"COMPARISON OF ONSET AND DURATION OF BLOCKADE AND POST OPERATIVE ANALGESIA OF ISOBARIC ROPIVACAINE 0.75% WITH FENTANYL AND ISOBARIC ROPIVACAINE 0.5% WITH FENTANYL IN FEMALE PATIENTS UNDERGOING LOWER ABDOMINAL SURGERIES UNDER EPIDURAL ANAESTHESIA - A ONE YEAR HOSPITAL BASED RANDOMISED CONTROLLED TRIAL"

By

REG NO.BA0114002

Dissertation

Submitted to the
KLE University, Belagavi, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
ANAESTHESIOLOGY

DEPARTMENT OF ANAESTHESIOLOGY,

JAWAHARLAL NEHRU MEDICAL COLLEGE,

BELAGAVI, KARNATAKA

APRIL– 2017

KLE UNIVERSITY, BELAGAVI, KARNATAKA

ENDORSEMENT

This is to certify that the dissertation entitled **"COMPARISON OF ONSET AND DURATION OF BLOCKADE AND POSTOPERATIVE ANALGESIA OF ISOBARIC ROPIVACAINE 0.75% WITH FENTANYL AND ISOBARIC ROPIVACAINE 0.5% WITH FENTANYL IN FEMALE PATIENTS UNDERGOING LOWER ABDOMINAL SURGERIES UNDER EPIDURAL ANAESTHESIA - A ONE YEAR HOSPITAL BASED RANDOMISED CONTROLLED TRIAL"** is a bonafide research work done by **REG NO.BA0114002.**

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LIST OF ABBREVIATIONS USED

ASA	-	American Society of Anaesthesiologists
C	-	Cervical
T	-	Thoracic
Mcg	-	Microgram
cc	-	Cubic centimeter
CNS	-	Central nervous system
CSF	-	Cerebrospinal fluid
CVS	-	Cardiovascular system
DBP	-	Diastolic blood pressure
ED	-	Effective dose
FDA	-	Food and Drug Administration
GA	-	General anaesthesia
HCO_3	-	Bicarbonate
HR	-	Heart rate
bpm	-	Beats per minute
I.V.	-	Intravenous
HCL	-	Hydrochloric Acid
KCl	-	Potassium chloride
kg	-	Kilogram
L	-	Lumbar
m	-	Meters
MAP	-	Mean arterial pressure
mg	-	Milligram
v/s	-	Versus

Min	-	Minutes
ml	-	Millilitre
NIBP	-	Non invasive blood pressure
O_2	-	Oxygen
$PaCO_2$	-	Partial pressure of carbon dioxide
S	-	Sacral
SAB	-	Subarachnoid block
SBP	-	Systolic blood pressure
SD	-	Standard deviation
Sec	-	Second
SpO_2	-	Peripheral saturation of oxygen
TNS	-	Transientneurologicalsymptoms
α	-	Alpha
β	-	Beta
δ	-	Delta
μ	-	Mu
cm	-	centimeter
G	-	Gauge
mEq	-	milliequivalents
Lt	-	litre
Dl	-	decilitre
V_{max}	-	maximum initial velocity or rate of a reaction.

ABSTRACT

Background and objective : Epidural anaesthesia is increasingly becoming popular as the neuraxial block of choice for lower abdominal and lower limb surgeries due to various advantages over sub arachnoid block. Ropivacaine, a newer amide local anaesthetic with excellent sensory blockade with less dense motor block and a much more cardiostable profile compared to bupivacaine is increasingly replacing the latter as the drug of choice in epidural anaesthesia. Opioids especially the highly lipid soluble fentanyl, provide synergistic action with local anaesthetics and are popular adjuvants for epidural block. The present study was done to compare the onset and duration of sensory block and post operative analgesia between 0.75% ropivacaine with 50 mcg fentanyl and 0.5% ropivacaine with 50 mcg fentanyl in female patients undergoing lower abdominal surgeries under epidural anaesthesia.

Methods: The present one year randomised clinical trial was undertaken at Department of Anaesthesiology, KLES Dr. Prabhakar Kore Charitable Hospital, Belagavi from January 2015 to December 2015. A total of 80 female patients undergoing lower abdominal surgeries under epidural anaesthesia were randomly allocated into two groups using a computer generated randomization chart as follows :Group A received 15 ml of 0.75% ropivacaine and 50 mcg fentanyl by epidural route, (n=40) while Group B received 15 ml of 0.5% ropivacaine and 50 mcg fentanyl by epidural route, (n=40)

Results : The demographic data was comparable in both the groups. The mean time of onset of sensory block in this study was significantly faster in group A(8.8$\pm$ 1.33 min) than in Group B(14.8 $\pm$ 0.97 min).The duration of sensory block was significantly longer in group A (150 $\pm$ 11.09 min) than in Group B (137.2 $\pm$ 9.93

min). The time of onset of motor block in this study was significantly faster in group A (14.4 ± 2.05 min.) than in Group B(19.1 ± 1.03 min). The duration of motor block was significantly longer in group A (164.7 ± 13.77 min.) than in Group B(152.2 ± 9.49 min). The time for rescue analgesia was significantly delayed in Group A (190.7 ± 15.91 min) as compared to Group B (163.7 ± 8.37 min). The total analgesic consumption was significantly lower in Group A (206.27 ± 73.54 mcg) than Group B (266.63 ± 63.43 mcg). There was a significant fall in heart rate, SBP and DBP in group A as compared to group B. No major side effects complications were encountered during the study.

Conclusion: Our study showed that 0.75% ropivacaine with fentanyl is significantly more potent than 0.5% ropivacaine with fentanyl in terms of onset and duration of sensory and motor block , however the overall sensory and motor block was found to be comparable. Also 0.75% ropivacaine with fentanyl provides significantly prolonged analgesia and significantly lower analgesic requirement in 24 hours than 0.5% ropivacaine with fentanyl.

The haemodynamic parameters including HR, SBP and DBP are more stable with 0.5% ropivacaine with fentanyl than 0.75% ropivacaine with fentanyl. Thus 0.5% ropivacaine with fentanyl can be used as an alternative to 0.75% ropivacaine with fentanyl for epidural anaesthesia without any major side effects/complications.

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INTRODUCTION

" Pain is inevitable , suffering is optional "

" Divine is the task to relieve pain " – Hippocrates

Pain is the most dreaded symptom of any surgical procedure. The International Association for Study of Pain defines it as an " unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage "

Providing pain relief is the principal function and duty of an anaesthesiologist.

With the field of anaesthesiology extending into the peri-operative period , expertise in acute postoperative pain management is a crucial weapon in an anaesthesiologist's armoury. Effective analgesia in both intraoperative as well as post – operative period is a cornerstone of " balanced anaesthesia " . A multimodal approach has been advised for analgesia and has more or less replaced any single technique for pain relief .

The type of anaesthesia during the intraoperative period plays a major role in providing effective postoperative analgesia which in turn is one of the most important determinants of postoperative morbidity

Neuraxial blockade is the anaesthetic technique of choice for most abdominal and lower limb surgeries. Traditionally , Sub arachnoid Block (SAB) has been preferred for these patients. Epidural anaesthesia when used was in combination with SAB.

In recent years however , more and more anaesthesiologists are trying isolated epidural anaesthesia for management of such patients.

As compared to SAB , epidural anaesthesia is more versatile and provides the anaesthesiologist with a flexibility in managing the case which is not possible with SAB. Epidural anaesthesia has a longer duration of action , ability to provide local anaesthetic topups if surgery extends beyond expected time, and ability to provide analgesic topups for post operative pain relief. It also provides better haemodynamic stability than SAB due to segmental nature of the block.[1]

Bupivacaine is a long acting amide local anaesthetic which has been the gold standard for use in all regional anaesthesia techniques including epidural anaesthesia. Its advantage is that it provides adequate sensory and motor blockade. However like all amide local anaesthetic agents , it is associated with cardiotoxicity especially when used in higher concentrations or on inadvertent intravascular injection. This has lead to a search for a safer yet effective alternative.

Ropivacaine is a relatively new long acting amide local anaesthetic . It is marketed as a pure S(-) enatiomer of its parent molecule – Propivacaine . Its apparent advantages over Bupivacaine include lesser cardiotoxicity and neurotoxicity and amore specific effect on sensory as compared to motor fibres. Both these features can be explained on the basis of lesser lipophilicity of Ropivacaine.[2]

Ropivacaine is available as 1%, 0.75% , 0.5% and 0.2% solutions. Traditionally , higher concentrations i.e 1% and 0.75% have been used for epidural anaesthesia while lower concentrations i.e 0.5% and 0.2% have been used for epidural analgesia.[2] Despite safer profile of Ropivacaine , side effects/toxicity can still occur with higher concentrations especially in epidural anaesthesia since the volume of drug injected is high.

This fine balance between safety and efficacy can be achieved by use of adjuvants , which favourably change the block characteristics of local anaesthetics , therefore reducing the required dose.[3] Adjuvants used in epidural anaesthesia broadly belong to two groups :

- Opiates (eg. Fentanyl, Morphine, Sufentanil)[4]
- α_2 - agonists (eg. Clonidine , Dexmedetomidine)[5]

Fentanyl , a selective μ receptor agonist has been one of the most commonly used adjuvant in neuraxial blockade.

There are numerous studies comparing various doses of ropivacaine with other amide local anaesthetics[6,7] and ropivacaine with various adjuvants in epidural anaesthesia[8,9]. However direct study comparing different concentration/doses of ropivacaine with an opioid adjuvant are lacking.

We therefore took up the present study to compare onset and duration of blockade and postoperative analgesia between two different concentrations of Ropivacaine(0.75% and 0.5%) along with Fentanyl in female patients undergoing lower abdominal surgeries under epidural anaesthesia .

OBJECTIVES

The objectives of the present study were :

Primary Objective: To compare the *onset and duration of sensory and motor blockade and post operative analgesia* between 0.75 % isobaric Ropivacaine with Fentanyl and 0.5 % isobaric Ropivacaine with Fentanyl in epidural anaesthesia in adult female patients undergoing lower abdominal surgeries .

Secondary objective: To study and evaluate associated complications.

REVIEW OF LITERATURE

The history of epidural anaesthesia goes back to 1901 , when two French clinicians Jean. E. Sicard and Fernand Cathelin working independently injected cocaine through the sacral hiatus thus pioneering caudal epidural block .Sicard applied the technique purely for non surgical purpose of pain relief in patients with sciatica and tabes. However, Cathelin used the technique for surgical anaesthesia, considering it to be a safer alternative to spinal anaesthesia for inguinal hernia repair.[1]

The caudal block thus given was found to be adequate for perineal surgeries but soon the clinicians realized that techniques should be developed to place epidural needles at lumbar or even thoracic areas if surgeries on abdomen and thorax were to be performed under regional anaesthesia.

For almost twenty years various methods were tried but none were found to be satisfactory in identifying the epidural space at higher levels.

Finally in 1921, Fidel Pages, a Spanish military doctor published a ground breaking article detailing a tactile technique to identify epidural space at all levels . He used a blunt needle and then “felt” and “ heard “ the entry of the needle through the ligamentum flavum to confirm its position in epidural space .[10]

A.M Dogliotti in 1931 used a saline filled syringe to identify the epidural space. The syringe, with a blunt needle was advanced through the ligaments of the back with a constant pressure on the plunger and the anaesthesiologist felt for a loss of resistance as the ligamentum flavum was breached . It was found to be more accurate than the previous tactile technique.[11,12]

One major drawback of neuraxial blockade at that time was short duration of action of procaine. To deal with this problem William Lemmon attached the malleable silver spinal needle to a rubber tubing and a syringe through a hole in the operating table. Injections of local anaesthetic were made at intervals to maintain spinal block for several hours.

Edward Tuohy threaded a ureteric catheter through a wide tipped spinal needle to provide continuous spinal anaesthesia.[12,13]

In 1940, Martin Curbelo of Havana used a Tuohy's needle and a ureteric catheter to provide the first continuous epidural anaesthesia. Since then many advances have been made in the needle as well as epidural catheters.[13]

While the techniques of epidural anaesthesia were being refined, a lot of developments were happening in the field of pharmacology too.

The first major breakthrough happened when Loefergen and Lundquist synthesized Lidocaine[14], an amide derivative of diethyl amino acetic acid. Later several other amide drugs like mepivacaine, bupivacaine , levobupivacaine and ropivacaine were also introduced. Amide local anaesthetics have several advantages over amino esters like better stability and longer shelf life.

However various serious side effects were reported with lidocaine . Most of them were due to CNS toxicity and were due to use of high doses.

Chiang Y.Y et al reported lidocaine toxicity in a healthy young man weighing 65 kgs undergoing circumcision under penile block with 2% lidocaine (total 600 mg). The patient developed features of CNS toxicity after injection – headache , tinnitus ,

vertigo , visual and auditory disturbances followed by trismus and rigidity of extremities.[15]

Due to these side effects and shorter duration of action, research was focussed to find a longer acting and safer alternative to lidocaine .

In 1957, A. F. Ekenstam and colleagues synthesized bupivacaine a long acting amide local anaesthetic. It has since then become a bulwark of regional anaesthesia and has been used extensively for intrathecal , epidural anaesthesia and peripheral nerve blocks.[16]

However a significant number of deaths attributable to cardiovascular collapse were reported due to regional anaesthesia with bupivacaine ; most of them due to accidental intravenous injection of the drug. The dose required to produce cardiotoxicity was close to the convulsant dose. Bupivacaine also has a selective cardio toxicity due to its slow dissociation from cardiac sodium channels . It was also shown that this cardiac toxicity was highly stereo specific, with S(-) enantiomers showing significantly less toxicity .

Thus two pure S congeners of bupivacaine –levobupivacaine and ropivacaine were developed. Based on 3 dimensional structure, both have a lower potential to cause cardiac as well as neuro toxicit .

In initial animal studies, ropivacaine was found intermediate in its cardiac depressant effect, between bupivacaine (highest) and lidocaine (lowest) . A favourable cardiotoxic profile of ropivacaine was confirmed in rabbits and pigs with a greater margin between convulsant and lethal dose.[17,18,19]

In another experimental study where healthy volunteers were administered intravenous ropivacaine and bupivacaine infusion the former was found to be less toxic . On the other hand , mild CNS symptoms and minor cardiovascular toxicity as measured by changes in myocardial contractility and conductivity occurred at lower dose and plasma concentration with bupivacaine as compared to ropivacaine [20]

Many other in vivo studies established that the cardiotoxic dose of bupivacaine and its pure S(-) congeners followed the order : ropivacaine> levobupivacaine > bupivacaine, making ropivacaine the most cardiostable of them all.[21]

Once the safety of ropivacaine was established in experimental studies , various studies were undertaken to compare its efficacy to bupivacaine .

In a study conducted by Crosby. E et al, 60 patients posted for caesarean section were divided into two groups with one receiving 22 ml of 0.5 % bupivacaine and the other receiving 22 ml of 0.5% ropivacaine via epidural route. Median onset for time of sensory block in surgically relevant dermatomes ($T_6 – S_3$) varied between 7.5 and 25 minutes in the ropivacaine group and 5 and 17.5 minutes in the bupivacaine group . The median duration of sensory block varied between 1.7 and 4.2 hours in ropivacaine group and 1.8 to 4.4 hours in bupivacaine group. The median time for onset of motor blockade was 15 minutes for ropivacaine and 12.5 minutes for bupivacaine. The median duration of motor blockade was 2.1 hours for ropivacaine and 2.4 hours for bupivacaine. Thus bupivacaine caused early onset and longer duration of both sensory and motor block as compared to ropivacaine.[22]

In another study by Kulkarni and colleagues efficacy of 15 ml 0.5% ropivacaine was compared to 15 ml 0.5% bupivacaine in elderly patients undergoing lower limb surgeries under epidural anaesthesia. Time required to achieve T_{10} sensory block was 8.75 $\pm$ 2.41 minutes in bupivacaine group as compared to 13.5 $\pm$ 1.9 minutes in ropivacaine group. The difference was statistically significant. The maximum level of sensory block was found to be T_8 in both the groups . Motor blockade was Bromage grade III in all but one patient in group Bupivacaine . However in group ropivacaine ,1 patient had grade III block , 17 had grade II block , 10 had grade I block while 2 patients had grade 0 block . Thus it was concluded that 0.5% ropivacaine provided less intense motor blockade than 0.5% bupivacaine. In group bupivacaine the HR fell from 82.27 $\pm$ 11.23bpm to 72.45 $\pm$ 11.48 bpm while in ropivacaine group it fell from 88.10 $\pm$5.89 to 87.60 $\pm$10.58 bpm. The SBP fell from 146.3 $\pm$21 mm of Hg to 120.5 $\pm$17.8 mm of Hg in bupivacaine group as compared to a fall from 150.0 $\pm$16.99 mm of Hg to 145.5 $\pm$ 16.99 mm of Hg in ropivacaine group. Both values were statistically significant thus suggesting that ropivacaine 0.5% was more cardiostable than bupivacaine 0.5%. The onset of two segment regression was 97.86 $\pm$8.53 minutes with bupivacaine and 78.25$\pm$5.13 minutes with ropivacaine. The difference was statistically significant suggesting a prolonged sensory block with 0.5% bupivacaine as compared to 0.5% ropivacaine.[23]

In another similar study by McGlade D.P. and colleagues, block characteristics of 20 ml ropivacaine 0.5% and 20 ml bupivacaine 0.5% given epidurally were compared in patients undergoing lower limb orthopaedic procedures. The onset and duration of analgesia at T_{10} dermatome (median , interquartile range) was 10 (5-15) minutes and 3.5 (2.7 – 4.3) hours with ropivacaine and was 10 (6-15)

minutes and 3.4 (2.5-3.8) hours with bupivacaine. This difference was not statistically significant. The maximum block height was T_6 in both groups. 9 patients receiving ropivacaine and 8 patients receiving bupivacaine had no apparent motor blockade. Incidence of grade III motor blockade was low in both groups : 4/27 with ropivacaine and 6/34 with bupivacaine and this difference was not statistically significant. In ropivacainegroup , sensory and motor block was satisfactory in 78% patients while in bupivacaine group it was 62% and 71% respectively. Cardiovascular changes were similar in both groups. Therefore this study found no statistically significant difference in any of the study parameters between 0.5% ropivacaine and 0.5% bupivacaine.[7]

Jain and co workers did a study comparing different concentrations of different local anaesthetics for cervical epidural for thyroid surgery. Patients were divided into three groups with one receiving 10ml 1% Lignocaine , second getting 10ml 0.25% bupivacaine and 10ml 0.5% ropivacaine. The upper limit of sensory block was at C_2 in all 3 groups. The caudal limit was T_5 in lignocaine and bupivacaine groups and T_4 in ropivacaine group. The median time to onset of sensory block was significantly shorter in lignocaine group [10minutes(5-10)] as compared to ropivacaine [15 minutes(10-20)] and bupivacaine [10 minutes (10-15)] groups. However, compared to other studies they found a more intense motor blockade with ropivacine as compared to lignocaine ($p=0.01$) and bupivacaine ($p=0.001$). The lignocaine group required significantly more number of topups to maintain anaesthesia , with $p < 0.001$ in comparison with both bupivacaine and ropivacaine. HR decreased much more in lignocaine group , 30 minutes post epidural placement than ropivacaine and bupivacaine but the fall was significant in all three groups

($p<0.001$). MAP was significantly low 30 minutes after epidural placement in all three groups.[6]

In another study conducted by Guler G et al in which 81, ASA I-II males, aged 60-80 years, undergoing transurethral resection of prostate were randomly assigned to three groups receiving epidural ropivacaine as Group I(15 ml) of 0.75% solution, group II (10ml) of 0.75% solution, and group III (10 ml) of 0.5% ropivacaine. The duration of sensory block was more in group I (172min.), and the time to achieve the T10 level was least in group I (17min.). Duration of motor block was significantly less in group III (87min.) than in groups I (95.8min.) and II (91.6min.).[24]

After studies comparing ropivacaine with bupivacaine, studies regarding effect of various adjuvants on the block characteristics were undertaken .

