"A COMPARATIVE STUDY TO KNOW THE EFFICACY OF INTRATHECAL NALBUPHINE VERSUS INTRATHECAL FENTANYL AS AN ADJUVANT TO BUPIVACAINE FOR LOWER LIMB SURGERIES"

By

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Dissertation submitted to BLDE (Deemed to be University), Vijayapura

In partial fulfilment of the requirements for the award of the degree of

DOCTOR OF MEDICINE

IN

ANAESTHESIOLOGY

Under the guidance of

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LIST OF ABBREVIATIONS

ASA	-	American Society of Anaesthesiologists
NB	-	Nalbuphine + Bupivacaine
FB	-	Fentanyl + Bupivacaine
BP	-	Blood pressure
BT	-	Bleeding time
C	-	Cervical
CVS	-	Cardiovascular system
CSF	-	Cerebrospinal fluid
CNS	-	Central nervous system
CT	-	Clotting time
ECG	-	Electrocardiogram
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
mcg	-	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
WDR	-	Wide Dynamic Range
yrs	-	Years

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INTRODUCTION

Spinal anaesthesia is the most widely used procedure for lower limb surgeries as it is inexpensive and simple to perform[1]. The brief duration of action and absence of postoperative analgesia restrict the benefits of subarachnoid block.

In recent years, adjuvants have been frequently used to complement local anaesthetics in order to reduce the dose of local anaesthetic, minimise adverse effects, and extend the duration of anaesthesia.[1,2] Intrathecal morphine was used as a predecessor of opioids added to local anaesthesia for spinal anaesthesia, which was first used in clinical practise in 1979. Intrathecal opioid injection, in conjunction with local anaesthetics, improves intraoperative analgesia and will have longer-lasting postoperative analgesia.[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, works shortly after intrathecal application. When injected intrathecally, it does not diffuse to the fourth ventricle in adequate concentration to elicit delayed respiratory depression.[6] When fentanyl is added to spinal anaesthesia, it causes synergistic analgesia for somatic and visceral pain without affecting sympathetic block.[7] Therefore, fentanyl provides better intraoperative analgesia and a safer alternative than morphine for management of early postoperative pain.

Nalbuphine is a lipophilic semi-synthetic opioid related to both oxymorphone and naloxone. Nalbuphine has relatively potent μ-antagonist and κ-agonist activity. κ-opioid receptors, which are found all across the brain and spinal cord, regulate nociception. Nalbuphine produces analgesia by attaching to κ-receptors in the brain. Nalbuphine's μ-antagonist characteristics contribute in fewer adverse events such as

respiratory depression, itching, nausea, and vomiting. As a result, nalbuphine is categorized as a combined agonist-antagonist. [8].

The purpose of this study was to assess and compare the characteristics of subarachnoid block and their adverse effects in adult patients undergoing lower limb operations who got a subarachnoid block with either bupivacaine with nalbuphine or bupivacaine with fentanyl.

AIMS AND OBJECTIVES OF THE STUDY

AIM:

The aim of the study is to assess the effects of intrathecal 0.5% hyperbaric Bupivacaine with Fentanyl 25mcg and 0.5% hyperbaric Bupivacaine with Nalbuphine 1mg in patients undergoing elective lower limb procedures under spinal anaesthesia.

OBJECTIVES

1. To compare the onset and duration of sensory block.
2. To compare the onset and duration of motor block.
3. To compare the haemodynamic changes like heart rate and blood pressure.
4. Time of rescue analgesia.
5. Side effects of study drugs.

REVIEW OF LITERATURE

HISTORICAL REVIEW OF SPINAL ANAESTHESIA

Cerebrospinal fluid was discovered by **Domenico Cotugno in 1764** and 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**",** is what he said.

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

On **16th of August 1898, in Keil, August Bier** performed the first planned spinal anaesthesia in man. He injected 3ml 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 anaesthesia. He also reported the use of intrathecal epinephrine to prolong the duration of spinal anaesthesia 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 anaesthesia.

Bupivacaine was first used for intrathecal block in 1966.

History of Spinal Anaesthesia

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

1891 Quincke (Germany) Lumbar Puncture

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

1905 H. Braun (Germany) Procaine Spinal Anaesthesia

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

1930 Jones (United Kingdom) - Dibucaine spinal anaesthesia

1935 Sise (USA) -Tetracaine Spinal Anaesthesia

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 anaesthesia

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:

Sharma DN, Padhy M, Kar M[9] in 2019 did a research to study the effects of intrathecal nalbuphine with l fentanyl as an adjuvant to bupivacaine for orthopaedic surgery on 60 adult patients categorised into two groups. The group A got 15mg of 0.5% bupivacaine with 1mg of nalbuphine, while the group B got 15mg of 0.5% bupivacaine with 25mcg of fentanyl intrathecally. The length of sensory block in group A was substantially more than in group B, while the duration of motor block was significantly higher (155.7±16.8 min) in group A compared to group B (133.1±12.4 min). The mean time period of postoperative pain relief was significantly higher than that of group B.

Kumkum Gupta, Bhawana Rastogi, Prashant K. Gupta *et al.*[10] in 2019 conducted a study on 68 patients and were split into 2 groups of 34 participants each to obtain either fentanyl 25 mcg (Group I) or nalbuphine 2 mg (Group II) with 3.5 mL 0.5 percent hyperbaric bupivacaine, amounting medication volume injected to 4 cc. The key end goals were sensory and motor block characteristics, as well as the time duration of analgesia. Adverse events like itching, nausea/vomiting, and respiratory depression were also studied. In patients of Group II, the time to two segment regression and the time to complete motor recovery were significantly prolonged, with a statistically significant difference ($P<0.05$). Also patients in Group II had a significantly longer duration of analgesia (378.0±35.72 min) than those in Group I (234.0±24.10 min), with a ststistically significant variation ($P<0.001$).

There were no adverse events in either group due to study drugs. They found that intrathecal nalbuphine 2mg as an adjuvant to 0.5% bupivacaine improved postoperative analgesia more effectively than fentanyl.

Shahedha Parveen, P Krishna Prasad, B Sowbhagya Lakshmi[11] In 2015, conducted a study on 60 patients who were between the ages of 30 and 60yrs and were randomised into two groups. Group B got intrathecal 0.5% hyperbaric bupivacaine 3ml (15 mg) + 0.5 ml sterile water; Group N received intrathecal 0.5% hyperbaric bupivacaine 3ml (15 mg) + 0.5 ml (1 mg) nalbuphine. The researchers came to the conclusion that intrathecal nalbuphine increased the quality of intraoperative and post-operative analgesia while having few side effects.

Manisha Sapate, Preety Sahu, W. S. Thatte *et al.*,[12] in 2013 conducted a study in 40 patients who belongs to ASA I and II aged between 50-70 years, posted electively for infra umbilicus surgeries. By using a lottery system, patients were divided into two equal groups of 20. Intrathecally, Group I got 3 mL of 0.5 percent hyperbaric bupivacaine + 0.5 mL nalbuphine (0.5 mg). Intrathecally, Group II got 3 mL of 0.5 percent hyperbaric bupivacaine + 0.5 mL of normal saline. They found that Nalbuphine offers a better quality of block than bupivacaine alone as an adjuvant to spinal bupivacaine in elderly patients, it also prolongs postoperative analgesia.

Pallavi Ahluwalia, Amit Ahluwalia, Rohit Varshney *et al.*,[13] in 2015 conducted a study on 70 adult patients scheduled for lower abdominal surgeries under subarachnoid block. Patients were divided into two groups (35 patients each); Group B, received bupivacaine heavy 0.5% (2.5 ml) + normal saline (0.5 ml) and in Group N, received bupivacaine heavy 0.5% (2.5 ml) + nalbuphine 0.8mg intrathecally.

The period of sensory blockade in Group B and Group N was 123.65 ± 21.23 min and 166.24 ± 29.84 min respectively with P value <0.05. While similar statistical significance was seen in between two groups for duration of motor blockade. Duration of analgesia in Group B (201.31 ± 34.31 min) was significantly lower compared to Group N (298.43 ± 30.92 min) with statistical significance ($P < 0.05$). They concluded

that post-operative analgesia was better taken care off with 0.8 mg intrathecal nalbuphine with minimal side-effects.

Bindra T K, Kumar P, and Jindal G[14] conducted a prospective, randomised, double-blind, and comparative investigation on 150 parturients with normal coagulation profiles who were undergoing caesarean section under spinal anaesthetic. Three groups of patients were chosen at random. Along with 0.5% hyperbaric bupivacaine 2ml, Group I got 0.4 ml nalbuphine (0.8 mg), Group II got 0.4 ml fentanyl (20 g), and Group III got 0.4 ml normal saline.

In Group I, effective analgesia lasted 259.20 ± 23.23 minutes, 232.70 ± 13.15 minutes in Group II, and 168.28 ± 7.55 minutes in Group III. In Group I, the number of rescue analgesics needed was markedly less ($P<0.001$) than in Groups II and III. According to the authors, intrathecal nalbuphine 0.8 mg and fentanyl 20 mcg are both better adjuvants to 0.5% hyperbaric bupivacaine in spinal block. Intrathecal nalbuphine, on the other hand, provides prolonged postoperative analgesia and could be utilized as a substitute to intrathecal fentanyl during caesarean sections.

Culebras.X *et al*[15] did a dose response clinical trial to assess the efficacy of analgesia and side effects of intrathecal nalbuphine, at three doses 0.2mg, 0.8mg and 1.6mg, and IT morphine, as adjuvant to bupivacaine for postoperative pain relief after caesarean deliveries in 90 patients. They concluded that 0.2mg, 0.8mg and 1.6mg of intrathecal nalbuphine prolong postoperative analgesic duration by 136 ± 22, 212 ± 72 and 193 ± 77min respectively. Morphine increases analgesic duration by 585 ± 446 min. The side effects noted in the intrathecal morphine group are pruritus, nausea and vomiting. These side effects were not noted in the nalbuphine groups. The additional increase in the dose of nalbuphine to 1.6mg did not increase the efficacy. Finally, it was discovered that intrathecal nalbuphine 0.8 mg offers effective post-operative pain

relief and prolongs early post-operative analgesia without raising the risk of adverse events.

Mukherjee A, Pal A, Agrawal J *et al*[16] did a prospective clinical study on 100 patients in 2011 who were scheduled for orthopedic surgery under spinal block to study the effective dose of Intrathecal nalbuphine as an additive to subarachnoid block. They were randomly divided into four groups A, B,C and D. Along with 12.5mg 0.5% hyperbaric bupivacaine, Group A - 0.5ml Normal Saline, Group B - 0.2mg Nalbuphine, Group C - 0.4mg Nalbuphine, Group D - 0.8mg Nalbuphine were injected intrathecally.

The time required for sensory and motor block, as well as the time period of sensory and motor block, were compared among groups. They applied the Bromage scale to evaluate motor block and for assessing pain, the visual analogue scale was employed. In the nalbuphine groups, the initiation time of sensory and motor blockade was significantly ($p<0.05$) shortened, but the length of block was extended. They reported that when nalbuphine was given as an adjuvant, the analgesic effect of bupivacaine was markedly prolonged. The authors also found that 0.4mg Nalbuphine is the most effective intrathecal dose for increasing post-operative analgesia without causing side effects.

Jyothi B, Shruthi Gowda, Safiya Shaikh[17] in 2014 did a clinical trial to compare the analgesic properties of various doses of intrathecal nalbuphine along with bupivacaine and bupivacaine alone for below umbilical surgeries". Hundred patients were enrolled and were randomly divided into four groups I, II, III and IV. Subarachnoid block was given with 3cc bupivacaine + 0.5ml NS (Group I) or 3cc of bupivacaine with either of nalbuphine 0.8mg, 1.6 and 2.5mg (Group II,III and IV). In nalbuphine groups, the time period for sensory block and the period of post operative analgesia were markedly increased. Postoperative pain levels were

significantly lower in groups II to IV than in group I (3.4±0.4 vs 4.08±0.5). They found that combining 0.8mg nalbuphine with 0.5% bupivacaine intrathecally gives better analgesia with no adverse effects. Nalbuphine has an analgesic ceiling effect at 0.8mg dose; increasing the dose did not enhance the analgesic efficacy.

Shehla shakooh, Pooja Bhosle[18] did a study to assess the efficacy of Intrathecal nalbuphine as an adjuvant for effective analgesia on 60 patients posted for elective below umbilical surgeries and were divided into two groups by slips in the box technique. Group N was given 0.5% heavy bupivacaine (3ml) with 0.8mg nalbuphine. Group B was given 0.5% heavy bupivacaine (3ml). And reported that the onset of sensory and motor block were rapid in group N with a statistically significant p value <0.001. The length of sensory & motor block and the postoperative analgesia duration were higher in group N as compared to group B. No major adverse events were seen among the two groups.

Ravikiran J Thote, Prashant Lomate, Shilpa Gaikwad *et al*[19] performed a prospective randomised controlled double blind study on sixty patients in 2015 to compare intrathecal fentanyl and nalbuphine as an adjuvant to bupivacaine and plain bupivacaine. They were categorised into three groups of 20 patients each using computer generated numbers. Group I received 25mcg of fentanyl, Group II received 500mcg nalbuphine, Group III received 0.5ml of normal saline along with 2.5ml of 0.5% bupivacaine in each group. The onset of sensory and motor block were significantly decreased in fentanyl and nalbuphine group. However the period of sensory block was increased with nalbuphine than compared to fentanyl group Arousable sedation was seen with nalbuphine without any respiratory depression.

Ananda Bangera, Krishna Prasad *et al*[20] did a clinical trial to compare Nalbuphine as an alternative to morphine in patients undergoing hysterectomy. Fifty

patients were included in the study and were divided randomly into two groups by closed envelope method. Injection diazepam 0.1mg/kg was given 30 minutes before induction of anaesthesia. General anaesthesia was given in both the groups. After preoxygenation Group N received 0.2mg/kg nalbuphine IV and Group M received 0.1mg/kg morphine IV. Patients in both groups were anaesthetised with propofol 2mg/kg and vecuronium 0.1mg/kg and maintained with O2/N2O/isoflurane. At the end of surgery, neostigmine 50mcg/kg and glycopyrrolate 10mcg/kg were used for reversal and extubation was performed. Period of analgesia was significantly more in nalbuphine group than compared to morphine group (437±63.87min vs 255±43.75min). The time for first rescue analgesia requirement was significantly more with intravenous nalbuphine in addition to good intraoperative hemodynamic stability.

