"A COMPARATIVE STUDY OF INTRATHECAL HYPERBARIC BUPIVACAINE 0.5% WITH FENTANYL VERSUS HYPERBARIC BUPIVACAINE 0.5% WITH BUPRENORPHINE IN LOWER LIMB AND LOWER ABDOMINAL SURGERIES"

By

DR. NITHYASHREE N

Thesis submitted to the

BLDE(DEEMED TO BE UNIVERSITY),

VIJAYAPURA, KARNATAKA

In partial fulfilment of the requirements for the degree of

DOCTOR OF MEDICINE

IN

ANAESTHESIOLOGY

Under the guidance of

Dr. VIJAY. V. KATTI MD

ASSOCIATE PROFESSOR .

DEPARTMENT OF ANAESTHESIOLOGY

B.L.D.E(DEEMED TO BE UNIVERSITY)

SHRI B.M.PATIL MEDICAL COLLEGE

HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

2020

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Date: 28-09-2020

Nithyashree N

Place: Vijayapur **DR. NITHYASHREE .N**

.

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Date: 28-09-2020

DR.VIJAY V. KATTI **M.D.**
ASSOCIATEPROFESSOR
DEPARTMENT Of ANAESTHESIOLOGY
B.L.D.E S**.(DEEMED TO BE UNIVERSITY)**
SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL&
RESEARCH CENTRE, VIJAYAPUR.

Place: Vijayapur

B. L. D. E.(DEEMED TO BE UNIVERSITY)
SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR. KARNATAKA

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Dr. Vidya Patil

DR. VIDYA PATIL$_{M.D}$
PROFESSOR & HEAD
DEPARTMENT OF ANAESTHESIOLOGY
B. L. D. E**.(DEEMED TO BE UNIVERSITY)**
SHRI. B. M. PATILMEDICAL COLLEGE
HOSPITAL &RESEARCH CENTRE,
VIJAYAPUR.

Date: 28-09-2020
Place: Vijayapur

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SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR. KARNATAKA

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Date: 28-09-2020
Place: Vijayapur

DR.ARVIND PATIL
PRINCIPAL
B. L. D. E.**(DEEMED TO BE UNIVERSITY)**
SHRI. B. M. PATILMEDICAL COLLEGE
HOSPITAL &RESEARCH CENTRE,
VIJAYAPUR.

B. L. D. E. .(DEEMED TO BE UNIVERSITY)
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Nithyashree N

DR. NITHYASHREE .N

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Nithyashree N

DR. NITHYASHREE.N

LIST OF ABBREVIATIONS

ASA	-	American Society of Anaesthesiologists
BB	-	Bupivacaine+ Buprenorphine
BF	-	Bupivacaine+Fentanyl
BP	-	Blood pressure
BT	-	Bleeding time
C	-	Cervical
CVS	-	Cardiovascular system
CSF	-	Cerebrospinal fluid
CNS	-	Central nervous system
CT	-	Clotting time
ECG	-	Electrocardiography
Hb	-	Haemoglobin
HR	-	Heart rate
ICU	-	Intensive care unit
IM	-	Intramuscular
IV	-	Intravenous
INJ	-	Injection
kg	-	Kilogram
L	-	Lumbar
L.A.	-	Local Anaesthetic
MAP	-	Mean arterial pressure
MIN	-	Minutes
mg	-	Milligram
mg/dL	-	Milli gram per deciliter
mmHg	-	Milli meter of mercury
µg	-	Microgram
NIBP	-	Non invasive Blood pressure
NS	-	Normal saline
PAP	-	Pulmoanay arterial pressure
PCWP	-	Pulmonary capillary wedge pressure
PR	-	Pulse rate
P/A	-	Per abdomen

pKa	-	Dissociation constant
RL	-	Ringer lactate
RS	-	Respiratory system
RR	-	Respiratory rate
RBS	-	Random blood sugar
S	-	Sacral
SBP	-	Systolic blood pressure
S.D	-	Standard deviation
SpO2	-	Oxygen saturation
TC	-	Total count
VAS	-	Visual analogue scale
yrs	-	Years

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INTRODUCTION

Spinal anesthesia is the most commonly used technique for lower abdominal surgeries as it is very economical and easy to administer [1]. The advantages of subarachnoid block are limited by its short duration of action and lack of postoperative analgesia.

In recent years, the supplementation of local anaesthetics with adjuvants is widely in practice, to reduce the dose of local anaesthetic, minimize side effects and prolong the duration of anaesthesia [1,2] .

Opioid added to local anaesthetic for spinal anaesthesia was first introduced into clinical practice in 1979 with intrathecal morphine as a forerunner. Neuraxial administration of opioids along with local anaesthetics improves the quality of intraoperative analgesia and also provide postoperative pain relief for longer duration[3,4].

Intrathecal morphine provides prolonged postoperative analgesia but is associated with increased risk of nausea, vomiting, itching and respiratory depression[5].

Fentanyl, a lipophilic opioid, has rapid onset of action following intrathecal administration. It does not tend to migrate to the fourth ventricle in sufficient concentration to cause delayed respiratory depression when administered intrathecally[6]. Addition of fentanyl to spinal anesthesia produces synergistic analgesia for somatic and visceral pain without increased sympathetic block[7]. Therefore, fentanyl provides better intraoperative analgesia and a safer alternative than morphine for management of early postoperative pain.

Buprenorphine is a centrally acting lipid soluble analogue of alkaloid thebaine. It exhibits analgesic property both at spinal and supraspinal level, when used

intrathecally in combination with bupivacaine it has known to improve the quality and duration of postoperative analgesia compared to bupivacaine alone [8,9].

This study was conducted to evaluate and compare the characteristics of spinal block and its side effects in adult patients undergoing lower abdominal surgeries who received a subarachnoid block with either bupivacaine with buprenorphine or bupivacaine with fentanyl.

OBJECTIVES OF THE STUDY

PRIMARY OBJECTIVES

1. To compare the onset and duration of sensory blockade.
2. To compare the onset and duration of motor blockade.
3. To compare the haemodynamic changes like heart rate and blood pressure.
4. Time of rescue analgesia.

SECONDARY OBJECTIVES

1. Side effects of study drugs.
2. Complications.

REVIEW OF-LITERATURE

HISTORICAL REVIEW OF SPINAL ANAESTHESIA

Cerebrospinal fluid was discovered by **Domenico Cotugno in 1764 a**nd circulation was described by **F.Magendie in 1825** who also named it.

Alexander Wood introduced hollow needle and glass syringe in 1853. Cocaine was isolated from Erythroxylon coca in **1860** by **Neimann and Lossen**. Its analgesic properties were described by **Schroff in 1862.** It was introduced in medicine as local analgesic for ophthalmology by **Carl Koller in 1884,** encouraged by Sigmund Freud.

The first spinal anaesthesia was performed in the year **1885, J. Leonard Corning,** a New York Neurologist. He injected cocaine into the subarachnoid space by accidentally piercing the dura while experimenting on a dog. Later he deliberately repeated the intradural injection for 60 minutes of 3% cocaine and suggested its use in surgery**.** "Be the destiny of this observation, what it may, had seemed to me, on the whole worth recording"**,** were his words.

Heinrich Iraneus Quinke 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, August Bier** performed the first planned spinal anesthesia in man. He injected 3 ml of 0.5% cocaine into the subarachnoid space of a 34 years old labourer for the operation on the lower limb. After using it on six patients, he and his assistant injected cocaine into each other's theca.

Heinrich Braun, a German Surgeon in **1905** reported the use of procaine for operative spinal anesthesia. He also reported the use of intrathecal epinephrine to

prolong the duration of spinal anesthesia but it was not accepted because of the fear of neurological complications.

It was only in **1945; Prickett** and his associates published their report on the neurological safety of intrathecal epinephrine to prolong the duration of spinal anesthesia.

Bupivacaine was first used for intradural block in 1966.

History of Spinal Anesthesia

1885 J L Corning (New York Neurologist) - Spinal Cocaine for pain relief

1891 Quincke(Germany)Lumbar Puncture

1898 August Bier (Germany) First Cocaine Spinal Anesthesia in six patients

1905 H. Braun (Germany) Procaine Spinal Anesthesia

1907 Barker (United Kingdom) - hyperbaric procaine (glucose); hypobaric procaine (alcohol)

1930 Jones (United Kingdom) -Dibucaine spinal anesthesia

1935 Sise (USA) -Tetracaine Spinal Anesthesia

1940 Lemmon (USA) - continuous spinal anesthesia

1945 Tuohy (USA) - continuous spinal anesthesia

1945 Prickett (USA) - report on neurologic safety of intrathecal epinephrine to prolong spinal anesthesia

1965 Re-emergence of use of spinal anaesthesia

1979 Intrathecal opioids first used in man

1994 Human study on the effects of cholinesterase inhibitors in SA.

1996 Studies in animals suggest that intrathecal clonidine is safe.

REVIEW OF CLINICAL STUDIES:

Pradeep Samuel Indurkar , Samala Saibaba[10](2017) Conducted a study on 60 patients of both sex between the age group of 18 to 65 years, ASA I or ASA II undergoing elective lower extremity and lower abdominal surgeries who were randamized into two groups . Group C(control group) receiving 0.5% hyperbaric Bupivacaine 13mg(2.6ml) alone and another group S(study group) receiving 0.5% hyperbaricBupivacaine 13mg(2.6ml) with Fentanyl 12.5mcg(0.25ml),they concluded in their study that the addition of 12.5mcg Fentanyl to 13mg of hyperbaric Bupivacaine 0.5% for spinal anaesthesia significantly decreases the onset of sensory block ,prolongs the maximum dermatome level and also prolongs the time to segment regression with better hemodynamic stability .

SapkalPravin S , D KulkarniKalyani , S RajurkarSampda , D NandedkarPrerna[11] (2013) conducted a comparative study on intrathecal Clonidine 60mcg versus intrathecal Buprenorphine 60mcg on 80 patients who were posted for elective or emergency lower limb surgeries, concluded that intrathecal Buprenorphine gives adequate analgesia which is significantly longer than that of intrathecal clonidine**.**

SoumyaSamal , P Rani ,LJ Chandrashekar ,Saubhagya Kumar Jena,ID Mail[12] (2014)conducted a study on 60 patients of ASA I and II aged between 18 and 50 years of both sexes scheduled for lower abdominal and lower limb surgeries. One group received 3ml of 0.5% (H) Bupivacaine with 150mcg Buprenorphine and another group 3ml of 0.5% (H) Bupivacaine with 15mcg Dexmedetomidine diluted to 0.5 ml. Concluded that the use of Bupivacaine with Buprenorphine (150mcg) in spinal anesthesia provides longer duration of postoperative analgesia as compared to intrathecal Bupivacaine and Dexmedetomidine.

NareshBhukya, Madhavi, PavaniKalyanam, Pandu Naik[13](2017) conducted a study in 100 ASA I and II patients of both sexes posted for various infraumbilical surgeries and the patients were divided into two groups of 50 each. Group F received 3mL of 0.5% Bupivacaine heavy with 0.5mcg/kg of Fentanyl and groupB received 3mL of 0.5% Bupivacaine heavy with 2mcg/kg of Buprenorphine. And they cocluded that Buprenorphine has higher efficacy with intrathecal Bupivacaine with prolonged duration of sensory and motor blockade with decreased incidence of side effects, better haemodynamic stability and intraoperative sedation and also analgesic sparing effect in the postoperative period when compared to Fentanyl .

B.DinakarRao , K.ChandraPrakash[14](2015) concluded that intrathecal Buprenorphine enhances sensory blockade of the local anesthetics without affecting the sympathetic activity. When compared to 0.5% Bupivacaine alone, 0.5% Bupivacaine along with low dosage of Buprenorphine has superior anesthetic effect than Bupivacaine alone.

PadmajaPallavi, Sanjay Choubey ,ArindamSarkar[15](2017) studied a total of 80 ASA Grade I/II patients aged >18 years were enrolled in the study and were randomized to two groups: Group I (n=40) received 0.5% hyperbaric Bupivacaine (3ml) with Fentanyl 25mcg (0.5 ml) intrathecally whereas Group II (n=40) received 0.5% hyperbaric Bupivacaine (3ml) diluted with 0.5 ml Normal Saline only. Median block level achieved was higher in Group I (T6) as compared to Group II (T8). However, mean duration of sensory and motor block was longer in Group I as compared to that in Group II. They concluded that Intrathecal adjuvant use of Fentanyl potentiated the post-operative analgesic effect and prolong sensory blockade without affecting motor block.

Uma Shankar Gupta ,Mayur Gupta[16](2018) conducted a prospective randomised study in 60 ASA I and ASA II adult patients, aged 18-60 years undergoing lower limb orthopaedic surgeries . Patients were randomly divided in to 2 groups , Group A receiving conventional dose of 0.5% Bupivacaine 3ml and Group B receiving low dose 0.5% Bupivacaine 2.5ml + 0.5ml Fentanyl . Concluded that addition of Fentanyl to low dose Bupivacaine prolongs the duration of sensory block , reduces intraoperative discomfort and produces more post operative analgesia , more hemodynamic stability and lower incidence of complications than conventional dose of 0.5% plain Bupivacaine .

BN_ Biswas, et al.,[17](2002) : Forty healthy women of ASA grade I scheduled for elective caesarean section were randomly allocated to receiver either 2m1 of 0.5% inj. Bupivacaine with 0.25 ml of normal saline (group A, n=20) or 0.25 ml (12.5 microgram) fentanyl with 2m1 of 0.5% inj. Bupivacaine (group B, n=20). Vital signs, sensory level, motor block, pain score and side effects were observed every 2 min for first 20 min, then at 15 min interval for remainder of operation, thereafter at 30 min interval until the patient complained of pain. Complete analgesia was longer in group B than group A . The effective analgesia (time from injection to first parenteral analgesic) was prolonged with the dose of intrathecal fentanyl 12.5 µg (248 ± 11.76). Pruritus was only 15% in fentanyl group. Hence, addition of fentanyl to bupivacaine improves the quality of spinal anaesthesia.

Sunil Dixit (2007) [18]. Conducted a study on sixty patients scheduled for elective caesarean section under spinal anesthesia. The patients belonging to Control group received 8.5mg (1.7ml) of 0.5% bupivacaine heavy and Study group received 8.5mg (1.7ml) of 0.5% bupivacaine heavy with 60 microgram buprenorphine (0.2ml). Concluded that intrathecal buprenorphine is a suitable drug for postoperative

analgesia, after cesarean section, it enhances the sensory blockade of local anaesthetics without affecting the sympathetic activity with minimal side effects.

F A Khan et al (2006)[19]. Conducted a study on sixty patients scheduled for elective transurethral resection of prostate (TURP). The included subjects were randomly assigned to three groups by the sealed-envelope technique, one group received 15 mg 2 ml of 0.75% hyperbaric bupivacaine (Group L) and second group received 10 µg of fentanyl mixed with 2 ml of 0.75% hyperbaric bupivacaine(Group F) and third group received 30 µg of buprenorphine mixed with 2 ml of 0.75% hyperbaric bupivacaine (Group B). Demonstrated that the use of bupivacaine with fentanyl (10µg), resulted in the earlier onset of both sensory and motor block compared to bupivacaine and buprenorphine 30µg. They concluded that the use of buprenorphine 30microgram in combination with bupivacaine 0.75% 2 ml provided postoperative analgesia in elderly patients undergoing urological procedures but with a clinically increased incidence of nausea and vomiting .

MS Khanna, Ikwinder KJP Singh,[20](2002): Forty patients (65 years and above) undergoing hip replacement or DHS were studied. Patients had spinal anaesthesia with 12.5 mg Bupivacaine plus saline (SS; n=20) or 25 µg Fentanyl (FN; n=20). Group FN had more pruritis ($p<0.02$) and lower Sa02 ($p<0.007$).Pain intensity at the time of analgesia request (TAR) was lower in group FN ($p<0.01$). Their results show that 25 µg Fentanyl during spinal anaesthesia to elderly patients premedicated with benzodiazepines for sedation, does not alter characteristics of motor block, prolongs the sensory block, improves intraoperative analgesia; produces postoperative pain relief; preserves the congnitive function, but induces pruritus and decreases O2 desaturation.

Jain K, Grover Vk, et al.[21], (2004): "conducted a study to evaluate haemodynamic stability, perioperative analgesia and neonatal outcome following intrathecal 0.5% Bupivacaine 7.5mg with varying doses of Fentanyl in parturients with pregnancy induced hypertension. Forty five patients with pregnancy induced hypertension scheduled for caesarean section were randomly allocated. Group I: Bupivacaine 7.5mg +1ml normal saline, Group II: Bupivacaine 7.5mg + Fentanyl 10µg, Group III: Bupivacaine 10mg + Fentanyl 20µg .Heart rate, blood pressure and sensory block were recorded at regular intervals. Pain, nausea, vomiting, pruritis and any other side effects were sought. Neonatal outcome was assessed using Apgar score and umbilical artery blood gas analysis. Adequate surgical anaesthesia was established in all three groups. There was significant fall in mean arterial pressure in all three groups within 4-6 minutes of subarachnoid block. Pain and discomfort during surgery were experienced more frequently in group 1 than in the latter groups. Duration of post operative analgesia was significantly longer in group III than group II and group I . They concluded that intrathecal Fentanyl with low dose Bupivacaine provides good surgical anaesthesia and prolongs the duration of analgesia without haemodynamic or neonatal compromise in PIH patients undergoing caesarean delivery"[18].

Raju G, Priyanka V, Dayananda V P(2014)[22]. Conducted a study on 200 patients undergoing various surgeries under spinal anaesthesia. Patients were randomly grouped into two groups. One group of 100 patients received 3cc of 0.5% hyperbaric bupivacaine with 100 µg of buprenorphine (Group B) and another group of 100 patients received 3cc of 0.5% hyperbaric bupivacaine with 100 µg of morphine (Group M). Concluded that that intrathecal buprenorphine (100 µg) with 3cc of 0.5% hyperbaric bupivacine provided prolonged post operative analgesia with much less

side effects compared to morphine. Hence buprenorphine can be safely used for post operative analgesia.

Sandhya Gujar et al (2014)[23]. Conducted a study on 60 patients ASA grades I and II scheduled for gynecological and orthopedic surgery. Patients were divided into 3 groups of 20 each, first group received 3.5 ml of 0.5% hyperbaric bupivacaine with 0.5ml normal saline (Group I) and the second group received 3.5 ml of 0.5 % hyperbaric bupivacaine + 75 μg of clonidine (Group II) and the third group received 3.5 ml of 0.5% bupivacaine + 150 μg buprenorphine (Group III). Concluded that intrathecal buprenorphine has more advantages as analgesia provided is more than 12 hours which is very important in post operative period and it is without the risk of respiratory depression.

Rashmi Pal, K. K. Arora et al[24]. Conducted a prospective, randomized and comparative study which included 90 ASA class 1 & 2 patients undergoing lower abdominal and lower limb surgeries under spinal anesthesia. The patients were randomly divided in three groups of thirty each using a computer random number sequence. Group BC which received 3.0ml of 0.5% of hyperbaric bupivacaine (15mg) + 50μg (0.33ml) of Clonidine + (0.17 ml normal saline). Group BF which received 3.0ml of 0.5% hyperbaric bupivacaine (15mg) +25μg (0.5ml) fentanyl. Group BB which received 3.0ml of bupivacaine heavy 0.5% (15mg) + buprenorphine 75μg (0.25ml) + normal saline (0.25ml). This study showed a significant difference in terms of duration of sensory, motor blockade and that of duration of analgesia in fentanyl and buprenorphine group as it was significantly prolonged in buprenorphine group with 'p' value 0.001.

Gajanan Chavan, Aparna Chavan, Alok Ghosh [25]. Conducted a study on 80 ASA grade I and II patients, scheduled for elective gynecological surgeries, patients were

assigned to receive either 3ml of 0.5% hyperbaric bupivacaine (Group I) or 3ml of 0.5% hyperbaric bupivacaine and 0.5ml of fentanyl 25microgram, (Group II). Two segment regression and the duration of analgesia was significantly prolonged in group II i.e.134.12±10.81 and 207±17.57 minutes respectively compared to group I i.e-89.85±10.98 and 192.12±21.04 minutes respectively, confirmed in their study that addition of fentanyl (25microgram) to 0.5% hyperbaric bupivacaine for spinal anesthesia would markedly improve the quality of intraoperative analgesia with minimal side effects.

ANATOMY OF SPINAL CORD[26-28]

For an anaesthesiologist , understanding the vertebral column anatomy and especially that of the lumbar vertebra is very important

The mean spinal cord length in males is 45 cm and 42 cm in female.

The mean weight is around 30 g.

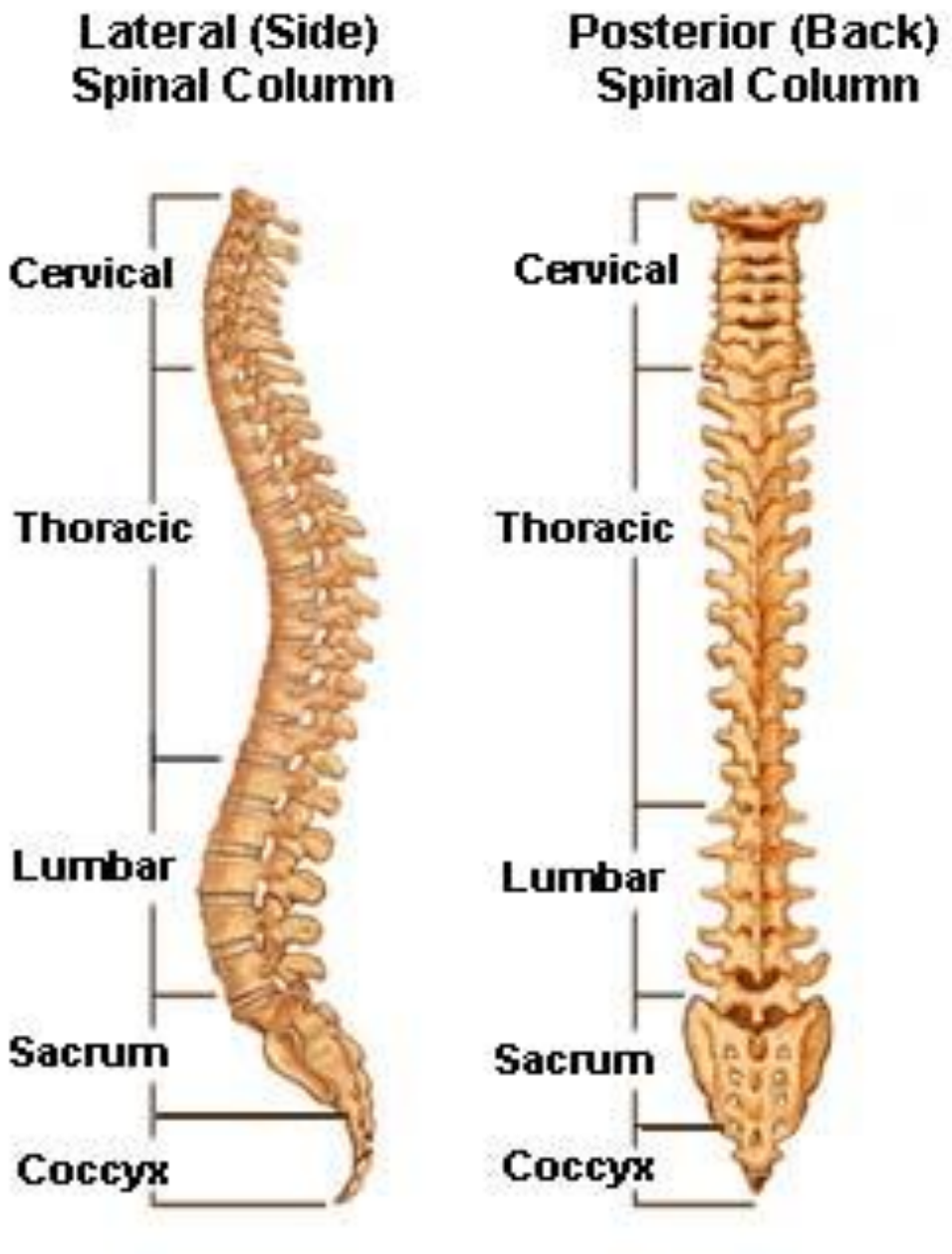


Fig:VERTEBRAL COLUMN

The vertebral column is formed by 33 Vertebrae

Cervical - 7

Thoracic - 12

Lumbar - 5

Sacrum - 5 (fused)

Coccyx - 4 (fused)

The curvature of the spine:

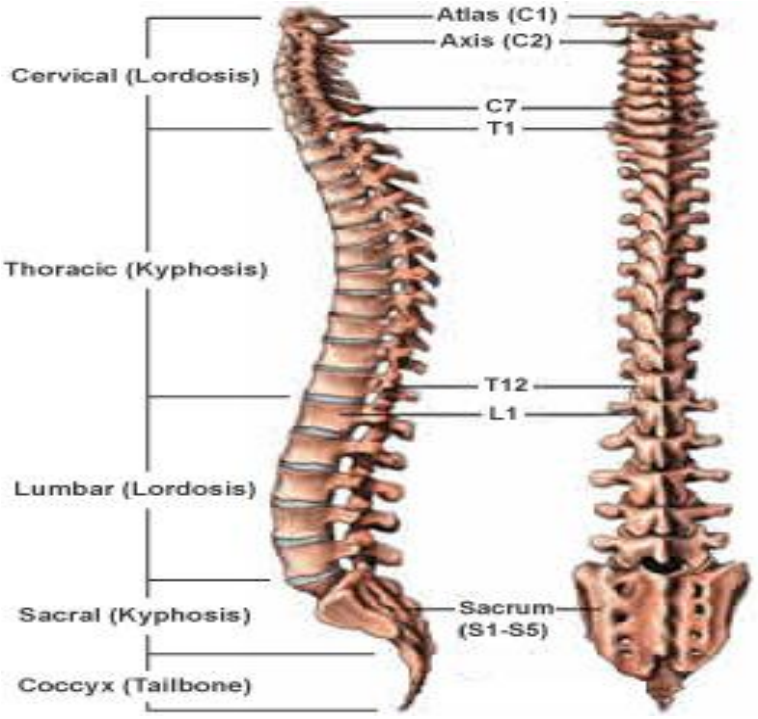
In adult, the normal vertebral column has 4 curves,

1. Cervical spine curve -- convexity anterior
2. Thoracic spine curve -- convexity anterior
3. Lumbar spine curve -- convexity posterior
4. Sacrococcygeal curve — convexity posterior

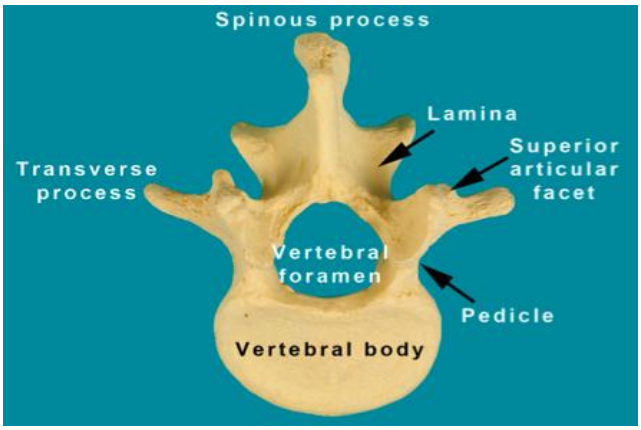
The curves of the spine are of additional importance when the patient is either in supine or horizontal position.

