"A COMPARATIVE STUDY OF INTRATHECAL BUPIVACAINE AND BUPIVACAINE WITH MIDAZOLAM IN LOWER ABDOMINAL AND LOWER LIMB SURGERIES"

By

DR ABHISHEK M. PATIL

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Under the guidance of

DR. VIJAY V. KATTI$_{MD}$
ASSOCIATE PROFESSOR
DEAPRTMENT OF ANAESTHESIOLOGY
B.L.D.E.U SHRI.B.M.PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE.
VIJAYAPUR -586103

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BLDE UNIVERSITY, VIJAYAPUR, KARNATAKA.

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Date:

Place: Vijayapur. **DR ABHISHEK M. PATIL**

BLDE UNIVERSITY, VIJAYAPUR, KARNATAKA.

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DR. VIJAY V. KATTI$_{MD}$

ASSOCIATE PROFESSOR,

DEPARTMENT OF ANAESTHESIOLOGY
BLDEU's Shri. B. M. Patil Medical College Hospital and Research Centre,
Vijayapur.

Date:

Place: Vijayapur.

BLDE UNIVERSITY, VIJAYAPUR, KARNATAKA.

ENDORSEMENT BY THE HOD

This is to certify that the dissertation entitled **"A COMPARATIVE STUDY OF INTRATHECAL BUPIVACAINE AND BUPIVACAINE WITH MIDAZOLAM IN LOWER ABDOMINAL AND LOWER LIMB SURGERIES"** is a bonafide research work done by **DR ABHISHEK M. PATIL** under the guidance of **DR. VIJAY V. KATTI$_{MD}$** Associate Professor, Department of Anaesthesiology.

DR.D.G.TALIKOTI **MD.,DA**

PROFESSOR AND HEAD OF DEPARTMENT OF ANAESTHESIOLOGY.
BLDEU's Shri. B. M. Patil Medical College, Hospital and Research Centre,
Vijayapur

Date:

Place: Vijayapur .

BLDE UNIVERSITY, VIJAYAPUR, KARNATAKA.

ENDORSEMENT BY THE PRINCIPAL

This is to certify that the dissertation entitled **"A COMPARATIVE STUDY OF INTRATHECAL BUPIVACAINE AND BUPIVACAINE WITH MIDAZOLAM IN LOWER ABDOMINAL AND LOWER LIMB SURGERIES"** is a bonafide research work done by **DR ABHISHEK M. PATIL** under the guidance of **DR. VIJAY V. KATTI$_{MD}$** Associate Professor, of Department of Anaesthesiology.

Dr. S. P. GUGGARIGOUDAR $_{MS}$
Principal
BLDEU's Shri. B. M. Patil Medical College, Hospital and Research Centre, Vijayapur

Date :

Place: Vijayapur

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Date: **DR ABHISHEK M. PATIL**

Place: Vijayapur

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Date:

Place: Vijayapur **DR.ABHISHEK M. PATIL**

LIST OF ABBREVIATIONS USED

ASA	-	American Society of Anaesthesiologists
B	-	Beta
CBF	-	Cerebral Blood Flow
CMRO2	-	Cerebral metabolic rate for oxygen
COPD	-	Chronic Obstructive Pulmonary Disease
CSF	-	Cerebrospinal fluid
CNS	-	Central Nervous System
CVS	-	CardioVascular System
DBP	-	Diastolic Blood Pressure
DM	-	Diabetes Mellitus
Δ	-	Delta
ECG	-	Electrocardiogram
GIT	-	GastroIntestinal Tract
ICP	-	Intracranial Pressure
GABA	-	Gamma-Amino-butyric acid
HTN	-	HYpertension
IV	-	Intravenous
IM	-	Intramuscular
Kg	-	Kilogram
MPC	-	Mallampatti classification
MAP	-	Maean Arterial Pressure
mcg/µg	-	Micrograms
ml	-	Milliliter

NIBP	-	Non Invasive Blood Pressure
PONV	-	Post-operative nausea and vomiting
PR	-	pulse Rate
RS	-	Respiratory System
SBP	-	Systolic Blood Pressure
SVR	-	Systemic Vascular Resistance
SD	-	Standard deviation
SpO_2	-	Arterial oxygen saturation
TNS	-	Transient Neurological Symptoms
VAS	-	Visual analogue score
Vs	-	Versus

ABSTRACT

Background & Objectives :

Subarachnoid blockade is the common form of centrineuraxial blockade performed for lower abdominal and lower limb surgeries. In order to maximize quality and duration of anaesthesia and post operative analgesia, a number of adjuvants have been added to spinal local anaesthetics. Intrathecal midazolam abolishes pain of somatic origin, produces selective sensory block, and depresses somatosympathetic reflexes without any neurotoxicity and other complications. It potentiates the blocking actions of local anaesthetics. The present study was conducted to compare the differences of action and complications of intrathecal hyperbaric Bupivacaine 0.5% (group B) and intrathecal hyperbaric Bupivacaine 0.5% and Midazolam 1mg in lower abdominal and lower limb surgeries.

Materials and Methods :

100 patients belonging to ASA grade – I and grade-II of both the sexes (each group 50 patients n=50) were randomly selected for the study. The time of onset of sensory and motor block, hemodynamic status, time for two dermatomal segments regression of sensory level and regression of sensory level to L_2 dermatome, time of first request of analgesics, visual analogue score and adverse effects were compared in both the groups.

Results :

The time of onset of sensory and motor block was significantly longer in group-BM than group-B ($P<0.001$) Hemodynamic changes did not differ in patient of either group ($P>0.05$). The time for two dermatomal segments regression of sensory level (group –B 87.50±4.4 minutes and group –II 122.00± 3.6 minutes) and regression

of sensory level to L_2 dermatome (Group-B 87.2±3.4 minutes and group-BM 122.6±3.6 minutes) were statistically longer in group BM (P<0.001). The time of first request of analgesics by the patient in group-B was 139.6±8.7 minutes and in group BM was 263.8±35.8 minutes which was statistically significant (P<0.001). The VAS scores were significantly less in group-BM at 3 hours (p<0.001), 6 hours (P<0.001) and 12 hours (P<0.001) compared to group-B. The side effects were minimal in both the groups.

Conclusion :

From the present study it can be concluded that addition of intrathecal midazolam with bupivacaine significantly improves the quality of anaesthesia, duration of analgesia without prolonging the recovery from the anaesthesia.

Keywords: Intrathecal, midazolam, bupivacaine, visual analogue score, quality ofanalgesia, post operative analgesia.

INDEX

LIST OF TABLES

TABLE OF FIGURES

INTRODUCTION

Subarachnoid block is one of the most versatile regional anaesthesia techniques available today. Regional anaesthesia offers several advantages over general anaesthesia—blunts stress response to surgery, decreases intra-operative blood loss, lowers the incidence of postoperative thromboembolic events, and provides analgesia in early postoperative period. Subarachnoid block provides adequate anaesthesia for patients undergoing lower abdominal and lower limb surgeries.

In order to maximize quality of anesthesia and post-operative analgesia, a number of adjuvants have been added to local anesthetics. Among the various methods of providing post-operative analgesia, the benefits of intrathecal opioids and non-opioids as adjuncts in spinal anesthesia are well documented. The addition of intrathecal opioids is however associated with dose related adverse effect such as respiratory depression, nausea, vomiting, urinary retention, pruritus and sedation[1.]

Therefore, use of non-opioids such as ketamine, clonidine, neostigmine, magnesium sulphate, midazolam has become popular adjuncts for post-operative analgesia[2]. Intrathecal Midazolam abolishes pain of somatic origin produces selective sensory block and depresses somatosympathetic reflexes without any neurotoxicity. It potentiates the blocking actions of local anesthetics. It improves the quality of sensory and motor block, without prolonging the recovery and also provides good post-operative analgesia.

The subarachnoid Midazolam was originally shown to have anti-nociceptive properties in studies performed in animals in early 1980's[3].The subarachnoid

Midazolam has been used in humans since 1986 and doses up to 2mg have been described[4].

There are many clinical studies in favour of intrathecal Midazolam which has added advantages since it produces sedation, amnesia and anti-nociceptive effects without any neurotoxicity or other side effects. Hence this study was designed to evaluate the efficacy, to know the duration of pain relief, to know the incidence of adverse effects and complications when Midazolam is given along with Bupivacaine intrathecally.

AIMS AND OBJECTIVES

The aim of the study is to compare the following factors in two groups i.e, Hyperbaric Bupivacaine 0.5% and 0.2ml of normal saline with

Hyperbaric Bupivacaine 0.5% and Midazolam 1mg when given intrathecally.

Onset and duration of analgesia:

Speed of onset as determined by lack of appreciation of pin-prick and duration of analgesia as determined by regression of sensory level by two dermatomal segments.

Motor blockade:

Speed of onset and duration of motor blockade as assessed by Bromage scale.

Intraoperative discomfort:

As determined by perception of dragging sensation or pain and need for any systemic analgesic agents.

Post-operative period:

Analgesic requirements and post-operative complications such as nausea, vomiting, hypotension, shivering, pruritus, seizures and respiratory depression.

REVIEW OF LITERATURE

Maged L. Boules, Josepph M. Botros (2016)[5] conducted the study to compare efficacy and duration of analgesia produced by adding magnesium sulfate to intrathecal bupivacaine (10 mg) plus midazolam (1 mg) in patients undergoing cesarean section.

In their study, 60 patients aged 18–35 years of ASA class I and II were scheduled for a caesarean section under an intrathecal block and divided randomly into two groups: Midazolam group (group M): A total of 30 patients received 10mg/2ml intrathecal 0.5% hyperbaric Bupivacaine, Midazolam (1mg/0.2 ml), and 0.8 ml normal saline and magnesium and Midazolam group (group MM): A total of 30 patients received 10 mg/2ml intrathecal 0.5% hyperbaric Bupivacaine, Midazolam (1 mg/0.2 ml), Magnesium sulfate(50 mg/0.5 ml), and 0.3 ml normal saline. The onset and duration of both sensory and motor block, the total dose of analgesia, and adverse effects were recorded.

The onset of sensory block was significantly delayed in the MM group compared with the M group (6.05 ± 1.1 vs. 3.5 ± 0.45 min, $P = 0.024$), the duration of sensory block was longer in the MM group compared with the M group (132.4 ± 7.8 vs. 115.3 ± 6.60 min, $P = 0.018$). In addition, the onset of motor block was delayed in the MM group (7.05 ± 1.3 min) compared with the M group (5 ± 0.65 min, $P = 0.028$) as well as its duration (149.9 ± 8.67 vs. 126.3 ± 5.35 min, $P = 0.005$).

They concluded that addition of magnesium sulfate to intrathecal bupivacaine plus midazolam led to a significant delay in the onset of both sensory and motor blockade, and also prolonged their duration without side effects.

Riham S. Ebieda, Mohamed Z. Alia, Maged L. Boulesb, Yasser M. Samhana (2016)[6] conducted prospective, randomized, double-blind study involved 60 ASA physical status II-III patients aged over 60 years scheduled for elective endoscopic urologic procedures under spinal anesthesia with hyperbaric Bupivacaine 0.5% (5 mg/ml). They were randomized into one of three equal groups of 20 patients each. The first group, control group (group C), received 7.5 mg hyperbaric Bupivacaine 0.5% in a volume of 1.5 ml, the second group, Fentanyl group(group F) received 7.5 mg hyperbaric Bupivacaine 0.5% in a volume of 1.5 ml and 10 μg fentanyl (0.1 ml); and the third group, Fentanyl Midazolam group (group FM),received 7.5 mg hyperbaric Bupivacaine 0.5% in a volume of 1.5 ml and 10 μg Fentanyl (0.1 ml) plus 1.0 mg of Midazolam (0.2 ml). Sensory and motor effects were assessed. Postoperative pain, sedation, and adverse effects were also recorded.

The three studied groups were comparable in demographic and clinical characteristics. They were hemodynamically stable. There was no significant difference between the three groups in the onset of sensory ($P = 0.721$) and motor block ($P = 0.342$), duration of motor block ($P = 0.286$), and sedation score ($P = 0.229$). Duration of sensory block was prolonged in group F compared with the control group ($P < 0.001$) and prolonged more in group FM compared with the F group ($P = 0.065$). Time to first request of rescue analgesic was significantly longer in group F compared with the C group ($P = 0.033$) and in FM compared with the F

group ($P < 0.001$). All patients reported excellent or good degree of satisfaction with anesthetic procedure ($P = 0.547$).

The result of study was "Adjuvant intrathecal Midazolam resulted in intraoperative hemodynamic stability and safely potentiates postoperative analgesic effect of Bupivacaine Fentanyl spinal anesthesia in elderly patients undergoing endourologic procedures."

Venkatesh Selvaraj, TapanRay (2016)[7]conducteda prospective randomized control double-blind study in American Society of anesthesiology I and II surgical population. The primary objective of the study was to evaluate the effect of intrathecal Midazolam as an adjuvant to spinal Lignocaine in terms of quality and duration of spinal sensory blockade. The secondary objectives are to study the effect on hemodynamics and the incidence of TNS.

Hundred healthy adult patients scheduled for elective infraumbilical surgery were randomly assigned to group A patients received spinal anesthesia with 1.5 ml of 5% Lignocaine heavy with 0.4 ml of 0.9% saline and group B (control group) received spinal anesthesia with 1.5 ml of 5% heavy Lignocaine with 0.4 ml of preservative-free Midazolam.

The result was Midazolam resulted in improved quality of sensory blockade in terms of early onset, increased duration of effective analgesia and delayed two segment regression time and also decreases the incidence of TNS with intrathecal lignocaine. And concluded Midazolam is an effective adjuvant to intrathecal lignocaine.

Anshu Gupta, Hemlata Kamat, Utpala Kharod (2016)[8] conducted a study "Efficacy of intrathecal midazolam in potentiating the analgesic effect of intrathecal fentanyl in patients undergoing lower limb surgery". In a double‑blind study design, 75 adult patients were randomly divided into three groups: Group B, 3 ml of 0.5% hyperbaric Bupivacaine; Group BF, 3 ml of 0.5% hyperbaric Bupivacaine + 25 mcg of Fentanyl; and Group BFM, 3 ml of 0.5% hyperbaric Bupivacaine + 25 mcg of Fentanyl + 1 mg of Midazolam. Postoperative analgesia was assessed using visual analogue scale scores and onset and duration of sensory and the motor blockade was recorded.

They found mean duration of analgesia in Group B was 211.60 ± 16.12 min, in Group BF 420.80 ± 32.39 min and in Group BFM, it was 470.68 ± 37.51 min. There was statistically significant difference in duration of analgesia between Group B and BF (*P*= 0.000), between Group B and BFM (*P* = 0.000), and between Group BF and BFM (*P* = 0.000). Both the onset and duration of sensory and motor blockade was significantly prolonged in BFM group.

They concluded intrathecal midazolam potentiates the effect of intrathecal fentanyl in terms of prolonged duration of analgesia and prolonged motor and sensory block without any significant hemodynamic compromise.

Chattopadhyay Anirban *et al* (2013)[9] conducted a study to compare the analgesic efficacy of intrathecal Bupivacaine alone (2.5 ml of hyperbaric Bupivacaine 0.5%+0.4 ml normal saline 0.9%) with intrathecal bupivacaine Midazolam (2.5ml of hyperbaric bupivacaine 0.5%+0.4 ml midazolam) combination in patients undergoing elective infraumbilical surgery. The study group includes 90 patients aged 18-60 years

with ASA I-II. They concluded that the combination of both drugs prolong the duration of effective analgesia as compared to Bupivacaine alone and delays the need for postoperative rescue analgesics without having sedative effects, pruritus or respiratory depression.

Kulkarni Malavika, Kurdi Madhuri, Itagimath Savithri, Sujatha DA, Muralidhar MK (2012)[10] conducted a study to know the effect of intrathecal Midazolam in prolonging post-operative analgesia when used as an adjunct with Bupivacaine. The study groups includes 150 pateints of ASA I-II scheduled for lower abdominal surgeries and urological surgeries. They concluded that the duration of effective analgesia when Midazolam is added to intrathecal Bupivacaine is significantly prolonged thereby proving that Midazolam is useful adjunct to intrathecal Bupivacaine for post-operative analgesia.

Suchita A Joshi, Venkatesh V Khadke, Rajesh D Subhedar, Arun W Patil, Vijay M Motghare (2012)[11] conducted a study to assess the comparative efficacy, safety and duration of analgesia produced by low-dose clonidine and midazolam when used as adjuvant for spinal anesthesia. Study includes 50 ASA grade I and II patients posted for lower abdominal surgery. They concluded that Postoperative analgesia with clonidine is short lived with some bradycardia. Intratheal Midzolam provides superior analgesia without clinically relevant adverse effects.

Shadangi B K, Garg R, Pandey R, Das T (2011)[12] conducted a study compared intrathecal Bupivacaine with and without Midazolam to assess its effect on the duration of sensory block, motor block and pain relief. The Study includes 100 patients of ASA I-II scheduled for lower abdominal surgeries, lower limb surgeries

and gynaecological surgeries. They concluded that the addition of preservative-free Midazolam to Bupivacaine intrathecally resulted in prolonged postoperative analgesia without increasing motor block.

PrakashS, Joshi N, Gogia AR, Prakash S, Singh R (2006)[13] conducted a study to evaluate the postoperative analgesic efficacy of two doses of intrathecal Midazolam as an adjunct to Bupivacaine for spinal anesthesia in sixty patients undergoing elective caesarean delivery under spinal anesthesia and were allocated randomly to 3 groups: group B, 2ml hyperbaric Bupivicaine 0.5%; group BM1, 2ml Bupivacaine plus Midazolam1mg (preservative free); and group BM2, 2ml Bupivicaine plus Midazolam 2mg. They concluded that intrathecal Midazolam 2mg provided a moderate prolongation of postoperative analgesia when used as an adjunct to Bupivacaine in patients undergoing caesarean delivery. Intrathecal Midazolam 1mg and 2mg, decreased postoperative nausea and vomiting.

Agarwal Nidhi, Usmani A, Sehgal R, Kumar Rakesh, Bhadoria Poonam (2005)[14]conducted a study to know the effect of intrathecal Midazolam Bupivacaine combination for postoperative analgesia on 53 adult aged 18-60years of ASA I-II patients scheduled for lower abdominal surgeries and urological surgeries. They concluded that intrathecal combination of Midazolam and Bupivacaine provides longer duration of post-operative analgesia as compared to intrathecal Bupivacaine alone, without prolonging duration of dermatomal sensory block.

Tucker AP, Lai C, Nadeson R, Goodchild CS (2004)[15] investigated the potential of intrathecal Midazolam to produce symptomatology suggestive of neurological damage. This study compared two cohorts of patients who received

intrathecal anesthesia with or without intrathecal Midazolam (2mg). Eighteen risk factors were evaluated with respect to symptoms representing potential neurological complications. The definitions of these symptoms were made wide to maximize the chance of counting patients with neurological sequelae after intrathecal injections. Eleven hundred patients were followed up prospectively during the first postoperative week by a hospital chart review and 1 month later by a mailed questionnaire. Symptoms suggestive of neurological impairment, including motor or sensory changes and bladder or bowel dysfunction were investigated. Intrathecal Midazolam was not associated with an increased risk of neurologic symptoms. In contrast, neurologic symptoms were found to be increased by age > 70 years (relative risk 8.72) and the occurrence of a blood stained spinal tap (relative risk, 8.07). The administration of intrathecal midazolam 2mg, did not increase the occurrence of neurologic or urologic symptoms, as suggested by some preclinical animal experimentation.

Bharti N, Madan R, Mohanty PR, Kaul HL (2003)[16] studied the effect of addition of Midazolam to intrathecal Bupivacaine on the duration and quality of spinal blockade.

Fourty ASA I or II adult patients undergoing lower abdominal surgery were selected for the study. The patients were randomly allocated to receive 3 ml of 0.5% hyperbaric Bupivacaine intrathecally either alone or with 1mg of Midazolam using a combined spinal epidural technique. The duration and quality of sensory and motor block, perioperative analgesia, hemodynamic changes and sedation levels were assessed.

They concluded that the addition of intrathecal Midazolam to Bupivacaine significantly improves the duration and quality of spinal anaesthesia and provides prolonged perioperative analgesia without significant side effects.