Lefevre B, Freysz M *et al*[21] did a study to Compare nalbuphine and fentanyl as an intravenous analgesics for ASA PS III and IV patients undergoing oral surgery and published in 1992. It was a double-blind randomised study done on 24 patients who were scheduled for oral surgery. They were divided into two groups. One group received 0.2mg/kg nalbuphine IV as an analgesia, whereas the other received 2mcg/kg fentanyl IV analgesia. After 3min Local anaesthetic was injected to both groups. Before and during surgery, the patient's vitals were monitored. Quality of analgesia, sedation scores, and respiratory depression were assessed. The researchers found that there were no significant differences between the two study drugs in terms of analgesia and sedation. They also reported that nalbuphine causes lesser respiratory depression compared to fentanyl and that it should be used as an alternative of fentanyl in ASA III and IV patients posted for oral surgeries.

Hala Mostafa Gomaa, Nashwa nabil Mohamed *et al*[22] performed a study in 2013 to compare post-operative analgesia among intrathecal nalbuphine and fentanyl

with bupivacaine after LSCS on 60 pregnant females posted for elective Lower Segment Caesarean Section under the ASA PS II. The patients were divided randomly into two groups. Group F got 2ml of 0.5% hyperbaric bupivacaine with 0.5ml fentanyl (25µg) intrathecally. Group N got 2ml of 0.5% hyperbaric bupivacaine with 0.5ml nalbuphine hydrochloride (0.8mg) intrathecally. The onset of sensory blockade was statistically insignificant in the two groups. They came to the opinion that the period of intraoperative analgesia and early postoperative pain relief was high in group N compared to group F.

Faure E *et al*[23], in 1982 performed a study to determine whether nalbuphine added to intrathecal fentanyl would prolong analgesia and attenuate the side effects. The study was carried out on 70 patients with full term pregnancy. Group 1 received intrathecal fentanyl 50µg, group 2 received intrathecal fentanyl 50µg with nalbuphine 1mg and group 3 received intrathecal fentanyl 50µg with nalbuphine 2mg. At 5 min, all pain scores had come down to < 3. The mean VAS scores in group 3 were significantly more at 10 and 15 min than the scores in group 2. ($p = 0.003$, $p = 0.008$). Group 2 and 3 had pruritus scores 3 and fewer incidence of pruritus than did group 1. The patient satisfaction scores were significantly more in groups 1 and 2 compared to group 3 at 10, 15, and 30 min. They reported that addition of 1mg nalbuphine reduced the incidence and intensity of pruritus after intrathecal fentanyl and enhanced patient satisfaction.

Manjula R, Chaithra GV, Amit Gandhi, Upakara Selvin Rajan *et al*[24]**,** did a randomised double blind study on 60 patients, who were scheduled for elective lower limb surgeries under spinal anesthesia. Patients were split into 2 groups, group B got 15mg of 0.5% hyperbaric bupivacaine + 0.1ml of normal saline and group N got 15mg of hyperbaric bupivacaine + 0.1ml of nalbuphine (1mg). Length of motor and sensory

block was assessed using modified bromage scale and pin prick method respectively. There was insignificant variation observed in onset of motor and sensory block among the two groups, but duration of post operative analgesia in group N was statistically significant than group B (P<0.001). They reported that intrathecal nalbuphine at dose of 1mg can be utilised as an adjuvant along with 0.5% of hyperbaric bupivacaine intrathecally to have better post-operative pain relief.

Tiwari AK *et al*[25], conducted a dose response study to find the effective IT dose of nalbuphine in patients posted for infra umbilical surgeries. Seventy-five patients were randomly divided into 3 groups of 25 each. Along with 2.5 mL of 0.5% hyperbaric bupivacaine, Group A got 1 mL sterile water; group B got 1 mL (200 μg) nalbuphine; group C got 1 mL (400 μg) nalbuphine intrathecally. Mean time duration of analgesia (in minutes) in Group A, B & C were 170 ± 5.85, 213.8 ± 6.70 & 237.3 ± 5.64 respectively. They found that 400 μg of nalbuphine hydrochloride along with 2.5 ml of 0.5% hyperbaric bupivacaine significantly lengthens the duration of sensory block and postoperative analgesia without any influence on onset of sensory or motor block.

ANATOMY OF VERTEBRAL COLUMN & SPINAL CORD: [26-28]

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

Anatomy of vertebral column:

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

The mean weight is around 30g.

The vertebral column is formed by 33 Vertebrae.

Cervical - 7

Thoracic - 12

Lumbar - 5

Sacrum - 5 (fused)

Coccyx - 4 (fused)

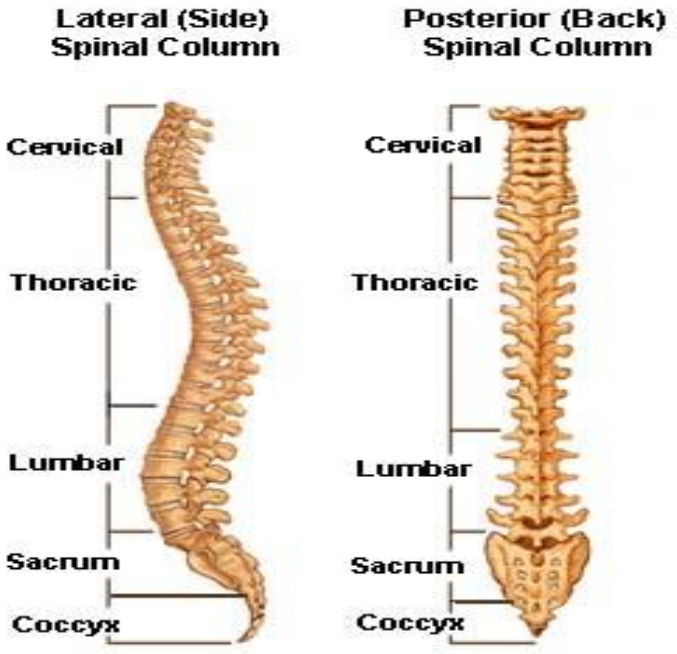

Fig 1: VERTEBRAL COLUMN

The curvature of the spine:

In adult, the normal vertebral column has 4 curves,

1. Cervical spine curve – convexity anterior (lordosis)
2. Thoracic spine curve – convexity posterior (kyphosis)
3. Lumbar spine curve – convexity anterior (lordosis)
4. Sacrococcygeal curve — convexity posterior (kyphosis)

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.

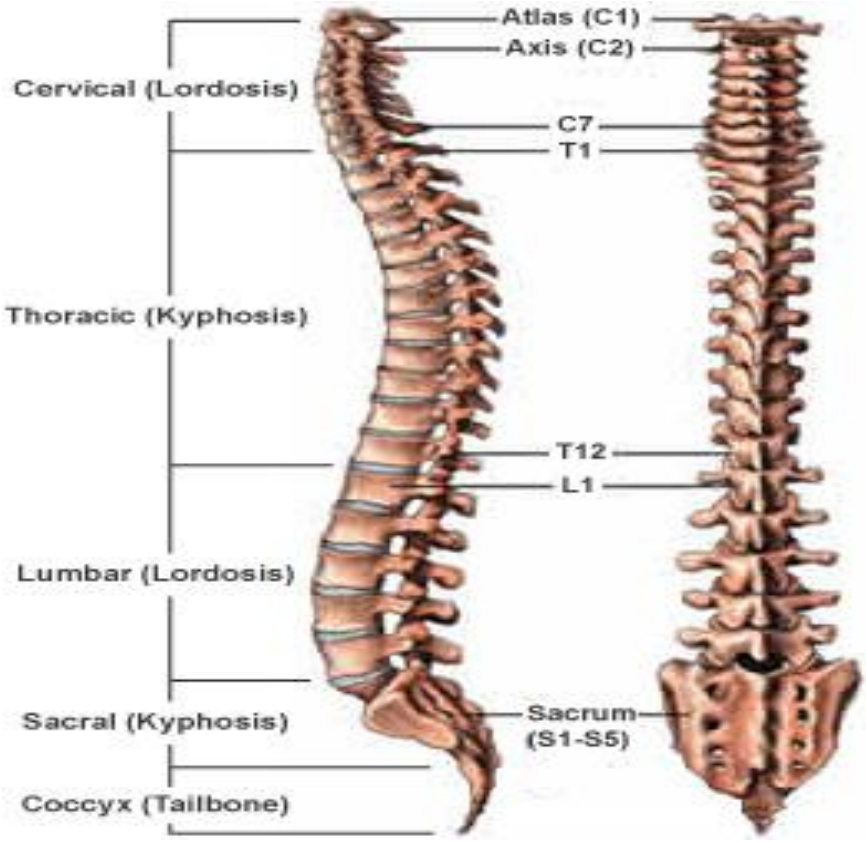

Fig 2: CURVATURE OF SPINE

The vertebrae:

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 archadhered to the body, consisting of two pedicles anteriorly and two lamina posteriorly, surrounding and protecting the spinal cord.
3. The transverse processes are at the junction of pedicles and laminae, and the spinous process is where the laminae meet. There are 2 transverse processes and 1 spinous process to those ligaments and muscles are attached.
4. Articular processes are four in number – superior 2 and inferior 2.

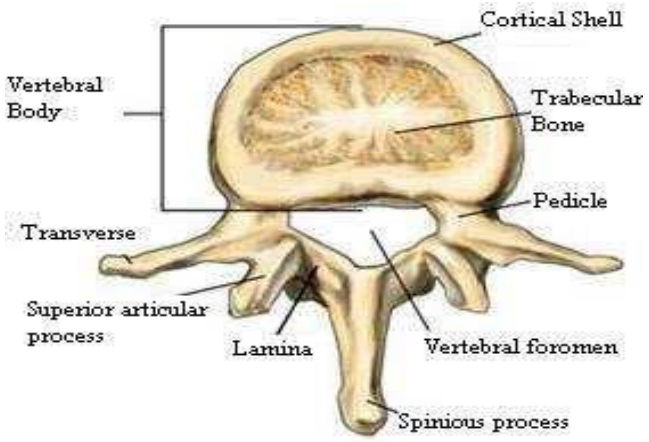

Fig 3: CROSS SECTION OF VETEBRA

Intervertebral discs:

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

The Lumbar Vertebrae: Is different from other vertebrae:

- Lumbar vertebrae bodies are bigger and kidney shaped.
- The vertebral foraminae are triangular & medium in size between those in the cervical and thoracic parts.
- The pedicles are thick and short.
- Length of transverse processes increases from L1 to L3 and then decreases.
- 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.

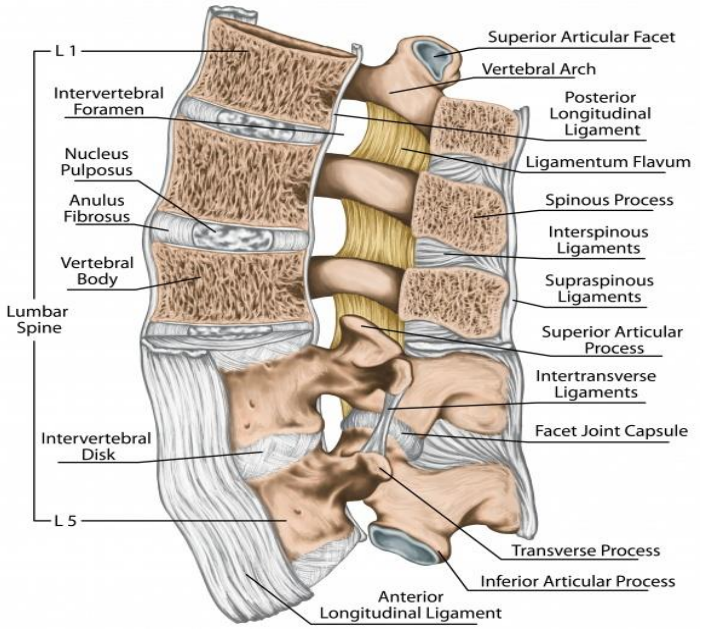

Fig 4: LUMBAR VERTEBRAL COLUMN

The Vertebral Ligaments:

It is must for an anaesthesiologist to have good knowledge of the ligaments of vertebral 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.

- **Supraspinous ligament:** Is a continuation of ligamentum nuchae, strong thick dense fibrous cord that connects the apices of spines from the 7^{th} cervical vertebrae to the sacrum. This may get ossified in old age and make difficult to pass spinal needle through it.
- **Interspinous 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 and occupies half of the vertebral canal's

posterior wall. Cervical region has the thinnest ligamentum flavum and lumbar region has the thickest.

Functionally, these ligaments are muscle spares that help to recover from effect of 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 extends along the dorsal surfaces of the vertebral bodies, separated by the basivertebral veins.

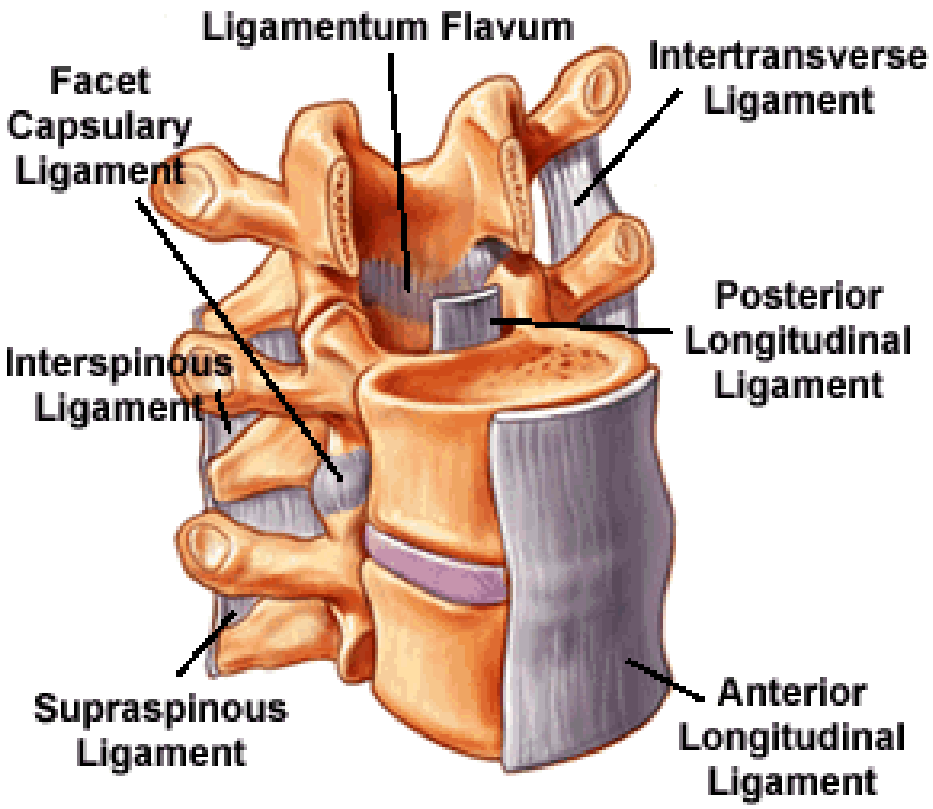

Fig 5: VERTEBRAL LIGAMENTS

Vertebral Canal:

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

Vertebral canal contents:

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

The Spinal cord:[29-31]

It is an expanded component of the central nervous system that comprises the upper two-thirds of the spinal canal, has a length of 42-45 cm, and weighs around 30g. It runs from the upper border of the atlas vertebra to the lower border of the first lumbar vertebra or the upper border of the second lumbar vertebra above it, and trimmed into a conical conus medullaris below it.