The 3rd lumbar vertebrae (L3) is the highest point of the spinal curve and the 5th thoracic vertebrae (T5) is the lowest point.

The Curvature of the spine



The typical vertebrae: (Fig 1)



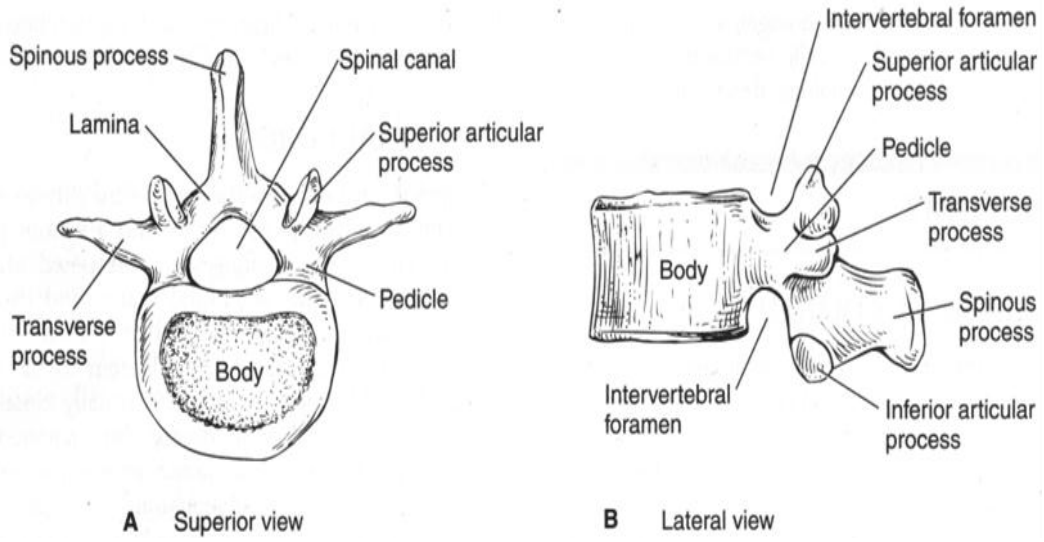
It is composed of,

1. Anteriorly, the body that bears and transfers the weight and is separated by intervertebral disc from adjacent vertebral bodies

2. The vertebral arch adhered to the body , containing of two pedicles anteriorly and two lamina posteriorly , encircling and protecting the spinal cord .

3. .Articular processes are four in number – 2-superior and 2-inferior.

The Lumbar Vertebrae[29]:



The lumbar vertebrae differ from other vertebrae:

- Lumbar vertebrae bodies are large and kidney shaped.
- The vertebral foraminae are triangular & intermediate in size between those in the cervical and thoracic region.
- The pedicles are thick and short.
- Length of transverse processes increases from L1 to L3 and then decreases agian
- The laminae are short and along its posterior and inferior borders, the lumbar spinous process is almost horizontal, quadrangular and thickened & oblong to not overlap each other.

- The fifth vertebra produces the lumbosacral angle. Its transverse processes although short & thick are strong and arises not only from the arch but also from the side of the vertebral body.

Intervertebral discs:

The intervertebral discs account for about onefifth of the vertebral column length composed of outer fibrous cover, the annulus fibrosus enclosing the nucleus pulposus, a core of soft-pulpy gelatinous material. The intervertebral disc offers flexibility to the spinal column and acts as shock absorber. Osteoporosis of the vertebra in addition to atrophy of the intervertebral discs leads to kyphotic old age deformation and reduced height.

FIG 2-LATERAL VIEW OF LUMBAR VERTEBRAL COLUMN

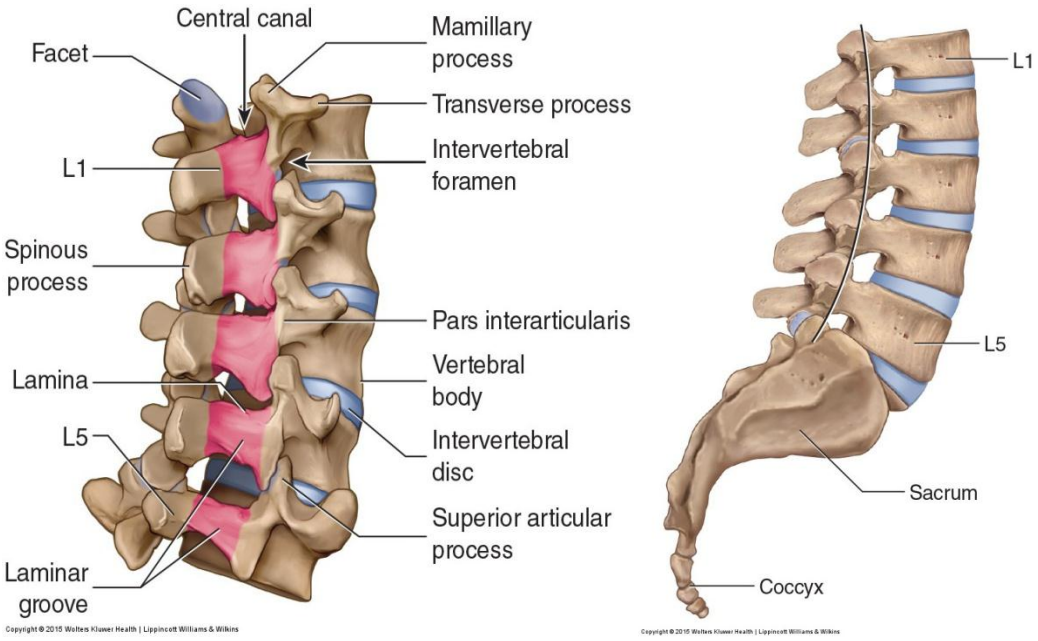


FIG 4:CROSS SSECTION OF VERTEBRA

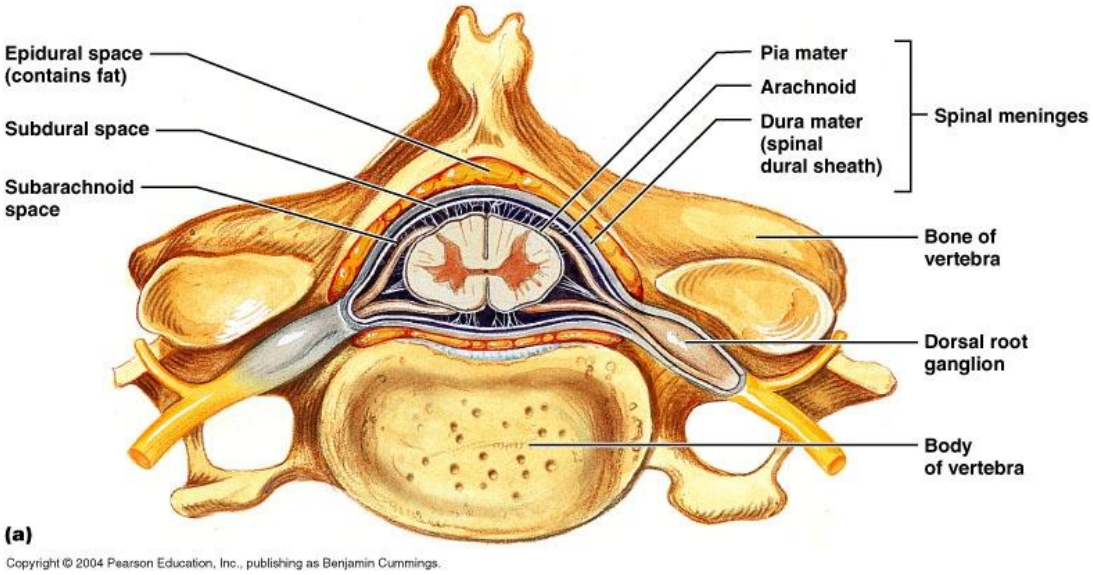
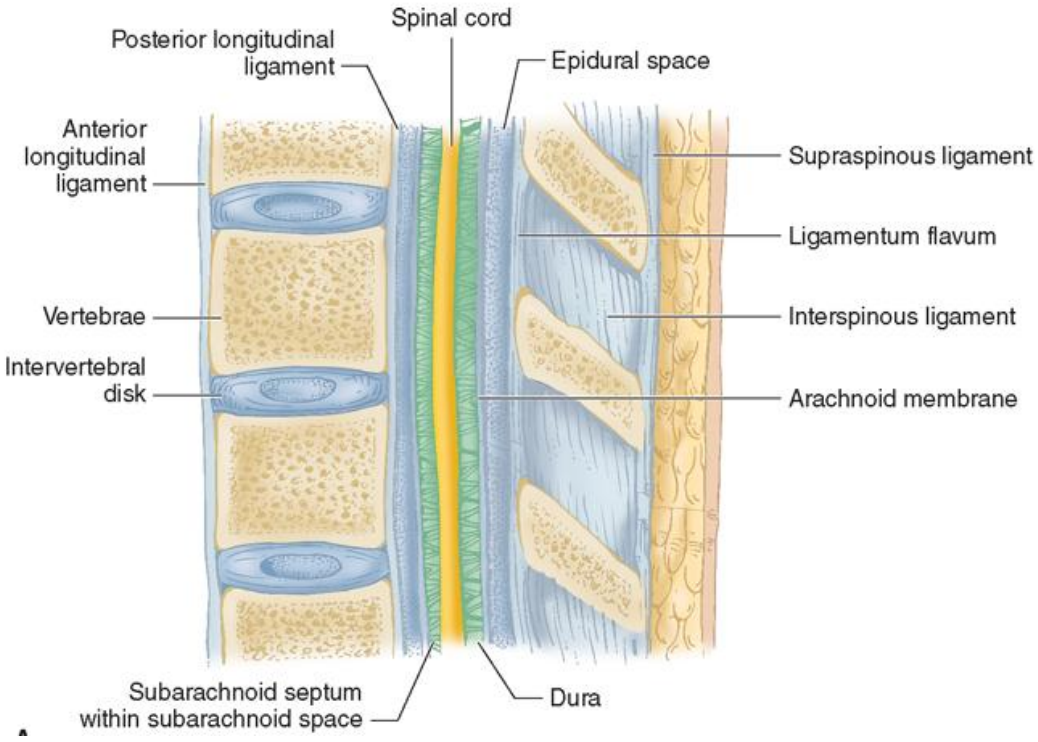
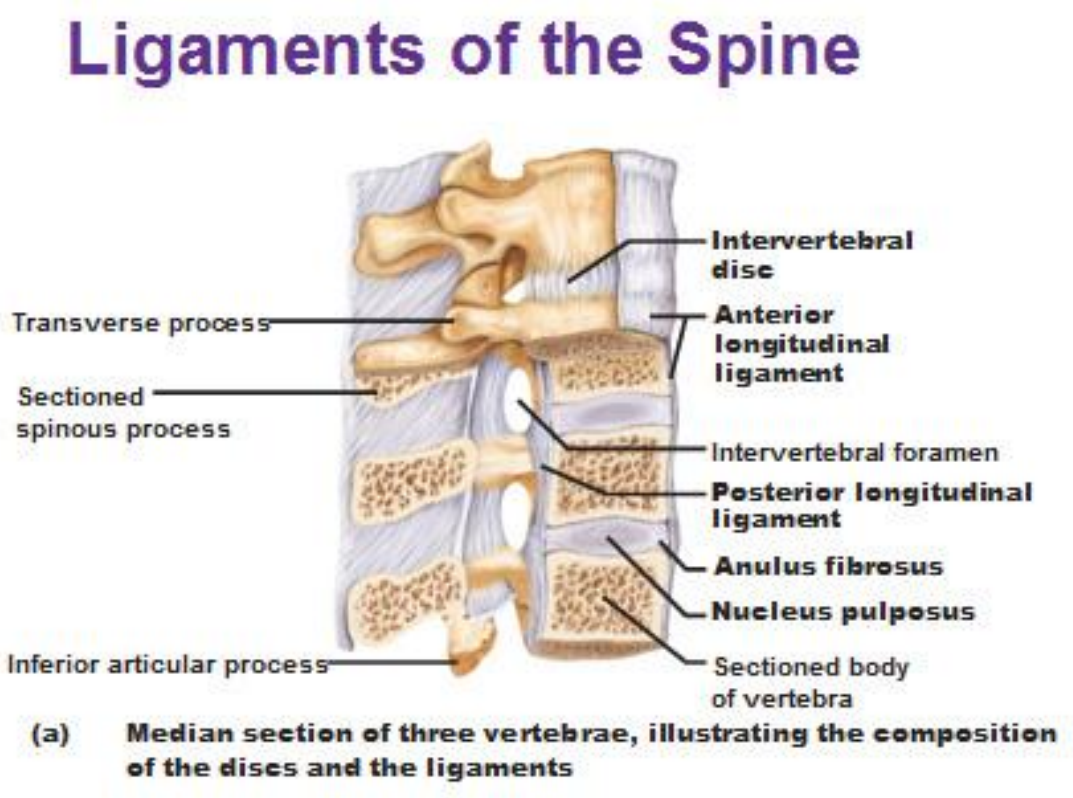


FIG 5:LONGITUDINAL SECTION OF VERTEBRA



VERTEBRAL LIGAMANETS



(a) **Median section of three vertebrae, illustrating the composition of the discs and the ligaments**

The Vertebral Ligaments:

For practicing spinal anaesthesia, it is must for an anaesthesiologist to have good knowledge of the ligaments of the spinal column by which the spinal needle passes.

The distinct sensations of resistance that these ligaments produce to the advancing needle can be felt with experience by the operator.

- **Supra-spinous ligament:** Is a continuation of ligamentum nuchae, strong thick dense fibrous cord that connects the apices of spines from the sevength cervical vertebrae to the sacrum. This can get ossified in old age and make difficult to pass spinal needle through it.

- **Inter-spinous ligament:**

  It joins spinous processes adjacent to it. Subsequently they fuse posteriorly with the supraspinous ligament and anteriorly with ligamentum flavum .

- **Ligamentum flavum:**

It extends from the inner surface and lower border of one lamina to the outer surface and upper border of the lamina below. It is made up of elastic yellow fibers.

It occupies over half of the vertebral canal's posterior wall, the remaining bony lamine. In he cervical region has the thinnest ligamentum flavum and lumbar region has thickest .Functionally, these ligaments are muscle spares that help to recover from effect posture after bending and enables an erect posture.

- **Anterior longitudinal ligament:**

It runs from C2 to sacrum along the anterior surface of vertebral bodies .

- **Posterior longitudinal ligament** :

It stretches along the posterior surfaces of the vertebral bodies from which the basivertebral veins separate it.

Vertebral Canal:

It starts from the foramen magnum to the sacrum's tip. Anteriorly bounded by the vertebral bodies and intervertebral discs.The laminae, the ligamentum flavum, and the vertebral arch posteriorly.

vertebral canal contents:

- Meningeal layers which enclose the spinal cord and CSF.
- Spinal nerve roots.
- Fat, vessels and areolar tissue of the extradural space.

Spinal cord[30-32]:

It is an extended part of the central nervous system that occupies upper two thirds of the vertebral canal, span of 42-45 cms in length, and weighs about 30 gms. It extends from the upper border of the atlas vertebra to that of the lower border of 1st lumbar vertebra or upper border of the 2nd lumbar vertebra above it, the medulla oblongata continues and below it tapers into a conical conus medullaris. A delicate fibrous filament descends from apex of conus medullaris to back of first segment of coccyx is known as the filum terminale. The cord has two enlargements cervical and lumbar corresponding to the nerve supply of the upper and lower limbs. The cervical enlargement extends from C3 to T1 and lumbar enlargement from L1 to S2.

At birth, the tip of spinal cord end at the level of lower border of L3 vertebra and in the adult, it ends at L1-L2 vertebra.

The meninges:

The spinal cord is surrounded by three layers from the outside to the inside

1) **Duramater:** is a circular sac or sleeve that surrounds the spinal cord. It is made up of theInner (meningeal) layer which is the cranial duramater continuation and the outer (endosteal) layer which is the vertebral canal periosteum lining, and is separated from the spinal dura by the extradural space. Above, it is tightly attached to the circumference of the foramen magnum. Below it usually streches to the lesser border of S2 vertebra, and then continues as the coating of filum terminale to end by attaching to the periosteum on back of the coccyx. Main fibres of the duramater are longitudinal; lumbar puncture needle should be inserted with its bevel separating rather than cutting these fibres.

2) **Arachnoid mater:**

It is a delicate non-vascular membrane which is closely applied to the dura mater. It is separated from the duramater by subdural space and from piamater by subarachnoid space. Above it continues with cerebral arachnoid, below it widens out, invests the cauda equina and ends at the lower border of S2 vertebra.

3) **Pia mater:** It is the innermost membrane is a vascular sheath which closely invests the brain & spinal cord and sends delicate septa into its substance. The spinal pia is thickened anteriorly into the linea splendens along the length of anterior median fissure, on either side it forms ligamentum denticulatum which projects into subarachnoid space and is attached by series of pointed processes to the dura as far down as the first lumbar nerve.

Subarachnoid space:

It is space between the arachnoid and pia mater .Cobweb trabeculae, cranial & spinalnerves cross this space. These are bathed by the spinalfluid . The space in the cranial and thoracic is annular and is approximately 3 mm deep.It's circular below the first lumbar.

The space communicates with the tissues around the vessels in the piamater that accompany them as they enter the cord. These continuations have been described as the breaking up into fine ramifications, which surround individual nerve cells (Virchow robin space) and this has been considered as pathway by which a spinal anesthetic solution penetrates cord.

Spinal segments:

The pair of spinal nerves which emergefrom it divide the cord into segments. These pairs are 31 in number and are : Cervical—08 , Thoracic —12 , Lumbar - 05, Sacral --05, Coccygeal -- 01.

There are no epineural sheaths in the nerve roots within the dura and are therefore easily affected by the doses of analgesic drugs brought into contact with them.

Spinal nerves:

"Anterior root & posterior root these two fuse together making spinal nerves. Efferent and motor is the anterior root.Sympathetic preganglionic axons emerge from T1 -L2 cells in the spinal cord's intermediolateral horn .Inhibition these fibers affects some of the endocrine glands ' reaction to surgical stress. The posterior root is larger than anterior and afferent impulses from whole body including the viscera passes through these roots.

Each posterior root has a ganglion and carries fibersof pain, touch, temperature, deep sensation from bone joints and muscles and tendons / efferent from viscera (accompanying sympathetic) and vasodilator fibers. Pain and temperature nerve-fibers enter the posterior horn and end around the cell in gray mater, then cross to the contralateral side of the within three segments and rise in the lateral spinothalamic.

In the posterior column and spinocerebellar tracts, deep or muscle sensory impulses ascend In the posterior column, the vibration impulses ascend"[29-32].

Sensitivity of different fibres:

Local anesthetics affects all nerve fibres,but within any one fiber type, there is a tendency for smaller,slower conducting fibers to be more easily blocked than large, fast conducting fibres.Myelinated preganglionic B fibres which have a faster

conduction time are about three times more sensitive to local anesthetics than the slower non myelinated postganglionic Cfibres.

Large A fibres the most resistant to local anaesthetics, they are Aδ fibres, they are more susceptible to subservient pain and temperature than C fibres, though they conduct rapidly.

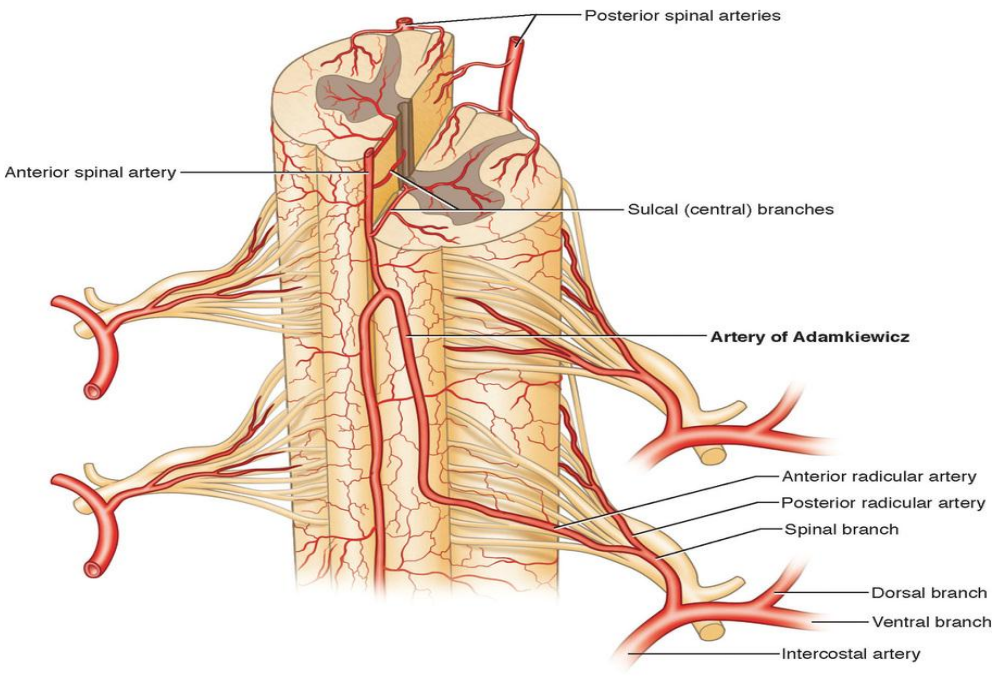
Sensory Aα fibers seem to be more susceptible to blocking than motor Aα fibers, even though at the same velocity of conduction. This may be because sensory fibres conduct at a higher frequency.

