IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 20, Issue 3 Ser.13 (March. 2021), PP 05-09
www.iosrjournals.org

Comparison of Efficacy of Midazolam With 0.5% Bupivacaine Heavy To 0.5% Bupivacaine Heavy Alone Intrathecally for Surgeries below the Level of Umbilicus: A Prospective Randomised Study.

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Abstract
Background: *Subarachnoid block with local anaesthetics and adjuvants has been extensively used for surgery. Intrathecal midazolam produces antinociception and potentiates the effect of local anaesthetics. We compared intrathecal bupivacaine with and without midazolam to assess its effect on the duration of sensory block, motor block and pain relief.*
Methods: *This is a prospective randomised single blinded study. Hundred patients were enrolled ad divided into two groups having 50 patients in each group. Group A received 0.5% Bupivacaine with Midazolam 2mg intrathecal; Group B received 0.5% Bupivacaine with 0.9% normal saline. Onset and duration of sensorymotor block, two segment regression, hemodynamics, postop analgesic requirement, complications if any has been observed.*
Results: *Demographic profile ad duration of surgery was comparable between the groups. The onset of sensory and motor blockade was significant in midazolam group. The duration of effective analgesia was prolonged in midazolam group. Sedation was also comparable in between two groups.*
Conclusion: *The addition of preservative free midazolam to 0.5% bupivacaine intrathecally resulted in prolonged postoperative analgesia without any sideffects.*
Keywords: *spinal anaesthesia, benzodiazepine's, nociceptive receptors, lowerlimb surgeries.*

Date of Submission: 16-03-2021 Date of Acceptance: 31-03-2021

I. Introduction

Spinal anesthesia is a reliable mode of regional anesthesia technique for surgeries below level of umbilicus over ages it has been tested and is safe, reliable, reproducible mode of surgical anesthesia. It has relatively easy technique with rapid onset fewer side effects, less failure rates. Reason for popularity is it has well defined end points and also reproducible.[1]

The distribution of local anesthetic within subarachnoid space determine extent of block/ time of onset/ duration of action along with sympathetic, sensory and motor blockade depending on the dose, concentration, volume of drug but the use of local anesthetics has limited by its duration of action and dose dependent adverse effects, so to prolong its action adjuvants can be added along with local anesthetics[2].

A wide variety of adjuvants like opioids, alpha adrenergic agents, magnesium sulphate, ketamine, midazolam are used as they potentiate the effect of local anesthetics along with post-surgical analgesia[3]. However their use is limited due to adverse effects such as pruritis, urinary retention, respiratory depression, hemodynamic instability, nystagmus, and severe nausea and vomiting.

Opioids are the first and foremost most commonly used drug as adjuvant, however research has supported a number of non-opioid adjuvants such as midazolam has antinociception and potentiate the effect of local anesthetic when give in spinal anesthesia which prolongs the duration of spinal anesthesia without significant side effects.

In this study we compared midazolam plus 0.5% bupivacaine heavy with 0.5%bupivacaine heavy alone in order to assess analgesic effect, sedation, intraoperative analgesic duration, postoperative analgesia and other added benefits, side effects.

II. Materials And Methods

After obtaining Institutional Ethical Committee approval Lr.No.36/2017, this study was carried out as a prospective randomised comparative study. patients included in sample size were explained about anesthetic procedure, a written informed consent was obtained from all patients on day before surgery.

Patients of both sexes belonging to American Society of Anaesthesiologists physical status I and II, In between the age group of 18-55 years were included. Patients with gross spinal deformity, peripheral neuropathy or had any neuraxial contraindications, psychiatric illness, local/systemic infections, coagulation disorders, morbidly obese, hypovolemia, raised intracranial pressure, uncontrolled hypertension, pregnant women were excluded from our study.

A routine and detailed pre-anaesthetic evaluation of all subjects conducted as per protocol and was randomly allocated into two groups as and when the cases were posted. All patients prior to surgery, routine aspiration prophylaxis given with tab. ranitidine150mg, tab.alprazolam 0.5mg night before surgery and kept nil per oral for 8hours prior to surgery, on day of surgery after shifting to operating theatre, after patients attached to standard ASA monitors and baseline values are recorded, WHO surgical safety checklist confirmation. An 18G IV cannula is secured on no dominant hand and were preloaded with ringer's lactate 10ml/kg 15min before the procedure.

According to prior randomization done using a computer- generated random number and sealed in an envelope. The slip was taken out by the consultant on duty not involved in the study and the drug prepared according to the coded slip.

Group A - 15mg of 0.5% bupivacaine heavy + Midazolam 2mg.

Group B- 15mg of 0.5% bupivacaine + 0.9% Normal saline.

Both assessor and the patients were blinded. Under all aseptic precautions, lumbar puncture was performed using 25G spinal needle in sitting position. After obtaining a clear and free flow of cerebrospinal fluid, 2.5 mL of the study drug was injected and the patient was turned in supine position.

The sample size of the study determined by considering the alpha error of 0.05 and power of study 80% was calculated to be 56 in each group with a total sample size of 112. With around 10-12% dropout rate due to prolonged duration of surgery, the sample size decreased to 100 with 50 patients in each group.

STATISTICAL ANALYSIS

A descriptive statistics was used to measure mean, standard deviation. Unpaired student "t" test used to measure difference between two groups, paired "t" test used for comparison between intra groups. ANOVA for group's vs sessions together. All the data was analysed Using SPSS package (version 20.0 SPSS INC., Chicago, IL, USA) software for windows, the study parameters were expressed in Mean± SD and Median wherever applicable. In all the parameters, $p<0.05$ was considered to be significant.

III. Results

The demographic profile which included age, sex, weight and ASA grade were similar in all the three groups and was not statistically significant. In our study the mean duration of surgery was 94.10±25.69 in group A, 95.88±21.97 in group B, which is statistically not significant.

	Group A	Group B	P value
Age (Mean ± SD)	35.48±10.63	34.40±9.99	>0.05
Duration of Surgery (minutes)	94.10±25.69	95.88±21.97	>0.05
Onset of Blockade (Sensory)	3.16±0.53	5.05±0.79	<0.001
Onset of Blockade (Motor)	3.44±0.54	5.24 ± 0.80	<0.01
Time for two Segment regression	153.60 ± 20.83	138.28 ± 18.39	<0.01

P>0.05 Not Significant, P<0.01 statistically significant.

Table: 2 Mean Pulse Rate

Mean pulse rate/Min	Pre-op	0 min	10 min	20 min	30 min	60 min	90 min	End of surgery
Group A	81.2 ± 7.36	80.3 ±6.48	78.5 ± 7.73	77.0 ± 7.86	78.1 ± 6.51	78.6 ± 6.84	78.98 ±7.03	79.36 ±5.32
Group B	81.2 ± 7.99	80.5 ±7.52	79.7 ± 8.27	77.6 ± 9.36	78.2 ± 8.88	78.9 ± 6.44	79.70 ± 6.90	79.72 ± 6.21

P >0.05 Not Significant

The above table shows that both the groups were comparable with regards to preoperative vitals – pulse, No statistically significant difference is found between two groups (P>0.05).

Table: 3 Mean Non Invasive Blood Pressures

Mean Non Invasive Blood Pressure	Pre-op	0 min	10 min	20 min	30 min	60 min	90 min	End of surgery
Group A	95.18 ±6.26	93.12 ± 6.16	89.93 ± 9.69	89.41 ± 5.19	90.15 ± 4.05	90.39 ± 3.71	90.50 ± 2.82	91.19 ± 2.87
Group B	94.95 ± 6.71	92.08 ± 4.68	90.25 ± 6.17	89.57 ± 6.12	90.64 ± 4.90	90.35 ± 4.29	91.17 ± 4.18	90.62 ± 3.87

P<0.01 Statistically significant.

The above table shows that both the groups were comparable with regards to preoperative vitals – Non Invasive Blood Pressures, statistically significant difference is found between two groups (P<0.01).

Table: 4 Mean Respiratory rate

Respiratory Rate	Pre-op	0 min	10 min	20 min	30 min	60 min	90 min	End of surgery
Group A	18.06 ± 1.15	17.94 ± 1.08	18.00 ± 1.12	18.10 ± 1.20	17.90 ± 1.07	18.14 ± 1.13	18.14 ± 1.07	18.14 ± 1.13
Group B	17.66 ± .98	17.8 8± 1.14	17.88 ± 1.04	17.98 ± 1.13	18.14 ± 1.07	18.04 ± 1.14	18.00 ± 1.12	17.84 ± 1.11

P <0.01 Statistically significant

The above table shows that both the groups were comparable with regards to preoperative vitals parameters in respiratory rate and there is statistically significant difference found in between two groups (P<0.01).