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. Cervical expansion ranges from C3 to T1, and lumbar expansion ranges 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 the Inner (meningeal) layer which is the cranial duramater continuation and the outer (endosteal) layer which is the vertebral canal periosteum lining and the epidural space differentiates it from the spinal dura.. Above, it is tightly attached to the circumference of the foramen magnum. Below it usually stretches 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. The duramater's major fibres are vertical; the spinal injection needle should be introduced with its tip separating instead of cutting these fibres.
2) **Arachnoid mater:** Is a fragile non-vascular membrane that is tightly wrapped around the dura mater. Subdural space divides it from the dura mater, and subarachnoid space differentiates it from the piamater. Above, it extends with the cerebral arachnoid; below, it broadens, engages in the cauda equine, and terminates at the lower border of the S2 vertebra.
3) **Pia mater:** It is a vascular membrane's innermost layer that closely wraps the brain and spinal cord and sends fragile septa into its content. The spinal pia thickens anteriorly into the linea splendens along the course of the anterior median fissure, forming ligamentum denticulatum on either side, which expands into the subarachnoid space and is linked to the dura by a sequence of pointed processes as far down as the first lumbar nerve.

Subarachnoid space:

It is space between the arachnoid and pia mater. Cobweb trabeculae, cranial & spinal nerves cross this space. These are immersed in spinal fluid. The circumferential space in the cranial and thoracic regions are roughly 3 mm deep. It is round and located beneath the first lumbar vertebra.

The space communicates with the tissues around the vessels in the piamater that accompany the m 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 bigger than the anterior, and afferent impulses from the entire body, including the viscera, stream through it.

Each posterior root contains a ganglion that transports fibres of pain, touch, temperature, deep feeling from bone joints and muscles and tendons / efferent from viscera (together with sympathetic) and vasodilator fibres. Pain and temperature nervefibers enter the posterior horn and end around the c ell in gray mater, then cross to the contralateral side of the within three segments and r ise in the lateral spinothalamic.

In the posterior column and spinocerebellar tracts, deep or muscle sensory imp ulses 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 with a quicker conduction time are approximately three times more responsive to local anaesthetics than nonmyelinated postganglionic C fibres.

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 c onduct rapidly.

Sensory Aα fibers seem to be more susceptible to blocking than motor Aα fib ers, 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 blockad e.

Blood supply of the spinal cord: [31]

The spinal cord artery is formed of one anterior and two posterior arteries that flow down from the level of the foramen magnum.

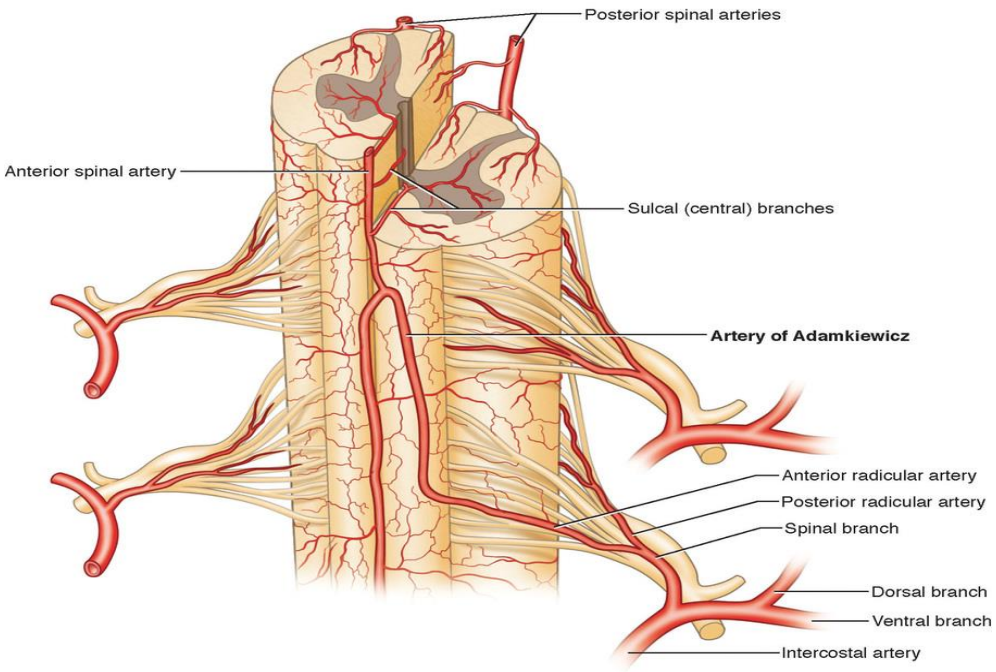

Fig 6: BLOOD SUPLLY OF SPINAL CORD

Anterior spinal artery: is a single artery ,it is formed by union of each vertebral artery at the foramen magnum and passes the full length 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 o

ften from subsequent inferior cerebellar arteries. Posterior 1/3rd 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):[31]

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:[31]

The following structures are pierced when a needle is introduced into the subarachnoid space from posterior to anterior direction:

- 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 seen on a line crossing the spine of L4 (in the erect position) or L4-L5 interspace (in the lateral decubitus position). This line is known as the topographic line of Tuffier[34].

PHYSIOLOGY OF NEURAXIAL BLOCKADE:[28,29,33,37]

Subarachnoid block's well recognised physiological sequels are often 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.[28,33]

- 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 th e 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 le vel 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 sp inal anaesthesia but is of longer duration than the levels arising from rapid inje ction.

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 agent to 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 su barachnoid space, i.e. below L3.Hyperbaric solutions travel to the most dependent po rtion of the subarachnoid space when the patient's position changes from the horizont al.With changes in position, isobaric solutions are considered not to spread and anest hesia levels are independent of positioning. The solution is puddling close the injectio n site.

In comparison to hyperbaric solutions, hypobaric solutions are affected by pat ient 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 amou nt of fluid in the subarachnoid space.The second stage of concentration reduction is d ue to the diffusion of the agent in the spinal fluid owing to its molecular motion. Som e 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 u ptake of local anesthetic from the spinal fluid and nerve fibers into the vascula r 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 anaesthetics include:

[34,36]

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 block:[36]

1. Vasomotor block --- skin vessels dilates and increased 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 reverse 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:[37]

Cardiovascular System:

The most significant physiological response of spinal anaesthesia 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 determ ines 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 pregan glionic sympathetc fibers paralysis that transmits motor impulses to the peripheral va sculature's smooth muscles.

Fall in BP level was proportional to the blocked number of sympathetic fibers. It was not understood the exact mechanism by which sympathetic blockade reduced b lood 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 h eart.

While both theories are right, neither is sufficient in itself to explain all the changes i nduced 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 15-20 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 perio d, 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 i s a result of compensatory circulatory activity mediated by the blocked proportions of sympatheticoutflow andpossibly by a slight r eturn of smooth muscle tone in the denervated part of the peripheral vasculature.

Heart Rate:

Spinal anaesthesia is typically associated with slowing of the heart rate. The degree of bradycardia can be approximately correlated with the extent of sympath etic 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 Anaesthesia:[38]

"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 intrin sic 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 anaesthesia. Thus, venous pooling in the periphery in spinal anaesthesia 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".[44]

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 c erebrovascular 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 re spiratory center with reduction of sensory input. Lowered arterial and venous tone als o 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. Because S2-S3 includes small autonomic fibres, whose paralysis lasts longer than that of bigger sensory and motor fibres, post-spinal urine retention may be moderately protracted. 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 labour. Due to decreased extradural space, lesser doses of local anaesthetics 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: [30-32,39]

Pain is described as an unpleasant sensory and emotional perception that is accompanied with or explained in terms of real or potential tissue 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 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:**

- Spinoreticular tract - it is thought to mediate arousal and autonomic response to pain
- Spinothalamic tract - activates hypothalamus and evokes emotional behavior to pain.
- 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.

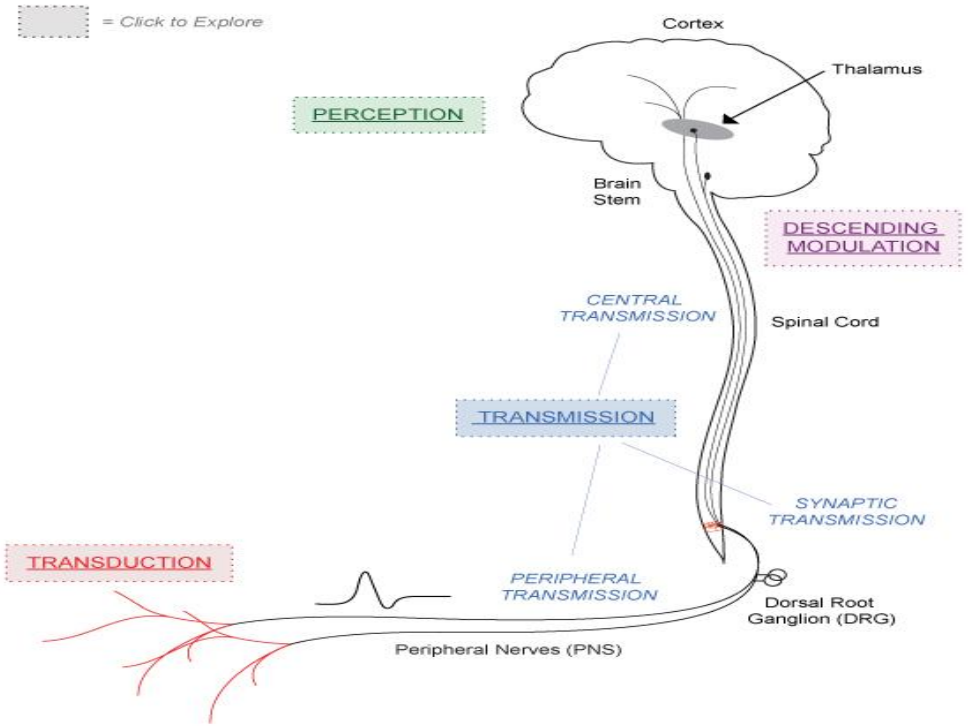

Fig 7: PAIN PATHWAY

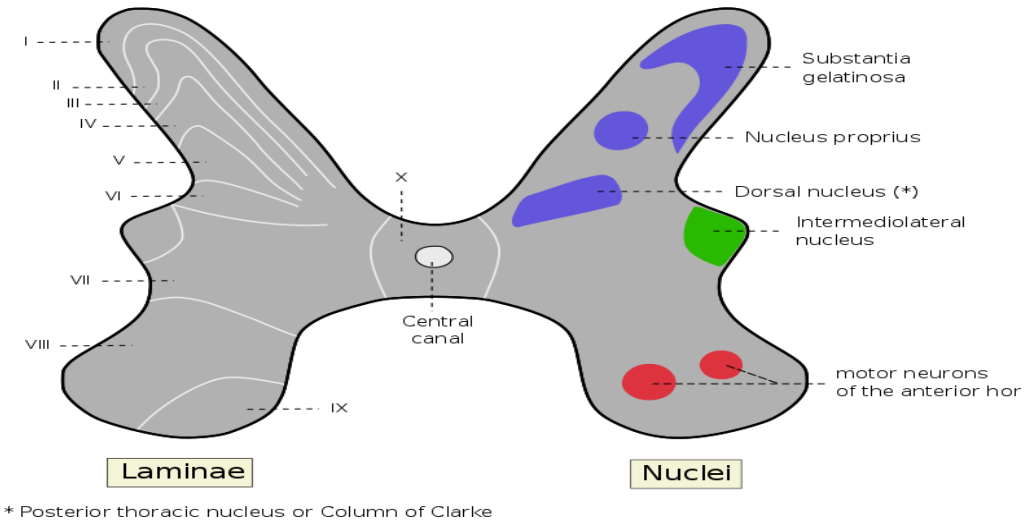

FIG 8: REXED'S SPINAL CORD LAMINAE

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,Aδ	Nucleus proprius
4	Mechano reception	Aβ, $A\delta$	Nucleus proprius
5	Visceral and Somatic Nociception and Mechano reception	Aβ,Aδ, (C)	Nucleus proprius WDR neurons
6	Mechano reception	Aβ	Nucleus proprius
7	Symphathetic		Intermediate column
8		Aβ	Motor horn
9	Motor	Aβ	Motor horn
10		Aβ	Central canal

Modulation of pain: [40,41]

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: [42]

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: [43]

Proposed by Melzack and Wall in 1965 and then later modified by them in 1982. They first considered proof of physiological specialisation, central aggregation, patterning regulation of input and the influence of psychological variables.

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:[45]

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. Sertürner studied the isolation of a pure component in opium in 1806, which he termed morphine after Morpheus, the Greek deity 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

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:[46]

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:[47]

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 decreases excitatory transmitter discharge (glutamate and substance P) from presynaptic C fibre synapses but not A fibre endings, leading to a decreased 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 decrease the discharge of gamma aminobutyric acid (GABA) and glycine from dorsal horn neurons via a calcium-independent mechanism. 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.