Preganglionic, heat, pain,touch, proprioception, and motor fibres appear to be the order of sensitivity to blockade.

Blood supply of the spinal cord[32]:

The artery supplying the spinal cord is derived from one anterior and two posterior arteries that descend from level of foramen magnum.

FIG 7:BLOOD SUPLLY OF SPINAL CORD



Anterior spinal artery - is a single artery ,it is formed by union of each vertebral artery at the foramen magnum and passes the full lengh of spinal cord length . It receives lumbar communications, as well as from other small arteries in the cervical and thoracic regions, there are usually 23 communications, and there is only one unilateral Artery, the radicular magna (Adam Kiewicz Artery) supplying lumbar enlargement. It supplies lateral and the anterior columns about 3/4 of the substance of the cord.

Posterior spinal artery-- are two in number one on each side. They derived directly from the vertebral artery at the base of the brain or more often from subsequent inferior cerebellar arteries. Posterior $1/3^{rd}$ of the spinal cord is supplied by these arteries.

This supply is supplemented by vertebral, ascending posterior cervical intercostal, lumbar, and lateral sacral arteries passing through the intervertebral foramina.

Venous drainage:

Anterior and posterior spinal veins drain into segmental veins in the neck, the azygous veins in the thorax, lumbar veins in the abdomen, and lateral sacral veins in the pelvis.

Nerve supply of the meninges:

The posterior aspect of the dura and arachnoid mater contain no nerve fibres and so no pain is appreciated on dural puncture.

Sinovertebral nerves supplies the anterior element, each of these enters an intervertebral foramina and passes up for a segment and down for two segments.

Cerebrospinal fluid (CSF)[32]:

The term CSF was first coined by French Physiologist F.Magandie in the year 1825. It is a clear & colourless fluid which fills all the cavities and space around the CNS. It is isotonic with plasma. It is mainly formed by ultrfiltration from the choroid plexus of the lateral ventricle ,third and fourth ventricle & is reabsorbed by the arachnoid villi & granulations.

In a normal adult CSF is formed at a rate of 25 ml/hr or 600 ml/day. The replacement of total spinal fluid under ordinary normal physiological circumstances is every 6 hours.

Characteristics of CSF:

Specific gravity at 37°C	1.006 (1.003-1.009)
Volume	130-150 mL
Vol. in subarachnoid space	25 — 35 mL
Pressure	70-180 cm of water

Composition of CSF:

pH	-	7.32 (7.27 — 7.37)
Glucose	-	50-80 mg/dL
pCO2	-	48 mmHg
Bicarbonate	-	25-30 mg/mL
Cells	-	< 5 cells / mm3
Chloride	-	120- 130 mEq/L
Sodium (NA^+)	-	140-150 mEq/L
Non protein nitrogen	-	20-30mg/dL
Protein	-	15-45 mg/dL

Circulation: Fromed in the lateral ventricles following which CSF passes through the foramina of Munro to the third ventricles, through the aqueduct of sylvius to the fourth ventricle. Then via foramen of Magendie to cisterna magna and via two foramen of Luschka then into cisterna ponti. From the fourth ventricles it also passes into central canal of spinal cord and subarachnoid space, after it reaches spinal subarachnoid space through the foramen magnum CSF is absorbed into cranial venous sinuses through arachnoid villi.

Functions of CSF:

- It acts as cushion between the soft and delicate brain substance and rigid cranium
- Drainage of metabolites
- Nutrition and oxygen supply to nerve cells to some extent.

TECHNICAL ASPECTS[32]:

When a needle is inserted in to the subarachnoid space the following are traversed,

- Skin
- Subcutaneous tissue
- Supraspinous ligament
- Interspinous ligament
- Ligamentum flavum
- Areolar tissue or epidural space
- Spinal dura mater

- The highest point of the iliac crests is usually on a line crossing the spine of L4 (in the upright position) or L4-L5 interspace (in the lateral decubitus position). This line is called the topographic line of Tuffier[35].

PHYSIOLOGY OF CENTRAL NEURAXIAL BLOCKADE.[29,30,34-38]

Subarachnoid block's well recognized physiological sequels are often erroneously called complications. It is essential to make a clear difference between physiological effects of anaesthetic technique and complications that cause some damage to patients.

The various factors, which control the different effects of a spinal anaesthetic technique, are.[29,34]

- Type of drug and amount of drug
- Solution volume
- Injection site
- Injection rate
- Specific gravity of solution - baricity and density
- Barbotage

Amount of drug:

With greater amounts of drug there is an increase in the duration, height and intensity of spinal anaesthesia. There is an upper limit to the total amount of agent that may be used regardless of the volume and it is determined by the amount of that drug which may produce neurological damage.

Type of Local anesthetic agents:

The various agents can be classified as:

1. Agents of low anaesthetic potency and short duration of action: Procaine.
2. Agents of intermediate anaesthetic potency and intermediate duration of action : Lidocaine, Mepivacaine
3. Agents of high anaesthetic potency and prolonged duration of action: Bupivacaine, Tetracaine.

Volume of solution:

Increasing the volume may increase the extent of anesthesia if the amount of drug is maintained the same. If the total volume is less, the effect of volume augmentation is limited.

Site of injection:

When all other circumstances are constant, taking 1 or 2 spaces greater than the usual L4 L5 inter-vertbral space offers a greater level of anaesthesia.

Rate of injection:

This is most important factor in determining the height of anesthesia . The level is low with slow injections. Very rapid injections can cause anaesthesia to reach the thoracic level.

The slow injection of hyperbaric solution produces adequate distribution and generally results in lower level anaesthesia.

The slow injection of a hypobaric solution produces greater levels of spinal anaesthesia but is of longer duration than the levels arising from rapid injection.

Barbotage:

The term is derived from the puddling or mixing of the French word ' barboter.

This is the stirring method for increasing turbulence, mixing injected solution and incr easing Subarachnoid Block distribution.

The movement to and fro mates the injectate in the spinal fluid and mixes the agent, to carry the agentto higher levels more enormously.

Specific gravity, Density and Baricity:

When using hyperbaric solutions in horizontal plane with patient supine, the a nesthetic will preferably travel into the lumbosacral concavity to the low points of subarachnoid space, i.e. below L3.Hyperbaric solutions travel to the most dependent portion of the subarachnoid space when the patient's position changes from the horizontal.With changes in position, isobaric solutions are considered not to spread and anesthesia levels are independent of positioning. The solution is puddling close the injection site.

In comparison to hyperbaric solutions, hypobaric solutions are affected by patient gravity and position. They are administered while patient is in prone position.

Pharmacokinetics of spinal anaesthesia:

There is a fall in the concentration soon following the injection of anaesthetic agent into the subarachnoid space. The reason being,

1. Dilution and mixing of CSF.
2. Diffusion and distribution to neural tissues
3. Uptake and fixation by neural tissues
4. Vascular absorption and elimination

- Through arachnoid villi

- Directly from capillary bed of parenchyma.

Initially, there is a quick reduction in drug concentration, that happens shortly after drug injection within 2-3 minutes. This is due to mixing and dilution with CSF, which depends on the drug injection force or rate and the volume or amount of fluid in the subarachnoid space.The second stage of concentration reduction is due to the diffusion of the agent in the spinal fluid owing to its molecular motion. Some of the agent is absorbed in the nervous tissue at the same time.

This absorption takes place along a gradient of concentration to 3 sites.

1. The nerve roots bathed directly by anesthetics
2. By diffusion through the pia mater directly into the spinal cord surface.
3. Through Virchow-Robin spaces into the deeper areas of the spinal cord parenchyma.The uptake of local anesthetic from the spinal fluid and nerve fibers into the vascular compartment represents the third stage of slow decline in total concentration of agent in the spinal fluid.

The significant part of the drug leaves the subarachnoid space through venous drainage, while a small part passes through tiny lymphatic channels. Very less amount or no breakdown of local anesthetic agents occurs in the CSF or in the subarachnoid space.

The various factors that affect the spread of local anesthetics include[35,37]:

1. Position
2. Age
3. Height
4. Configuration of spinal column
5. CSF volume
6. Injection site
7. Spread of injected drug
8. Needle direction
9. Dose of local anesthetics
10. Baricity of local anaesthetics
11. Volume of local anesthetics

The sequence of nerve modality block[37]:

1. Vasomotor block --- skin vessels dilatation and elevated cutaneous blood flow
2. Temperature fibers --- first cold and then warmth.
3. Pain --- First pin prick fibers
4. Tactile sensation loss
5. Paralysis of Motor nerve
6. Loss of temperature discrimination
7. Pressure sensation
8. Vibratory and Proprioceptic sensation

During the recovery, return of sensations is in the inverse sequence.

The significant determinant of physiological response to spinal anesthesia is sympathetic blockade. Indirect effects of spinal anaesthesia may be regarded as a result of paralysis of sympathetic nerves.

Effect of Spinal Anaesthesia on Various Organs[38]:

Cardiovascular System:

The most significant physiological response of spinal anesthesia is on the cardiovascular system.

They are mediated by mixed autonomic denervation and greater levels of neural blockade and added vagal nerve intervention effects.

Sympathetic Denervation:

The sympathetic blockade level determines the extent of cardiovascular responses to spinal anesthesia. The higher the neural blockade level, the higher the cardiovascular parameters would change.There is a reflex increase in sympathetic activity in sympathetically intact areas in the presence of partial sympathetic blockad. The outcome is vasoconstriction that tends to compensate in sympathetically denerved sites for peripheral vasodilatation.

Arterial Circulation:

Sympathetic denervation on the arterial side of circulation results in more arterial and physiologically significant arteriolar vasodilatation of vascular smooth muscles.

As a consequence of this total peripheral vascular resistance in normal subjects reduces only about 15% to 18% in the presence of total sympathetic denervation provided that the cardiac output and other blood pressure determinants are maintained normal.

Venous Circulation:

After pharmacological denervation, veins and venules with only a few smooth muscles on their walls will not retain significant residual tone.

They can vasodilate to the maximum.Intraluminal hydrostatic pressure determines this.

Intraluminal hydrostatic pressure is dependent on gravity on the venous sides of the circulation.If the denervated veins are below the right atrium level, this causes the blood to flow back to the heart. Therefore,preloading to the heart depends on the patient's position during spinal anaesthesia.

.Physiology of Hypotension:

The most common and immediate complication of spinal anaesthesia is hypotension.

Hypotension following spinal anesthesia is predominantly the result of preganglionic sympathetc fibers paralysis that transmits motor impulses to the peripheral vasculature's smooth muscles.

Fall in BPlevel was proportional to the blocked number of sympathetic fibers. It was not understood the exact mechanism by which sympathetic blockade reduced blood pressure. Two schools of thought existed:

- One postulated that widespread arterial and arteriolar dilatation resulted in a decrease in peripheral vascular resistance that was sufficient to account for the vital portion of the decrease in peripheral vascular resistance.
- Others assumed that the hypotension was secondary to a reduction in cardiac production due to peripheral pooling and a decline in venous blood return to heart.

While both theories are right, neither is sufficient in itself to explain all the changes induced by spinal anaesthesia in circulatory physiology.The sympathectomy resulting in spinal anaesthesia technique depends on the block's height.

The question left unanswered at which level of arterial blood pressure is acceptable after the central neuraxial block.

If the blockade extends above the level of T5, the hemodynamic transition will gradually become more difficult to compensate and the blood pressure will decrease significantly.

Hypotension develops usually during the first 1520 minutes during spinal anaesthesia ; left untreated BP reaches its lowest level within 20 - 25 minutes after subarachnoid injection.

Forthis reason, the first ½hour of a spinal anesthesia is considered its dangerous period, although in some individuals the initial fall in B.P may develop with alarming rate.

After the BP has reached its lowest point , the systolic B.P often rises 5-10 mm Hg spontaneously over the next 10-15 minutes , after which the roots have worn off their concentrations and remain comparatively fixed until the anaesthetic nerve effect.This slight rise is a result of compensatory circulatory activity mediated by the blocked proportions of sympatheticoutflow andpossibly by a slight return of smooth muscle tone in the denervated part of the peripheral vasculature.

Heart Rate:

Spinal anesthesia is typically associated with slowing of the heart rate. The degree of bradycardia can be approximately correlated with the extent of sympathetic denervation as well as the frequency with which it occurs.

Marked bradycardia is most commonly noted when cardiac output and arterial B.P have considerably reduced during anaesthesia.

Bradycardia during high Spinal Anesthesia[39]:

"There is one factor that affects pulse rate and BP during spinal anesthesia. A decrease in venous return outcomes in a decrease in cardiac output and cardiac output is one of the major determinants of blood pressure levels during spinal anesthesia.

One of the three mechanisms may cause decreased venous return to the heart causing bradycardia.

First, the right heart's hydrostatic pressure influences heart rate through intrinsic chronotropic stretch receptors in the right atrium wall. These baroreceptors , independent of neural connection to the CNS, form intracardiac reflexes where the heart rate is proportional to the stretch of the pacemaker.

By generating a compensatory tachycardia (Marey's law) through vagal afferent and efferent pathways, the baroreceptors normally respond to a drop in blood pressure.

Most patients exhibits bradycardia under spinal anesthesia. Thus, venous pooling in the periphery in spinal anesthesia decreases stimulation of the nerves of the volume receptor. The outcome is vagal preponderance and heart rate slowing. The rise in pressure in the great veins or the right atrium generates reflex tachycardia through stretch receptors and vice versa. There are nerve endings within the walls of the ventricles that can be activated mechanically either through ventricular distension and stretching or through vigorous and rapid systolic contractions. The reflex, also known

as the "Bezold Jarisch Reflex," originates from mechanoreceptors and chemoreceptors discovered mainly in the inferoposterior wall of left ventricle"[45].

Cerebral Blood Flow:

Two main factors govern the cerebral blood flow. Mean arterial blood pressure in the cerebral vessels and local blood flow resistance in cerebral vessels. Theoretically, spinal anesthesia may affect cerebral blood flow, altering either blood pressure or cerebrovascular resistance or both.The autoregulatory mechanism of the cerebrovascular system maintains cerebral blood flow in humans at steady levels in the presence of wide Variations in mean arterial blood pressure. "Cerebral blood flow will become pressure dependent until the Mean Arterial Pressure (MAP) drops below 55mmHg". In the sympathetic nervous system, cerebrovascular auto-regulation is independent. In normal persons ,cerebral blood flow continues unaffected even when mean arterialpressure during spinal anesthesia declines from 90 to 60 mm Hg.

The Respiratory system:

The phrenic nerve that supplies the diaphragm is derived from the anterior root, root of C3-C5, and should not be encroached into spinal anaesthesia, but phrenic paralysis may happen. Apnea may be due to medullary ischemia or in extradural blocks owing to toxic impacts of the drug. Breathing becomes quite and tranquil during spinal anaesthesia.

This is not only due to motor blockade, but also due to differentiation in the respiratory center with reduction of sensory input. Lowered arterial and venous tone also diminishes the work of heart and relives any existing pulmonary congestion.The relationship of ventilation perfusion during extradural block is not significantly changed and the impact on respiratory function is comparatively low with no evidence of change in the proportion of FRC or V/Q. The exchange of pulmonary gas is

preserved. Intercostal paralysis is compensated by enhanced diaphragm descent, which is facilitated by a lax abdomen.

The Gastrointestinal system:

T5-L1 sympathetic pre-ganglionic fibers are gut inhibitors. There is no impact on the esophagus, which is vagal in the innervation. The small intestine is contracted with the removal of sympathetic inhibitory impulses, the vagus being all-powerful. The sphincters are relaxed and though not more frequent, peristalsis is active. There is enhanced pressure within the lumen of the bowel. Handling of small bowel by the surgeon may cause it to dilate, as may the injection of atropine before the operation. Due to the hypotension, nausea and vomiting can happen and generally occurs in waves that last about a minute and pass spontaneously.

Causes of Nausea and Vomiting:

1. Increased peristalsis
2. Traction on nerve endings, in particular vagus
3. The presence of bile in the stomach caused by pyloric sphincter relaxation
4. Narcotic analgesics (pre medication)
5. Psychological effects
6. Hypotension
7. Hypoxia

The Spleen :

When its sympathetic efferent fibers are paralyzed, the spleen enlarges 2-3 times in high level blocks. Following spinal anaesthesia, colonic blood supply and oxygen availability in animals are improved, perhaps a significant factor in preventing anastomotic breakdown following gut resection.

The Liver:

There are no significant effects. It is not known the degree of hypotension that affects liver function. If the liver is diseased, a reduction in MAP effects the liver blood flow and also amide anesthetics metabolism.

Endocrine system:

Spinal block delays adrenal responses to injury and trauma, so the levels of 17-hydroxy corticosteroids do not change. Spinal block suppresses the surgery and stress induced hyperglycemic response and is therefore helpful in diabetic patients. Insulin response is increased, one should be conscious of hypoglycemia risk. IV-infused glucose is well utilized.

Genitourinary system:

Via the lower splanchnic nerve, sympathetic supply to the kidney is from T11-L1. Any effects on renal function are caused solely due to fall in blood pressure, the renal blood flow decreases but does not cease until blood pressure drops to about 80 mm Hg. These changes are temporary and disappear when Blood pressure increases again. Due to paralysis of Nervi erigenti(S2-S3), the penis is often engorged and flaccid, and this is also a favorable indication of a sucessful block. Post-spinal urine retention may be moderately prolonged sinceS2-S3 includes small autonomic fibers and their paralysis remains longer than that of larger sensory and motor fibers. The bladder must be palpated during prolonged blockade of lumbar and sacral segments so that catheterization can be done if needed. Sometimes spermatorrhoea is seen.

Uterus:

The tone of the uterus is not significantly altered during pregnancy following spinal anaethesia. The blocking of nerves from T11 results in painless labor. Due to decreased extradural space, lesser doses of local anesthetics are required in late pregnancy.

Body temperature:

Vasodilation causes heat loss, lack of sweating causes hyperpyrexia in a warm setting, catecholamine secretion is decreased hence heat loss is generated by metabolism.

Electrolyte status:

Salt and water are retained after surgery and trauma. Continuous extradural block in patients undergoing upper abdominal surgeries abolishes sodium retention but not water retention.

THE PATHOPHYSIOLOGY OF PAIN[31-33,40]

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

Psychological pain occurs when a noxious stimulus activates high threshold sensory receptors (nociceptors). This informs the body of potential or actual damage and correlates with withdrawal reflexes.

Pathological pain occurs in response to non-noxious stimulus or even in the absence of a definable stimulus. This promotes healing by avoidance of all stimuli but is truly pathological in its chronic form

The sensory component of pain: Pain signals are received by the nociceptors at the periphery and transmitted by thinly myelinated a-delta fibers and unmyelinated C fibers.

Nociceptors:

Nociceptors are receptors that transduce noxious stimuli. Most nociceptors are free nerve endings that sense heat, mechanical pressure and tissue damage.

Types of nociceptors:

a) Mechano-nociceptors: respond to pin prick & touch
b) Silent nociceptors: responds only when inflammation occurs
c) Polymodal mechano-nociceptors: most common and responsive to excessive stress, temperature extremes and substance-generating pain.
d) Cutaneous nociceptors: available in somatic and visceral tissue
e) Deep nociceptors: Less sensitive than cutaneous nociceptors but readily sensitized by inflammation. Dull and poorly localized pain arises from these receptors.
f) Visceral nociceptors: Generally insensitive tissues that contain mostly silent nociceptors. Brain lacks nociceptors altogether, but meningeal coverings do contain nociceptors.

A & B fibers -Only mechanically sensitive, conduct at 5-25 m/sec and transduce fast or first pain, which causes withdrawal from the source of pain.

C fibers - Conduct at less than 2m/sec and convey the messages generated by tissue damage, (slow or second pain) which may cause immobilization. They are Polymodal because they respond to noxious, thermal, mechanical and chemical stimuli.

Pain Pathways :(Fig. 8)

Pain is conducted along the three neuronal pathways that contain noxious stimuli from the periphery to cerebral cortex.

1. **First order neuron:**

Majority of these neurons send their axons into the spinal cord via the dorsal spinal root at each cervical, thoracic and sacral level. In the dorsal horn they may synapse with interneurons, sympathetic neurons and motor neurons

2. **Second order neurons:**

They synapse in the thalamic nuclei with third order neurons. Rexed divided spinal cord gray matter into 10 laminae. First six laminae make up dorsal horn, receive all afferent neural activity and represent the principal site of modulation of pain.

a) **Spinothalamic tract:** (STT) Axons of most second order neurons cross the midline close to their level of origin to the contra lateral side of the spinal cord to become spinothalamic tract. This ascending tract can be divided into Lateral and Medial. Lateral STT projects mainly to the ventral-postero-lateral nucleus of thalamus and carries discriminative aspects of pain such as location, intensity and duration. The medial STT projects into medial thalamus and is responsible for mediating the autonomic and unpleasant perceptions of pain.

b) **Alternate pain pathways:**

a) Spinoreticular- tract it is thought to mediate arousal and autonomic response to pain

b) Spinothalamic tract-activates hypothalamus and evokes emotional behavior to pain.

c) Spinocervical tract-ascends uncrossed to lateral cervical nucleus where it relays fibers to conventional thalamus and is an alternate pathway

3. Third order neuron:

Sends projections through the internal capsule and corona radiata to the posterior central gyrus of the cerebral cortex. Perception and discrete localization of pain takes place in these cortical areas.

