial vasodilatation, but because of the large amount of blood in the venous system (approximately 75% of the total volume of blood), the venodilatation effect predominates as a result of the limited amount of smooth muscle in venules; in contrast, the vascular smooth muscle on the arterial side of the circulation retains a considerable degree of autonomous tone.

After neuraxial block–induced sympathectomy, if normal cardiac output is maintained, total peripheral resistance should decrease only 15% to 18% in normovolemic healthy patients, even with nearly total sympathectomy. The heart rate during a high neuraxial block typically decreases as a result of blockade of the cardio accelerator fibers arising from T1 to T4. The heart rate may decrease because of a fall in right atrial filling, which decreases outflow from intrinsic chronotropic stretch receptors located in the right atrium and great veins.

The clinical question of what level of decrease in arterial blood pressure after a neuraxial block is acceptable remains to be answered. It will probably remain speculative because conducting ethical human investigations designed to define a dose-response curve of decreased arterial blood pressure accompanying neuraxial blockade would be difficult.

Prevention of decrease in mean arterial pressure of greater than 30% has some basis, but it is important to remember that these data were derived from severely hypertensive, presumably untreated patients. For normotensive and treated hypertensive patients, a wider undocumented margin of safety probably exists.

After arterial blood pressure decreases to a level at which treatment is believed to be necessary, ephedrine, a mixed adrenergic agonist, provides more appropriate therapy for the noncardiac circulatory sequelae of neuraxial block than a pure α-adrenergic agonist does, unless the patient has a specific and defined blood pressure requirement. That the decrease in arterial blood pressure after neuraxial block can be minimized by the administration of crystalloids intravenously is probably not a valid concept. Specifically, 250- to 2000-mL preblock hydration regimens appear to temporarily increase preload and cardiac output without consistently increasing arterial blood pressure or preventing hypotension.

Respiratory Effects

Tidal volume remains unchanged during spinal anaesthesia and vital capacity decreases by a small amount. The decrease in vital capacity is due to decrease in expiratory reserve volume[ERV] related to paralysis of the abdominal muscles necessary for forced exhalation rather than a decrease in phrenic or diaphragmatic function. This minimal impact on pulmonary function also holds for elderly patients undergoing lumbar and thoracic epidural anaesthesia.

The rare respiratory arrest associated with spinal anaesthesia is due to hypotension associated hypoperfusion of respiratory centers in medulla, rather than phrenic nerve or other respiratory muscle paralysis. It is observed that apnea disappears once fluid therapy and vasopressors restore BP and cardiac output.

Neuraxial block should be used cautiously in respiratory cripples because of paralysis of the respiratory muscles. Except for severely compromised patients with respiratory failure, inspiratory muscle function during neuraxial blocks should be adequate to maintain ventilatory function. The physiologic consideration related to muscle paralysis with neuraxial block should focus on the expiratory muscles in these severely compromised patients because these muscles are important for effective coughing and clearing of intrapulmonary secretions.

Gastrointestinal Effects

Another organ system affected during neuraxial blockade is the gastrointestinal tract. Nausea and vomiting may be associated with neuraxial block in up to 20% of patients and are primarily related to gastrointestinal hyperperistalsis caused by unopposed parasympathetic (vagal) activity. Atropine is effective in treating nausea associated with high (T5) subarachnoid anaesthesia. This gastrointestinal hyperperistalsis has the advantage of providing excellent surgical conditions because of a contracted gut. An often-cited advantage of regional anaesthesia in patients with compromised gastrointestinal function (e.g., hepatic dysfunction) is that less physiologic impairment is possible than with general anaesthesia.

Nevertheless, it appears that if intra-abdominal surgery is performed, the magnitude of the decrease in hepatic blood flow parallels the site of surgery rather than the anaesthetic technique chosen. The decrease in hepatic blood flow during spinal anaesthesia parallels the decrease in mean arterial blood pressure.

Renal Function

Renal function has a wide physiologic reserve. Despite small decreases in renal blood flow following spinal anaesthesia, the decrease is of little physiologic importance. One aspect of genitourinary function that is of clinical importance is the belief that neuraxial blocks are a frequent cause of urinary retention, which delays discharge of outpatients and necessitates bladder

catheterization in inpatients. Lower concentrations of local anaesthetic are necessary for paralysis of bladder function than for paralysis of motor nerves to the lower extremities. However, some studies do not support this belief. For example, in orthopedic patients undergoing hip replacement, it was demonstrated that bladder catheterization was no more frequent after neuraxial (spinal or epidural) block than after general anaesthesia and narcotic analgesics. In any case, it is prudent to avoid administration of excessive volumes of crystalloid solutions intravenously to patients undergoing spinal anaesthesia and to individualize the requirement for voiding before discharge in low-risk ambulatory surgery patients after short-acting spinal or epidural anaesthetics are used.

Table-4: Drug Selection for Hyperbaric Spinal Anaesthesia

Local Anaesthetic Mixture	**Dose (mg) ***		**Duration (min)**	
	To T10	**To T4**	**Plain**	**Epinephrine, 0.2 mg**
Lignocaine [5% in 7.5% dextrose]	50-60	75-100	60	75-100
Tetracaine [0.5% in 5% dextrose]	6-8	10-16	70-90	100-150
Bupivacaine [0.75% in 8.5% dextrose]	8-10	12-20	90-120	100-150
Ropivacaine [0.5% in dextrose]	12-18	18-25	80-110	—

Local Anaesthetic Mixture	Dose (mg) *		Duration (min)	
	To T10	To T4	Plain	Epinephrine, 0.2 mg
Levobupivacaine	8-10	12-20	90-120	100-150

* Doses are for use in a 70-kg adult male of average height

Spinal Anaesthetic Additives

Some physicians are concerned that the use of additives, particularly vasoconstrictors, may be risky. The concept is that epinephrine and phenylephrine have such potent vasoconstrictive action that they place the blood supply of the spinal cord at risk. There are no human data supporting this theory. Kozody and colleagues have shown that administering subarachnoid epinephrine (0.2 mg) or phenylephrine (5 mg) does not decrease spinal cord blood flow in dogs. These traditional vasoconstrictors are not the only adrenergomimetic agents being studied.

Clonidine, an α_2-agonist, prolongs the motor block associated with tetracaine spinal anaesthesia in dogs as much as epinephrine does while prolonging sensory blockade for an even longer interval. The mechanism for this prolongation may involve vasoconstriction and antinociception from α-adrenergic stimulation. Another drug investigated for spinal use as an additive is neostigmine. This acetyl cholinesterase inhibitor inhibits the breakdown of acetylcholine and thereby induces analgesia. It also prolongs and intensifies the

analgesia through release of nitric oxide in the spinal cord. Despite the side effect of nausea and prolongation of motor block when combining it with local anaesthetics, it is slowly gaining acceptance clinically.

The interaction of various vasoconstrictors and local anaesthetics is better understood. Traditionally, epinephrine was thought to prolong tetracaine spinal anaesthesia but not bupivacaine or lidocaine spinal anaesthesia. This theory was postulated because of differences in the vasodilatory action of the local anaesthetic drugs; plain lidocaine and bupivacaine cause vasodilatation, whereas plain tetracaine does not. The original investigations of spinal anaesthetic duration used two-dermatome regression in the thoracic dermatomes to establish duration. Since that time it has become clearer that two-dermatome regression in the middle to high thoracic dermatomes may be misleading when measuring spinal anaesthetic duration in the lower thoracic and lumbar dermatomes. Some data indicate that lidocaine spinal anaesthesia is prolonged by epinephrine when measured by two-dermatome regression in the lower thoracic dermatomes and by occurrence of pain at the operative site for procedures carried out at the level of the lumbosacral dermatomes.

When epinephrine has been compared with phenylephrine as a means of prolonging spinal anaesthesia, conflicting information has resulted. Concepcion and coworkers compared epinephrine (0.2 and 0.3 mg) and phenylephrine (1 and 2 mg) added to tetracaine and did not find a difference in increased duration with the two vasoconstrictors. . Phenylephrine has been

shown to prolong lidocaine spinal anaesthesia, but it appears that the length of prolongation is more similar to that produced with epinephrine · The duration of bupivacaine spinal anaesthesia does not appear to be prolonged by phenylephrine. Whichever local anaesthetic solution and additives are selected for subarachnoid injection, special care should be taken to ensure that the clinician knows what substance is being injected and that all procedures have been carried out aseptically.

THE ROLE OF NEURAXIAL ANAESTHESIA IN ANAESTHETIC PRACTICE

Almost all operations below the neck can be performed under neuraxial anaesthesia. However, because intrathoracic, upper abdominal and laparoscopic operations can significantly impair ventilation, general anaesthesia with endotracheal intubation is also necessary. So why do we need a regional anaesthetic for these cases, or for any other cases?

Some clinical studies suggest that postoperative morbidity and possibly mortality may be reduced when neuraxial blockade is used either alone or in combination with general anaesthesia in some settings. Neuraxial blocks may reduce the incidence of venous thrombosis and pulmonary embolism, cardiac complications in high-risk patients, bleeding and transfusion requirements, vascular graft occlusion, and pneumonia and respiratory depression following upper abdominal or thoracic surgery in patients with chronic lung disease.

Neuraxial blocks may also allow earlier return of gastrointestinal function following surgery. Proposed mechanisms include amelioration of the hypercoagulable state associated with surgery, sympathectomy-mediated increases in tissue blood flow, improved oxygenation from decreased splinting, enhanced peristalsis, and suppression of the neuroendocrine stress response to surgery.

For patients with coronary artery disease, a decreased stress response may result in less perioperative ischemia and reduced morbidity and mortality. The increasing use of perioperative β-blockade to reduce perioperative cardiac complications, however, may minimize or eliminate the potential advantage of neuraxial anaesthesia in this setting. Reduction of parenteral opioid requirements may decrease the incidence of atelectasis, hypoventilation, and aspiration pneumonia.

Table: 5- CONTRAINDICATIONS OF SPINAL ANAESTHESIA

Absolute
Infection at the site of injection
Patient refusal
Coagulopathy or other bleeding diathesis
Severe hypovolemia
Increased intracranial pressure
Severe aortic stenosis
Severe mitral stenosis
Relative
Sepsis
Uncooperative patient
Preexisting neurological deficits
Demyelinating lesions
Stenotic valvular heart lesions
Severe spinal deformity
Controversial
Prior back surgery at the site of injection
Inability to communicate with patient[1]
Complicated surgery
Prolonged operation
Major blood loss
Maneuvers that compromise respiration

Table:6- Factors Influencing Block Height
Controllable Factors
Dose (volume × concentration)
Site of injection along the neuraxis
Baricity of the local anaesthetic solution
Posture of the patient
Factors Not Controllable
Volume of cerebrospinal fluid
Density of cerebrospinal fluid

Factors Probably Unrelated to Height of the Spinal Anaesthetic Block
Added vasoconstrictor
Coughing, straining, or bearing down
Barbotage
Rate of injection
Needle bevel
Gender
Weight

COMPLICATIONS OF SUBARACHNOID BLOCK

Immediate complications:-

- Hypotension.
- Bradycardia.
- Toxicity due to intravascular injection.
- Allergic reaction to local Anaesthetic.
- Hypoventilation (brain stem hypoxia).

Late complications:-

Backache

Postoperative backache is common following spinal and epidural anaesthesia. The etiology of backache is not clear, although needle trauma, local anaesthetic irritation, and ligamentous strain secondary to muscle relaxation have been offered as explanations.

Postdural Puncture Headache

The incidence of PDPH is as high as 25%. PDPH is characteristically mild or absent in supine position but becomes severe on standing or head end elevation. Occasionally cranial nerve symptoms (e.g. diploplia, tinnitis) and nausea and vomiting are also present. The headache is due to loss of cerebrospinal fluid through the meningeal hole created by the spinal needle. In the upright position the brain sags in the cranial vault putting traction on pain-sensitive structures.