Bajwa et al compared epidural ropivacaine(Group R) to epidural ropivacaine – clonidine combination (Group RC) in patients undergoing elective caesarean sections . Group R received 20ml of 0.75% ropivacaine whereas group RC received 20ml of 0.75% ropivacaine with 75 mcg of clonidine – an α - 2 agonist. The onset of analgesia at T_{10} was faster in group RC (8.64$\pm$ 2.56 minutes) as compared to group R (11.36 $\pm$ 3.30 minutes). Time to complete motor blockade was 21.70 $\pm$/ 4.20 minutes for group R as compared to 17.34 $\pm$ 4.48 minutes for group RC. Time for 2 segmental regression was found to be shorter for group R (88.32 $\pm$ 16.52 minutes) as compared to group RC (102.80 $\pm$ 18.38 minutes). Time for first rescue analgesia was lower for group R (117.49 $\pm$ 22.34 minutes) as compared to group RC (138.46 $\pm$ 25.42 minutes). All these values were statistically significant with p values < 0.05. There was comparable maternal tachycardia for first 20 minutes in both groups which was followed by continuing increase in group R while a fall in heart rate in group RC

which was statistically significant. The difference in heart rate remained significant until the block regressed . The fall in MAP was also significantly more in RC group. 9 patients complained of dry mouth in group RC as compared to none ingroup R, which was statistically significant.[25]

Thimappa and colleagues carried out a similar study comparing ropivacaine(R) alone with ropivacaine clonidine (RC) and ropivacaine dexmedetomidine (RD) combinations for epidural anaesthesia in patients undergoing lower abdominal and lower limb surgeries. Patients were divided into three groups as follows- group R received 19ml of 0.75% ropivacaine with 1ml normal saline , group RC received 19ml of 0.75% ropivacaine with 1ml (75 mcg) clonidine and group RD received 19ml of 0.75% ropivacaine with 1ml (75 mcg) dexmedetomidine .

Time for onset of analgesia at T_{10} was 12.33 $\pm$ 1.56 minutes for group R , 9.17 $\pm$1.21 minutes for group RC , and 8.90 $\pm$0.99 minutes for group RD. Time for complete motor blockade was 21.37 $\pm$2.13 minutes for group R , 16.47 $\pm$1.38 minutes for group RC and 15.77 $\pm$ 1.25 minutes for group RD . Time for 2 segment regression least forgroup R (94.57 $\pm$6.98 minutes) followed by group RC (120.63 $\pm$17.59 minutes) and group RD (163.67 $\pm$15.20 minutes). Duration of analgesia was shortest for group R (200.33 $\pm$17.07 minutes), followed by group RC (261.00 $\pm$17.68 minutes) and group RD (291.33 $\pm$27.79 minutes). Thus dexmedetomidine and clonidine provided a significantly early onset and prolonged duration of both sensory and motor blockade as compared to plain ropivacaine. Out of the two α_2 -agonists ,dexmedetomidine provided more favourable block characteristics. A significant number of patients in RD group had bradycardia (33%) as compared to RC group

(13.3%) and none in group R. Also sedation was found to be significantly higher in RD group[8]

Opioids have been another regular group of drugs used as adjuvants in epidural anaesthesia. Bajwa and co-workers compared the effects of fentanyl with dexmedetomidine long with ropivacaine for epidural anaesthesia in patients undergoing lower limb orthopaedic surgeries. Group RF received 15ml of 0.75% ropivacaine with 1 mcg/kg of fentanyl while group RD received 15ml of 0.75% ropivacaine with 1mcg/kg of dexmedetomidine via epidural route. Onset of sensory loss at T_{10} was significantly quicker in group RD (7.12 $\pm$2.44 minutes) than in group RF (9.14 $\pm$2.94 minutes). Time for complete motor blockade was significantly more for group RF (22.98 $\pm$4.78 minutes) compared to group RD (18.16 $\pm$4.52 minutes). Time for 2 dermatomal regression was 110.84$\pm$9.48 minutes in group RF as compared to 140.32 $\pm$10.21 minutes in group RD. Time for rescue analgesia was also significantly shorter in RF group (242.16 $\pm$23.86 minutes) as compared to group RD (366.62 $\pm$24.42 minutes). There was however a higher incidence of dry mouth in group. RD (14%). Group RD also had a significantly high incidence of sedation score of >= 2. Bradycardia and fall in MAP were seen in significant number of patients in both groups and the data was comparable.[9]

Thus we see a few studies comparing 0.75% Ropivacaine with and without various adjuvants and comparing 0.5% Ropivacaine with different local anaesthetics , but a direct comparative study between the two different concentrations of the drug with an opioid adjuvant are missing. Thus we undertook our study :

"COMPARISON OF ONSET AND DURATION OF BLOCKADE AND POST OPERATIVE ANALGESIA OF ISOBARIC ROPIVACAINE 0.75% +

FENTANYL AND ISOBARIC ROPIVACAINE 0.5% + FENTANYL IN FEMALE PATIENTS UNDERGOING LOWER ABDOMINAL SURGERIES UNDER EPIDURAL ANAESTHESIA - A ONE YEAR HOSPITAL BASED RANDOMISED CONTROLLED TRIAL" to fill this knowledge gap .

BASIC SCIENCES

Applied Anatomy

An anaesthesiologist requires to have an accurate and in depth knowledge of the anatomy of vertebral column and its contents for a safe and successful administration of epidural anaesthesia, not only in terms of performance but also in terms of spread of drug in epidural space and level of block achieved.

Vertebral column

Main function of vertebral column is to protect the spinal cord. There are 33 vertebrae in vertebral column which includes

- Cervical - 7
- Thoracic - 12
- Lumbar - 5
- Sacrum - 5 (fused)
- Coccyx - 4 (fused)

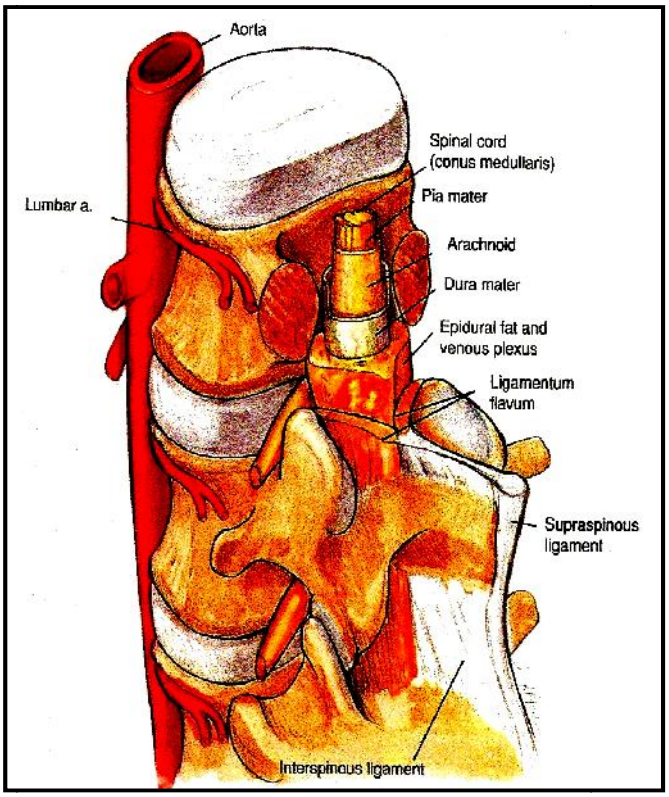
Curves of spine

In adults, curves of vertebral column have significant effect on spread of drugs in subarachnoid space and these curves are:[26]

- Cervical curve - Convexity anterior
- Thoracic curve - Concave anterior
- Lumbar curve - Convexity anteriorly

Cervical (C) five and lumbar (L) five are the highest points of cervical and lumbar curves in supine position and the lowest points of thoracic and sacral are at thoracic (T) five and sacral (S) two respectively.[26]

Figure 1: Vertebral Column

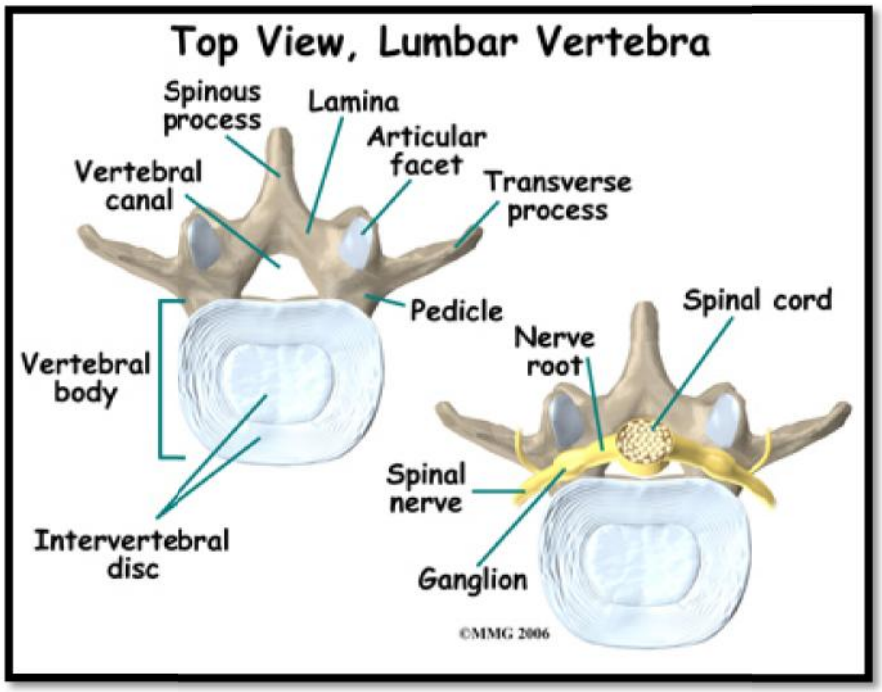


Lumbar vertebrae

A typical lumbar vertebra consists of:

- A kidney shaped body.
- Two pedicles directed backwards from the upper part of the body.
- Two transverse processes
- Two laminae meeting posteriorly and enclosing the triangular vertebral foramen.
- Thick, broad and quadrilateral spinous processes.
- Two upper and lower articular processes which prevent rotation but allow limited flexion and extension between contiguous vertebrae.

Figure 2: Typical lumbar vertebra



Thoracic vertebrae :

- A heart shaped body
- A small costal demi facet on superior border of lateral side of body and a larger demi facet on the inferior surface
- Shallow superior vertebral notches and deeper inferior vertebral notches
- Transverse processes are directed backwards and laterally , carrying a costal facet for articulation with ribs.

Vertebral ligaments

The following overlapping ligaments provide stability to the vertebral column and protect the spinal cord :

Supraspinous ligament: This is a strong fibrous cord which connects apices of spinous processes from sacrum to C_5 where it is continued as the ligamentum nuchae . The width depends upon the width of the spinous process – in lumbar region it might

be upto 1 cm wide. In elderly people and manual labourers this ligament calcifies thus making the midline approach difficult.

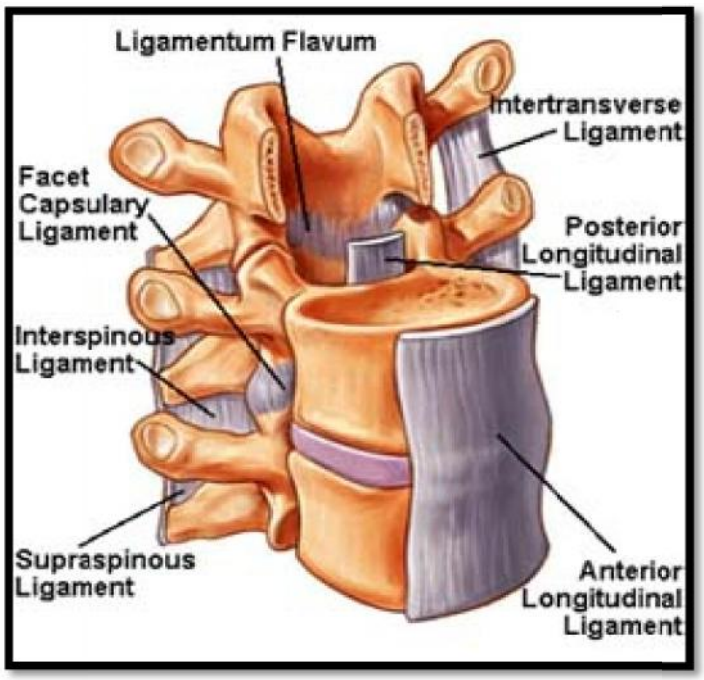
Interspinous ligament: This is a thin membranous ligament running obliquely and connecting spinous processes blending anteriorly with ligamentum flavum and posteriorly with supraspinous ligament . In the lumbar region , thisligament is rectangular in shape leading to the characteristic and identifiable “loss of resistance” feel to air or saline.

Ligamentum flavum: This ligament comprises of yellow elastic fibres and connects adjacent laminae. Laterally, this ligament begins at the root of articular processes and extends posteriorly and medially to the point where laminae join to form spinous process. It provides the classic springy resistance in the lumbar region.

Longitudinal ligaments: There are two longitudinal ligaments (anterior and posterior) that bind vertebral bodies together.

For epidural anaesthesia, needle pierces the first three ligaments when midline approach is used . In paramedianapproach , only the ligamentum flavum is encountered.

Figure 3 :Vertebral ligaments



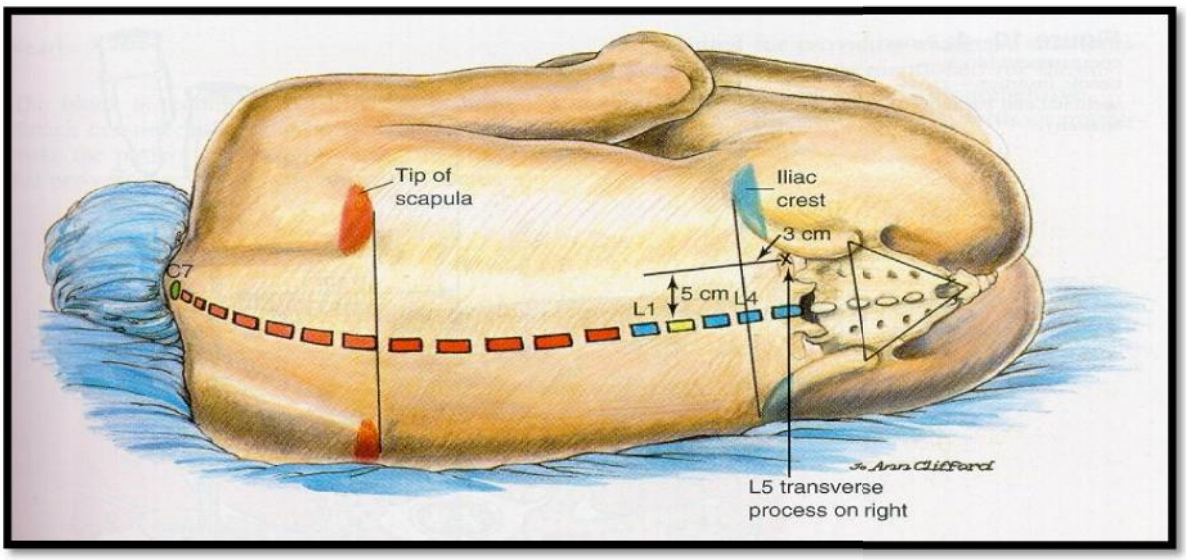
Intervertebral Discs[27]

These are principle connecting link between vertebral bodies. They form about 25% of the length of the spine. They consist of two parts - The outer fibrous part called the *annulus fibrosus*(made up of fibrous tissue), while the *nucleus pulposus* is the softer core. The discs serve as shock absorbers and lend flexibility to the vertebral column.

Topographical Line of Tuffier[27]

This is a horizontal line across the back between the crests of the iliac bone passing over the spine of the 4th lumbar vertebra in the upright position. In a patient lying in the lateral position it may also pass through L4 and L5 interspaces. The superior iliac crest is used to identify the L4 and L5 interspace during epidural anesthesia.

Figure 4: Topographical line of Tuffier



Vertebral canal:

The vertebral canal is bound by the vertebral bodies and intervertebral discs anteriorly , the laminae , ligamentum flavum and laterally by pedicles and laminae.

The contents of vertebral canal are as follows :

- Spinal cord
- Spinal nerve roots
- Meninges
- Cerebrospinal fluid
- Vessels
- Fat
- Loose areolar tissue

Spinal cord[26]

The average length of the spinal cord in males is 45 centimetres (cms) and in females it is 42 cms. The average weight is approximately 30 gm.

The spinal cord is a continuation of the medulla oblongata below the level of foramen magnum and it tapers off into a conical extremity known as conus medullaris. Filum terminale descends to the back of first segment of coccyx from apex of conus medullaris.

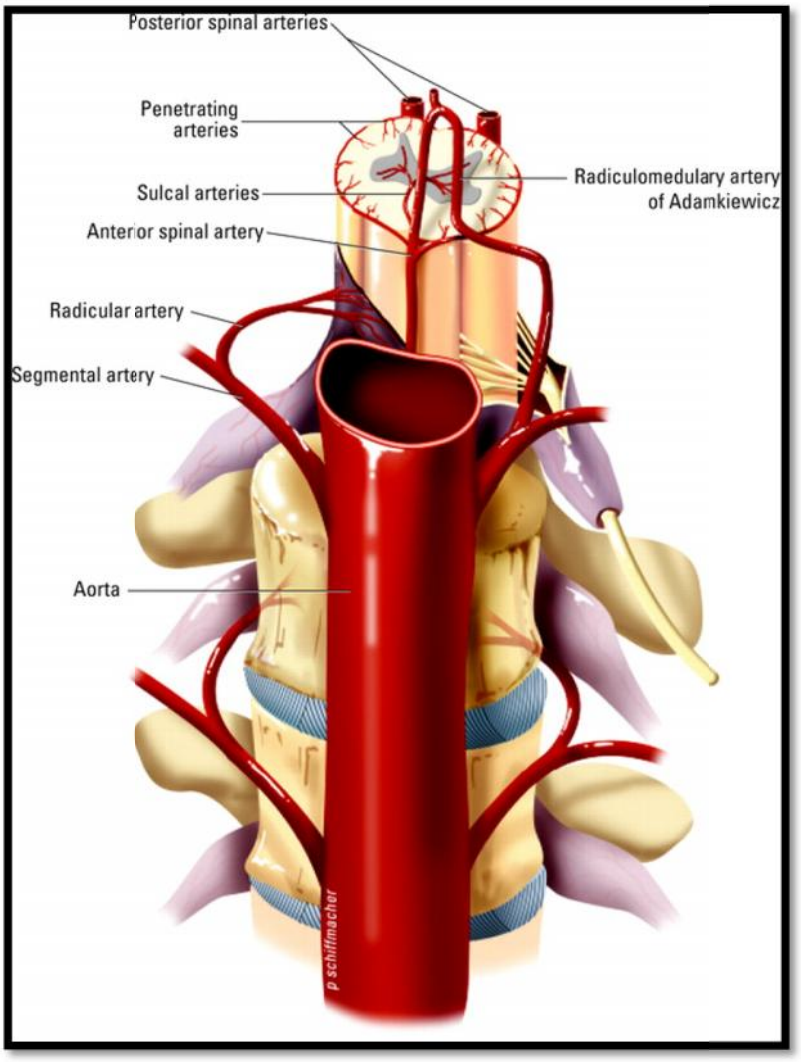
At birth, Spinal cord ends at the level of lower border of lumbar (L) three vertebra and in adults, it is as follows;

- Lower border of L1 - 50%
- Upper border of L2 - 40%
- Upper border of L3 - 3%

From the spinal cord arise 31 pairs of spinal nerves, each made of a ventral and a dorsal root. These anterior and posterior roots after crossing the subarachnoid space, pass through the dura and extradural space independently and unite at the level of intervertebral foramen to form spinal nerve trunks, which further divide into anterior and posterior primary divisions.

The amount of white matter declines progressively from the cervical region down to the lumbar region. The gray matter is greatly increased in the both the lumbar and cervical enlargement.

Figure 5: Blood supply of spinal cord



Blood Supply of Spinal Cord:[27]

The spinal cord receives its blood supply from anterior and posterior spinal arteries. The anterior spinal artery is a single vessel lying in front of the anterior median fissure. It is formed by two small arteries, one given off from each vertebral artery at the level of the foramen magnum. It receives small communications from the intercostal and lumbar arteries; to provide the extra blood supply needed in the cervical, thoracic and lumbar enlargements.

There are two posterior spinal arteries-one on each side. They are derived from the vertebral artery or more often from a primary branch of each vertebral artery. They supply the posterior one-third of the spinal cord. This supply is augmented by spinal branches of vertebral, ascending cervical, posterior intercostals, lumbar and lateral sacral arteries, which pass through the intervertebral foramina.

Venous drainage is through a plexus of anterior and posterior veins in the neck, azygous veins in the thorax, lumbar veins in the abdomen, and lateral sacral veins in the pelvis. There is no anastomosis between the anterior and posterior spinal arteries.