Chemical mediators of pain :

Several neuropeptides and excitatory amino acids function as neurotransmitters for afferent neuron sub serving pain . The most important of these peptides are Substance P, Calcitonin Gene Related Peptide (CGRP) and Glutamate, which have an excitatory effect on nociception of which glutamate, is the most important excitatory amino acid. GABA and glycine are the major inhibitory neurotransmitters

FIG 8:PAIN PATHWAY

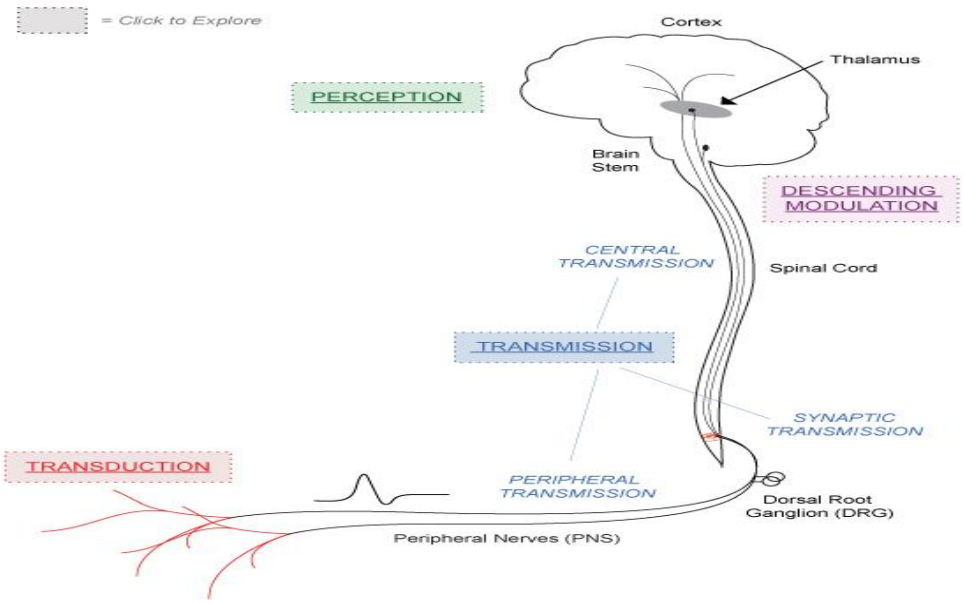


FIG 9: REXED'S SPINAL CORD LAMINAE

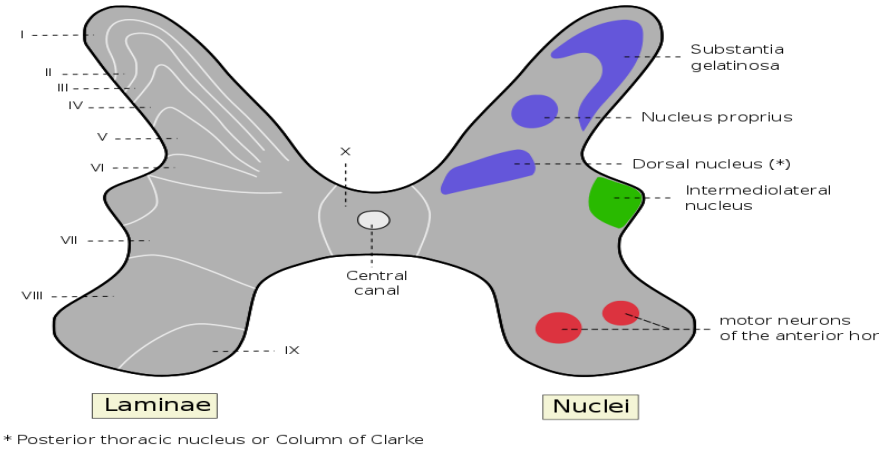


TABLE -1: SPINAL CORD LAMINAE OF REXED

LAMINA	PREDOMINANT FUNCTION	INPUT	NAME
1	Somatic Nociception Thermoception	Aδ,C	Marginal layer
2	Somatic Nociception Thermoception	C,Aδ	Substantia gelatinosa
3	Somatic mechano reception	Aβ	Nucleus proprius
		Aδ	
4	Mechano reception	Aβ, A	Nuclear
5	Visceral and Somatic Nociception and Mechano reception		Wide dynamic range neurons
6	Mechano reception	Aβ	Nucleus proprius
7	Symphathetic		Motor horn
8		Aβ	Motor horn
9	Motor	Aβ	Motor horn
10		Aβ	Central canal

Modulation of pain[41,42]:

a) **Peripheral modulation:** Nociceptors and their neurons show sensitization after repeated stimulation and this sensitization may appear as an enhanced response to noxious stimuli..

b) Central modulation

Facilitation by at least three mechanisms:

a) Windup and sensitization of second order neurons

b) Receptor field expansion

c) Hyper excitability of flexion reflexes

Preemptive analgesia[43]

The importance of peripheral and central modulation in nociception has fostered the concept of 'preemptive analgesia' in patients undergoing surgery. This may involve infiltration of the wound with LA, central neuraxial blockade or the administration of opioids to name a few.

Theories of pain :

Although the exact mechanism of pain relief is not clear, various theories have been put forward .Of all the theories, the Gate control theory of pain is the most widely accepted.

Gate control theory of pain[44]:

Proposed by Melzack and Wall in 1965 and then later modified by them in 1982. They initially took into consideration the evidence of physiological specialization, central summation, patterning modulation of input and the influence of psychological factors.

The theory states that

1. A spinal gating mechanism in the dorsal horn modulates the transmission of nerve impulses from afferent fibers to spinal cord T cells.
2. The mechanism of spinal gating is influenced by the relative amount of activity in large diameter (L) and small diameter fibers, and activity in large fibers tends to inhibit transmission, thus closing the gate, while activity in small fibers tends to promote transmission, thereby opening the gate.
3. The mechanism of the spinal gating is influenced by the nerve impulse that descends from the brain.
4. A central control trigger carries precise information about the nature and location of the stimulus, which occurs rapidly. This rapid transmission makes it possible for the brain to identify, evaluate, localize and selectively modulate the sensory input before the action system is activated.
5. When the output of the spinal cord transmission (T) cells exceeds a critical level , it activates the action system in those neural areas that underline the complex sequential pattern of behavior and thereby experience characteristics of pain .

Melzack and Wall modified their theory, which includes excitatory and inhibitory links from the substantia gelatinosa to the transmission cells as well as the descending inhibitory control from the brain stem system Melzack and Wall theories though have deficiencies, have proven to be among the most important development in the field of pain research. They also have stimulated much psychological and physiological research and have proved the development of newer approaches to pain therapy.

Effects of postoperative pain:

- Respiratory: Atelectasis, sputum retention and hypoxemia due to ineffective cough
- CVS: Increased myocardial oxygen demand and ischemia
- GIT: Decreased gastric emptying, reduced gut motility and constipation
- Genitourinary: urinary retention
- Neuro-endocrine: Hyperglycemia, protein catabolism and sodium retention
- Musculoskeletal: Reduced mobility, pressure sores and increased risk of Deep Vein Thrombosis
- Psychological: Anxiety and fatigue

PHARMACOLOGICAL REVIEW

OPIOIDS[46]

The term opioid refers broadly to all compounds related to opium. The word "opium" is derived from opos, the Greek word for juice, as the drug is derived from the juice of the opium poppy Papaver somniferum.

The first undisputed reference to opium is found in the writings of Theophrastus in the third century. During the Middle Ages, many of the uses of opium were appreciated. Opium contains more than 20 distinct alkaloids. In 1806, Sertürner reported the isolation of a pure substance in opium that he named morphine after Morpheus, the Greek god of dreams. By the middle of the 19th century, the use of pure alkaloids rather than crude opium preparations began to spread throughout the medical world.

Opioid Receptors[46]

In 1973, based on radioligand binding assays, three types of opioid receptors were postulated. They were named μ for the morphine type, κ for the ketocyclazocine type, and σ for the SKF10047 (N-allylnormetazocine) type. In addition, a high-affinity receptor for enkephalins was found in the mouse vas deferens and designated the δ-receptor. Furthermore, an ε-receptor was proposed as the binding site for β-endorphin in the rat vas deferens.

MECHANISM OF ACTION OF OPIOIDS[47]

Opioid analgesics act at both supra spinal and spinal levels. Supra spinal action may activate descending inhibitory pathways. In spinal cord, the primary site of nociceptive input is the dorsal horn. The greatest abundance of opioid receptors is in the substansia gelatinosa, where they are present on the pre synaptic terminals of primary afferent sensory neurons and on the dendrite of the postsynaptic inter-neurons

that modulate spinothalamic transmission. These pre synaptic receptors inhibit release of substance P, glutamate and other neuro transmitters and post synaptic receptors decrease the evoked excitatory post synaptic potential (EPSP).

'mu and delta' receptors open potassium ion channels causing hyperpolarisation and decreased neuronal firing. At the nerve terminal the action potential plateau will shorten and so reduce calcium ion influx and neuro transmitter release. In contrast 'Kappa' receptors, close calcium channels.

Intrathecal opioids[48]

Intrathecal opioids bind to a family of G-protein-linked pre- and postsynaptic opioid receptors in Laminae I and II of the dorsal horn. Receptor activation leads to G-protein-mediated potassium channel opening (mu and delta) and calcium channel closure (kappa), with an overall reduction in intracellular calcium. This reduces the release of excitatory transmitters (glutamate and substance P) from presynaptic C fibres, but not A fibre terminals with consequent reduction in nociceptive transmission. There are significantly greater number of opioid receptors located presynaptically compared with postsynaptically. Binding of opioids to postsynaptic receptor sites in the dorsal horn results in potassium channel opening and indirect activation of descending pathways from the brainstem. Other possible target sites for intrathecal opioids have been proposed:

1. Phenylpiperidine opioids, including fentanyl and meperidine (pethidine), exhibit close structural similarities to local anaesthetics. Fentanyl has demonstrable local anaesthetic effect on sensory C primary afferent nerve fibres, which may facilitate analgesic effects.
2. An increase in lumbosacral adenosine concentrations in human cerebrospinal fluid (CSF) has followed intrathecal morphine injection in animals and

humans. Adenosine is known to open potassium channels with consequent hyper polarization of nerve fibres and reduction in neuronal activity.

3. Intrathecal opioids reduce the release of gamma amino butyric acid (GABA) and glycine by a calcium-independent process from dorsal horn neurones. This would appear to counter what we intuitively assume to be a damping down of neuronal activity in the context of an analgesic effect. However, it is conceivable that opioids may disinhibit inhibitory pathways, thereby reducing nociceptive transmission. This gives us new insight into the complexities of opioid mechanisms in the dorsal horn.

FENTANLY[49,50,51]

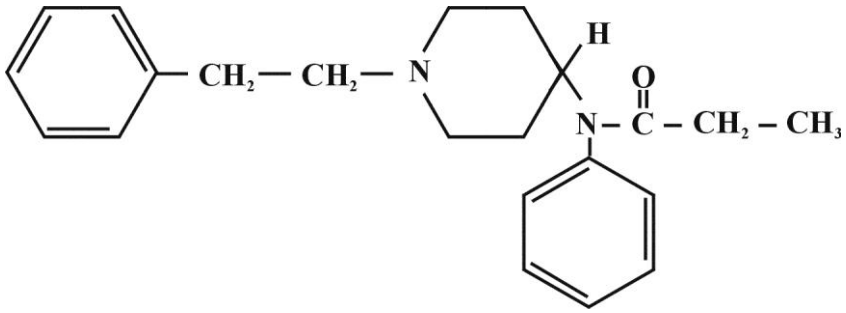


Fig.8: Chemical structure of Fentanyl

Fentanyl is a phenylpiperidine derivative synthetic opioid agonist that is structurally related to pethidine. As an analgesic, fentanyl is 75-125 times more potent than morphine. Fentanyl is highly lipid soluble and has a low molecular weight.

Fentanyl is a popular drug in anaesthetic practice because of its shorter time to peak analgesic effect, rapid termination of effect after small bolus doses and relative cardiovascular stability[48].

PRARMACOKINETICS:

After IV administration the onset of action of fentanyl is 1-2 minutes with duration of action for about 60 minutes. After epidural route duration is 3-4 hours. After intrathecal administration the onset is within 5 minutes and duration of action is of 60 minutes[48].

The greater potency and more rapid onset of action reflect the greater lipid solubility compared to morphine, which facilitates its passage across the blood brain barrier. The short duration of action reflects its rapid redistribution to inactive tissue sites such as adipose tissue and skeletalmuscles, with an associated reduction in plasma concentration of drug. The lungs also acts as a inactive storage site, with an estimated 75% of the initial fentanyl dose undergoing first pass pulmonary uptake.

Progressive saturation of these inactive tissue locations happens when numerous IVdoses of fentanyl are administered or when the drugs are continuously infused. This results in slow decrease in the plasma concentration of fentanyl and the duration of analgesia and depression of ventilation, may be prolonged[50].

METABOLISM AND ELIMINATION[50]:

Fentanyl is extensively metabolized by N- demethylation to nor-fentanyl, excretion occured by kidneys and can be present in urine for 72 hours after a single IV dose of fentanyl.

Despite its short duration of action, its elimination half time is prolonged. This is because of larger volume of distribution of fentanyl. This larger volume of distribution is due to greater lipid solubility and thus more rapid passage into tissue. The plasma level of fentanyl is maintained by slow reuptake from inactive tissue locations, resulting in persistent drug effects that parallel the extended half time

elimination. The longer elimination half time of fentanyl in elderly patients is due to reduced clearance of the opioid in comparison to younger adults.

CONTEXT SENSITIVE HALF TIME:

As the length of ongoing fentanyl infusion rises beyond 2 hours, this opiod's context sensitive half time improves. This resuits in saturation of inactive tissue sites when fentanyl infusion prolonged and return of the opioid from theses tissues to plasma.

PHARMACOLOGICAL ACTIONS[50]:

a) **Central nervous system:** Fentanyl produces analgesia, drowsiness, change in mood and mental clouding. It produces modest decrease in the cerebral metabolic rate when used with barbiturates and nitrous oxide.

b) **Cardiovascular system:**

I. Heart rate: Due to stimulation of central vagal nucleus there is a decrease in the heart rate. It is dependent on dose and speed of injection. It can be effectively prevented by premedication with parasympatholytic agent such as glycopyrolate or atropine. Fentanyl also blocks sympathetic stress response that includes increase in heart rate by decrease in CNS sympathetic vasoregulatory flow.

II. Blood pressure: Minor reductions in blood pressure are seen primarily due to a reduction in systemic vascular resistance through centrally mediated reduction in sympathetic tone and often associated with bradycardia.

III. Cardiac electrophysiological effects: Fentanyl slows AV conduction, prolongs RR interval, AV node refractory period and the duration of purkinje fiber action potential.

IV. Coronary vasomotion and myocardial metabolism: Fentanyl has no effect on coronary vasomotion or myocardial metabolism and does not diminish ability of large coronary arteries or coronary arterioles to respond to vasoactive agents.

c) Respiratory system: Fentanyl produces dose related depression respiration.

d) Rigidity: It occurs frequently during IV induction of anaesthesia with larger doses, but with intrathecal fentanyl no such complication is seen.

e) Gastrointestinal tract: Intestinal motility is decreased and constipation can be the problem. It can increase the tone of sphincter of oddi and produce increased pressure in biliary ducts, occasionally producing pain. The effects are produced by combination of peripheral actions.

Adverse effects[50]:

1. Bradycardia : Due to stimulation of vagal nuclei in medulla
2. Hypotension: Is unlikely as fentanyl does not evoke release of histamine even at large doses.
3. Respiratory depression: Dose dependent depression of ventilation due to direct depressant effects on brainstem ventilation centers.
4. Spasm of biliary smooth muscles
5. Gastrointestinal system: Spasm of gastrointestinal smooth muscles occures, leads to number of side effects including constipation, biliary colic and delayed gastric emptying.
6. Nausea and vomiting: It is due to direct stimulation of chemoreceptor trigger zone.
7. Urinary retention: Due to increase tone of vesicle sphincter.

Therapeutic efficacy:

Fentanyl is potent and safe. Its therapeutic index of 323 is much greater than that of morphine (69) and pethidine (4.8).

Clinical uses/ dose[50]:

- Analgesia — fentanyl 1-2µg/kg 1V
- As an adjuvant to inhaled anaesthetics to blunt circulatory response to laryngoscopy and intubation. 2- 20µg/kg 1V
- For surgical anaesthesia 50-150µg/kg 1V
- To decrease preoperative anxiety- transmucosal preparation in a delivery device to deliver 5-20µg /kg.
- Intradural or extradural administration to potentiate the action of local anesthetics and to provide post operative analgesia.

Contraindication and Cautions:

1. Should not be administered to patients who have taken MAO inhibitors within previous 14 days.
2. Bronchial asthma
3. Myasthenia gravis

Counter measures for adverse effects:

- Respiratory depression can be treated with naloxone and by mechanical ventilation.
- Pruritis, nausea and urinary retention can be reversed by naloxone, antihistaminic, antiemetic and by catheterization.

Side effects of intrathecal fentanyl:

a) Pruritis

b) Urinary retention

c) Depression of ventilation

d) Sedation

e) Central nervous system excitation

f) Neonatal morbidity

g) Delayed gastric emptying

h) Sexual dysfunction

i) Water retention

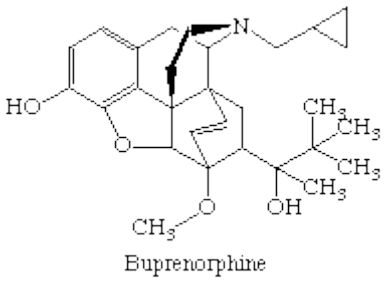
BUPRENORPHINE[52]

Buprenorphine is a thebaine derivative, μ-receptor partial agonist and similar in structure to morphine but approximately 33 times more potent.

PHYSIOCHEMICAL PROPERTIES [53]

The volume of distribution of buprenophine is 2.8 L/kg and its clearance is 20 mL/kg/min.

Fig 9: Chemical structure of Buprenorphine



Buprenorphine

MECHANISIM OF ACTION OF BUPRENORPHINE[54]

Buprenorphine is a partial agonist at the mu opioid receptor and an antagonist at the kappa receptor. It has very high affinity and low intrinsic activity at the mu receptor and will displace morphine, methadone, and other opioid full agonists from the receptor.

Opioid partial agonists are drugs that activate receptors, but not to the same degree as full agonists. Increasing the dose of a partial agonist does not produce as great an effect as does increasing the dose of a full agonist. The agonist effects of a partial agonist reach a ceiling at moderate doses and do not increase from that point, even with increases in dosage.

Its partial agonist effects imbue buprenorphine with several clinically desirable pharmacological properties: lower abuse potential, lower level of physical dependence (less withdrawal discomfort), a ceiling effect at higher doses, and greater safety in overdose compared with opioid full agonists.

At analgesic doses, buprenorphine is 20–50 times more potent than morphine. Because of its low intrinsic activity at the mu receptor, however, at increasing doses, unlike a full opioid agonist, the agonist effects of buprenorphine reach a maximum and do not continue to increase linearly with increasing doses of the drug—the ceiling effect. One consequence of the ceiling effect is that an overdose of buprenorphine is less likely to cause fatal respiratory depression than is an overdose of a full mu opioid agonist.

DOSE RESPONSE CURVE[55]

The buprenorphine dose-response curve is sometimes submaximal, or even bell-shaped,in nociceptive assays, depending upon the nature and intensity of the noxious stimulus. Moreover,buprenorphine, when administered with full agonists, such as morphine, antagonizes the action of these drugs. Partial agonism at the mu opioid receptor and, in some cases, antagonism at the kappa or delta opioid receptor have been considered as possible underlying mechanisms for the ceiling effect and bell-shaped dose-response curve of buprenorphine. While ceiling effects can be explained by partial agonist activity of buprenorphine, the bell-shaped dose-response curve cannot be a consequence of this property of the drug. Recently, buprenorphine has been shown to activate the opioid receptor-like (ORL-1; also known as NOP) receptor. Supraspinal activation of the ORL-1 receptor counteracts the antinociceptive and rewarding actions of morphine, raising the possibilitythat these actions of buprenorphine can also be altered by its ability to concomitantly activate the ORL-1 receptor.

DURATION OF ACTION[56]

Buprenorphine is a long-acting drug with a terminal elimination half-life of 24 to 37 hours. Peak clinical effects occur one to four hours after sublingual administration. Typically effects will continue to be experienced for up to 12 hours at low doses (2 mg), but as long as 48 to 72 hours at higher doses (16 or 32 mg). The prolonged duration of effect at high doses enables alternate-day, and even 3-days-a week dispensing regimes.

METABOLISIM AND EXCRETION

Peak plasma concentrations are achieved one to two hours after sublingual administration. Buprenorphine undergoes extensive first pass metabolism when taken orally. The major metabolite, norbuprenorphine, has some opioid activity but the extent of its contribution to the effects of buprenorphine is unknown.

Buprenorphine is principally metabolised by two hepatic pathways: conjugation with glucuronic acid and N-dealkylation, mediated by the cytochrome P450 3A4 isozyme. The metabolites are excreted in the biliary system, with enterohepatic cycling of buprenorphine and its metabolites. Most of the drug is excreted in the faeces and, to a lesser extent, in the urine.

SIDE EFFECTS ;

The side effects of buprenorphine are similar to those of other opioids (Lofwall et al 2005), the most common being:

- Constipation
- disturbed sleep
- drowsiness
- sweating
- headaches
- nausea

DRUG INTERACTIONS:

The principal drug interactions of buprenorphine relate to its opioid activity.

Other sedatives: Buprenorphine exerts additive sedative effects when used in conjunction with other sedating medications. These include other opioids, benzodiazepines, alcohol, tricyclic antidepressants, sedating anti-histamines, and

major tranquillisers. The combination of buprenorphine with benzodiazepines, alcohol and other sedatives has been associatedwith fatal overdoses.

Opioid antagonists (naloxone and naltrexone): Buprenorphine has affinity for mu opioid receptors similar to the opioid antagonists. In the event of overdose of buprenorphine, very high doses of naloxone may be required to partially reverse its effects. Cases have been reported in which naloxone in doses of 10 to 35mg was required, while in other cases doses of 2mg or less were reported to be effective in reducing respiratory depression . Because of the uncertain response to naloxone, prolonged ventilatory support may be required in overdoses involving buprenorphine. Naltrexone can precipitate a withdrawal reaction in patients on buprenorphine, although the effect may be delayed (2 to 4 hours, occasionally up to 8 hours).

Opioid agonists: Buprenorphine exerts a degree of blockade to the effects of full agonist opioids, which may complicate the use of additional opioids for analgesia. The initial dose of buprenorphine can precipitate opioid withdrawal in patients who have recently used an opioid drug.

Hepatic enzyme inducers and inhibitors: Buprenorphine metabolism can be influenced by the presence of drugs and other compounds that are also metabolised by or affect the activity of the cytochrome system . Patients who are concurrently prescribed or using inhibitors of cytochrome P450 3A4 may have increased buprenorphine blood concentrations, and those taking inducers may have decreased blood concentrations. Such interactions are probably seldom of clinical significance.

PHARMACOLOGY OF LOCAL ANAESTHETIC [56-61]

INTRODUCTION:

Local anesthetics are drugs that reversibly block nerve conduction, when locally to nerve tissue in appropriate concentrations.

General Properties of Local Anesthetics:

The structure of anesthetic drug consists of a lipophilic aromatic ring and a hydrophilic tertiary amine. The intermediate link is cither by an ester or an amide.

Local anesthetics have to cross the axonal membrane to reach the binding site.

A swift change in the valency of amino nitrogen moiety lakes place for penetration. High concentration of base is required for penetration and cation moiety is required for action on target organ.

$R{=}N + H^+ \longleftrightarrow R = NH^+$

(Unchanged base (changed base water soluble)

Water insoluble)

Local anesthetics exist in an aqueous solution in a chemical equilibrium between base and cation. This depends on pH of solution and pKa of drug. pH can change the equilibrium but pKa is constant.

When pH= pKa, Cation base.

At physiological pH (7.4), concentration of cation is more than that of the base. Increase in the pH causes increase in base and hence increases penetration.

Mode of Action of Local Anesthetics:

Local anesthetics prevent generation and conduction of nerve impulses in all excitable tissues. It affects the permeability of the nerve to Na+ and K+.

Local anesthetics probably inhibit Na+ flux by specific interaction with voltage gated Na-i- channels. It is hypothesized to act on the outer and inner surface

of the axonal membrane. Uncharged local anesthetics enter the axoplasm and become positively charged to become an active cation. It acts as a receptor, blocking the Na+ channel.

Another theory **is 'The membrane expansion theory'.** Drugs, which do not form cations at physiological pH, act by penetration the axonal membrane. The membrane swells and blocks Na+ channel. During the resting phase, interior of the peripheral nerve fibre has a potential difference of about -70mV relative to the outside. When the nerve is stimulated there is a rapid increase in the membrane potential to approximately +20mV, followed by immediate restoration of the resting level. This depolarization/ repolarization sequence lasts for 1-2 ms and produces the action potential associated with the passage of a nerve impulse.

Depolarization is the result of sudden increase in membrane permeability to Na+, which enters the cell through Na+ channels that are closed during resting phase. This increases the membrane potential to approximately +20mV. when the electrochemical and concentration gradients of Na+ balance each other and the channels close. This gradient favors the movement of K+ outside the cell till resting potential is reached.

The impulse is transmitted along the axons because a local current flows between depolarized (positive charge) and non-depolarized (negative charge) segment of the nerve. The voltage change because of these current causes configurationally changes in the BA+ channel in the next segment, so that action potential is propagated along nerve.