Traction on cranial nerves is believed to cause the cranial nerve palsies occasionally seen.

The incidence of PDPH decreases with increasing age and with the use of small diameter spinal needles with noncutting tips. Inserting cutting needles with the bevel aligned parallel to the long axis of the meninges has also been shown to decrease the incidence of PDPH. Some authors have suggested that parallel insertion spreads dural fibers, whereas perpendicular insertion cuts the fibers resulting in a larger meningeal hole. However, the collagen fibers of the dura mater are arranged randomly; therefore, as many fibers will be cut with parallel insertion as with perpendicular insertion. A more likely explanation arises from the fact that the dura mater is under longitudinal tension. Thus, a slit-like hole oriented perpendicular to this longitudinal tension will tend to be pulled open while a hole oriented parallel to this tension will be pulled closed.

Some studies have suggested that women are at greater risk of developing PDPH. However, if age differences are accounted for, there does not appear to be a gender difference in the incidence of PDPH. Finally, use of fluid, instead of air, for loss of resistance during attempted epidural anaesthesia does not alter the risk of accidental meningeal puncture, but does markedly decrease the risk of subsequently developing PDPH. PDPH usually resolves spontaneously in a few days to a week for most patients. However, there are reports of PDPH persisting for months following meningeal puncture. Bed rest

and analgesics are the mainstay of conservative management. Caffeine has also been shown to provide symptomatic relief.

Table-7: Relationships Among Variables and PDPH

Factors That May Increase the Incidence of Post–spinal Puncture Headache	
Age	Younger more frequent
Gender	Females > males
Needle size	Larger > smaller
Needle bevel	Less when the needle bevel is placed in the long axis of the neuraxis
Pregnancy	More when pregnant
Dural punctures (no.)	More with multiple punctures
Factors Not Increasing the Incidence of Post–spinal Puncture Headache	
Continuous spinals	
Timing of ambulation	

Epidural Blood Patch.

Epidural blood patch forms a clot over the meningeal hole, and thus prevents further CSF leak 10 to 20 mL of autologous blood is injected aseptically into epidural space at or near the interspace at which meninges was punctured. This is effective in relieving symptoms within 1 to 24 hours in 85% to 95% of patients; ~90% of patients who fail an initial blood patch will respond

to a second patch. The most common side effects of blood patch are backache and radicular pain, although transient bradycardia and cranial nerve palsies have also been reported.

The timing of epidural blood patch has been controversial. Early studies suggested that prophylactic blood patch in patients at high risk for PDPH was ineffective. This led several authors to suggest that blood patch should not be performed before patients develop symptoms of PDPH. Subsequent studies, which used larger volumes of blood in the epidural space (15 to 20 mL), have shown that prophylactic blood patch is effective in preventing PDPH in patients in whom the meninges were accidentally punctured during attempted epidural anaesthesia. Prophylactic blood patch is not appropriate for most patients but is worth considering in high-risk outpatients for whom a return trip to the hospital for epidural blood patch would be difficult.

Epidurally administered fibrin glue has been shown to be an effective alternative to blood .The incidence of postdural puncture headache decreases as patient age increases. When using beveled needles, the incidence is higher than average at any given age if the needle is inserted perpendicular to the spinal meninges and lower if inserted parallel to the spinal meninges.

Hearing Loss

Lamberg et al demonstrated that a transient (1 to 3 days) mild decrease in hearing acuity [>10 dB] is common after spinal anaesthesia with an incidence of around 42% and a 3:1 female: male predominance. Similarly,

Gültekin et al demonstrated a 45% incidence of hearing impairment in subjects undergoing prilocaine spinal anaesthesia but a much lower incidence (18%) in patients having bupivacaine spinal anaesthesia. The mechanism of hearing loss in these studies is not clear.

Total Spinal

Total spinal anaesthesia occurs when local anaesthetic injected intrathecally spreads cephaled enough to block the entire spinal cord or even the brainstem. Bradycardia and profound hypotension are common secondary to complete sympathetic blockade. Apnea may occur as a result of respiratory muscle paralysis or dysfunction of brainstem respiratory control centers. Management includes delivering 100% O2 via controlled ventilation, treating hypotension with intravenous fluids and vasopressors, atropine to treat bradycardia. If the cardiovascular and respiratory consequences are managed appropriately, total spinal block will resolve without sequelae.

Neurologic Injury

Multiple large series of spinal and epidural anaesthesia report that neurologic injury occurs in ~0.03% to 0.1% of all central neuraxial blocks, although in most of these series the block was not clearly proven to be causative. Paresthesias and motor weakness are the most common injuries, but *cauda equina syndrome* also occurs rarely. Injury results from direct needle trauma to spinal nerves or spinal cord, from cord ischemia, by introduction of

infection into the subarachnoid or epidural space, from accidental injection of neurotoxic drugs or chemicals, or rarely from epidural hematoma.

Hyperbaric 5% lidocaine has been implicated as a cause of multiple cases of cauda equina syndrome following subarachnoid injection through small-bore ("microspinal") catheters during continuous spinal anaesthesia. Hyperbaric solutions injected through these high-resistance catheters have been shown to produce very little turbulence and thus poor mixing of the local anaesthetic within the CSF. Nerve injury is believed to result from pooling of toxic concentrations of undiluted lidocaine around dependent cauda equina nerve roots. Microspinal catheters and high concentrations of lidocaine have clearly been implicated in causing cauda equina syndrome, this complication has also occurred when using larger (20 gauge) catheters, 2% lidocaine, and 0.5% tetracaine.

Transient Neurologic Symptoms (TNS)

In addition to cauda equina syndrome, the occurrence of *transient neurologic symptoms* (TNS) or *transient radicular irritation* (TRI) has also emerged as a concern following central neuraxial blockade. Transient Radicular Irritation is defined as pain, paresthesia, or both in the lower limbs , buttocks after spinal anaesthesia and was first proposed as a recognizable entity by Schneider. All local anaesthetics have been shown to cause TRI although the risk appears to be greater with lidocaine than other local anaesthetics. In a large epidemiologic study of nearly 2,000 patients, Freedman et al characterized the

clinical picture of TRI. They found that patients receiving lidocaine were significantly more likely to develop TRI than were patients receiving spinal tetracaine or bupivacaine although TRI did occur with these latter two drugs as well. Additional risk factors for TRI included surgery in the lithotomy position when lidocaine, but not when bupivacaine or tetracaine, was used, and outpatient status; obesity was a borderline risk factor. Variables shown not to increase the risk of TRI included lidocaine dose, type of spinal needle, addition of epinephrine to lidocaine, paresthesia, hypotension, and blood tinged CSF among others. The pain usually resolved spontaneously within 72 hours but a very few patients required 6 months.

The mechanism responsible for TRI is unknown; however, it would be inappropriate to conclude that TRI is simply a milder manifestation of cauda equina syndrome. Differences in clinical presentation, risk factors, and so on suggest that these are not simply two points along a continuum of the same process.

CIRCULATORY EFFECTS OF SUBARACHNOID BLOCK

The subarachnoid block can influence the cardiovascular system, as follows.

1) Vasodilatation of resistance and capacitance vessels.
2) Block of cardiac efferent sympathetic fibers from T1 to T4 resulting in loss of chronotropic and inotropic drive and fall in cardiac output.

3) A further cause of bradycardia is the lowering of pressure in the right atrium consequent to diminished venous return (Bain Bridge reflex).
4) Bezold–Jarisch reflex where by baroreceptors located in the inferoposterior wall of the left ventricle respond to increase in ventricular contractility induced by reduction in preload and ventricular volume. Stretch of these baroreceptors paradoxically increases vagal output resulting in bradycardia.
5) Vasodilatation and β-adrenergic blockade of myocardium with fall in cardiac output, following systemic absorption of the local anaesthetic drug.

PHYSIOLOGY OF PAIN

The widely accepted definition of pain was developed by a taxonomy task force of the International Association for the Study of Pain: "Pain is an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage or described in such terms."

AUTONOMIC NERVOUS SYSTEM RESPONSES:-

Painful stimulation may evoke reflex increase in sympathetic nervous system efferent activity. It is possible that associated vasoconstriction leads to acidosis, tissue ischemia, and release of chemicals that further activate pain receptors. Resulting sustained, painful stimulation produces further increases in sympathetic nervous system activity and the vicious cycle termed ***reflex***

sympathetic dystrophy (complex regional pain syndrome) may develop. After certain types of nerve injury, pain may occur without activation of pain receptors. Spontaneous firing that occurs from injured peripheral nerves, especially in response to sympathetic nervous system stimulation may reflect a proliferation of alpha-adrenergic receptors on the increased number of neuroma sprouts (Devor, 1983). Spontaneous firing may also occur from dorsal root ganglia whose peripheral projections have been interrupted, as after nerve transection or limb amputation.

Neuromodulators:

The activity of dorsal horn relay and projection neurons is modulated by several inhibitory inputs, including chemical modulators. They are as follows:

1. Gamma amino butyric acid (GABA): It is a major source of pre and post synaptic inhibition of nociceptive input. The interneurons releasing GABA are concentrated in the superficial laminae of the dorsal horn.

2. Glycine: Intrinsic neurons containing glycine are also inhibitory but are more widely distributed in the gray mater.

3. Endogenous opioids: There are three families of endogenous opioids:

(a) β endorphin.

(b) (leu) enkephalin and (met) enkephalin.

(c) Dynorphin A and B.

These three families of opioid peptides have distinct anatomical distribution in the CNS and differing affinities for opioid receptors which are classified into **μ, δ, κ, ε** and **σ** receptors.

4. Descending pathway originating in the brainstem also modulate the activity of dorsal horn relay and projection neurons. Descending catecholaminergic pathways from locus coeruleus and ventrolateral horns and medulla inhibit nociceptive spinal neurons. Descending control may also be derived from dopamine containing regions of the hypothalamus and caudal thalamus.

5. Cholinergic binding sites have been identified in the dorsal horn. These spinal cholinergic receptors are involved in mediating antinociceptive effects. These antinociceptive effects are independent of opioid and α receptor system and these receptors are primarily muscarinic and not nicotinic cholinergic receptors. Acetylcholine has been found to act upon these muscarinic receptors which are of subtype M1 and M3 .

METHODS OF PAIN MEASUREMENT:

Merskey of International Association for the Study of Pain (IASP) defined pain "*as the sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage*". One cannot determine for the individual patient how much nociception occurs in response to tissue damage for which we have to rely on the expression of the patient to accurately measure the subjective nature of pain.

Loser, of multidisciplinary pain centre, University of Washington put forward a multifaceted model. The core of the model is the immeasurable nociception resulting from tissue damage. The next layer is the human experience of emotional and sensory components integrated pain which is not available for direct inspection. Pain leads to suffering and suffering leads to painful behaviours which is available for observation in the form of

-Withdrawing, Grimacing, Crying, Asking for analgesics.

Thus if one relies on the patient's report of pain it is possible to measure pain intensity and the response to analgesic medications.

Introspective Method:

Patient or trained attender attempts to assess pain.

Behavioural Method:

Some physical parameters which get altered in the presence of pain are objectively measured and correlated with the severity of pain like tachycardia, tachypnea and increased blood pressure.

