

“A Prospective Randomised Comparative Study Of 0.5% Heavy Bupivacaine 15mg With 0.9% Saline AND 0.5% Heavy Bupivacaine 15mg WITH 2mg Midazolam Intrathecally in Lower Abdominal Surgeries and Lower Limb Surgeries”

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ABSTRACT-

BACKGROUND-spinal anaesthesia using local anaesthetics is a common procedure for surgeries below the umbilical level and some time adding additives to get some additional effects is also common in spinal anaesthesia.

AIMS&OBJECTIVES-Our aim is to assess the analgesic effect, sedation and to note the enhancement of postoperative analgesia by the use of a benzodiazepine like Midazolam as an adjuvant to local anaesthetic – 0.5% hyperbaric Bupivacaine and also to assess any another benefits and adverse effects ov intrathecal Midazolam.

METHODOLOGY-It is a randomized prospective study ,done in hundred patients ,where fifty patients were given 0.5% heavy Bupivacaine 15mg with 0.9%saline and in another fifty patients 0.5% heavy Bupivacaine with 2mg and comparing the effect of the addition of Midazolam to Bupivacaine to increase the analgesic effects of the spinal blockade in patients undergoing lower abdominal and lower limb surgeries done in the Department of Anaesthesiology at Sri Venkateswara Ram Narayana Ruya Government General Hospital ,Tirupathi.

RESULTS- The present study was conducted on 100 patients of either sex in the age group between 18-60 years belonging to ASA Grade I and II. These patients were posted for elective lower abdominal and lower limb surgeries.The patients were divided into two groups of fifty each. Group -A - received 0.5% hyperbaric bupivacaine 3ml + 0.4ml 0.9% normal saline Group -B - received 0.5% hyperbaric bupivacaine 3ml + 0.4ml preservative free Midazolam (2mg). The following parameters were compared between the 2 groups. Time of onset of sensory block,The maximum level of blockade, Duration of sensory block, The onset of motor blockade,Duration of analgesia,Time of first voiding as a measure of sympathetic recovery, The incidence of the complications was also compared between two groups.The present study across the group did not vary much with respect to age,sex, and duration of surgery.

CONCLUSION- The onset of the sensory blockade and motor blockade was faster with the addition of midazolam to bupivacaine as compared to bupivacaine. The mean time of two segment regression, mean time of voiding is prolonged in Midazolam group as compared to Group -A,The mean time of postoperative analgesia was significantly prolonged with the addition of 2mg midazolam to bupivacaine.

KEYWORDS- SA-Spinal Anaesthesia ,PONV-Postoperative nausea &vomiting,GABA-Gamma Amino Butyric Acid. CSF -Cerebrospinal fluid

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I. Introduction

Spinal anaesthesia is a method of regional anesthesia that will perform by blocking the nerves at root level in intrathecal space for lower limb surgeries. The main reasons for the popularity of spinal block are that the block has well-defined endpoints and the anesthesiologist can produce the blocks reliably with a single injection¹. Spinal anaesthesia with hyperbaric bupivacaine 0.5% is a popular method. Instead, 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 and to know the incidence of adverse effects and complications when midazolam is given along with bupivacaine intrathecally.

II. Aims & Objectives

Our aims&objectives are- To determine the clinical advantages of sub-arachnoid administration of Midazolam to qualitative regional blocks with Bupivacaine with regard to the provision of adequate intra-operative analgesia in lower limb and lower abdominal surgeries.

&To assess the analgesic effect, sedation and to note the enhancement of postoperative analgesia by the use of a benzodiazepine like Midazolam as an adjuvant to local anaesthetic – 0.5% hyperbaric Bupivacaine&To study the other added benefits of using Midazolam as an adjuvant.

III. Materials And Methods

A clinical study comparing the effect of the addition of Midazolam to Bupivacaine to increase the analgesic effects of the spinal blockade in patients undergoing lower abdominal and lower limb surgeries done in the Department of Anaesthesiology at Sri Venkateswara Ram Narayana Ruya Government General Hospital ,Tirupathi. The study was undertaken after obtaining Hospital Ethics Committee clearance as well as written, informed consent from all patients after explaining and reassuring about the spinal procedure. A hundred patients posted for various elective lower limb and lower abdominal surgeries were studied in a randomized prospective manner.

Inclusion criteria-Patients between the age 18 – 55 years of both sexes , Patients belonging to American Society of Anesthesiologists physical status I/II , Patients posted for elective lower limb and lower abdominal surgeries.

Exclusion Criteria

Patients with a history of known sensitivity to the drugs used. Patients with gross spinal deformity, peripheral neuropathy or had any contraindication to neuraxial block - local / Systemic infections, coagulation disorders, hypovolemia, signs of raised intracranial tension, uncontrolled hypertension.

Pre-anaesthetic Evaluation A thorough pre-anaesthetic evaluation with general physical and systemic examination was done the evening before the proposed surgery. General examination included recording pulse rate, blood pressure, airway assessment, examination of the respiratory and cardiovascular systems, spinal deformities and local infection at the lumbar puncture site.

Following investigations were carried out in all patients: Complete Blood Picture, Hemoglobin % , Bleeding and Clotting time Random or fasting blood sugar , Blood urea , Serum Creatinine ,Urine analysis for albumin, sugar and microscopy ,Electrocardiogram and Chest X-ray as and when required

All the patients were graded according to the American Society of Anesthesiologists classification. After explaining the anaesthetic procedure to the patient, informed written consent was taken to include them in the study. All patients have prescribed 0.5 mg of Alprazolam and Ranitidine 150mg orally the previous night. Patients were advised to be nil orally from 10 pm onwards on the previous day of surgery. On the day of surgery, intravenous access was secured with 18 gauge venous cannula for fluid administration before the block. NIBP, ECG, Pulse oximeter monitors were connected & baseline pulse rate, blood pressure, ECG, respiratory rate and SPO2 were recorded.

Patients were randomly allocated to 2 groups. All blocks were performed by the person conducting the study. All patients were given 500ml of Ringer's lactate or Isotonic saline before performing the spinal anaesthesia.

Technique

A lumbar subarachnoid block was performed under strict aseptic precautions with the patient in the right lateral position with a pillow under the head and the table flat or, in the sitting position, when the patient could not be placed in the lateral position. Lumbar tap was made in the L3-4 inter-space, midline approach, using 23 Gauge Quincke needle, after local infiltration of skin using 2% Xylocaine. After obtaining a clear flow of CSF, the drug was injected slowly, after negative aspiration for blood. 0.4ml of Midazolam and 0.4ml of 0.9% normal saline were measured using Insulin syringe. Patients were made to lie supine immediately after the completion of the injection. The time of injection of the drug was recorded as 0 minutes. During surgery, all patients were given intravenous fluids-Isotonic saline and ringers lactate for maintenance.

Intraoperative Monitoring

NIBP, ECG, Pulse Oximeter were the intraoperative monitors used. The Heart rate and SpO2 were monitored continuously. Blood pressure was recorded every 2 minutes for the first 20 minutes, every 5 minutes for the rest of the operation. Time intervals at which hypotension, bradycardia or other complications occurred were noted. Oxygen 4L/min via face mask was administered to all patients throughout the procedure.

Respiratory rate was monitored. Sedation score was recorded every 10 minutes the first hour and every 30 minutes next till end of surgery.

0= wide awake

1= Sleeping comfortably, responding to verbal commands

2= Deep sleep but arousable

3= Deep sleep, not arousable

Parameters studied -The following parameters were studied

1. Assessment of sensory blockade: Sensory blockade was assessed by pinprick and time noted for the block to reach different dermatomal level.

a) The onset of sensory block

b) Maximum height reached

c) Duration of analgesia

2) Assessment of onset of motor blockade

3) The patients were carefully monitored for any untoward effects like inadequate block, hypotension, bradycardia, respiratory distress, nausea, vomiting, restlessness, pruritis, shivering, anaphylactic reaction intraoperatively.

Hypotension was treated with the following measures:

a) Oxygen via mask 6litres / minute

b) Rapid infusion of intravenous fluids

c) Mephentermine intravenously at a 6mg increment

d) Injection Atropine 0.6mg if associated with bradycardia.

Bradycardia was treated by the following measures:

a) If the heart rate was reduced to <60/minute, associated with any associated with any hypotension-inj. Atropine 0.6mg I.V

b) If the heart rate reduced to <50/minute – Inj. Atropine 0.6mg I.V.

c) Rapid infusion of intravenous fluids

Nausea & vomiting were treated with Inj. Ondansetron 4mg I.V. **Shivering** was treated with warm drapes and warm intravenous fluids Patients were shifted to the postoperative ward and observed till the first administration of analgesic (Diclofenac sodium 1.5mg/kg, intramuscularly was given when the patient demanded it) and for the next 72 hours postoperatively .Delayed complications – If present were recorded Urinary retention ,Transient Neurological symptoms and Post-dural puncture headache.

IV. Results

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on mean \pm SD (Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. Paired t test is used to find the significance of study parameters between two groups of patients and chi-square test has been used to find the significance of study parameters on categorical scale between two groups. Statistical software spss 20.0 were used for the analysis of the data and Microsoft word and excel have been to generate graphs, tables etc. The results and interpretations are explained below

Table No. 1: Age wise distribution

AGE(years)	GROUP-A	GROUP-B
18-25	10	11
26-35	14	16
36-45	16	16
46-55	10	7
TOTAL NUMBER OF PATIENTS	50	50
Mean \pm SD	35.48 \pm 10.63	34.40 \pm 9.99

Note : P > 0.05 not significant

The mean age in Group A is 35.48 \pm 10.63 years with a minimum age of 18 years and maximum age of 55 years.

The mean age group in Group B is 34.4 \pm 9.99 years with a minimum age of 18 years and maximum age of 55 years. The age difference between the groups is not statistically significant(p>0.05)

Table No. 2 :Duration of surgery

DURATION OF SURGERY(MINUTES)	GROUP-A	GROUP-B
40-70	12	9
71-100	17	22
101-130	20	18

Above 130	1	1
TOTAL NUMBER OF PATIENTS	50	50
Mean ± SD	94.10±25.69	96.88±21.97

P>0.05 (Not significant)

The mean duration of surgery is 94.1 in Group A, 95.88 in Group B. The minimum duration is 40 min and maximum is 145 min. The differences between the groups, with regards to duration of surgery, is not significant(p>0.05)

Table No. 3 :Onset of sensory block

TIME IN MINUTES	GROUP-A	GROUP-B
Minimum	4	2
Maximum	6	4
Mean± SD	5.05±0.79	3.16±0.53

**p<0.001 significant at 0.001 level.

The mean time for onset of sensory block in Group A is observed to be 5.05±0.79 minutes compared to 3.16±0.53minutes in Group B, statistically significant at p <0.001 level.

Table No. 4 :Height of Analgesia

MAXIMUM LEVEL	GROUP - A	GROUP-B
T6	19	25
T8	15	17
T10	16	8
TOTAL NUMBER OF PATIENTS	50	50

Majority of the patients in both groups the maximum level of sensory block reached is T6 (38% in Group A and 50 % in Group B).

Table No. 5 Onset Of Motor block

ONSET OF MOTOR BLOCK(MINUTES)	GROUP-A	GROUP-B
3-4	0	27
4.1-5.9	27	23
>6	23	0
TOTAL NUMBER OF PATIENTS	50	50
Mean ± SD	5.24 ± 0.80	3.44±0.54

P<0.001 significant at 0.01 level;

In 54 % of patients in Group B the onset of motor block is between 3-4 minutes, whereas in Group A in 0% of patients it is between 3-4 minutes and in 27% of patients it is between 4.1 – 5.9 minutes, in 23% of patients in Group A it is more than 6 minutes as compared to 0% in group II, with a mean time of 5.24 minutes in Group A and 3.44 minutes in Group B which is statistically significant(P<0.001).

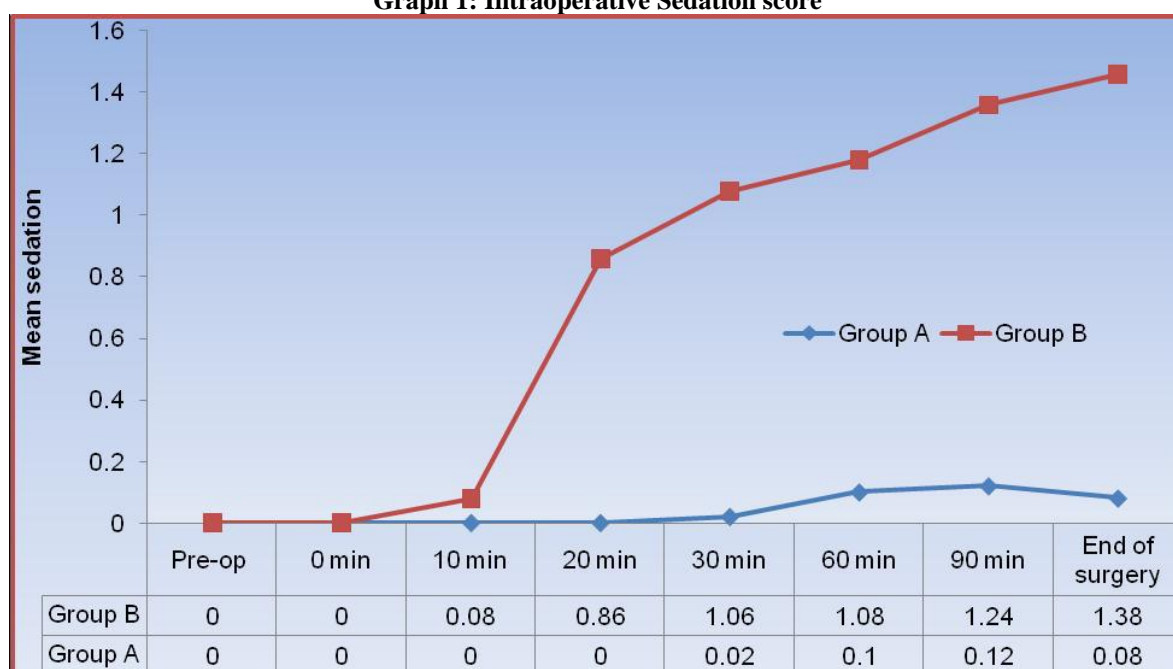
Table - 6 : Duration of postoperative analgesia

DURATION OF ANALGESIA IN MINUTES	GROUP-A	GROUP-B
UPTO 200	27	0
201-300	19	7
301-400	4	30
>400	0	13
TOTAL NUMBER OF PATIENTS	50	50
Mean± SD	214.60 ± 43.637	360.86 ± 56.215

P < .001 (Highly Significant)

In our study the mean time for rescue analgesic is 360.86±56.21 minutes in Group-B as compared to 214.60±43.63 minutes in group I. This is significant on statistical analysis p value < .001.In Group A in only 8% of patients the duration of analgesia is between 301-400 minutes whereas in Group II in 60% of patients duration of analgesia is between 301 – 400 minutes and in 26% of patients it is more than 400 minutes. In2 patients the duration of analgesia is more than 500 minutes.

Graph 1: Intraoperative Sedation score



Patients in the midazolam group had higher sedation scores as compared to those in group A. 12% of patients in Group A required intraoperative supplementation in the form of intravenous sedation, whereas the patients in Group B were calm and sedated and did not require any supplementation.

Table No 7: Complications

COMPLICATIONS	GROUP-A	GROUP-B
NILL	38	42
HYPOTENSION	2	2
BRADYCARDIA	3	2
SHIVERING	3	2
HYPOTENSION+BRADYCARDIA	2	1
NAUSEA+SHIVERING	2	1
TOTAL	50	50

In both groups hypotension is observed in 4% of patients (2 patients), Bradycardia is observed in 6% (3 patients) of Group A and in 4% (2 patients) in Group B. Hypotension and bradycardia is observed in 4% of Group A and 2% of Group B. Incidence of shivering is observed in 6% (3 patients) in Group A and 4% (2 patients) in the Midazolam group. Incidence of nausea and shivering is observed in 4% (2 patients) in Group A and 2% (1 patient) in Group B. Intraoperative complications are not statistically significant ($p > 0.05$).

V. Discussion

Local anaesthetics like Bupivacaine commonly used for the subarachnoid block purpose have various side effects and less duration of analgesia. There is a need for an adjuvant which increases the duration of analgesia, reducing intraoperative sedation, thus prolonging postoperative analgesia, reducing postoperative analgesic requirements, facilitating early ambulation to the patient, reducing the

hospital stay of the patient. Intrathecal midazolam is a water-soluble imidazo benzodiazepine almost meets the above requirements. The gate theory of pain has considerable influence in the management of pain by focusing attention on binding sites of benzodiazepine molecules are GABA receptors on the dorsal horn of the spinal cord. Intrathecally administered drugs can provide analgesia without some of the systemic side effects of intravenously administered drugs. Aggressive methods are often used to minimize pain to facilitate hospital discharge and a rapid return to normal functional activity.² Spinal anaesthesia has the definitive advantage that profound nerve block can be produced in a large part of the body by the relatively simple injection of a small amount of local anaesthetic³.

Bupivacaine introduced by Ekenstam in 1957 seems to fulfill the requirement of an ideal anaesthetic agent. Subarachnoid block with Bupivacaine is administered routinely for lower abdominal and lower limb surgeries. The ensuing sensory block is sufficient to ensure the patient's well-being, while motor block facilitates the surgeon's work. It also provides effective pain relief in the early postoperative period⁴. One of the methods to

prolong postoperative analgesia by additives such as vasoconstrictors, opioids - morphine is used as an adjuvant to intrathecal Bupivacaine in as early as 1979, it is observed to prolong the postoperative analgesia but is associated with some major side effects like delayed respiratory depression, other adjuvants like clonidine, ketamine, neostigmine etc have also been tried because of their adverse effects these adjuvants are not established in regular clinical use. However, each drug has its limitations and a need for alternative methods of drugs always exists.⁵ Benzodiazepines are usually not considered to be analgesics. Because it causes high blood levels of the drug when it administered by any given route, it is hard to demonstrate analgesic effects over and above their effects on consciousness and anxiety. However, one may confine the action of Midazolam to the spinal cord by giving it intrathecally, thus allowing access to GABA receptors that mediate analgesia, the measurement of which is not confused by changes in the level of consciousness.⁶ The impetus to develop a novel approach is typically based on accidental observations.⁷ The first human report about spinally mediated analgesia with a benzodiazepine is a case report in which diazepam is accidentally

administered epidurally.⁸ Discovery of benzodiazepine receptors in the spinal cord and the advent of a water-soluble benzodiazepine like Midazolam which could be used intrathecally unlike Diazepam for analgesia. The problems associated with the administration of diazepam into the intrathecal or epidural space are that the agent is not water soluble and that it is quite irritating to tissues. Of the clinically available benzodiazepines only Midazolam is water soluble and its tissue irritability is not significant.⁸ Midazolam hydrochloride is a potent imidazo benzodiazepine presented as an aqueous solution. Several investigations have shown that intrathecal or epidural administration of Midazolam produces a dose-dependent modulation of spinal nociceptive processing in animals and humans and is not associated with neurotoxicity or respiratory depression.

Benzodiazepine receptors are present throughout the nervous system including the spinal cord.⁹

Niv et al demonstrated that administration of exogenous benzodiazepines into the CSF around the spinal cord reached the benzodiazepine receptor in high concentration and could have a pronounced effect on local GABA activity.¹⁰ Thus benzodiazepines can gain access to analgesic system mediated by GABA_A. GABA is synthesized from glutamate in the pre-synaptic nerve ending and is generally inhibitory in effect. GABA on binding with GABA receptor opens ligand gate chloride channels cause increased chloride conductance which leads to hyper polarization of pre-synaptic inhibition of afferent terminals in the spinal cord. This results in less central propagation of action potential carrying nociceptive stimuli information. Subsequently a number of experimental investigations were carried out to study the effects of intrathecal Midazolam and it was found to produce reversible, segmental anti-nociception without any evidence of neurotoxicity in both animals and humans.¹⁰ Early clinical trials conducted in humans showed depression of the sympathetic nervous system in man following intrathecal Midazolam.¹¹ Later it is used with local anaesthetics for postoperative pain relief in both adults and

children.^{11,12,13} It is demonstrated by Nishiyama et al in 1998 that adding Midazolam to a continuous epidural infusion of Bupivacaine resulted in better analgesia and greater amnesia and sedation than Bupivacaine alone without any side effects in patients undergoing laparotomy.¹⁴ Nishiyama et al in 1999 demonstrated that spinally administered Midazolam, even in large doses, does not cause acute neurotoxicity/inflammation of the spinal cord.¹⁵ In 2003 Nishiyama & Hanaoka demonstrated that in both acute thermal and inflammatory-induced pain, intrathecally administered Midazolam and

Bupivacaine produced synergistic analgesia with decreased side effects in intrathecally catheterized rats.¹⁶ Intrathecal Midazolam has also been used in a continuous infusion with doses < 6 mg /day for long term period in patients with refractory neurogenic and musculoskeletal pain. Intrathecal Midazolam has been shown to be effective for 3 days in relieving backache in humans. These studies reported superior analgesia with the use of combination of Midazolam and Bupivacaine. Recovery to first analgesia times were longer than Bupivacaine alone and demand for rescue analgesics was markedly reduced. Drug interaction studies have shown the potentiation of the anti nociceptive effects of Midazolam with intrathecal local anaesthetics.¹⁷ To increase the duration of analgesia produced by local anaesthetics a number of adjuvants have been added by central neuraxial route. Administration of

intrathecal Midazolam by central neuraxial route has been shown to produce segmental antinociception. It abolishes pain of somatic origin, produces selective sensory block and blocks somato sympathetic reflexes without any neurotoxicity.¹⁸ In view of the above considerations this clinical study was undertaken to assess the behavior and feasibility of administration of intrathecal Midazolam as an adjuvant to intrathecal Bupivacaine in patients undergoing lower limb and lower abdominal

surgeries. Intrathecal Midazolam has been used in humans and doses of 1 mg and 2 mg have been described to provide pain relief without any side effects. A dose of 2 mg Midazolam is used intrathecally to relieve chronic low backache in adults. This dose is found to be free of respiratory depression and

sedation but produced anti-nociceptive sensory block up to mid thoracic region.¹⁹ Kim, Lee compared 1 mg and 2 mg of Midazolam intrathecally and found that 2 mg is safe and effective.²⁰ A cohort study

investigating the safety of intrathecal Midazolam by Tucker et al 2004, found that 2mg of Midazolam given intrathecally did not increase the occurrence of symptoms suggestive of neurological damage compared with conventional therapies.²¹ The clinical literature emphasizes that the addition of Midazolam in doses of approximately 2mg intrathecally has positive effects on peri-operative and postoperative pain therapy. Current reports suggest that the use of Midazolam in a dose not exceeding 1-2 mg at concentrations not exceeding 1mg/ml, delivered either alone or as an intrathecal adjuvant is not accompanied by an increase in the incidence of adverse effects.⁷ Hence in the present study Midazolam at the dose of 2mg is used intrathecally as an adjuvant to Bupivacaine. 100 patients were taken in this clinical study, posted for elective lower limb and lower abdominal surgeries belonging to ASA physical status I & II, in the age group 18-55 years of both sexes

Results of the present study

In this study, the patients across the group did not vary much with respect to age, sex, height. In both groups, all the parameters were kept identical to avoid intraoperative and postoperative variations. In both groups, surgeries performed were almost identical

Table 15: Results of the present study

	GROUP -A	GROUP-B
Mean age (years)	35.48±10.63	34.40±9.99
Mean duration of surgery (mins)	94.10±25.69	95.88±21.97
Mean Onset of sensory block (mins)	5.05±0.79	3.16±0.53
Mean Onset of the motor blockade (mins)	5.24±0.80	3.44±0.54
Meantime for two segment regression (mins)	138.28±18.39	153.6±20.83
Meantime of postoperative analgesia (mins)	214.60±43.63	360.86±56.21
Meantime for Voiding (mins)	243.03±49.76	363.08 ± 49.79
Hypotension %	2	2
Bradycardia %	3	2
Shivering %	3	2
Nausea + shivering %	2	1
Hypotension % + Bradycardia %	2	1

Observations comparing the present study with other studies as follows:

Table -16: Observations comparing onset of sensory block

Studies	GROUP-A	GROUP-B
Vaswani et al	3.41	2.26
Yegin A and et al	3.10	2.22
Present study	5.05±0.79	3.16±0.54

Table - 18: Observations comparing the duration of analgesia

Studies	GROUP-A	GROUP-B
Kim et al 2001	234	502.2
Bhattacharya et al 2002	210 ± 10.12	300 ± 11.82
Bharti et al 2002	103	199
Nidhi et al 2005	249	105.6
S premalatha et al	225	329
Indrajith et al	161	230
Shadangi et al	121.3	222.1
Present study	214.60	360.86

In the present study patients in the midazolam group had higher sedation score as compared to those in the control group. They were less anxious, more calm and sedate and required no additional supplementation (intravenous).

However 12% (6 patients) in Group I were anxious and needed iv supplementation to calm them.

Yegin A, Sanli et al, Sen A, Rudra A, et al observed that patients who received intrathecal Midazolam were high sedation score as compared to the control group

In present study incidence of shivering was observed in 6% (3 patients) in Group I and 4 % (2 patients) in the Group II. The incidence of nausea and shivering was observed in 4% (2 patient) in the Control group, 2% (1 patient) was observed in the Midazolam group.

Midazolam group had less PONV than in Bupivacaine group observed by Anirbhan et al and Abdul muthalib et al

No incidence of nausea/vomiting following intrathecal Midazolam (1mg and 2mg) reported by Kim. Lee.

VI. Conclusion

On the basis of Anatomy, Neurophysiology, pathophysiology, pharmacology and the development of more effective techniques for the effective management of intraoperative analgesia, most of the patients suffer from pain in the postoperative period. It is proven that relief of pain with a subarachnoid block with a local anaesthetic like Bupivacaine alone, is limited to the initial postoperative period.

When a combination of bupivacaine and an adjuvant-like Midazolam is used, pain relief can be extended well into the postoperative period.

On the basis of this study, the conclusion is

1. Midazolam added with bupivacaine shows the faster onset of both sensory and motor block than bupivacaine alone
2. The superior quality of surgical anaesthesia
3. Intraoperative sedation is adequate with an addition of intrathecal midazolam, decreases the additional supplementation of sedatives
4. Good hemodynamically stability.
5. The postoperative analgesic requirement is decreased by prolonging the duration of analgesia
6. Minimal side effects.

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