PHARMACOLOGY OF BUPIVACAINE [62-65]

BUPIVACAINE

Bupivacaine, an amino amide local anaesthetic was first synthesized in the year 1957 in Sweden by A.F Ekenstam and his colleagues . First report of its use was by L.J Teluvio in the year 1963 . It is one of the long acting local anaesthetic agents available, which is extensively used for intrathecal, extradural and peripheral nerve blocks. It is a white crystalline powder soluble in water

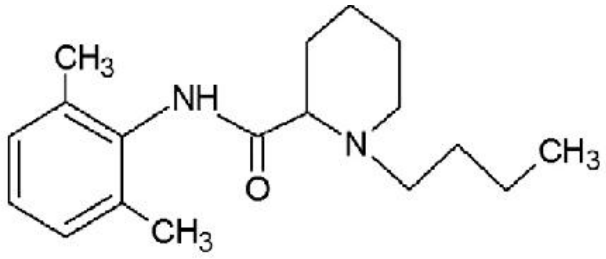


FIG.12: CHEMICAL STRUCTURE OF BUPIVACAINE

Bupivacaine has an IUPAC nomenclature of 1-butyl-n-(2,6- dimethyl phenyl) piperidine-2-carboxamide.

Physiochemical properties:

- Molecular formula C18 H28 N2OHC1
- Molecular weight 288.43 g/mol
- Solubility in water 25mg/m1
- pH of saturated solution 5.2
- pKa 8.1
- specific gravity 1.201 at c37^{0}C
- melting point 247-258^{0}C

Mechanism of action [43,44]:

Mechanism of action of bupivacaine is same to that of any other local anaesthetic. The main action of local anaesthetics is on the cell membrane axon, on which it produces electrical stabilization. Bupivacaine prevents conduction of nerve impulses by inhibiting transfer of sodium ions through ion-selective sodium channels in nerve membranes. For the local anaesthetics the particular receptor is sodium channel.

Failure to raise the permeability of sodium ion channel slows down the pace of depolarization so that threshold potential is not reached and therefore there is no propagation of action potential. Local anaesthetics do not change the resting transmembrane potential or threshold potential.

Other site of action targets:

- Voltage dependent potassium ion channels
- Calcium ion currents (L-type most sensitive)
- G protein coupled receptors

Dosage depends on:

- Area to be anaesthetized
- Number of nerve segments to be blocked
- Individual tolerance
- Technique of local anaesthesia
- Vascularity of area

Bupivacaine is available in the following concentrations:

- 0.25%. 0.5%and 1%
- 0.25% and 0.5% solution in isotonic saline
- 0.5% solution in 8% dextrose

Dosage is 2mg/kg limited to 150 mg in four hours the intrathecal minimum local analgesic dose of Bupivacaine is 2.37 mg.

Type of block	**Concentration**	**Dosage in ml**	**Dosage in mg**
Sub arachnoid block	0.5 — 0.75%	2- 4	10 – 20
Epidural block	0.25 — 0.5%	15 — 30	50 – 200
Caudal block	0.25 — 0.5%	15 - 30	75 – 150
Brachial plexus block	0.25 — 0.5%	15 — 30	75 – 225
Intercostals nerve block	0.25 — 0.5%	3 — 5 / nerve	15 — 20 mg per nerve
Local infiltration	0.25 — 0.5%	5 — 20	Upto 175 mg

Repeatation of these doses can be done in 3 -4 hrs but it should not exced 400 mg which is the maximum dose, in 24 hrs. To prolong the the duration of action vasoconstrictors can be added . However the peak blood concentration is significantly decreased, thereby reducing the systemic toxicity.

ANESTHETIC POTENCY:

Hydrophobicity appears to be a primary determinant of intrinsic anesthetic potency and Bupivacaine is highly hydrophobic, hence is very potent

ONSET OF ACTION:

The onset of conduction blockade is dose dependent or concentration dependent. The onset of action of Bupivacaine is 4-6 mins and peak effect occures between 15 — 20 minutes.

DURATION OF BLOCK :

Duration of anesthesia varies according to the type of block, the average duration of peridural block is about 3.5 — 5 hours, for nerve blocks, it is about 5 — 6 hours.

Pharmacokinetics:

The level of Bupivacaine in blood is determined by :

- The quantity of drug injected .
- The rate at which absorption occurs from the site of administration .
- The rate of tissue distribution and the rate of biotransformation and excretion of Bupivacaine.

Bupivacaine is detectedable in the blood within 5 mins of infiltration or following epidural or intercostals nerve blocks. The level of bupivacaine in plasma are related to the total dose administered , peak levels of 0.14 to 1.18 µg/ml were found within 5 mins to 2 hrs, which gradually declined to 0.1 to 0.34 µg/m1 by 4 hrs.

In plasma, Bupivacaine is 70 -90% protein bound . The rank order of protein binding for this and its homologues is Bupivacaine> mepivacaine > lidocaine. Conversely, the unbound active fraction is one seventh of lidocaine and one fifth of mepivacaine.

Absorption:

The systemic absorption of Bupivacaine depends upon:

- The dose injected .
- Vasoconstriction
- Site at which the drug is being injected .

- The highest blood concentration of Bupivacaine is dependent on the total dose given at any specific site and absorption is greater in areas with high vascularity.

Toxicity:

The toxic plasma concentration is set at 4 - 5 µg/ml, maximum plasma concentration rarely approach toxic levels.

Distribution:

The two-compartment model can describe this. It is thought that the rapid distribution phase-α is associated with intake by rapid equilibrating tissue i.e., tissues that have rich blood supply. The slow phase β is primarily a function of distribution to slowly equilibrating tissue, biotransformation and excretion of the compound.

The organs having rich blood supply show higher concentrations of the drug, rapid excretion occurs by lung tissue. Skeletal muscle is the largest biggest of the drug but does not show any specific affinity towards Bupivacaine.

Distribution characteristics:

T1/2 α	2-7 minutes (uptake by rapid equilibrium tissue)
T1/2β	28 minutes (distribution by slowly perfused tissues)
T1 /2γ	3-5 hours (metabolism and elimination)
VDSS	72 liters (volume of distribution at steady state)

Pharmacodynamics:

Central Nervous System:

Bupivacaine readily crosses the blood brain barrier, on crossing the blood brain barrier it causes CNS depression following higher doses. The early symptoms of CNS toxicity are light-headedness and giddiness followed by visual and auditory discomfort. There may be disorientation , drowsiness and other signs like shivering, muscular twitches and tremors and perioral numbness . At further increased concentration of drug it leads to cardiovascular or respiratory arrest. Acidosis enhances the likelihood of CNS toxicity from Bupivacaine, due to an increase in $PaCO_2$ there is increase in blood flow to brain leading to more anesthetic being delivered to the brain in short period.

Autonomic nervous system:

Bupivacaine does not inhibit the Noradrenalin uptake and hence has no sympathetic potentiating effect. Myelinated preganglionic B fibers have and are more sensitive to action of Bupivacaine as they are having faster conduction time. All local anesthetics, specially Bupivacaine shows higher incidence of sensory blockade than motor fibers.

Cardiovascular System:

Electrophysiological studies on the effect of local anesthetic have demonstrated that bupivacaine is associated with more pronounced depolarization changes. Bupivacaine blocks cardiac sodium channels and alters mitochondrial function. Its high degree of protein binding makes resuscitation prolonged and difficult.

Bupivacaine is highly arrythmogenic. This drug reduces the cardiac contractility. This is done by blocking the calcium transport. Low concentration of bupivacaine produces vasoconstriction while high doses cause vasodilatation.

Respiratory System:

At higher plasma concentrations respiratory depression may occur which in turn results in depression of medullary receptor center. Paralysis of respiratory muscles of diaphragm leads to respiratory depression as occurs in high spinal or total spinal anesthesia.

Biotransformation and Excretion:

Bupivacaine undergoes enzymatic metabolism in the liver. The excretion occurs by the kidney. Less than 5% of Bupivacaine is excreted via the kidney unchanged in urine. The major part of injected agent excreted in urine in the form of 2,6 pipecolyoxylidine (ppx) which is a n-dealkylated metabolite of bupivacaine. Renal clearance is inversely related to its protein binding capacity and pH of urine.

Adverse Effects:

Adverse effects are encountered in clinical practice mostly due to overdose, inadvertent intravascular injection or slow metabolic degradation.

- CNS signs includes excitation or depression. The first manifestation to be seen is nervousness, dizziness, blurring of vision , tremors, drowsiness followed by generalized tonic clonic convulsions, unconsciousness and respiratory arrest.
- CVS : myocardial depression, hypotension, arrhythmia, ventricular type conduction defect, SA node depression and cardiac arrest
- Allergic reactions such as urticaria, bronchospasm and hypotension
- Other signs includes nausea, vomiting, chills, constriction of pupil and auditory symptoms like tinnitus

CARDIOVASCULAR / CNS RATIO :

The CC / CNS dose ratio for Bupivacaine is 3.7 ± 0.5 indicating that 3 times drug is required to induce irreversible cardiovascular collapse as was needed to produce convulsions. It has also been suggested that some of the enhanced cardiac toxicity is due to enhanced myocardial uptake. Treatment: mainly is symptomatic and to maintain circulation and to support ventilation with oxygen and controlled ventilation. Supportive treatment with IV Fluids and vasopressors. Convulsions may be controlled with diazepam or muscle relaxants. Corticosteroids if allergic reactions suspected

METHODOLOGY

After taking written and informed consent ,this clinical trial was done on 60 patients aged between 18- 60 yrs with ASA grade 1 and 2 who were posted for elective urological ,lower abdominal ,lower limb and gynecological procedure under spinal anaesthesia after getting clearance from ethical committee at Shri B.M. Patil Medical College Vijaypura over a period of one and half year.

Patients were randomly assigned into two groups by a slip generated by computer with 30 patients in each.

Group "BB"- 0.5% hyperbaric bupivacaine 15mg +60μg Buphrenorphine

Group "BF" -0.5% hyperbaric bupivacaine 15mg + 25μg Fentanyl

INCUSION CRITERIA:

- Patients aged between 18 to 60 yearsof both sex planned for lower limb and lower abdominal surgeries
- Patients belonging ASA grade 1 and 2

EXCLUSION CRITERIA:

- Patient refusal
- Infection at site of injection
- Hypersensitivity to study drugs
- Coagulopathy or other bleeding disorders
- Patients with heart blocks
- Patients with peripheral neuropathy
- Patients with cardiac ,hepatic, pulmonary, renal failure

Method of study:

Patient's detailed history, general physical examination and systemic examination was carried out during preoperative visit. History of any significant medical illness was elicited. Airway, respiratory system and cardiovascular system were assessed. Intraoperative ECG, NIBP, SPO2 was monitored.

FOLLOWING INVESTIGATIONS WERE DONE:

- Routine blood- Hb%, TC, DC, ESR, Bleeding time, Clotting Time.
- Fasting blood sugar, Blood urea, serum creatinine .
- Urine analysis, chest x-ray, ECG if required.
- HIV and HbsAg.

Preliminaries:

- Written informed consent was taken.
- Nil per oral status was confirmed.
- Intravenous access was secured with a 18 guage I.V cannula .

PROCEDURE:

After shifting of the patient to the OT table IV access with 18 guage cannula was obtained on the forearm and RL infusion started IV before the block. The monitors were attached to the patient which include NIBP ,pulse oximeter and baseline PR, BP, RR and SpO2 were recorded.

The patients were placed in left lateral or sitting position. Under all aseptic precautions,lumbar puncture was done by midline approach using disposable Quincke spinal needle (25G) at L3-L4 intervertebral space and study drug was injected after confirming CSF free flow. Patients were monitored intraoperatively using NIBP, pulse oximeter and ECG. Oxygen (5L/min) by facemask was given after spinal anaesthesia and fluid therapy was maintained with RL.

Image 1:spinal tray

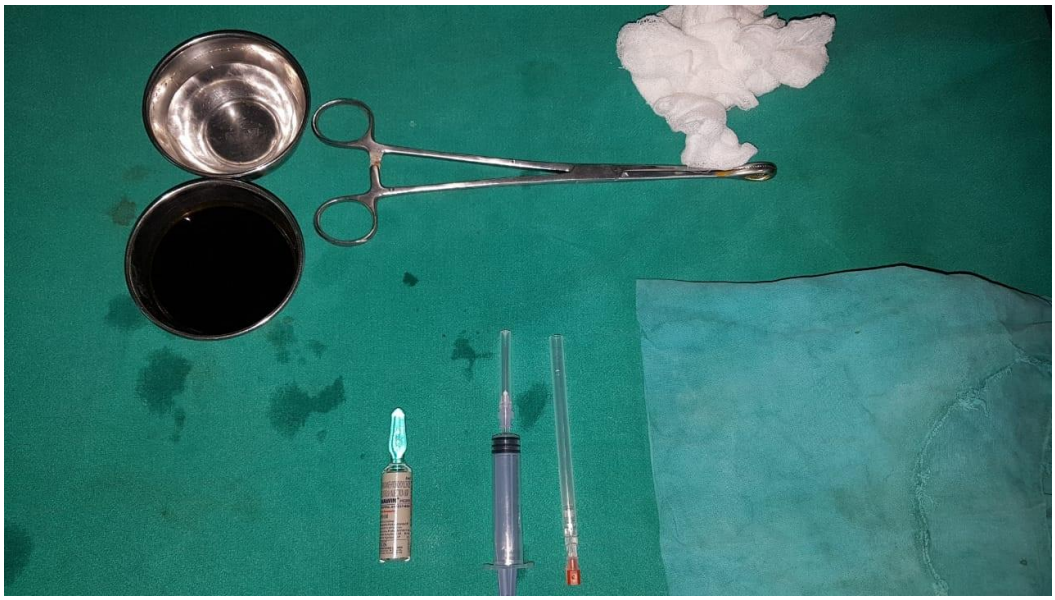
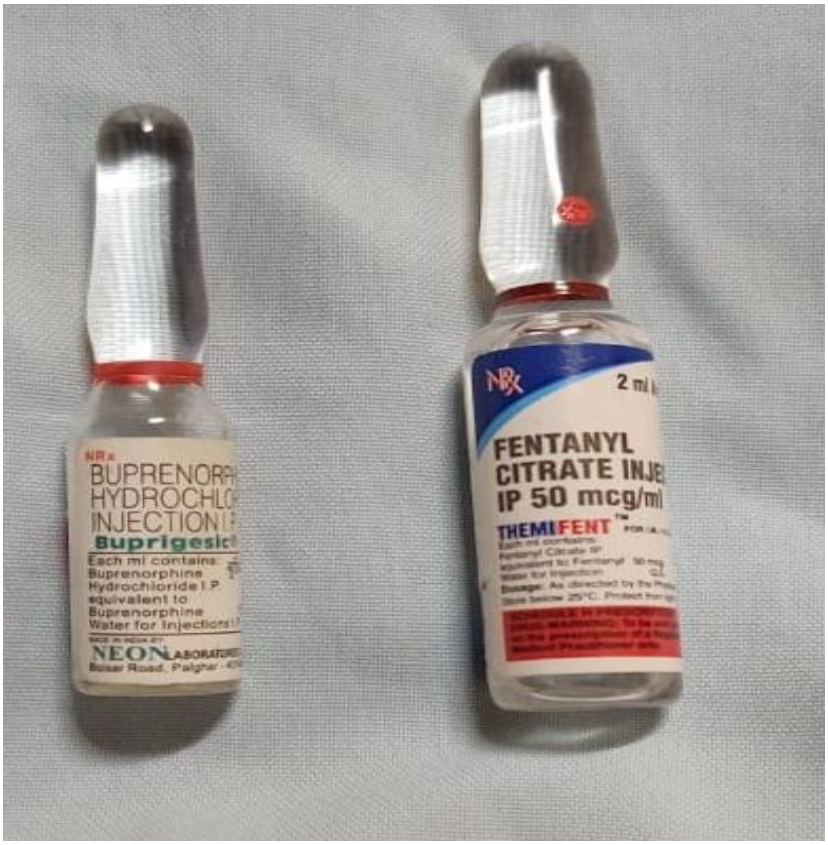
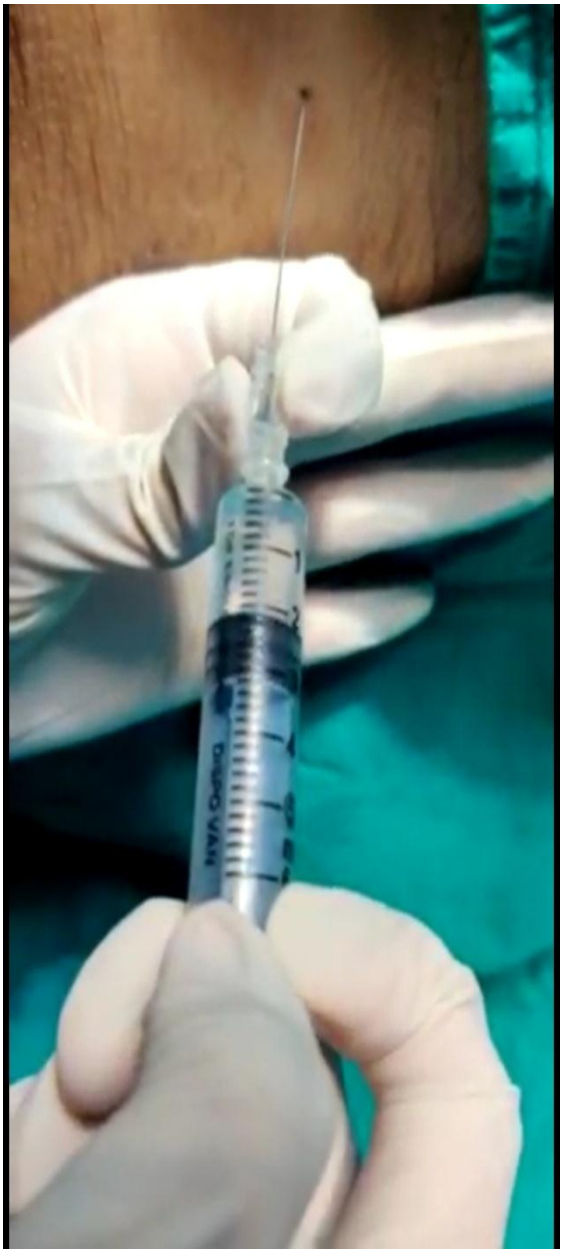


Image 2 :study drugs





Study drug being injected

We noted the following parameters:

HEMODYNAMIC CHANGES: Pulse rate, Systolic BP, Diastolic BP, Respiratory rate and SPO_2 were monitored at 0,5,10,15,30,60 and 120 minutes.

ASSESMENT OF SENSORY BLOCKADE:

Onset of sensory blockage was assessed by

pin-prick method using hypodermic needle and the time of onset was considered from the time of administration of drug into subarachnoid space until loss of pin prick sensation. After assessing the highest level of sensory blockade and time for two dermatomal segment regression of sensory level and duration of sensory block were recorded.

ASSESMENT OF MOTOR BLOCKADE:

This motor blockade was assesed by Bromage scale. Time interal between injection of drug into subarachnoid space,to the patients inability to lift the straight extended leg was taken as onset time(br.3).the duration of motor was taken from the time of injection to complete regression of motor block

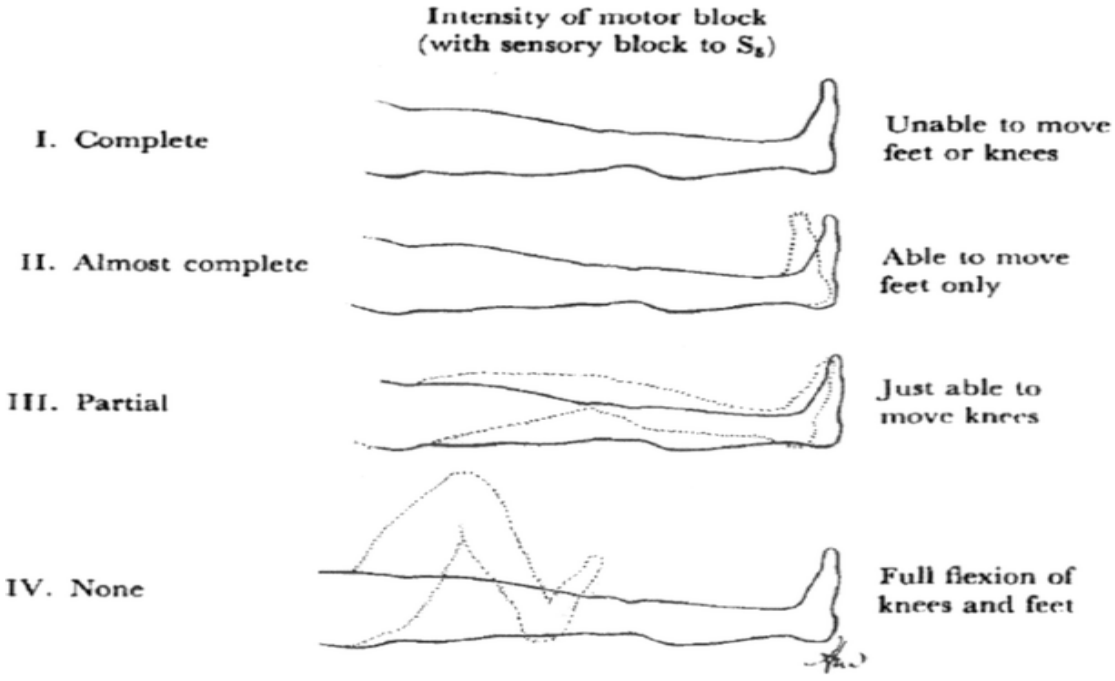


FIG 13:Bromage scale for assesing motor block and degree of paralysis

Modified Bromage Scale[67]:

“Grade 0 -Able to raise leg straight, full flexion of knees and feet.

Grade 1-Inability to raise leg, just able to flex knees, full flexion of feet.

Grade 2-Unable to flex knees, but some flexion of feet possible.

Grade 3-Unable to move the legs or feet.”

ASSESSMENT OF PAIN: Painhas been evaluated by using visual analogue score[68]. VAS consist of a 10 cm line anchored at one end by a label such as “NO PAIN” and at other end by a label “WORST PAIN IMAGINABLE” The patient simply marks the line to indicate the pain intensity and the provider then measures the length of line to mark a point scale. All the patients were given instructions about VAS and to point out the intensity of pain on the scale in the preoperative visit .

0-NO PAIN, 10-WORST PAIN.”

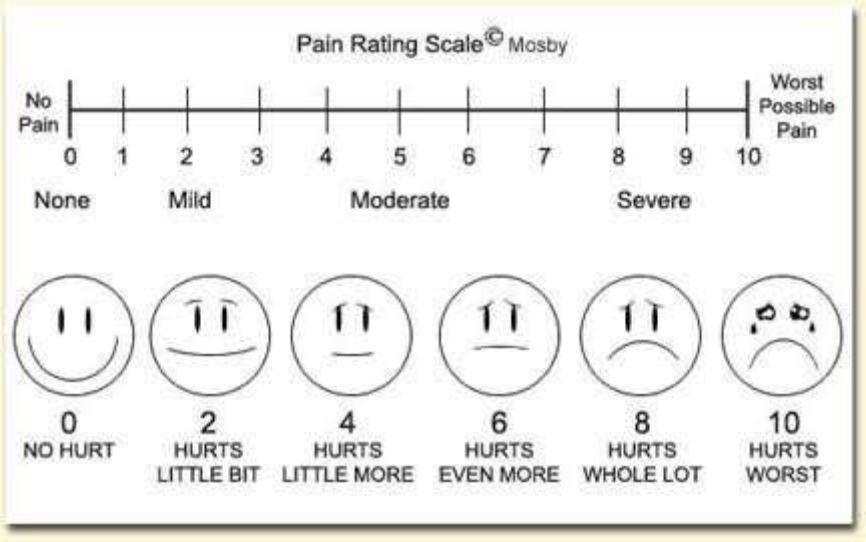


FIG 14: Linear Visual Analog Scale Score

Statistical analysis:

The data obtained were entered in a Microsoft Excel sheet, and statistical analysis was performed using statistical package for the social sciences (Verson 17). Results are presented as drawings, Mean±SD, counts and percentages. Results were compared using Independent t test, Mann Whitney U test and Friedman test with Dunn's post hoc test.