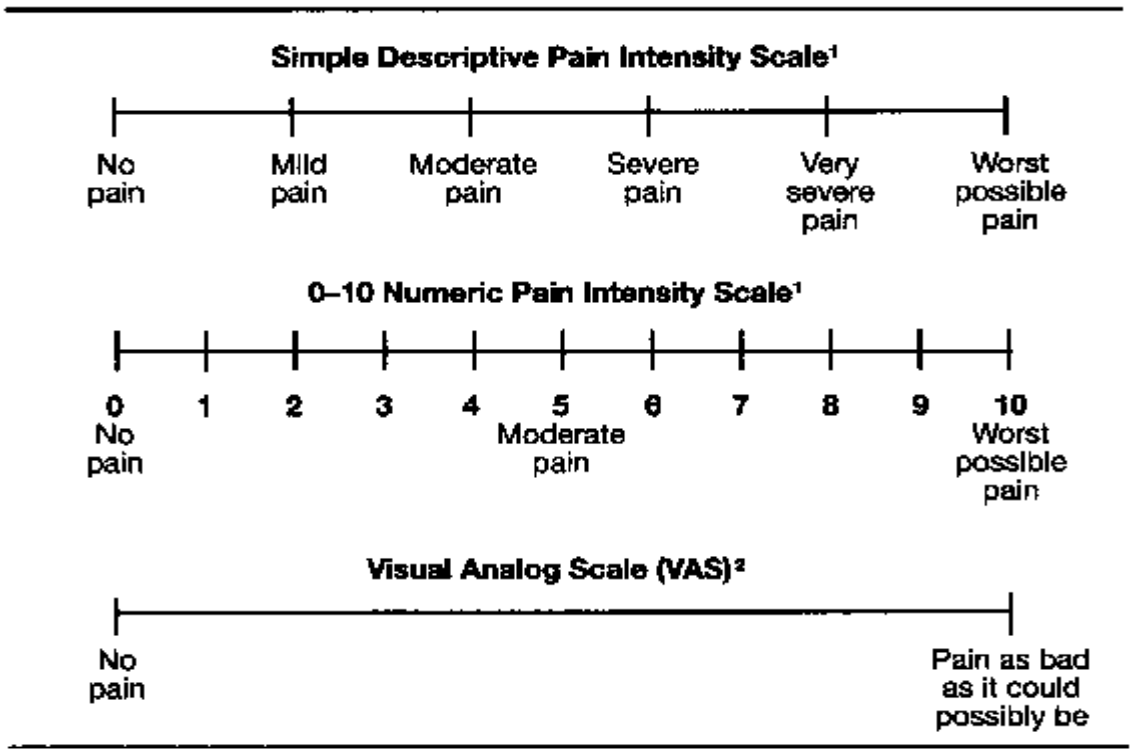
PAIN AS SELF -REPORT ON A SINGLE DIMENSION:

Verbal Descriptor Scales: Melzack and Torgerson introduced the following scale for pain intensity; “Mild, Discomforting, Distressing, Horrible, Excruciating."

Numeric Rating Scale (NRS): Here patients are asked to indicate how strong their pain is on a scale from 0 to 10 on which 0 represents "no pain at all"

and 10 "the worst pain imaginable".

Visual Analogue Scale (VAS): Currently, the most commonly used method, first described by AITKEN in 1966.The subject makes a mark on a 10cms line – horizontal or vertical, one end of which is marked as "No pain" and the other as "The worst pain one can imagine". The position of the mark on the line measures how much pain the subject experiences.



[1]If used as a graphic rating scale, a 10 cm baseline is recommended.
[2]A 10-cm baseline is recommended for VAS scales.

Oral Analogue Scale (OAS): First put forward by AUSTIN et.al.It is a simple and clinically relevant rating scheme. Absence of pain, presence of pain, and if the patient desired more analgesics are rated 0, 1 and 2 respectively.

PAIN AS SELF-REPORTS ON MULTIPLE DIMENSIONS:

McGill Pain Questionnaire: It scales pain in three dimensions: Sensory, Affective and Evaluative.

West Haven-Yale Multidimensional Pain inventory: This has been designed to be briefer and more classical in its psychometric approach.

Brief Pain Inventory: is a quick, multidimensional pain measurement that has demonstrated reliability and validity.

Memorial Pain Assessment Card: It scales pain, pain relief and mood on VAS and adds a set of adjectives reflecting pain intensity.

Cross-Modality Matching: a psychophysical technique in which a sensory experience is quantified by matching it to the experience of a precisely controlled stimulus in a different sensory modality.

Pain Perception Profile: is based on cross modality matching.

The preoperative personality assessment is also helpful in assessing the patient's psychological background and his psycho to surgery and the pain that follow it. Although there is no absolute consensus on how clinical pain should be measured, there is enough agreement that clinicians and researchers do not have to despair of being able to measure the subjective phenomenon of pain.

METHODS OF POSTOPERATIVE PAIN RELIEF:

Preventive Analgesia

Central sensitization and hyperexcitability develop after the surgical incision and result in amplification of postoperative pain. Although experimental studies convincingly confirm the concept of preemptive analgesia in decreasing post injury pain, the results of clinical trials are mixed. Definitions of preemptive analgesia include what is administered before the surgical incision, what prevents the establishment of central sensitization resulting from incisional injury only (i.e., intraoperative period), what prevents central sensitization resulting from incisional and inflammatory injury (i.e., intraoperative and postoperative periods), or the entire perioperative period encompassing preoperative interventions, intraoperative analgesia, and postoperative pain management (i.e., preventive analgesia).

Timing of the intervention may not be as clinically important as other aspects of preventive analgesia (i.e., intensity and duration of the intervention). An intervention administered before the surgical incision is not necessarily preemptive if it is incomplete or insufficient such that central sensitization is not prevented.

A variety of drugs and technique] have been used to study preemptive analgesia. By preventing central sensitization, preemptive analgesia along with

intensive multimodal analgesic interventions could theoretically reduce acute postoperative pain/hyperalgesia and chronic pain after surgery.

Multimodal Approach to Perioperative Recovery

The analgesic benefits of controlling postoperative pain are generally maximized when a multimodal strategy to facilitate the patient's convalescence is implemented.The use of epidural anaesthesia and analgesia is an integral part of the multimodal approach because of the superior analgesia and physiologic benefits conferred by epidural analgesia.

A multimodal approach to perioperative recovery to control postoperative pathophysiology and facilitate rehabilitation may result in accelerated recovery and decreased length of hospitalization. Patients undergoing major abdominal or thoracic procedures and who participate in a multimodal strategy have a reduction in hormonal and metabolic stress, preservation of total-body protein, shorter times to extubation, lower pain scores, earlier return of bowel function, and earlier fulfilment of intensive care unit discharge criteria.

TREATMENT METHODS:

Many options are available for treatment of postoperative pain. By considering patients' preferences and individualized assessment of the risks and benefits of each treatment modality, the clinician can optimize the postoperative analgesic regimen for each patient.

1) Systemic Analgesic Techniques:

a) **Opioids:** Opioid analgesics are cornerstone options for the treatment of postoperative pain. Opioids may be administered by oral, intravenous, intramuscular, subcutaneous, transcutaneous or transmucosal routes.

b) Nonopioids Analgesics:

c) **Nonsteroidal Anti-inflammatory Agents (NSAIDS):** Used as sole agents, NSAIDS generally provide effective analgesia for mild to moderate pain.

2) Regional Analgesic Techniques:

a) Central Neuraxial Blockade: The administration of local anaesthetics, opioids, spinal adjuvants such as neostigmine or a combination neuraxially (subarachnoid or epidurally) is an excellent technique for managing postoperative pain following abdominal, pelvic, thoracic, or orthopaedic procedures on the lower extremities.

b) Peripheral Regional Analgesia: This includes various nerve blocks. It can be administered as single shot or continuous infusions through peripheral nerve catheters.

3) Other Techniques: such as transcutaneous electrical nerve stimulation (TENS), acupuncture and psychological approaches can be used .

PHARMACOLOGY OF BUPIVACAINE

INTRODUCTION:-

It is an aminoamide local anaesthetic..It is chemically known as 1-butyl 2-piperidyl formo-2'6'-xylidine hydrochloride.It was first synthesised by Swedish investigator Boaf Ekenstam.

CHEMICAL STRUCTURE:-

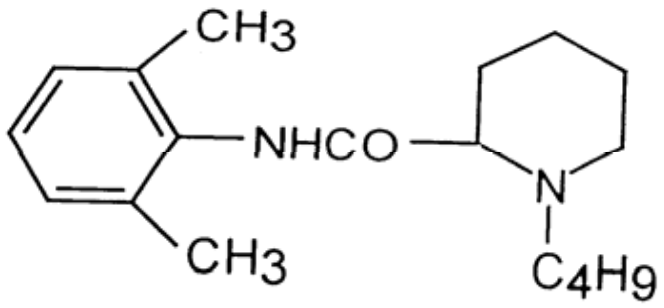


Fig:8- Chemical structure of bupivacaine

PHYSICAL AND CHEMICAL PROPERTIES:-

1. Chemically it is an amide – 2,6 methyl amide
2. Molecular weight - 325
3. pH of saturated solution - 5.2
4. Specific gravity - 1.025 at 37^0 C
5. Stability and sterilization - highly stable, can withstand repeated autoclaving.
6. Melting point - 247 to 258^0 C.

MECHANISM OF ACTION:-

Mechanism of action of bupivacaine is similar to that of any other local anaesthetics. The primary action of local anaesthetic is on the cell membrane of the axon on which it produces electrical stabilization. The large transient increase in permeability to sodium ions necessary for propagation of the impulse is prevented. Thus the resting membrane potential is maintained and depolarization in response to stimulation is inhibited.

DISTRIBUTION:-

Rapid distribution phase (alpha)-In this phase the drug is distributed to highly vascular region, $t^{1/2}$ being 2.7 minutes. Slow disappearance phase (beta)-In this phase the drug distributes with slowly equilibrating tissues, $t^{1/2}$ of Beta is 28 minutes .Biotransformation and excretion phase- half time of γ is 3.5 hours.

BIOTRANSFORMATION:-

Possible pathways of metabolism of bupivacaine include aromatic hydroxylation and conjugation. Only the N-alkylated metabolite, N-butyl bupivacaine has been measured in blood or urine after epidural or spinal anaesthesia. Alpha-1 acid glycoprotein is the most important plasma protein binding site of bupivacaine. Excretion is through the kidney 4-10% of the drug is excreted unchanged.

TOXICITY:-

Toxicity is related to plasma level of unbound drug and more likely due to inadvertent intravenous injection. Systemic toxicity reactions primarily involve CNS and CVS. The blood level required to produce CNS toxicity is less than that to produce circulatory collapse.

CENTRAL NERVOUS SYSTEM TOXICITY:-

Early symptoms are dizziness, tongue paresthesia, circumoral numbness. Blurred vision and tinnitus usually occurs. . Skeletal muscle twitching precedes the onset of seizures. Respiratory arrest often follows. The excitatory reactions are a result of selective blockade of inhibitory pathways. Benzodiazepines and hyperventilation raises the threshold of local anaesthetic induced seizure activity. Thiopentone (1–2 mg/kg) effectively terminates seizure activity. Adequate ventilation and oxygenation must be maintained

CARDIOVASCULAR TOXICITY:-

In general, all local anaesthetics depress myocardial automaticity. These effects result from direct cardiac muscle membrane changes (cardiac sodium channel blockade) and inhibition of the autonomic nervous system. Bupivacaine produces smooth muscle relaxation, which causes some degree of arteriolar vasodilatation. Accidental intravenous injection of bupivacaine ensues combination of bradycardia, heart block, and hypotension may culminate in cardiac arrest.

PHARMACOLOGY OF NEOSTIGMINE

INTRODUCTION:-

Neostigmine methylsulfate was synthesized by Aeschliman and Reinest in1931.It is available as bromide and methylsulfate salts.

PHYSICAL PROPERTIES:-

It is a synthetic quaternary ammonium compound. It consists of carbamate moiety and quaternary ammonium Group. The former provides covalent bonding in acetylcholinesterase. The latter renders the molecule lipid insoluble so that it cannot pass through blood brain barrier.