FENTANYL:[48,49,50]

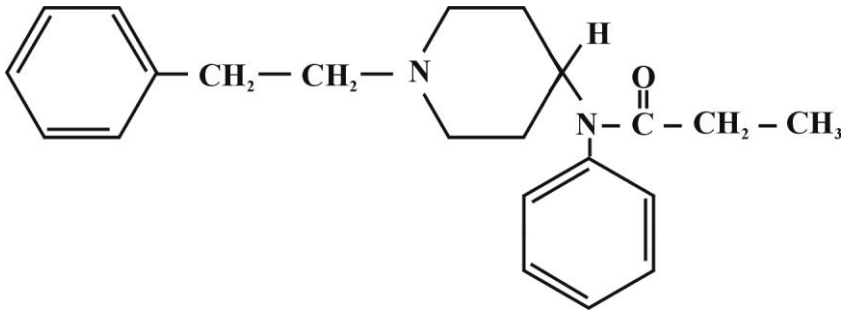

Fig 9: Chemical structure of Fentanyl

Fentanyl is a synthetic opioid agonist with a phenylpiperidine derivative and its chemical structure similar to pethidine. Fentanyl is 75-125 times more effective than morphine as an analgesic. 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.[47]

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.[47]

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 numero us 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.[49]

Metabolism and elimination:

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 increased volume of distribution is owing to increased lipid solubility and, as a result, faster transit 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:

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: The heart rate is reduced as a result of activation of the central vagal nucleus. It is determined by the injection dose and speed. Premedication with a parasympatholytic drug like glycopyrolate or atropine can effectively prevent it. Fentanyl also inhibits the sympathetic stress response, which results in an increase in heart rate due to a decrease in sympathetic vasoregulatory flow in the CNS.

II. Blood pressure: Minor drops in blood pressure are seen predominantly as a result of a decrease in systemic vascular resistance caused by a centrally controlled reduction in sympathetic tone, and are frequently accompanied by 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 it does not reduce the ability of major coronary arteries or coronary arterioles to respond to vasoactive drugs.

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

d) **Rigidity:** It occurs more often while IV induction with higher doses, but with intrathecal injection there are no such adverse events noted.

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:

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 a potent and safe opioid. It has a therapeutic index of 323, which is significantly higher than morphine (69) and pethidine (4.8).

Clinical uses/ dose:

- Analgesia — fentanyl 1-2µg/kg 1V
- As an adjuvant to inhaled anaesthetics to reduce the 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. Not indicated in patients who are on MAO inhibitors within previous 14 days.
2. Bronchial asthma
3. Myasthenia gravis

Counter measures for adverse effects:

- Naloxone and mechanical ventilation can be used to alleviate respiratory depression.
- Antihistaminic, antiemetic, and catheterization can all help with pruritis, nausea, and urine retention respectively.

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

NALBUPHINE:[8]

Nalbuphine hydrochloride, a phenanthrene-series synthetic narcotic agonist-antagonist analgesic. It is chemically related to naloxone, an opioid antagonist, and oxymorphone, an opioid agonist. Nalbuphine is only available as an injectable solution and is soluble in water at 25 degrees, ethanol at 0.8 percent.

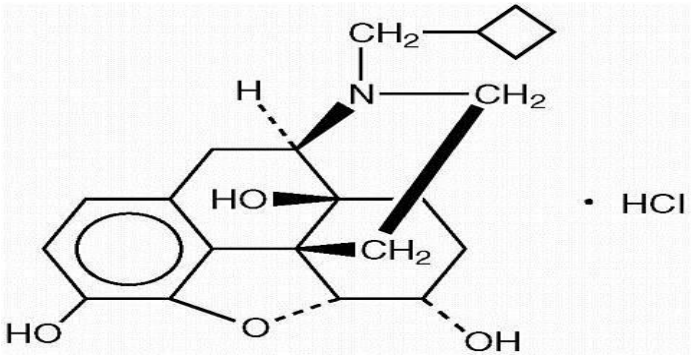

Fig 10: Molecular structure of nalbuphine

Chemical name:

17-(cyclobutylmethyl)-4,5-epoxy-,morphinan-3,6,14-triol, hydrochloride

Receptor interaction:

Nalbuphine binds to mu(μ), kappa(κ), and delta(δ) receptors, but do not bind to sigma receptors. Nalbuphine is primarily an analgesic that works as both κ agonist and μ antagonist. On a milligramme for milligramme basis, Nalbuphine has an analgesic potency[51] similar to morphine. Nalbuphine has one-fourth the potency of nalorphine and ten times the potency of pentazocine as a narcotic antagonist. When given after or simultaneously with agonist opioids (e.g., morphine, fentanyl), nalbuphine may partly negate their effect or inhibit the agonist analgesic's opioid-induced respiratory depression.

Mechanism of action:

Because of its agonist effect, nalbuphine activates κ-receptors, limiting the neurotransmitter release such as substance P, which mediate pain. It functions as a post-synaptic regulator on the Spino-thalamic tract's "inter neurons and output neurons," which carry nociceptive impulses.

Pharmaceutical information:

Molecular formula - C21 H27 NO 4 .HCl

Molecular Mass - 393.91 g/mol

pKa - 8.71

Pharmacokinetics:

Nalbuphine is ineffective when taken orally, hence the intravenous route is the preferred method of delivery. It can also be given intramuscularly, subcutaneously, or neuraxially.

Bio-availability is approximately 80%.

Volume of distribution is 3.8litres/kg.

Onset of action:

Intravenous administration is within 2-3 mins

Subcutaneous, intramuscular < 15 mins

Plasma half life - 5 hrs

Duration of analgesia - 3 to 6 hours

Nalbuphine is largely metabolised in the liver, with the metabolites eliminated through the kidney. As a result, nalbuphine dosage should be reduced in individuals with kidney and liver failure.

Uses of nalbuphine:

- As an adjuvant to general anesthesia
- As an adjuvant to neuraxial anesthesia
- Obstetric analgesia during labor and delivery
- As an adjuvant to peripheral nerve blocks.
- In the management of postoperative pain.

Off label uses:

- Opioid induced pruritus.
- Opioid induced respiratory depression[52]
- Post anaesthesia shivering
- Sickle cell anemia with crisis

Preparations and storage:

- Available as 10mg, 20mg solutions in 1ml ampoule.
- Should be stored at room temperature (15°c to 30°c).
- Protect from excessive light.

Inj. Nalbuphine Ampule

Adverse effects:

The common adverse effects of nalbuphine are sedation, sweating, nausea, vomiting, dizziness, vertigo, dry mouth, headache. Other effects are decrease in heart rate and blood pressure, urinary urgency. Due to its ceiling effect.[53] nalbuphine produces less respiratory depression compared to other opioids. It is classified as category ‘B’ drug in pregnancy. It is contraindicated in patients who are allergic to the drug or its components.

LOCAL ANAESTHETICS:[54-59]

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

General Properties of Local Anaesthetics:

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

Local anaesthetics 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 Anaesthetics:

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

Local anaesthetics 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 anaesthetics 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 favours 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.

BUPIVACAINE: [60-63]

Bupivacaine, an amino amide local anaesthetic was first synthesized in the year 1957 in Sweden by A.F Ekenstam and his colleagues. Its first documented use was by L.J Teluvio in the year 1963. It is a long acting local anaesthetic substance available, that is widely used for intrathecal, extradural and peripheral nerve blocks. It is a white crystalline powder which dissolves in water.

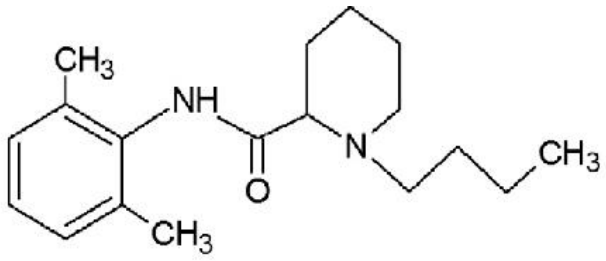

Fig 11: MOLECULAR STRUCTURE OF BUPIVACAINE

Chemical name:

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: [42,43]

Mechanism of action of bupivacaine is same to that of any other local anaesthetic. Local anaesthetics primarily act on the cell membrane axon, where it promotes electrical stability. Bupivacaine blocks nerve impulse conduction by limiting sodium ion transport across 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. The resting transmembrane potential or the threshold potential are not affected by local anaesthetics.

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**
Subarachnoid 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

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

Anaesthetic potency:

Hydrophobicity appears to be a primary determinant of intrinsic anaesthetic 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 min and peak effect occurs between 15 - 20 minutes.

Duration of block:

Duration of anaesthesia varies according to the type of block, the average duration of peridural block is about 3.5 - 5 hours and 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 found in the blood within 5 mins of local administration 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 higher in areas with high blood supply.

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 PaCO2 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:

Overdosage, unintentional intravascular injection, and delayed metabolic clearance are the most common causes of adverse effects in clinical practise.

- 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 collapse (CC) / 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:

Source of data:

After taking valid written informed consent, the randomised comparative clinical study was done on 70 patients aged between 18- 60 yrs with ASA grade 1 and 2 who were posted for elective lower limb surgeries under spinal anaesthesia after

getting clearance from Institutional ethical committee at B.L.D.E (DU)'s Shri B.M. Patil Medical College, Vijaypura from December 2019 to September 2021.

Sample size:

Seventy (35 per group) patients are required to have a 90% chance of detecting, as significant at the 5% level.

Calculation based on the formula:

$$\mathbf{n = f(\alpha/2, \beta) \times 2 \times \sigma^2 / (\mu_1 - \mu_2)^2}$$

Where $\mu 1$ and μ_2 are the mean outcome in the study groups respectively, σ is the standard deviation.

Randomization:

The study population of 70 patients age and sex matched were randomly divided by computer generated slip into 2 groups with 35 patients in each group.

- Group **NB** got 0.5% heavy Bupivacaine 3ml + Nalbuphine 1mg.
- Group **FB** got 0.5% heavy Bupivacaine 3ml + Fentanyl 25 mcg.

Incusion criteria:

- Patients with valid written informed consent.
- Patients aged between 18 to 60 years of both sex planned for elective lower limb 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 and renal failure

Method of study:

Patient's detailed history, general physical examination and systemic examination was carried out during preoperative evaluation. 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.

METHOD:

After shifting of the patient to the operation table IV access with 18 guage cannula was secured on the forearm and Ringer Lactate infusion started IV before the block. The monitors were attached to the patient which include ECG, non invasive

blood pressure (NIBP), pulse oximeter and baseline PR, BP, RR and SpO2 were recorded.

The patients were positioned in left lateral or sitting posture. 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 intrathecally 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 ringer's lactate solution

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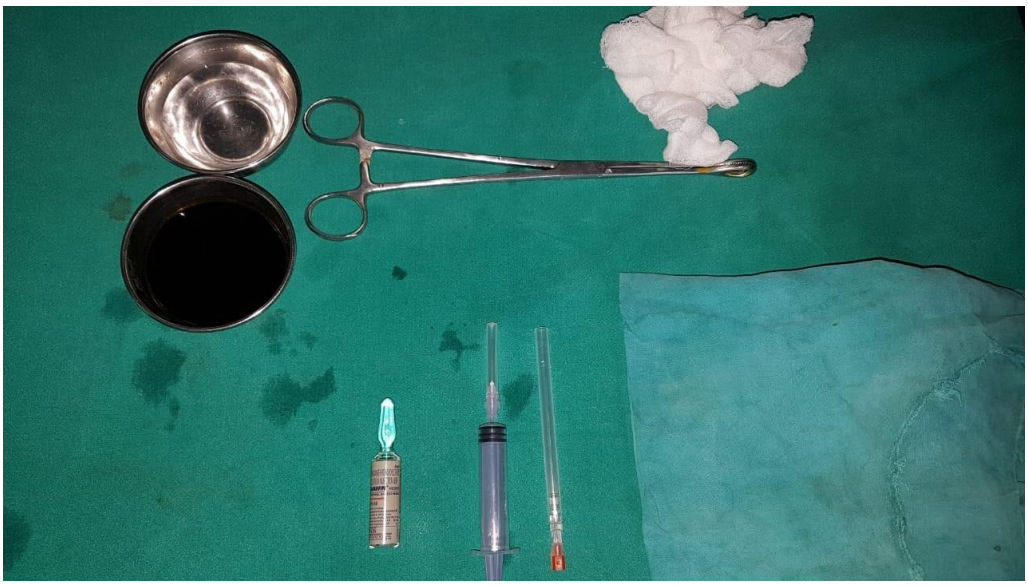

Image 1: Spinal tray

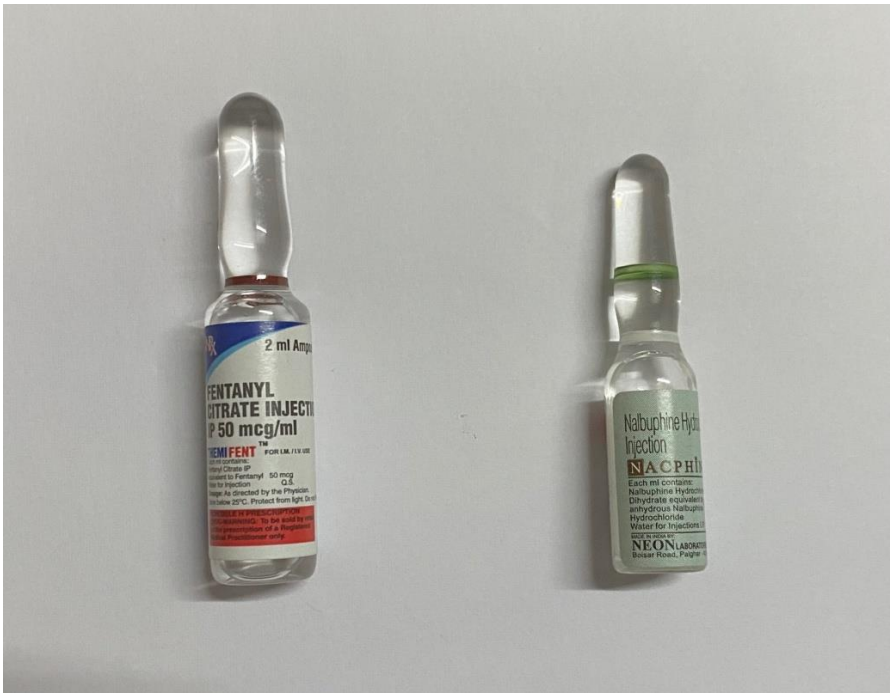

Image 2: Study drugs

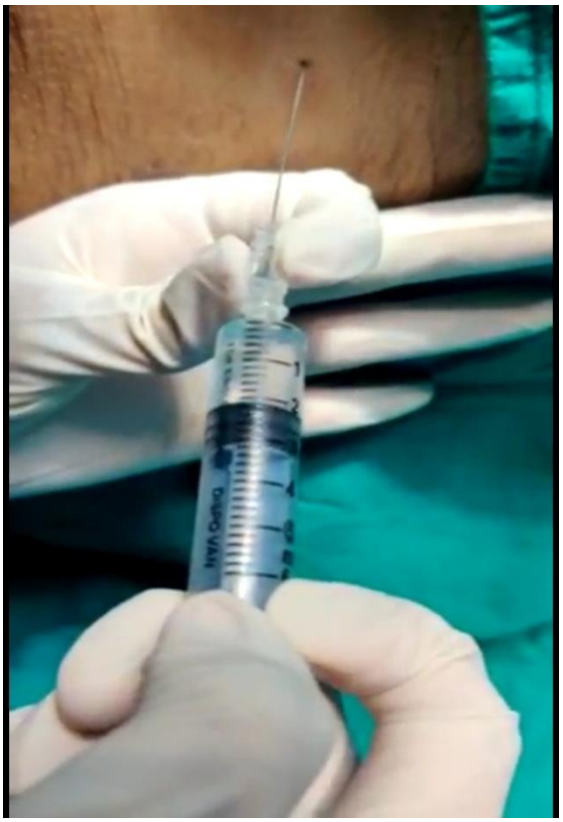

Image 3: Study drug being injected intrathecally

Following parameters were noted:

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

Onset of sensory blockade: 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: was done by Modified 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 of motor block. The duration of motor was taken from the time of injection to complete regression of motor block.