IV. Discussion

Subarachnoid block is currently widespread popular anaesthetic technique available today. Spinal anaesthesia has the definitive advantages like profound nerve block that can be produced in a large part of the body by the relatively simple injection of a small amount of local anaesthetic[4]. Local anaesthetics like Bupivacaine commonly used for this purpose has less duration of analgesia, various side effects.

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. In order to maximize the duration of analgesia and minimize side effects, many adjuvants have been used one of them is Intrathecal midazolam a water-soluble Imadazo benzodiazepine almost meets the above requirements.

opioids - morphine are most commonly used as an adjuvant to intrathecal Bupivacaine since 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 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 ofconsciousness.[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 triggered the use of intrathecal Midazolam for analgesia.

The problems associated with the administration of diazepam into the intrathecal or epidural space are that it is not water soluble and 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].

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[10].

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.

Demographic parameters like age, sex, height were similar in between the groups, duration of surgeries performed were almost identical in both groups and statistically not significant.

SENSORIMOTOR BLOCKADE

	Group A(Midaz)	**Group B(plain)**	**P value**
Onset of Blockade (Sensory)	3.16±0.53	5.05±0.79	<0.001
Onset of Blockade (Motor)	3.44±0.54	5.24 ± 0.80	<0.01
Time for two Segment regression	153.60 ± 20.83	138.28 ± 18.39	<0.01
Duration of Post op Analgesia	360.86 ± 56.215	214.60 ± 43.637	<0.01

In our study onset of sensory block was assessed by pin prick and it was faster in patients receiving intrathecal midazolam along with 0.5% bupivacaine heavy (3.16min) compared to 0.5% bupivacaine alone (5.05min). Onset of motor block was assessed by modified bromage scale, the onset was faster in patients receiving midazolam (3.44 min) compared to patients receiving bupivacaine heavy alone (5.24min) and it is statistically significant. The results were similar when compared to Indrajit et al[11].

REGRESSION OF BLOCK

Two segment regression in present study with patients receiving midazolam along with 0.5% bupivacaine heavy 153.6±20.83 and in patients with 0.5% bupivacaine alone a mean of 138.28±18.39 and it is statistically significant. This was not described in any previous studies whereas regression of blockade was faster in control groups as in described by I Punjabi et al[12] and Anirban et al[13].

POST OP ANALGESICS REQUIREMENT

Requirement of analgesics in the form of intravenous administration was more in patients who received 0.5% bupivacaine alone. The mean time duration was 214.60 ± 43.637 minutes compared to 360.86± 56.21 in patients who received adjuvant intrathecally. Nidhi et al observed that time to rescue analgesic was more than 24 hours in the Midazolam group, in as many as 18 out of 29 patients as compared to 4 hours in the Bupivacaine group; inspite of the fact that sensory dermatomal block had receded in 2.5 hours. They also quote that none of the other human studies had reported this aspect. Present study results concur with the results observed by premalatha et al[14].

INTRAOPERATIVE MONITORING

Monitoring of heart rate, blood pressure, SpO_2, respiratory rate and sedation score were done to assess the hemodynamic and respiratory effects of intrathecal Midazolam.

In the present study, the intraoperative hemodynamic parameters were comparable in both groups hypotension was equal in both groups with 2 patients had a fall in blood pressure in both Groups .Hypotension and bradycardia was seen in both group without much variation compared in both groups as 4% in midazolam group and 2% in bupivacaine heavy alone group.

POSTOPERATIVE COMPLICATIONS

None of our patients reported any postoperative complications like nausea, vomiting, urinary retention, transient neurological symptoms, post dural puncture headache on observing for 72hrs postoperatively.

V. Conclusion

From the results of present study we conclude that midazolam 2mg along with 0.5% bupivacaine heavy intrathecally produces faster onset of blockade and prolongs duration of postoperative analgesia with minimal side effects.

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