CHEMICAL STRUCTURE:-

Fig:9- Chemical structure of Neostigmine

INTRATHECAL NEOSTIGMINE:-

Intrathecal neostigmine inhibits metabolism of spinally released acetylcholine and produces analgesia in animals and humans. It increases blood pressure and heart rate by direct stimulation of preganglionic sympathetic neurons in spinal cord. It reduces the uterine activity by β adrenergic effects and

reduces the uterine blood flow by α adrenergic action.

Potency of intrathecal neostigmine is increased in post-operative period, because descending noradrenergic or cholinergic antinociceptive spinal system is activated by ongoing pain causing an increase in release of acetylcholine, which, in presence of neostigmine results in augmented selective analgesia.

Neurological effects:-

Motor weakness and reduction in deep tendon reflex are shown in subjects receiving high dose of neostigmine. Motor effects are consistent with cephalad spread of neostigmine in CSF and it is due to direct action on motor fibres, rather than to ischemia or neurotoxicity. Neostigmine in large doses do not reduce spinal blood flow. Intrathecal neostigmine did not cause changes in attention, motor coordination or memory.

Gastrointestinal effects: -

Vomiting and nausea occur in a dose related manner after intrathecal neostigmine. The most likely site of action is brain stem. A peripheral site of action of intrathecal neostigmine is unlikely, because plasma concentration after small intrathecal doses would be very low. Also systemic administration of glycopyrrolate was ineffective in treating the nausea. Nausea and vomiting are the most important side effect of intrathecal neostigmine.

Cardiovascular system:-

Higher dose can cause bradycardia. Blood pressure is minimally affected.

Respiratory effects:-

Respiratory system is minimally affected even with higher doses.

Genitourinary effects:-

Urinary retention has occurred after higher doses, but only for brief periods.

NITROGLYCERINE TRANSDERMAL SYSTEM

Nitroglycerine is 1,2,3-propanetriole trinitrate.

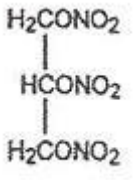


Fig-10: Chemical structure of nitroglycerine

Molecular weight of NTG is 227.09. It is a vasodilator of both arteries and veins.

The Nitroglycerine Transdermal System provides slow sustained release of nitroglycerine through skin. The rate of release of nitroglycerine is dependent upon the area of the system; each square centimetre of applied system delivers approximately 0.02 mg of nitroglycerine/ hr. Thus, the 18cm2 and 10cm2 systems deliver approximately 0.4mg and 0.2mg of nitroglycerine/hour respectively. Each 10cm2 system contains 20mg of nitroglycerine. The transdermal NTG system delivers 12% of its initial content of nitroglycerine by 12 hours.

The Nitroglycerine Transdermal System comprises of three layers. These layers are 1) impermeable polypropylene layer and 2) nitroglycerine in an adhesive acrylic- polymer matrix which acts as a source of NTG.3) A peelable protective layer on the outer surface which has to be removed to attach to skin.

Fig:11-Cross section of Transdermal NTG system:

Nitroglycerine Transdermal System- Clinical Pharmacology:-

The action of nitroglycerine is relaxation of vascular smooth muscles and dilatation of peripheral veins/arteries, [mainly veins]. Venous dilatation promotes peripheral pooling of blood and venous return to the heart decreases. This reduces preload. Arteriolar dilatation decreases systemic vascular resistance, systolic BP, and mean BP (afterload).Vasodilatation occurs in the coronary arteries also.

Pharmacokinetics:-

The volume of distribution of nitroglycerine is about 3.2 L/kg, and nitroglycerine is cleared rapidly from circulation. The initial metabolites of nitroglycerine are inorganic nitrates and 1,2 and1,3-dinitroglycerol. These are further metabolised to mononitrates and finally to carbon dioxide and glycerol. Upon removing the patch, the plasma concentration declines with a half-life of about an hour.

TRANSDERMAL NITROGLYCERINE IN SPINAL ANAESTHESIA

The transdermal NTG patch releases nitric oxide during degradation to organic nitrates. According to clinical research, nitric oxide generators do not

produce analgesia but recent researches provides evidence of acetylcholine, stimulating NO synthesis in the spinal cord, which is necessary for the expression of analgesic effect secondary to the cholinomimetics.. This mechanism of action is mediated through second messengers like cGMP. Neurons in the superficial spinal dorsal horn shows decreased response after exposure to cGMP. Therefore, analgesic effect would be due to predominant action on superficial spinal cord layers.

Precautions:-

Postural hypotension may occur particularly in the elderly. Hypotension induced by nitroglycerine may be accompanied by paradoxical bradycardia and this can increase the incidence of angina pectoris.

Drug Interactions:-

The vasodilating effects of nitroglycerine may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Adverse Reactions:-

Adverse reactions to nitroglycerine are generally dose related, and almost all of these reactions are the result of nitroglycerine's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Transient episodes of light headedness occurs. Hypotension occurs infrequently but warrants discontinuation in some patients.

PATIENTS AND METHODS

After obtaining approval from Ethical Committee, the study was conducted in RAJA MIRASDAR HOSPITAL [Thanjavur medical college] over a period of 5 months. After obtaining informed consent, the study was conducted on 78 patients aged 30 to 60 years of ASA grade I and II, planned for hysterectomies. Patients were allocated into 3 groups, each group containing consisting 26 patients.

Group C: Patients received 15mg [3ml] of intrathecal bupivacaine.

Group N: Patients received 15mg [3ml] of intrathecal bupivacaine and 25μg [1ml] of neostigmine.

Group P: Patients, in addition to 15mg [3ml] of intrathecal bupivacaine and 25μg [1ml] of neostigmine, received transdermal NTG patch [5mg/24hours] at chest wall in non-anaesthetized area 15 minutes after intrathecal administration of drug solution.

Visual analogue scale [VAS] was used as pain score, 0 = no pain and 10 = worst pain. After preloading the patients with Ringer Lactate 10ml/kg, spinal anaesthesia was performed at L3-L4 level, with 25 gauge Quincke needle and 4ml of drug volume was injected intrathecally.

Sensory level was assessed by pinprick. BP was recorded every 5 minutes during the surgery. Inj. ephedrine 6mg IV was given when systolic BP

decreases below 15% of base line. Pulse rate and SpO2 were observed continuously. Fall in heart rate below 60 per minute was treated with Inj. atropine 0.2mg IV. Intraoperative vomiting was treated with Inj. Metoclopramide 10mg IV. Postoperatively VAS score was used to assess pain in subjects every 30 minutes. Patients were given rescue analgesia at VAS score of 4.

Other adverse effects like vomiting, nausea, sedation bradycardia, hypotension, sweating, headache and palpitation were also monitored.

Inj Pentazocine 30 mg was administered intramuscularly as rescue analgesic. Duration of analgesia was calculated from the time of intrathecal drug administration till VAS score reaches 4.

Data thus obtained were analyzed using Microsoft Excel software.

Statistical Tools

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2010)** developed by Centre for Disease Control, Atlanta.

Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's chi square test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

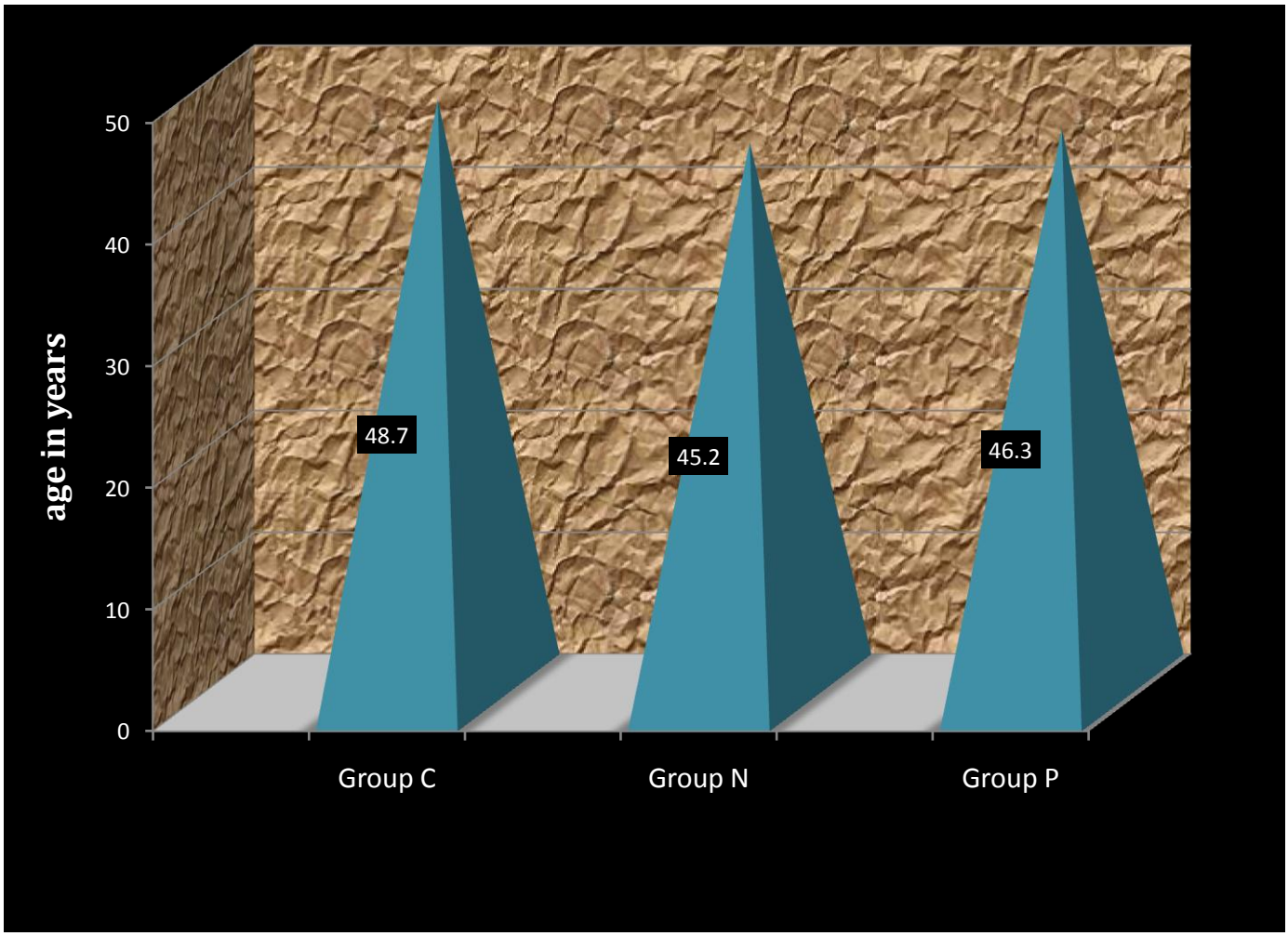
RESULTS

A : Characteristics of cases

Table 8 : Age distribution

Age group	Group C		Group N		Group P	
	no:	%	no:	%	no:	%
Upto 40 years	3	11.5	8	30.8	9	34.6
41-50 years	14	53.8	14	53.8	10	38.5
51-60 years	9	34.6	4	15.4	7	26.9
Total	26	100	26	100	26	100
Range	38-58 years		33-55 years		35-60 years	
Mean	48.7 years		45.2 years		46.3 years	
SD	5.6 years		6.1 years		7.3 years	
'p' value	0.1348 Not significant					