Modified Bromage Scale:[64]

0 – Able to raise leg straight, full flexion of knees and feet.

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

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

3 – Unable to move the legs or feet.

Assessment of pain: was done by using **Visual Analogue Scale (VAS)**[65]. VAS consist of a 10 cm line anchored at one end by a label such as "NO PAIN" and at other end by "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 on the 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."

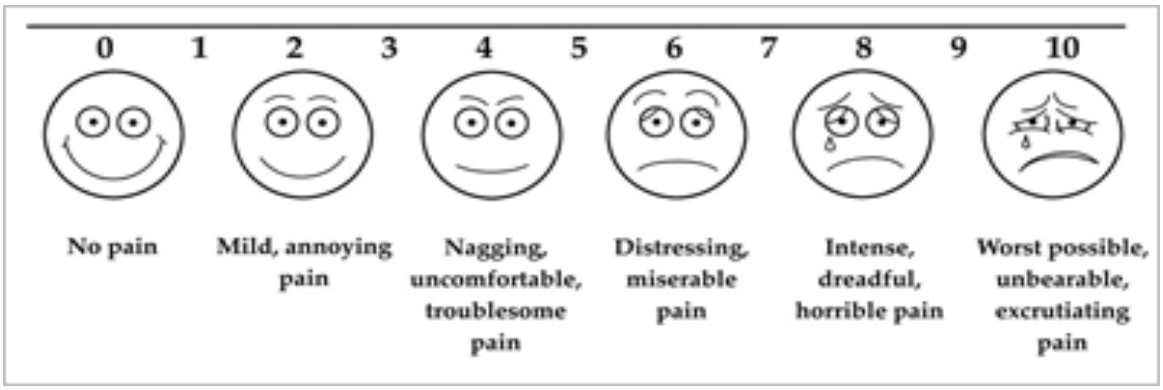

FIG 12: Visual Analog Scale

STATISTICAL ANALYSIS[66-68]

The data was processed into a Microsoft Excel data sheet and analysed with SPSS 22 software. Frequencies and proportions were used to express categorical data. For qualitative data, the Chi-square test was employed as a test of significance. The mean and standard deviation were used to describe continuous data. As a test of significance, the independent t test was employed to assess the mean difference between two quantitative variables and two qualitative variables, respectively.

Graphical representation of data: MS Excel and MS Word were used to generate different graphs such as bar graphs and line graphs.

After applying all statistical test procedures, a **P value** (probability that the result is true) of 0.05 was declared statistically significant.

Statistical software: MS Excel and SPSS version 22 (IBM SPSS Statistics, Somers, NY, USA) have been used to interpret data.

OBSERVATION AND RESULTS

In our study, a total of 70 study participants who are scheduled for elective lower limb surgeries under spinal anaesthesia, were taken in our institute from December 2019 to September 2021. The data was collected and statistical analysis was performed. The results were as follows;

DEMOGRAPHIC PROFILE

Table 1: Mean Age Comparison between two groups

	Group				p value
	Group NB		Group FB		
	Mean	SD	Mean	SD	
Age(yrs)	38.97	12.43	40.26	11.06	0.649

Mean Age in Group NB was 38.97 ± 12.43 and in Group FB was 40.26 ± 11.06. Statistically significant difference not found in mean Age comparison between two groups.

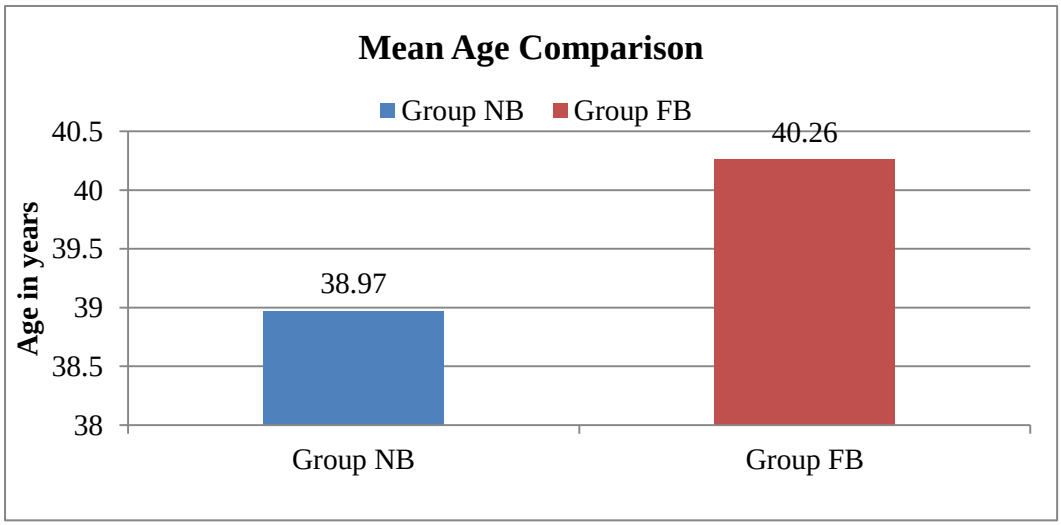

Figure 1: Bar Diagram Showing Mean Age Comparison between two groups

Table 2: Sex Distribution between two groups

		Group			
		Group NB		Group FB	
		Count	%	Count	%
Sex	Female	8	22.86%	11	31.43%
	Male	27	77.14%	24	68.57%

$\chi 2 = 0.65$, df = 1, p = 0.42

In Group NB, 22.86% were female and 77.14% were male.

In Group FB, 31.43% were female and 68.57% were male.

Significant difference was not observed in Sex Distribution among two groups.

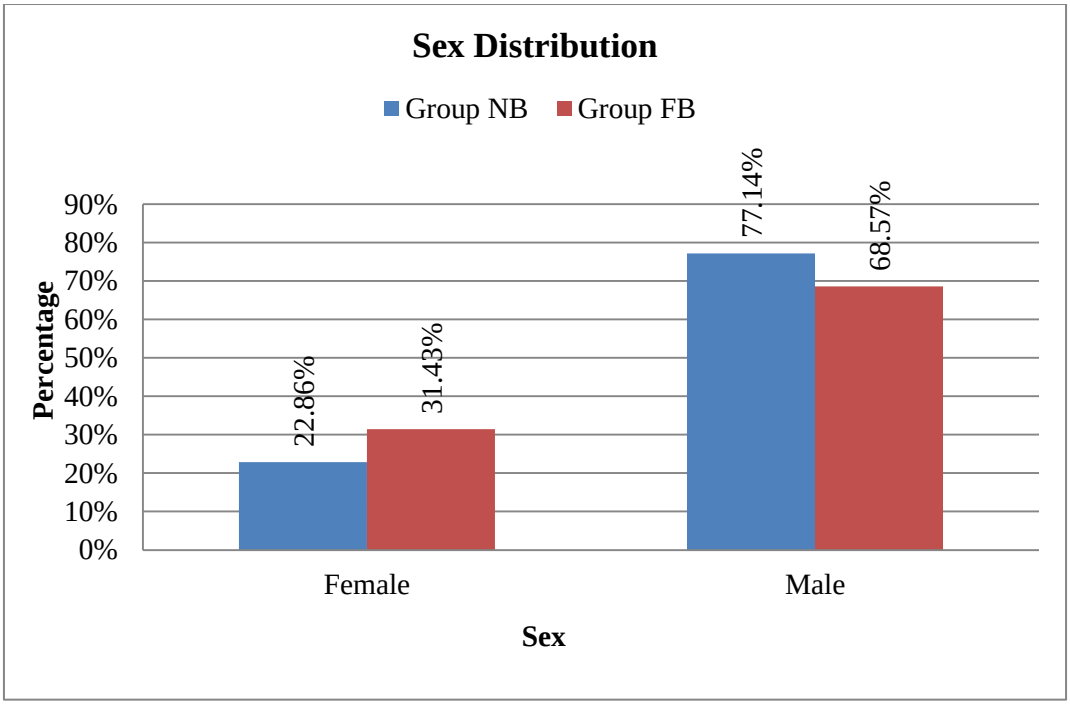

Figure 2: Bar Diagram Showing Sex Distribution between two groups

Table 3: ASA Distribution between two groups

		Group			
		Group NB		Group FB	
		Count	%	Count	%
ASA	1	21	60.00%	24	68.57%
	2	14	40.00%	11	31.43%

$\chi 2$ = 0.56, df = 1, p = 0.454

In Group NB, 60.00% had ASA Grade 1 and 40.00% had ASA Grade 2.

In Group FB, 68.57% had ASA Grade 1 and 31.43% had ASA Grade 2.

There was no significant difference in ASA Distribution between two groups.

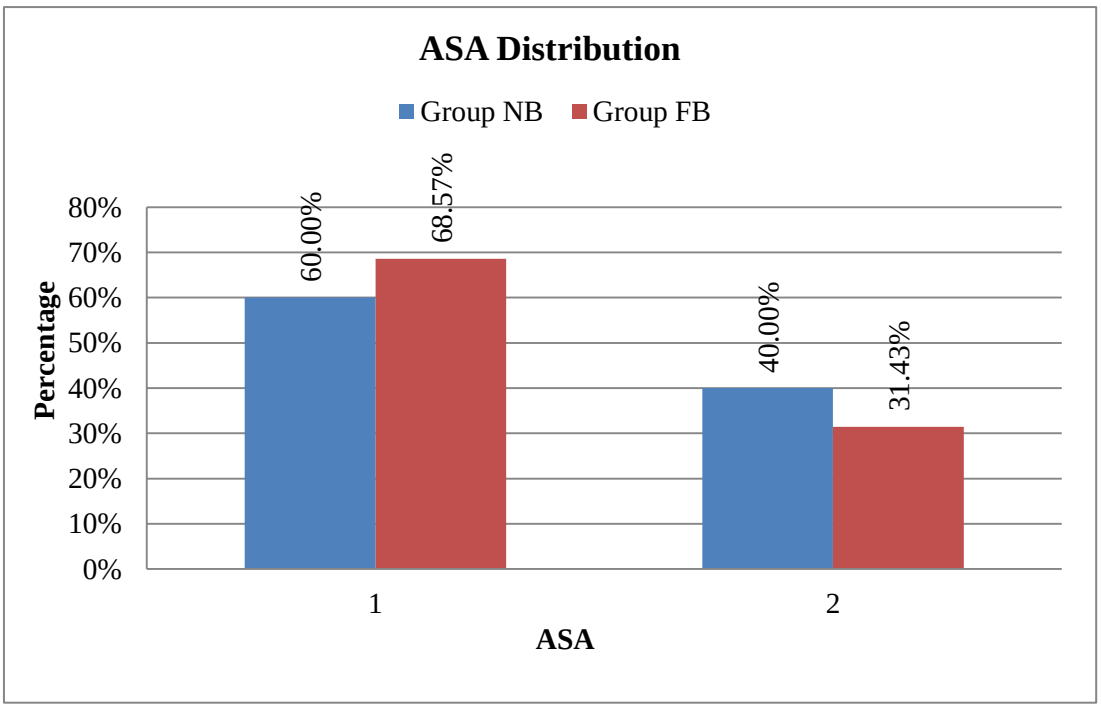

Figure 3: Bar Diagram Showing ASA Distribution between two groups

Table 4: Mean BMI Comparison between two groups

	Group				p value
	Group NB		Group FB		
	Mean	SD	Mean	SD	
BMI	22.91	1.98	22.37	2.16	0.285

Mean BMI in Group NB was 22.91 ± 1.98 and in Group FB was 22.37 ± 2.16.

There was no significant difference in mean BMI comparison between two groups.