. For all tests, significant was achieved at $p<0.05$.

OBSERVATION AND RESULTS

A total of 60 patients belonging to ASA grade 1 and 2 posted for lower abdominal and lower limb surgeries were randomly selected the patients were divided into two groups of 30 each.

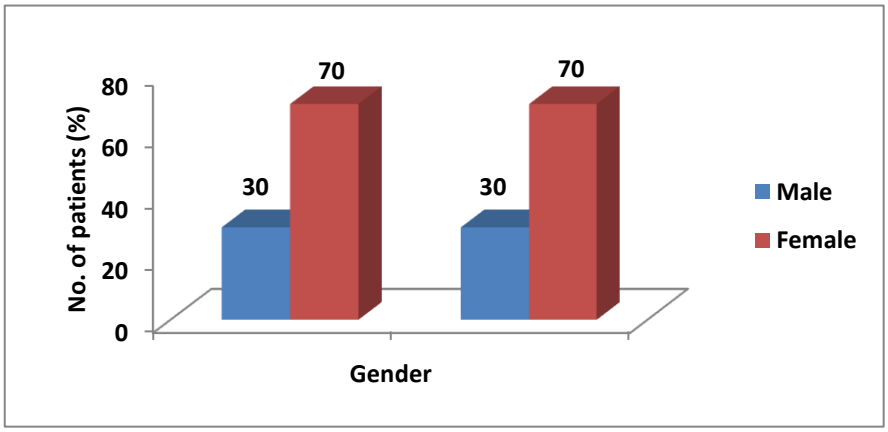
- Group "BB" received 0.5% hyperbaric Bupivacaine 3ml + Buprenorphine 60µg
- Group "BF" received 0 .5% hyperbaric Bupivacaine 3ml + Fentanyl 25µg

DEMOGRAPHIC PROFILE

Table: 1 Distribution of patients according to Gender in two groups

Gender	BUPIVACAINE + BUPRENORPHINE		BUPIVACAINE+ FENTANYL		Chi square test	P value
Female	9	30.0	9	30.0	X^2=0.000	P=1.0
Male	21	70.0	21	70.0		0
Total	30	100.0	30	100.0		
Insignificant						

Values are expressed as Mean ±SD. NS: Not significant, HS: Highly significant

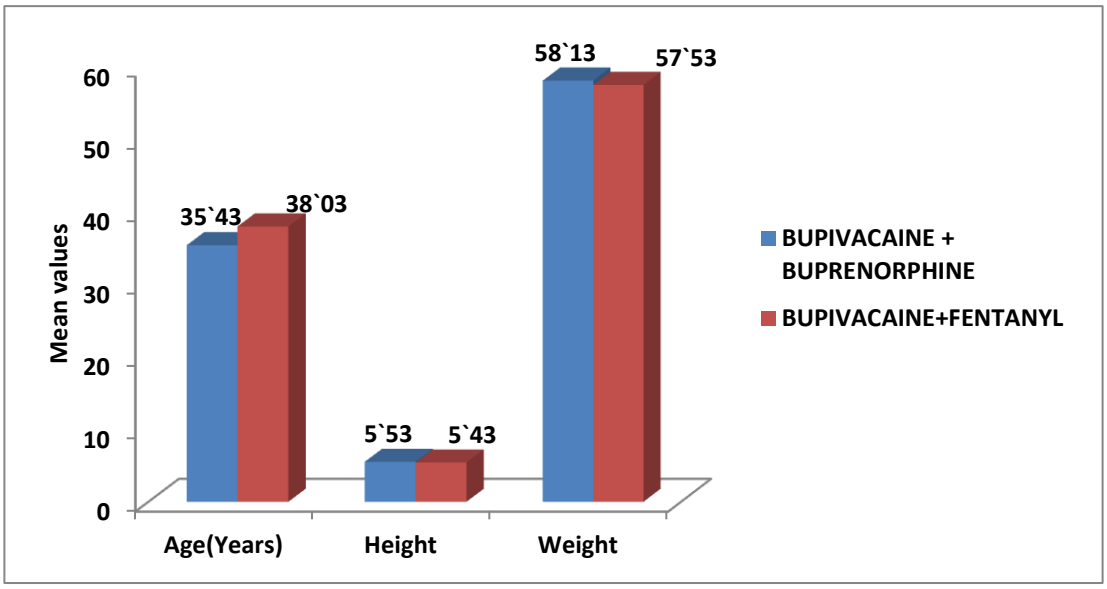


In BB group there were 21 males and 9 females and BF group 21 males and 9 females.

We did not observe any statistically significant difference in both the groups with regards to gender .

Table: 2 Comparison of basic variables between two groups

Basic variables	BUPIVACAINE + BUPRENORPHINE		BUPIVACAINE +FENTANYL		Unpaired t test/Mann Whitney U test	P value
	Mean	±SD	Mean	±SD		
Age(Years)	35.43	12.461	38.03	11.801	t=0.810	P=0.410
Height	5.53	.507	5.43	.302	U=415.000	P=0.595
Weight	58.13	7.394	57.53	8.460	t=0.292	P=0.771
Insignicant						



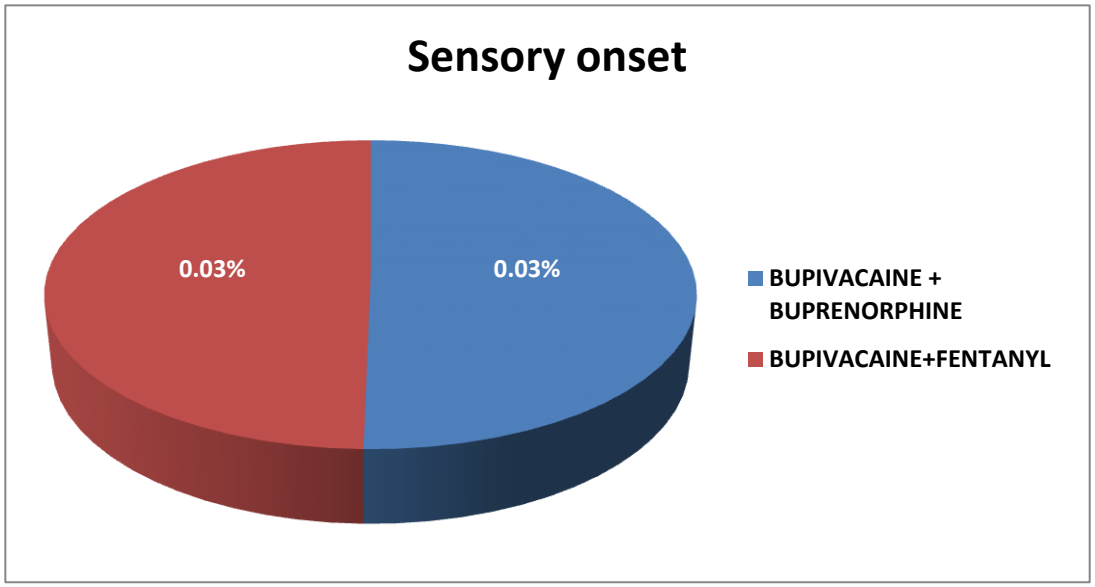
The mean age of patient in group BB was 35.43±12.461 years and in group BF was38.03±11.801 years.

The mean height of patient in group BB was 5.53±0.507 feet and in group BF was 5.43±0.302 feet.

The mean weight of patient in group BB was 58.13±7.394 kg and in group BFwas 57.53±8.460 kg. We did not observe any statistically significant difference in both the groups with regards to age , height and weight.

Table 3: ONSET OF SENSORY BLOCK

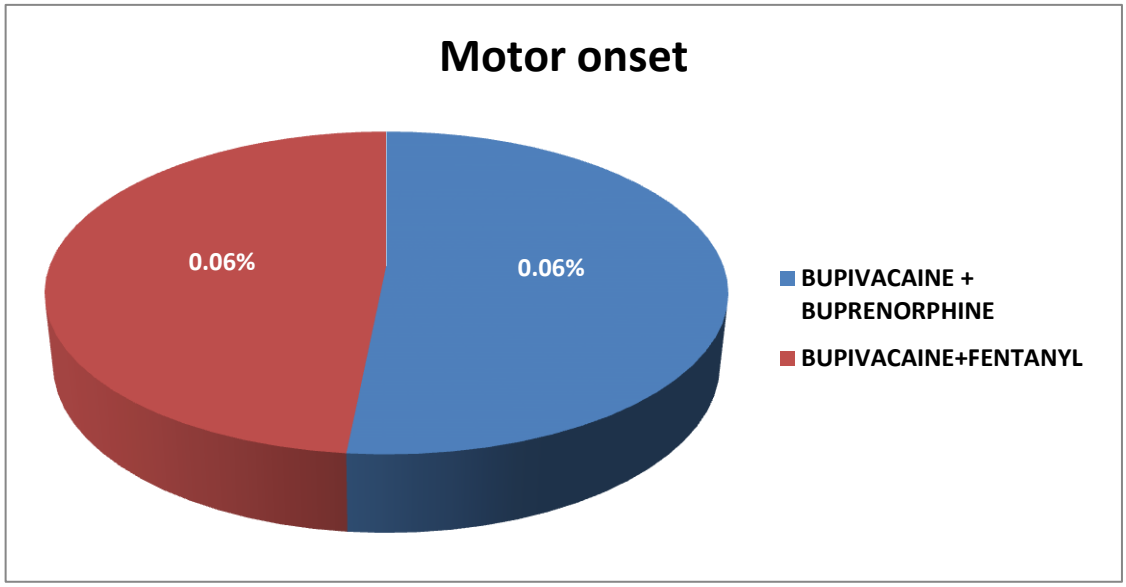
Basic variables	BUPIVACAINE + BUPRENORPHINE		BUPIVACAINE+ FENTANYL		Mann Whitney U test	P value
	Mean	±SD	Mean	±SD		
Sensory onset	3.27	0.980	3.23	0.728	U=443.500	P=0.919



The mean time for onset of sensory block in group BB was 3.27±0.980 minutes and in group BF was 3.23±0.728 min. The onset of sensory block in both groups was statistically not significant.

Table 4: ONSET OF MOTOR BLOCK

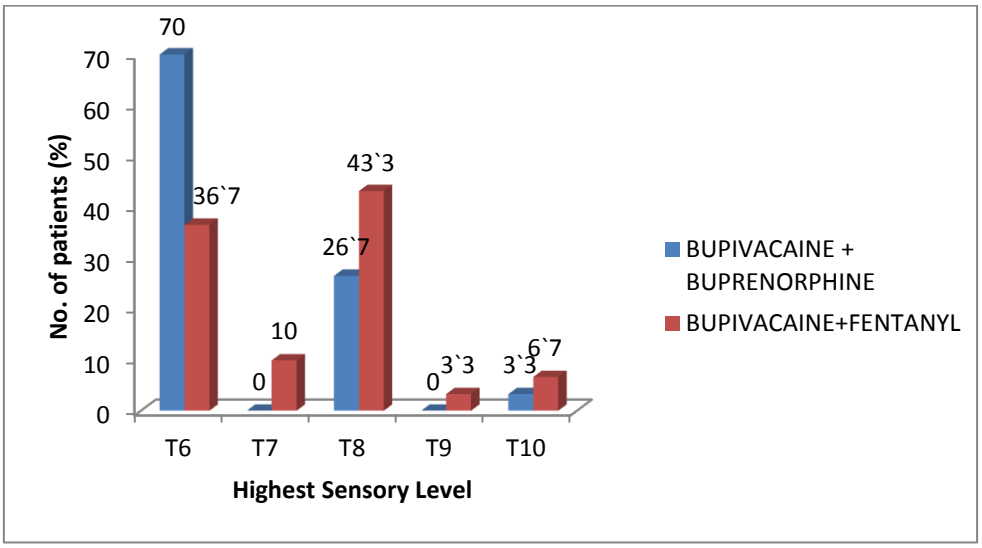
Basic variables	BUPIVACAINE + BUPRENORPHINE		BUPIVACAINE + FENTANYL		Mann Whitney U test	P value
	Mean	±SD	Mean	±SD		
Motor onset	6.07	1.363	5.70	1.119	U=382.000	P=0.301



The mean time for onset of motor block in group BB was 6.07±1.363 min. and in group BF was 5.70±1.119 min. There was no statistically significant difference in two groups with regard to onset of motor block.

Table 5: HIGHEST LEVEL OF SENSORY BLOCK

Highest Sensory Level	BUPIVACAINE + BUPRENORPHINE		BUPIVACAINE+ FENTANYL		Chi square test	P value
T6	21	70.0	11	36.7	X^2=8.469	P=0.0757
T7	0	0	3	10.0		
T8	8	26.7	13	43.3		
T9	0	0	1	3.3		
T10	1	3.3	2	6.7		
Total	30	100.0	30	100.0		
Insignicant						

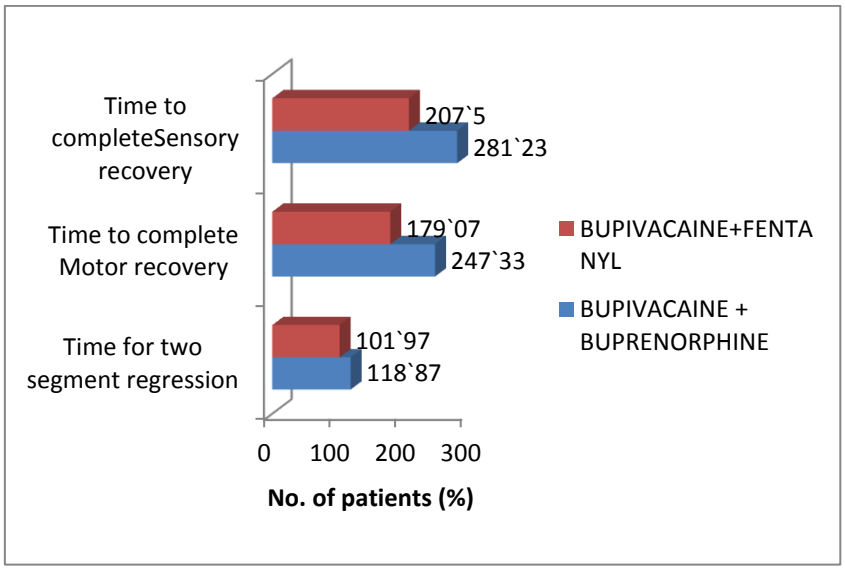


In our study the highest sensory level attained, patients in group BB 70% achieved T6 level, 26.7% achieved T8 level and 3.3% achieved T10 level.

In group BF 36.7% achieved T6 level, 10% achieved T7 level,43.3% achieved T8, 3.3% achieved T9 and 6.7% achieved T10. This implied that with regard to sensory level block there is no difference between the two groups.

Table 6: RECOVERY PARAMETERS

Basic variables	BUPIVACAINE + BUPRENORPHINE		BUPIVACAINE+ FENTANYL		Mann Whitney U test	P value
	Mean	±SD	Mean	±SD		
Time for two segment regression	118.87	6.996	101.97	7.972	U=42.000	P=0.001*
Time to complete Motor recovery	247.33	15.522	179.07	11.209	U=0.500	P=0.001*
Time to complete Sensory recovery	281.23	16.245	207.50	14.248	U=0.000	P=0.001*
*:Statistically significant						



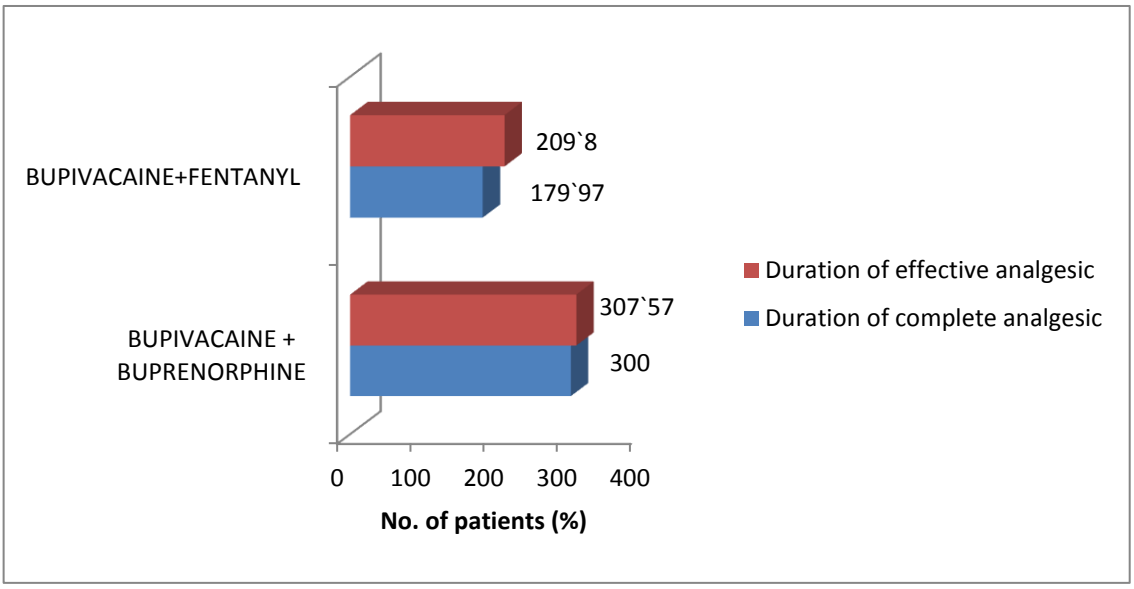
The time for two segment regression was considerably slower in group BB with 118.87±6.996 min compared to group BF which was 101.97±7.97 min. The difference was statistically significant.

The mean duration of motor block (time for complete motor recovery) in group BB was 247.33+15.522 min and in group BF was 179.07+11.209 min .There was statistically significant difference in duration of motor recovery.

The mean duration of sensory recovery in group BB was 281.23±16.24 min. and in group BF was 207.50±14.24 min. There was highly significant difference between two groups regarding sensory recovery.

Table -7: DURATION OF ANALGESIA

Basic variables	BUPIVACAINE + BUPRENORPHINE		BUPIVACAINE+ FENTANYL		Mann Whitney U test	P value
	Mean	±SD	Mean	±SD		
Duration of complete analgesic	300.00	17.019	179.97	19.595	U=0.000	P=0.001*
Duration of effective analgesic	307.57	12.244	209.80	25.185		
*:Statistically significant						

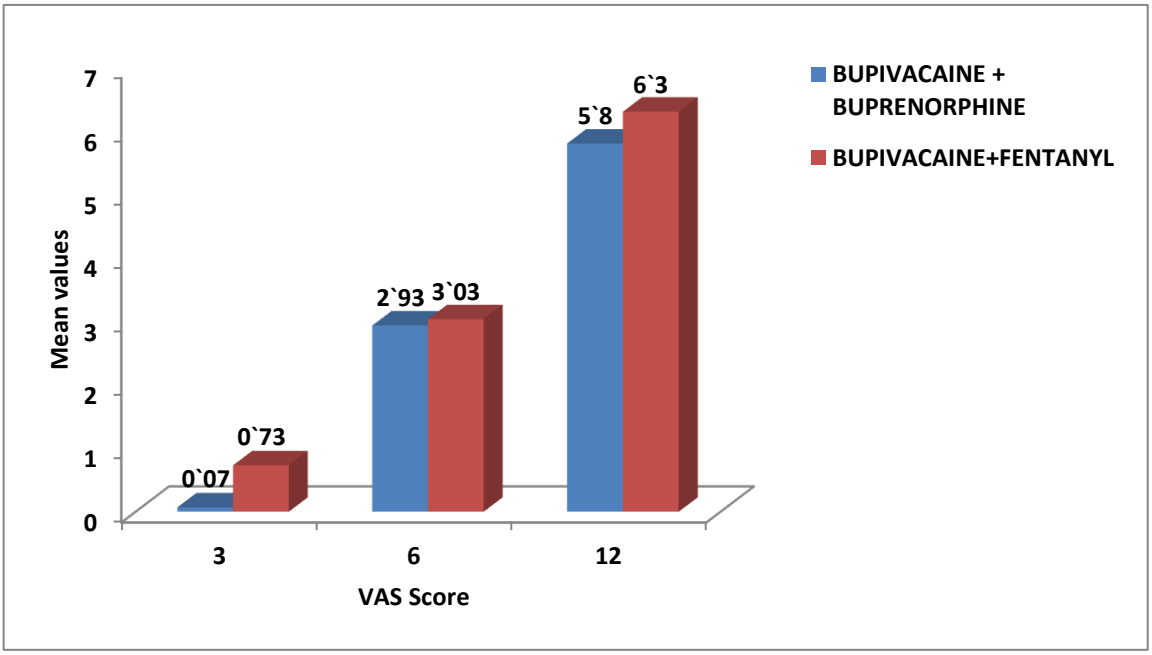


The mean duration of complete analgesia in group BB was 300 ±17.019 min and in group BD was 179.97±19.595 min.There was statistically significant difference in both groups with regards to duration of complete analgesia.

The mean duration of effective analgesia in group BB was 307.57 ±12.24 min. and in group BF was 209.80±25.18min.There is highly significant difference in between two groups with regard to effective analgesia.