Graph -1: Age distribution



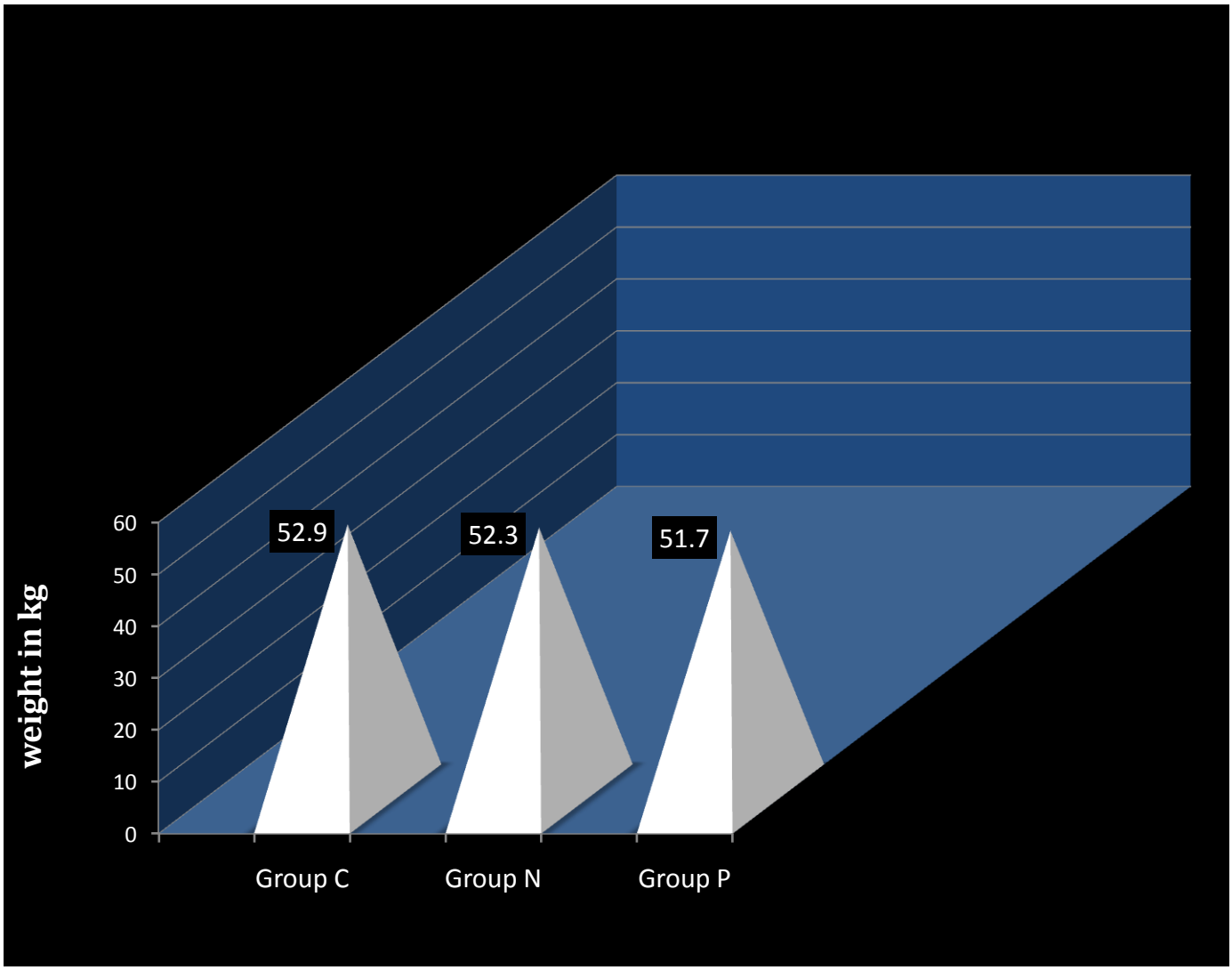
- There was no statistically significant difference in the distribution of age among the three groups.

Table- 9: Distribution of weight among the three groups

Group	Weight (in kg)		
	Range	**Mean**	**SD**
Group C	45 - 70	52.9	6.1
Group N	45 - 60	52.3	4.7
Group P	40 - 66	51.7	5.8
‘p’ value	0.8163 Not significant		

Graph -2: Comparison of mean weight among the three groups.

.



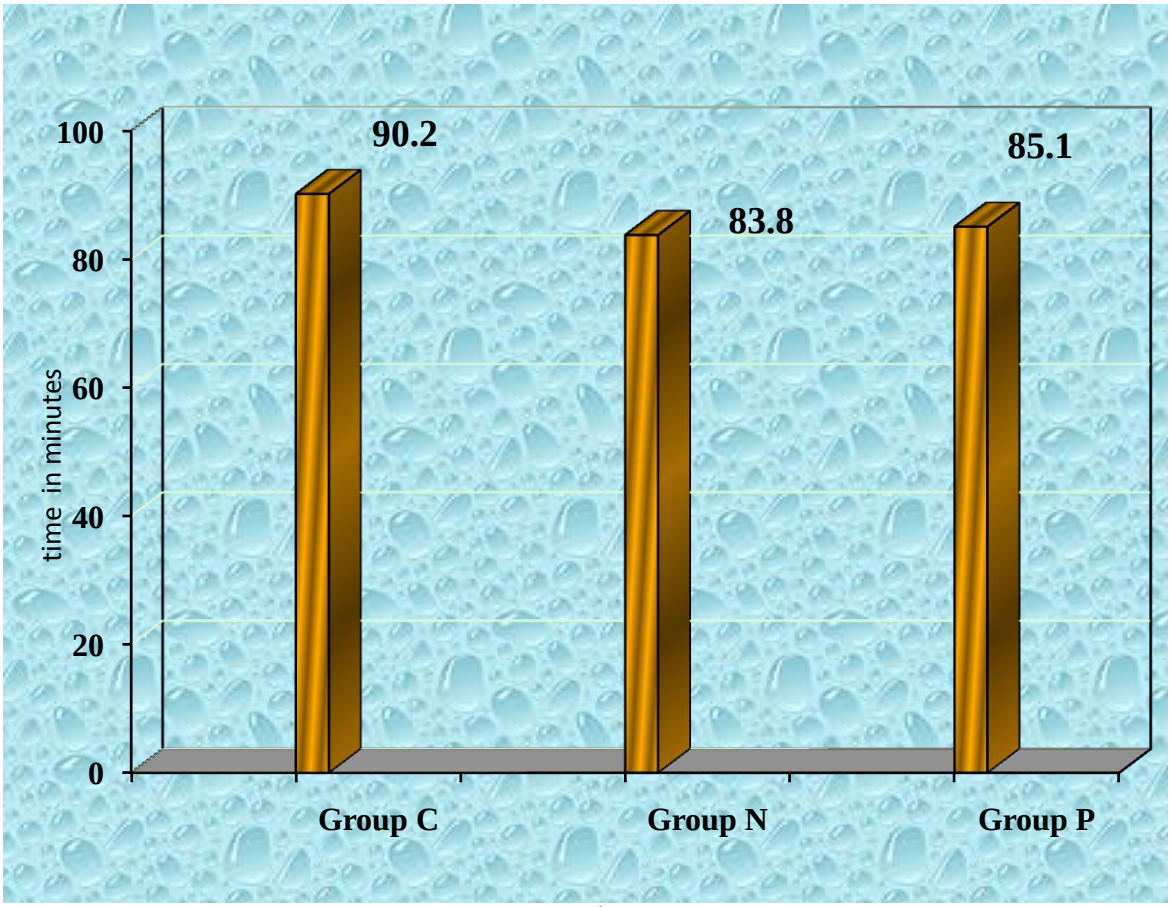
There was no statistically significant difference between the distribution of weight among the three groups…….

Table -10: Duration of surgery

Group	Duration of surgery in minutes		
	Range	Mean	SD
Group C	55 - 130	90.2	18.1
Group N	60 - 120	83.8	18.0
Group P	60 - 120	85.1	18.4
'p' value	0.3675 Not significant		

There is no statistically significant difference between duration of surgery among the three groups..

Graph-3: Mean duration of surgery in minutes..

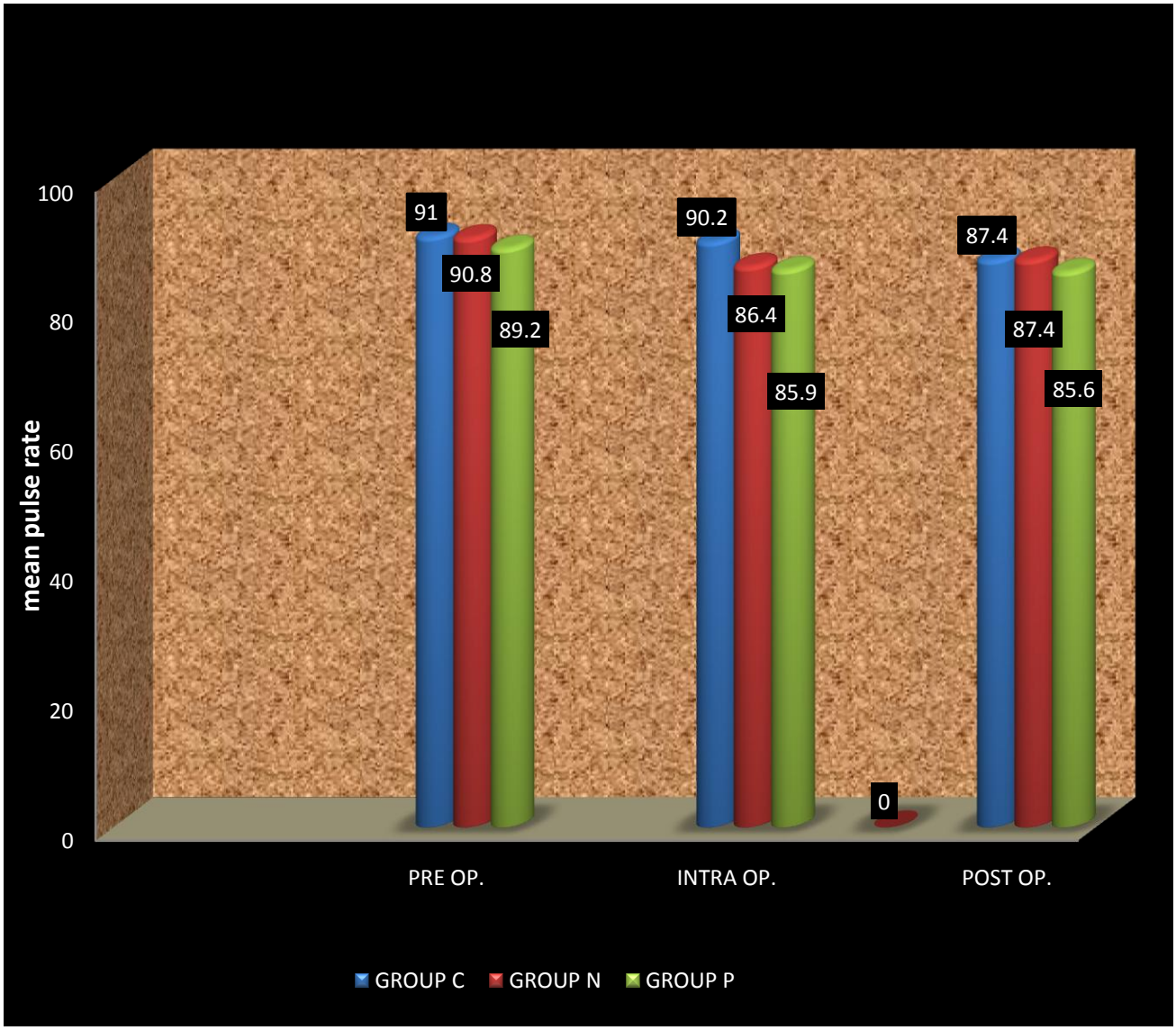


COMPARISON OF THREE REGIMEN

Table 11: Changes in pulse rate

Pulse rate	Pulse rate						'p' value between Groups			
	Group C		Group N		Group P					
	Mean	SD	Mean	SD	Mean	SD	C,N & P	C &N	C & P	N &P
Pre operative	91	10.4	90.8	11.6	89.2	12.8	0.7195 Not significant.	0.5701 Not significant.	0.481 Not significant.	0.6604 Not significant.
Intra operative	90.2	11.1	86.4	10.7	85.9	12.7	0.1723 Not significant	0.0714 Not significant	0.156 Not significant	0.927 Not significant
Post operative	87.4	10.5	87.4	11.4	85.6	12.6	0.7125 Not significant	0.5704 Not significant	0.5159 Not significant	0.5518 Not significant
Decrease	3.5	2.4	3.3	5.0	3.6	7.3	0.7623 Not significant	0.4809 Not significant	0.5704 Not significant	0.9416 Not significant