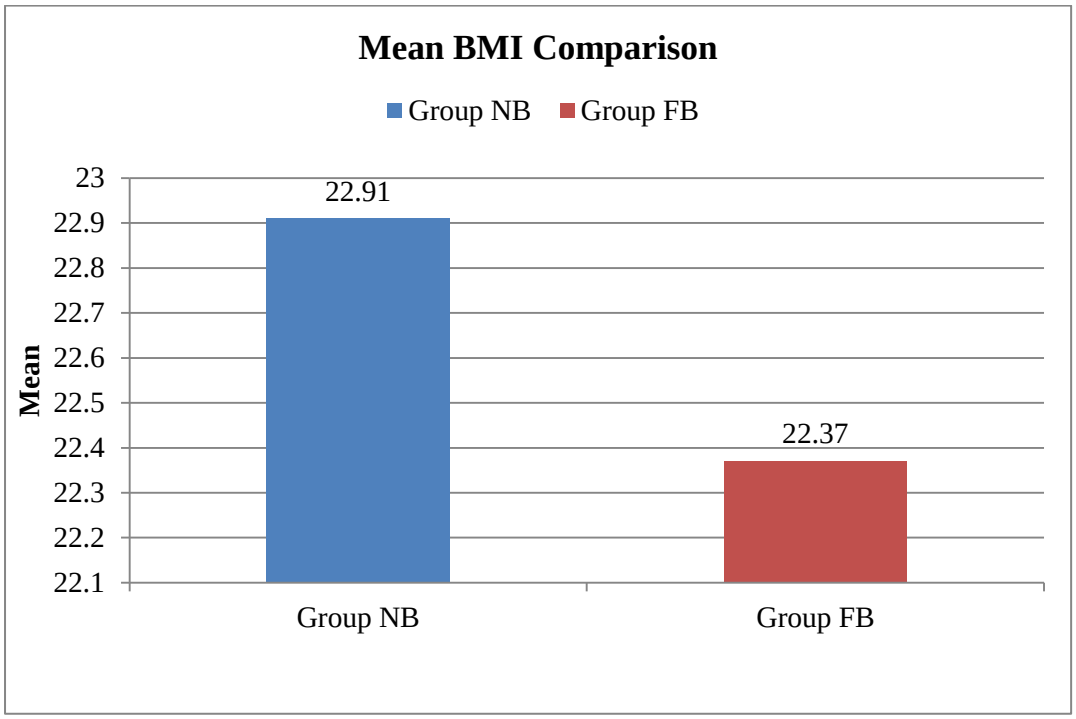

Figure 4: Bar Diagram Showing Mean BMI Comparison between two groups

Table 5: Mean time of Onset of Sensory Block Comparison between two groups

ONSET OF SENSORY BLOCK (seconds)	Group				p value
	Group NB		Group FB		
	Mean	SD	Mean	SD	
	178	14.97	174.4	12.57	0.28

Mean Onset of Sensory block in Group NB was 178 ± 14.97 seconds and in Group FB was 174.4 ± 12.57 seconds. There was no significant difference in mean Onset of sensory block comparison between two groups.

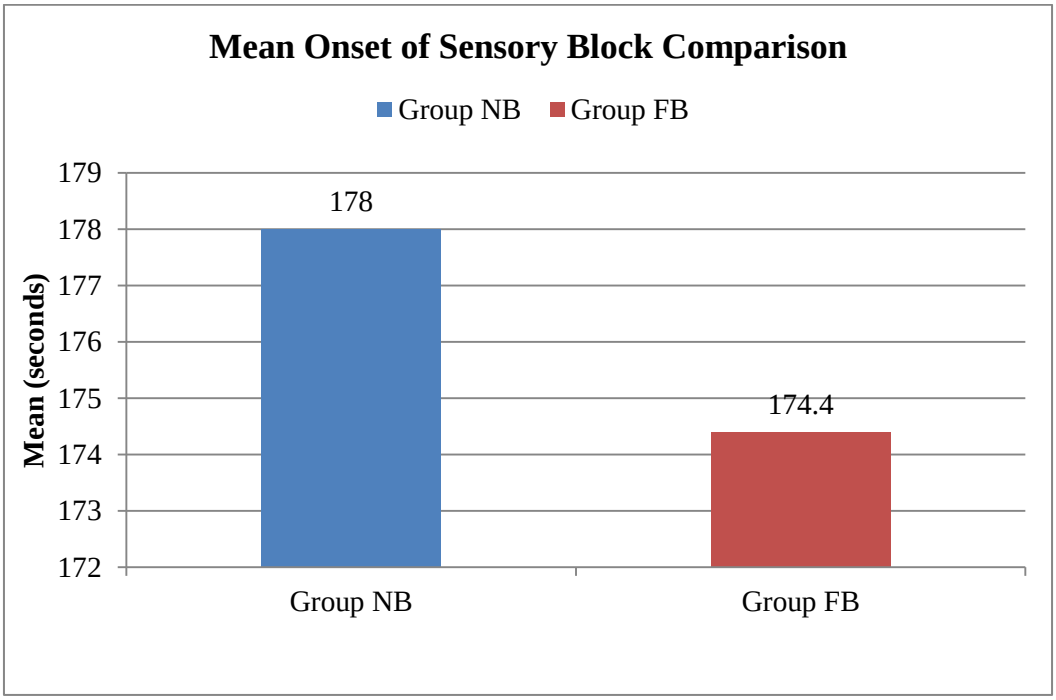

Figure 5: Bar Diagram Showing Mean Onset of Sensory Block Comparison between two groups

Table 6: Mean time of Onset of Motor Block Comparison between two groups

Onset of Motor Block (seconds)	Group				p value
	Group NB		Group FB		
	Mean	SD	Mean	SD	
	318.09	13.36	322.23	16.29	0.249

Mean Onset of Motor Block in Group NB was 318.09 ± 13.36 seconds and in Group FB was 322.23 ± 16.29 seconds.

There was no significant difference in mean time of Onset of Motor Block comparison between two groups.

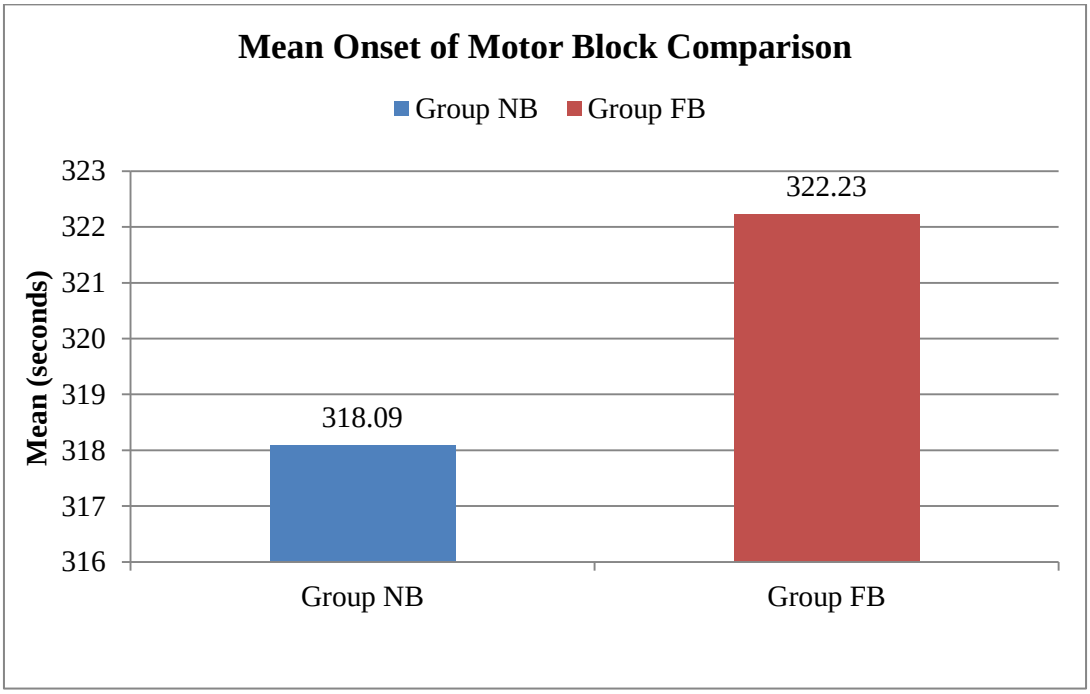

Figure 6: Bar Diagram Showing Mean Onset of Motor Block Comparison between two groups

Table 7: Mean Duration of Sensory Block Comparison between two groups

DURATION OF SENSORY BLOCK (min)	Group				p value
	Group NB		Group FB		
	Mean	SD	Mean	SD	
	126.06	6.52	103.34	3.7	< 0.001*

Mean Duration of Sensory Block in Group NB was 126.06 ± 6.52 min and in Group FB was 103.34 ± 3.7 min.

There was a significant difference in mean Duration of Sensory Block comparison between two groups.

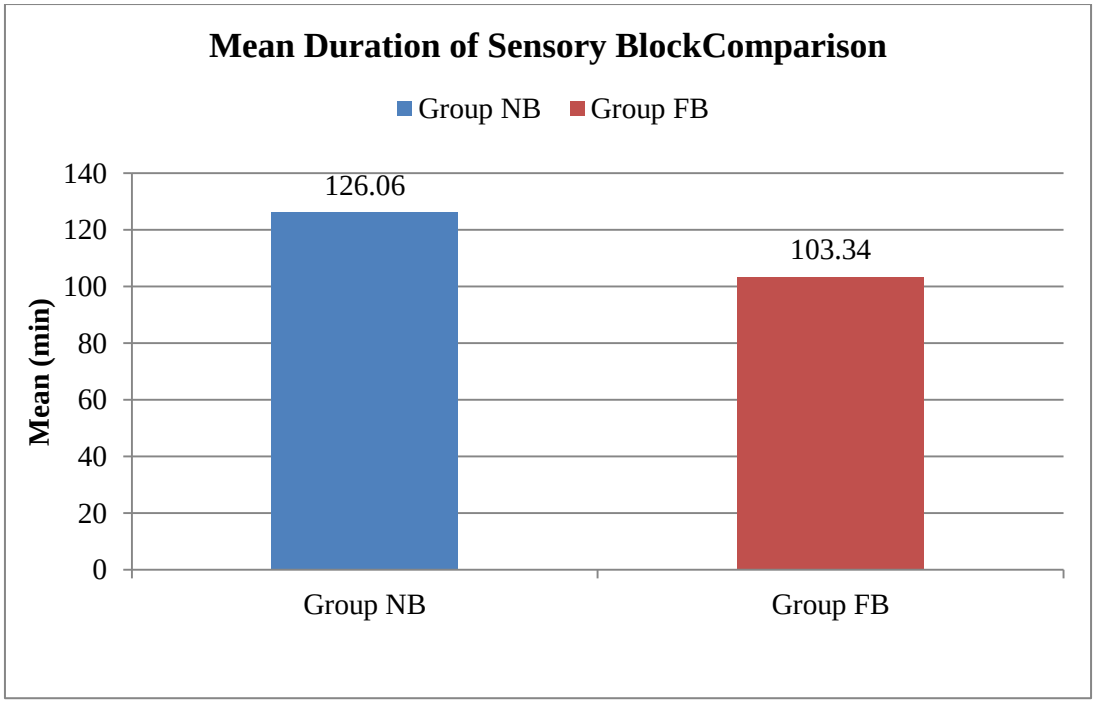

Figure 7: Bar Diagram Showing Mean Duration of Sensory block Comparison between two groups

Table 8: Mean Duration of Motor Block Comparison between two groups

DURATION OF MOTOR BLOCK (min)	Group				p value
	Group NB		Group FB		
	Mean	SD	Mean	SD	
	156.66	9.31	135.43	6.63	< 0.001*

Mean Duration of Motor Block in Group NB was 156.66 ± 9.31 min and in Group FB was 135.43 ± 6.63 min.

There was a significant difference in mean Duration of Motor Block comparison between two groups.

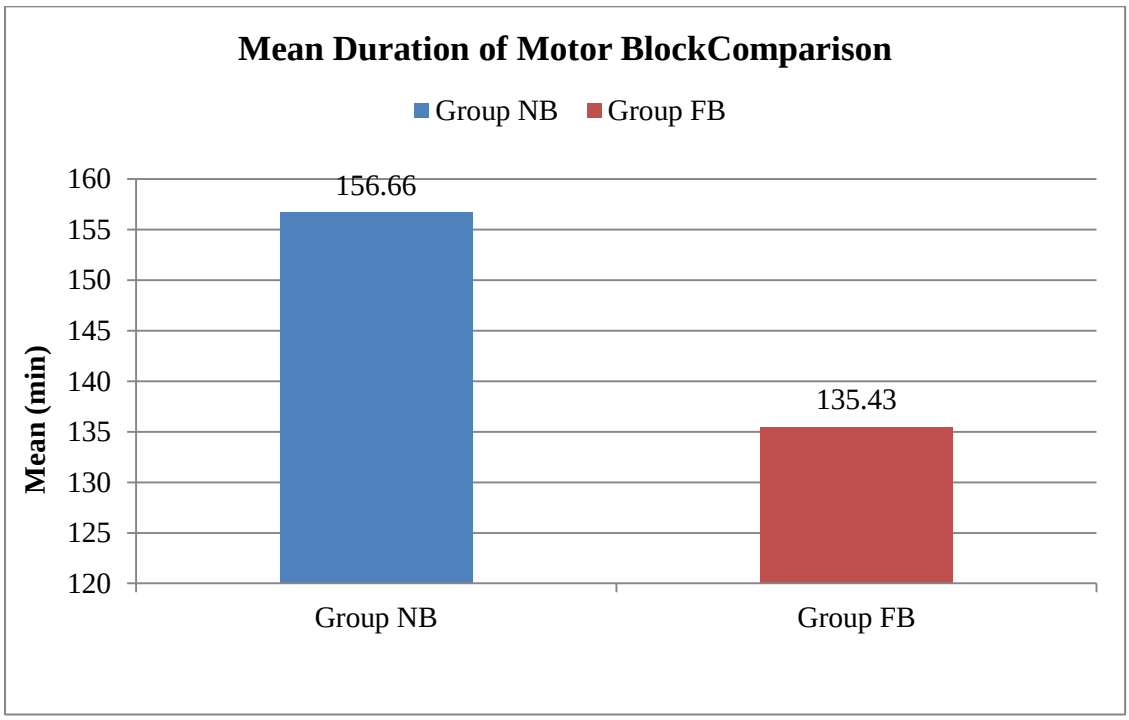

Figure 8: Bar Diagram Showing Mean Duration of Motor Block Comparison between two groups

Table 9: Mean Duration of Analgesia Comparison between two groups

Duration of Analgesia (min)	Group				p value
	Group NB		Group FB		
	Mean	SD	Mean	SD	
	278.31	9.58	230.83	7.98	< 0.001*

Mean Duration of Analgesia in Group NB was 278.31 ± 9.58 min and in Group FB was 230.83 ± 7.98 min.

There was a significant difference in mean Duration of Analgesia comparison between two groups.

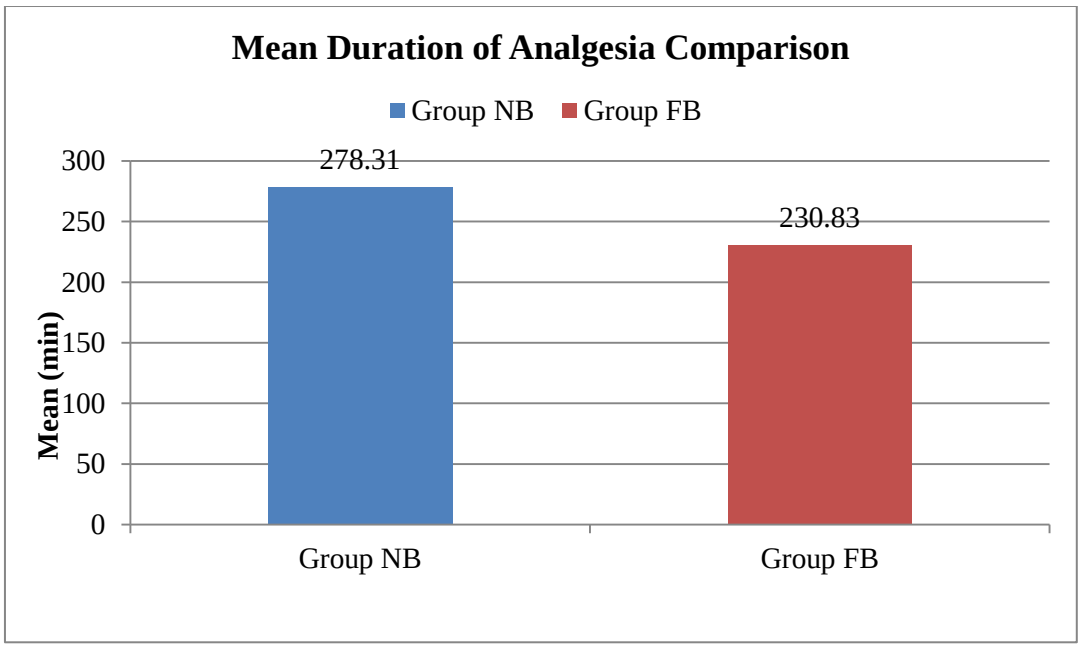

Figure 9: Bar Diagram Showing Mean Duration of Analgesia Comparison between two groups

Table 10: Mean Heart Rate Comparison between two groups at different intervals of time

Heart Rate	Group				p value
	Group NB		Group FB		
	Mean	SD	Mean	SD	
0 min	76.74	6.8	76.17	8	0.748
5 min	80.83	12.91	78	8.57	0.284
10 min	88.66	19.39	83.46	14.21	0.205
15 min	89.06	17.53	84.71	14.26	0.26
30 min	84	12.73	81	9.79	0.273
60 min	79.86	9.85	78.09	7.45	0.399
120 min	77.69	6.84	76.03	6.64	0.307

The mean Heart Rate of the two groups at different time intervals did not differ significantly at any period.

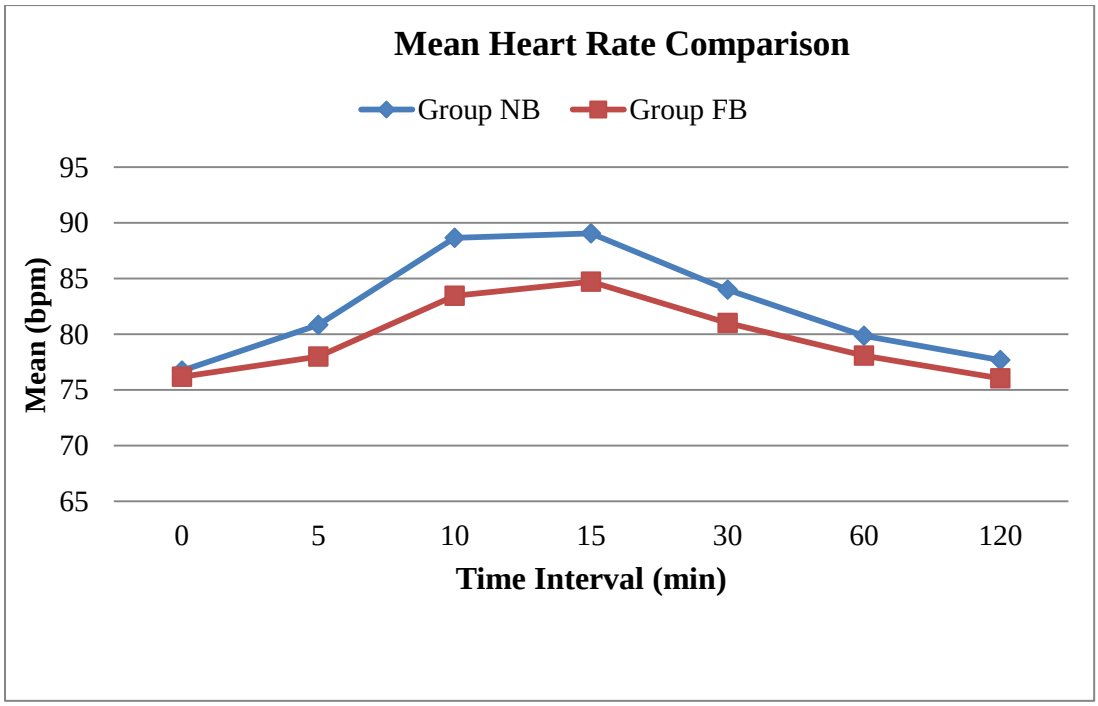

Figure 10: Line Graph Showing Mean Heart Rate Comparison between two groups at different intervals of time

Table 11: Mean Systolic Blood Pressure Comparison between two groups at different intervals of time

SYSTOLIC BLOOD PRESSURE	Group				p value
	Group NB		Group FB		
	Mean	SD	Mean	SD	
0 min	120.37	7.12	119.17	8.23	0.516
5 min	114.34	8.87	111.31	13.39	0.269
10 min	111.14	11.87	109.31	12.72	0.536
15 min	114.51	7.96	114.03	10.33	0.826
30 min	117.2	7.18	115.89	8.22	0.479
60 min	118	6.45	117.37	7.62	0.711
120 min	117.8	5.95	118.17	7.43	0.818

The mean Systolic Blood Pressure of the two groups at different time intervals did not differ significantly at any period.

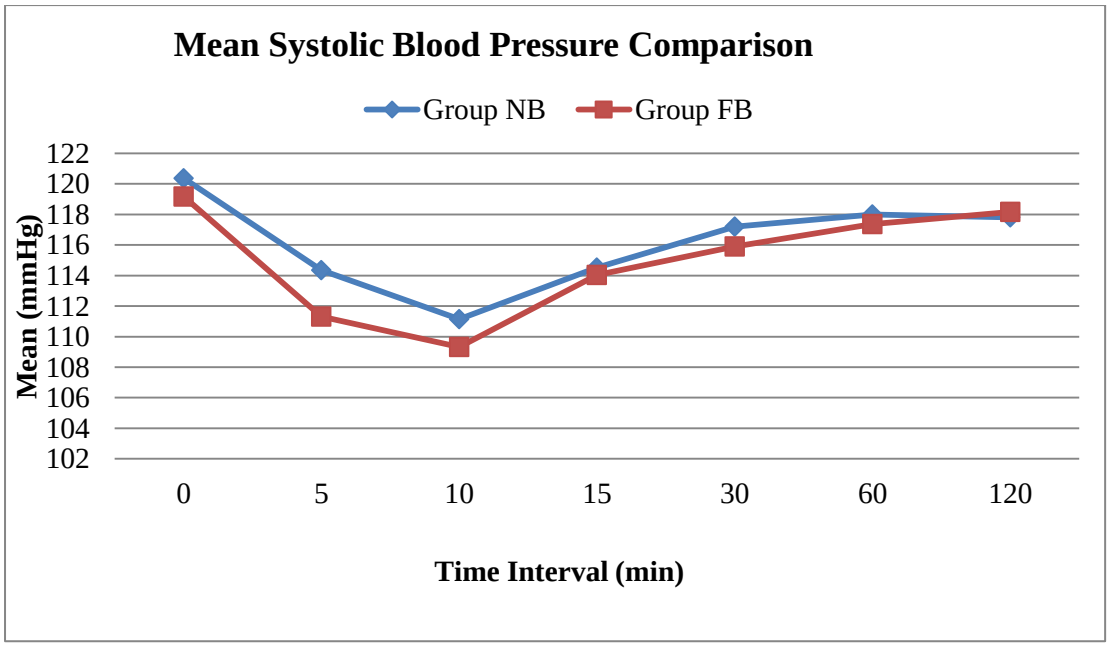

Figure 11: Line Graph Showing Mean Systolic Blood Pressure Comparison between two groups at different intervals of time

Table 12: Mean Diastolic Blood Pressure Comparison between two groups at different intervals of time

DIASTOLIC BLOOD PRESSURE	Group				p value
	Group NB		Group FB		
	Mean	SD	Mean	SD	
0 min	75.23	5.47	74.29	5.13	0.459
5 min	73.57	6.12	70.2	8.42	0.059
10 min	72.54	6.99	70.2	7.12	0.169
15 min	73.4	6.05	71.4	5.87	0.165
30 min	73.37	5.88	72.43	5.8	0.502
60 min	73.11	5.31	73.29	4.97	0.89
120 min	74.14	5.6	75	5.21	0.51

The mean diastolic blood pressure of the two groups at different time intervals did not differ significantly at any period.

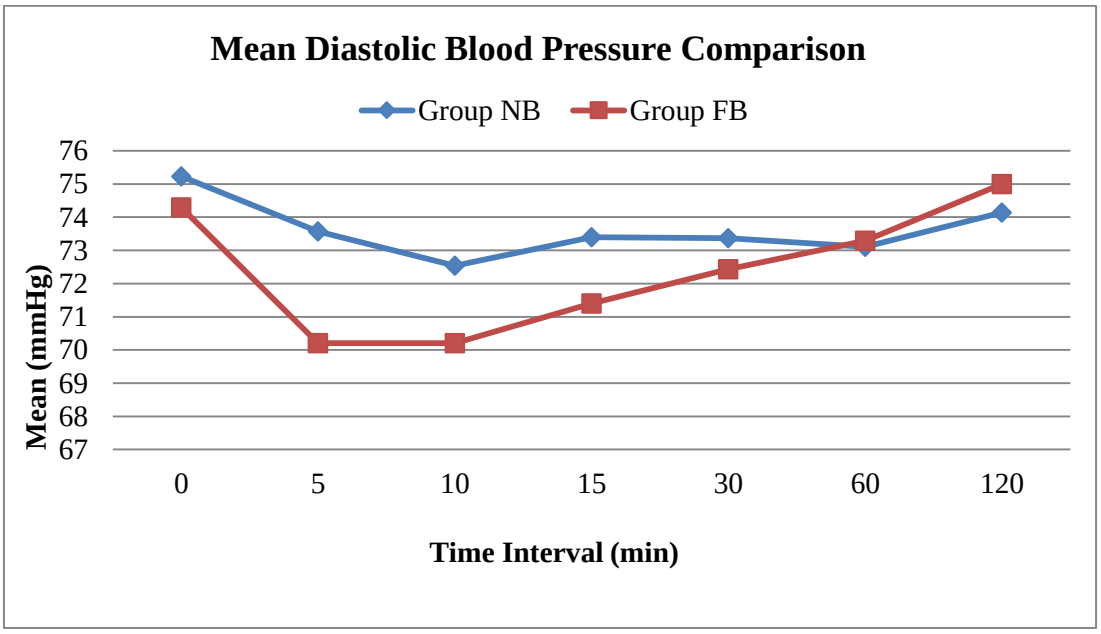

Figure 12: Line Diagram Showing Mean Diastolic Blood Pressure Comparison between two groups at different intervals of time

Table 13: Mean VAS Score Comparison between two groups at different intervals of time

VAS Score	Group				p value
	Group NB		Group FB		
	Mean	SD	Mean	SD	
0 hrs	0	0	0	0	-
2 hrs	0.4	0.6	0.49	0.66	0.572
4 hrs	1.29	1.07	2.86	1.38	< 0.001*
6 hrs	3.63	0.91	3.71	0.96	0.702

At 4 hours, there was a significant difference in the mean VAS Score Comparison between the two groups. There was no significant change at other intervals.

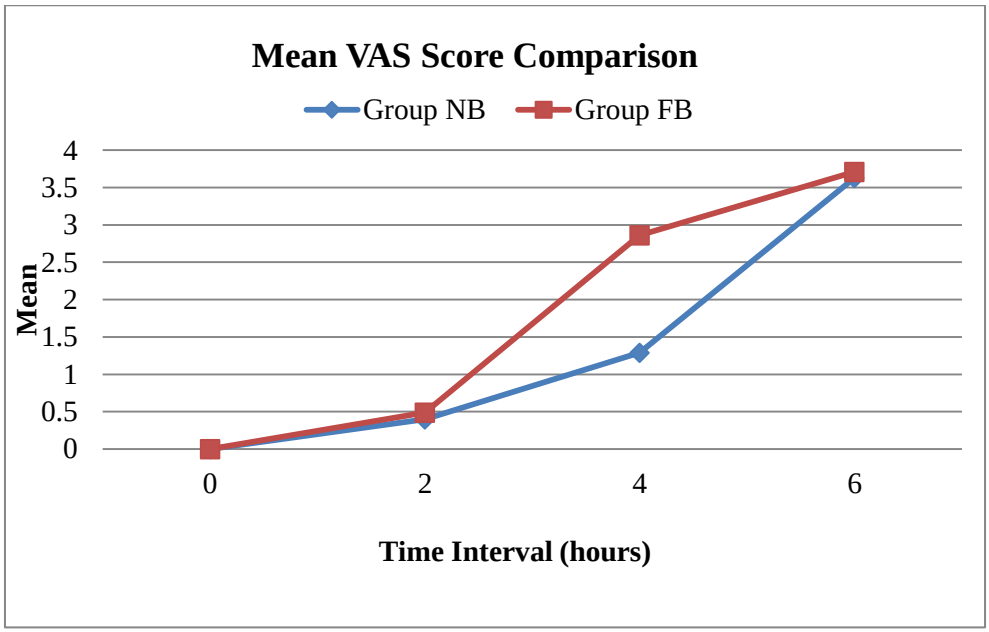

Figure 13: Line Diagram Showing Mean VAS Score Comparison between two groups at different intervals of time

Table 14: Side Effects Distribution between two groups

SIDE EFFECTS		Group				Chi Square
		Group NB		Group FB		
		Count	%	Count	%	
Nausea	No	27	77.14%	28	80.00%	0.771
	Yes	8	22.86%	7	20.00%	
Vomiting	No	31	88.57%	31	88.57%	1.000
	Yes	4	11.43%	4	11.43%	
Bradycardia	No	31	88.57%	31	88.57%	1.000
	Yes	4	11.43%	4	11.43%	
Hypotension	No	22	62.86%	22	62.86%	1.000
	Yes	13	37.14%	13	37.14%	

There was no statistically significant difference seen in Side Effects Distribution between two groups.