Table: 8 Comparison of VAS Score between two groups

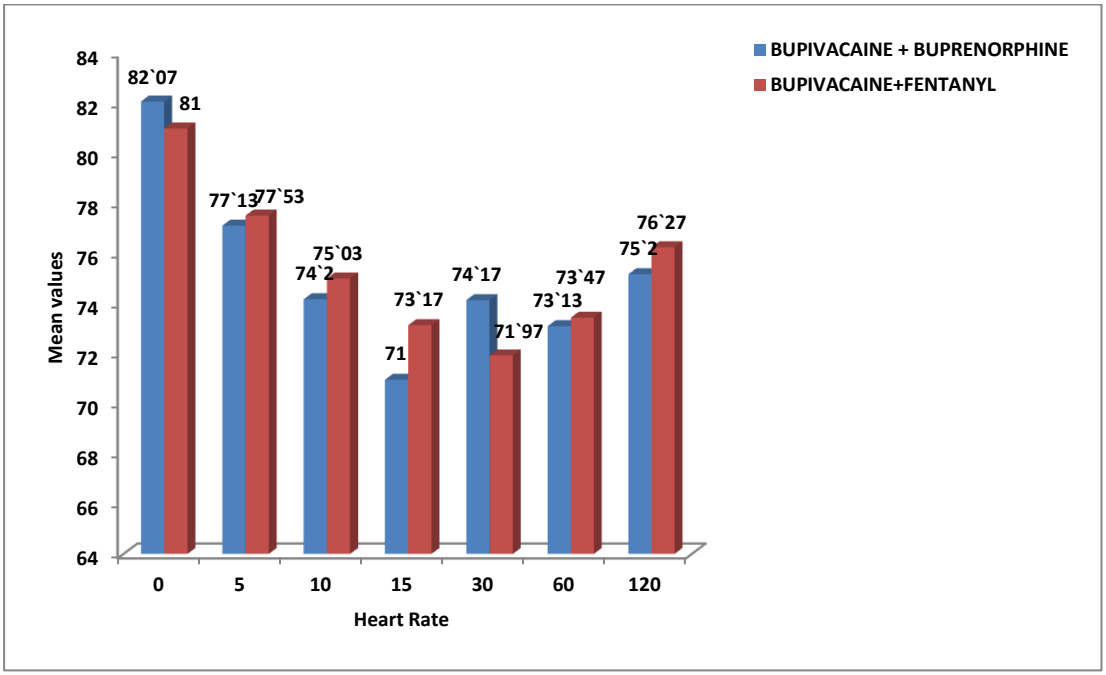
VAS Score	BUPIVACAINE + BUPRENORPHINE		BUPIVACAINE+ FENTANYL		Mann Whitney U test	P value
	Mean	±SD	Mean	±SD		
3	0.07	0.254	0.73	1.048	U=306.000	P=0.003*
6	2.93	1.413	3.03	0.890	U=-429.000	P=0.748
12	5.80	0.887	6.30	0.837	U=317.500	P=0.039*
*:Statistically significant						



VAS at the end of 3hrs in group BB 0.07±0.25 was and group BF was 0.73±1.04VAS at end of 6 hrs in group BB was2.93±1.43and group BF was3.03±0.89 .VAS at end of 12hrs in group BB was 5.80±0.887 and group BF was 6.30±0.837 .VAS were statistically significant at the end of 3hrs and 12 hrs showing patient in group BB(lower VAS) had better pain relief than group BF in postoperative period

Table:9 Comparison of Heart Rate (Min) between two groups

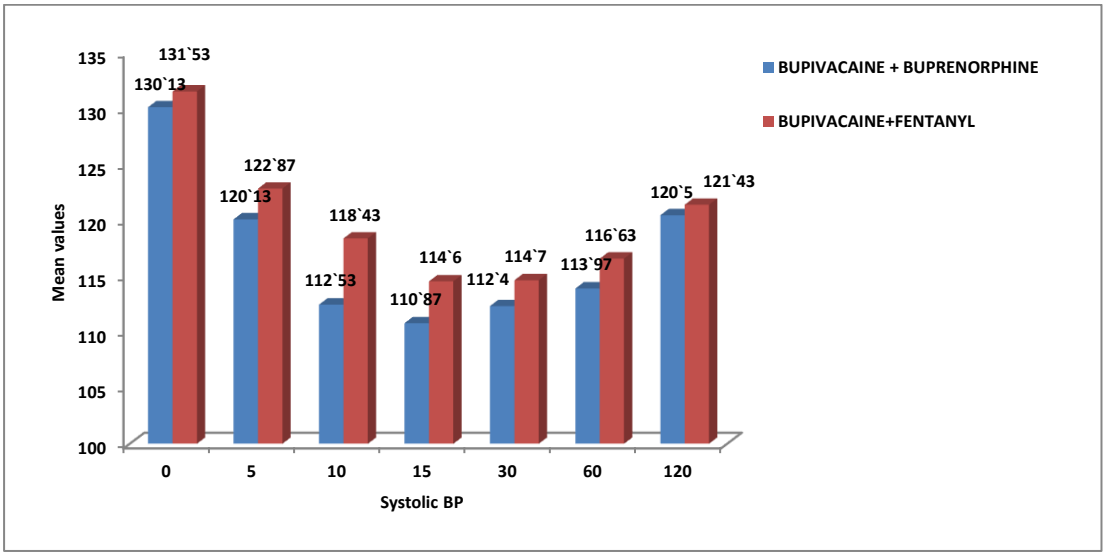
Heart Rate (Min)	BUPIVACAINE + BUPRENORPHINE		BUPIVACAINE+ FENTANYL		Mann Whitney U test	P value
	Mean	±SD	Mean	±SD		
0	82.07	7.455	81.00	11.453	U=445.000	P=0.940
5	77.13	8.673	77.53	10.553	U=435.000	P=0.823
10	74.20	7.355	75.03	8.876	U=414.000	P=0.592
15	71.00	7.456	73.17	10.124	U=386.000	P=0.341
30	74.17	5.534	71.97	8.298	U=311.000	P=0.038*
60	73.13	5.431	73.47	9.005	U=421.500	P=0.671
120	75.20	4.831	76.27	8.828	U=426.500	P=0.725
*:Statistically significant						



At any interval the two groups did not differ significantly with respect to heart rate. In group BB three patients had bradycardia which was treated by 0.6mg Atropine successfully. In group BF no incidence of bradycardia**.**

Table:10 Comparison of Systolic BP between two groups

Systolic BP min	BUPIVACAINE + BUPRENORPHINE		BUPIVACAINE+FENTANYL		Mann Whitney U test	P value
	Mean	±SD	Mean	±SD		
0	130.13	9.684	131.53	13.893	U=410.500	P=0.557
5	120.13	12.079	122.87	14.569	t=0.791	P=0.432
10	112.53	11.614	118.43	15.030	t=1.071	P=0.094
15	110.87	11.670	114.60	13.016	U=359.000	P=0.176
30	112.40	9.733	114.70	10.774	t=1.153	P=0.443
60	113.97	8.962	116.63	9.445	U=401.500	P=0.471
120	120.50	8.799	121.43	9.224	U=438.500	P=0.864
Insignificant						

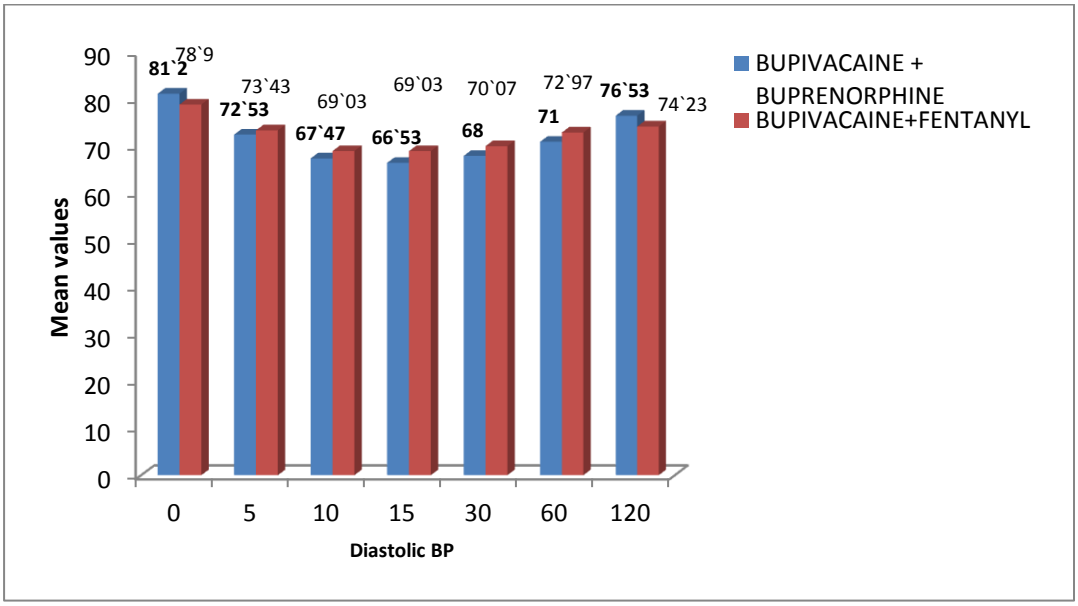


The mean SBP in group BB decreased from baseline 130mmHg to 120mmHg at 5 min,112mmHg at 10 min,110 mmHg at 15 min,112 mmHg at 30 min ,113mmHg at 60 min and which gradually increased to 120mmHg at the end of 120 min.

The mean SBP in group BF decreased from baseline 131 mmHg to 122 mmHg at 5 min, 118 mmHg at 10min, 114 mmHg at 15 min, 114 mmHg at 30 min, 116mmHg at 60 min and which gradually increased to 121 mmHg at the end of 120 min.

Table:11 Comparison of Diastolic BP between two groups

Diastolic BP min	BUPIVACAINE + BUPRENORPHINE		BUPIVACAINE+ FENTANYL		Mann Whitney U test	P value
	Mean	±SD	Mean	±SD		
0	81.20	7.941	78.90	7.932	U=397.000	P=0.427
5	72.53	8.386	73.43	6.694	t=-0.459	P=0.648
10	67.47	9.380	69.03	7.346	U=400.500	P=0.461
15	66.53	8.287	69.03	7.641	t=-1.215	P=0.229
30	68.00	7.066	70.07	6.812	U=1.153	P=0.254
60	71.00	4.449	72.97	6.014	U=332.500	P=0.076
120	76.53	4.424	74.23	6.786	t=1.555	P=0.125
Insignificant						

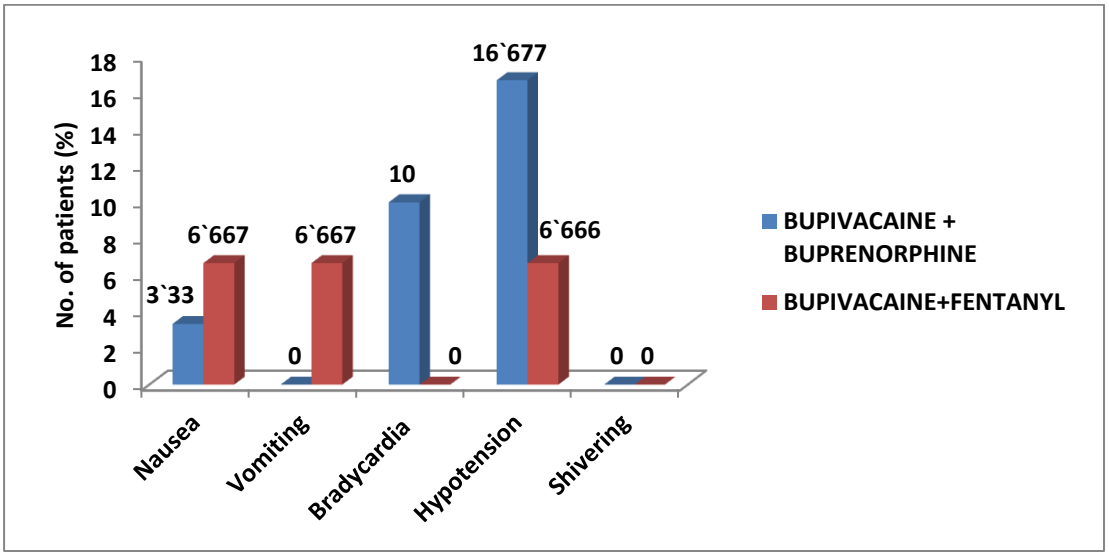


The mean baseline DBP in group BB was 81 mmHg which decreased to 72 mmHg at the end of 5 min, 67 mmHg at the end of 10 min,66 mmHg at the end of 15 min, after that BP started rising slowly from 68mmHg to 71 mmHg to 76mmHg at 30 min ,60 min and 120 min respectively.

The mean baseline DBP in group BF was 78 mmHg which decreased to73 mmHg at the end of 5 min, 69 mmHg at the end of 10 min,69 mmHg at the end of 15 min, after that BP started rising slowly from 70mmHg to 72mmHg to 74mmHg at 30 min ,60 min and 120 min respectively.

Table 12 :Distribution of patients according to Side Effect in two groups

Adverse effect	BUPIVACAINE + BUPRENORPHINE		BUPIVACAINE+FENTANYL		Chi square test	P value
Nausea	1	3.33	2	6.667	X^2=0.000	P=1.00
Vomiting	0	0	2	6.667		
Bradycardia	3	10	0	0		
Hypotension	5	16.677	2	6.666		
Shivering	0	0	0	0		
Total	9	100.0	6	100.0		
Insignificant						



In BB group 3.3% patients had nausea, 10% patients had bradycardia, 16% patients had hypotension.

In BF group 6.66% patients had nausea, 6.66% had vomiting , 6.66% patients had hypotension

DISCUSSION

"Spinal anaesthesia is the gold standard for lower abdominal surgeries. It has got the advantage of being, cost-effective, easy administration technique, rapid onset of action, with relatively less adverse effects and most importantly patient remaining aroused throughout the procedure . But at times short duration and uncomfortable postoperative period offset the above advantages. Therefore, in order to extend the intraoperative analgesia into postoperative period, following spinal anaesthesia, various spinal adjuvants like morphine, buprenorphine and fentanyl, clonidine, ketamine are being used in anaesthetic practice"[5].

" Opioid added to local anaesthetic for spinal anaesthesia was first introduced into clinical practice in 1979. Neuraxial administration of opioids along with local anaesthetics improves the quality of intraoperative analgesia and also provides postoperative pain relief for longer duration"[17]

Spinal opioids and local anaesthetics have been shown to act synergistically at the spinal level in animal studies[59]. The advantage of combining the two types of agents in this manner is thought to be explained by their different analgesic properties and their ability to block pain at two different sites. Opioids produce analgesia by specifically binding and activating the opiate receptors in the substantia gelatinosa, whereas local anaesthetics provide analgesia by blocking impulse transmission at the nerve roots and dorsal root ganglia[68]

Fentanyl , a lipophilic opiod agonist when used as an adjuvant prolongs the duration of spinal anaesthesia . Fentanyl is a lipophilic μ-receptor agonist opioid . Intrathecally , fentanyl exerts its effect by combining with opioid receptor in the dorsal horn of spinal cord and may have supra-spinal spread and action. Buprenorphine is a mixed agonist-antagonist type of opioid with a long duration . The

high lipid soluability , high affinity for opioid receptors end prolonged duration of action makes buprenorphine a suitable choice for intrathecal and peripheral nerve site administration . Therefore , the present study was performed to compare fentanyl and buphrenorphine in their efficacy as adjuvents to spinal anaesthesia[13] .

The aim of this study is to compare the efficacy of buprenorphine and fentanyl as adjuvants to bupivacaine for lower limb and lower abdominal surgeries consisting of 60 patients with ASA 1 and 2 aged between 18-60 yrs posted for lower abdominal and lower limb surgeries.

Group BBreceived 0.5% hyperbaric bupivacaine 3ml + 60µg buprenorphine

Group BFreceived 0.5% hyperbaric bupivacaine 3ml +25µg fentanyl.

The following parameters were observed:

1. **Sensory and motor blockade–**Onset and Highest level of sensory blockade.
2. **Recovery parameters**- Time for two segment regression and Time for complete sensory and motor recovery.
3. **Analgesia Duration of complete analgesia, effective analgesia and Quality of analgesia.**
4. **Adverse effects**

DEMOGRAPHIC PROFILE ACROSS THE GROUP :

In our study ,in both the groups majority of patients were middle aged . The mean weight and the height,sex were identical in both groups. The type of surgeries performed were also identical in either groups .To avoid variations in intraoperative and postoperative results of patients these parameters were kept identical in both the group .

ONSET OF SENSORY AND MOTOR BLOCKADE:

In our study, The mean time for onset of sensory block in group BB was 3.27±0.980 minutes and in group BF was 3.23±0.728 min.

The mean time for onset of motor block in group BB was 6.07±1.363 min. and in group BF was 5.70±1.119 min. There was no statistically significant difference in two groups with regard to onset of sensory and motor block. Our study correlate with following studies .

Bhukya N , Madhavi ,KalyanamP et al[13]conducted a study on 100 patients to evaluate the effect between buprenorphine and fentanyl as intrathecal adjuvant to bupivacaine and concluded that there was statistically no significant difference with onset of sensory between two groups while the onset of motor block was higher in group fentanyl and was statistically significant with a p value of < 0.001 which did not match with my study .

Rashmi Pal , K.K.Arora , N.S.Doneria et al[24]conducted study on about 90 patient to evaluate the effect of adding clonidine, fentanyl and buprenorphine to intrathecal bupivacaine on spinal block and concluded that there was statistically no significant difference with onset of sensory and motor blockade in between two groups.

HIGHEST SENSORY LEVEL BLOCKADE:

In our study the highest sensory level attained, patients in group BB 70% achieved T6 level, 26.7% achieved T8 level, 3.3% achieved T10level .

In group BF 36.7% achieved T6 level, 10% achieved T7 level,43.3% achieved T8, 3.3% achieved T9 and 6.7% achieved T10. This implied that with regard to sensory level block there is no difference between the two groups.

Gajanan Chavan, Aparna Chavan et[25] in their study concluded that the peak sensory level was T6(T4-T10) in Buprenorphine group and T6(T3-T8) in fentanyl group, without significant difference between the group.

F A Khan et al[19] found that the time taken to achieve maximum sensory level in fentanyl group(fentanyl 10 microgram with hyperbaric bupivacaine 0.75% 2ml) which was significantly faster compared to the buprenorphine group (buprenorphine 30microgram with hyperbaric bupivacaine 0.75% 2 ml) which did not match with our study wherein the mean time to reach highest sensory level was comparable in both the groups.

Our result correlates with above mentioned studies. Hence we conclude that sensory level block achieved by addition of buprenorphine and fentanyl to intrathecal hyperbaric bupivacaine is same.

TIME FOR TWO SEGMENT REGRESSION:

RECOVERY PARAMETERS-The time of two segment regression was considerably slower in group BB with 118.8±6.99 min compared to group BF which was 101.97±7.972 min.Which was statistically significant.

Bhukya N , Madhavi ,KalyanamP et al [13]conducted a study on 100 patients to evaluate the effect between buprenorphine and fentanyl as intrathecal adjuvant to bupivacaine and concluded that time for two segment regression from highest sensory level in buprenorphine group was slower 226±41.83 min compared to fentanyl group 187±8.142 min which was statistically significant($p<0.001$).

Rashmi Pal , K.K.Arora , N.S.Doneria et al[24]conducted study on about 90 patient to evaluate the effect of adding clonidine, fentanyl and buprenorphine to intrathecal bupivacaine on spinal block and concluded that time for two segment

regression from highest sensory level in buprenorphine group was slower 267±30.18 min compared to fentanyl group 174.33±23.44 min which was statistically significant($p<0.001$).

Our study correlates with above mentioned study. Hence we conclude that block regression was significantly slower by addition of buphrenorphine intrathecally as compared to intrathecal fentanyl.

TIME FOR COMPLETE SENSORY RECOVERY:

The mean duration of sensory block (time for complete sensory recovery) in group BB was 281.23+16.245 min and in group BF was 207.50+14.248 min .There was statistically significant difference in duration of sensory recovery.

Bhukya N , Madhavi ,KalyanamP et al [13]conducted a study on 100 patients to evaluate the effect between buprenorphine and fentanyl as intrathecal adjuvant to bupivacaine and concluded that time for complete sensory recovery in buprenorphine group was slower compared to fentanyl group .

Rashmi Pal , K.K.Arora , N.S.Doneria et al[24]conducted study on about 90 patient to evaluate the effect of adding clonidine, fentanyl and buprenorphine to intrathecal bupivacaine on spinal block and concluded that time for complete sensory recovery in buprenorphine group was slower compared to fentanyl group .

Our study result correlates with above mentioned studies, we concluded that addition of buprenorphine to hyperbaric bupivacaine intrathecally prolongs the sensory blockade as compared to intrathecal fentanyl with hyper baric bupivacaine.

TIME TO COMPLETE MOTOR RECOVERY:

The mean duration of motor recovery in group BB was 247.33±15.522 min. and in group BFwas179.07 ±11.209min. There was significant difference between two groups regarding motor recovery.

Rashmi Pal, K. K. Arora et al[24] in a study titled "Intrathecal Buprenorphine, Clonidine And Fentanyl As Adjuvants To 0.5% Hyperbaric Bupivacaine In Lower Abdominal And Lower Limb Surgeries: A Prospective, Randomized And Comparative Study" found that the mean duration of motor blockade in fentanyl group who received 3.0ml of 0.5% hyperbaric bupivacaine +25µg fentanyl to be 151.27±12.0 minutes and that in buprenorphine group who received 3.0ml of bupivacaine heavy 0.5% + buprenorphine 75µg (0.25ml) to be 222.66±24.3 minutes in which it was significantly prolonged , which is in accordance with our study.

Bhukya N , Madhavi ,KalyanamP et al [13]conducted a study on 100 patients to evaluate the effect between buprenorphine and fentanyl as intrathecal adjuvant to bupivacaine and concluded that time for complete motor recovery in buprenorphine group was slower 205±37.718 compared to fentanyl group 159.2±8.311

Our study result correlates with the above mentioned study. Hence we conclude that addition of buprenorphine to hyperbaric bupivacaine intrathecally prolongs the motor blockade compared to addition of fentanyl intrathecally.

DURATION OF ANALGESIA:

The mean duration of complete analgesia in group BB300.0±17.019 min.and in group BF was179.97 ±19.595min.

There was statistically significant difference in both groups with regards to duration of complete analgesia.

The mean duration of effective analgesia in group BB was 307.57±12.244 min. and in group BF was 209.80±25.185 min.

There was statistically significant difference in between two groups with regard to effective analgesia .

Bhukya N , Madhavi ,KalyanamP et al [13]conducted a study on 100 patients to evaluate the effect between buprenorphine and fentanyl as intrathecal adjuvant to bupivacaine and concluded that time to first of analgesia in buprenorphine group was 292±35 min as compared to fentanyl group which was 169 ±10.69 min.

Rashmi Pal , K.K.Arora , N.S.Doneria et al[24]conducted study on about 90 patient to evaluate the effect of adding clonidine, fentanyl and buprenorphine to intrathecal bupivacaine on spinal block and concluded that time to first request of analgesia in bupivacaine group was 294±17.93 min compared to fentanyl group which was 195.83±7.30 min

Our results correlates with above mentioned study hence we concluded that intrathecal buprenorphine has longer duration of analgesia than intrathecal fentanyl .

POSTOPRATIVE ANALGESIA:

At the end of 3 hour VAS in group BB was 0.07±0.254 and0.73 ±1.048 in group BF.VAS at end of 6 hours in group BB was2.93 ±1.413 and in group BF was 3.03±0.890.VAS at the end of 12 hours in group BB was 5.80±0.887 and 6.30±0.837 in group BF.VAS was statistically significant at the end of 3hous and 12 hours implying patient in group BB had better pain relief (lower VAS) in post operative period than group BF

Bhukya N , Madhavi ,KalyanamP et al [13]conducted a study on 100 patients to evaluate the effect between buprenorphine and fentanyl as intrathecal adjuvant to

bupivacaine and concluded that VAS score was less in buprenorphine group compared to fentanyl group at 6hour ,12hour and 18 hour which was statistically significant.

Rashmi Pal , K.K.Arora , N.S.Doneria et al[24]conducted study on about 90 patient to evaluate the effect of adding clonidine, fentanyl and buprenorphine to intrathecal bupivacaine on spinal block and concludedthat VAS score was less in buprenorphine group compared to fentanyl group which was statistically significant.

Our study results correlate with above mentioned studies. Hence we conclude that addition of buprenorphine to bupivacaine intrathecally results in significant prolonged duration of complete analgesia, effective analgesia and time to first pain medication is longer with improved quality of analgesia and reduced requirements of analgesics postoperatively as compared to intrathecal fentanyl.

VITAL PARAMETERS::

HAEMODYNAMICS-HEART RATE:

At any interval the two groups did not differ significantly with respect to heart rate. In group BB three patients had bradycardia which was treated by 0.6mg Atropine successfully. In group BF no incidence of bradycardia .

Bhukya N , Madhavi ,KalyanamP et al [13]conducted a study on 100 patients to evaluate the effect between buprenorphine and fentanyl as intrathecal adjuvant to bupivacaine and concluded that in their study six patients developed bradycardia in buprenorphine group and no patient developed bradycardia in fentanyl group .

Rashmi Pal , K.K.Arora , N.S.Doneria et al[24]conducted study on about 90 patient to evaluate the effect of adding clonidine, fentanyl and buprenorphine to intrathecal bupivacaine on spinal block and concluded no significant variation in the

hemodynamics between fentanyl group (25microgram) and buprenorphine group (75microgram) which is similar to our study.

Our result correlates with the above mentioned study. Hence we conclude that there is no difference in heart rate in buprenorphine group and fentanyl group.

BLOOD PRESSURE:

The mean SBP in group BF decreased from baseline 130mmHg to 122mmHg at 5 min,118mmHg at 10 min,116 mmHg at 15 min,114 mmHg at 30 min ,116mmHg at 60 min and which gradually increased to 121mmHg at the end of 120 min.

The mean SBP in group BB decreased from baseline 130 mmHg to 120 mmHg at 5 min, 112mmHg at 10min, 110 mmHg at 15 min, 112 mmHg at 30 min, 113mmHg at 60 min and which gradually increased to 120 mmHg at the end of 120 min.

The mean baseline DBP in group BF was 78 mmHg which decreased to 73 mmHg at the end of 5 min, 69 mmHg at the end of 10 min,69 mmHg at the end of 15 min, after that BP started rising slowly from 70mmHg to 72 mmHg to 74mmHg at 30 min ,60 min and 120 min respectively.

The mean baseline DBP in group BB was 81 mmHg which decreased to 72 mmHg at the end of 5 min, 67 mmHg at the end of 10 min,66 mmHg at the end of 15 min, after that BP started rising slowly from 68mmHg to 71 mmHg to 76mmHg at 30 min ,60 min and 120 min respectively

F A Khan et al[19] in a study titled " Comparison of Intrathecal Fentanyl and Buprenorphine in Urological Surgery" noted no significant difference in the hemodynamic variables like heart rate, blood pressure, respiratory rate between fentanyl group (10microgram) and buprenorphine group (30microgram). This is in accordance with our study.