Shah FR, Halbe AR, Panchal ID, Good Child CS (2003)[17] conducted a study to compare the efficacy of the addition of Midazolam to a mixture of Buprenorphine and Bupivacaine used for spinal anesthesia. The duration of sensory block (i.e time to regression to the S_2 segment) was significantly longer in the Midazolam group than the control group (218 min Vs 165 min; P< 0.001). The duration of motor block was also prolonged in the Midazolam group as compared with the control group (P<0.01). In 90% of the patients in the Midazolam group, the quality of block was adequate during the intra-operative period as compared with only 65% of the patients in the control group (P<0.05). The duration of effective analgesia was longer in the Midazolam group than in the control group (199 Vs 103 min, p<0.01). Blood pressure, heart rate, oxygen saturation and sedation scores were comparable in both groups. No neurological deficit or other significant adverse effects were recorded.

The study was prospective, randomized and observer blinded. It involved 60 patients (30 per group), ASA I and II, age 20-40 year, undergoing minor and intermediate lower abdominal surgery under spinal anesthesia. Patients were randomized into two groups, the control group received a spinal injection of hyperbaric Bupivacaine (15 mg) plus Buprenorphine (0.15 mg) and the experimental group received a spinal injection of the same two drugs and doses but supplemented with intrathecal Midazolam (2mg).

The duration of postoperative analgesic in the control group was 9.24 +/-2.57 h (mean ± SEM) and 21.33 ± 12.69 h in the Midazolam treated group (p<0.001)

patients treated with intrathecal Midazolam had better pain relief judged by visual analogue score on coughing ($p=0.0013$) and a nursing mobility score ($p<0.0001$). Adverse effects were minor and their incidence was similar in both groups.

They concluded that intrathecal Midazolam 2mg improves the quality and duration of postoperative pain relief afforded by intrathecal Buprenorphine and Bupivacaine.

D. Battacharya *et al* (2002)[18] conducted a randomized, double blinded, placebo controlled study to evaluate the effect of intrathecally administered Midazolam with Bupivacaine on duration of analgesia in patients undergoing major gynaecological surgeries. The study comprised of 50 patients randomly allocated to group A, who received 3mL of 0.5% of Bupivacaine and 0.4mL of normal saline and group B, who received 3mL of 0.5% of Bupivacaine and 0.4mL of Midazolam. The subarachnoid block was performed in right lateral position with 25G Quincke's needle at L3-4 interspace. Post operatively VAS score was noted every 30 minutes till 6hours. The postoperative analgesic were given on patient demand or when VAS score was more than 40mm. Sedation score was noted.

The two groups were comparable with respect to the height, weight, and duration of surgery. The duration of analgesia or pain free period in group A was 210± 10.12 minutes were as in group B it was 300 ± 11.82 minutes ($p<0.05$).

There were no clinically significant changes observed in heart rate, blood pressure, respiratory rate and sedation score either of the group intra operatively or postoperatively. A significantly higher VAS score (10 ± 0.3 to 64 ± 0.23) was observed on group B (3.5 ± 0.23 to 43 ± 0.21) $p<0.01$. None of the patients had any postoperative complication like itching, respiratory depression or lower limb

weakness. They concluded that intrathecal administration of Midazolam with hyperbaric Bupivacaine increases the analgesic effects of spinal blockade without clinically significant changes in heart rate, blood pressure, respiratory rate, sedation score either in intra-operative or in postoperative period.

Anjana Sen *et al* (2001) [19] studied the effect of intrathecal Midazolam for postoperative pain relief in patients coming for caesarean section delivery. The study comprised of 40 patients who were divided in to group A of 20 patients receiving 1.5mL of 5% heavy Lignocaine only and group B of 20 patients receiving the mixture of 1.5mL of 5% heavy Lignocaine with 2mg Midazolam(preservative free) through intrathecal route. The subarachnoid block was performed at L3-4 interspace with sitting position with a 25G Quincke's needle. Post operatively rescue analgesics were provided on specific pain complained by patients. The total pain free period was considered from the completion of the intrathecal injection to the time of request by patients for the rescue analgesic.

There were no significant difference observed between the groups regarding heart rate, systolic/diastolic blood pressure and SpO2 intra operatively ($p>0.05$). One patient in group A experienced vomiting and most of them were talking during operation.

The pain free period observed in the group A was 56.2 ± 5.8 minutes whereas in the patients of group B it was 196.5 ± 3.3 minutes which was highly significant ($p<0.001$). The authors concluded that intrathecal Midazolam produced highly significant postoperative pain relief together with antiemetic effect and tranquility of patients of caesarean section delivery.

Batra-YK; Jain-K; Chari-P; Dhillon MS; Shaheen-B; Reddy-GM (1999)[20] designed a study to evaluate the postoperative analgesic effects of intrathecal Midazolam and Bupivacaine mixture in patients undergoing knee arthroscopy.

Thirty healthy patients scheduled for knee arthroscopy were divided into two groups to receive either Midazolam Bupivacaine mixture (Group M; n=15) or Bupivacaire alone (group B; n=15) intrathecally. Level of sensory block, sedation score, assessment of pain using visual analogue score were recorded in both groups at regular time intervals. Time to block regression, recovery to ambulation and ability to void were recorded and noted before discharge.

A significantly higher VAS score was seen in group B patients as compared to the score observed in group M. Group B at a mean duration of 258+/–46.8 minutes whereas only one patient in group M required supplemental analgesia within this period. Time to regression of sensory analgesia to L_5–S_1 level was longer in group M (26.7+/–67.38) as compared to group B (229.8+/– 41.4) ($P<0.05$). Blood pressure, heart rate, oxygen saturation and sedation score showed no differences between the groups. Neither motor block nor time to void were prolonged with the addition of Midazolam to Bupivacaine.

They concluded that addition of Midazolam to Bupivacaine intrathecally provided better postoperative analgesia without any adverse effects.

Murat Bahar MD *et al* (1997)[21] examined in an animal model whether intrathecal Midazolam alone or with Fentanyl can achieve anaesthesia sufficient for laprotomy, comparable to Lidocaine. Effects on consciousness and whether anaesthesia was segmental were also examined. Both groups that received intrathecal

Midazolam alone and combined with Fentanyl, developed effective segmental sensory and motor blockade of the lower limb and abdominal wall, sufficient for pain free laprotomy procedure. They concluded that Midazolam when injected intrathecally produces reversible segmental spinally mediated antinociception sufficient to provide balanced anaesthesia for abdomen.

Valentine M J *et al* (1996)[22] conducted a study to know the effect of intrathecal Midazolam on postoperative pain relief on 50 patients posted for elective caesarean section under spinal anaesthesia. They concluded that intrathecal midazolam appears to be safe and has clinically detectable analgesic properties.

Goodchild *et al* (1996)[23] conducted a study on rats to demonstrate the antinociceptive effects of intrathecally administered drugs in spinal cord by measurements of electrical threshold for avoidance behavior with the help of chemically implanted lumbar intrathecal catheters. They concluded that intrathecal Midazolam caused spinally mediated antinociception in rats by a mechanism involving δ opioid receptor activation.

Edwards M, Serrao JM, Gent JP, Good child CS (1990)[24] studied the mechanism by which midazolam causes spinally mediated analgesia.

The effects of a benzodiazepine antagonist and a gamma-aminobutyric acid (GABA) antagonist on the analgesic effects of equivalent doses of Midazolam, Fentanyl and ketocyclazocine were studied in rats. These were the minimum doses producing maximal segmental analgesia when given intrathecally. Flumazenil administration caused a parallel shift to the right of the dose response curve for Midazolam spinal analgesia. Segmental analgesia following Midazolam was also

significantly attenuated (P less than 0.05) when the selective GABA antagonist Bicuculline was given intrathecally at the same time as Midazolam. The highest dose of Bicuculline used (50pmol) caused no significant attenuation of the segmental analgesic effects of either ketocyclazocine or Fentanyl.

Goodchild CS, Serrao JM (1987)[25] investigated the possible analgesic effect of Midazolam as a result of interruption of those spinal cord pathways taken by pain afferents. Experiments were performed on 15 male Wistar rats with chronically implanted lumbar subarachnoid catheters. The threshold for pain induced by brief passage of electric current between pairs of electrodes placed on the tail and the skin of the neck was measured before and after subarachnoid injections of Midazolam. Intrathecal Midazolam caused a significant (p less than 0.02) increase in the threshold for pain in the tail, but not in the neck, this response was not produced by intrathecal injections of vehicle and was blocked by prior intraperitoneal injections of the benzodiazepine antagonist. They also performed experiments on frog sciatic nerves which showed that Midazolam did not have a local anesthetic action.

They concluded that intrathecal Midazolam causes spinally mediated analgesia by binding to benzodiazepine receptors in the spinal cord.

SPINAL ANESTHESIA

The vertebral column consists of thirty three vertebrae. They are seven cervical, twelve thoracic, five lumbar five cervical and four or five coccygeal, the sacral and coccygeal vertebrae are fused in adults. The vertebral columns has four curves, of which thoracic and sacral are primary and are concave anteriorly, thus, when spine is fully flexed, cervical and lumbar are obliterated. The cervical and lumbar are convex anteriorly. In supine position, third lumbar vertebrae marks the highest point of lumbar curve, while the fifth thoracic is the lowest point of the lumbar curve. Kyphosis, scoliosis, lardosis and hypertrophic arthritis of the spine may upset the curves and make the lumbar puncture difficult.

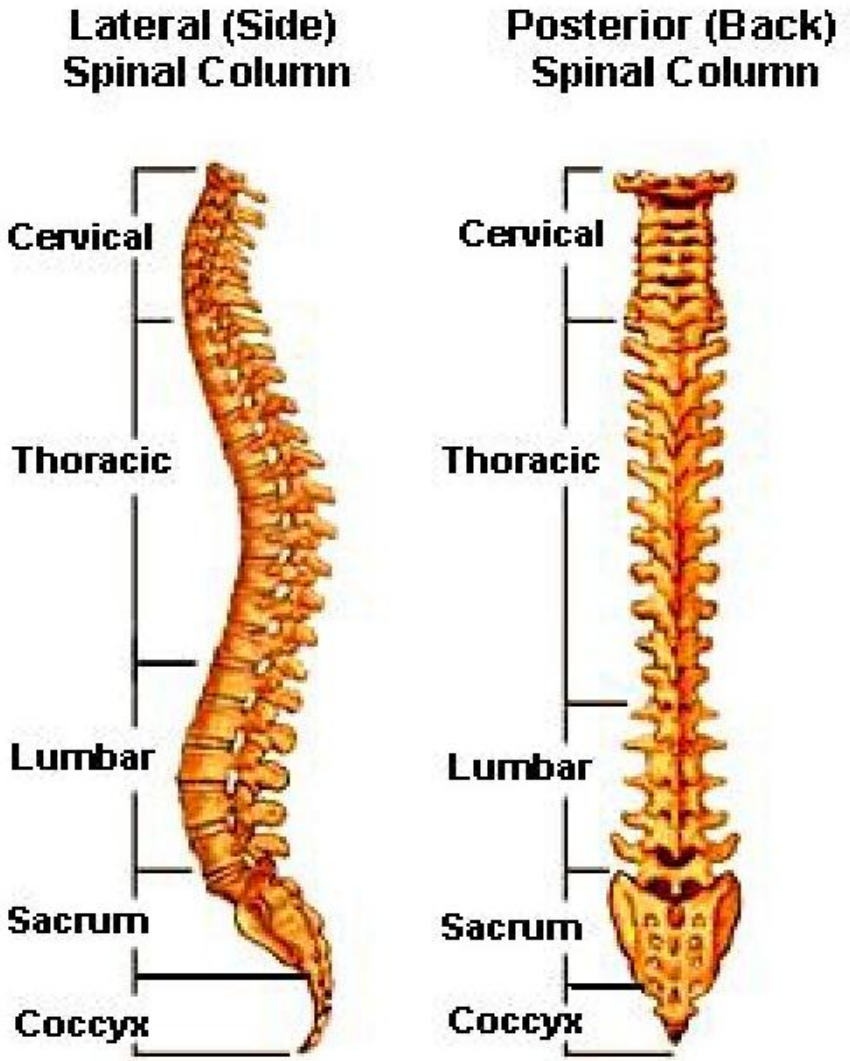
VERTEBRAL CANAL:

The vertebral canal is bounded in front by bodies of the vertebrae and intervertebral discs, posteriorly by the laminae, ligamentum flavum and arch which bear spinous process and the ligaments between them called the interspinous ligaments, laterally by pedicles and laminae. The size and shape of vertebral canal vary in cervical and lumbar regions.

The vertebral canal consists of:

1. Roots of spinal nerves
2. Spinal membrane with their enclosed cord and CSF
3. Structures- vessels, fat and areolar tissue of the extradural space.

FIGURE 1: VERTEBRAL COLUMN LATERAL AND POSTERIOR VIEWS



LIGAMENT BOUNDING THE VETEBRAL COLUMN

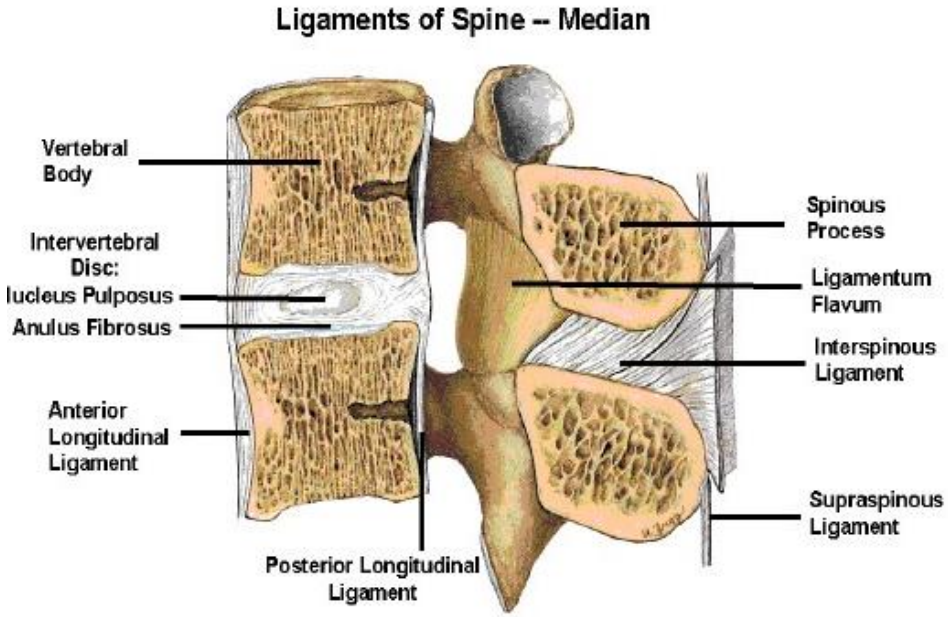
These are:

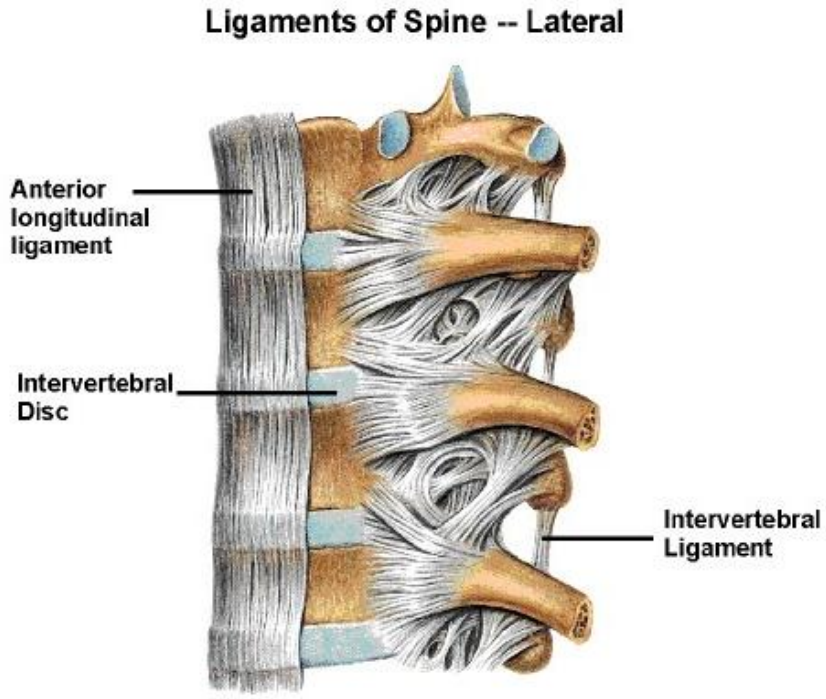
1. **Supraspinous ligament**: Is a continuation of ligament nuchae and joints together the tips of the spinous process from the 7^{th} cervical vertebrae to the sacrum. It is the thickest and widest in the region.
2. **Interspinous ligament**: These ligaments connect adjoining spinous process from their tips to the roots. They fuse with the supraspinous ligament posteriorly and with ligament flavum anteriorly. In the lumbar region they are wide and dense.
3. **Ligament flavum**: It is composed of yellow elastic fiberes which accounts for its name. It is placed on either side of spinous process and extends laterally to blend with capsule of joints between the superior and inferior processes. It runs from anterior and inferior aspects of laminae below. It comprises over half of the posterior wall of the vertebral canal, the bony laminae accounting for the reminder. Ligamentum flavum is the thinnest at cervical region and thickest in lumbar region. Functionally these ligaments are muscle spares, assisting in recovery of posture after bending and maintaining erect posture.
4. **Posterior longitudinal ligament**: Lies within the canal on posterior surface of bodies of vertebra from which it is separated by basivertabral veins. This ligament is thinnest in cervical and lumbar region.
5. **Anterior longitudinal ligament**: It is more of anatomical interest than anaesthetic interest. It runs along the front of vertebral bodies to which, as also to the intervertebral discs, it is adhered.

It is essential for the anesthesiologist practicing spinal anaesthesia to have an accurate knowledge of these ligaments. The different sensations of resistance these ligaments impart to the advancing needle can be appreciated by the operator and are invaluable aid to a successful technique.

In midline subarachnoid block, the spinal needle pierces the skin, subcutaneous tissue, supraspinous, interspinous ligaments and ligamentum flavum, duramater, arachnoid mater and enters subarachnoid space. In the lateral spinal puncture, the spinal needle pierces the skin, subcuteneous tissue, lumbar muscles, ligamentum flavum, duramater, arachnoid mater and enters subarachnoid space.

Figure 2 : Vertebral ligaments





SPINAL CORD:

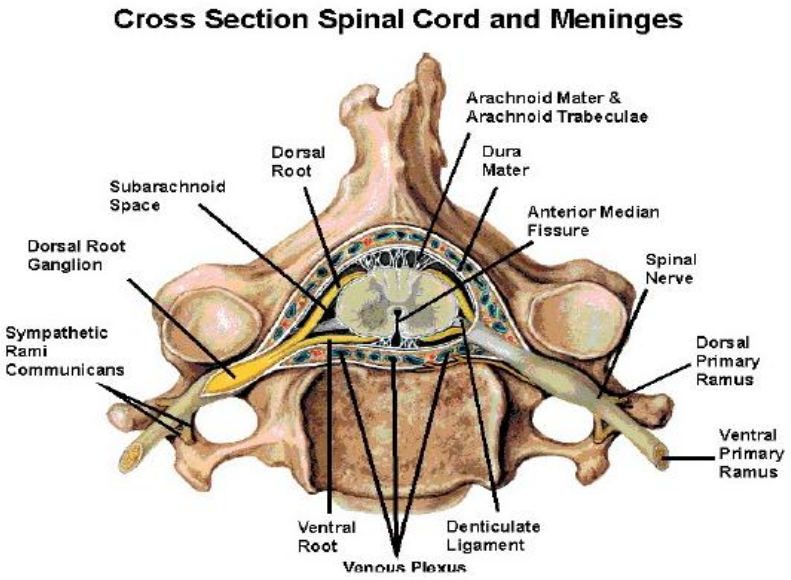
The spinal cord is elongated part of the central nervous system which occupies upper two thirds of the vertebral canal. In adults it measures 42-45cm in length. It extends from upper border of the atlas to the upper border of the second lumbar vertebra. Its position is lower in infants when compared with the adults. At its rostral end, it continuous with medulla oblangata, below ends in conus medullaris from which filum terminale descends as far as coccyx.

In foetal life length of the spinal cord corresponds with that of vertebral canal, but the canal grows more rapidly than the cord. Thus nerve roots which pass out transversely in early foetal life becomes more and more oblique in direction in adult life. The lumbar and sacral nerves descend almost vertically to meet their foramina and known as cauda equina. The cord has two enlargements, the cervical and the lumbar, corresponding to the nerve supply of the upper and lower limbs. The cervical enlargement extends from C3 to T2 and lumbar enlargement from T9 to T12.

SPINAL SEGMENTS

The spinal cord is divided into segments by a pair of spinal nerves which arise from the cord. There are thirty one pairs of spinal nerves. These are eight cervical, twelve thoracic, five lumbar, five sacral and one coccygeal. The nerve roots within the dura have no epineural sheath and are therefore easily affected by doses of analgesic drugs brought in to contact with them.

Figure 3 : Cross section of spinal cord and meninges



SPINAL MENINGES

Spinal cord is ensheathed by three membranes from without in wards

a. Dura mater

b. Arachnoid mater

c. Pia mater

a) Duramater

This is a strong fibrous layer forming a tubular sheath, attached above to margin of foramen magnum and ending below at the lower border of the second sacral vertebrae. It is separated from the bony wall of vertebral column by extradural space which contains fat, areolar tissue, venous plexus, anterior and posterior roots of spinal nerves. Its main fibers are longitudinal so that the lumbar puncture needle should be introduced with its needle separating rather than dividing.

b) Arachnoidmater:

This is the membrane of spider web delicacy which lines dural sheath and sends prolongation along each nerve root, subdural space being merely a capillary layer.

c) Piamater:

This is the inner most of the three membranes, is a vascular connective tissue sheath which closely invests the brain, spinal cord and projects in to their sulci and fissures. This is separated from the arachnoidmater by subarachnoid space filled with CSF. The spinal pia is thickened anteriorly in to the linea splendens along the length of anterior median fissure, on either sides, it forms ligamentam denticulatum, a series of triangular fibrous strands attached at their apices to dural sheath. The piamater ends as a prolongation, filum terminale which pierces the distal end of the dural sac and is attached to the periosteum of the coccyx.

BLOOD SUPPLY :

The spinal cord is supplied by anterior and posterior spinal arteries.

The arteries descend from the level of foramen magnum.

The anterior spinal artery is a midline vessel lying on the anterior median fissure in the substance of piamater. It is formed by the union of a branch from each vertebral artery. It is longer of the two vessels and supplies the lateral columns, anterior columns and three fourth of the substance of spinal cord.

The posterior spinal arteries comprise two vessels on either side derived from posterior inferior cerebellar arteries and descend medial to the posterior nerve roots, sending penetrating twigs to the posterior white column.

They supply posterior columns on both side and remainder of the posterior grey columns. These arteries are reinforced by arteries which passes through the intervertebral foramina from the vertebral, ascending cervical, posterior intercostal, lumbar, lateral sacral arteries. The spinal veins are gathered together into anterior and posterior venous plexus. They drain along the nerve roots through intervertebral foramina into vertebral, azygus and lumbar veins.

NERVE SUPPLY OF THE MENINGES

The posterior aspect of the dura and arachnoid mater contains no nerves and no pain is felt on dural puncture. The anterior aspect s is supplied by sinuvertebral nerves, each of these enters an intervertebral foramen and passes up for a segment and down for two segments.

CEREBROSPINAL FLUID

It is an ultrafiltrate of the plasma with which it is in hydrostatic and osmotic equilibrium. It is a clear, colourless fluid found in the spinal canal, cranial subarachnoid spaces and in the ventricles of the brain. At 37ºC, its specific gravity is 1003 to 1009, and pH is 7.0 to 7.6. The total volume in adult ranges from 120 to 150ml, of which 25ml to 35ml is in spinal subarachnoid space. In horizontal position, the pressure of CSF ranges from 60 to 80mm of water.

The cerebrospinal fluid is formed by secretion or ultrafiltration from the choroid arterial plexuses of the lateral, third and fourth ventricles. The normal daily secretion is believed to be equal to the volume present (150ml). It has been shown that after removal of small volumes of CSF, it is reformed at an increased rate of approximately 0.3ml min-1 (432ml per day).

The circulation, elimination of CSF are important for understanding and treatment of postdural puncture headache. Although the choroid plexus are present in all the 4 ventricles, the bulk of the CSF is formed in lateral ventricles and then passes in to the third ventricle. In the fourth ventricle, it departs through two foramen of Luschka and circulates upwards over the surface of the brain. It also passes through the median foramen of Magendie to proceed downward into the medullary and spinal cord areas.

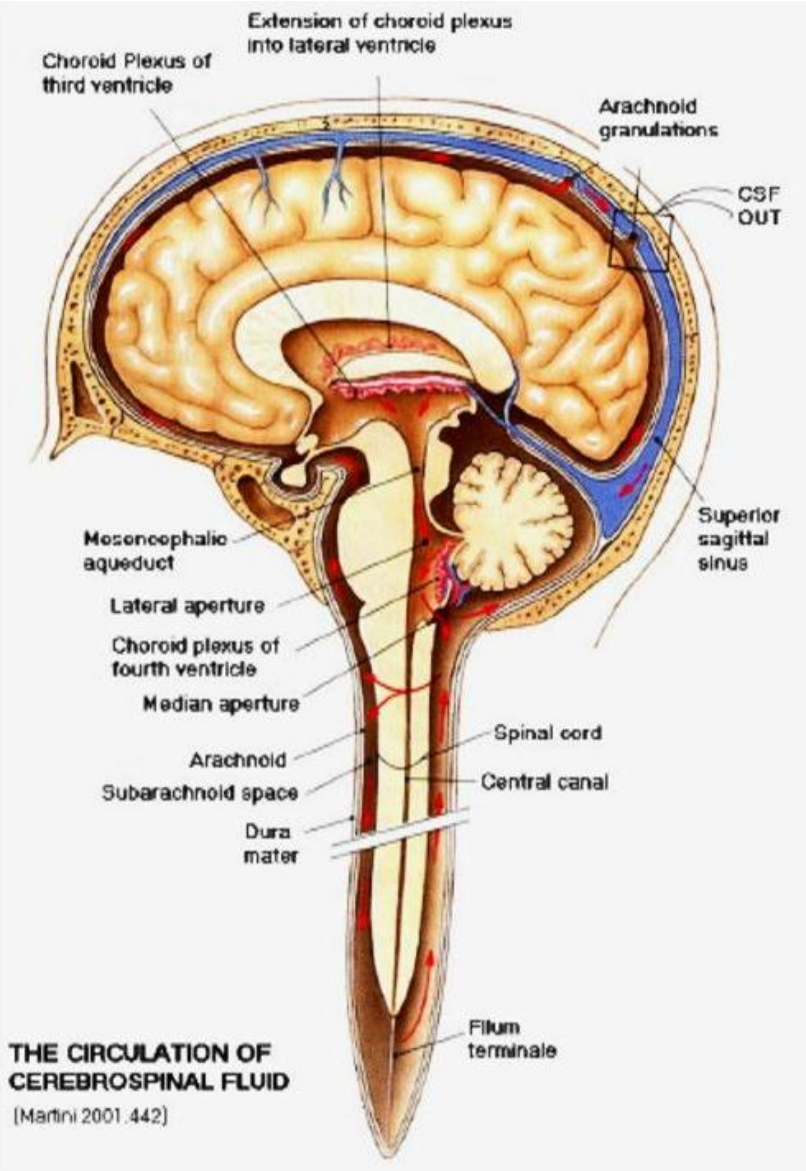
Composition of CSF

Protein	15-45mg%
Glucose	50-80 mg%
Non protein nitrogen	20-30 mg%
Chloride	120-140mEq L-1
Sodium	140-150mEq L-1
Bicarbonate	24-30mEq L-1
pH	7.4-7.6

Functions of the CSF :

1. The brain and spinal cord (CNS) are rendered buoyant by the cerebrospinal fluid medium in which they are suspended. This provides the nervous system with support and protection against rapid movements and trauma.
2. The CSF is believed to be nutritive for both neurons and glial cells.
3. The CSF provides a vehicle for removing waste products of cellular metabolism form the nervous system. In this capacity, it functions like a lymphatic system.
4. The CSF plays a role in maintaining the constancy of the ionic composition of the local microenvironment of the cells of the nervous system.

FIGURE 4: CSF PRODUCTION AND CIRCULATION



FUNDAMENTAL CONSIDERATIONS

Spread of local anaesthetics in the subarachnoid space:

The spread of local anesthetic agents injected in to the subarachnoid space is influenced by multitude of factors, primarily, the physical principles of fluid dynamics related to the subarachnoid block. The dispersion is the actual mixing of the injected material with the CSF;

The dispersion is the actual mixing of the injected material with the CSF, therefore it is primarily a function of injection of given volume of solution.

The barbotage certainly has an effect on dispersion. The spread of solution is as much function of their volume as of their specific gravity. Apart from these purely physical factors, there are number of other anatomical physiological, and technical factors with which anesthesiologist must be familiar, if he has to have control over anaesthesia. The examples of uncontrolled factors; curvatures and calcification of vertebral column, the age of the patient, intraabdominal pressure (affected by pregnancy, obesity, tumour, ascites) and pH of the CSF. The factors that anaesthesiologist can control include, specific gravity of the solution, dose of the drug injected, site of injection, and position of the patient during and after injection. The other considerations influencing the above factors include site and duration of surgical procedure, physical status of the patient and position of the patient during surgery.

Fate of local anaesthetic solution in the subarachnoid space:

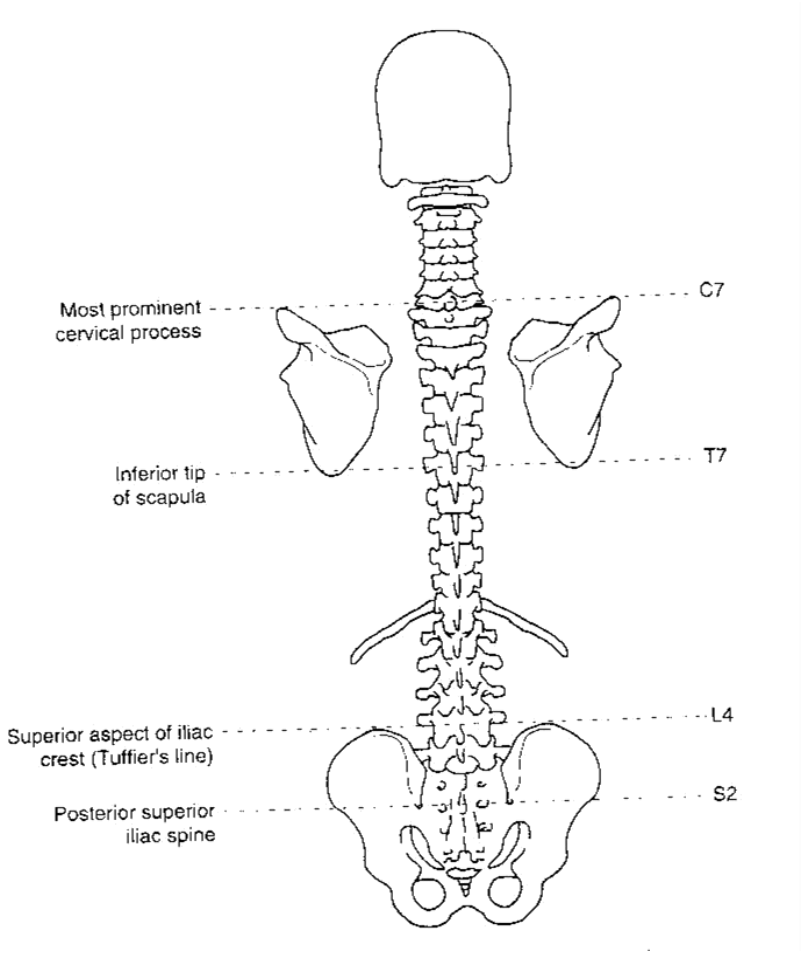
Immediately following the injection of local anaesthetic solution into subarachnoid space, there is a rapid decrease in the concentration of the anesthetic agent in the CSF at the point of injection. The greatest decrease occurs within 5 minutes, followed by a more gradual decline. The amounts present in solution are

however, so small that after 20 to 30 minutes, they are insufficient to produce spinal anesthesia. The hyperbaric solutions spread predominantly to the cephalad direction when the patient is in the supine position in level table.

As the local anesthetic solution spreads, a differential block occurs that is a zone where the concentration of local anesthetic solution is highest, all the motor and sensory modalities are blocked; at the most cephalad extent, however, only the sympathetic nerves are involved in the blockade.

A differential block exists between motor and sensory levels, averaging two spinal segments. Immediately after the injection, the local anesthetic agent is taken up by neural elements. It accumulates along the posterior and lateral aspects of the spinal cord itself and as well as in the spinal nerve roots. The egress is primarily by vascular absorption with no hydrolysis or degradation taking place in the spinal fluid. Depending upon the type of local anesthetic injected, the drug is metabolized either in the plasma by pseudocholinesterase (e.g.-procaine and tetracaine) or in the liver (e.g. – lignocaine, other amide local anesthetic agents)[26].

Figure-5: Surface landmarks of vertebral segments Scapular position is with arms hanging by sides



PHYSIOLOGY

In spinal anesthesia, the anesthetic agent is brought into contact with neural structures in the subarachnoid space. 3 sites of action of local anesthetics in the subarachnoid space in order of importance;

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

Sequence of nerve modality block:

1. Vasomotor block- dilatation of skin vessels and increased cutaneous blood flow.
2. Block of cold temperature fiberes.
3. Sensation of warmth by patient –due to above.
4. Temperature discrimination is next lost.
5. Slow pain.
6. Fast pain.
7. Tactile sense lost.
8. Motor paralysis.
9. Pressure sense abolished.

Most of the physiologic side effects of spinal anesthesia are a consequence of the sympathetic blockade. A thorough understanding of these physiologic effects is necessary for the safe and successful application of spinal anesthetic. Although some of them may be deleterious and require treatment, others can be beneficial for the patient or can improve operating conditions[27].

Factors affecting spread of local anesthetics in the subarachnoid space.

1. Major factors affecting CSF spread Patient age.

   Patient height, Patient position, Spinal cord Configuration of spine.

   Volume of CSF.

   Site of injection.

   Speed of injection

   Direction of needle

   Local anesthetic baricity

   Local anesthetic dose

   Local anesthetic volume.

2. Factors not affecting CSF spread

   Patient weight

   Patient gender

   Local anesthetic concentration

   CSF composition

   CSF circulation

   Vasoconstrictors

In practice, the following topographic landmarks are used for determining the sensory pinprick level of anesthesia.

- Anesthesia to inguinal ligament and crest of ileum includes L1 and overlaps to T_{12}.
- Anesthesia to umbilicus indicates the level of T_{10}.
- Anesthesia to xiphoid cartilage includes block to T_6 segment.
- Anesthesia to nipple line indicates block to T_4 segment.
- Anesthesia to clavicles indicates block to T_1 segment.

Difference in levels of block according to fibre type:

Generally, the sympathetic paralysis is more diffuse and will extend 2 to 4 segments above the sensory block. This sympathetic block is usually first in onset and last to disappear. On the other hand, motor nerve blockade is usually one to four segments below the sensory levels.

Complications during spinal anesthesia:

Blood pressure

A reduction in blood pressure is an invariable accompaniment of spinal anesthesia. In general diastolic pressure is not decreased remarkably. The systolic pressure falls, and there is no proportional fall in diastolic pressure. The blood pressure decreases an average of 2.5% per spinal segment blocked.

Primary mechanism of hypotension:

Paralysis of the sympathetic vasoconstrictor fibres to blood vessels best explains the hemodynamic changes and hypotension during spinal anesthesia. This decreased vasomotor tone occurs at the preganglionic level and affects both arterioles

and veins. Thus, hypotension may be induced predominantly either by arteriolar paralysis or by postarteriolar bed paralysis.

Various theories to explain hypotension;

1 Hematogenous intoxication.

2 Direct action on medullary centers.

3 Paralysis of adrenal nerve

4 Respiratory depression.

5 Loss of skeletal muscle tone.

Cardiac effects

Bradycardia

It results from block of the cardioaccelerator nerves and decreased venous return. Levels of spinal anesthesia that block the T_1–T_4 dermatomes not only inhibit the cardioaccelerator nerves but also result in total preganglionic sympathetic blockade that produces venodilation and reduces venous return. Decreased venous return reflex slows the heart rate by activating receptors in the right atrium and great veins[28]

Cardiac output:

Cardiac output decreases in all patients after spinal anesthesia. The fall in mean arterial blood pressure is due to a decrease in cardiac output, which results from venodilatation and decreased stroke volume. Pressure in the right auricle falls regularly. Patients show a significant reduction in left ventricular work.

Effects on oxygen, utilization and transport:

Oxygen consumption is reduced. This is explained by the fact that hypotensive states are associated with a drop in basal metabolic rate and there should be a reduction in oxygen needs proportional to the mass of relaxed musculature.

The central arteriovenous oxygen difference is increased. This is the result of greater oxygen extraction from a slowing of the rate of blood flow through tissues in the anesthetized fixed areas.

Arterial oxygen saturation is not changed significantly. Hematocrit values are reduced slightly by 1 to 2% due to displacement and stagnation of red blood cells in capillary beds. An increase in oxygen extraction also occurs in the splanchnic bed.

Respiratory System:

Low SAB has no effect on the respiratory system. Motor blockade extending to the roots of the phrenic nerves ($C_{3–5}$) causes apnoea.

Blocks which reach the thoracic level cause loss of intercostal muscle activity. This has little effect on tidal volume (because of diaphragmatic compensation), but there is a marked decrease in vital capacity resulting from a significant decrease in expiratory reserve volume. The patient may experience dyspnoea, difficulty in taking a maximal inspiration or in coughing effectively.

Gastrointestinal system:

The vagus nerve supplies parasympathetic fibres to the whole of the gut as far as the transverse colon. Spinal blockade causes sympathetic denervation and unopposed parasympathetic action, lead to a constricted gut with increased peristaltic activity. This is regarded by some as advantageous for surgery.

Nausea, retching or vomiting may occur in the awake patient and are often the first symptoms of in impending or established hypotension[29]

PHARMACOLOGY OF BUPIVACAINE

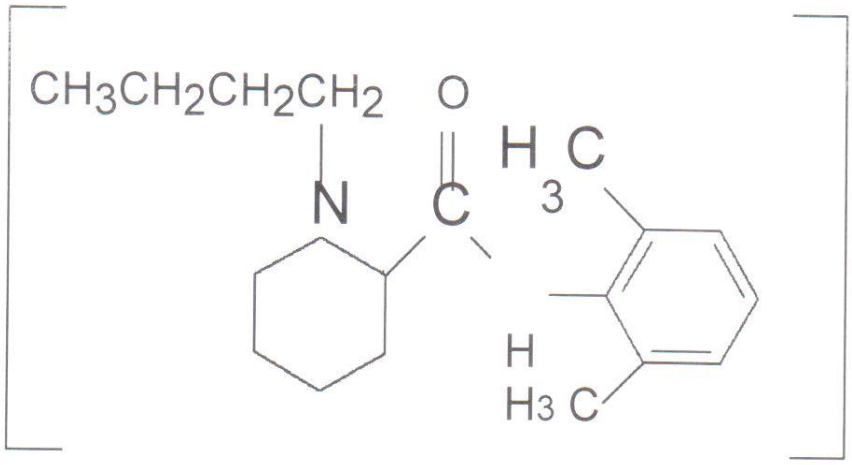
Introduction:

The bupivacaine was prepared by A.F.Ekestam in 1957. The Telir and Widmann were the first to report its use in 1963.

Chemistry:

The molecular weight of Bupivacaine hydrochloride salt is 325 and that of the base form is 288. It has a melting point of 258ºC. The Bupivacaine and solutions have a pH of about 3.5. Chemically, it is N-butyl pipecolic 2, 6 dimethyl xylidide hydrochloride.

Structural Formula:



Physiochemical properties :

The Bupivacaine base is sparingly soluble in water highly soluble in lipid, but the hydrochloride is readily soluble in water. Bupivacaine is highly stable and can withstand repeated autoclaving.

Pharmacokinetics:

The onset of action of the drug is intermediate. The Bupivacaine can be detected in the blood within 5 minutes of infiltration or following epidural or intercostal blocks. The pKa of Bupivacaine is 8.1 which determine the onset of action. The plasma levels are related to the total dose administered, peak levels of 0.14 to 1.18µg ml -1 were found within 5 minutes to 2 hours after the administration of anaesthesia, and they gradually decline to 0.1 to 0.34µg ml-1 by four hours. The tissue blood partition coefficient of Bupivacaine 1:28, and has a clearance of 0.47L min-1. The elimination half-life of Bupivacaine is 3.5 hours in adults and 8.1 to 14 hours in neonates.

Pharmacodynamics:

The onset of action of Bupivacaine is between 4 and 6 minutes, and maximum anaesthesia is obtained between 15 to 20 minutes. The duration of anaesthesia varies according to the block; the average duration of peridural block is about 3.5 to 5 hours and for nerve blocks, it is about 5 to 6 hours.

In subarachnoid block, the onset of action is about 3 to 4 minutes, and complete anesthesia occurs in 5 minutes and lasts for 3.5 to 4 hours. The motor blockade is definitely inferior to Tetracaine.

Plasma binding

In plasma drug is avidly bound to protein to the extent of 70 to 90%. The rank order of protein binding for this and its homologues is Bupivacaine → Mepivacaine → Lidocaine. Conversely the unbound active fraction is one-seventh that of Lidocaine and one-fifth that of Mepivacaine

Metabolism and elimination:

The liver is the primary site of Bupivacaine metabolism. The drug is metabolized partly by N-dealkylation. The debutylation of Bupivacaine results in production of pipecolyl xylidine, which undergoes further breakdown. This product is 1/8th as toxic as the parent drug. When compared to ester local anesthetics the metabolism of Bupivacaine is more complex and slower. Therefore, there may be sustained elevations of plasma concentrations and hence systemic toxicity is more likely.

It crosses placental barrier as any local anesthetic by passive diffusion, but the lowest level of placental diffusion is reported for this drug (umbilical vein/maternal ratio is 0.31 to 0.44). The high protein binding capacity of this agent is probably the reason why less diffusion occurs across the placenta. No effects on foetus have been noted.

The renal elimination is limited because of poor water solubility and less than 5% of injected dose may be excreted unchanged.

Systemic Effects:

At plasma concentrations of 1.0 to 2.0µg ml-1, the heart rate increases significantly. The mean arterial pressure increased from 87 to 100 mmHg, while cardiac output is decreased about 20%. The blood concentration of glucose, lactose,

plasma cortisol, and fatty acids do not change significantly. In addition, intravenous Bupivacaine has been shown to inhibit cardiac sympathetic nerve activity. The lung is capable of extracting Bupivacaine. The pulmonary extraction limits the concentration of drug which reaches the systemic circulation.

Sympathetic effects:

1. Definitive β-adrenergic receptor block
    a) The hypertensive effect of isoproterenol is inhibited.
    b) The pressor effect of adrenaline is enhanced
    c) Intestinal smooth muscle tone is enhanced
    d) The chronotropic effect of isoproterenol is decreased
    e) The ionotropic effect of isoproterenol is decreased.

2. No α- adrenergic receptor blocking properties
3. No effect on pressor effect of noradrenaline.

Anaesthetic properties:

The Bupivacaine is approximately three to four times more potent than Lidocaine and eight times more than procaine. The duration of action of local anesthetic is two to three times longer than that of Mepivacaine or Lidocaine and 20 to 25 times longer than that of Tetracaine. The anesthetic index of Bupivacaine is 3.0 to 4.0. The Bupivacaine is reliable drug for nerve block and subarachnoid block. It appears to have slow nerve penetrating power. It produces excellent sensory anaesthesia for prolonged duration.

Dosage:

The recommended concentrations for various types of procedures is as follows

I. **Infiltration:** A concentration of 0.125% to 0.25% is used for infiltration block. The onset is rapid. The duration of action is 200 to 400 minutes.

II. **Peripheral nerve blocks.**

A concentration of 0.25% to 0.5% is used. The onset of action is slow (10-20minutes) with very wide variation. 0.5% solution is preferred as it produces satisfactory motor block also. The duration of action is 350 to 400 minutes.

III. Caudal blocks:

For obstetric analgesia and perineal surgery, the 0.25% solution is effective. It is preferred over Lidocaine because of association of higher incidence of neurobehavioral defects with Lidocaine in newborn, and low placental distribution ratio. A volume up to30ml may be used by caudal technique. For surgery of lower extremities, the 0.5% solution must be used if good motor block is desired.

IV. Epidural block:

For obstetric analgesia and perineal surgery, 20ml of 0.25% solution is effective. For lower extremity surgery, up to 20ml 0f 0.5% solution is satisfactory. For abdominal surgery good conditions are achieved only by the use of 0.75% solution up to a volume of 20ml.

V. Subarachnoid block:

The 0.5% hyperbaric Bupivacaine is effective for subarachnoid block. The maximum recommended dose is 200mg. The dose may be repeated in 3 to 4 hours, but maximum 400mg in 24 hours.

Adverse effects:

There are no serious adverse effects reported at clinical doses. The incidence of hypotension and bradycardia are not greater than Mepivacaine and Lidocaine. The shivering is more frequent with Bupivacaine than other local anaesthetics. Convulsions have followed accidental injection of large volume of the drug in to blood vessels or after relative over dosage.

Toxicity:

The minimum toxic blood concentration is 2 to 4µg ml-1. Bupivacaine is 15 times more toxic than Lidocaine. Higher concentration of Bupivacaine produce ECG changes, commonest being,

1. Wide QRS complex
2. Bradycardia, regardless of dose.
3. Refractory asystole
4. Ventricular tachycardia
5. Electro mechanical dissociation
6. Fibrillation.

Toxicity is enhanced by,

1. Hypercarbia
.
2. Hypoxia.
3. Acidosis.

The suggested mechanism is blockade of cardiac sodium channels. The Bupivacaine remains bound to Na+ Channels longer with a dissociation constant 110 to 115 times greater than that of Lidocaine.

Advantages of Bupivacaine:

1. Long acting
2. Less tachyphylaxis
3. Less cumulative effect.
4. Selective, differential, segmental block.
5. Less crossing of blood brain barrier
6. Less crossing of placenta
7. Less Female/Male ratio of 0.3 which helps in labour analgesia[30]

PHARMACOLOGY OF MIDAZOLAM

Midazolam an imidazobenzodiazepine derivative is utilized as a premedicant, sedative, and an anaesthetic induction agent. The unique chemical structure of Midazolam confers a number of physiological properties that distinguish it from other benzodiazepines in terms of its pharmacologic and pharmacokinetic properties. The drug was synthesized in 1976 by Fryer and Walser[31].

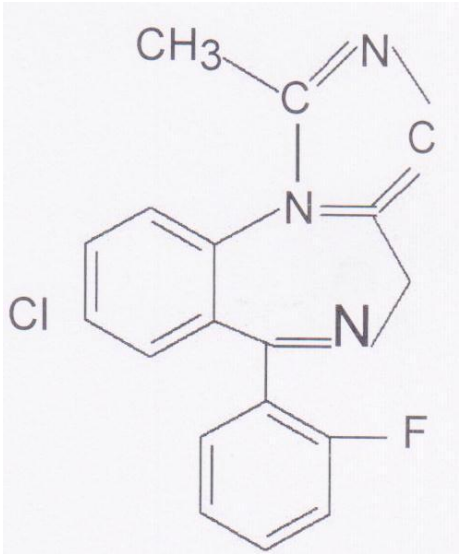
Chemical properties:

Midazolam (molecular weight =362) has a fused imidazole ring that is different from classic benzodiazepines. The imidazole ring accounts for the baricity, stability of an aqueous solution and rapid metabolism. The Pka of Midazolam is 6.15. In acidic aqueous media; Midazolam is water soluble, thereby allowing the parentral formulation to exclude lipoidal such as propylene glycol. At physiologic PH, on the other hand Midazolam becomes highly lipophilic and is one of the most lipid soluble of benzodiazepines. It's compatible with D5W, normal saline and lactated ringer's solution and can be mixed with acidic salts of other drugs (eg: morphine, scopolamine, and atropine).

The high lipophilicity has a number of clinical consequences, including rapid absorption of Midazolam from the gastrointestinal tract and rapid entry of Midazolam into brain tissue after intravenous administration. Some studies suggest that opening of the benzodiazepine ring may occur when Midazolam is in acidic solution. However this physiochemical change ring may occur when Midazolam is in acidic solution. However this physiochemical change reversible[31.]

Midazolam extensively binds to plasma proteins (96-97%) and is independent of the dose and plasma concentrations of Midazolam.

Structural Formula:



Effects and mechanism of action:

Central nervous system:

Midazolam has anxiolytic effects. The mammillary body may be the site of antianxiety activity. The affinity of the benzodiazepines for glycine receptors in brainstem correlates with their antianxiety potency.

Midazolam has anticonvulsant action, which is through the enhanced action of GABA on motor circuits in brain.

Midazolam has anterograde amnestic actions, site and mechanism of action of this effect is not known.

Midazolam given by intrathecal or epidural injection can produce antinociceptive effects. This could be GABA mediated because GABA has been shown to have analgesic properties. Midazolam reduces in dose related manner, cerebral metabolic rate for oxygen (CMRO2) and cerebral blood flow. The reductions

in CMRO2 and CBF suggest that Midazolam can protect against cerebral hypoxia and be useful for patients who have impaired intracranial compliance or increased intracranial pressure (ICP). The protection offered by Midazolam is superior to diazepam but less than Phenobarbital[32]

Respiratory system:

Midazolam causes some respiratory depression. It appears to be a CNS effect, since both ventilatory response to and the mouth occlusion pressure to CO_2 are depressed and there's is little effect on respiratory mechanics. Low sedative doses of Midazolam i.e. 0.075 mg/kg IV does not affect the ventilatory response to CO_2, suggesting that, in lower doses (i.e. in doses used for premedication or sedation clinically important respiratory depression does not occur. There is a concern of apnoea following Midazolam administration. Apnoea probably is a dose related and also a function of the speed of the injection, the higher the dose and more rapid the administration, the higher is the probability that apnoea will occur after Midazolam. apnoea is more likely to occur when Midazolam is administered to patients premedicated with opioids[31].

Cardiovascular effects:

In normal humans, midazolam 0.15mg/kg iv over 15s produces statistically significant reductions in systolic and diastolic blood pressure and increases in heart rate (18%). The cardiac index and left and right heart filling pressures usually are maintained after Midazolam, but the systemic vascular resistance may change.

The severity of a patient's cardiac disease does not appear to significantly influence the hemodynamic response to induction with Midazolam. The cardiovascular pharmacology of Midazolam involves direct and indirect (reflex)

action. A decrease in systemic vascular resistance (SVR), venodilation and a transient change in portal blood flow combine to reduce the cardiac filling. Midazolam also reduces myocardial contractility by direct action. The reduction in blood pressure presumably activates the baroreflexes, simultaneously, simultaneously increasing heart rate and contractility with mobilization of splanchnic and other blood volumes into the central circulation[31.]

Pharmacokinetics:

The high lipophilicity of Midazolam at physiologic PH causes it to have a rapid onset of activity after intravenous administration. The volume of distribution generally averages between 1 and l/kg. After the distribution equilibrium is achieved elimination of Midazolam proceeds rapidly with half-life ranging from 1to 4h in healthy individuals[31].

After oral administration Midazolam is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations generally are achieved within 1 hour of ingestion and the onset of clinical effects after oral administration is correspondingly rapid. Owing to the rapid hepatic clearance of Midazolam the absolute systemic availability after oral administration is significantly less than 100%. On the average only 40-50% of an orally administered dose reaches the systemic circulation in its nonmetabolized form. This is because of extensive first pass hepatic extraction. Thus the oral dose of midazolam must be approximately twice as high as the intravenous dose to achieve clinically comparable effects. The elimination half-life on the other hand is similar or identical to that observed after intravenous administration, indicating that the rate of elimination is independent of route of administration.

Factors influencing pharmacokinetics.

Obesity:

The volume of distribution greatly increases in obese patients because of the greatly enhanced distribution of Midazolam in adipose tissues. This in turn causes highly significant prolongation of elimination half-life but no change in the total metabolic clearance. For obese patients each single intravenous dose should be increased at least in proportion to body weight. The rate of continuous infusion however should be adjusted to the ideal rather than total weight[31].

Age:

The volume of distribution is slightly increased in the elderly, and the volume of distribution was larger in women than in men regardless of age. The various studies suggest that a reduction in dose of Midazolam is not required in elderly patients based on pharmacokinetics alone. Since continuous infusion is based on patient's clearance, infusion rates in the elderly should be reduced by 50% to compensate for their reduced clearance.

Dosage:

Induction : 15 - 0.400 mg/kg iv

Premedication: 0.07 - 0.10 mg /kg im

10 - 15 mg oral

Intravenous sedation: 0.05-0.15 mg/kg

Outpatient use :

The relatively rapid onset and brief half-life of Midazolam make it suitable drug for use in short duration anaesthesia. After use of Midazolam the initial awakening in the recovery room is more prolonged than Thiopentone but its gradual and infrequently associated with nausea vomiting or emergence excitement phenomena. Discharge times were similar.

Undesirable effects :

Fewer side effects have been associated with Midazolam like hiccoughs, coughing, nausea and vomiting. Occasionally erythema and pain at the site of intramuscular injection is seen. The incidence of thrombophlebitis which is reportedly higher with other benzodiazepines has been reported less frequently with Midazolam[31].

MATERIALS AND METHODS

SOURCE OF DATA:

One hundred patients undergoing elective and operative procedures under spinal anesthesia for lower abdominal and lower limb surgeries at Department of Anaesthesiology, B.L.D.E.U'S Shri. B. M. Patil Medical College, Hospital and Research Centre, Vijayapur. Study was conducted from December 2014 to June 2016.

The study was approved by the Hospital's ethical committee.

Inclusion criteria:

1) Patients belonging to ASA Class I & II
2) Patients of either sex aged between 20 to 45 years.
3) Patients undergoing lower abdominal and lower limb surgeries.

Exclusion criteria:

1) Patients belonging to ASA Class III & IV.
2) Pregnant patients.
3) Patients with hypersensitivity to the study drugs.
4) Patients on long term analgesic therapy and chronic alcoholics.
5) Patients with gross spinal abnormality, localized skin sepsis, haemorrhagic diathesis, neurologic involvement or diseases.

Preoperative Period:

On the evening of the surgery all the patients were visited and detailed pre-anesthetic examination including history, clinical examination, systemic examination of cardiovascular, respiratory, central nervous systems and examination of spine for deformity, infection was carried out.

The anesthetic procedure was briefly explained to the patient.

An informed written consent was obtained from the patient or his/her relatives.

Routine investigation:

Haemogram, total leucocyte count, differential leucocyte count, complete urine examination, random blood sugar, blood grouping, blood urea, serum creatinine, electrocardiogram and chest X-ray (if required) were done.

The patients were also introduced to the Visual Analogue Scale (VAS) and were taught how to use it.

Intra operative period:

Once the patient was shifted to the operating room, the patient was connected to the routine monitors which included NIBP, pulse oximeter and electrocardiogram.

All resuscitation equipments like intubation trolley with airways, laryngoscopes, endotracheal tubes along with drugs like atropine, mephentermine were kept ready. The anesthesia machine was also checked along with the oxygen delivery system.

Hypotension- If BP less than 20% of basal reading is considered as hypotension and treated accordingly.

Bradycardia- If pulse rate is less than 50bpm.

Patients were allocated into two groups viz;

Patients were randomly allocated into two groups using computer generated slip.

Group-B: Fifty patients receiving 3ml of hyperbaric Bupivacaine 0.5% with 0.2ml of normal saline.

Group-BM: FIfty patients receiving 3ml of hyperbaric Bupivacaine 0.5% with 0.2 ml (1mg) of Midazolam.

The patients were kept nil orally for 8-10 hours before surgery.

Base line pulse rate, blood pressure, respiratory rate, SpO_2 were recorded.

An intravenous access was obtained and secured with 18G IV canula. All patients were preloaded with 15ml/kg of Ringer's lactate prior to spinal anesthesia.

The patients were then put in left lateral or sitting position. Under strict aseptic precautions, lumbar puncture was performed by midline approach by using disposable Quincke's Babcock spinal needle 26G at L_3–L_4 intervertebral space.

Patients were continuously monitored using NIBP, pulse oxymeter and electrocardiogram.

After spinal anesthesia, the patient's pulse rate and blood pressure were recorded at 0, 5, 10, 20, 30, 45, 60, 90 and 120 minutes.

Assessment of Sensory blockade:

This was tested by pin-prick method. The time of onset was taken from time of injection of the drug into the subarachnoid space to loss of pin-prick sensation. The time to achieve maximum sensory block was noted from time of injection of drug to loss of pin-prick sensation at highest dermatomal level. The time for two dermatomal segments regression of sensory level was noted. Duration of sensory blockade was recorded from time of onset to time of return of pin prick sensation to L_2 dermatomal area.

Assessment of motor blockade:

Motor blockade was assessed by Bromage scale. The time interval between injection of drug into subarachnoid space, to the patient's inability to lift the straight extended leg were taken as onset time. The time to achieve maximum motor blockade was noted from time of injection of the drug to maximum degree of motor block.

Bromage Scale:

Grade-I No block:	Full-flexion of knees and ankle joint possible
Grade-II Partial block :	Just able to flex knees, but still full flexion of ankle joint possible
Grade-III:	Unable to flex knees. Flexion of ankle joint Almost complete block possible.
Grade-IV :	Unable to flex knees or ankle joint Complete block

Sedation score:

Sedation score was assessed every 15min both intra and post operatively using a The sedation score is assessed by scoring system of Chernic *et al*.[37] four point scale (1= awake, 2=drowsy but responding to verbal commands, 3=drowsy but responding to physical stimulus, 4=unresponsive to verbal/ physical stimulus). Post-operatively, monitoring of vital parameters, VAS scores and sedation scores were continued every 15min until the time of regression of sensory block to first sacral dermatome. The incidence of hypotension, bradycardia, pruritus, urinary retention, nausea and vomiting were monitored in the recovery room.

Post-operative analgesia was assessed using visual analogue scale (VAS). The patient was asked to mark on a 10cm horizontal scale with no pain corresponding to

zero at one end, the worst and unbearable, excruciating pain at the other end. This was explained to the patient in his vernacular language. The patient's mark of severity of pain on the line was measured. The duration of effective analgesia was taken from time of intrathecal drug administration to the time of first supplementation with rescue analgesic. Injection Diclofenac sodium 1.5 mg/kg intramuscular is the rescue analgesic given if VAS was found to be 4 or more.

Visual Analogue Scale[32]:

Since the perception of pain is highly subjective, this variable was standardized by using data from visual analogue scale.

First advocated by Revill and Robinson in 1976, VAS consists of a 10cm line anchored at one end by a label such as no pain and at the other end by a label such as the 'Worst pain Imaginable' or 'Pain as bad as can be'. The patient simply marks the line to indicate the pain intensity and the provider then measures the length of the line to mark on a point scale.

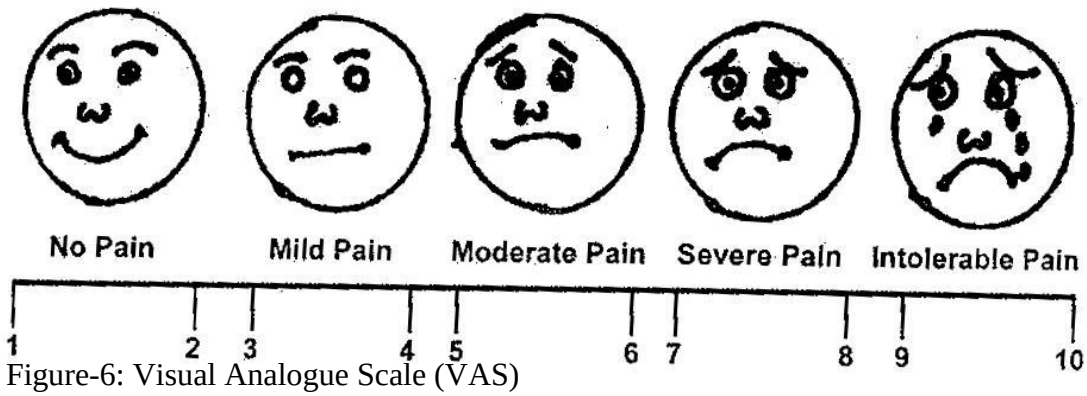


Figure-6: Visual Analogue Scale (VAS)

The side effects of intrathecal Midazolam like nausea and vomiting, hypotension, respiratory depression, shivering, pruritus, motor weakness and seizures are noted.

RESULTS

The effect of hyperbaric Bupivacaine 0.5% (n-50) and hyperbaric Bupivacaine 0.5% with Midazolam 1 mg intrathecally was compared in 100 patients belonging to ASA grade-I and II, posted for elective lower abdominal and lower extremity surgeries.

Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of N, mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries. Chi-square (χ^2)/Fisher exact test was employed to determine the significance of differences between groups for categorical data. The difference of the means of analysis variables was tested with the unpaired t-test. If the p-value was < 0.05, then the results were considered to be significant. Data were analyzed using SPSS software v.23.0.

The results are as follows:

Table 1: Percent Distribution of Age in two study groups

Age group	Bupivacaine		Bupivacaine+Midazolam	
	N	%	N	%
21-25	12	24.0%	12	24.0%
26-30	10	20.0%	11	22%
31-35	12	24.0%	11	22.0%
36-40	6	12.0%	7	14.0%
41-45	10	20.0%	9	18.0%
Total	50	100.0%	50	100.0%

Figure 7: Percent Distribution of Age in two study groups

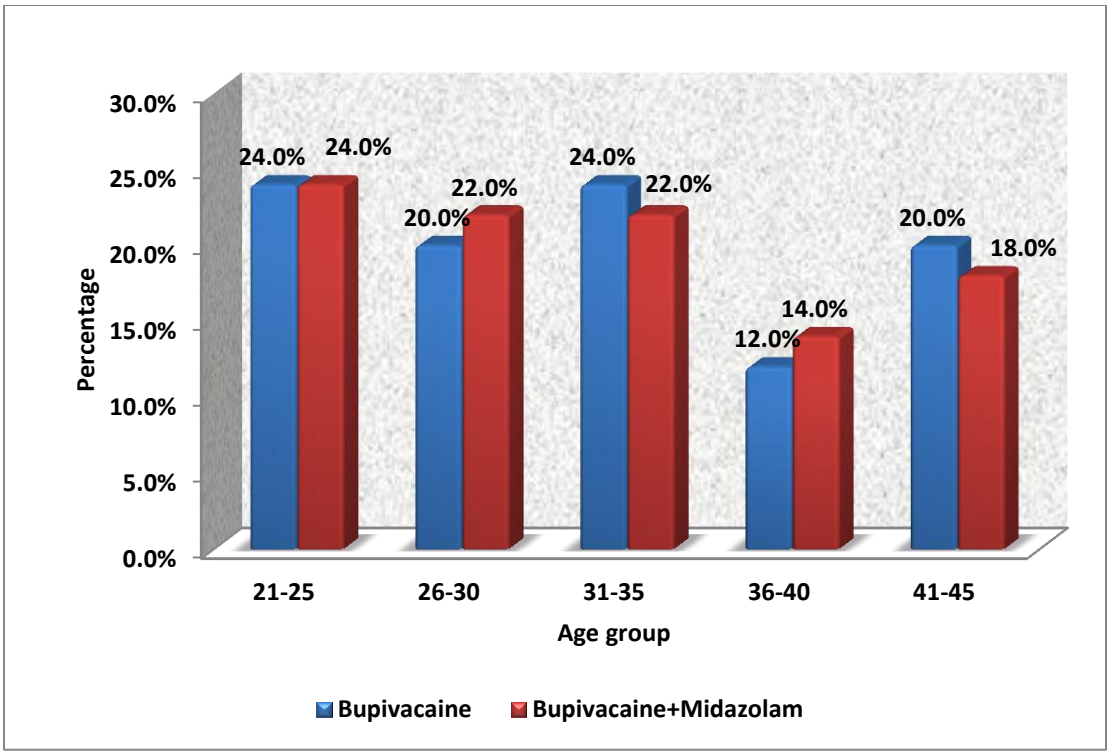


Table 2: Percent Distribution of Sex in two study groups

SEX	Bupivacaine		Bupivacaine+Midazolam	
	N	%	N	%
Male	29	58.0%	25	50.0%
Female	21	42.0%	25	50.0%

Figure 8: Percent Distribution of Sex in two study groups

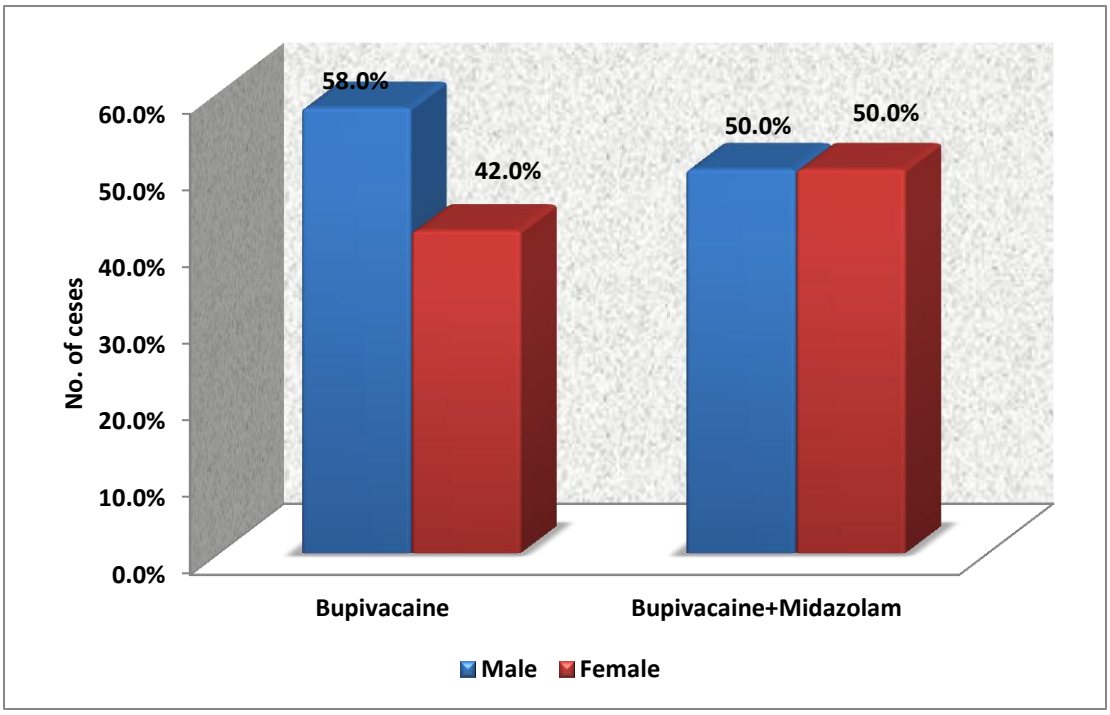


Table 3: Percent Distribution of ASA grade in two study groups

ASA GRADE	Bupivacaine		Bupivacaine+Midazolam		p value
	N	%	N	%	
I	40	80.0%	32	64.0%	0.075
II	10	20.0%	18	36.00%	
Total	50	100.0%	50	100.0%	

Figure 9: Percent Distribution of ASA grade in two study groups

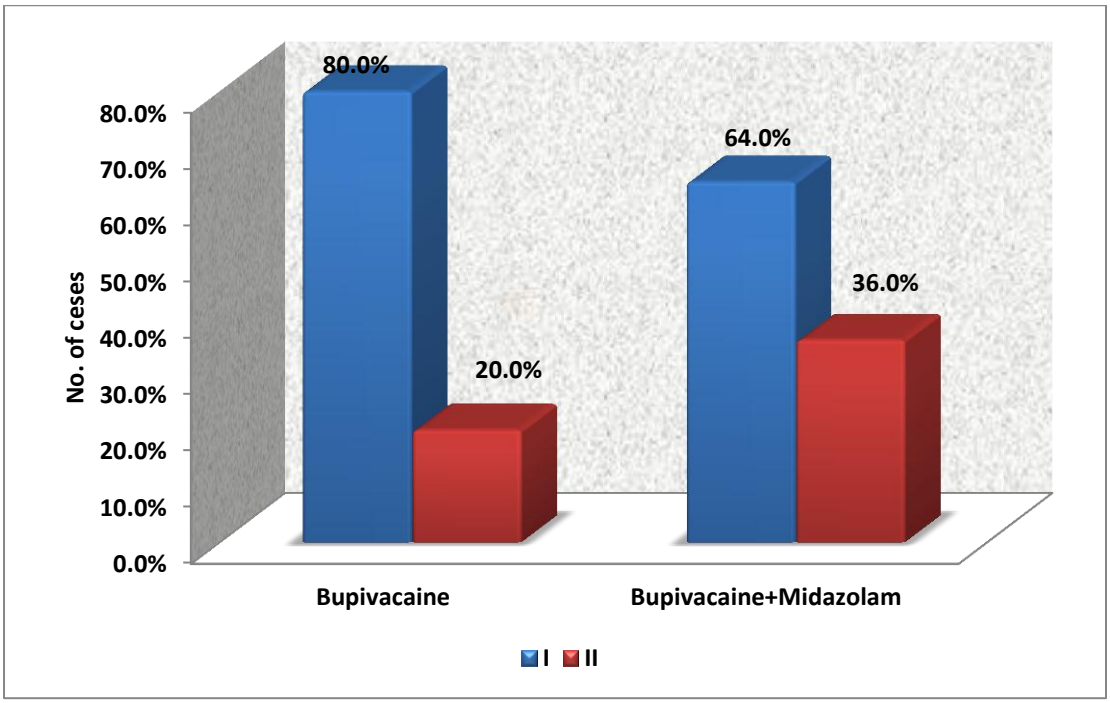


Table 4: Percent Distribution of Max Level in two study groups

MAX LEVEL	Bupivacaine		Bupivacaine+Midazolam		p value
	N	%	N	%	
T1	0	0.0%	0	0.0%	0.363
T6	12	24.0%	8	16.0%	
T7	20	40.0%	21	42.0%	
T8	13	26.0%	16	32.0%	
T9	5	10.0%	5	10.0%	
Total	50	100.0%	50	100.0%	

Figure 10 : Percent Distribution of Max Level in two study groups

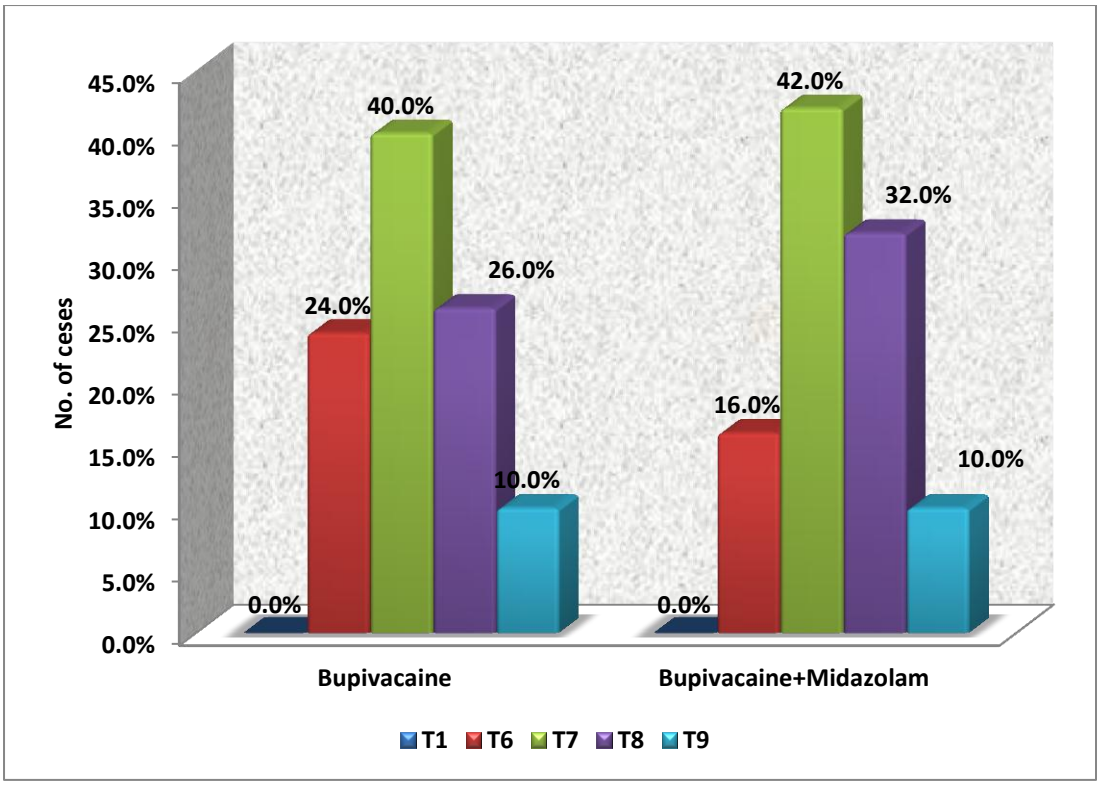
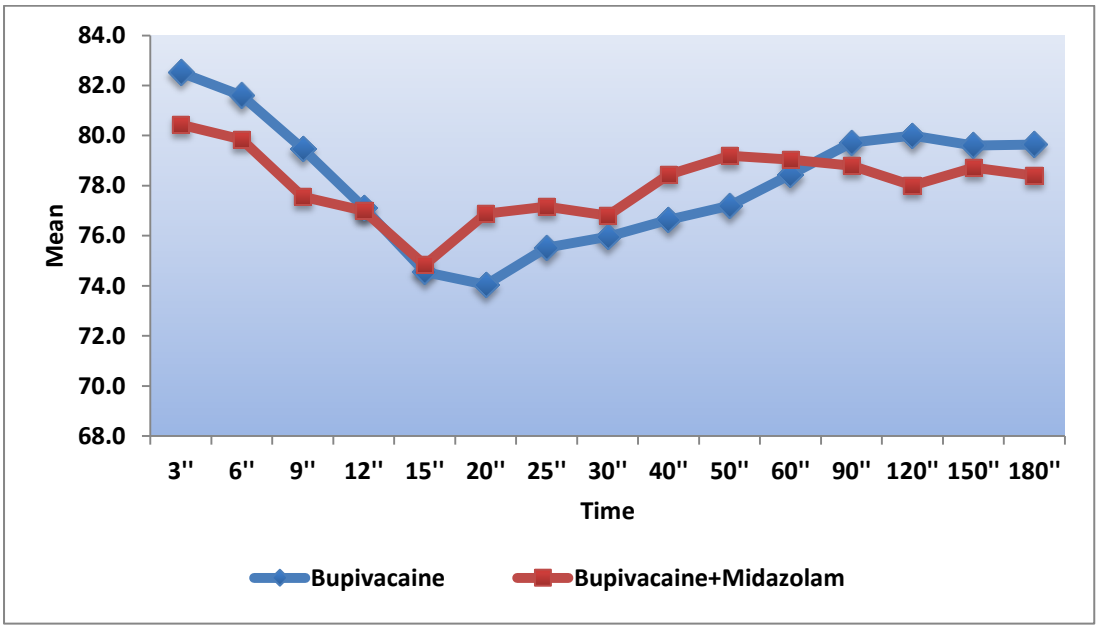


Table 5: Comparison of Means of Heart Rate in two study groups by different time (Min)

Time (Min)	Bupivacaine		Bupivacaine+Midazolam		Mean Difference	p value	95% Confidence Interval	
	Mean	SD	Mean	SD			Lower	Upper
3	82.5	10.3	80.4	13.0	2.1	0.377	-2.6	6.7
6	81.6	9.4	79.8	11.5	1.8	0.403	-2.4	5.9
9	79.5	8.2	77.6	10.1	1.9	0.299	-1.7	5.6
12	77.1	9.2	77.0	8.4	0.1	0.946	-3.4	3.6
15	74.6	9.4	74.8	8.7	-0.3	0.877	-3.9	3.3
20	74.0	8.9	76.9	9.4	-2.8	0.124	-6.5	0.8
25	75.5	8.6	77.2	10.2	-1.6	0.386	-5.4	2.1
30	76.0	8.3	76.8	10.5	-0.8	0.659	-4.6	2.9
40	76.6	8.4	78.4	9.6	-1.8	0.320	-5.4	1.8
50	77.2	7.9	79.2	8.8	-2.0	0.234	-5.3	1.3
60	78.4	8.3	79.0	8.9	-0.6	0.728	-4.0	2.8
90	79.7	8.1	78.8	7.8	0.9	0.564	-2.2	4.1
120	80.0	7.9	78.0	8.7	2.0	0.232	-1.3	5.3
150	79.6	8.0	78.7	7.9	0.9	0.582	-2.3	4.0
180	79.6	7.2	78.4	7.1	1.2	0.387	-1.6	4.1

Figure 11: Comparison of Means of Heart Rate in two study groups by different time (Min)



The difference between the groups at different time intervals studies were statistically insignificant (P>0.05)

Table 6: Comparison of Means of Blood Pressure in two study groups by different time (Min)

Time (Min)	BP	Bupivacaine		Bupivacaine+ Midazolam		Mean Difference	p value	95% Confidence Interval	
		Mean	SD	Mean	SD			Lower	Upper
3	SBP	120.2	13.3	124.5	13.9	-4.3	0.114	-9.7	1.1
	DBP	71.2	11.2	79.3	9.9	-8.0	<0.01*	-12.2	-3.8
6	SBP	122.9	10.6	127.1	10.8	-4.2	0.053	-8.4	0.0
	DBP	77.2	9.1	79.8	9.1	-2.6	0.163	-6.2	1.1
9	SBP	122.0	9.6	129.2	8.6	-7.2	<0.01*	-10.8	-3.5
	DBP	73.3	7.6	77.2	8.2	-3.9	0.016*	-7.0	-0.7
12	SBP	120.9	13.0	127.8	10.3	-6.9	0.004*	-11.6	-2.3
	DBP	71.7	10.6	79.1	13.9	-7.4	0.003*	-12.3	-2.5
15	SBP	121.2	9.6	124.2	11.0	-3.1	0.139	-7.2	1.0
	DBP	71.6	10.1	77.4	12.3	-5.8	0.011*	-10.3	-1.4
20	SBP	120.5	11.5	124.1	10.4	-3.6	0.104	-8.0	0.8
	DBP	71.0	9.2	78.8	9.4	-7.8	<0.01*	-11.5	-4.1
25	SBP	121.5	11.8	124.3	10.0	-2.8	0.204	-7.1	1.5
	DBP	72.7	10.6	75.2	14.2	-2.5	0.322	-7.5	2.5
30	SBP	122.5	10.4	124.6	10.6	-2.1	0.325	-6.3	2.1
	DBP	71.0	9.1	78.2	8.6	-7.2	<0.01*	-10.7	-3.7
40	SBP	123.8	9.0	124.3	9.7	-0.5	0.773	-4.3	3.2
	DBP	72.4	9.3	77.6	8.8	-5.3	0.004*	-8.9	-1.7
50	SBP	121.8	9.6	125.5	9.6	-3.7	0.058	-7.5	0.1
	DBP	70.6	10.1	79.9	8.8	-9.2	<0.01*	-13.0	-5.5
60	SBP	121.0	8.2	126.1	10.0	-5.2	0.006*	-8.8	-1.5
	DBP	72.2	9.3	78.3	8.2	-6.1	0.001*	-9.6	-2.6
90	SBP	120.6	10.5	125.7	10.2	-5.1	0.016	-9.2	-1.0
	DBP	72.3	10.6	79.3	8.1	-7.0	<0.01*	-10.7	-3.2
120	SBP	122.0	10.2	125.1	9.3	-3.1	0.113	-7.0	0.8
	DBP	74.1	11.4	78.7	7.8	-4.6	0.021*	-8.5	-0.7
150	SBP	122.0	8.9	124.3	8.7	-2.3	0.198	-5.8	1.2
	DBP	74.4	9.8	78.7	6.5	-4.3	0.011*	-7.6	-1.0
180	SBP	122.1	8.9	122.7	9.3	-0.6	0.726	-4.3	3.0
	DBP	74.3	9.8	78.7	6.4	-4.4	0.009*	-7.7	-1.1

Note: *statistically significant difference at 5% level of significance

Figure12 : Comparison of Means of Systolic Blood Pressure in two study groups by different time (Min)

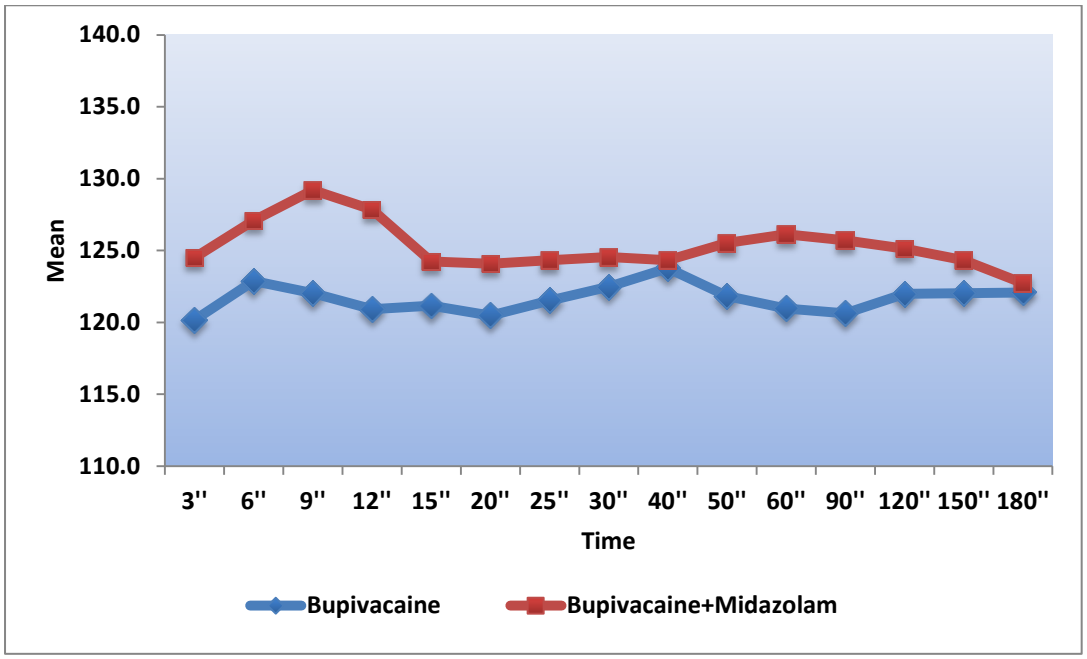


Figure 13: Comparison of Means of Diastolic Blood Pressure in two study groups by different time (Min)

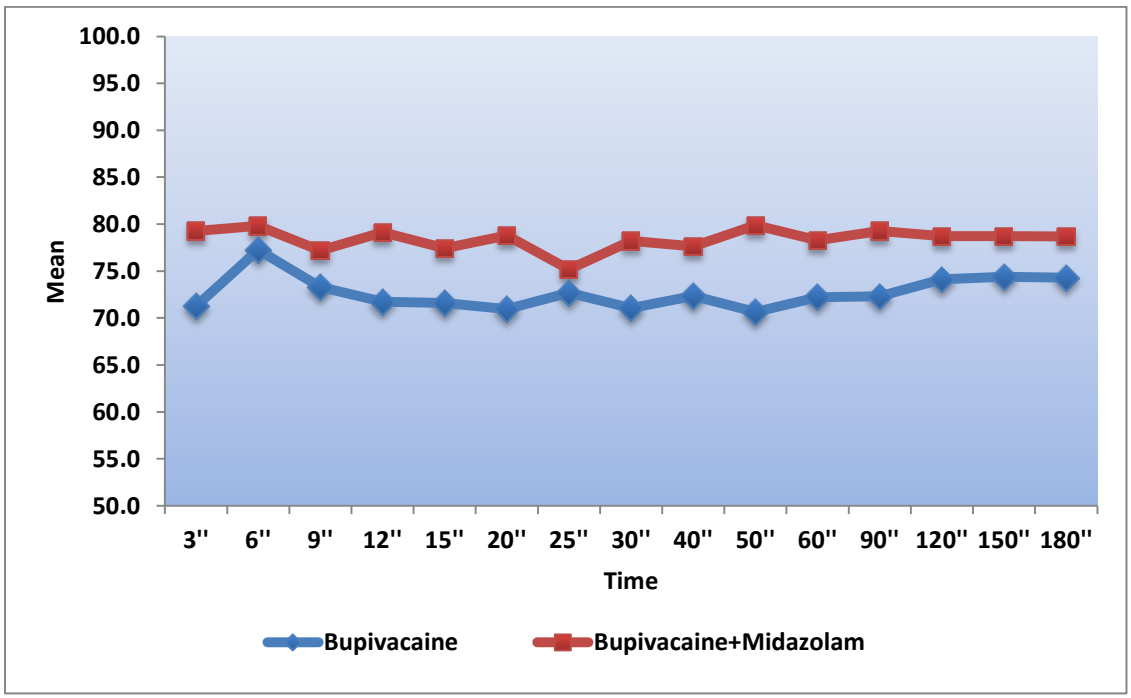


Table 7: Comparison of Means of Oxygen Saturation in two study groups by different time (Min)

Time	Bupivacaine		Bupivacaine+ Midazolam		Mean Difference	p value	95% Confidence Interval	
	Mean	SD	Mean	SD			Lower	Upper
3	98.1	0.8	98.8	0.4	-0.7	<0.01*	-0.9	-0.4
6	98.3	1.7	98.8	0.4	-0.6	0.027*	-1.1	-0.1
9	98.7	0.6	98.8	0.4	-0.1	0.217	-0.3	0.1
12	98.7	0.5	98.9	0.4	-0.1	0.160	-0.3	0.0
15	98.8	0.5	98.9	0.3	-0.1	0.112	-0.3	0.0
20	98.9	0.5	98.9	0.3	0.0	0.801	-0.2	0.1
25	98.9	0.3	99.0	0.0	-0.1	0.042*	-0.2	0.0
30	98.8	0.5	98.9	0.3	-0.1	0.112	-0.3	0.0
40	98.7	0.4	98.9	0.3	17.7	0.323	-17.7	53.0
50	98.7	0.5	98.8	0.4	-0.1	0.239	-0.3	0.1
60	98.8	0.5	98.9	0.3	17.7	0.323	-17.6	53.0
90	98.7	0.6	98.9	0.3	-0.2	0.012*	-0.4	-0.1
120	98.7	0.5	98.9	0.2	-0.3	0.001*	-0.4	-0.1
180	98.7	0.5	98.9	0.3	-0.2	0.005*	-0.4	-0.1

*statistically significant difference at 5% level of significance

Figure 14: Comparison of Means of Oxygen Saturation in two study groups by different time (Min)

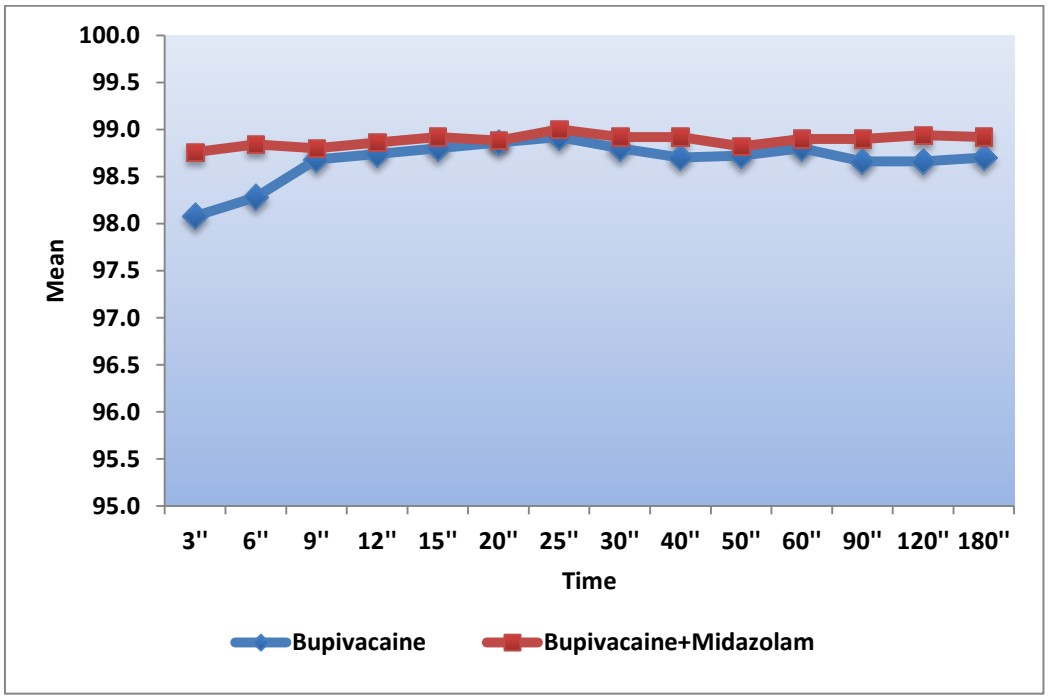
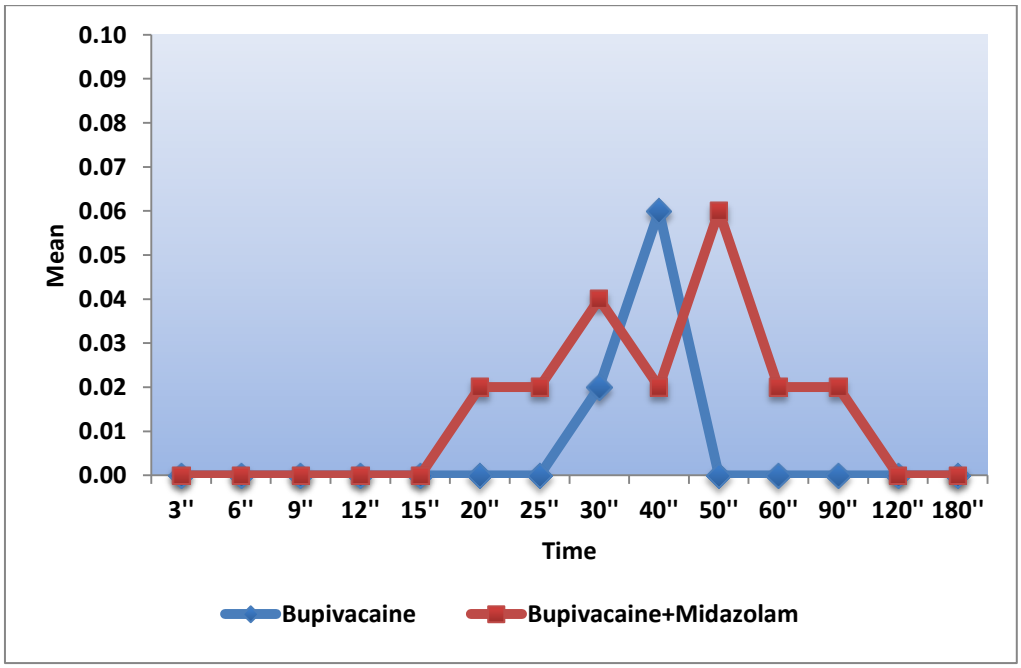


Table 8 : Comparison of Means of Sedation Score in two study groups by different time (Min)

Time	Bupivacaine		Bupivacaine+ Midazolam		Mean Difference	p value	95% Confidence Interval	
	Mean	SD	Mean	SD			Lower	Upper
3	0.0	0.0	0.0	0.0	-	-	-	-
6	0.0	0.0	0.0	0.0	-	-	-	-
9	0.0	0.0	0.0	0.0	-	-	-	-
12	0.0	0.0	0.0	0.0	-	-	-	-
15	0.0	0.0	0.0	0.0	-	-	-	-
20	0.0	0.0	0.0	0.1	0.0	0.320	-0.1	0.0
25	0.0	0.0	0.0	0.1	0.0	0.320	-0.1	0.0
30	0.0	0.1	0.0	0.2	0.0	0.562	-0.1	0.0
40	0.1	0.2	0.0	0.1	0.0	0.312	0.0	0.1
50	0.0	0.0	0.1	0.2	-0.1	0.080	-0.1	0.0
60	0.0	0.0	0.0	0.1	0.0	0.320	-0.1	0.0
90	0.0	0.0	0.0	0.1	0.0	0.320	-0.1	0.0
120	0.0	0.0	0.0	0.0	-	-	-	-
180	0.0	0.0	0.0	0.0	-	-	-	-

Figure15: Comparison of Means of Sedation Score in two study groups by different time (Min)



The difference between the groups was insignificant (P>0.32)

Table 9: Comparison of Onset of Sensory Block (Sec) between two study groups

ONSET OFSENSORY BLOCK (SEC)	Bupivacaine		Bupivacaine+Midazolam		Mean Difference	p value
	Mean	SD	Mean	SD		
	153.2	8.2	173.0	5.8	-19.8	<0.001*

*statistically significant difference at 5% level of significance

FIGURE 16: ONSET OF SENSORY BLOCKADE

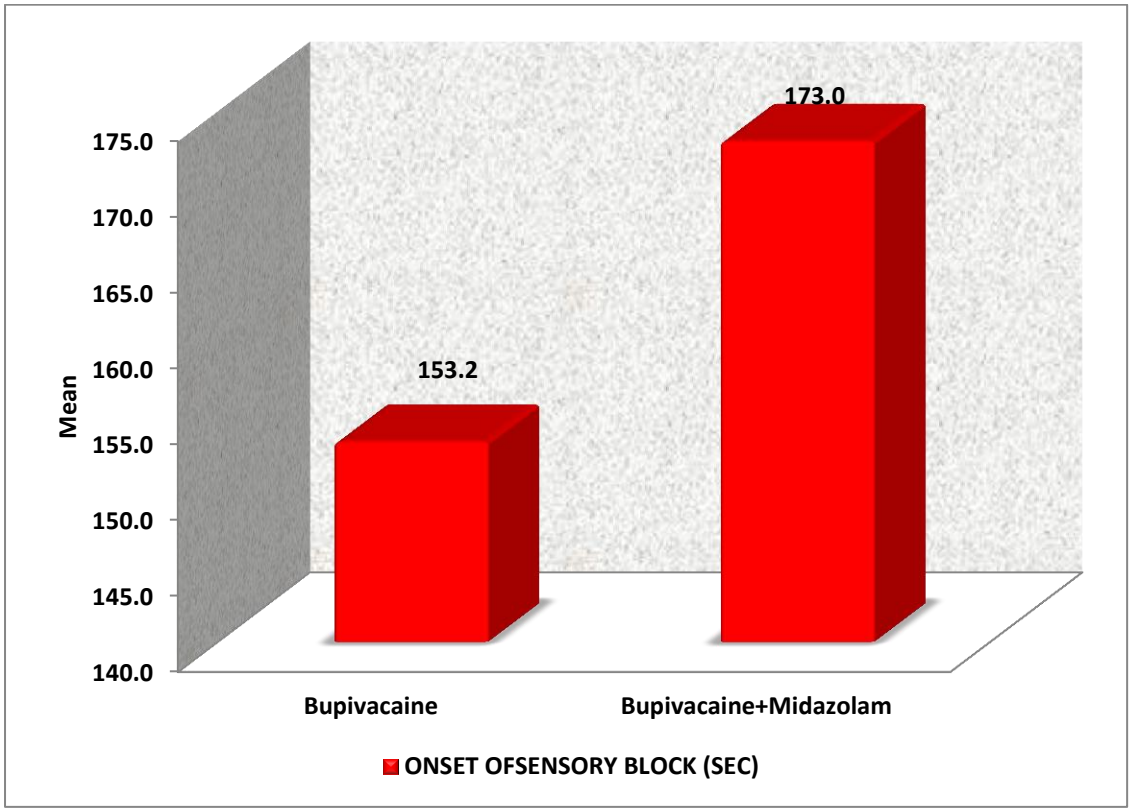


Table 10: Comparison of Onset of Motor Block (Sec) between two study groups

ONSET OF MOTOR BLOCKADE (SEC)	Bupivacaine		Bupivacaine+Midazolam		Mean Difference	p value
	Mean	SD	Mean	SD		
	220.4	7.3	240.4	4.6	-20.0	<0.001 *

*statistically significant difference at 5% level of significance

FIGURE 17: ONSET OF MOTOR BLOCKADE

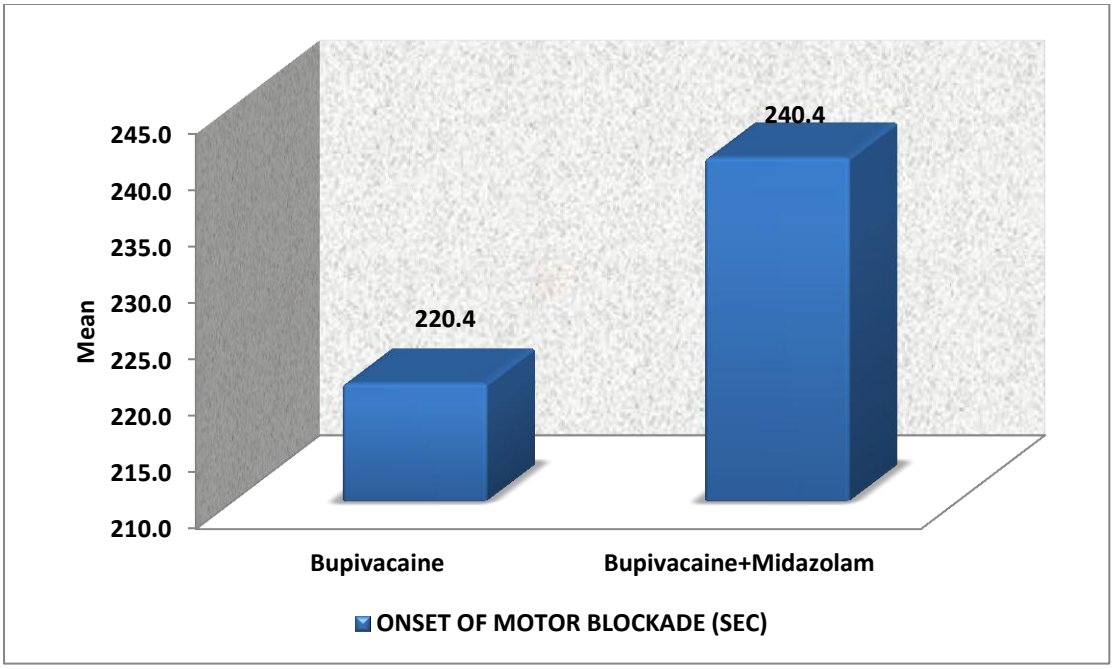


Table 11: Comparison of Two Segment Regression (Min) between two study groups

TWO SEGMENT REGRESSION (min)	Bupivacaine		Bupivacaine+Midazolam		Mean Difference	p value
	Mean	SD	Mean	SD		
	87.2	3.4	122.6	3.6	-35.4	<0.001 *

FIGURE 18: TWO SEGMENT REGRESSION.