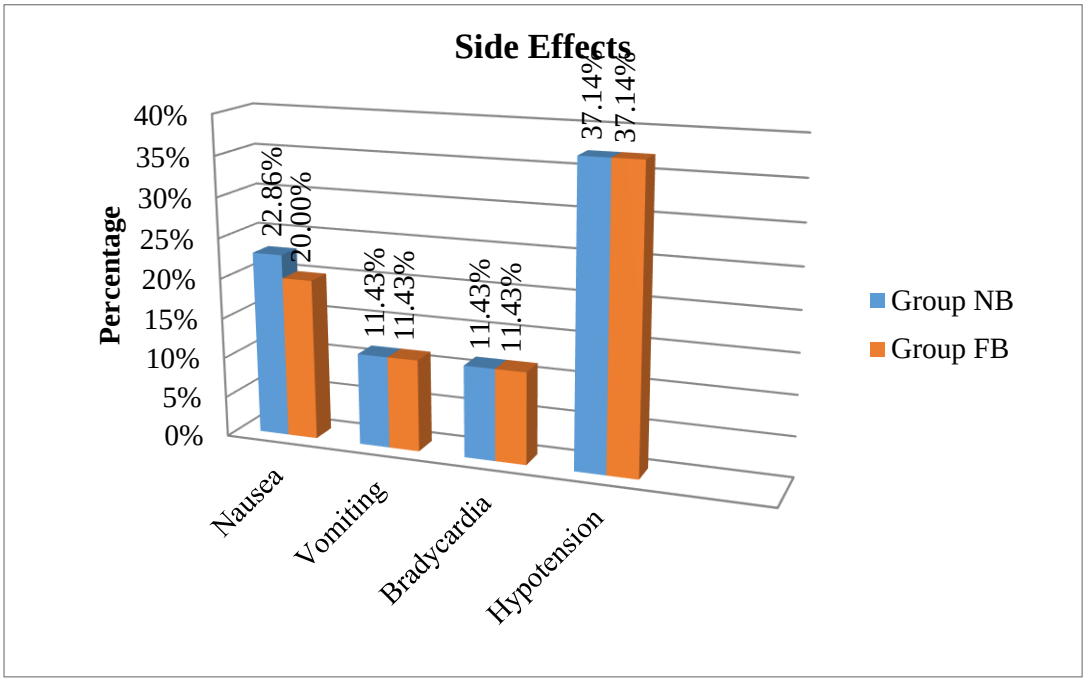

Figure 14: Bar Graph Showing Side Effects Distribution between two groups

DISCUSSION

Subarachnoid block has been used more extensively in lower limb procedures. The use of adjuvants, particularly opioids such as fentanyl and nalbuphine, in conjunction with hyperbaric bupivacaine has been demonstrated to minimise its dose required in subarachnoid block with a lower incidence of adverse effects and a lower dose of analgesia requirement. The main benefit is selective pain blockade without considerable sympathetic and motor block, allowing for greater haemodynamic stability, early ambulation of patients, and elimination of catastrophic side effects such as cardiovascular collapse.

Subarachnoid block is the choice of anaesthesia considered for lower abdominal and lower extremity surgeries. Subarachnoid block with local anaesthetics alone has shorter duration of post operative analgesia. To extend post-operative analgesia, opioid additives such as fentanyl, morphine, and buprenorphine have been explored. Intrathecal opioids can give longer-lasting post-operative analgesia while causing less negative effects than systemic opioids.[69] The commonly administered opioids are typically agonist agents with extremely good analgesic efficacy but with a variety of μ accompanying adverse effects. Later, it was discovered that strong analgesia can be produced by acting on kappa binding sites without causing any μ related side effects.[70,71] There were studies on opioids like Nalbuphine which is kappa agonist/partial μ antagonist analgesic[72] as an adjuvant in spinal anaesthesia.

So, We conducted a randomized comparative study to compare the efficacy intrathecal nalbuphine 1mg and fentanyl 25μg as adjuvants to 0.5% heavyc bupivacaine in patients scheduled for elective lower limb procedures.

Culebras *et al*.[15] contrasted intrathecal morphine to nalbuphine in doses of 0.2 mg, 0.8 mg, and 1.6 mg, reporting that intrathecal nalbuphine 0.8 mg gives greater intraoperative and early pain relief with no adverse effects. They also discovered that raising the intrathecal nalbuphine dose to 1.6 mg did not improve analgesic effects but did raise the adverse effects in this group. It claims that raising the dose of nalbuphine enhances its analgesic impact only up to a certain level, after which there is no subsequent rise in its analgesic action. i.e. it exhibits a ceiling effect. So in this study we have taken 1 mg nalbuphine to compare with fentanyl 25μg.

In this current study, the onset of sensory block was comparable in group NB (178 ± 14.97 seconds) and group FB (174.4 ± 12.57 seconds) and there has been no significant difference between the 2 groups in terms of reaching T8 sensory block level (P=0.280). Gomaa *et al*.[22] observed no significant variation in the initiation of sensory block between the fentanyl and nalbuphine groups when compared intrathecal nalbuphine 0.8 mg and fentanyl 25 g. Similarly, Gupta *et al*.[10] also reported no statistically significant difference among nalbuphine and fentanyl groups.

The mean time for motor block development in group NB was 318.09 ± 13.36 seconds comparing to 322.23 ± 16.29 seconds in group FB, which was not significant (p=0.249). Gupta *et al*.[10] and Bindra *et al*.[14] also observed insignificant difference for time of onset of motor block among the two groups. But Gomaa *et al*,[22] in their study observed that the onset of motor block was significantly faster with fentanyl than with nalbuphine.

In our study, the mean duration of sensory block was longer (126.06 ± 6.52 min) in patients of group NB than patients of group FB (103.34 ± 3.7 min) and it was statistically significant (P< 0.001). Gurunath *et al*.[73] and Gupta et al.[10] in their study

discovered that the time of 2 segment sensory regression in the nalbuphine group was much longer than in the fentanyl group.

The duration of motor block in patients of group NB (156.66 ± 9.31 min) was more than that of group FB (135 ± 6.63 min) which is statistically significant ($p<0.001$). Gupta *et al.*[10] and Ahulwalia P *et al.*[13] also found similar results in their study that nalbuphine group had prolonged duration of motor block compared to fentanyl group.

In this study we have found that patients who received intrathecal nalbuphine 1mg as an adjuvant had a significantly prolonged duration of analgesia than in patients with intrathecal fentanyl 25µg ($p<0.001$). The mean duration of analgesia in group NB was 278.31 ± 9.58 min and in group FB was 230.83 ± 7.98 min. Tiwari *et al.*[25] in their study have found that nalbuphine had longer duration of analgesia compared to fentanyl and was ststistically significant. Gomaa *et al.*[22] compared postoperative analgesia between intrathecal fentanyl 25µg with nalbuphine 0.8 mg and it was prolonged in nalbuphine group but it was not significant difference statistically.

There was no statistically significant difference in vitals like Heart Rate, Systolic Blood Pressure and Diastolic Blood Pressure at 0, 5, 10, 15, 30, 60 and 120 min time intervals among two groups. Chawla R *et al.*[74] in 1989, studied the effects of different intrathecal pentazocine doses combined with 1% bupivacaine and did not find any significant changes in hemodynamic condition. Our findings were identical to those of the previous study.

In this study there was no significant difference in mean VAS score between two groups from 0 to 2 hours, at 4 hours mean VAS Score was higher in Group FB compared to Group NB. Bindra TK *et al.*[14] found that in the nalbuphine group, the mean VAS score for postoperative pain was lesser than in the fentanyl group. Mostafa

et al.[75] and Naaz *et al*.[76] found that patients who received intrathecal nalbuphine required a much smaller amount of rescue analgesics.

Side effects such as nausea, vomiting, bradycardia and hypotension following administration of spinal anaesthesia with the above intrathecal opioids were minimal in both the groups and did not differ much among the two groups and was statistically insignificant. In their trial, Singh *et al*.[77] found that adding nalbuphine to intrathecal bupivacaine maintained sensory block and post-operative analgesia without worsening side effects or complications. Gurunath *et al*.[73] compared intrathecal nalbuphine to fentanyl as a spinal adjuvant and found that individuals receiving nalbuphine had less side effects than those received fentanyl.

CONCLUSION

On the basis of the present clinical comparative study, we can conclude that the addition of 1mg Nalbuphine 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.

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ANNEXURE-I

ETHICAL COMMITTEE CLEARANCE

IEC/NO-131/2019
22-11-2019

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

(Declared vide notification No. F.9-37/2007-U.3 (A) Dated. 29-2-2008 of the MHRD, Government of India under Section 3 of the UGC Act, 1956)

The Constituent College

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

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The ethical committee of this college met on 13-11-2019 at 3-15 pm to 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 been accorded Ethical Clearance

Title: A comparative study to know the efficacy of intrathecal nalbuphine versus intrathecal fentanyl as an adjuvant to bupivacaine for lower limb surgeries

Name of PG student: Dr. Swathi N R, Department of Anaesthesiology

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

DR RAGHVENDRA KULKARNI
CHAIRMAN

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

Following documents were placed before Ethical Committee for Scrutinization:

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

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B.L.D.E.(Deemed to be University)
SHRI B.M.PATIL MEDICAL COLLEGE,VIJAYAPUR-586103
INSTITUTIONAL ETHICAL COMMITTEE

Date : 13-11-2019

1. Name of UG/PG Students/Researcher: Dr. Swathi N R
2. Department : Anaesthesiology
3. Title : A Comparative Study To Know The Efficacy Of Intrathecal Nalbuphine Versus Intrathecal Fentanyl As An Adjuvant To Bupivacaine For Lower Limb Surgeries
4. Guide/Co-Guide/Principle Researcher: Dr. Vijay. V. Katti, Associate Prof
5. Date of Admission (PG Only) :

Observation :

- No ethical issues observed

I.E.C. Remarks : Ethical Clearance accorded/be Chairman after corrected revised version is submitted by stipulated time.
1. Any alternation in Synopsis protocol should be intimated to E.C. in writing for review & approval.
2. Any adverse effects to subject of the study should be intimated in writing to E.C.
3. If study is stopped or an included patient is out of study inform E.C. the same with reason.

Signature of the Committee Members :

1. Dr Raghavendra Kulkarni, Chairman
2. Dr Tejaswini Vallabha
3. Dr Akram Naikawadi
4. Dr P.B.Jaju
5. Dr Chandrashekhar Bhuyyar
6. Dr Pranesh Jahagirdar
7. Dr Manjunatha Aithala
8. Dr Satish Patil
9. Dr Mohammed Shannawaz

ANNEXURE – II

SAMPLE INFORMED CONSENT FORM

BLDE (DEEMED TO BE UNIVERSITY)'s SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPURA – 586103, KARNATAKA

TITLE OF THE PROJECT **:** "A COMPARATIVE STUDY TO KNOW THE EFFICACY OF INTRATHECAL NALBUPHINE VERSUS INTRATHECAL FENTANYL AS AN ADJUVANT TO BUPIVACAINE FOR LOWER LIMB SURGERIES".

PRINCIPAL INVESTIGATOR **:** Dr. SWATHI N R
Department of Anaesthesiology

PG GUIDE **:** Dr. VIJAY V KATTI
Associate Professor,
Department of Anaesthesiology
BLDE (DEEMED TO BE UNIVERSITY)
Shri B M Patil Medical College and Research Centre, Sholapur Road, VIJAYAPURA-03

PURPOSE OF RESEARCH:

I have been informed that this, study is **:"** A COMPARATIVE STUDY TO KNOW THE EFFICACY OF INTRATHECAL NALBUPHINE VERSUS INTRATHECAL FENTANYL AS AN ADJUVANT TO BUPIVACAINE FOR LOWER LIMB SURGERIES**".**

I have been explained about the reason for conducting this study and selecting me/my ward as a subject for this study. I have also been given free choice for either being included or not in the study.

PROCEDURE:

I understand that I will be doing ‘‘A COMPARATIVE STUDY TO KNOW THE EFFICACY OF INTRATHECAL NALBUPHINE VERSUS INTRATHECAL FENTANYL AS AN ADJUVANT TO BUPIVACAINE FOR LOWER LIMB SURGERIES’’

RISKS AND DISCOMFORTS:

I understand that I/my ward may experience hypotension while doing the procedure and I understand that necessary measures will be taken to reduce these complications as and when they arise.

BENEFITS:

I understand that I/my wards participation in this study will help in finding out**.** **“**A COMPARATIVE STUDY TO KNOW THE EFFICACY OF INTRATHECAL NALBUPHINE VERSUS INTRATHECAL FENTANYL AS AN ADJUVANT TO BUPIVACAINE FOR LOWER LIMB SURGERIES**”**

CONFIDENTIALITY:

I understand that medical information produced by this study will become a part of this Hospital records and will be subjected to the confidentiality and privacy regulation of this hospital. Information of a sensitive, personal nature will not be a part of the medical records, but will be stored in the investigator’s research file and

identified only by a code number. The code key connecting name to numbers will be kept in a separate secure location.

If the data are used for publication in the medical literature or for teaching purpose, no names will be used and other identifiers such as photographs and audio or video tapes will be used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time.

Dr SWATHI N R is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me.

And that a copy of this consent form will be given to me for keep for careful reading.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I also understand that **Dr SWATHI N R** will terminate my participation in this study at any time after he has explained the reasons for doing so and has helped arrange for my continued care by my own physician or therapist, if this is appropriate

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/my ward, resulting directly to my participation in this study, if such injury were reported promptly, then medical treatment would be available to me, but no further compensation will be provided.

I understand that by my agreement to participate in this study, I am not waiving any of my legal rights.

I have explained to _____, the purpose of this research, the procedures required and the possible risks and benefits, to the best of my ability in patient's own language.

Date: Dr. VIJAY V KATTI (Guide) Dr. SWATHI N R (Investigator)

STUDY SUBJECT CONSENT STATEMENT:

I confirm that **Dr SWATHI N R** 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

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 [ ]

MONITORING

Time (min)	Pulse Rate /min	B.P (mmHg)	Resp Rate /min	SpO_2 %
0 min				
5 min				
10 min				
15 min				
30 min				
60 min				
120 min				

Time of first rescue analgesia will be noted.

Study ends when patient demands for analgesic in postoperative period.

DATE: STAFF SIGNATURE