Graph-4: Changes in pulse rate

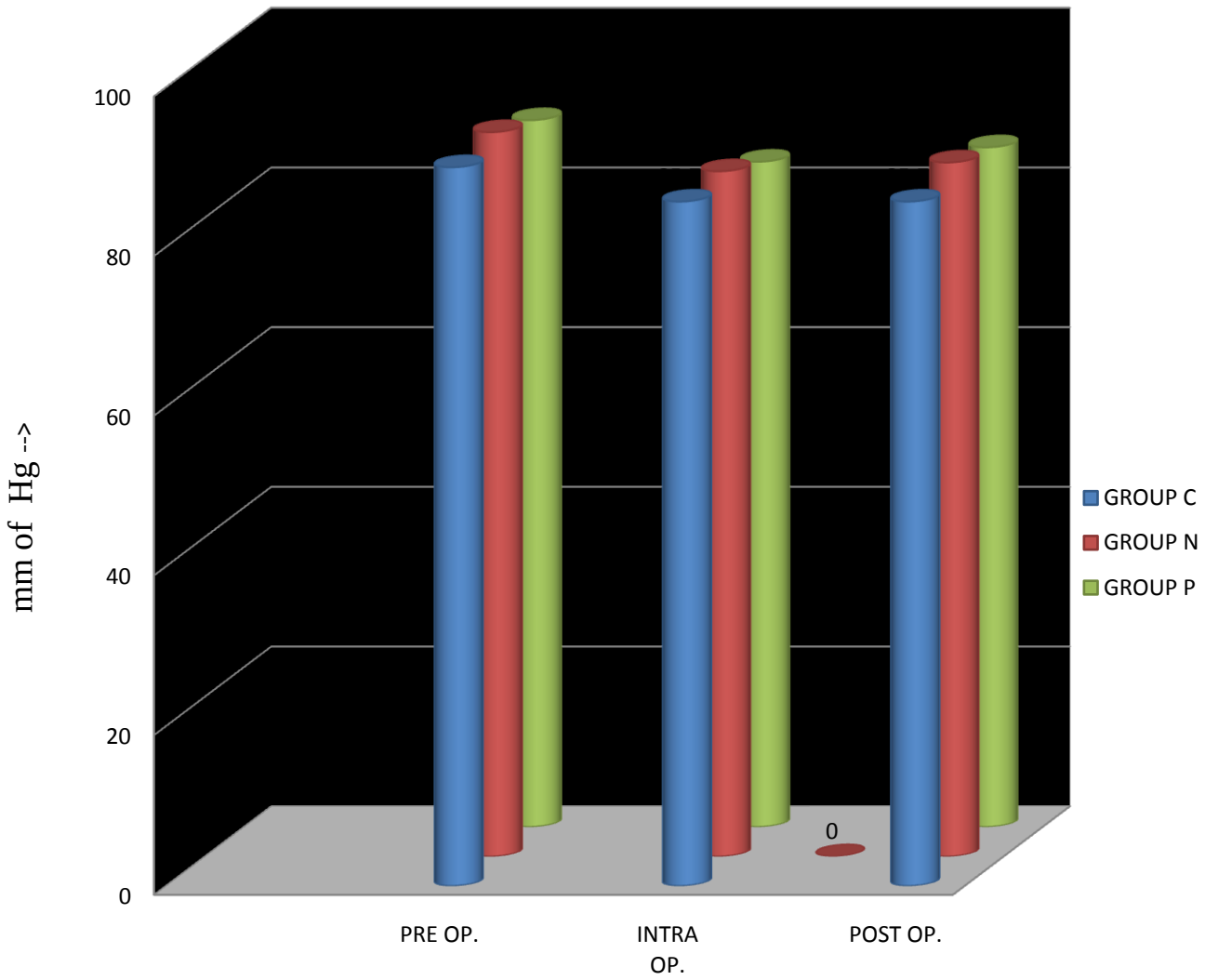


There is no statistically significant difference in the heart rate among the three groups…..

Table -12: Changes in Mean Arterial Pressure among the three groups

MAP	MAP of						'p' value between Groups			
	Group C		Group N		Group P					
	Mean	SD	Mean	SD	Mean	SD	C,N & P	C &N	C & P	N &P
Pre operative	90.0	5.2	90.7	5.2	88.5	6.8	0.4273 Not significant.	0.3696 Not significant.	0.558 Not significant.	0.234 Not significant.
Intra operative	85.7	5.5	85.8	5.4	83.3	6.7	0.2021 Not significant.	0.8836 Not significant.	0.148 Not significant.	0.1033 Not significant.
Post operative	85.7	5.6	86.9	4.6	85.1	6.6	0.7111 Not significant.	0.4474 Not significant.	0.9416 Not significant.	0.5099 Not significant.
Decrease	3.9	1.7	3.7	4.2	3.4	2.2	0.118 Not significant.	0.9271 Not significant.	0.1102 Not significant.	0.4207 Not significant.

Graph-5 : Changes in MAP

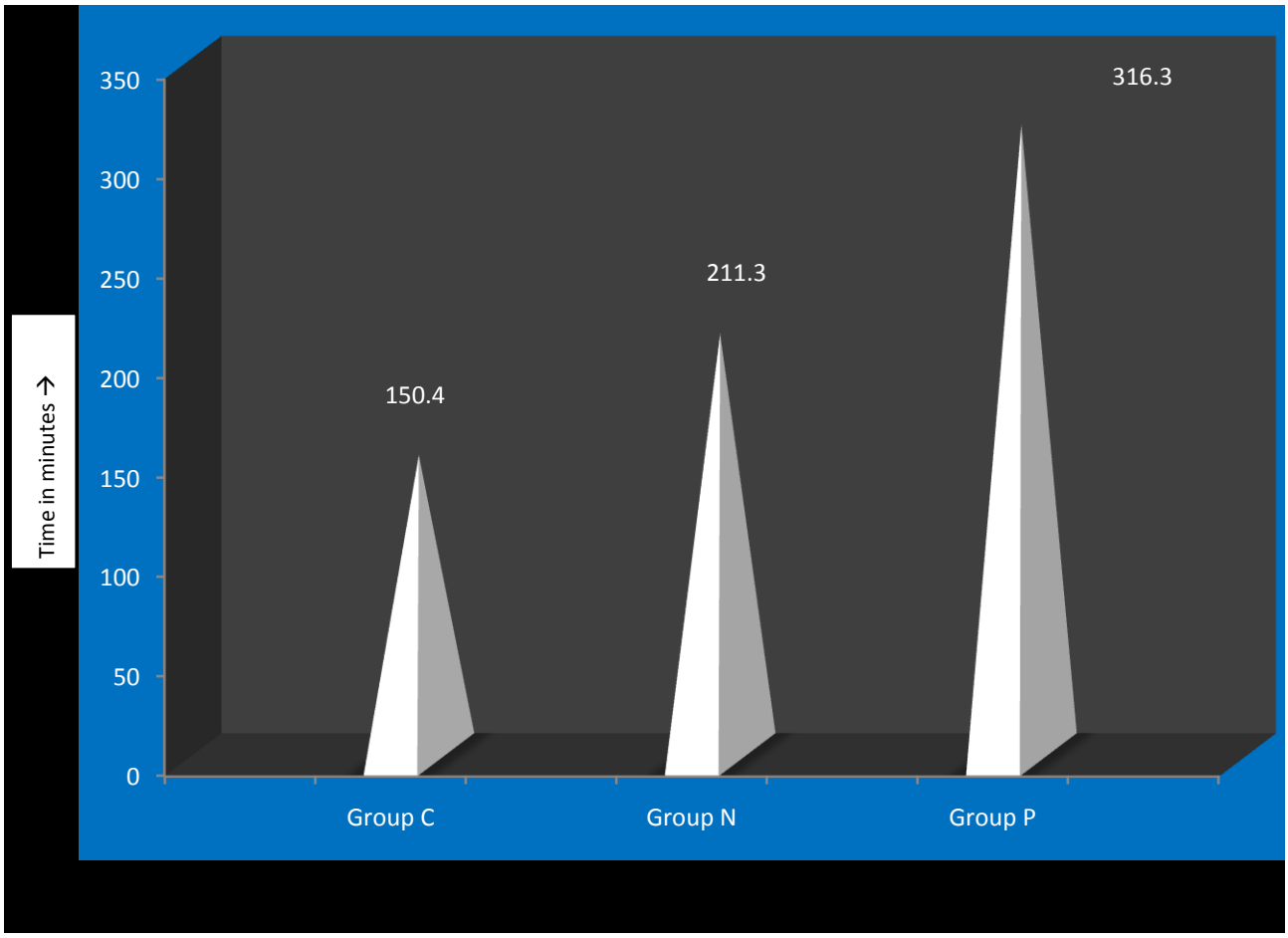


There is no statistically significant difference in the mean arterial pressure among the three groups…..

Table- 13: Comparison of Duration of Analgesia

Group	Duration of Analgesia in minutes		
	Range	Mean	SD
Group C	120 - 180	150.4	15.7
Group N	180 - 250	211.3	22.8
Group P	200 - 400	316.3	48.0
'p' value between Groups C,N & P	0.0001 - Significant		
C & N	0.0001 Significant		
C & P	0.0001 Significant		
N & P	0.0001Significant		

Graph-6: Comparison of Duration of Analgesia



- **Duration of analgesia was longest in Group P in comparison to other two groups and this difference was statistically significant. …**

- **Duration of analgesia was longer in Group N in comparison to Group C and this difference was also statistically significant…..**

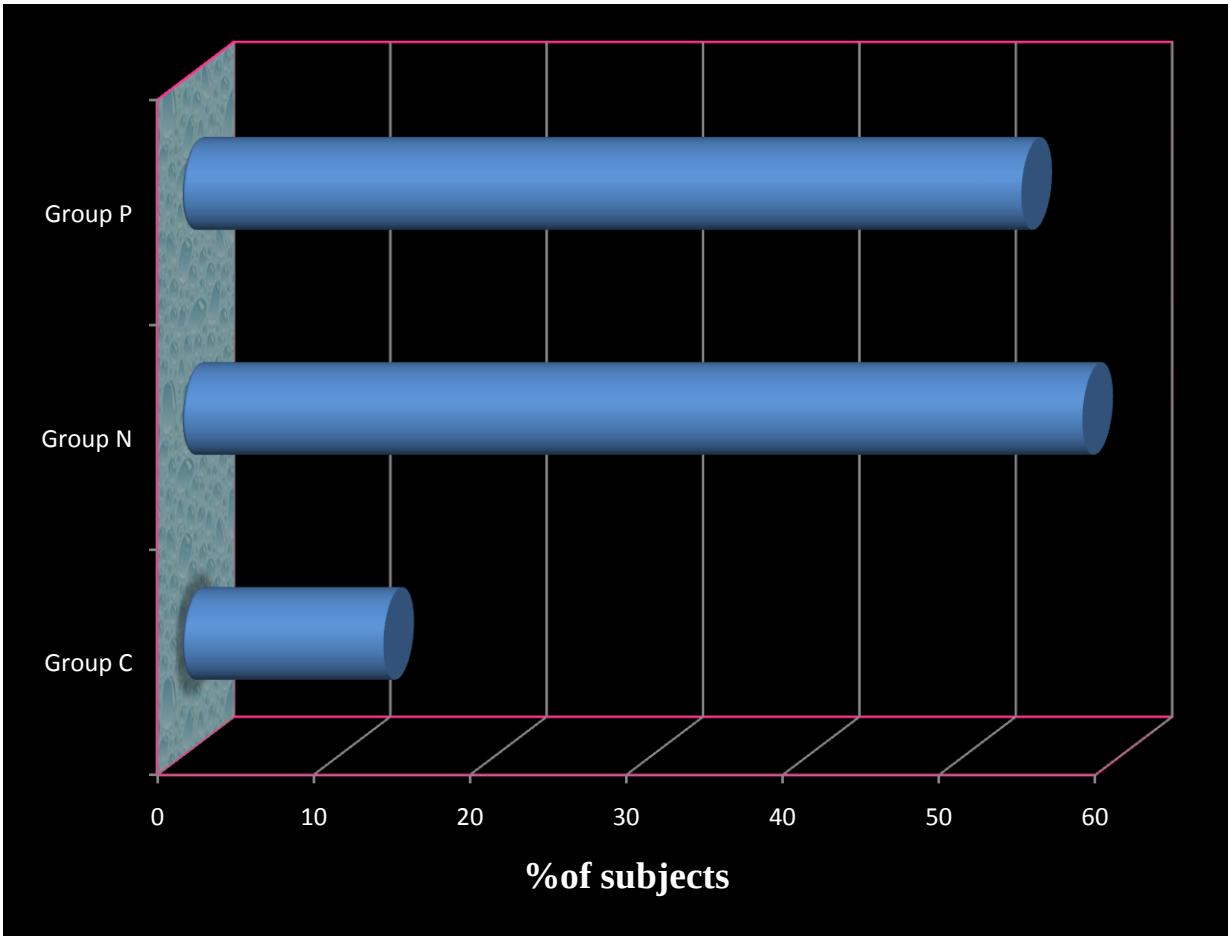
Table -14 a: Adverse effects

	GROUP-P		GROUP-N		GROUP-C
NAUSEA	8		8		2
VOMITING	6		7		1
HYPOTENSION	3		2		3
BRADYCARDIA	2		2		1

Table -14b: Comparison of adverse effects

Group	**Nausea and vomiting**			
	Yes		**No**	
		%		**%**
Group C	3	11.5	23	88.5
Group N	15	57.7	11	42.3
Group P	14	53.8	12	46.2
‘p’ value between Groups C & N C & P N & P	0.0238 – Significant 0.046 – Significant 0.7822 - Not significant			

Graph-7: Incidence of nausea and vomiting



Incidence of nausea and vomiting was higher in Group- N and Group-P when compared with Group- C and this difference is statistically significant. There was no statistically significant difference in the incidence of nausea and vomiting among Group-P and Group-N.

DISCUSSION

Various drugs have been tried in the subarachnoid space along with local anaesthetics with the aim of improving the duration of post-operative analgesia. The cholinesterase inhibitor neostigmine is one among such adjuvants.

Even though neostigmine has shown to produce an increase in duration of analgesia, it was also associated with many unwanted side effects particularly nausea and vomiting, especially in higher doses. So to reduce the incidence of adverse effects and to prolong post operative analgesia other adjuvants have been used along with neostigmine.

The aim of this study was to systematically review the current evidence of analgesic enhancement of intrathecal neostigmine by the addition of transdermal nitroglycerine patch on bupivacaine spinal anaesthesia

Analgesic effect of intrathecally administered neostigmine is by release of acetylcholine in the spinal cord. Increased acetylcholine due to surgical stimuli and acetylcholine preserved from anticholinesterase activity of intrathecal neostigmine, binds to nicotinic and muscarinic nerve terminals in the spinal cord. Studies have proved that cholinergic agonists produce inhibitory effects on spinal dorsal horn neurons, including spinothalamic tract .This suggest that a spinal cholinergic system plays an important inhibitory role in the modulation of pain pathways.

Since NO was shown to be a CNS neurotransmitter, there has been reports of relationship between Nitric Oxide and pain processing in the CNS. It is accepted that Nitric Oxide may occupy an important position in the mediation of pain. Acetylcholine induces analgesia by activation of the arginine-Nitric Oxide-cGMP pathway. Enzyme Guanylate Cyclase activity in the CNS is markedly stimulated by Nitric Oxide generated from L-arginine or provided through transdermal NTG ,an exogenous source as in the present study. Nitric Oxide formation occurs during degradation of organic nitrates from transdermal NTG.

This study was designed to find out whether the analgesic effect of intrathecal neostigmine will be enhanced by transdermal NTG, which acts as an exogenous source of nitric oxide. In this study the duration of analgesia was analyzed as period from intrathecal drug administration till VAS score reaches 4. On statistical analysis, patient belonging to Group C complained of pain earlier than other groups, duration of analgesia being 2.5hours. There was statistically significant delay in the onset of pain in Group N and Group P. Our study showed a mean duration of 3.5 hours in patients belonging to Group N and 5.2 hours in patients belonging to Group P.

Lauretti, Gabriela R. et al. in 2000 conducted a study to determine whether association of transdermal nitroglycerine would enhance analgesia from a low dose of intrathecal neostigmine in patients undergoing gynaecologic surgery during spinal anaesthesia. They concluded that neither intrathecal 5 μg

neostigmine alone nor transdermal nitroglycerine alone (5 mg/day) delayed the time to administration of first rescue analgesics, but the combination of both provided an average of 550 min of effective postoperative analgesia after vaginoplasty. There was no significant difference in the incidence of adverse effects.. They suggested that transdermal nitroglycerine and the central cholinergic agent neostigmine may enhance each other's antinociceptive effects which correlate with findings of my study. The increased incidence of adverse effects in my study may be due to usage of higher dose of neostigmine.

Gurvinder Kaur, Narjeet Osahan, Lalita Afzal in 2007 conducted a study to examine the effect of transdermal NTG patch (5mg/24hours) on intrathecally administered neostigmine (5μg) along with 15mg bupivacaine and incidence of untoward effects. They found that average duration of analgesia in intrathecal neostigmine Group [Group I] was 6.5 hours and in neostigmine and transdermal nitroglycerine patch Group [Group II] was 9.10 hours. Duration of analgesia was significantly higher in patients in Group II as compared to Group I. The incidence of nausea was higher in Group I than in Group II. The enhancement of analgesia of intrathecal neostigmine by transdermal NTG in this study correlates with my study. The increased incidence of nausea and vomiting in my study may be due to usage of higher dose of neostigmine.

Fareed Ahmed.et. al. 2010 conducted a study to determine the effect of transdermal nitroglycerine patch on intrathecal neostigmine. Patients were

allocated into four groups with Group I received 15 mg bupivacaine intrathecally, Group II received 15mg of bupivacaine with 5µg neostigmine intrathecally, patients in Group III received 15mg of bupivacaine with 1ml of normal saline intrathecally and transdermal NTG patch (5 mg/24 hours). Patients in Group-IV received 15 mg bupivacaine with 5µg of neostigmine intrathecally and transdermal NTG patch [5 mg/24 hours]. The mean duration of analgesia was 202.2min, 407.6min, 207.8 min and 581.6 min in Group [1] , Group [II], Group [III] , Group [IV] respectively.

In my study intrathecal bupivacaine – transdermal nitroglycerine patch group was omitted since the above studies substantiated that transdermal nitroglycerine patch do not show analgesic potential of its own. The enhancement of analgesia by intrathecal neostigmine and potentiation of analgesic effect of intrathecal neostigmine by transdermal NTG patch correlates with the findings of my study. No change in perioperative hemodynamic parameters which was observed in this study also correlates with my study. The increased incidence of nausea and vomiting in my study may be due to usage of higher dose of neostigmine.

CONCLUSION

On the basis of this study the following conclusions were drawn:-

1) Spinal anaesthesia with 3ml 0.5% bupivacaine provided 2.5±0.26hrs of analgesia.

2) Addition of intrathecal 25µg neostigmine to bupivacaine spinal anaesthesia significantly prolonged the duration of analgesia [3.52±0.38hrs].

3) Addition of transdermal nitroglycerine patch [5mg/24hrs] and intrathecal 25µg neostigmine to bupivacaine spinal anaesthesia provided the longest duration of analgesia [5.27±0.8 hrs].

4) Addition of intrathecal neostigmine and transdermal nitroglycerine patch to bupivacaine spinal anaesthesia did not produce any significant change in hemodynamic parameters

5) Addition of intrathecal 25µg neostigmine to bupivacaine spinal anaesthesia significantly increased the incidence of nausea and vomiting.

BIBLIOGRAPHY

1) Yaksh TL, Dirksen R, Harty GL. Antinociceptive effects of intrathecally injected cholinomimetic drugs in rats and cats. Eur J Pharmacol 1985; 117(1): 81-88

2) Naguib M, Yaksh TL .Antinociceptive effects of spinal cholinesterase inhibition and analysis of its interaction with μ and α2 receptor systems. Anesthesiology 1994; 80: 1338-48.

3) BouazizH, Eisanach JC, Tong C. Post operative analgesia from intrathecal neostigmine in sheep. Anesth Analg1995; 80: 1140-4.

4) Abram SE, Winne RP. Intrathecal acetylcholinesterase inhibitors produce analgesia that is synergistic with morphine and clonidine in rats. Anesthesiology1995; 81:501-7.

5) Hood DD, Eisenach JC, Tuttle R. Phase I safety assessment of intrathecal neostigmine methylsulfate in humans. Anesthesiology 1995; 82:331-343.

6) Hood DD, Eisenach JC, Tong C, Tommasi E, Yaksh TL. Cardiorespiratory and spinal cord blood flow effects of intrathecal neostigmine methylsulfate, clonidine and their combination in sheep. Anesthesiology 1995;82: 428-435.

7) GR Lauretti, Prado WA, Rais MP, Klamt JG. Dose response study of intrathecal morphine versus intrathecal neostigmine, for post operative analgesia in patients undergoing vaginoplasty.AnesthAnalg 1996; 83: 1182-6.

8) Lauretti GR, Lima ICPR. The effects of intrathecal neostigmine on somatic and visceral pain: Improvement by association with a peripheral

anticholinergic. AnesthAnalg 1996; 82: 617-20.

9) Lauretti GR and Azevedo VMS. Intravenous ketamine or fentanyl prolongs post operative analgesia after intrathecal neostigmine. AnesthAnalg 1996; 83: 766-70.

10) Krukowski JA, Hood DD, Eisenach JC, Mallak KA, Parker RL: Intrathecal neostigmine for post-cesarean analgesia section analgesia -Dose response. Anesth Analg 1997; 84:1269–75.

11) Klamt JG, Slullitel A, Garcia IV, Prado WA. Post operative analgesic effect of intrathecal neostigmine and its influence on spinal anaesthesia. Anaesthesia 1997; 52:547-551.

12) Chapman, C Richard and Karen L. Syrjala. Measurement of pain and Management of Pain. (Philadelphia United states of America): 1990, 580-594

13) American Journal of Physical Medicine & Rehabilitation: October 2001 Volume 80 – Issue 10 - p 717.

14) Oral analogue scale as an outcome measure after displaced intra-articular calcaneal fractures; Foot Ankle Int. 1998 Oct;19(10):694-7

15) The McGill Pain Questionnaire: major properties and scoring methods; Pain. 1975 Sep; 1(3):277-99.