Rashmi Pal , K.K.Arora , N.S.Doneria et al[24]conducted study on about 90 patient to evaluate the effect of adding clonidine, fentanyl and buprenorphine to intrathecal bupivacaine on spinal block and concluded no significant variation in the hemodynamics between fentanyl group (25microgram) and buprenorphine group (75microgram) which is similar to our study.

In our study there is no significant difference with respect to change in mean systolic blood pressure in both the groups. But with regard to DBP there is statistical significant difference in reduction of mean DBP but not clinically (to become clinically significant, reduction in BP should be more than 20% of baseline) .

CONCLUSION

On the basis of the present clinical comparative study, we can conclude that the addition of 60µg buprenorphine to hyperbaric Bupivacaine for spinal anaesthesia appears to be an attractive alternative as compared to 25µg Fentanyl. It provides longer duration of both sensory and motor blockade, good quality of both Intraoperative and postoperative analgesia with minimal side effects and better hemodynamic stability.

SUMMARY

We performed this prospective randomized study titled with "**A COMPARATIVE STUDY OF INTRATHECAL HYPERBARIC BUPIVACAINE 0.5% WITH FENTANYL VERSUS HYPERBARIC BUPIVACAINE 0.5% WITH BUPRENORPHINE INLOWER LIMB AND LOWER ABDOMINAL SURGERIES"** to assess the impacts of addition of Buprenorphine to hyperbaric- Bupivacaine versus Fentanyl to hyperbaric-Bupivacaine with respect to onset and duration of sensory and motor blockade, duration and quality of analgesia and adverse effects. 60 patients with the age group of 18 to 60 yr and ASA grade 1-2 posted for elective lower limb, lower abdominal urological surgeries were assigned randomly into two groups .

- Group "BB"-0.5% hyperbaric Bupivacaine 3ml + 60µg Buprenorphine
- Group "BF"-0.5% hyperbaric Bupivacaine 15 mg + 25µg Fentanyl

Demographic profile: Both groups were similar in terms of age, sex, height and ASA grading and undergone similar surgical procedures.

Sensory and motor blockade: We observed that in both the groups no statistically significant difference with respect to onset and highest level of sensory and motor blockade.

Recovery parameters: Group **BB** showed prolonged duration for two segmental regression which is 118 min. and in **BF** group 101 min. Time required for full sensory recovery by **BB** group was prolonged 281 min thangroup **BF** 207 min. **BB** group showed prolonged motor recovery 247min compared to **BF** group 179 min.

Analgesia: We found that duration of complete analgesia in **BB** group was 300 min. and **BF** group showed 179 min. Effective analgesia of group **BB** was307 min and

group **BF** was 209 min. In **BB** group time for first request of post-operative analgesia was significantly delayed thus reduced need of immediate post-operative analgesics. As the VAS was lesser in **BB** group indicating better quality of analgesia than group **BF**.

Side effects: Group **BB** had more hypotension and bradycardia .Group **BF** had nausea and vomiting.

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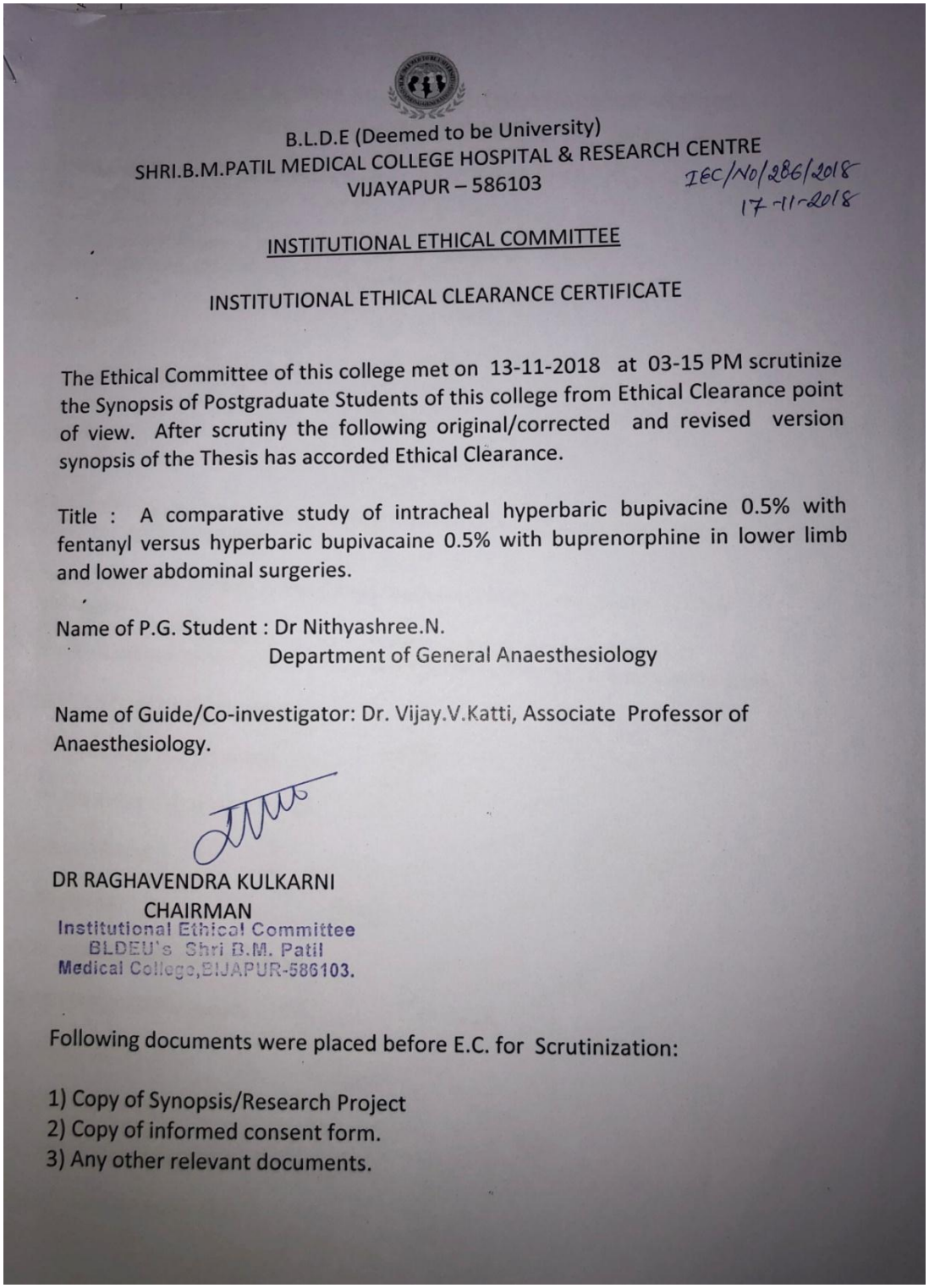
ANNEXURE-I

ETHICAL COMMITTEE CLEARANCE



B.L.D.E (Deemed to be University)
SHRI.B.M.PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE
VIJAYAPUR – 586103

IEC/No/286/2018
17-11-2018

INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 13-11-2018 at 03-15 PM scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.

Title : A comparative study of intracheal hyperbaric bupivacine 0.5% with fentanyl versus hyperbaric bupivacaine 0.5% with buprenorphine in lower limb and lower abdominal surgeries.

Name of P.G. Student : Dr Nithyashree.N.
Department of General Anaesthesiology

Name of Guide/Co-investigator: Dr. Vijay.V.Katti, Associate Professor of Anaesthesiology.

DR RAGHAVENDRA KULKARNI
CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College,BIJAPUR-586103.

Following documents were placed before E.C. for Scrutinization:

1) Copy of Synopsis/Research Project
2) Copy of informed consent form.
3) Any other relevant documents.

ANNEXURE-II

CONSENT FORM

STUDY SUBJECT CONSENT STATEMENT:

I confirm that **Dr NITHYASHREE,N** has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project.

_____ _____

(Participant) Date

_____ _____

(Witness to above signature) Date

ANNEXURE-III

PROFORMA

PROFORMA

Patient name - Date -

Address-

I.P. number -

Age - Sex - Male/Female Weight –

Height –

Diagnosis -

Proposed Surgery -

ASA - Consent -

Medical and surgical history -

Examination in brief -:

General Physical

Examination

Vitals -: Pulse-

Respiratory rate: B.P. - Airway assessment -

Systemic examination -:

R.S. - C.V.S. -

C.N.S. - P/A -

PREOPERATIVE INVESTIGATIONS -:

Hb -

TLC/DLC -

Platelet count - BT/CT -

RBS - mg/dl

Blood Urea :

Serum Creatinine :

Chest x ray if required :

ECG:

Other investigations:

Monitors Attached:

Pulse :

B.P.:

SpO2:

ECG:

PARAMETERS OBSERVED INTRA-OP:

Onset time of sensory blockade: (Min)

Onset time of motor blockade: (Min)

Duration of sensory blockade: (Min)

Duration of motor blockade: (Min)

Duration of Analgesia : (Min)

Quality of blockade:

Side effects: Nausea[ ] / vomiting[ ]

Bradycardia [ ]/hypotension[ ]

Shivering [ ]

MONITORING

Time	PulseRate Permin	B.P (mmHg)	Res.Rate/ min	SpO_2 %
0min				
5min				
10 min				
15min				
30 min				
60 min				
120				

Time of first rescue analgesia will be noted.

Study ends when patient demands for analgesic in postoperative period.

MASTER CHART

BUPIVACAINE+FENTANYL GROUP -BF

GROUP	NAME	AGE	SEX	HEIGHT	WEIGHT	SENCORY ONSET	MOTOR ONSET	HEGHEST SENSORY LEVEL	VAS intra op	Quality of intra op analgesia	Time for two segment regression	Motor recovery	Sensory recovery	Duration of complete analgesic	Duration of effective analgesic	Heart Rate (min)							Systolic							Diastolic BP							VAS Post op (hrs)		
																0	5	10	15	30	60	120	0	5	10	15	30	60	120	0	5	10	15	30	60	120	3	6	12
BF	SIDAPPA	21	M	6	69	3	4	T10	0	4	100	185	210	160	210	82	72	68	62	58	58	70	148	142	138	120	122	130	132	92	90	88	78	80	82	80	3	3	6
BF	UMESH	44	M	5`7	68	2	5	T10	0	3	95	180	200	150	200	60	64	62	58	60	62	64	150	148	145	146	138	140	132	80	74	70	72	68	75	80	2	3	6
BF	Bifani	22	F	5`2	51	4	6	T6	0	4	110	170	190	200	200	60	60	58	56	60	60	64	148	140	130	120	110	124	126	72	75	65	62	60	70	72	2	2	5
BF	DASTAGEER	52	M	5`4	57	4	5	T8	0	4	110	190	225	190	240	84	80	88	88	86	88	82	134	124	120	118	120	122	126	80	76	78	77	81	80	80	0	5	8
BF	VISHAL	52	M	5	43	2	5	T8	0	3	106	182	220	180	190	84`	86	74	70	70	70	80	148	150	142	130	120	126	124	84	80	78	64	68	72	76	2	3	5
BF	THIMAPPA	35	M	5	51	4	6	T8	0	4	100	170	205	170	160	76	72	66	64	64	64	70	142	126	124	128	120	122	130	82	74	76	74	70	78	80	0	3	6
BF	MADAYYA	38	M	5`6	59	4,	6	T6	0	4	102	182	210	150	200	80	82	78	66	70	72	76	140	130	122	118	124	110	130	80	78	62	68	70	80	84	2	5	7
BF	MEENAKSHI	44	F	5`4	57	3	5	T6	0	3	110	185	215	180	210	62	60	58	58	66	66	64	146	140	138	140	142	134	140	89	80	78	80	84	80	88	2	4	7
BF	SHIVAJI	29	M	5	44	3	5	T8	0	4	120	210	240	170	190	80	84	84	92	100	104	107	100	100	130	122	126	127	112	70	68	70	78	73	76	77	2	3	6
BF	CHANDRASHEKAR	36	M	5`8	58	2	4	T6	0	3	100	184	210	180	210	70	70	72	74	76	74	80	130	116	110	104	120	121	110	70	68	66	54	70	72	72	2	4	6
BF	SHRUTHI	23	F	5`4	56	3	4	T6	0	4	106	170	205	175	230	120	106	82	100	88	90	94	130	102	108	106	104	104	107	80	60	72	80	60	62	60	1	2	5
BF	GURUBASAPPA	42	M	5..6	51	3	6	T9	0	4	96	185	225	200	210	75	68	71	73	70	70	78	126	116	128	122	122	110	120	90	80	70	80	84	80	82	0	3	6
BF	KASTURI	35	F	5`4	60	3	5	T8	0	4	106	180	200	200	240	72	76	80	80	72	76	72	130	121	108	106	110	108	140	82	68	62	64	64	66	58	3	3	7
BF	MALAKAPPA	58	M	5`7	51	2	4	T6	0	3	80	150	175	210	250	76	70	80	84	74	76	82	100	98	90	104	108	110	112	60	62	60	70	72	78	80	0	5	6
BF	JAGDEESH	41	M	6	74	4	6	T8	0	3	84	160	180	190	240	80	76	74	70	76	80	84	140	128	126	122	120	118	110	80	76	72	70	68	60	66	0	4	7
BF	NEELAWWA	27	F	5`4	67	4	7	T8	0	4	95	194	210	200	230	84	80	84	80	70	72	78	126	116	96	120	124	128	126	80	74	70	72	76	74	76	1	3	8
BF	KASHIBAI	32	F	5`2	45	3	5	T8	0	4	100	180	220	210	240	87	88	90	80	74	74	72	124	110	112	116	110	120	128	74	70	68	74	70	78	70	0	3	5
BF	RAMCHANDRA	32	M	5`1	51	3	6	T6	0	4	110	190	225	195	180	88	70	70	72	72	74	80	130	124	126	110	116	112	124	80	82	78	74	76	80	74	0	3	6
BF	HANAMAPPA	35	M	5`2	72	4	8	T6	0	4	105	175	200	190	160	90	80	82	74	72	72	74	128	130	118	110	98	108	110	84	70	58	60	64	72	80	0	3	7
BF	PATHIMA	47	F	5`3	55	3	6	T8	0	4	100	170	190	170	240	100	102	88	80	76	80	82	120	112	100	90	102	110	118	70	72	60	62	66	70	74	0	3	7
BF	MALLIKARJUN	50	M	5`4	57	4	7	T6	0	3	100	180	210	150	230	80	76	70	72	72	74	80	150	140	146	120	122	108	110	90	82	70	72	76	70	80	0	2	6
BF	NAMRATA	23	F	5`5	64	3	6	T6	0	4	95	175	200	160	190	84	80	82	80	74	78	80	110	100	102	90	98	106	118	72	70	58	56	68	70	68	0	3	7
BF	GOPAL	44	M	5`8	59	4	7	T6	1	3	108	170	205	156	200	80	82	70	68	66	68	70	122	116	112	114	100	106	112	70	76	72	70	74	78	72	0	2	6
BF	MALLIKARJUN	23	M	5`3	61	3	5	T8	0	3	100	180	210	183	210	78	74	70	70	74	74	70	130	120	116	122	110	114	116	80	70	72	66	64	70	74	0	2	6
BF	RAJKUMAR	60	M	5`4	48	4	6	T8	0	4	106	175	200	190	180	90	70	72	64	70	70	74	110	102	96	98	100	104	110	68	60	56	58	60	64	68	0	3	6
BF	DEVAKAMMA	59	F	5	52	3	5	T8	0	4	105	195	225	170	174	80	70	70	74	70	70	76	144	130	122	106	110	118	120	86	76	70	72	68	76	74	0	2	7
BF	PRADEEP	19	M	5`8	62	4	7	T7	1	3	100	175	195	200	230	90	92	80	82	72	74	74	128	116	100	96	110	117	120	90	70	70	72	66	72	68	0	2	7
BF	AMOGHI	45	M	5`1	49	3	5	T7	0	4	110	185	210	210	240	80	82	76	68	65	68	70	130	120	122	124	110	118	126	70	72	60	58	62	70	68	0	2	5
BF	DEVENDRA	40	M	5`8	65	2	7	T8	1	4	105	170	195	150	200	78	72	64	66	72	74	70	140	136	110	106	112	118	130	86	80	70	74	76	72	76	0	3	7
BF	SAHEBGOWDA	33	M	5`7	70	4	8	T7	0	3	95	175	220	160	210	80	82	88	70	70	72	71	142	133	116	110	113	106	124	76	70	72	60	64	62	70	0	3	6

MASTER CHART
BUPIVACAINE + BUPRENORPHINE GROUP - BB

GROUP	NAME	AGE	SEX	HEIGHT	WEIGHT	SENSORY ONSET	MOTOR ONSET	HIGHEST SENSORY LEVEL	VAS intra op	Quality of intra op analgesia	Time for two segment regression	Motor recovery	Sensory recovery	Duration of complete analgesic	Duration of effective analgesic	Heart Rate (min)							Systolic							Diastolic BP							VAS Post op (hrs)			TIME FOR FIRST RESCUE ANALGESIA
																0	5	10	15	30	60	120	0	5	10	15	30	60	120	0	5	10	15	30	60	120	3	6	12	
BB	SHRIKANTH	30	M	5`6	57	3	4	T6	0	4	135	250	290	300	310	74	70	70	62	72	72	78	124	110	100	98	96	100	110	80	64	50	60	72	70	72	0	4	5	310
BB	BASALINGAMMA	50	F	5`5	60	4	6	T6	0	4	120	240	260	270	300	80	76	74	80	80	79	74	118	106	94	102	108	101	100	80	60	58	60	62	68	70	1	5	5	300
BB	RISHIKESH	32	M	5`8	65	2	4	T6	0	4	130	260	280	300	320	90	80	70	72	70	70	78	130	124	122	120	110	112	130	90	72	74	80	74	80	82	0	5	5	320
BB	IRAPPA	33	M	6	70	4	7	T8	0	4	127	220	240	340	300	100	96	90	85	76	76	80	136	120	122	120	124	118	122	90	80	78	80	80	76	78	0	4	6	325
BB	DUNDAPPA	44	M	5`9	64	3	5	T6	0	4	125	260	300	330	310	74	64	65	62	61	61	68	118	104	100	96	98	100	110	70	62	60	62	58	64	70	0	5	5	330
BB	SHIVAPPA	60	M	5`4	56	2	4	T6	0	4	120	210	260	260	270	84	82	85	77	78	78	80	136	130	124	120	132	126	130	78	76	80	70	70	74	80	0	5	7	280
BB	JATTEPA	46	M	5`4	52	4	5	T8	0	3	125	270	305	300	320	80	72	74	70	70	70	70	130	120	112	106	116	120	126	80	64	60	68	66	72	80	1	4	6	320
BB	SHARANAPPA	50	M	5`8	60	4	7	T8	0	3	117	250	270	280	290	80	78	82	80	76	76	74	130	122	120	126	110	112	124	80	72	80	70	80	68	74	0	5	6	292
BB	RAVINDRA	23	M	5`5	54	3	8	T8	0	4	118	235	285	310	320	78	70	80	70	76	76	78	130	106	108	110	110	108	112	70	60	56	60	72	70	80	0	4	6	320
BB	ASLAM	20	M	6	70	5	7	T6	0	3	110	240	260	275	290	78	80	72	60	72	70	80	120	106	104	100	108	110	112	70	72	60	50	64	68	80	0	4	6	295
BB	RAMESH	22	M	5	48	2	5	T8	0	3	108	220	260	290	300	80	86	70	72	67	66	70	130	132	110	104	100	110	118	70	70	60	70	60	64	78	0	3	7	310
BB	LAXMAN	32	M	5`4	60	5	8	T8	0	4	120	250	280	300	310	78	70	72	62	70	68	80	120	108	110	110	114	110	108	70	72	68	64	66	70	72	0	2	7	310
BB	SAINATH	52	M	5`5	54	3	6	T6	0	4	120	245	275	290	310	78	70	68	70	72	70	76	118	112	102	100	102	116	120	72	68	50	54	58	70	74	0	4	5	320
BB	MUTHAWWA	30	F	5	46	3	5	T6	0	3	120	230	300	310	320	74	72	72	68	63	62	70	110	102	100	102	100	98	110	74	68	64	64	60	72	78	0	2	7	325
BB	MEENA	23	F	5`2	50	4	6	T6	0	4	115	260	290	308	314	98	70	68	64	79	78	70	120	122	100	96	106	110	116	80	60	64	62	70	70	80	0	4	6	320
BB	GANGADHAR	20	M	5`8	66	2	4	T6	0	4	110	280	308	320	322	70	74	80	84	79	78	80	134	120	110	108	110	112	122	90	70	60	56	62	70	74	0	2	4	330
BB	VITHOBA	26	F	5`4	48	3	5	T6	0	4	120	240	270	290	295	90	80	74	68	72	70	74	134	110	108	110	114	120	130	80	70	58	62	60	68	80	0	1	6	300
BB	AYYAPPA GOWDA	50	M	5`8	60	3	5	T6	0	3	122	250	290	300	310	78	76	62	64	66	66	70	138	118	108	110	112	108	118	86	70	68	64	70	68	74	0	2	5	320
BB	SIDHANNA	58	M	5`5	52	5	8	T6	0	4	110	240	295	300	310	82	80	70	76	82	80	84	140	144	120	110	114	130	132	94	80	82	70	74	78	76	0	1	6	310
BB	SANJU	35	M	5`6	61	5	8	T6	0	3	114	240	270	320	320	78	70	66	64	74	74	70	110	106	94	90	102	108	112	74	60	62	60	64	74	78	0	2	5	320
BB	LAKSHMI	28	F	5`4	60	3	8	T8	0	3	115	250	270	295	304	90	82	90	70	74	72	70	132	118	106	112	110	118	128	78	80	70	68	72	66	70	0	1	5	300
BB	MALAKARI	27	M	5`6	68	3	6	T6	0	2	120	240	275	294	300	100	106	90	92	82	80	86	140	142	128	110	124	130	128	90	88	86	70	74	76	80	0	3	7	315
BB	MANTAYYA	50	M	5`6	56	2	5	T6	1	3	110	245	278	295	300	86	74	70	70	72	72	70	136	126	120	110	106	112	116	80	76	70	72	70	76	70	0	3	5	300
BB	SARASWATHI	36	F	5`3	58	4	6	T6	0	4	125	260	295	325	330	84	76	70	66	72	70	74	140	122	100	106	110	112	116	86	90	70	72	78	80	82	0	1	7	330
BB	MAHANTESH	30	M	5`2	60	3	7	T6	0	4	120	250	290	300	310	80	86	80	70	76	76	78	136	114	120	116	122	110	117	90	80	70	74	68	70	86	0	2	5	320
BB	SHARADA	50	F	5	48	2	5	T6	0	4	124	245	270	290	300	78	82	70	68	76	74	76	150	142	134	136	128	130	132	96	84	70	72	74	70	72	0	1	7	300
BB	Savitri	40	F	5`3	54	3	6	T6	0	4	106	250	285	300	310	78	70	76	70	82	80	76	140	128	126	130	132	128	130	90	76	74	78	70	74	80	0	3	7	310
BB	MAHABEEBA	22	M	5`8	77	2	7	T10	0	4	110	270	300	306	320	80	82	70	74	82	82	80	132	120	116	110	124	120	134	78	70	68	50	58	62	70	0	2	5	320
BB	SHREESHAIL	24	M	5`3	55	3	8	T8	0	4	125	250	286	292	300	80	70	72	70	80	78	70	140	130	138	140	120	110	128	80	82	80	78	56	72	76	0	1	6	300
BB	LAKSHMI	20	F	5`3	55	4	7	T6	0	4	125	270	300	310	312	82	70	74	70	74	70	72	132	140	120	118	110	120	124	90	80	74	76	78	70	80	0	3	5	325

Date: 28-09-2020 Signature: