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

Anaesthesiology

Dr. T. Chandrakala* M.D., Assistant Professor, Department of Anaesthesiology, Kurnool Medical College/GGH, Kurnool. *Corresponding Author

Dr. M. Sarada M.D., Assistant Professor, Department of Anaesthesiology, Kurnool Medical College/GGH, Kurnool

ABSTRACT

Background: Spinal anaesthesia is unable to maintain postoperative analgesia for a longer period with commonly used drugs. Various adjuvants have been added to intrathecal bupivacaine to prolong the duration of analgesia. Here, in this study we added midazolam to assess the duration of analgesia.

Aims And Objectives: To compare intrathecal bupivacaine alone and midazolam combined with bupivacaine for the duration and the quality of spinal anaesthesia in patients undergoing lower abdominal and lower limb surgeries.

Results: Intrathecal midazolam augments onset of action, prolongs the duration of analgesia of the intrathecal bupivacaine and also enhances the analgesic effect of used along with it.

Conclusion: The addition of preservative free midazolam to bupivacaine for subarachnoid block in lower abdominal and lower limb surgeries prolong the duration of effective analgesia compared to bupivacaine alone.

KEYWORDS

Intrathecal bupivacaine, Intrathecal midazolam, Lower abdominal surgeries

INTRODUCTION

Spinal anaesthesia is a form of regional anaesthesia involving injection of a local anaesthetic into the cerebrospinal fluid of the patient's subarachnoid space to anaesthetize the spinal nerve roots running through it. Spinal anaesthesia has many advantages over general anaesthesia which makes it the anaesthesia of choice in the present surgical practice. Adequate muscle relaxation is obtained following spinal and blood loss is reduced which makes it superior to general anaesthesia. It may also allow earlier return of gastrointestinal function following surgery. Following spinal anaesthesia there is reduction of the hypercoagulable state associated with surgery, sympathectomy mediated increases in tissue blood flow, improved oxygenation from decreased splinting, enhanced peristalsis and suppression of the neuroendocrine stress response to surgery.

Spinal anaesthesia is also unable to maintain postoperative analgesia for a longer period with commonly used drugs which has been identified as one of the most serious deficiencies in pain management today. Despite the availability of effective analgesic agents, patients continue to suffer severe postoperative pain. With the conventional practice of supplementing with opioids intramuscularly, in the postoperative period, the analgesia many patients receive is simply too little or too late.

Various adjuvants have been added to intrathecal bupivacaine like Morphine, Clonidine and Neostigmine to prolong the duration of spinal anaesthesia. Intrathecal Morphine prolonged the duration of postoperative analgesia but at the same time had other adverse effects like itching, nausea, urinary retention, sedation, ileus and life-threatening respiratory depression.

There are many clinical studies in favour of intrathecal midazolam which has added advantages since it produces sedation, amnesia and antinociceptive effects without any neurotoxicity or other side effects. Hence this study is 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.

AIMS AND OBJECTIVES

The aim of the study is to compare intrathecal bupivacaine alone and midazolam combined with bupivacaine for the duration and the quality of spinal anaesthesia in patients undergoing lower abdominal and lower limb surgeries.

Specific objectives:
1. Speed of onset of analgesia
2. Duration of analgesia
3. Onset of motor blockade
4. Duration of motor blockade
5. Time required for need of post operative analgesia
6. Intra operative complications like nausea, vomiting, hypotension, brady cardia, shivering, respirative depression, seizures.
7. Perioperative sedation

PATIENTS AND METHODS

After approval by the hospital ethics committee and obtaining written informed consent , 60 patients (ASA grade I and II) of either sex, aged between 20 to 60 years, scheduled to undergo elective lower abdominal and lower limb surgeries were included in this study.