16) On the utility of the West Haven-Yale Multidimensional Pain Inventory; 1995 Apr 15;20(8):956-63

17) Buerkle H, Boschin M, Marcus MAE, Brodner G, wusten R, Aken HV. Central and peripheral analgesia mediated by the acetylcholinesterase-inhibitor

neostigmine in the rat inflammed knee joint model. AnesthAnalg 1998; 86:1027-32.

18) Lauretti GR, Hood DD, Eisenach JC, Pfeifer BL.A mulitcenter study of intrathecal neostigmine for analgesia following vaginal hysterectomy .Anesthesiology 1998; 89: 913-8.

19) Cho SS, Kim JS, Chung CJ, Han IS, Jang SC. Effect of intrathecal neostigmine on Post-Cesarean Section Analgesia. KoreanAnesthesiology.1998 Sep; 35(3):545-552

20) Liu SS, Hodgson PS, Moore JM, TrautmanWJ, Burkhead DL. Dose response effects of spinal neostigmine added to bupivacaine spinal anaesthesia in volunteers. Anaesthesiology 1999:90:710-7.

21) Dwivedi A, Jain PN, Dasgupta D. Intrathecal neostigmine for post operative pain analgesia. IJA 2000;44-36-39.

22) Lauretti, Gabriela R., Oliveira, Ana-Paula M.,Julião, Maria-do-CarmoC.,Reis, Marlene P. Pereira, Newton L. .Transdermal Nitroglycerine Enhances Spinal Neostigmine Postoperative Analgesia following Gynecological Surgery Anaesthesiology: October-2000 ;Volume 93 :943-6.....

23) Saini S, Sethi S, Malhotra N. Evaluation of intrathecal neostigmine for post operative analgesia. J Anaesthclinpharmacol 2006; 22(1): 35-40.

24) GurvinderKaur, , LalitaAfzal NarjeetOsahan: Effect of Transdermal Nitroglycerine Patch on Analgesia of intrathecally administered Neostigmine . Anaesthesia journal of Clinical Pharmacology 2007; 23(2): 159-162

25) Farid Ahmed, Mamta Khadelwal ,Vipul Chawla Ashish Garg.. Transdermal NTG patch enhances analgesic effect of intrathecal neostigmine sulphate following hysterectomies.. Indian Journal of Anaesthesia. 2010 ,Jan-54:24-8.

PROFORMA

A STUDY OF EFFICACY OF TRANSDERMAL NITROGLYCERINE PATCH IN ENHANCING ANALGESIA OF INTRATHECAL NEOSTIGMINE FOLLOWING HYSTERECTOMIES UNDER BUPIVACAINE SPINAL ANAESTHESIA

NAME: IP-no: DATE:

AGE/SEX: WEIGHT: UNIT:

DIAGNOSIS: GROUP PROCEDURE:

PREOPERATIVE EXAMINATION **INVESTIGATIONS**

ASA GRADE

SPINAL ANAESTHESIA

TIME OF INTRATHECAL DRUG INJECTION:

DRUG/DOSE

POSITION

SPACE

INTRA OPERATIVE MONITORING:

Time	PR	MAP	Sp02	Adverse effects	Drugs

RESULTS

1.DURATION OF SURGERY:

2.POST OPERATIVE BP and PR:

TIME	MAP	PR	VAS score

.

3.HEMODYNAMIC PARAMETERS:

	MEAN BP	MEAN PULSE RATE
PRE OPERATIVE		
INTRA OPERATIVE		
POST OPERATIVE		

4.DURATION OF ANALGESIA:

5.ADVERSE EFFECTS:

							MASTER CHART- Group-C							
NO:	IP NO	AGE	WEIGHT	Duration of		PR				MAP			Adverse	duration of
				surgery		Pre op	intra op	post op		pre op	intra op	post op	effects	Analgesia
1	214191	55	45	120		98	97.7	93.3		96.5	94.2	98.2	nausea	140
2	214209	45	70	110		88	84.8	86.2		98.2	94.6	94.2	nil	135
3	211957	43	48	130		100	97.4	95.6		83.3	76.6	79.9	NIL	150
4	214119	40	51	90		97	96.6	96.9		88.6	80.2	83.3	NIL	170
5	210827	48	49	80		94	93.3	92.3		93.4	90.6	92.4	nil	160
6	215925	38	45	100		76	66.8	68.9		90.6	86.6	88.8	bradycardia	170
7	212791	50	48	110		72	68.6	72.3		96.6	93.6	96.8	NIL	170
8	216112	47	54	90		96.6	98.8	98.3		96.6	90.4	95.6	NIL	120
9	209928	38	56	75		89	83.3	87.3		86.2	82.3	86.9	NIL	130
10	210820	42	58	60		115	112.5	110.6		77.9	74.5	73.3	hypotension	150
11	215165	55	54	55		110	102.3	98.7		90.6	84.6	97.6	NIL	130
12	203456	54	49	100		94	96.9	98.9		87.6	85.9	88.2	VOMITING	170
13	198287	46	56	90		88	89.4	90.4		93.2	89.5	92.1	nil	150
14	213498	55	60	80		95	94.3	98.3		87.6	84.3	82.3	nil	160
15	213498	42	54	95		82.3	79.4	82.3		86.6	82.3	84.3	nil	150
16	215912	49	47	90		79	84.3	87.6		91.2	87.8	89.1	nil	140
17	200149	55	52	95		76	70.6	78.5		84.4	80.2	83.3	nausea	180
18	199610	52	47	65		80.2	86.3	80.4		92.1	89.4	90.6	nil	140
19	200314	50	55	70		96.6	100.4	95.5		86.5	76.5	82.3	hypotension	130
20	245198	49	59	75		93.3	90.3	95.5		88.5	84.4	83.3	nil	160
21	215819	55	46	85		99.9	95.4	100.2		95.5	92.3	95.5	nil	130
22	200139	58	54	100		91.3	85.6	90.9		87.7	83.3	88.8	hypotension	145
23	206781	47	52	95		88.3	90.3	92.3		86.5	83.8	85.5	nil	160
24	204156	50	46	100		100	106.8	105.1		95.6	90.6	93.3	nil	160
25	213418	52	62	110		85.6	89.3	90.4		87.6	85.3	88.9	nil	160
26	201892	50	59	75		80.3	83.3	85.6		80.4	84.4	87.7	nil	150

							MASTER	CHART		GROUP-N				
	AGE	IP NO	WEIGHT	DURATION		MEAN PR				MAP			duration	adverse
				OF SURGERY		PREOP	INTRA OP	POST OP		PRE OP	INTRA OP	POST OP	of analgesia	effects
1	48	210833	50	60		94	84.4	81.6		88	74.4	77.6	210	hypotension
2	40	200822	46	65		118	112.8	116.8		103	94.4	91.9	200	vomiting
3	45	214913	56	75		93	90.4	88.2		92.3	90.3	91.6	180	NIL
4	48	197674	52	90		90	82.2	88.1		93.3	84.4	91.6	180	vomiting
5	35	207380	60	80		120	110.6	109		92.3	91.3	92.6	240	nausea
6	38	202416	48	60		94	87.6	95		92.3	83.3	83.6	190	NIL
7	45	207927	50	70		98	88.3	83.3		95	82.2	86.6	180	vomiting
8	40	210692	58	90		86	83.3	83.3		98	89.9	93.3	220	NIL
9	50	208782	53	70		96	94.4	96.6		92	82.6	83.3	230	nausea
10	40	209920	47	60		77	72.3	85.2		77	70.3	78.9	230	hypotension
11	45	212136	60	75		74	73.3	73		90	89.2	87.2	180	nausea
12	33	209921	48	75		80	76.6	73.3		85.9	85.2	83.2	180	NIL
13	45	219845	45	60		110	108.6	112.6		92.2	87.3	85.6	210	nausea
14	52	212390	49	90		84	83.2	84.6		89.4	86.4	83.9	210	NIL
15	50	211100	56	120		82	78.4	78.3		92.6	89.4	87.3	220	vomiting
16	48	205130	55	90		82	79.4	75.4		84.6	82.7	78.6	220	nausea
17	47	198479	55	80		80	76.4	78.3		90.6	86.5	88.3	185	NIL
18	47	205146	49	100		93	90.6	93.3		93.6	89.3	88.2	230	nausea
19	53	207941	53	80		86	79.3	81.6		91.3	87.3	86.4	180	NIL
20	55	198908	56	90		90	84.6	83.3		96.6	94.6	96.9	250	nil
21	45	207836	56	110		86	82.5	82.7		92	89.6	86	220	NIL
22	40	200819	48	75		94	87.5	86.6		80.7	80.6	88.3	220	nausea
23	35	207099	46	110		96	88.5	88.3		86.3	82.3	83.6	240	NIL
24	50	209739	49	120		74	73.4	72.4		89.3	85.4	86.6	220	bradycardia
25	45	206147	54	100		90	86.4	90.2		89.3	84.6	89.9	230	nausea
26	55	208280	60	85		93	92.2	92.6		89.3	86.3	88.5	240	NIL

			MASTER CHART GROUP P										
						PR			MAP			Adverse	Duration of
NO:	IP NO	AGE	WEIGHT	Duration of Surgery		Pre op	intra op	post op		pre op	intra op	post op	effects	analgesia
1	208058	45	52	65		83.2	79.4	81.6		90.6	81.5	85.6	nausea	330
2	209516	45	54	72		102.6	104.8	104.6		93	82	89	nausea	370
3	211074	39	56	75		94.5	98.8	93.9		96	93	92.3	NIL	370
4	208665	38	55	75		98.4	98	110		79	76	71.1	nausea	280
5	203233	40	45	70		115.4	116	112		80	79	78.8	NIL	400
6	209797	40	49	75		79.5	76	75.00		80	78	77	NIL	340
7	204376	47	52	60		104.8	91.8	96		98.3	82.3	87.4	nausea	310
8	205494	36	53	70		79.6	77.4	78		80	75.6	77.2	NIL	330
9	203834	42	50	80		92.3	86.8	85		87.5	86.6	84	nausea	300
10	204831	43	46	70		89.7	89.8	92		76.6	67.8	75.5	hypotension	270
11	207923	40	40	60		90.5	83.4	85		84	79.5	81.3	NIL	300
12	202426	39	66	70		74.9	70.3	72.4		96.6	87.3	94.3	NIL	320
13	197664	60	55	105		64.1	61.6	60.3		86	82.3	82.9	vomiting bradycardia	380
14	193782	47	56	100		76.5	69.4	70.2		88	84.3	84.2	NIL	340
15	206156	40	50	75		78.9	79	76		96	94.6	94.4	NIL	380
16	210813	50	55	110		90.7	81.8	80.6		94.7	88.9	91.7	vomting	330
17	200707	54	45	110		75.6	76.4	77.3		92	90.8	91.8	nausea	350
18	206524	50	59	120		94.3	90.6	94.3		89.2	84.6	87.6	vomiting	200
19	207606	53	45	70		96.1	89.4	95		100.7	92.3	96.8	NIL	270
20	206181	35	50	75		88.5	94.6	95		84.6	78	83.3	nausea, hypotension	290
21	209216	50	45	110		85.9	86.4	87		91.7	90.4	90.4	NIL	330
22	205494	45	45	90		112.2	104.7	94.8		82.3	80.3	81.3	NIL	320
23	205168	60	54	90		86.4	85.5	79		87.2	84.3	85.5	vomiting	290
24	205163	55	60	100		72.4	65	70.6		96.2	92.3	93.6	nausea, bradycardia	300
25	197812	55	54	105		108.9	92.4	82.3		90.7	79.6	87.7	NIL	205
26	203274	50	54	110		82.3	83.9	78		81.3	73.3	79.4	vomiting	320