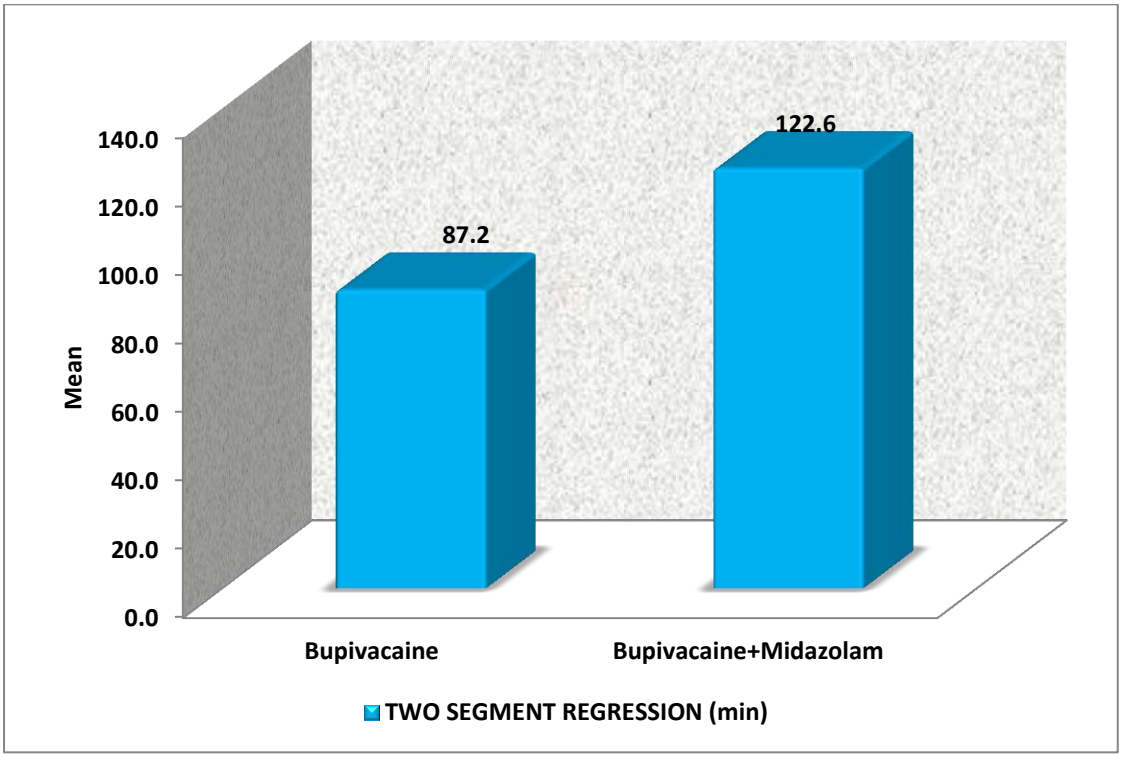


Table 12 : Comparison of Duration Of Analgesia (min) between two study groups

DURATION OF ANALGESIA (min)	Bupivacaine		Bupivacaine+Midazolam		Mean Difference	p value
	Mean	SD	Mean	SD		
	139.6	8.7	263.8	35.8	-124.2	<0.001 *

*statistically significant difference at 5% level of significance

FIGURE 19: DURATION OF ANALGESIA

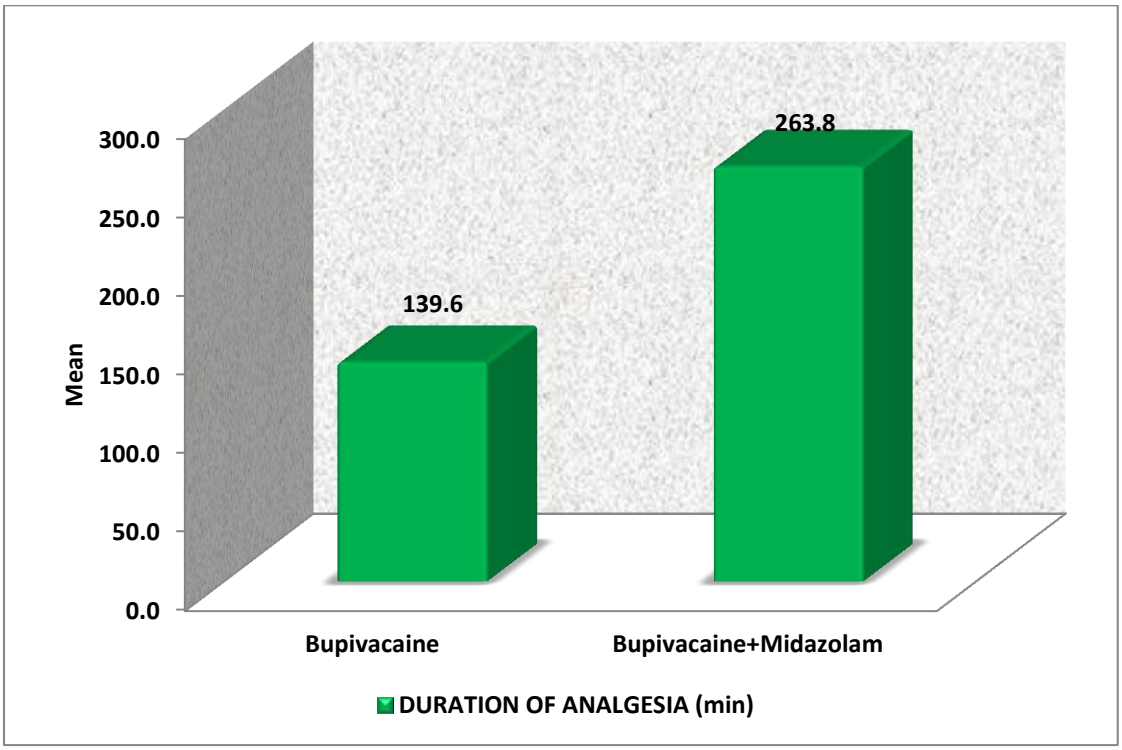
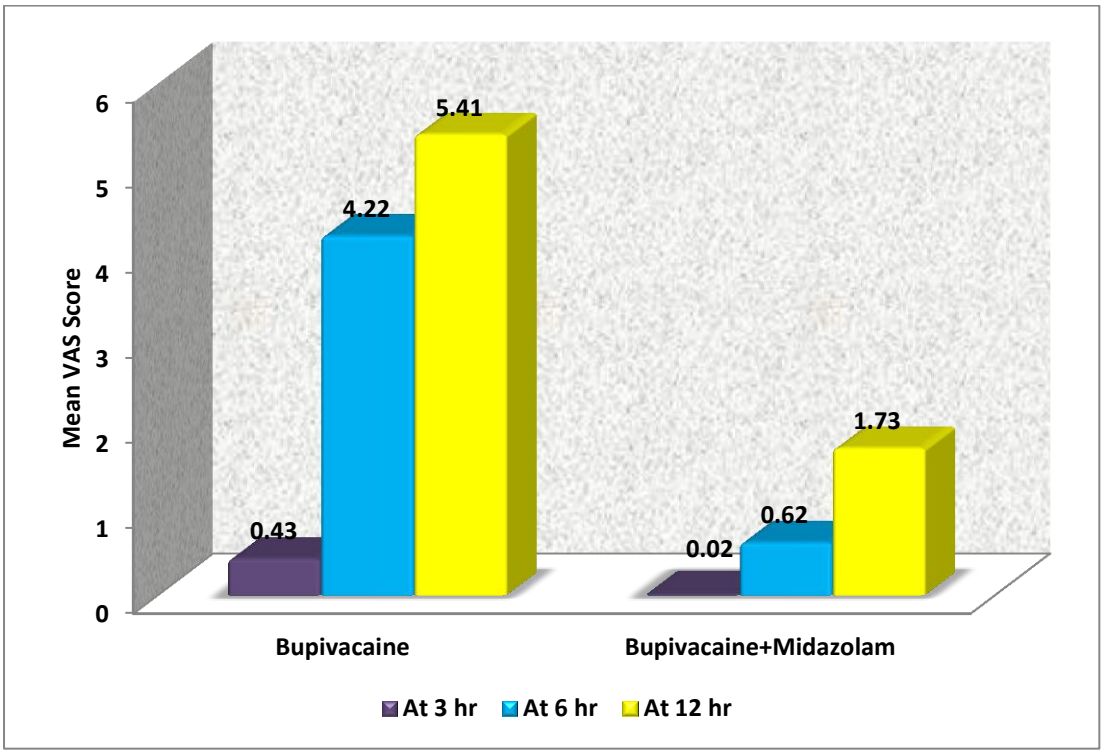


Table 13 : Comparison of Visual Analogue Scores at different time interval between two study groups

Time in hours	Bupivacaine		Bupivacaine+Midazolam		Mean Difference	p value
	Mean	SD	Mean	SD		
3	0.43	0.78	0.02	0.43	0.5	<0.001*
6	4.22	0.51	0.62	0.65	-19.8	<0.001*
12	5.41	0.42	1.73	0.56	-20.0	<0.001 *

FIGURE 20 : Visual Analogue Scale

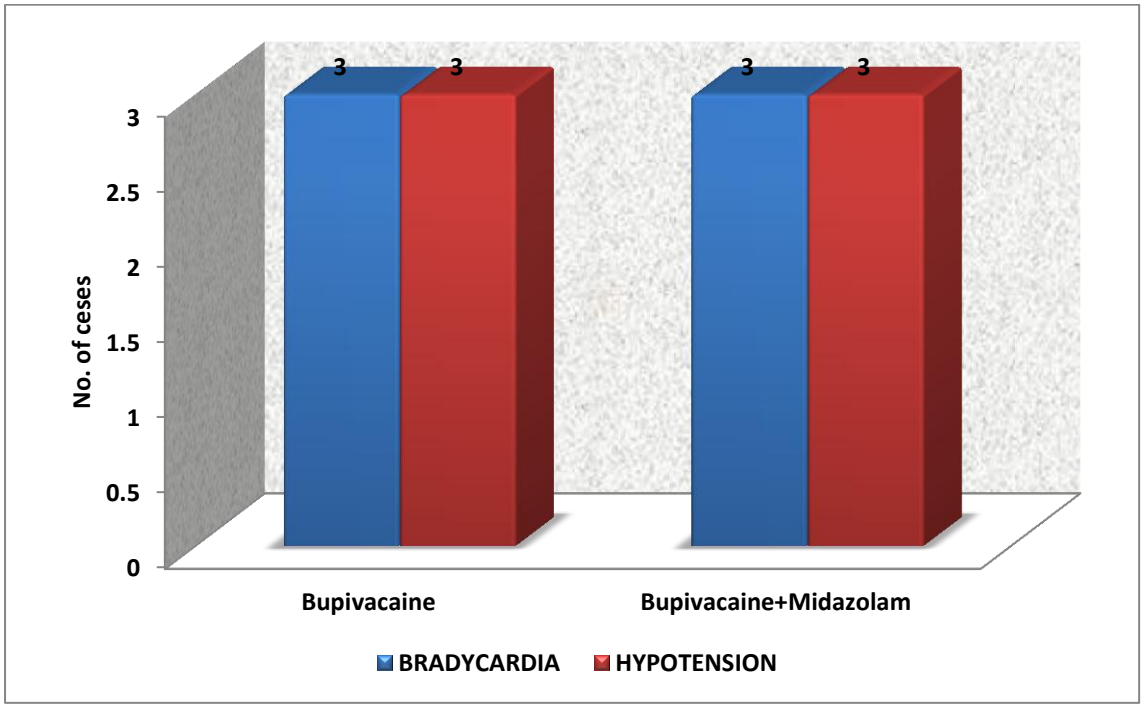


The difference between the groups was statistically highly significant.

Table 14 : Percent Distribution of Complications in two study groups

COMPLICATIONS	Bupivacaine		Bupivacaine+Midazolam		p value
	N	%	N	%	
BRADYCARDIA	3	50.0%	3	50.0%	0.999
HYPOTENSION	3	50.0%	3	50.0%	
Total	6	100.0%	6	100.0%	

Figure 21: Percent Distribution of Complications in two study groups



DISCUSSION

The subarachnoid blockade is the common form of centrineuraxial blockade performed for lower abdomen and lower limb surgeries. The ensuing nerve block ensures the patient wellbeing, while motor block facilitates the surgeon's work. Hyperbaric bupivacaine 0.5% produces longer duration of anaesthesia with good muscle relaxation. It provides effective pain relief in initial post-operative period.

In order to maximize postoperative analgesia, a number of adjuvants have been added to spinal local anaesthetics. Midazolam is a newer water soluble imidazo - benzodiazepine derivative which has been tried since early 1980's. It had been tried widely and antinociceptive effect with neurological safety had been well established in animals and humans.

The intrathecal benzodiazepine induced analgesia is spinally mediated. The binding sites benzodiazepine molecules are GABA receptors which are abundant in dorsal root nerve cells of spinal cord. The maximum concentration of GABA receptors are found within lamina II of dorsal nerve cells, a region which plays prominent role in processing nociceptive and thermoceptive stimulation. Acting over the GABA receptors benzodiazepines induce changes in chloride conductance and enhance GABA induced presynaptic inhibition of primary afferent terminals.

The present clinical study is a randomized clinical trial in 100 patients belonging to age group 20- 45 years of both the sexes and of ASA Grade I and II who were scheduled to undergo various elective lower abdomen and lower limb surgeries under subarachnoid anesthesia. The patient group B received 3ml of hyperbaric Bupivacaine0.5% with 0.2ml normal saline subarachnoid anesthesia. The patient group BM received 3ml of hyperbaric bupivacaine0.5% with 0.2ml (1mg preservative free) Midazolam intrathecally.

Patient characteristics across the groups:

The patients studied across the group did not vary much with respect to age, sex or height. The type of surgeries performed were almost identical in both the groups. These parameters were kept identical in both the groups to avoid variations in the intraoperative and postoperative outcome of the patients.

Changes in the perioperative cardiovascular parameters:

In the present study, the incidence of hypotension was equal in both groups with 3 patients had a fall in blood pressure in group-B and 3 patients in group-BM of the study. Hypotension was corrected by administration of injection Mephentermine 6mg IV in incremental doses, giving IV fluids and raising the foot end side of the operating table to facilitate venous return.

Heart rate, systolic and diastolic blood pressure in both the groups did not vary significantly.

In our study even though the statistical data for blood pressure was significant, but it is clinically not significant.

Goodchild CS, Noble J in 1987, Bahar M *et al* (1997), Batra Y.K *et al* in 1999 and Bharti N *et al* (2003) found no difference in the hemodynamic responses to the drugs used correlating with the present study.

From the above studies we can conclude that use of Midazolam 2 mg along with Bupivacaine causes no gross hemodynamic changes.

Changes in respiratory parameters:

None of the patients in the present study had respiratory depression Bahar M *et al*(1997) found no changes in the arterial blood gases or respiratory rate when given intrathecal midazolam in animal model.

Sen A *et al*(2001) observed that intrathecal Midazolam 2mg and 5% Lignocaine 1.5 ml produces better tranquility of patients of caesarian section delivery without much sedation and respiratory depression. Apgar score of baby in 1^{st} and 5^{th} minute of delivery was found to be normal.

Bharti N *et al* (2003) studied the effect of intrathecal 1mg of Midazolam with hyperbaric Bupivacaine in patients undergoing lower abdominal surgery and found no change in oxygen saturation.Not only Midazolam enhances the postoperative analgesia it also potentiates the analgesic effects of Fentanyl.

Sanaa M *et al* (2015) conducted Comparative study of intrathecal Midazolam versus Fentanyl as adjuvants to Ropivacaine for lower-limb surgery. They concluded Adding Midazolam to hyperbaric Ropivacaine in spinal anesthesia for lower-limb surgeries is considered a good alternative for improving the duration of sensory block and decreasing the analgesic requirement in the early postoperative period with minimal side effects compared with hyperbaric Ropivacaine alone or Fentanyl combined with hyperbaric Ropivacain.

Anshu Gupta *et al* (2016) conducted the study to know the efficacy of intrathecal Midazolam in potentiating the analgesic effect of intrathecal Fentanyl in patients undergoing lower limb surgery. They concluded intrathecal Midazolam potentiates the effect of intrathecal Fentanyl in terms of prolonged duration of analgesia and prolonged motor and sensory block without any significant hemodynamic compromise.

The above observations were similar to our study results. We conclude that intrathecal Midazolam 1mg is safe to use without causing respiratory depression.

Changes in the onset of sensory and motor blockade:

In the present study the onset of sensory blockade in group-B was 153.2± 8.2 seconds compared to 173.0 ± 5.8 seconds in group-BM which was statistically highly significant (P< 0.001). It shows that addition of Midazolam to local anesthetic delays the onset of analgesia. Similarly the onset of motor blockade in group-B was 220.4 ± 7.3 compared to 240.4 ± 4.6 seconds in group-BM which was also statistically highly significant (P< 0.001) i.e., the addition of Midazolam to local anesthetic delays the onset of motor blockade.

Yegin A *et al* (2004) have found in their study that addition of 2mg of Midazolam to hyperbaric Bupivacaine in spinal anesthesia does not delay onset of sensory and motor blockade compared to hyperbaric Bupivacaine alone in patients undergoing perianal surgery.

From the above study we conclude that there is variation in the onset of sensory and motor blockade in different studies. Though it is statistically significant in our study it does not have any clinical implications.

Time for two dermatomal segments regression of sensory level:

In the present study, the two segment regression of sensory level in group B was 87.50 ± 4.4 minutes compared to 122.00 ± 3.6 minutes in group-BM which was statistically highly significant (P<0.001). This shows that addition of Midazolam increases the duration of sensory blockade.

Bharti N *et al* (2003) found that duration of sensory block (ie. time to regression to S_2 segment) was significantly longer in the Midazolam group than the control group (218 min vs 165min, P< 0.001)

Venkatesh Selvaraj, Tapan Ray (2015) Studied Midazolam as an adjuvant to intrathecal Lignocaine: A prospective randomized control study Midazolam and found, an improved quality of sensory blockade in terms of early onset, increased duration of effective analgesia, and delayed two segment regression time and also decreases the incidence of TNS with intrathecal Lignocaine.

Thus we can conclude that intrathecal Midazolam increases the duration of sensory blockade.

Time of first request of analgesics

In the present study, the time of first request of analgesics in group-B was 139.00±8.77 minutes compared to 263.8±35.8 minutes in group-BM which was statistically highly significant ($P<0.001$). This shows that there was significantly longer period of analgesia with intrathecal Midazolam.

Valentine J.M. J *et al* (1996), Bharti N *et al* (2003), Shah FR *et al* (2003) found prolonged duration of postoperative pain relief in Midazolam group.

Thus we can conclude that intrathecal Midazolam along with Bupivacaine prolongs the duration of analgesia thus prolonging the first request of supplemental analgesics in the postoperative period.

Midazolam acts through the GABA receptors which are present in the dorsal horn of spinal cord. Administration of exogenous benzodiazepines in to the CSF around the spinal cord reached the GABA receptors in the high concentration and could have potentiated the effects of local anesthetics. Therefore, benzodiazepines can gain access to the analgesic system mediated by Gama amino butyric acid. GABA is synthesized from glutamate in the pre synaptic ending and it is generally inhibitory in effect. GABA on binding with $GABA_A$ receptor opens the ligand gate chloride

channels. Chloride conductance increased, leading to hyper polarization and presynaptic inhibition of afferent terminals in spinal cord. This results in less central propagation of action potentials carrying nociceptive stimuli information. Intrathecal Midazolam has been used in humans and the doses of 1 mg and 2 mg have been described to provide pain relief. Addition of Midazolam through epidural intrathecal infusion provides better analgesia, than local anaesthetics , which confirms by present study also[35]

Kim MH *et al* (2001) found significantly greater time to first analgesia in the Midazolam group in patients undergoing haemorrhoidectomy.

Amr M *et al* (2003)[33] showed the time required for first postoperative analgesic intake was prolonged when 25 µg preservative free Fentanyl or 2mg preservative free Midazolam is added to 0.5% heavy Bupivacaine in patients undergoing knee arthroscopy.

Yegin A *et al* (2004)[34] studied the effect of intrathecal Midazolam and hyperbaric Bupivacaine in comparison to hyperbaric Bupivacaine alone and found significantly longer time until the first dose of additional analgesic requirement in Midazolam group.

Visual Analogue Score:

In the present study, there is significant reduction in the visual analogue score of the patients in group-BM in comparison with higher VAS in group-B recorded at 3 hours, 6 hours and 12 hours of spinal anesthesia.

Shah FR *et al* in 2003 showed that patients treated with intrathecal Midazolam had better pain relief judged by visual analogue score on coughing ($P=0.0013$) and a nursing mobility score ($P<0.0001$).

Yegin A *et al* (2004) found significantly lower visual analogue pain scores in midazolam group at the first 4 hours.

Valentine J.M. J *et al* (1996), Sen A *et al* (2001), Bharti N *et al* (2003), Amr M *et al* (2003) found significantly decreased frequency of postoperative analgesic intake in those receiving intrathecal midazolam.

From the above studies we can conclude that intrathecal midazolam potentiates the sensory blockade of bupivacaine, thereby reduce the visual analogue scores in the early postoperative period bringing about better postoperative outcome.

Sedation Score.

The sedation score is assessed by scoring system of Chernic *et al* [36]

Table 15 :

SCORE	CHARECTERISTICS
1	AWAKE
2	DROWSY BUT AROUSABLE
3	DROWSY,BUT RESPONDING TO PHYSICAL STIMULUS
4	UNRESPONSIVE TO VERBAL/ PHYSICAL STIMULUS

In the present study the sedation score ranged from 0 to 1 in both the groups. Most of the patients in group B were calm and sleeping comfortably were as most of the patients in the group BM were awake and alert.

Nishiyama T (1995)[37] Midazolam is used in a variety of clinical setting for pre and postoperative settings for sedation. The studies of have shown that the sedation scores were higher in the patients receiving Midazolam the epidural or intrathecal route.

Vaswani *et al (*2002)[38] reported that sedation was earlier with maximum sedation level of short duration if Midazolam is given intravenously. The sedation scores were less but more sustained when the Midazolam is administered intrathecally. Anjana Sen *et al*[19] also reported the higher sedation scores with intrathecal Midazolam.

The results of present study are consistent with both the authors though the duration of the sedation in less. This may be because of different doses of the drug.

Adverse Effects:

In the present study, 3 patients had hypotension, 1 patient had shivering and nausea vomiting in group-BM compared to 3 patients of hypotension, 2 patients of shivering and 1 patient of nausea vomiting in group-B. This signifies that adverse effects are minimal with intrathecal Midazolam.

Erdine S *et al* (1999)[39] conducted neurotoxicologic animal studies and showed neurotoxic effects of Midazolam by studying histologic and vascular lesions in spinal cord and recommended for avoidance of intrathecal Midazolam in humans.

Subsequent studies in humans by valentine JMJ *et al*(1999), Sen A *et al* (2001), Bharti N *et al* (2003), Shah FR *et al* (2003), Amr M *et al* (2003), Tucker AP *et al* (2004), Yegin A *et al* (2004) found no adverse neurological symptoms in those received intrathecal Midazolam. They also found that intrathecal Midazolam has mild sedative and antiemetic effect.

With all the above observations we conclude that addition of Midazolam to Bupivacaine provides prolonged analgesia, superior pain relief and better sedation with minimal side effects compared to Bupivacaine alone in spinal anesthesia.

CONCLUSION

In the present study, the sensory and motor characteristics of 3ml hyperbaric Bupivacaine0.5% alone and 3ml hyperbaric Bupivacaine 0.5% with 1mg of intrathecal Midazolam were studied.

The results of the present study suggests that the combination of inj.Midazolam1mg with inj. Bupivacaine 0.5% (hyperbaric),

- Superior quality of analgesia
- Prolongs the duration of analgesics.
- Does not associated with any significant hemodynamic changes
- Does not increases the incidence of complications such as bradycardia, drowsiness, hypotension, postoperative nausea and vomiting, and neurotoxicity.
- Reduced postoperative analgesic requirements.

SUMMARY

The study was conducted to compare the effect of intrathecal hyperbaric Bupivacaine 0.5% and hyperbaric Bupivacaine 0.5% with Midazolam 1 mg in lower abdominal and lower limb surgeries.

One hundred patients belonging to American Society of Anesthesiologists (ASA) classification I & II, aged between 20-45 years, posted for elective lower abdominal and lower limb surgeries were randomly allocated for the study.

Group-B: Fifty patients received intrathecal hyperbaric Bupivacaine 0.5 only.

Group-BM : Fifty patients received intrathecal hyperbaric Bupivacaine 0.5% and Midazolam 1mg.

The patients studied across the group did not vary much with respect to age, sex or height.

The onset of sensory blockade was delayed by about 20 seconds in group-BM and the onset of motor blockade was delayed by about 20-25 seconds in group-BM compared to group-B.

The time for two dermatomal segments regression of sensory level was prolonged in group-BM compared to group-I and also time for regression of sensory level to L_2 dermatome was prolonged in group-BM compared to group-B thus increasing the duration of analgesia.

The time of first request of analgesics by the patients in group-BM is prolonged compared to group-B thus prolonging the duration of analgesia.

Visual analogue scores were significantly lower in group-BM compared to group-B thus reducing the frequency of supplemental postoperative analgesics.

The adverse effects observed in the study were minimal.

With the present study we can summarize that intrathecal Midazolam potentiates Bupivacaine thereby bringing about better quality and longer duration of analgesia, better sedation, and better postoperative outcome with minimum side effects.

BIBILOGRAPHY

1. Ramkumar V, Prasad KN. Management of post-operative pain. *Indian j anaesth* 2006;50:345-54.
2. Agarwal N, Usmani A, Sehgal R, Rakesh K, Bhadoria P. Effect of intrathecal midazolam bupivacaine combination on postoperative analgesia. *Indian J anaesth* 2005;49:37-9.
3. Whitwam DN, Loh L. Depression of nociceptive sympathetic reflexes by intrathecal administration of Midazolam. *Br J Anaesthe* 1983;55:541-546.
4. Goodchild CS, Noble J. The effect of intrathecal Midazolam sympathetic nervous system reflexes in man-A pilot study. *J clin pharmacol* 1987;23(3):279-85.
5. Maged L. Boules, Josepph M, Botros Comparative study between the effect of intrathecal midazolam versus intrathecal midazolam plus magnesium sulfate on the effi cacy and duration of analgesia in patientsundergoing cesarean section. *Ain-Shams Journal of Anesthesiology* 2015, 08:70–75.
6. Riham S, Ebieda, Mohamed Z. Alia, Maged L, Boulesb, Yasser M. Samhana Does intrathecal midazolam improve hyperbaric bupivacaine fentanyl anesthesia in elderly patients? *Ain-Shams Journal of Anesthesiology* 2015, 08:602–607.
7. Venkatesh Selvaraj, Tapan Ray Midazolam as an adjuvant to intrathecal lignocaine: A prospective randomized control study. *Saudi Journal of Anesthesia* 2015; 4:393-396.
8. Anshu Gupta, Hemlata Kamat1, Utpala KharodEfficacy of intrathecal midazolam in potentiating the analgesic effect of intrathecal fentanyl in

patients undergoing lower limb surgery. *Anesthesia: Essays and Researches;* 9(3); Sep-Dec 2015.

9. Chattopadhyay A, Maitra S, Sen S, Bhattacharjee S, Layek A, Pal S *et al*. Study to compare the analgesic efficacy of intrathecal bupivacaine alone with intrathecal bupivacaine midazolam combination in patients undergoing elective infraumbilical surgeries. *Anesthesiol Res Pract* 2013;1-5.
10. .Kulkarni M, Kurdi M, Itagimath S, Sujatha D, Muralidhar M. The role of intrathecal midazolam as an adjunct to bupivacaine in providing post-operative pain relief. *International Journal of Health and Allied Sciences* 2012;1(4):231.
11. Joshi S, Subhedar R, Motghare V, Khadke V, Patil A. Comparative evaluation of intrathecal midazolam and low dose clonidine: Efficacy, safety and duration of analgesia. A randomized, double blind, prospective clinical trial. *Indian J Pharmacol* 2012;44(3):357-61.
12. Shadangi BK, Garg R, Pandey R, Das T. Effects of intrathecal midazolam in spinal anaesthesia: a prospective randomized case control study. *Singapore Med J 2011;52*(6):432.
13. Prakash S, Joshi N, Gogia AR, Prakash S, Singh R. Analgesic efficacy of two doses of intrathecal midazolam with bupivacaine in patients undergoing cesarean delivery. *Regional Anesthesia & Pain Medicine* 2006;31(3):221-6.
14. Nidhi Agarwal, Usmani A, Sehgal R, Rakesh Kumar and Poonam Bhadoria2005: "Effect of intrathecal midazolam bupivacaine combination on post operative analgesia". *Indian J Anaesth*: 49(1): 37-39.
15. Tucker AP, Lai C, Goodchild CS. Intrathecal Midazolam II: combination with intrathecal fentanyl for labor pain. *Anesth Analg* 2004;98:1521–7.

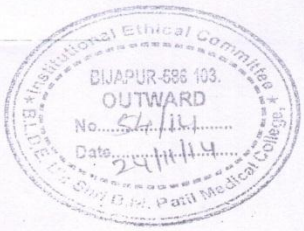
16. Bharti N, Madan R, Mohanty PR, Kaul HL. Intrathecal Midazolam added to Bupivacaine improve the duration and quality of spinal anaesthesia. *Acta Anaesthesiol Scand* 2003;47(9):1101-5.
17. Shah FR, Halbe AR, Panchal ID, Goodchild CS. Improvement in postoperative pain relief by the addition of Midazolam to an intrathecal injection of Buprinorphine and Bupivacaine. *Eur J Anaesthesiol* 2003;20(11):904-10.
18. D. Bhattacharya, B Biswas, A.Banergy 2002: "Intrathecal midazolam with bipivacaine increases the analgesic effect of spinal blockade after major gyenaecological surgery". *J. Anaesth Clin Pharmacol* 18(2): 183-86.
19. Anjana Sen, A.Rudra, santhosh Kumar Sarkar, B Biswas 2001: "Intrathecal Midazolam for Postoperative Pain Relief in Caesarian Section Delivary*" J Indian med Assoc*, 99(12): 683-86.
20. Batra YK, Jain K, Chari P, Dillon MS, Shaheen B, Reddy GM. Addition of intrathecal Midazolam to Bupivacaine produces better postoperative analgesia without prolonging recovery. *Int. J. Clin Pharmacol. Ther*. 1999;(37):519-23.
21. Bahar M, Cohen ML, Grinshopon Y, Chanimov M. Spinal anaesthesia with Midazolam in the rat. *Can J. Anaeshes* 1997;44(2):208-15.
22. Valentine JMJ, Lyons G, Bellamy MC. The intrathecal Midazolam on post-operative pain. *Eur J Anaesthesiolgy* 1996;13(6):589-93.
23. C.S Good Child, Z Guo A Musgreave and J.P Gent 1996: "Antinociception by intrathecal midazolam involves endogenous neurotransmitters acting at spinal cord delta opioid receptors*" Br J Anaesth*, 77: 758-763.

24. Edwardi M, Serrao JM, Gent JP, Goodchild CS. On the mechanism by which midazolam causes spinally mediated analgesia. *Anesthesiology* 1990 Aug; 73(2): 273-7.
25. Goodchild CS, Serrao JM. Intrathecal midazolam in the rat: Evidence for spinally mediated analgesia. *Br. J. Anesth*. 1987 Dec; 59(12): 1563-70.
26. Michael J Cousins, Phillip O Briendenbaugh: chapter 7 in "Spinal, Subarachnoid and Neural Blockade" chapter 7 in Neural Blockade in Clinical *Anaesthesia and management of pain*, 1st edition, J.B Lippincott company, Philadelphia, United states America, 1980:151-59.
27. Prithviraj P. *Spinal anesthesia* in: Clinical practice of regional anesthesia, 1st Edition, Vol. 2, Churchill Livingstone, 1991.
28. Longnecker DE, Tinker JH, Morgan GE. Spinal anesthesia in: Principles and *Practice of Anaesthesiology*, 2nd Edition, Vol. 2, St. Louis, Missouri, Mosby, 1998
29. .Aitkenhead AR, Rowbotham DJ, Smith G. *Central Nerve Blocks*, in: Textbook of Anaesthesia, 4th Edition, Eidnburg, Churchill Livingstone, 2001
30. Vincent J Collins: *"Local Anaesthetics*" Chapter 42 in Principles of Anaesthesiology general and regional anaesthesia, 3rd edition, Lea and Febiger USA, 1993;1233-1281
31. Reeves J.G, Robert J Fragen, Ronald Vinik H, David Greenblatt J, "Midazolam: Pharmacology and uses". Anaesthesiology 1985; 62:310-324.
32. Loeser JD, Butler SH, Chapman CR, Turk DC. Measurement of pain 'Bonica's Management of Pain, 3rd Edition, Philadelphia, Lippincott Williams & Wilkins.

33. Amr M Abdelfatah, Ahmed A Fawaz, Hesham M Al-Azazi. The postoperative analgesic effect of intrathecal fentanyl versus midazolam in knee arthroscopy. *Eng. J. Anaesth*. 2003; 19: 173-177.
34. Yegin A, Sanli S, Dosemeci L, Kayacan N, Akbas M, Karsli B. The analgesic and sedative effects of intrathecal midazolam in perianal surgery. *Eur J Anaesthesiol*. 2004 Aug; 21(8): 658-62.
35. A Sen, A Rudra 2002; " Intrathecal Midazolam to Prevent Nausea-Vomiting During Caesarean Delivary with Spinal Anaesthesia". *J.Anaesth. Clin. Pharmacol*18(1); 21-25.
36. Chernic DA, Gilling D, Laine H et al 1990; "validity and liability of observer's assessment of alertness and sedation scale; Study with intravenous midazolam. *J Clin Physicol Pharmacol* 10; 244-257.
37. Nishiyama T 1995; " The postoperative analgesic action of midazolam following epidural administration"; *Eur J Anaesth* 12(4): 369-374.
38. RK Vaswani, Lalit Kumar Raiger, Richa Purohit and Pramila Bajaj 2002; "The Effect of Intrathecal Midazolam on Postoperative Pain Relief in Orthopaedic Surgery. *Hospitals Today*. Vol 4: 150-153.
39. Erdine S, Yucel A, Ozyalcin S, Ozyuvaci E, Talu GK, Ahiskali B et al. Neurotoxicity of midazolam in the rabbit. Pain 1999 Mar; 80(1-2): 419-23.

ANNEXURES

ETHICAL CLEARANCE CERTIFICATE



B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 22-11-2014 at 3-30 pm. to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.

Title "A Comparative Study of Intrathecal Bupivacaine and Bupivacaine with Midazolam in Lower Abdominal and Lower Limb Surgeries."

Name of P.G. student Dr. Abhishek M. Patil
Dept of Anaesthesiology

Name of Guide/Co-investigator Dr Vijay. V. Katti Asso Professor.
Dept of Anaesthesiology

for

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

CONSENT FORM

CONFIDENTIALITY:

I understand that medical information produced by this study will become a part of this hospital records and will be subjected to the confidentiality and privacy regulation of this hospital. Information of a sensitive, personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code key connecting name to numbers will be kept in a separate secure location.

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

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. **Dr. ABHISHEK.M.PATIL** is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

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

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

REFUSAL OR WITHDRAWL OF PARTICIPATION:

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

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

INJURY STATEMENT:

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

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

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

Date: Dr. VIJAY V.KATTI Dr. ABHISHEK.M.PATIL

(Guide) (Investigator)

STUDY SUBJECT CONSENT STATEMENT:

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

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

_____ _____

(Participant) Date

_____ _____

(Witness to above signature) Date

PROFORMA

Patient Name : I.P. No:

Age : Weight:

Height : Gender:

Date of Operation: Occupation:

Address : Anaesthesiologist:

PRE-ANAESTHETIC EVALUATION :

Chief Complaints:

Past History-

a. HTN / DM / Asthma / Epilepsy / Drug allergy

b. Drug therapy

c. Previous exposure to anaesthesia

Family history

General Physical Examination

Pallor / Icterus / Clubbing / Lymphadenopathy / Edema

PR: BP:

RR:

Musculoskeletal disorders

Jaw movements: Teeth:

Airway assessment: Spine:

Systemic examination

RS: CNS:

CVS: GIT:

Investigations:

Hb%: Total count:

Differential count: Bleeding time:

Clotting time:

Urine routine:

Others:

Preoperative physical status: ASA Grade I II

Diagnosis:

Proposed surgery:

Pre-operative baseline:

Heart rate: **pulse rate:**

Monitors attached

Pulse Oximeter: YES/NO Non invasive blood pressure: YES/NO

ECG: YES/NO

1. Group: Group B / Group BM

2. Vital parameters

Time (Min)	Heart rate	Blood pressure	SPO_2
3			
6			
9			
12			
15			
20			
25			
30			
40			
50			
60			
90			
120			
150			
180			
End of surgery			

3.

Time of drug injection in MIN	Sensory block	Motor block	Maximum dermatomal level achieved
0			
5			
10			
15			
20			
25			
30			

4. Sedation score table

Time(Min)	Sedation score
15	
30	
45	
60	
75	
90	
105	
120	
End of surgery	

5. Time to two segment regression (min) :

6. Time for rescue analgesia (hours) :

ANY COMPLICATION DURING THE OPERATIVE PROCEDURE:

a) Nausea and vomiting : YES/ NO

b) Neurological sequeale : YES/ NO

c) Sedation and dizziness : YES/ NO

d) Hypotension : YES/ NO

e) Bromage index

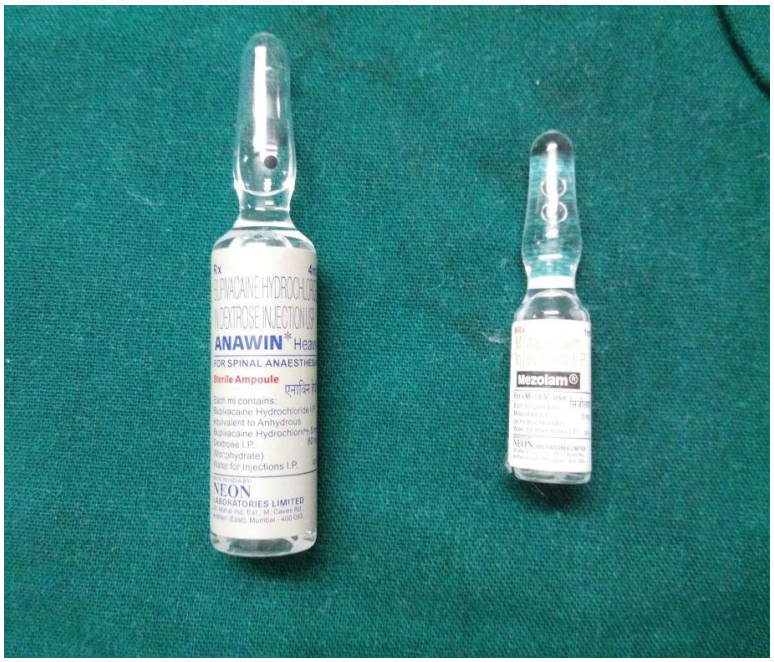
Grade-I No block: Full-flexion of knees and ankle joint possible

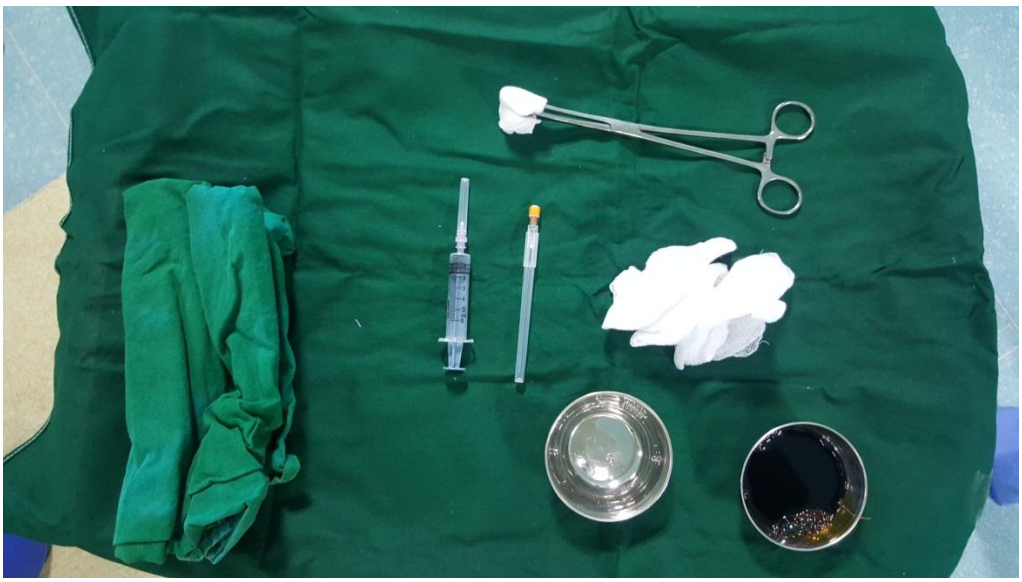
Grade-II Partial block: Just able to flex knees, but still full flexion of ankle joint possible

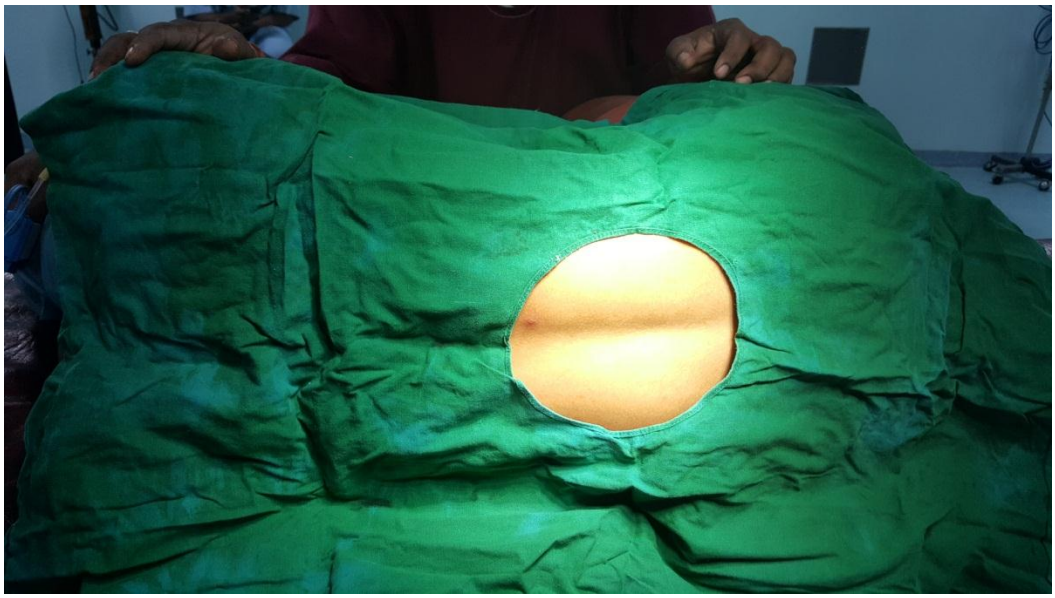
Grade-III Almost complete block: Unable to flex knees. Flexion of ankle joint possible.

Grade-IV Complete block: Unable to flex Knees or ankle joint

PHOTO GRAPHS







KEY TO MASTER CHART

S/L no-……Serial number

I/P No-……Indoor patient number

ASA……American Society of Anesthesia

M/L…….Maximum Level

OMB……...Onset Of Motor Blockade

OSB……Onset of Sensory Blockade

TSR…….Two Segment Regression

DA……..Duration of Analgesia

MIN……Minute

SEC……Seconds

VAS……...Visual Analogue score

%.....Percent

HYPO…….. Hypotension

BRAD…….. Bradycardia

CMP……..Complication