The longest of the feeder arteries is the radicularis magna (artery of Adamkiewicz), which supplies the anterior spinal artery in the area of the lumbar enlargement of the cord. It enters by way of a single intervertebral foramen (78% of the time on the left) between the T8 and L3 foramina.

Meninges[28]

The spinal cord is covered by three membranes from inward to outward, they are the pia mater, the arachnoid mater and the dura mater. The dural sac is the continuation of meningeal layer of the cranial dura mater. It is a circular sac or sleeve surrounding the spinal cord. Above, it is attached firmly to the circumference of the foramen magnum.

Duramater[29]

It is the outermost membrane, the fibres of which run longitudinally. Although continuous, it can be described in two parts: the cranial and the spinal. The cranial dura consists has two layers, outer endosteal layer, which lines the skull, and an inner

meningeal layer, which invests the brain and folds inward to form the falxcerebri and tentorium cerebelli.

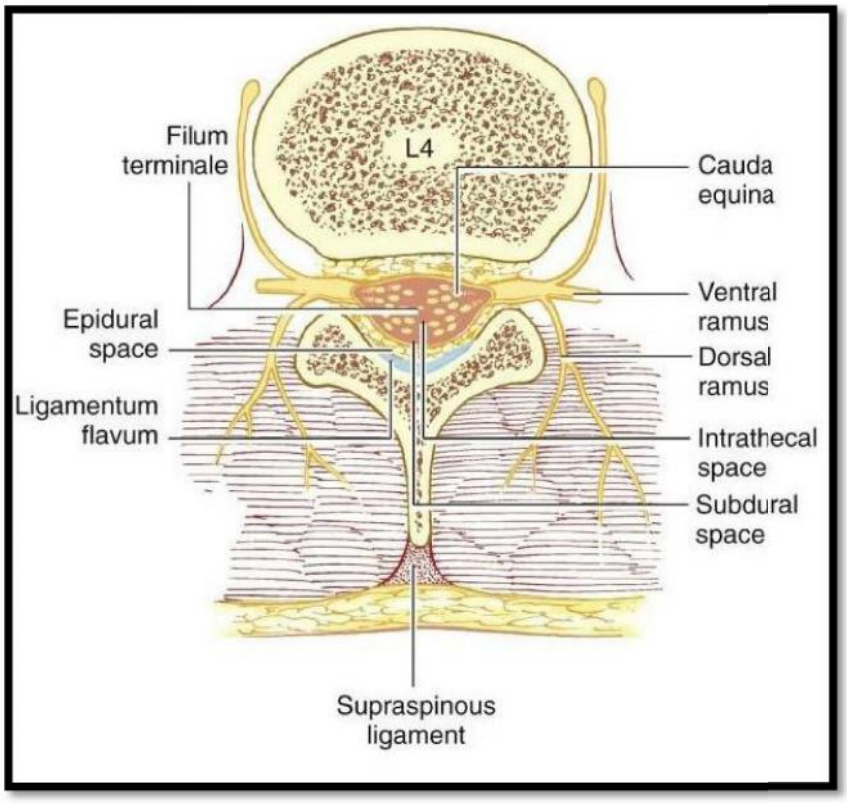
Arachnoid Mater[28]

The arachnoid mater is a delicate non-vascular membrane applied closely to the dura mater. The lower extent of dural sac is as follows;

Below this the dura continues as the filum terminale. The subarachnoid space is the space between the arachnoid and pia mater. This space is occupied by the cranial and spinal nerves and by the cobweb trabeculae. The space is annular in the cranial and thoracic vertebrae and is about three mm deep. Below the first lumbar vertebrae it is circular in shape.

EPIDURAL SPACE[30]

Figure 6 : Epidural Space



Boundaries of the epidural space

The epidural space is bounded

Superior: by foramen magnum , where speriosteal and spinal layers of duramater fuse.

Inferior: by sacroccygeal membrane and sacral hiatus .

Anterior : by the posterior longitudinal ligament, vertebral bodies and discs

Posterior : by ligamentum flavum , periosteum of anterior surface of laminae and connecting ligaments.

Lateral : by periosteum of pedicles and intervertebral foramina.

Rarely, a fold of duramater divides the space into ventral and dorso – medial compartments leading to patchy or unilateral analgesia or missed segments.

Shape and size: These are largely determined by the shape of the lumbar vertebral canal and the position and size of the dural sac within it.

Cervical : 1.5 mm

Upper thoracic : 2.5 – 3 mm

Lower thoracic : 4-5 mm

Lumbar : 5-6 mm

Types of epidural space[30]

The epidural space can be categorized into cervical, thoracic, lumbar and sacral epidural spaces. These spaces can be defined according to their margins. At the cervical epidural space, there is a fusion of the spinal and periosteal layers of dura mater at the foramen magnum to lower margin of the 7th cervical vertebra. While the

thoracic epidural space is formed by the lower margin of C_7 to the upper margin of L_1, the lumbar epidural space is formed by the lower margin of L_1 vertebra to the upper margin of S_1 vertebra. The sacral epidural space is formed by the upper margin of S_1 to sacrococcygeal membraneand sacral hiatus.

Contents of the epidural space :

Contains semi liquid fat , lymphatics , arteries , loose areolar tissue spinal nerve roots and a very rich plexus of veins.

Fat[31]

The epidural space is filled with semi fluid , lobulated fat tissue. Fat cells are also abundant in the dura that forms the sleeves around spinal nerve roots but they are not embedded within the laminae that form the dura mater of the dural sac. The fat in the epidural space buffers the pulsatile movements of the dural sac and protects nerve structure, creates a reservoir of lipophilic substances, and facilitates the movement of the dural sac over the periosteum of the spinal column during flexion and extension.The areolar tissue of this space has a very rich blood supply with small capillaries forming a network in its substance . Drugs stored in fat, inside dural sleeves, could have a greater impact on nerve roots than drugs stored in epidural fat, given that the concentration of fat is proportionally higher inside nerve root sleeves than in the epidural space, and that the distance between nerves and fat is shorter. Similarly, changes in fat content and distribution caused by different pathologies may alter the absorption and distribution of drugs injected in the epidural space. The maximum amount of fat is present posteriorly , where it assumes triangular capsular shapes and is linked to the midline of the ligamentum flavum by a vascular pedicle. Drugs with high lipid solubility like bupivacaine have a high affinity for fatty tissue

and thus remain in epidural fat for a longer time thus leaving a small quantity of the drug to interact with nerve roots at any time .Uptake of local anaesthetic by fat competes with it's vascular and neural uptake .

Lymphatics

The lymphatics of the epidural space are mostly found in the region of the dural roots where they remove foreign materials including microorganisms from the subarachnoid and epidural spaces.

Vertebral venous plexus[32]

The internal vertebral venous plexus consists of four interconnecting longitudinal vessels, two anterior and two posterior. The external vertebral plexus (EVP) in contrast, lies peripheral to the vertebrae and is made of the anterior and posterior external vertebral plexuses.The EVP is situated anterior to the vertebral bodies and in relation to the laminae, spinous processes, transverse processes and articular processes respectively. These veins communicate with the segmental veins of the neck, the intercostal, azygous and lumbar veins. With the veins of bones of the vertebral column, the internal and external vertebral plexuses form Batson's plexus.These veins are predominantly in the antero-lateral part of the epidural space, and ultimately drain into the azygous system of veins. As the whole system is valveless, increased intrathoracic or intra-abdominal pressure (e.g. ascites, pregnancy, tumours etc.) can lead to major congestion and vessel enlargement within the spinal canal. The epidural venous plexus is surrounded by sparse quantity of fat.

The anterior epidural space is entirely occupied by a rich venous plexus (valveless system of veins). The plexus communicates with the intracranial sigmoid sinus, basilar venous sinus, basivertebral vein, occipital vein, and the azygous system.

The plexus is linked to the abdominal and thoracic veins by the intervertebral foramina and through this connection transmit intraabdominal and intrathoracic pressure to the epidural space. The venous plexus is also connected to the iliac veins through the sacral venous plexus. Obstruction of the inferior vena cava, advanced pregnancy or intra abdominaltumors can cause distension of the venous plexus leading to an increased risk of being traumatized during needle and/or catheter placement in the epidural space. These veins are more prominent along the lateral wall of the vertebral canal usually they are out of reach of a correctly placed needle by midline approach. The dose and rate of local anaesthetic should also be reduced in any case of increased intraabdominal pressure / inferior vena cava obstruction as the resultant engorgement of the venous plexus would reduce the effective volume of the epidural space . The injected drug may therefore spread rapidly upwards or downwards along the epidural space.

Epidural arteries[33]

The epidural arteries located in the lumbar region of the vertebral column are branches of the ilio-lumbar arteries. These arteries are found in the lateral region of the space and therefore accidental puncture is uncommon by midline approach.

Spinal arteries :

As already discussed , the spinal cord is supplied by one anterior spinal and two posterior spinal arteries. The spinal branches of the subclavian , aortic and iliac arteries cross the epidural space on the way to sub arachnoid space. The largest of them , the artery of Adamkiewicz supplies the anterior spinal artery at the lumbar level. This artery enters the epidural space between $T_8 – L_3$ levels and any damage to

itwoul cause ischaemia of entire lumbar region of the cord. In general , anterior spinal artery is more susceptible due to it being unpaired .

Pharmacokinetics Of Epidural Blockade[34]

Epidural anaesthesia results from the interaction of local anaesthetics with nerve structures located within the epidural space. Local anaesthetics can reach the sites of action along various distribution pathways. Uptake into extraneural tissues like epidural fat and systemic absorption compete with neural tissue distribution thereby affecting the clinical potency and duration of action. Therefore, epidural doses of local anaesthetics are much higher than spinal doses.

Specifically, drugs may 1) exit the intervertebral foramina to reach the paraspinous muscle space, 2) drugs may diffuse into epidural fat, 3) drugs may diffuse into ligaments and finally, 4) drugs may diffuse across the spinal meninges.

The only mechanism by which drugs redistribute from the epidural space to the spinal cord is diffusion through the spinal meninges and the cellular arachnoid mater is the principal meningeal barrier to diffusion accounting for 95% of the resistance to meningeal permeability.

Meningeal permeability is not the only determinant of a drug spinal cord bioavailability after epidural administration. Drugs can partition into various environments in the epidural space and be unavailable for transfer across the spinal meninges.

Lipid soluble drugs have a tendency to get sequestrated into epidural fatty tissue. The dura mater is an important site of drug clearancespecially in humans where dura mater is a highly vascular structure. As lipid soluble molecules traverse

capillaries more readily than do more hydrophilic molecules, lipid soluble drugs may be cleared by this mechanism more readily than less lipid soluble drugs.

Meninges contain multiple enzyme systems, which are capable of drug metabolism. In addition, the meninges express enzymes capable of metabolizing neurotransmitters, including epinephrine, norepinephrine, acetylcholine and neuropeptides. After epidural administration, local anesthetics need to cross the spinal meninges to reach their site of action

Epidurally administered drugs that reach the CSF, also can diffuse back across the meninges into the epidural space, but this happens only when the drug concentration in the epidural space falls below that in the CSF . Diffusion is dependent mainly on the drug's physicochemical properties, particularly, lipid solubility.

Physiological Effects Of Epidural Blockade[26]

The physiological responses to epidural anaesthesia are mainly due to sympathetic blockade accompanied by sensory and motor blockade to various degrees. Some of the most important (but not all) physiological effects of epidural blockade can be discussed in relation to either sympathetic blockade of vasoconstrictor fibres (below T_4) and/or of cardiac sympathetic fibres. Major sympathetic blockade can be avoided by trying to keep the block level around or below T_{10} .Lower abdominal , urologic , gynaecological and lower limb surgeries can be carried out satisfactorily with acceptable sympathetic blockade.

Zone of differential blockade :[35]

Erlanger and Gasser showed that action of local anaesthetics on nerve fibres is by "differential conduction blockade ".The nerve fibres are of three types viz A, B , C

A minimum length of myelinated nerve fibres should come in contact with local anaesthetic for conduction blockade. In myelinated fibres , the blockade occurs at nodes of Ranvier and three consecutive nodes need to be blocked for impulse conduction to be completely interrupted .

All types of nerve fibres are affected by local anaesthetics. but within any one fibre type, there is tendency for small, slower conducting fibers to be more readily blocked than large, fast conducting fibres. Between fibre types however, these rules do not hold good. Myelinated preganglionic B fibres which have a faster conduction time are about three times more sensitive to local anaesthetics than the slower non-myelinated post ganglionic C fibers.

Sensory Aα fibres appear to be more sensitive to blockade than motor A_β fibres, although of the same conduction velocity, this may be because sensory fibres conduct at a higher frequency. It has been suggested that this selectivity for sensory fibres exhibited by Bupivacaine and Ropivacaine is a function of frequency dependent block.

Sensory

In intradural block sympathetic fibres are blocked two or three segments higher than sensory fibres. In extradural block, the relationship is complex. Level of sympathetic block is the same as (or lower than) sensory with epidural blockade. Sympathetic block will be greater when more concentrated solutions are used or when adrenaline added, as this has similar effect.

Motor

In intradural block, the difference between sensory and motor block is slight (two segments). In extradural block, the difference in levels is greater, depending on nature of local anaesthetic solution.

Factors influencing height and distribution of local anaesthetic :

Patient characteristics :

- Age : Study done by Bromage shows a correlation between age and dose , an increase in dose from age 4-18 years followed by a gradual decrease from 19 year onwards.
- Height : A simple thumb rule is to use 1ml per segment for height of 150 cm and then add 0.1 ml per segment for each 5 cm over 150 cm.
- Weight :Under normal circumstances , there is not much correlation between spread of analgesia and the weight . However in morbidly obese patients a given dose of local anaesthetics can cause a higher than normal block due to compression of epidural space due to increased intra abdominal pressure.
- Intra abdominal pressure : epidural venous engorgement in pregnancy , obesity , tumours can cause a higher blockade with a given dose due to narrower epidural space
- Posture : In sitting position there is slight propensity of the drug to spread caudally and higher doses may be required .
- Gender

Technique of injection :

- Site of injection : Rapid onset and denser blockade is seen when the point of injection was nearer to nerve roots . Lumbar epidural injection has a better cephalad spread than caudal epidurals.
- Direction of bevel
- Rate of injection :A rapid injection of local anaesthetic produces a rapid but incomplete and more extensive block. Injection rate of 0.3 – 0.75 ml/sec results in most reliable block .

Characteristics of anaesthetic solution :

- Amount : Earlier epidural anaesthesia was considered to be equivalent to multiple paravertebral blocks and the tendency was to give a large volume of diluted drug. However studies by Bromage showed that increasing dosage linearly increases the degree of sensory blockade.
- Concentration : An increase in the drug concentration increases the density of motor blockade .
- Density
- Temperature
- Use of adjuvants

Effects of epidural anaesthesia on various organ systems :

Cardiovascular System :

The action of epidural anaesthesia on cardiovascular system depends on the level of block:

1. If the level of block is below T_4 there is dilation of resistance and capacitance vessels due to loss of sympathetic tone. This causes a fall in BP. However if there

is a blockade of cardiac efferent sympathetic fibres from T_1 to T_4 there is a loss of chronotropic and inotropic drive resulting in a fall in cardiac output.

2. The activation arterial or Bainbridge reflex causing bradycardia -The lowering of blood pressure in the right atrium consequent to diminished venous return [Bainbridge (1874-1921) effect]

3. The operation of Mary's law causing tachycardia.

4. Depression of vascular smooth muscle and β adrenergic blockade of myocardium with fall in cardiac output.

Block not extending above T4 is not always associated with fall of blood pressure in fit young adults. However elderly may suffer significant hypotension when moderate volumes are injected into the epidural space

Slowing heart rate is caused if any of the anterior roots carrying sympathetic cardiac accelerator fibres are blocked(T_1– T_4). Activation of Bainbridge reflex may further contribute to bradycardia which is more frequent than tachycardia .

Theories of causation of fall in blood pressure

1. Diminished cardiac output consequent on reduction of venous return to heart due to failure of peripheral pump – calf muscles .

2. Dilatation of post arteriolar capillaries and small venules due to paralysis of vasoconstrictors, compensatory vasoconstriction takes place in areas not anaesthetized via carotid sinus reflexes. In high spinal blocks, majority of vasoconstrictor fibres including those to arm (T2-T10), are paralyzed, hence low blood pressure.

3. Paralysis of sympathetic nerve supply to heart T_1-T_4. Bradycardia may give rise to fall in cardiac output.

4. Paralysis of sympathetic nerve supply to adrenal glands splanchnic nerves, with consequent catecholamine depletion.

5. Absorption of drug into circulation. Seen more commonly with epidural blockade due to the larger volume of drug used .

6. Pre existent hypovolemia, if present, may cause precipitous hypotension after central neuraxialblockade . Compression of great vessels within abdomen, by the pregnant uterus, abdominal tumours or abdominal packs may cause severe hypotension in presence of central neural blockade.

Respiratory System:

The phrenic nerve supplying diaphragm arises from the anterior roots of C_3, C_4, C_5 and should not be encroached upon during neuraxial blockade. Lumbar and even mid thoracic epidurals usually do not cause much effects on respiratory system. . During epidural anaesthesia, breathing becomes quiet and tranquil. This is not only due to motor blockade, but also to differentiation with reduction of sensory input to respiratory center.

The ventilation perfusion during extradural block is not greatly altered and effects on respiratory functions are relatively small with no effect on FRC or V/Q ratio. The lung volumes and capacities (tidal volume , vital capacity) are basically unchanged during epidural anaesthesia. Abdominal muscle and intercostals muscle paralysis is compensated by diaphragm moving down . The pulmonary gas exchange is preserved.

The patient may stop breathing so that respiratory support by IPPV and, if necessary the tracheal intubation maybe required. Causes may be:

- Inadequate medullary blood flow due to inadequate cardiac output-a serious situation demanding immediate cardiorespiratory support.
- Massive epidural spread.
- Accidental subdural injection
- Toxic effects of local analgesic drug.
- Injecting narcotic analgesic drugs

Gastrointestinal System :

Pre ganglionic sympathetic fibres from T5 to L1 are inhibitory to gut, there is no effect on oesophagus, the innervations of which is vagus. The small gut is contracted as the sympathetic inhibitory impulses are removed, the vagus being all powerful, Sphincters are relaxed and peristalsis is active although not more frequent. Pressure within the bowel lumen is increased.

Nausea and vomiting due to the hypotension may occur in upto 20% of patients andusually come on in waves-lasting a minute or so and then passing away spontaneously. Stimuli arising in the upper abdomen might not be blocked causing discomfort. Colonic blood supply and oxygen availability are increased, perhaps an important factor in the prevention of anastomotic breakdown following gut resection.

1. Theories of causation of nausea and vomiting:
1. Hypotension: corrected using fluid boluses and vasopressor drugs
2. Increased peristalsis
3. Traction on nerve endings and plexuses, especially via vagus (usually upper abdomen)

4. Presence of bile in stomach due to relaxation of pyloric and bile-duct sphincters
5. Narcotic analgesics (premedication)
6. Psychological factors
7. Hypoxia

Liver

There are no specific effects of significance. The degree of hypotension that compromises liver function is not known. Liver disease may interfere with the metabolism of local anaesthetic drugs.

Endocrine system

Surgical stress produces a variety of changes in endocrine system and metabolic function. There is an increased catabolism of proteins and oxygen consumption. Increased plasma concentrations of catecholamines, vasopressin, growth hormones, renin, angiotensin, glucose ,Anti diuretic hormone (ADH) and Thyroid Stimulating Hormone (TSH) are noted and this is referred to as surgical stress response.

Neuraxial blocks in general suppress the increase of ADH .It also delays adrenal response to trauma, whereas operations under GA cause a rise in steroids.

In any case, either regional or general, there is no difference in the postoperative period once the effects of the block are discontinued. Spinal block suppresses the hyperglycemic response to surgery and stress and so is useful in diabetic patients but this does not extend into postoperative period. The response to insulin is augmented and anaesthetist should be aware of possibility of hypoglycemia.

Epidural block prevents lymphopenia and granulocytosis after operation, thus inhibiting the metabolic endocrine response to surgery and preventing immune depression.

Genito urinary system

Sympathetic supply of kidney is from T_{11} to L_1 via the lowest splanchnic nerves. As renal blood flow is maintained by autoregulation , epidural anaesthesia has very little effect on renal function.Any effects on renal function if seen is due to severe and intractable hypotension. Auto regulation of renal blood flow is impaired if mean arterial pressure falls below 50 mmHg. These changes are transient and disappear when blood pressure rises again. Sphincters of bladder are not relaxed, so soiling of table by urine is not seen and tone of ureters is not greatly altered.In fact there is urinary retention till block wears off and cathetreizing the patient should be considered. Retention of urine may be moderately prolonged as L_2 and L_3 contain small autonomic fibres and their paralysis lasts longer than of the larger sensory and motor fibres. The penis is often engorged and flaccid due to paralysis of the Nervi erigentes (S_2 and S_3). This is a useful positive sign of successful block.

Body temperature

Vasodilatation favors heat loss. Absence of sweating favours hyperpyrexia in hot environments. Catecholamine secretion is depressed, hence less heat is produced by metabolism. Extradural space is a temperature sensitive zone, whereas intradural space is not. Cold solutions injected into extradural space may induce shivering

ROPIVACAINE

INTRODUCTION

Ropivacaine is a newer, longer acting local anaesthetic agent which belongs to the amino amide group. It was first synthesized by Ekenstam in 1957[36] ; however it was first introduced for clinical practice only since 1996. Chemically it belongs to the same group as bupivacaine and mepivacainei. epipecoloxylidide local anaesthetic.

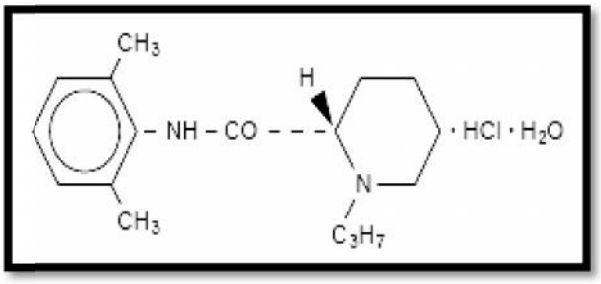
It was found that butyl derivatives of pipecoloxylidides (example bupivacaine) were more cardiotoxic than propyl derivatives, causing a significant number of cardiac arrests.[37]

Thus ropivacaine was developed as a pure S – enantiomeric form of pipecoloxylidides. Though ropivacaine has been available internationally for over three decades , it is a relative new entrant in the Indian market .

It is becoming increasingly popular among anaesthesiologists and has been used extensively in almost all modes of regional anaesthesia: infiltration , peripheral nerve blocks , spinal anaesthesia , epidural anaesthesia as well as caudal epidural blocks in paediatric patients.[2]

CHEMICAL STRUCTURE

Figure 7: Chemical structure of ropivacaine



Ropivacaine is an amino amide local anaesthetic agent, chemically described as S-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate. The *International Union of Pure and Applied Chemistry* name is (S)-N-(2,6-dimethylphenyl) -1-propylpiperidine-2-carboxamide. It's molecular formula is $C_{17}H_{26}N_2O{\bullet}HCl{\bullet}H_2O$ and it has a molecular weight of 328.89.

PHYSICAL PROPERTIES

Ropivacaine is a white crystalline powder .At 25°C ropivacaine hydrochloride has a solubility of 53.8 mg/mL in water and a distribution ratio between n-octanol and phosphate buffer at pH 7.4 of 14:1. The pKa of ropivacaine is 8.07 which is very similar to that of bupivacaine (8.1) .

However, ropivacaine has a much lesser lipid solubility as compared to bupivacaine and mepivacaine. This can be explained on the basis of presence of a propyl (3 Carbon) side chain in ropivacaine as compared to a butyl (4 Carbon) side chain in the other two local anaesthetics. This lower lipid solubility of ropivacaine has a significant effect on the block characteristics of ropivacaine as discussed ahead.[38]

MECHANISM OF ACTION AND CORELATION WITH STRUCTURE[39,40]

Ropivacaine reversibly inhibits the voltage gated sodium channels present on the nerve cell membranes thus preventing the influx of sodium ions into the cells. This:

I) Block generation and conductance of nerve impulses.

II) Slows propagation of nerve impulses

III) Reduces the rate of rise of action potential

Almost all local anaesthetic agents block the unmyelinated C and myelinated Aδfibres, which transmit pain impulses, at the same rate.

The rate of blockade of motor fibres (Aα and Aβ), however depends upon the physio chemical properties like pKa and lipid solubility of the individual drug. As ropivacaine is less lipid soluble than bupivacaine, the Aα and Aβ blockade is slower and hence motor blockade is less potent . Studies of lumbar epidural block in humans have confirmed that equal volumes and concentrations of bupivacaine and ropivacaine produce similar degree of sensory block but the motor block produced by ropivacaine is slower in onset, lesser in intensity and shorter in duration.

Clinically the order of blockade of nerve fibres is autonomic, sensory and motor, while the regression of the block occurs in reverse order.

The nerve impulse transmission is lost in the following order :

The order of the loss of nerve function is

1. Pain
2. Temperature
3. Touch
4. Proprioception
5. Skeletal muscle tone.

PHARMACOKINETICS[2]

Absorption :[40,41]

The systemic concentration of ropivacaine depends on the total dose and concentration of drug given, the route of administration, the patient's haemodynamic state and the vascularity of the site of administration. When administered in the epidural space ,ropivacaine has a biphasic absorption. The half lives of the two phases (mean± SD) are 14±7 minutes and 4.2 ±0.9 hours respectively.

Distribution :

After intravascular infusion, ropivacaine has a steady state of distribution of 41 ± 7 litres. It is 94% protein bound, mainly to α_1-acid glycoprotein. In case of continuous epidural infusion of ropivacaine the plasma concentration can rise due to increased protein binding and reduced clearance. Ropivacaine can easily cross the placenta.

Metabolism and excretion :

Ropivacaine is extensively metabolized by the liver, predominantly by the cytochrome P_{4501A} mediated aromatic hydroxylation to produce 3 – hydroxyl ropivacaine. After a single IV dose, approximately 37% of the total dose is excreted in the urine as both free and conjugated 3-hydroxy ropivacaine. An additional unquantified amount of 2 – hydroxyl – methyl ropivacaine has also been identified s a metabolite.

Ropivacaine metabolites are mainly excreted via kidney. After i.v. administration 86% of the dose is excreted in urine of which only 1% is in unchanged form. Following i.v.administration, ropivacaine has a mean ± SD total plasma clearance of 387 ± 107 mL/min, an unbound plasma clearance of 7.2 ± 1.6 L/min and

a renal clearance of 1 mL/min. The mean ± SD terminal half life is 1.8 ± 0.7 h and 4.2 ±1.0 h after i.v. and epidural administration respectively.

PHARMACODYNAMICS

Central Nervous System &CardioVascularSystem :

Ropivacaine has ahigher threshold for both cardiac as well as neuro toxicity as compared to bupivacaine due to its lower lipid solubility and stereo - selective properties. This holds good for both isomers of ropivacaine which have been shown to be less cardio depressant than respective bupivacaine isomers in animal studies.

CNS toxicity occurs earlier than cardiac toxicity on iv infusion in healthy volunteers.

Potency :

Lipid solubility of a local anaesthetic correlates well with it's potency and toxicity. Compounds which are more lipophilic penetrate the nerve cell membrane more readily . Thus fewer molecules are required to produce the desired conduction blockade .

Others :

Continuous epidural infusion of 0.375 % and 0.188% ropivacaine has been shown to inhibit platelet aggregation in plasma.

ADVERSE EFFECTS

Excessive plasma levels are due to over dosage, unintentional intravascular injection or slow metabolic degradation. The mean doses at which CNS symptoms of toxicity begin to occur in human beings are 4.3 and 0.6 mcg/mL of total and free plasma concentrations respectively. When prolonged blocks are used the risks of

reaching a toxic plasma concentration or inducing local neural injury are increased. Various possible side effects include

a. Injection site pain

b. **Cardiovascular system toxicity:** Vasovagal reaction, syncope, postural hypotension, non-specific ECG abnormalities which include wide QRS complexes , increased conduction time and reduced contractility.

c. **Gastrointestinal system toxicity:** Faecal incontinence, tenesmus, nausea, vomiting.

d. **Central nervous system toxicity:** Tremor, Horner's syndrome, dyskinesia, neuropathy, vertigo, convulsion and coma. Because of depressant effect of ropivacaine on medulla, excitatory stage of CNS might not occur.

e. **Liver and Biliary system toxicity:** Jaundice

f. **Metabolic disorders:** Hypomagnesemia

ADVANTAGES OVER OTHER LOCAL ANAESTHETICS

Ropivacaine produces a more differential blockade allowing better separation between sensory and motor block and is therefore a better choice for use in labour analgesia and post operative pain relief. When compared to bupivacaine it produces less dense motor blockade of shorter duration and hence permits earlier mobilization and discharge thus reducing both morbidity as well as cost of treatment. It has a lower systemic toxicity than bupivacaine and a better,cardiostable profile. Ropivacaine has been developed to offer a safer alternative to bupivacaine while retaining the desirable blocking properties of racemic bupivacaine.

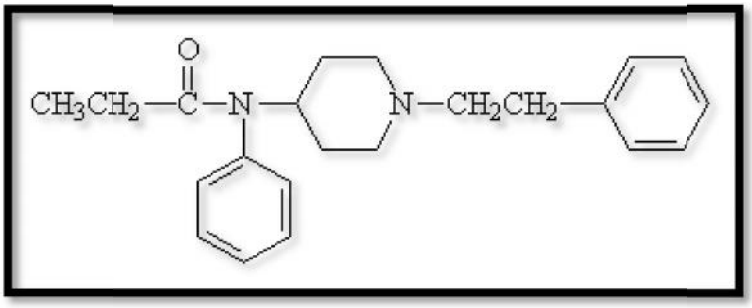
FENTANYL[42]

INTRODUCTION :

Fentanyl is a synthetic opioid analgesic , which was first synthesized by Janssen Pharmaceutics in 1960 . Chemically it is a phenyl piperidine derivative of Mepiridine(a reversed ester of Pethidine).It primarily acts on μ opioid receptors in CNS to cause analgesia . In addition , it also causes decreased heart rate , depression of ventilation , euphoria and dependence due to action on the same receptors.

CHEMICAL STRUCTURE :

Figure 8: Chemical structure of fentanyl



Fentanyl is available as a citrate salt . Chemically it is N 1,4- Piperidyl anilide dihydrogen citrate , ($C_{22}H_{28}N_{20}C_6H_8O_7$)

Molecular weight of Fentanyl is 528.6 g/mol)

PHYSIOCHEMICAL PROPERTIES :

Fentanyl occurs as a white , crystalline powder . It has a very high lipid solubility as compared to its sparing water solubility . In fact due to its much higher lipid solubility as compared to Morphine , it crosses the blood brain barrier more easily. This is the cause for Fentanyl havin an analgesic property 75 – 125 times that of Morphine.

pH of the commercial preparations ranges between 7 to 7.5 while the pKa value is 8.4. At physiologic pH of 7.4 less than 10% is unionized. It is highly plasma protein bound (84%). Solution should be protected from light and stored at 15 to 30° C. It is also available as intrabuccal, transdermal and aerosolized preparations.

MECHANISM OF ACTION :

Fentanyl is primarily a μ receptor agonist and these μ receptors are present in the brain, (periaqueductal gray matter of brain stem, amygdala, corpus striatum and hypothalamus), spinal cord (substantia gelatinosa) and peripheral nerves. These receptors are involved with pain perception, integration of pain impulses and responses to pain.

At cellular level it binds to its specific binding site on μ receptors , increasing potassium conductance across the cell membrane causing hyper polarisation or inactivation of calcium channels or both. This causes the depression of adenyl cyclase activity thus decreasing intracellular cAMP levels.

Opioids act as agonists at stereospecific opioid receptors at presynaptic and postsynapatic sites. The most likely mechanism of these peripheral actions appears to be activation of opioid receptors on primary afferent neurons, Fentanyl mimics the actions of endogenous ligands by binding to receptors resulting in activation of pain modulating system. Opioid receptor activation leads to decrease in neurotransmission. This decrease occurs largely by presynaptic inhibition of neurotransmitter (acetylcholine, dopamine, norepinephrine, substance P) release.

To a lesser extent , Fentanyl also binds to the κ - opioid receptors mediating sedation and miosis.

PHARMACOKINETICS :

Absorption :After I.V administration the onset of action is much more rapid with shorter duration of action. A single I V dose of Fentanyl has a more rapid onset than Morphine (around 30 seconds) . This can be explained on the basis of higher lipid solubility of the former. Similarly for the same reason Fentanyl has a much lesser duration of action as it gets redistributed quickly .

Distribution : Fentanyl has high lipid solubility, so distributes widely throughout the body to inactive sites. Initially it distributes to vascular organs such as heart, lungs and brain, then to skeletal muscles and fat. Lungs also serve as inactive storage site with estimated 75% of initial dose undergoing first pass pulmonary uptake. Volume of distribution for Fentanyl after administration is 4 ± 0.4 liters/kg.

Metabolism and Excretion :The main seat for metabolism is liver where it undergoes N – de methylation and hydroxylation to produce Norfentanyl and 4-N amilinonopiperidine& propionic acid respectively.

Fentanyl undergoes significant first pass metabolism in lungs which transiently take up 75% of injected dose of Fentanyl. 80% of Fentanyl is bound to plasma proteins (approximately 50% to α – acid glycoprotein).

Fentanyl is excreted mainly in the urine as metabolite and less than 8% is excreted as unchanged drug. The mean clearance after i/v administration is between the range of 34-53 litershour^{-1} or approximately 13 ml min^{-1} kg^{-1}. Mean terminal half lives are between 2.5 and 8 hours.

PHARMACODYNAMICS:

Central Nervous System : In the absence of hypoventilation, fentanyl decreases cerebral blood flow and in turn decreases intracranial pressure. Myoclonus during administration may resemble grand mal seizures. It can produce thoracic and abdominal skeletal muscle rigidity. Miosis can also occur as most of μ and κ agonists causes constriction of pupil by an excitatory action on the parasympathetic nerve innervating the pupils.

It causes pruritus when administered for central neuraxial blockade. . Pruritus produced by neuraxial opioids is likely due to cephalad migration of opioids in cerebrospinal fluid and subsequent interaction with opioid receptors in trigeminal nucleus.

Cardio Vascular System :

Fentanyl can cause a depression of cardiovascular system leading to hypotension,, syncope and drug induced bradycardia.Hypotension after fentanyl is due to decrease in systemic vascular resistence and bradycardia . Bradycardia due to the drug can be explained due to central sympathetic soutflowblockade .

Fentanyl causes enhanced entry of calcium ions during plateau phase of action potential and decrease in outward potassium movement thus slowing A-V conduction. This can cause prolonged Q-T interval , asystole and bradycardia.

Respiratory System :

Fentanyl causes dose dependent depression of ventilation and this effect can be more prolonged than the analgesic action and can even continue in the post

operative period. Such patients may require treatment with opioid antagonists (Naloxone) or respiratory stimulants (Doxapram).

Rigidity of respiratory muscles (chest wall) may require treatment with muscle relaxants. However the risk of respiratory depression following epidural administration of Fentanyl has been found to be very low .

Gastrointestinal system : Fentanyl decreases tone of lower oesophageal sphincter and increases gastric emptying time.

Hepatobiliary system : Causes a spasm of sphincter of oddi, increasing the biliary pressure .

Tolerance and physical dependence: Tolerance can occur without physical dependence but the reverse does not seem to occur. Cross tolerance develops between all the opioids.

ADVERSE EFFECTS :

1) Persistent and recurrent depression of ventilation
2) Hypotension and bradycardia
3) Muscle rigidity
4) Rarely can cause laryngospasm .

DOSE :

I.V. : 1 – 2 mcg/ kg body weight

Intrathecal : 25-40 mcg (adults)

Epidural : 25-50 mcg (adults)

METHODOLOGY

The present study titled **"COMPARISON OF ONSET AND DURATION OF BLOCKADE AND POST OPERATIVE ANALGESIA OF ISOBARIC ROPIVACAINE 0.75% WITH FENTANYL AND ISOBARIC ROPIVACAINE 0.5% WITH FENTANYL IN FEMALE PATIENTS UNDERGOING LOWER ABDOMINAL SURGERIES UNDER EPIDURAL ANAESTHESIA - A ONE YEAR HOSPITAL BASED RANDOMISED CONTROLLED TRIAL"** was conducted in the Department of Anaesthesiology , KLE's Dr. Prabhakar Kore Charitable Hospital , Belagavi during the period of January 2015 to December 2015 .

Source of data

Female patients between the age group of 18-60 yrs, belonging to ASA Grade I and II scheduled for elective lower abdominal surgeries at K.L.E`S Dr. Prabhakar Kore Charitable Hospital , Nehru Nagar, Belagavi between Jan 2015 to Dec 2015 were included.

Study Design:

A one year randomised controlled trial.

Study Period:

One year from January 2015 to December 2015.

Selection criteria

Inclusion:

- Female patients undergoing elective lower abdominal surgeries lasting 60 to 120 mins.
- Age: 18 to 60 years

- ASA Grade I and Grade II patients
- Patients providing consent
- Weight : 50 – 65 kgs
- Height : 150 – 165 cms.

Exclusion:

- Pregnant patients .
- Contraindications to epidural anaesthesia .
- Pre-existing neurological deficits in the lower extremities, and cardiovascular, respiratory, neurological, psychological, hepatic, or renal disease.

Sample size:

Total sample size is 80 patients.

0.75 % Ropivacaine-Fentanyl group = 40

0.5 % Ropivacaine-Fentanyl group = 40

Randomisation was achieved by computer generated randomisation chart.

Sample size calculation:

Using the formula, sample size =

$$\text{Sample Size (n)} = \frac{2 \times (Z\alpha + Z\beta)^2 (S_1^2 + S_2^2)}{(X_1 - X_2)^2}$$

Level of significance was taken as 5%

Power of the test used was taken as 80%

type I error rate $\alpha = 0.05$ and

type II error rate $\beta = 0.2$

Taking the level of significance at 5%(α=0.05), power of the test as 80%(β=0.2), and using one sided test we get Zα=1.65 and Zβ=0.84

$S_1$was S.D of 0.75 % Ropivacaine

$S_2$was S.D of 0.5 % Ropivacaine

$X_1$was time for onset of sensory blockade at T_{10} with 0.75 % Ropivacaine[25]

$X_2$was time for onset of sensory blockade at T_{10} with 0.5 % Ropivacaine[23]

Hence, Zα = 1.65

Zβ = 0.84

S_1= 3.30

S_2 = 1.90

X_1= 11.36

X_2 = 13.5

$$\text{Sample Size (n)} = \frac{2X(1.65+0.84)^2(3.30^2+1.9^2)}{(11.36-13.5)^2}$$

n = 39.27

For ease of calculations and sake of consistent result, sample size was taken as 40. There were thus two groups of 40 each.

Methodology

After obtaining the approval of ethical committee and written informed consent, a total of 80 female patients undergoing elective surgeries under epidural anaesthesia were included in the study.

After having met inclusion and exclusion criteria and having obtained informed consent, patients were randomized based on computer generated randomization table into one of the two groups.

- Group A
- Group B

All study drugs were prepared in identical sterile bowls by mixing isobaric 0.5% Ropivacaine 15 ml (75 mg) with Fentanyl 50 mcg and isobaric 0.75 % Ropivacaine 15 ml (112.5 mg) with Fentanyl 50 mcg . Study drugs were prepared by an anaesthesiologist not involved with subsequent administration and patient assessment.

A thorough Pre-Anaesthetic Evaluation was done. Detailed medical and personal history was obtained. A detailed physical examination was done. Patients were advised overnight fasting. Routine investigations such as Complete blood picture, Random Blood Sugar, Serum Creatinine, Blood Grouping and Typing, Chest X-ray, Electrocardiography were carried out.

In the preoperative holding area, a wide bore i.v. access was secured and patients preloaded with an infusion of 10ml/kg of crystalloid solution half hour before induction of anaesthesia. Anaesthetic techniques were standardized for all patients.

Inside the operation theatre, standard non – invasive monitors were attached and baseline HR , BP , SpO2 was recorded .

Under strict aseptic precaution the following procedure was carried out :

Group A: With the patient in lateral position, L2-L3 epidural space was identified using an 18G Tuohy's needle by loss of resistence to air technique . A test dose of 3 ml of 2% Lignocaine with Adrenaline was injected to confirm the presence of needle in the correct space . After waiting for 5 minutes to look for signs of intravascular/intrathecal injection of LA , with the bevel facing up epidural catheter was threaded in through Tuohy's needle and fixed at 4cms Inside the epidural space. The patient was then made supine and 15 ml of 0.75% Ropivacaine with 50 mcg of Fentanyl was injected through the catheter .

Group B : With the patient in lateral position, L_2-L_3 epidural space was identified using an 18G Tuohy's needle by loss of resistence to air technique . A test dose of 3 ml of 2% Lignocaine with Adrenaline was injected to confirm the presence of needle in the correct space . After waiting for 5 minutes to look for signs of intravascular/intrathecal injection of LA , with the bevel facing up epidural catheter was threaded in through Tuohy's needle and fixed at 4cms Inside the epidural space. The patient was then made supine and 15 ml of 0.5% Ropivacaine with 50 mcg of Fentanyl was injected through the catheter .

All patients were given Inj. Midazolam 1.5 mg. i.v. for sedation. The following parameters were then be monitored/measured :

A)Sensory Blockade : was assessed by alcohol swab in mid axillary line every minute till T_{10} block occurs , following which it was assessed at 10 minute intervals for next 2 hrs and at 15 minute intervals beyond 2 hrs till full regression occured .

Time taken for sensory blockade till T_{10} dermatome, highest sensory dermatome blocked , time for regression to 2 dermatomes from the highest dermatome reached and time for regression to S_2 were recorded.

Surgery was allowed to start once T_{10} dermatome had been blocked but GA was induced if this did not happen in 30 minutes. Such cases were labeled as block failure and excluded from final analysis .

B) Motor Blockade :was assessed immediately after sensory block assessment using a Modified Bromage scale.

Bromage 0:- free movement of legs and with ability to raise extended leg.

Bromage 1:-inability to raise extended leg and knee flexion is decreased, but full flexion of ankle and feet is present.

Bromage 2:-inability to raise leg or flex knees, flexion of ankle and feet present.

Bromage 3:-inability to raise leg, flex knee or ankle or move toes.

Motor block onset was taken as the time to reach modified Bromage score 3 and total duration of motor block was taken as the time for return to modified Bromage score 0.

In case patient didn't attain Bromage score of 3, the highest score attained was documented .

C) Post operative analgesia: Following surgery patient was not put on regular analgesics .

Time for first rescue analgesia was noted .As per institution protocol , Inj. Buprenorphine 150 mcg was given via the epidural catheter as rescue analgesia whenever patient complained of pain .

Further top up was given in the same dose after 12 hrs or on patient's complaining of pain whichever was later .

Any pain between 2 doses was treated with Inj. Diclofenac 75 mg. i.m

Total Buprenorphine consumption and extra Diclofenac if given were documented for the first 24 hrs post induction, which was the end of the study period .

The epidural catheter however remained in situ and further analgesia was provided to patient through it ,SOS . The catheter was removed after 72 hours as per institution protocol.

D) Vitals : HR , SBP , DBP and SpO_2 were monitored throughout the surgery .

Blood pressure and heart rate were recorded at 2, 4, 6, 8, 10, 15, 20, 25, 30 minutes and every 15 minutes till the end of surgery.

Hypotension was defined as decrease in systolic B.P by 20% from baseline values or a systolic B.P less than 90 mm of Hg and was treated with incremental intravenous boluses of Ephedrine 5 to 10 mg and a bolus administration of 250ml of Ringer Lactate solution over 10 mins.

Bradycardia was defined as decrease in heart rate less than 50 beats per minute and was treated with intravenous Atropine 0.6 mg.

Supplementary oxygen was given through face mask.

E) Side effects : Any side effects which occured were duly documented .

In case the effect of anaesthesiaweared off before the completion of surgery , patient was maintained on epidural bolus topups of a mixture of 2.5 ml. of the

original drug given + 2.5 ml. of 2 % Lignocaine with Adrenaline . Such patients were excluded from the final analysis .

Statistical Analysis

The data was tabulated and master chart was prepared (Annexure V). The categorical data was expressed as rates, ratios and percentages while continuous data was expressed as mean $\pm$ standard deviation. Student unpaired ‘ t ‘ test was used to find significance of study parameters on continuous scale between the two groups. Chi - square test was used to find association between different classes of variables. A p – value < 0.05 was considered statistically significant.

RESULTS

This one year randomised clinical trial was conducted in the Department of Anaesthesiology, during the period of January 2015 to December 2015 at KLES Dr. Prabhakar Kore Charitable Hospital, Belagavi attached to Jawaharlal Nehru Medical College, Belagavi.

A total of 80 female patients undergoing lower abdominal surgeries under epidural anaesthesia were randomly allocated into one of the two groups based on a computer generated randomisation chart :

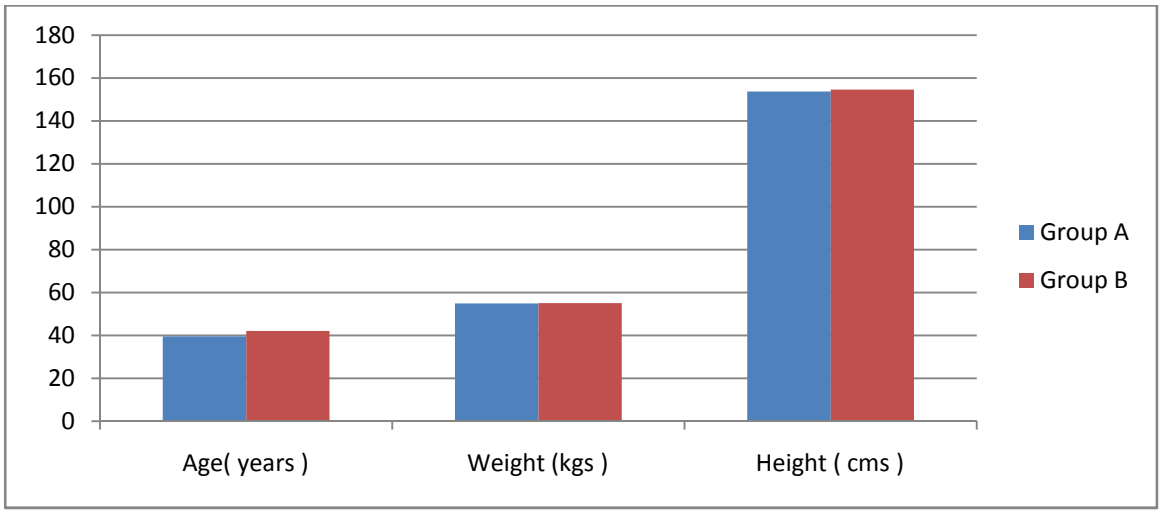
- Group A(n=40) : Patients received 15 ml of 0.75% Ropivacaine with 50 mcg Fentanyl via epidural catheter
- Group B (n=40) : Patients received 15 ml of 0.5% Ropivacaine with 50 mcg Fentanyl via epidural catheter

Data obtained was coded and analysed as below.

Table 1: Mean Age, Weight and Height

	Group A		Group B		P value
	Mean	Standard Deviation	Mean	Standard Deviation	
Age(years)	39.5	10.34	42.1	11.45	0.281
Weight(kgs)	54.9	3.47	55.1	2.93	0.255
Height(cms)	153.8	3.72	154.7	3.95	0.272

Graph 1 : Mean Age, Weight and Height



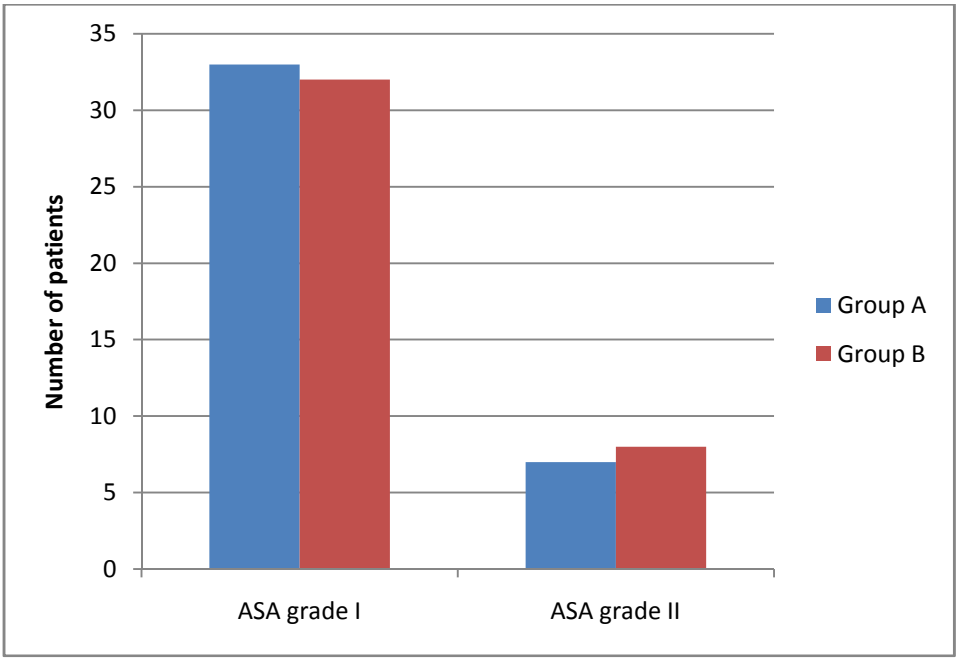
In the present study we found no statistically significant difference between group A and group B with regards to mean age (39.5 $\pm$ 10.34 and 42.1 $\pm$ 11.45 years respectively; p = 0.281), mean weight (54.9 $\pm$ 3.47 and 55.1 $\pm$ 2.93 kgs respectively; p = 0.255) and mean height (153.8 $\pm$ 3.72 and 154.7 $\pm$ 3.95 cms respectively; p =0.272)

Table 2: ASA Grade

	Group A		Group B	
	Number	Percent	Number	Percent
Grade I	33	82.5	32	80
Grade II	7	17.5	8	20
Total	40	100	40	100

x^2= 0.082 p= 0.775

Graph 2 : ASA Grade

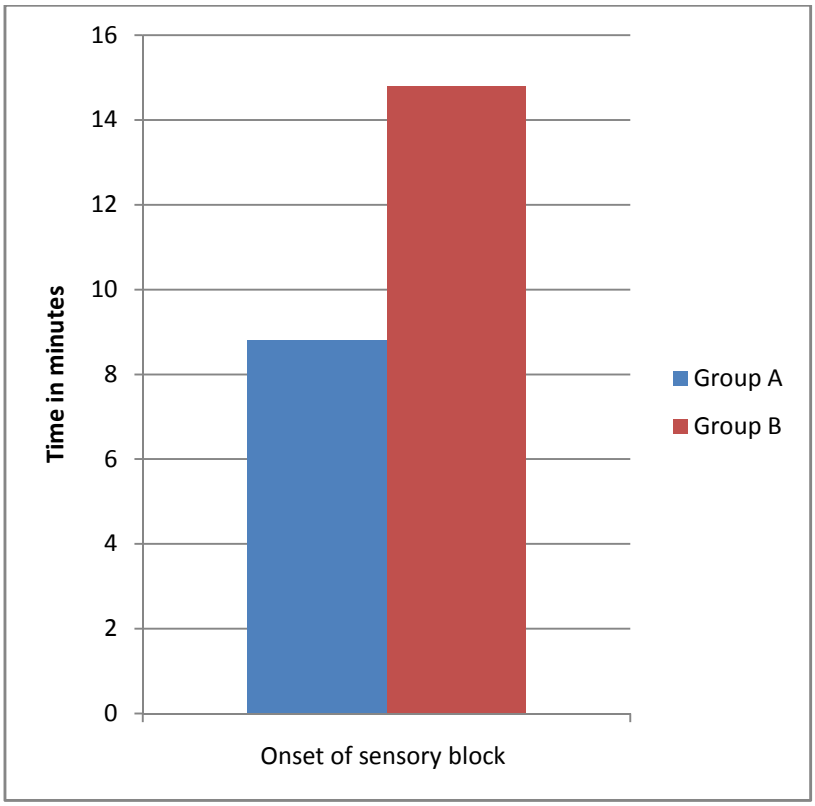


In group A 82.5 % patients were ASA grade I and 17.5 % were ASA grade II. In group B 80 % patients were ASA grade I while 20 % were ASA grade II.The data was comparable in both groups (x^2 = 0.082, p = 0.775)

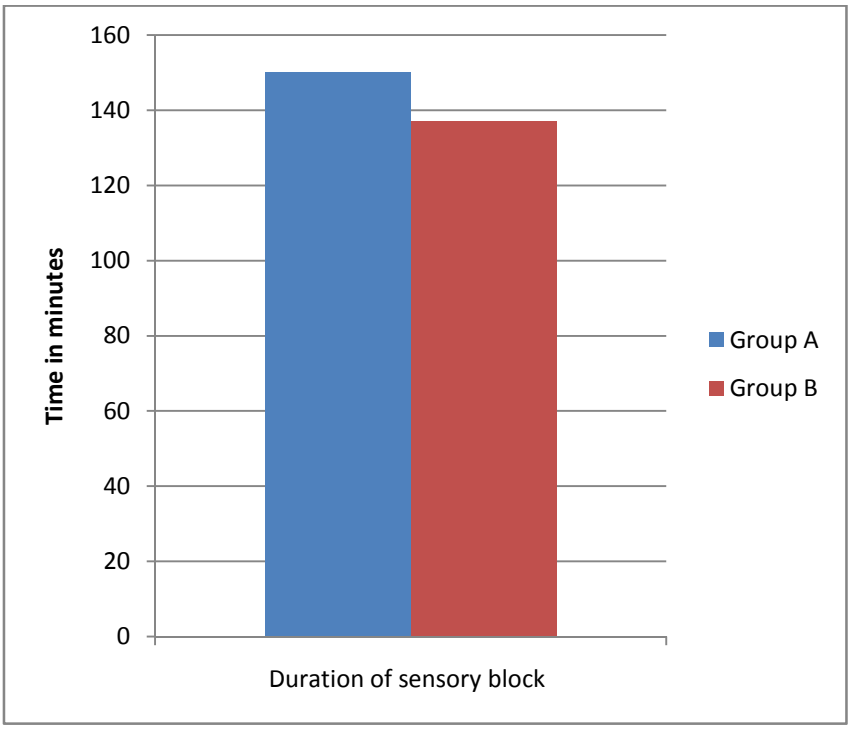
Table 3 Onset and duration of sensory block(Also refer Graphs 3,4)

	Onset(minutes)		Duration(minutes)	
	Mean	Standard Deviation	Mean	Standard Deviation
Group A	8.8	1.33	150	11.09
Group B	14.8	0.97	137.2	9.93
p value	< 0.001		< 0.001	

Graph 3 : Onset of sensory block



Graph 4: Duration of sensory block



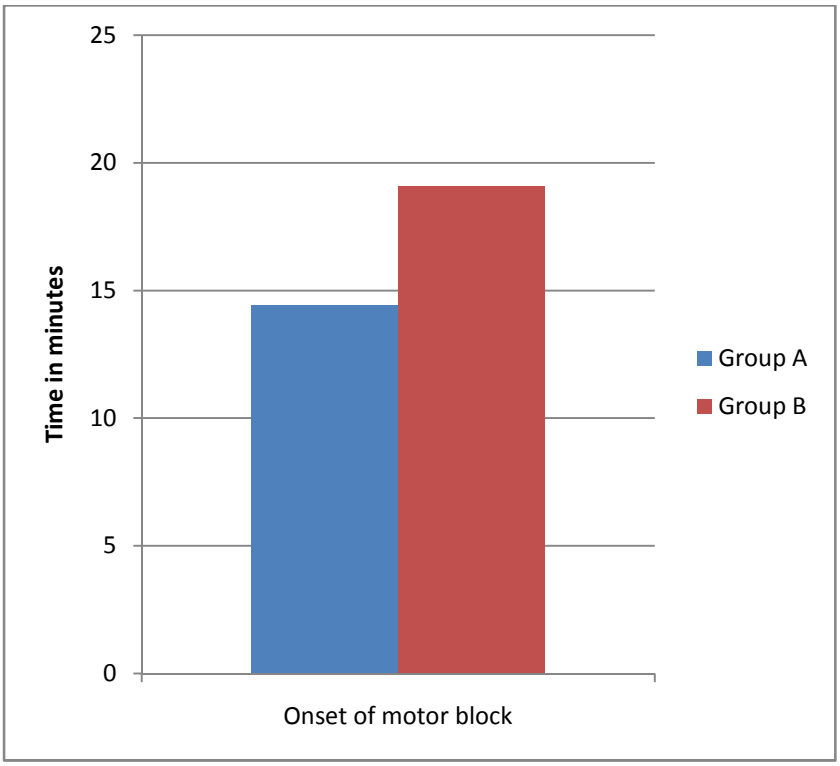
In our study, mean onset of sensory blockade was faster in group A (8.8 ± 1.33 min) than in group B (14.8 ± 0.97 min) and was statistically significant ($p < 0.001$).

The mean duration of sensory blockade was longer in group A (150± 11.09 min) than in group B (137.2 ± 9.93 min) and was statistically significant ($p < 0.001$)

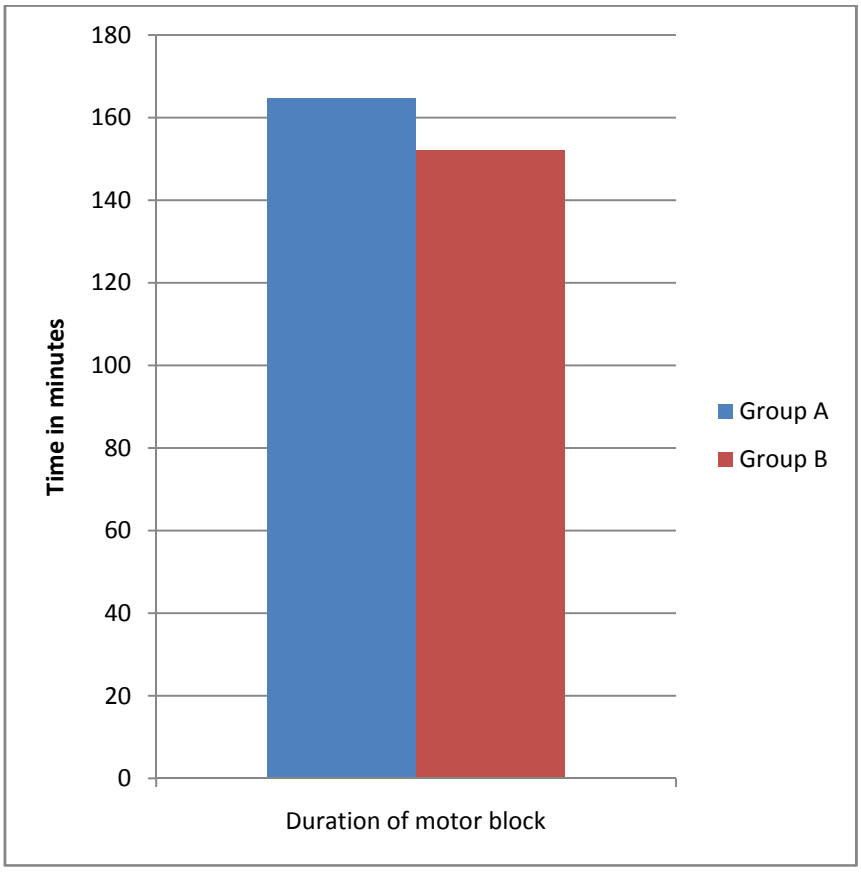
Table 4 : Onset and duration of motor block (Also refer graphs 5,6)

	Onset(minutes)		Duration(minutes)	
	Mean	Standard Deviation	Mean	Standard Deviation
Group A	14.4	2.05	164.7	13.33
Group B	19.1	1.03	152.2	9.49
p value	< 0.001		< 0.001	

Graph 5 : Onset of Motor Block



Graph 6 : Duration of Motor block



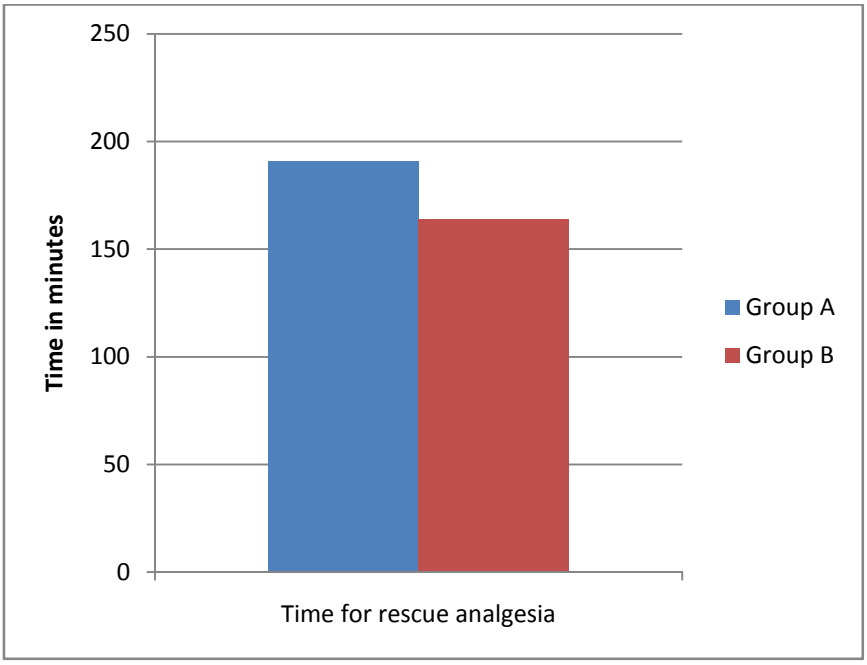
In the present study, mean onset of motor block was faster in group A (14.4 ±2.05 min) than group B (19.1 ± 1.03 min) and was statistically significant (p< 0.001).

The mean duration of motor block was longer in group A (164.7± 13.77 min) than group B (152.2 ± 9.49 min) and was statistically significant (p < 0.001)

Table 5 : Time for rescue analgesia

	Group A		Group B	
	Mean	Standard Deviation	Mean	Standard Deviation
Time for rescue analgesia (minutes)	190.7	15.91	163.7	8.37
p value	< 0.001			

Graph 7 : Time for rescue analgesia

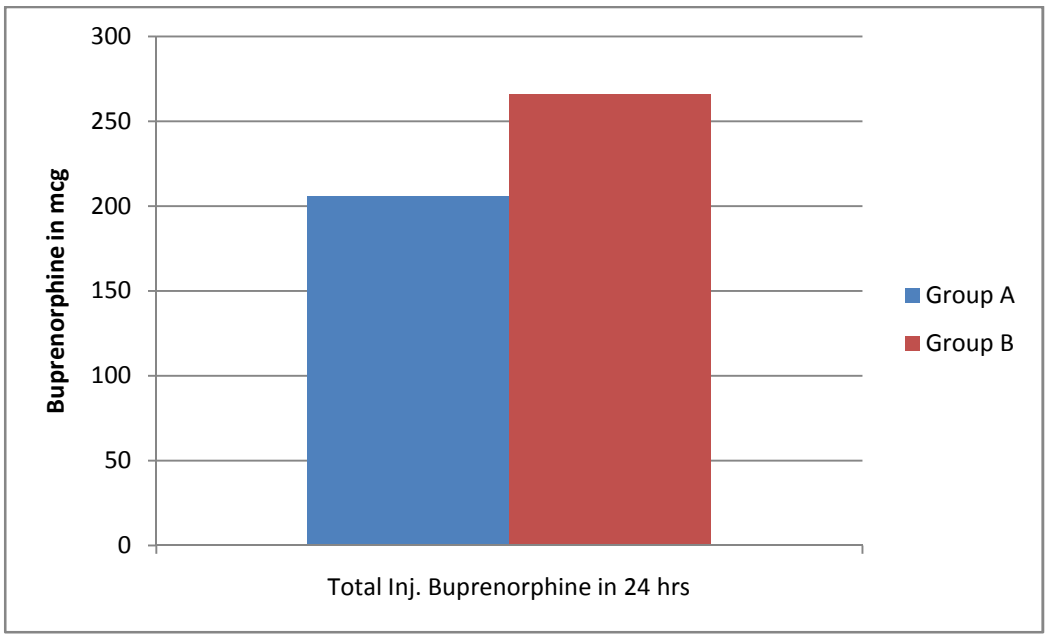


In the present study time for rescue analgesia was longer in group A (190.7 $\pm$ 15.91 min) than group B (163.7$\pm$ 8.37 min) and was statistically significant ($p < 0.001$)

Table 6 : Total dose of Inj. Buprenorphine in 24 hours

	Group A		Group B	
	Mean	Standard Deviation	Mean	Standard Deviation
Total dose of Inj. Buprenorphine in 24 hours (mcg)	206.2	73.54	266.63	63.43
p value	< 0.001			

Graph 8 : Total Inj Buprenorphine in 24 hours (mcg)



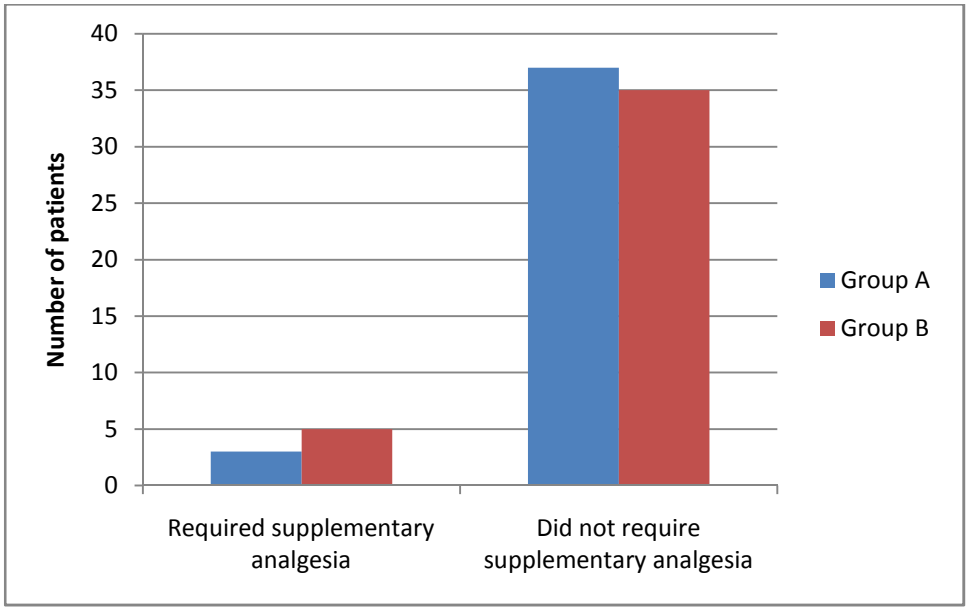
In the present study the total dose of Inj. Buprenorphine in 24 hours was less in group A (206.27 $\pm$ 73.54 mcg) than group B (266 $\pm$ 63.43 mcg) and was statistically significant ($p < 0.001$).

Table 7 : Requirement of supplementary analgesia

	Group A		Group B	
	Number	Percent	Number	Percent
Yes	3	7.5	5	12.5
No	37	92.5	35	87.5
Total	40	100	40	100

x^2= 0.139 p= 0.709

Graph 9 : Supplementary analgesia



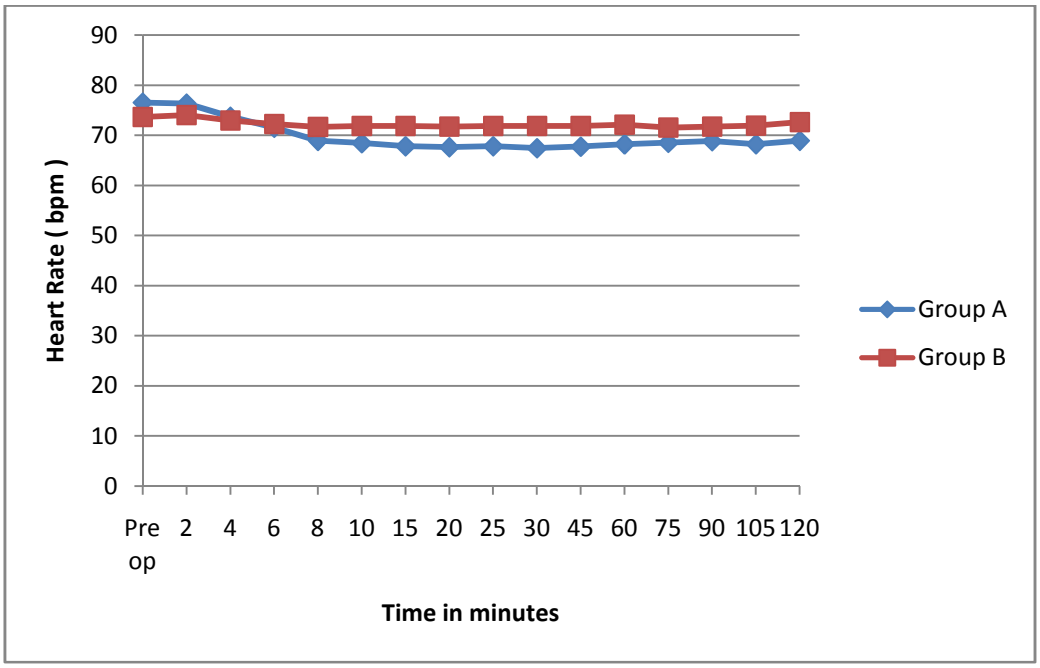
In group A 7.5 % of patients required supplementary analgesia between epidural topups . In group B 12.5 % patients required supplementary analgesia between epidural top ups.

The data was comparable between two groups (x^2 = 0.139 , p = 0.709)

Table 8: Comparison of mean heart rate at different time intervals (bpm)

Intervals(min)	Group A		Group B		p value
	Mean	SD	Mean	SD	
Pre op	76.5	6.93	73.6	7.19	0.07
2	76.3	7.39	74	7.46	0.17
4	73.7	6.87	72.9	7.57	0.655
6	71.5	7.05	72.2	7.59	0.671
8	68.9	8.07	71.6	6.44	0.109
10	68.4	8.14	71.8	8.06	0.066
15	67.8	7.59	71.8	7.64	0.02
20	67.6	7.07	71.7	7.5	0.017
25	67.8	7.08	71.8	7.45	0.017
30	67.4	8.26	71.8	7.77	0.016
45	67.7	8.17	71.8	7.99	0.024
60	68.2	7.90	72.1	8.49	0.034
75	68.5	7.68	71.5	7.57	0.078
90	68.8	8.09	71.7	6.54	0.085
105	68.2	8.07	71.9	6.54	0.026
120	68.9	8.39	72.6	6.38	0.035

Graph 10 : Comparison of mean heart rate at different intervals (bpm)



In this study the mean heart rate in the pre operative phase was 76.5 ±6.93 bpm in group A and 73.6 ± 7.19 bpm in group B and was comparable (p = 0.078).

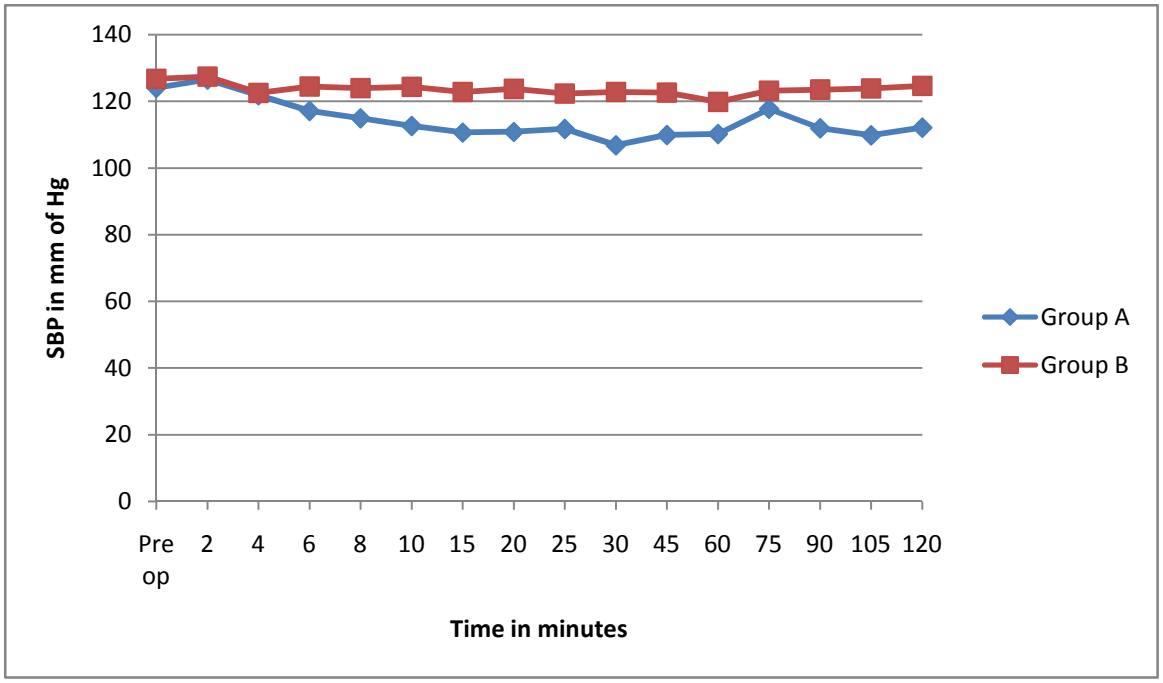
The heart rate fell to 68.2 ± 7.90 bpm at 60 minutes and 68.9 ± 8.39 bpm at 120 minutes in group A while it fell to 72.1 ± 8.49bpm at 60 minutes and 72.6 ± 6.38 bpm at 120 minutes in group B.

The heart rate was significantly lower in group A at 15, 20, 25, 30, 45, 60, 105 and 120 minutes (p values 0.021, 0.017, 0.017, 0.016, 0.024, 0.034, 0.026 and 0.035 respectively) than group B

Table 9: Comparison of systolic blood pressure at different time intervals (mm of Hg)

Intervals(min)	Group A		Group B		p value
	Mean	SD	Mean	SD	
Pre op	124	19.36	126.7	9.61	0.432
2	126.5	8.15	127.4	9.57	0.643
4	121.8	10.69	122.5	19.86	0.845
6	117.1	10.89	124.4	9.13	0.002
8	114.9	10.75	123.9	9.51	<0.001
10	112.6	9.09	124.3	9.41	<0.001
15	110.6	9.09	122.8	9.01	<0.001
20	110.8	9.00	123.7	8.9	<0.001
25	111.7	9.2	122.3	9.0	<0.001
30	106.8	17.99	122.8	9.85	<0.001
45	109.87	8.52	122.6	9.82	<0.001
60	110.2	8.31	119.8	19.96	0.006
75	117.7	9.76	123.2	10.56	<0.001
90	111.9	8.91	123.5	10.22	<0.001
105	109.8	17.26	123.8	9.49	<0.001
120	112.1	8.51	124.6	9.75	<0.001

Graph 11 : Comparison of systolic blood pressure at different intervals (mm of Hg)



In this study the mean systolic BP in the pre operative phase was 124 ± 19.36 mm of Hg in group A and 126.7 ± 9.61 in group B and was comparable (p = 0.432).

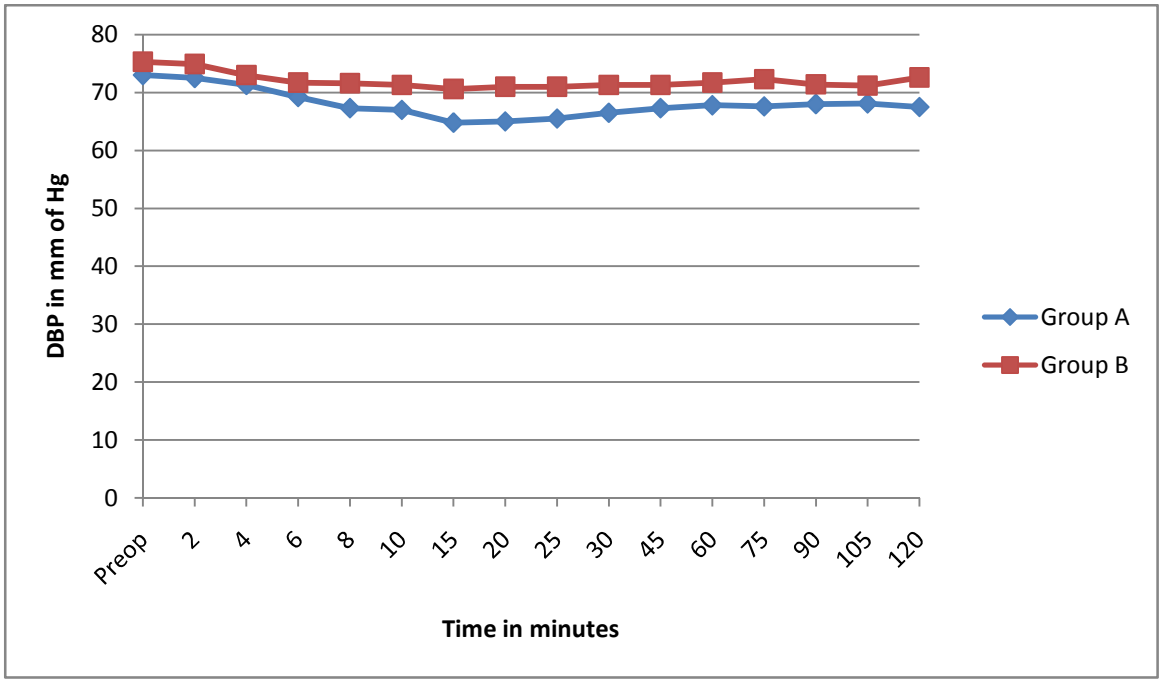
The systolic BP fell to 110.2 ± 8.31 mm of Hg at 60 minutes and 112.1 ± 8.51 mm of Hg at 120 minutes in group A while it fell to 119.8 ± 8.49 b19.96 mm of Hg at 60 minutes and 124.6 ± 9.75 mm of Hg at 120 minutes in group B.

The systolic BP was significantly lower in group A at 6, 8, 10, 15, 20, 25, 30, 45, 60, 105 and 120 minutes (p values< 0.05) than group B

Table 10: Comparison of diastolic blood pressure at different time intervals (mm of Hg)

Intervals(min)	Group A		Group B		p value
	Mean	SD	Mean	SD	
Pre op	73	5.87	75.3	5.72	0.07
2	72.5	5.02	74.9	6.11	0.054
4	71.3	4.63	73	6.12	0.165
6	69.2	5.59	71.7	5.03	0.045
8	67.3	5.35	71.6	4.96	<0.001
10	67	5.45	71.3	5.17	<0.001
15	64.8	10.75	70.6	4.65	0.003
20	65	10.00	71	9.0	0.003
25	65.5	8.9	71	9.0	0.002
30	66.5	5.27	71.3	4.37	<0.001
45	67.3	5.39	71.3	5.25	<0.001
60	67.8	5.62	71.7	4.67	0.006
75	67.6	5.09	72.3	5.90	<0.001
90	68	5.67	71.4	4.75	0.005
105	68.1	7.25	71.2	4.16	0.020
120	67.5	5.66	72.6	4.39	<0.001

Graph 12 : Comparison of diastolic blood pressure at different intervals (mm of Hg)



In this study the mean diastolic BP in the pre operative phase was 73 ± 5.87 mm of Hg in group A and 75.3 ± 5.72 mm of Hg in group B and was comparable (p = 0. 07).

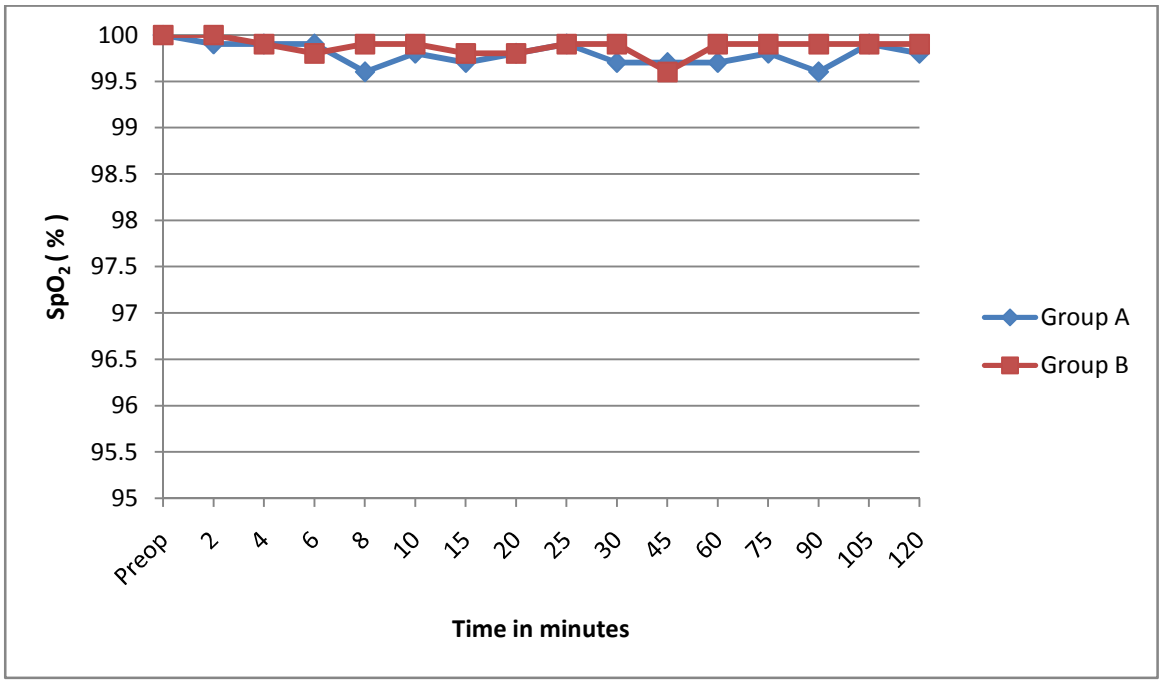
The diastolic BP fell to 67.8 ±5.62 mm of Hg at 60 minutes and 67.5 ±5.66 mm of Hg at 120 minutes in group A while it fell to 71.7 ± 4.67 mm of Hg at 60 minutes and 72.6 ± 4.39 mm of Hg at 120 minutes in group B.

The diastolic BP was significantly lower in group A at 6, 8, 10, 15, 20, 25, 30, 45, 60, 105 and 120 minutes (p values < 0.05) than group B

Table 11: Comparison of SpO_2 at different time intervals (%)

Intervals(min)	Group A		Group B		p value
	Mean	SD	Mean	SD	
Pre op	100	0	100	0	-
2	99.9	0.27	100	0	0.079
4	99.9	0.35	99.9	0.35	1
6	99.9	0.3	99.8	0.53	0.608
8	99.6	0.73	99.9	0.31	0.02
10	99.8	0.56	99.9	0.38	0.355
15	99.7	0.61	99.8	0.40	0.133
20	99.8	0.4	99.8	0.3	0.122
25	99.9	0.5	99.9	0.4	0.344
30	99.7	0.59	99.9	0.3	0.156
45	99.7	0.51	99.6	0.84	0.423
60	99.7	0.48	99.9	0.47	0.164
75	99.8	0.57	99.9	0.27	0.14
90	99.6	0.58	99.9	0.35	0.012
105	99.9	0.3	99.9	0.16	0.179
120	99.8	0.33	99.9	0.28	0.561

Graph 13 : Comparison of SpO_2 at different intervals (%)



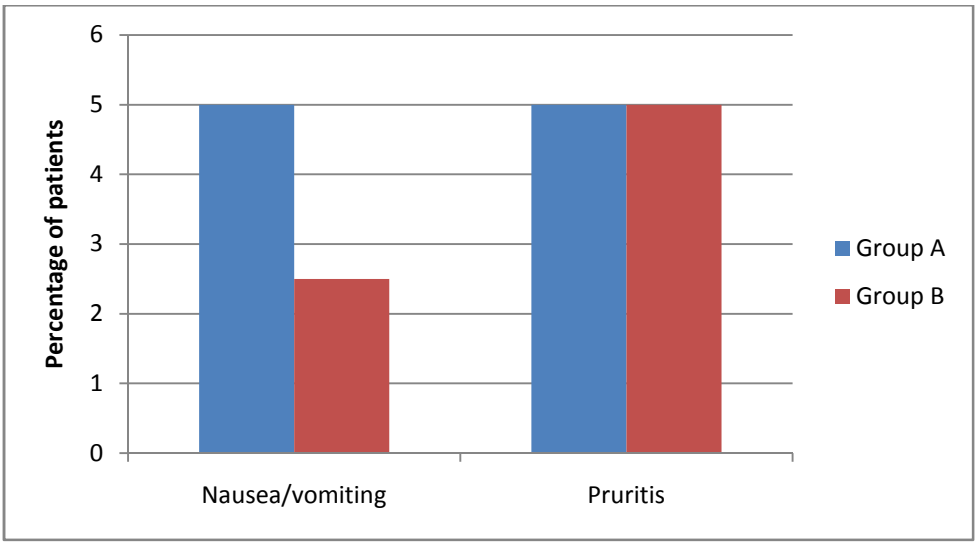
In this study the SpO_2 in the pre operative phase was 100 $\pm$ 0 % in both group A and group B and was thus identical.

The SpO_2 was comparable in both groups throughout the study period (p values > 0.05)

Table 12: Comparison of complications and side effects observed

	Group A	Percentage	Group B	Percentage
Hypotension	-	-	-	-
Nausea and vomiting	2	5	1	2.5
Pruritis	2	5	2	5
Bradycardia	-	-	-	-
Sedation	-	-	-	-

Graph 14 : Complications/ Side effects observed



In the present study, 5 % of patients in group A developed nausea and vomiting while 2.5 % patients in group B developed nausea and vomiting.

5 % patients in both group A and group B developed pruritis.

None of the patients in either group developed hypotension, bradycardia, sedation, urinary retention or respiratory depression

DISCUSSION

Neuraxial blockade has been the preferred anaesthetic technique for lower abdominal and lower limb surgeries. Sub arachnoid block has been the traditional neuraxial block technique for these patients, however in recent times epidural anaesthesia is being used more frequently for such procedures.

Epidural anaesthesia specially with placement of epidural catheter has certain distinct advantages over sub arachnoid block with the ability to titrate the dose of local anaesthetic to the desired level and duration of block and providing post operative analgesia being the most important ones. It also provides a better haemodynamic stability due to segmental nature of the block

Bupivacaine has traditionally been the drug of choice for epidural anaesthesia. However, bupivacaine has selective cardiotoxicity potential due to slow dissociation from cardiac sodium channels and significant number of deaths have been attributed to its use in regional anaesthesia – mainly due to inadvertent intravascular injection. This property was attributed to R(+) enantiomeric structure of bupivacaine.

Ropivacaine is a newer local anaesthetic which is available as pure S(-) enantiomer thus reducing it's cardiotoxic potential. The action of ropivacaine on Aα and $A_\beta$fibres is slower due to low lipid solubility thus producing a less dense motor block. The blockade of A_δ and unmyelinated C fibres however is comparable with bupivacaine thus producing comparable sensory block.

Various adjuvants have been tried along with local anaesthetics to provide a faster onset and prolonged duration of block. Opioids provide synergistic action with local anaesthetics and intensify the sensory block without much sympathetic block.

Fentanyl, a selective μ receptor agonist, is the most commonly used opioid adjuvant in neuraxialblock . Due to high lipid solubility it has a faster onset and shorter duration of action and is an excellent choice of adjuvant in epidural block.

The present one year randomized clinical trial was undertaken at Department of Anaesthesiology, KLES Dr. Prabhakar Kore Charitable Hospital, Belagavi from January 2015 to December 2015. A total of 80 female patients undergoing lower abdominal surgeries under epidural anaesthesia were randomly allocated into two groups using a computer generated randomization chart:

Group A: received 15 ml of 0.75% ropivacaine and 50 mcg fentanyl by epidural route, (n=40)

Group B: received 15 ml of 0.5% ropivacaine and 50 mcg fentanyl by epidural route, (n=40)

In our study we found no statistically significant difference between group A and group B with regards to mean age (39.5 $\pm$ 10.34 and 42.1 $\pm$ 11.45 years respectively; p value = 0.281), mean weight (54.9 $\pm$ 3.47 and 55.1 $\pm$ 2.93 kgs respectively; p value = 0.255) and mean height (153.8 $\pm$ 3.72 and 154.7 $\pm$ 3.95 cms respectively; p value =0.272)

In our study, onset of sensory block was defined as the time taken to achieve sensory block at T_{10} dermatomal level. The mean time of onset of sensory block in this study was8.8 $\pm$ 1.33 min in Group A as compared to 14.8 $\pm$ 0.97 min Group B. The difference between the groups was statistically significant (p-value < 0.001)

Bajwa et al in their study conducted in 2011, compared 100 patients undergoing lower limb orthopaedic surgeries under epidural anaesthesia, by dividing

them in two groups :Group ropivacaine – dexmedetomidine (RD) receiving 15 ml of 0.75 % ropivacaine with 1 mcg/kg dexmedetomidine and group ropivacaine – fentanyl (RF) receiving 15 ml of 0.75 % ropivacaine with 1mcg/kg fentanyl. Time to reach T_{10} block was 7.12 $\pm$ 2.44 minutes in ropivacaine – dexmedetomidine group while it was 9.14 $\pm$ 2.94 minutes in ropivacaine – fentanyl group.[9] These results are therefore similar to our study.

In a study conducted by Thimappa et al in 2014, 90 patients undergoing lower abdominal and and lower limb surgeries under epidural anaesthesia were randomly divided into three groups as follows : Group R received 19 ml of 0.75% ropivacaine with 1 ml normal saline, group RC received 19 ml of 0.75% ropivacaine with 75 mcg clonidine and group RD received 19 ml of 0.75% ropivacaine with 75 mcg dexmedetomidine. The time of onset of sensory block at T_{10} was 12.33 $\pm$ 1.56 minutes in group R, 9.17 $\pm$ 1.21 minutes in group RC and 8.90 $\pm$ 0.99 minutes in group RD.[8]As this study used ropivacaine without adjuvant in one group and ropivacaine with different α_2 - agonist adjuvants in the other two groups the onset of sensory block is different from our study.

Bajwa et al conducted another study on 51 patients undergoing caesarean section under epidural anaesthesia. Patients were divided into two groups randomly with one group receiving 20 ml of 0.75% ropivacaine while the second group received 20 ml of 0.75% ropivacaine with 75 mcg clonidine. The time of onset of sensory block at T_{10} was 11.36 $\pm$ 3.30 minutes in ropivacaine group and 8.64$\pm$ 2.56 minutes in ropivacaine – clonidine group.[25]. As this study used ropivacaine without adjuvant in one group and ropivacaine with clonidine in the other group instead of fentanyl, the onset of sensory block is slightly different from our study.

Kulkarni et al in 2013 conducted a study on elderly patients undergoing lower limb surgeries under epidural anaesthesia. Group B received 15 ml of 0.5% bupivacaine while group R received 15 ml of 0.5% ropivacaine via an epidural catheter. time of onset of sensory block at T_{10} was 8.73 $\pm$ 2.41 minutes in bupivacaine group and 13.55 $\pm$ 1.90 minutes in ropivacaine group[23]. Thus the onset of sensory block at T_{10} in this study is similar to our study.

In our study, duration of sensory block was defined as the time taken for regression of sensory block till S_2 dermatome. The mean duration of sensory block in this study was 150$\pm$11.09 minutes in Group A as compared to 137.2$\pm$9.93 minutes Group B. The difference between the groups was statistically significant (p-value < 0.001).

In the previously mentioned study by Bajwa et al[9], comparing ropivacaine with dexmedetomidine to ropivacaine with fentanyl, the duration of sensory block was 140.32 $\pm$ 10.21 minutes in ropivacainedexmedetomidine group and 110.84 $\pm$ 9.48 minutes in ropivacaine fentanyl group. The slight difference in the values can be attributed to this study using two segment regression as the end point for duration of sensory block as compared to regression to S_2 dermatome in our study.

In another study by Rastogi et al[43] comparing 15 ml of 0.75% ropivacaine along with 50 mcg fentanyl to 15 ml of 0.5% bupivacaine with 50 mcg fentanyl in high risk elderly patients undergoing hemiarthroplasty under epidural anaesthesia, the duration of sensory block was 130.6 $\pm$ 10.2 minutes in ropivacaine – fentanyl group and 175.8 $\pm$ 8.6 minutes in bupivacaine – fentanyl group. This result is similar to our study.

In previously mentioned study by Thimappa et al[8] comparing 0.75% ropivacaine alone , along with fentanyl and along with dexmedetomidine for lower abdominal and and lower limb surgeries, the mean duration of sensory block was 94.57 $\pm$ 6.98 minutes for ropivacaine group, 120.63 $\pm$ 17.59 minutes for ropivacaine – clonidine group and 163.67 $\pm$ 15.20 minutes for ropivacaine – dexmedetomidine group. The difference in the values from our study can be attributed to this study using ropivacaine alone and with α-2 agonist adjuvants instead of fentanyl and using two dermatomal regression as end point for sensory blockade instead of regression to S_2 dermatome.

In the study by Kulkarni et al[23] , the duration of sensory block was 97.86 $\pm$ 8.53 minutes for bupivacaine group and 78.25 $\pm$ 5.13 minutes for ropivacaine group. The use of fentanyl as an adjuvant and regression to S_2 dermatome rather than two dermatomal regression as end point in our study could be the cause of the difference observed in the values.

In our study, onset of motor block was defined as the time taken to reach modified bromagegrade 3. The mean time of onset of motor block in this study was 14.4 $\pm$ 2.05 minutes in Group A as compared to 19.1 $\pm$ 1.03 min Group B. The difference between the groups was statistically significant (p-value < 0.001)

In the previously mentioned study by Bajwa et al, comparing ropivacaine with dexmedetomidine to ropivacaine with fentanyl, the onset of motor block was faster in ropivacaine-dexmedetomidine group (18.16 $\pm$ 4.52 minutes)as compared to ropivacaine - fentanyl group (22.98 $\pm$ 4.78 minutes).[9] The results are comparable to our study.

In the previously stated study by Bajwa in patients undergoing caesarean section under epidural anaesthesia the mean onset of motor block was 21.70 ± 4.20 minutes for ropivacaine group and 17.34 ± 4.48 minutes in ropivcaine – clonidine group.[25] Absence of an adjuvant in one group and use of clonidine instead of fentanyl in the other can explain the difference of result seen from our study.

In the study done by Thimappa et al comparing 0.75% ropivacaine alone , along with fentanyl and along with dexmedetomidine for lower abdominal and and lower limb surgeries, the mean onset of motor block was 21.37 ± 2.13 minutes for ropivacaine group, 16.47 ± 1.38 minutes for ropivacaine – clonidine group and 15.77 ± 1.25 minutes for ropivacaine – dexmedetomidine group.[8] The difference in the values from our study can again be attributed to the use of ropivacaine alone and with α_2 - agonist adjuvants instead of fentanyl.

In our study, duration of motor block was defined as the time for return of modified bromage 0. The mean duration of motor block in our study was 164.7 ± 13.77 minutes in Group A as compared to 152.2 ± 9.49 minutes Group B. The difference between the groups was statistically significant (p-value < 0.001).

In the study by Bajwa et al the duration of motor block was 178.52 ± 23.29 minutes with ropivacaine – fentanyl and 259.62 ± 21.38 minutes with ropivacaine – dexmedetomidine.[9] The results are thus similar to our study.

In the previously stated study by on patients undergoing caesarean section under epidural anaesthesia by Bajwa et al, the mean duration of motor block was 131.40 ± 24.40 minutes for ropivacaine group and 173.50 ± 32.44 minutes in ropivcaine – clonidine group.[25] Addition of fentanyl instead of clonidine in our study could be the cause of this difference.

In the study done by Thimappa et al comparing 0.75% ropivacaine alone , along with fentanyl and along with dexmedetomidine for lower abdominal and and lower limb surgeries, the mean duration of motor block was 132.37 $\pm$ 12.59 minutes for ropivacaine group, 165.63 $\pm$ 14.73 minutes for ropivacaine – clonidine group and 213.83 $\pm$ 17.30 minutes for ropivacaine – dexmedetomidine group.[8] These results are slightly different from our study and can be due to the use of α_2- agonists in this study instead of an opioid.

The time for rescue analgesia was defined as the first time after surgery when the patient had pain and requested for an analgesic. It was 190.7 $\pm$ 15.91 minutes in group A and 163.7 $\pm$ 8.37 minutes in group B. The difference between the two groups was statistically significant (p-value < 0.001).

In a study by McGlade et al[7] comparing 0.5% ropivacaine with 0.5% bupivacaine in lumbar epidural anaesthesia for lower limb orthopaedic surgery, the median duration of analgesia was 3.5 hours (210 minutes) for ropivacaine group as compared to 3.4 hours (204 minutes) in bupivacaine group. The result was thus similar to our study.

In the previously mentioned study conducted by Thimappaet al[8] the duration of analgesia was 200.33 $\pm$ 17.07 minutes in ropivacaine group, 261.00 $\pm$ 17.68 minutes in ropivacaine – clonidine goup 291.33 $\pm$ 27.79 minutes. The duration of analgesia in ropivacaine group was comparable to our study even though they did not use any adjuvant.

In the previous study by Bajwaet al[25] in patients undergoing caesarean section under epidural anaesthesia the time for first epidural topup was 117.49 $\pm$ 22.34 minutes in ropivacaine group and 138.46 $\pm$ 25.42 minutes in ropivacaine – clonidine

group. The use of Fentanyl as adjuvant in our study could be the reason behind the difference in the result between the two groups.

The total dose of Inj. Buprenorphine given epidurally over 24 hours was tabulated and analysed in our study (150 µg in each bolus). The mean buprenorphine requirement in group A was 206.27 ± 73.54 mcg while it was 266.63 ± 63.43 mcg in group B.25 out of 40 (62.5 %) patients in group A required 1 topup in 24 hours while 9 out of 40 (22.5%) patients in group B required 1 topup.

In a study by Jain et al, comparing 1% lignocaine, 0.25% bupivacaine and 0.5% ropivacaine for cervical epidural anaesthesia in patients undergoing thyroid surgery, 25 out of 25 (100%) patients in lignocaine group , 4 out of 25 (16%) patients in ropivacaine group and 3 out of 24 (12.5%) patients in bupivacaine group required epidural topups.[6] Their result is quite similar to ours even though the site of surgery, the site of epidural catheter placement and the drug used are different.

In the present study, the baseline vital parameters – heart rate, systolic and diastolic blood pressure and SpO_2 were comparable amongst the two groups with p-values >0.05 .There was a significant fall in heart rate in group A as compared to group B starting at 15 minutes and persisted till the end of the procedure with p-values < 0.05. The absolute fall in heart rate however was not very much in either group. The preoperative mean heart rate was 76.5 ± 6.93 bpm while the lowest heart rate was 67.4 ± 8.26 bpm. The corresponding values for group B were 73.6 ± 7.19 bpm and 71.5 ± 7.57 respectively.

There was a significant fall in SBP in group A as compared to group B starting at 6 minutes which persisted till the end of the procedure with p-values < 0.05. The absolute fall in SBP however was not very much in either group. The preoperative

mean SBP in group A was 124 ± 19.36 mm of Hg while the lowest SBP was 106.8 ± 17.99 mm of Hg. The corresponding values for group B were 126.7 ± 9.61 mm of Hg and 119.8 ± 19.96 mm of Hg respectively.

There was a significant fall in DBP in group A as compared to group B starting at 6 minutes which persisted till the end of the procedure with p-values < 0.05. The absolute fall in DBP however was not very much in either group. The preoperative mean DBP in group A was 73 ± 5.87 mm of Hg while the lowest DBP was 64.8 ± 10.75 mm of Hg. The corresponding values for group B were 75.3 ± 5.72 mm of Hg and 70.6± 4.65 mm of Hg respectively.

SpO_2 values were comparable between group A and groupm B throughout the procedure. No patient in either group required any intervention to manage the fall in vital parameters.

In the present study, pruritis was the most commonly encountered side effect and was seen in 5% patients in each group. This is similar to the observation by Rastogi et al[43] , who in their previously mentioned study encountered pruritis in 6% of their patients who received ropivacaine – fentanyl and 10 % of patients who received bupivacaine- fentanyl.

Other side effect that we came across during this study was nausea and vomiting , seen in 5% patients in group A and 2.5% patients in group B. In the study done by Bajwa et al[9] the incidence of vomiting was found to be 12% and was thus similar to our study.

None of the patients developed sedation,urinary retention or respiratory depression in our study.

0.75 % ropivacaine has been used for epidural anaesthesiaboth with and without adjuvants. It provides good sensory and motor block and effective post operative analgesia. Even though ropivacaine has been considered as haemodynamically stable local anaesthetic, 0.75 % solution might cause some fall in HR and BP specially with the large volume injected via epidural route. The fall might be more pronounced when adjuvants specially opioids are used.

The present study was thus carried out to compare the sensory and motor block and postoperative analgesia of lower concentration (0.5%) ropivacaine with fentanyl with the above mentioned combination.

We found that 0.75 % ropivacaine – fentanyl provides significantly faster onset of sensory and motor block, significantly longer duration of sensory and motor block , significantly delayed time for rescue analgesia and significantly lower 24 hour analgesic consumption than 0.5% ropivacaine – fentanyl group. However, all patients in both groups achieved acceptable sensory and motor block (sensory level atleast at T_{10} dermatome and modified bromage grade 3).

There was a statistically significant fall in HR, SBP and DBP in group A as compared to group B.

We therefore recommend that the combination of lower concentration i.e 0.5% ropivacaine with fentanyl can be used as an alternative to 0.75% ropivacaine with fentanyl in elective lower abdominal surgeries. This might be of immense help in patients where minimal fluctuations in HR and BP are desirable like elderly patients, patients with valvular heart diseases and IHD and pregnant patients.

Further studies evaluating the use of α_{2}- agonistsas adjuvants with 0.5% ropivacaine may be useful and might help in reducing the time of onset of sensory and motor block when compared to opioid adjuvants.

CONCLUSION

Our study showed that 0.75% ropivacaine with fentanyl is significantly more potent than 0.5% ropivacaine with fentanyl in terms of onset and duration of sensory and motor block in female patients undergoing lower abdominal surgery under epidural anaesthesia. However the overall sensory and motor block was found to be similar in both groups.

0.75% ropivacaine with fentanyl provides significantly prolonged analgesia and significantly lower analgesic requirement in 24 hours than 0.5% ropivacaine with fentanyl.

The haemodynamic parameters including HR, SBP and DBP are more stable in 0.5% ropivacaine with fentanyl than 0.75% ropivacaine with fentanyl, which is a highly desirable feature, especially in elderly patients, patients with heart diseases and pregnant women.

Thus 0.5% ropivacaine with fentanyl can be used as an alternative to 0.75% ropivacaine with fentanyl for epidural anaesthesia without any major side effects/complications in elective lower abdominal surgeries.

SUMMARY

Epidural anaesthesia is fast emerging as the preferred neuraxial block technique for lower abdominal and lower limb surgeries. Epidural anaesthesia allows the anaesthesiologist to titrate the dose of drugs to the level of desired block and duration of surgery, maintain better haemodynamic stability and provide post operative analgesia to the patients. The newer local anaesthetic ropivacaine is fast gaining popularity in regional anaesthesia due its more cardiostable profile and dense sensory block. Various adjuncts along with local anaesthetics have been tried via epidural route to hasten the onset and prolong the duration of block. Opioids have been shown to have a synergistic effect along with local anaesthetics. Fentanyl, a short acting highly lipid soluble opioid, is one of the most commonly used adjuvants in epidural anaesthesia.

This one year randomised controlled trial was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Charitable Hospital Belagavi, during the period of January 2015 to December 2015. Total of 80 female patients undergoing lower abdominal surgeries were randomly allocated to two groups namely, Group A (n= 40) received 15 ml of 0.75% ropivacaine with 50 mcg fentanyl or Group B (n = 40) received 15 ml of 0.5% ropivacaine with 50 mcg fentanyl through epidural route. The onset and duration of sensory block, time for rescue analgesia , total analgesic consumption in 24 hours and vital parameters were studied. The haemodynamic parameters like heart rate, blood pressure and oxygen saturation were continuously monitored.

Demographic parameters were comparable in both groups. In this study, the onset of sensory block was faster in group A (8.8 $\pm$ 1.33 minutes) than in group B

(14.8 ± 0.97 minutes). The duration of sensory block was longer in group A (150 ± 11.09 minutes) than group B (137.2 ± 9.93 minutes). The onset of motor block was faster in group A (14.4 ± 2.05 minutes) as compared to group B (19.1 ± 1.03 minutes). The duration of motor block was longer in group A (164.7 ± 13.77 minutes) as compared to group B (152.2 ± 9.49 minutes). The time for the first rescue analgesic was significantly delayed in group A (190.7 ± 15.91 minutes) than in group B (163.7 ± 8.37 minutes). The total analgesic requirement in first 24 hours was lower in group A (206.2 ± 73.54 µg) as compared to 266.63 ± 63.43 µg), The pre operative heart rate, systolic BP, diastolic BP and SpO_2 were comparable in both groups. However fall in heart rate, systolic BP and diastolic BP were more in group A than group B intraoperatively. The side effects were comparable between two groups.

Overall, based on this study it may be concluded that 0.75% ropivacaine with fentanyl provides better sensory and motor block along with prolonged analgesia as compared to 0.5% ropivacaine with fentanyl but produces statistically significant fall in heat rate and BP as compared to the latter. Thus 0.5% ropivacaine with fentanyl can be used as alternative to 0.75% ropivacaine with fentanyl in elective lower abdominal surgeries under epidural anaesthesia.

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ANNEXURE I: CONSENT FORM

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr/Mrs/Miss. _____ we are requesting you to enroll yourself in **"COMPARISON OF ONSET AND DURATION OF BLOCKADE AND POST OPERATIVE ANALGESIA OF ISOBARIC ROPIVACAINE 0.75% WITH FENTANYL AND ISOBARIC ROPIVACAINE 0.5% WITH FENTANYL IN FEMALE PATIENTS UNDERGOING LOWER ABDOMINAL SURGERIES UNDER EPIDURAL ANAESTHESIA - A ONE YEAR HOSPITAL BASED RANDOMISED CONTROLLED TRIAL"**

Conducted by

Dr. _____, Post Graduate in M.D. Anaesthesiology under the guidance of Dr. _____, Professor , Department of Anaesthesiology, J.N. Medical College, Belgaum under KLE university, Belgaum.

Respected Sir/Madam we request you to enroll yourself to participate in our study as you are eligible for participating in the study. During the study you will be asked some questions regarding your present complaint and you are supposed to answer to the best of your knowledge.

The purpose of research is to compare the onset and duration of sensory and motor blockade and post operative analgesia with 0.75 % Ropivacaine with Fentanyl and 0.5 % Ropivacaine with Fentanyl in adultfemale patients undergoing lower abdominal surgeries .

Procedure Involved:

If you agree to enroll yourself in my study, you will be allocated to one of the two groups (A or B) randomly , as per a computer generated randomization chart. You will be interviewed regarding your present, past and family history. Then you will be clinically examined in detail and investigated accordingly. An 18 G Touhy's needle will be inserted in your back and a catheter will be passed through it and fixed . Following this you will receive either 15 ml of 0.75 % Ropivacaine with 50 mcg of Fentanyl (Group 1) OR 15 ml of 0.5 % Ropivacaine with 50 mcg of Fentanyl (Group 2) through this catheter . The procedure would thus involve mild discomfort / pain .

Benefits and Risks

The benefits of taking part in this research are that we can avoid GA with good quality of analgesia and early ambulation. In addition with the catheter in situ , you can receive topups of drugs for post operative pain relief for upto 72 hours after surgery . The risks are minimal which include hypotension, bradycardia, headache, backache, syncope, paraesthesia& infection. There are no observable risks associated with the study.

Voluntary participation / Withdrawal

Taking part in the study is voluntary; you may choose not to enroll in this study. Your decision will not change present or future health care services offered to you at Dr. Prabhakar Kore Hospital.

Alternatives

Even if you decline the participation in the study, you will get the routine line of management with either Spinal anaesthesia or General anaesthesia .

Confidentiality

All information collected about you during the course of the study will be kept Confidential. The code numbers will identify you in this Study records and the information from this study may be published but your identity will be confidential in any publication. The only people to know that you are a research subject are members of the research team. No information about you or information provided by you during the research will be disclosed to other without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

Authorization to Publish Results:

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will remain confidential.

Financial Incentives for participation

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

Compensation

In the event of injury, related to the study, treatment will be made available at Dr. Prabhakar Kore Hospital and MRC, Belgaum. No reimbursement, compensation or free medical care will be given by law.

Queries/ Contact details

In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact Dr. _____, Department of Anaesthesiology, KLES Hospital and MRC. Dr. _____ Professor, Dept. Of Anaesthesiology, KLES Hospital and MRC.

If you have any queries about your rights as a study subject, you may call Dr. Ganga Pilli, Professor, Dept. of Pathology as Chairman of J. N. Medical College Institutional Ethics Committee on Human Subjects Research, Phone No.9480275601 at J. N. Medical College, Belgaum

CONSENT FOR PARTICIPATION IN RESEARCH TRIAL

I, _____ voluntarily agree for the participation as a subject of study. By signing this consent form I am not giving up any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read form in vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name : _____

Signature or the Left Thumb Print of Subject :_____

Date: _____

Witness Name : _____ Signature: _____

Date:

Investigators Name: _____ Signature: _____

Date:

Place : _____

ANNEXURE II - PROFORMA

"COMPARISON OF ONSET AND DURATION OF BLOCKADE AND POST OPERATIVE ANALGESIA OF ISOBARIC ROPIVACAINE 0.75% WITH FENTANYL AND ISOBARIC ROPIVACAINE 0.5% WITH FENTANYL IN FEMALE PATIENTS UNDERGOING LOWER ABDOMINAL SURGERIES UNDER EPIDURAL ANAESTHESIA - A ONE YEAR HOSPITAL BASED RANDOMISED CONTROLLED TRIAL"

Patient Name: IP No.:

Age: Gender: Female

Height: cms Weight: kgs.

Date of Operation: Occupation:

Address: Anaesthesiologist:

Preanesthetic Evaluation:

1. Chief Complaints:
2. Past History: HTN / DM / Asthma / Epilepsy / Rx allergy/Other relevant history .
3. Treatment / Drug intake history :
4. History of previous surgeries and anaesthetic exposure
5. Family history

General physical examination

Pallor / Icterus / Clubbing / Cyanosis / Lymphadenopathy / Edema

Pulse Rate : BP :

Respiratory Rate : Temperature :

Systemic Examination

RS : CNS :

CVS : Abdomen :

Airway examination :

Jaw movements : Teeth :

Airway assessment : Spine :

Investigations

Hb : Total Leucocyte Count :

Platelet count : Serum Urea :

Serum.Creatinine: RBS:

ECG : Chest X-Ray:

Urine R/M : Others :

ASA GRADE : I II III IV V E

Diagnosis :

Proposed Surgery :

Preoperative baseline values :

Pulse: BP:

Monitors attached :

Pulse oximetry : NIBP :

ECG :

Intra – Op Vital parameters :

TIME	H.R.(bpm)	NIBP (mm of Hg)	SpO_2 (%)

Sensory Block :

Time for onset at T_{10} (mins.)	
Highest dermatome blocked	
Time for 2 dermatomal regression(min)	
Time for regression till S_2(mins.)	

Motor blockade :

Highest Bromage score reached	
Time to reach Bromage 3(mins)	
Time for regression to Bromage 0(mins)	

Post Operative Analgesia :

1) Time for first rescue analgesia in minutes. :
2) Total analgesic consumption in 24 hrs. (Inj. Buprenorphine in mcg) :

Inj. Diclofenac in mg , if any :

Side effects :

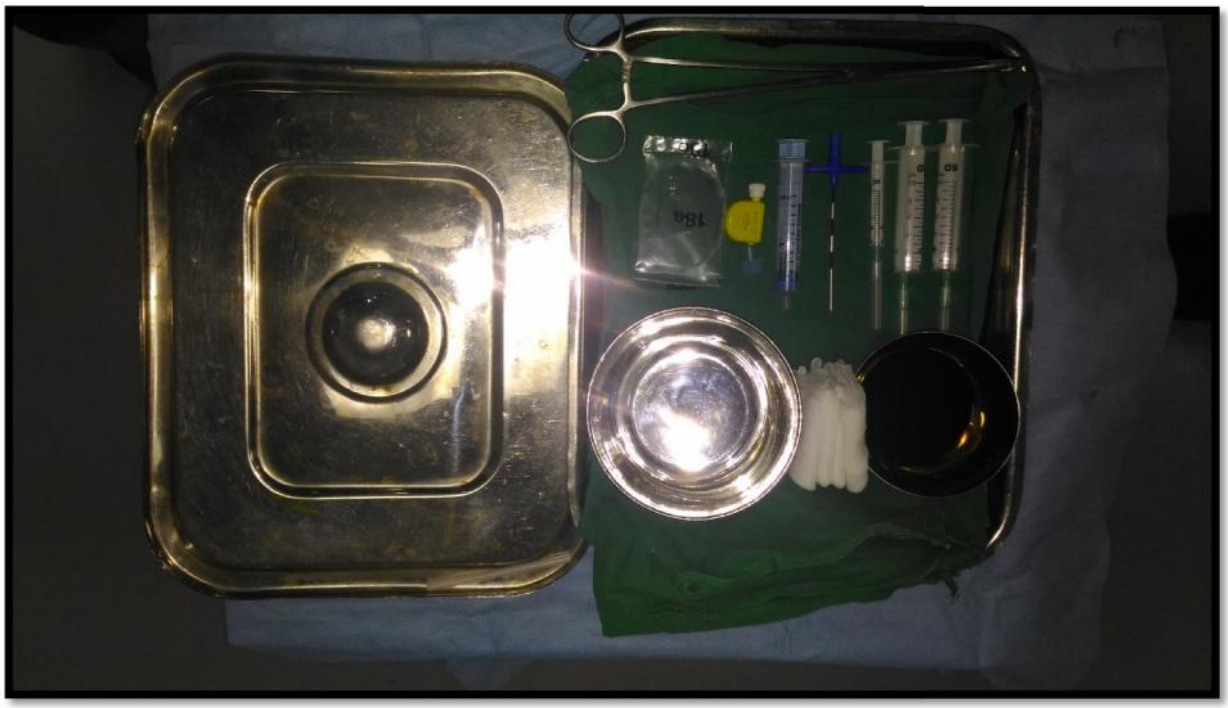
ANNEXURE III: PHOTOGRAPHS

Photograph 1: 0.75% Ropivacaine ampoule

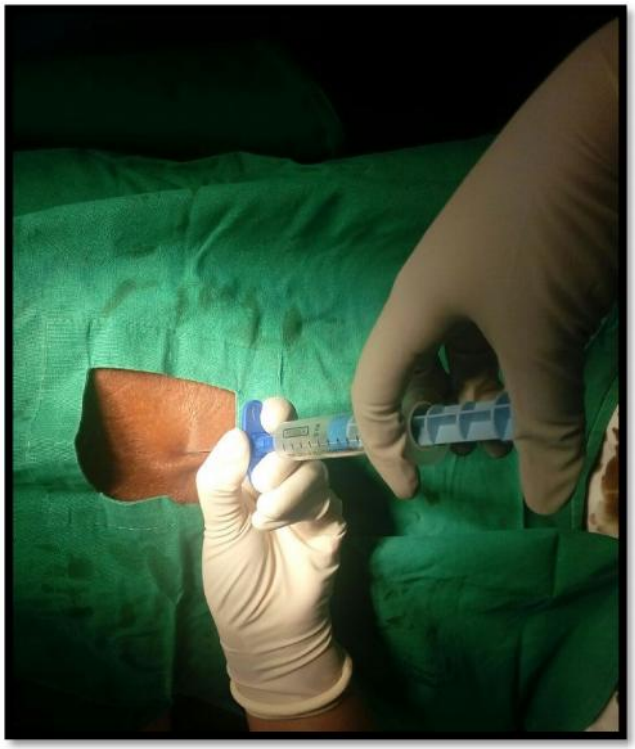
Photograph 2: 0.5% Ropivacaine ampoule

Photograph 3 : Fentanyl ampoule

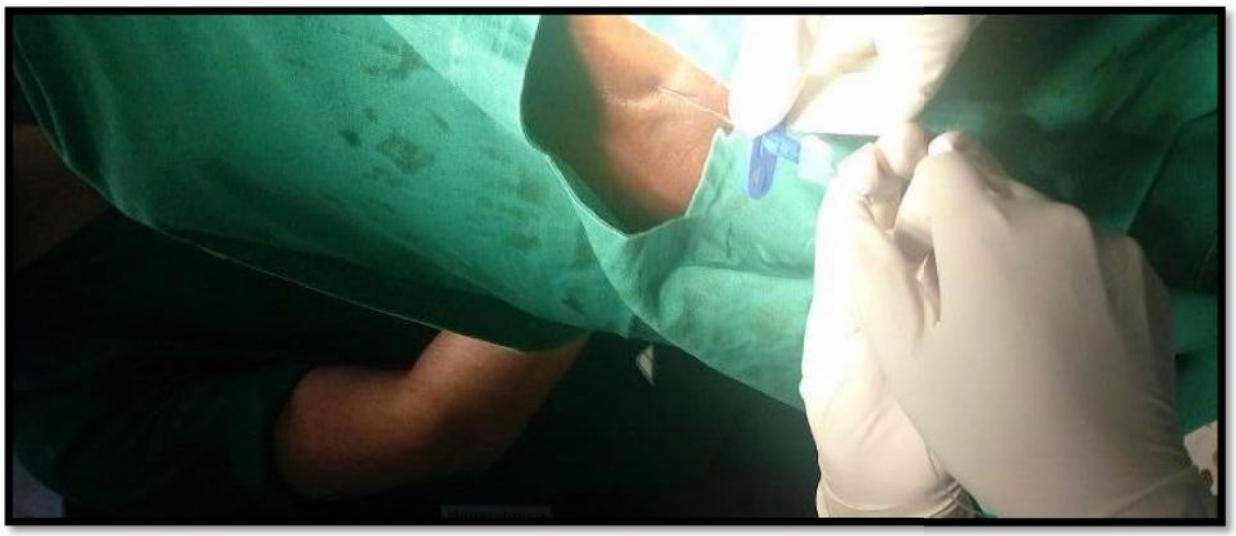
Photograph 4 : Epidural tray



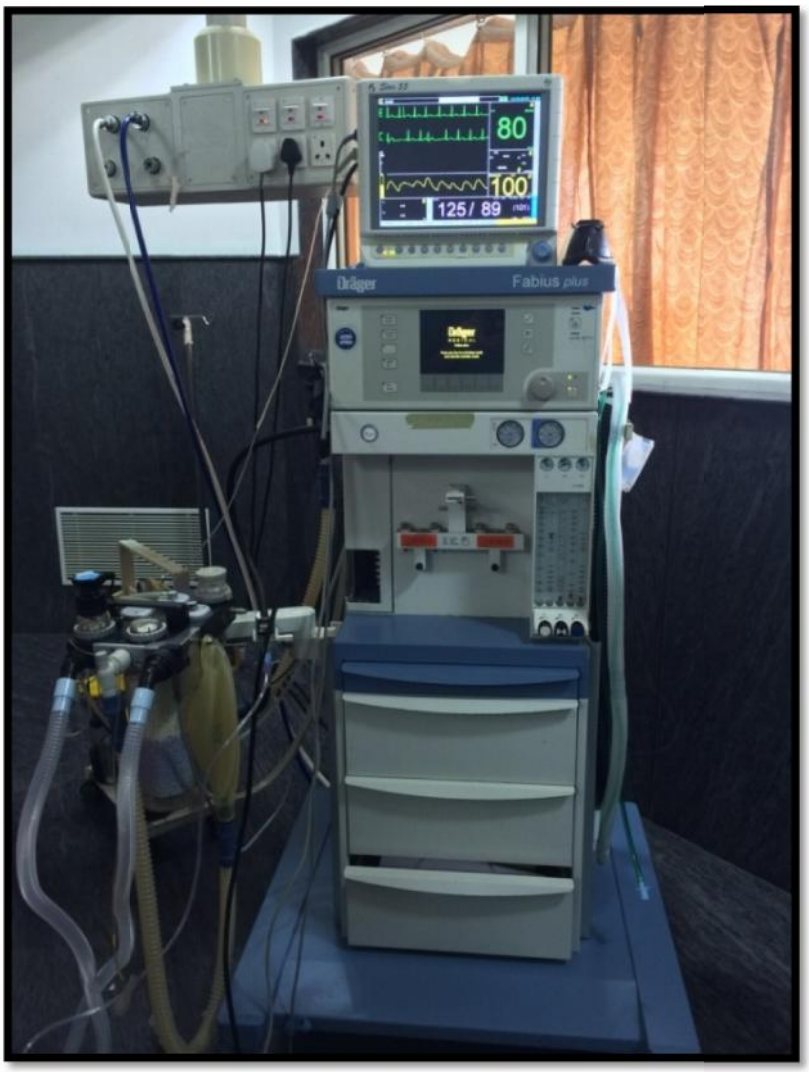
Photograph 5 A : Procedure of epidural (Loss of resistance technique)



Photograph 5 B : Procedure of epidural (Threading the epidural catheter)



Photograph 6 : Monitoring during surgery



ANNEXURE IV - KEY TO MASTER CHART

ASA	-	American Society of Anaesthesiologists
F	-	Female
HR	-	Heart Rate (bpm)
SBP	-	Systolic Blood Pressure (mm Hg)
DBP	-	Diastolic Blood Pressure (mm Hg)
SpO_2	-	Saturation of peripheral oxygen (%)
T	-	Thoracic sensory dermatomal level
mcg.	-	micrograms
min.	-	minutes
kgs.	-	kilograms
cms.	-	centimeters