Allocation Of Patients To Groups:

Patients were selected randomly by lottery method, where 'B' group received intrathecal bupivacaine only and group 'BM' received intrathecal bupivacaine with preservative free midazolam. Patients who were allocated to group 'B' received 3.5 ml of hyperbaric bupivacaine 0.5% + 0.4 ml of saline 0.9% intrathecally. Patients who were allocated to Group 'BM' received 3.5 ml hyperbaric bupivacaine 0.5% + 0.4ml preservative free midazolam(5mg/ml) intrathecally(Mezolam 1ml ampoule (5mg/ml) Neon Pharmaceuticals)

ANAESTHESIA

The patients were premedicated with injection ondensetron 4mg IV and injection ranitidine 50mg intravenously. The patient was placed in left lateral position. The skin over the back prepared with antiseptic solution and draped with sterile towel. The L3-L4 inter space was identified and 25G Quincke Babcock spinal needle was introduced in this space through midline approach. After confirming the free flow of CSF, the study drug was injected intrathecally and the patient was immediately made to lie in supine position. The time of intrathecal injection of drug was noted. All patients were supplemented with 4L of O2/min via polymask throughout the procedure.

ASSESSMENT

Assessment of sensory blockade:
This was tested by pin prick method. The time of onset of sensory analgesia was taken from time of injection of drug into the subarachnoid space to loss of pin prick sensation at the T10 dermatome. The time to achieve maximum sensory block was noted from the injection of the drug to loss of pin prick sensation at the highest dermatome level. Duration of sensory blockade was recorded from the time of onset to time of return of pinprick sensation at L2 dermatome level. These observations were assessed at 2 minutes interval for 15 min after intrathecal injection.

Assessment of motor blockade:
Motor blockade was assessed bilaterally using modified Bromage scale. Modified Bromage scale 0 - No block. Able to raise extended leg

against gravity 1 - Unable to raise extended leg, just able to flex knees 2 - Unable to flex knees, but able to flex ankle 3 - Total block. Inability to flex ankle / move leg. Assessment of motor block was started immediately after turning the patient supine. Onset of motor block was taken as the time to achieve Bromage score 1 from the time of injection. The duration of motor blockade was recorded from the onset of time to time when patient was able to lift the extended leg (Return of Bromage scale3 to 0).

Haemodynamic changes and the level of sedation was assessed every hour for 6 hours post operatively. Post operatively, in addition to the above, Visual Analogue Scale score for pain was noted at 4, 6 and 12 hours after surgery. The patients were asked to answer verbally and by pointing to where they would rate their pain using the visual Analogue scale.

Visual Analogue Scale:
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.

During the post operative period analgesics or opiods were avoided until demanded by the patient due to pain. Analgesics were administered when VAS score was four and above, if demanded by the patient. 75 mg of diclofenac sodium was given intramuscularly. Time to first analgesic and the total number of analgesics required in the first 12 hours postoperatively were recorded. Side effects like (nausea and vomiting, itching, shivering, respiratory depression, deep sedation and seizures) were recorded if any. Adverse effects if any were treated with the respective drugs. For nausea and vomiting, injection Ondansetron 4mg IV was given. As the study dealt with hysterectomy cases and long duration orthopedic procedures with Foley's catheter insitu, the problem of voiding does not arise.

OBSERVATION AND RESULTS

Collected data was analyzed by means of various statistical software such as SPSS and appropriate tests. Student's T-test (single tailed) has been used to find the significance of study parameters on continuous scale between two groups. Chi-square test has been used to find the significance of study parameters on categorical scale between the two groups. Significance was assessed at 5% level of significance. A total of 60 patients were taken for the study. In group-B, the mean age of patient was 39.77 ± 11.51 years, and mean height was 157.03 ± 7.68 cm. Female patients were 53.33% and male patients were 46.67% in group-B. In group-BM, the mean age of the patient was 41.97± 10.43 years, and mean height was 157.10 ± 7.80 cm. Female patients were 56.67% and male patients were 43.33% in group-BM. In both groups female patients were more than male patients. Duration of surgery in Group-B was 99.67 minutes and in Group-BM was 95.33 minutes.

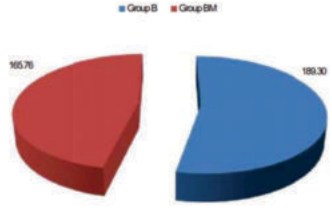
The average age (p value = 0.22) and height (p value = 0.49) in both groups were similar and insignificant.

In both groups female patients were significantly larger in number than the male patients.

There was no clinically significant difference between two groups regarding systolic blood pressure and diastolic blood pressure(P > 0.05) measurements.

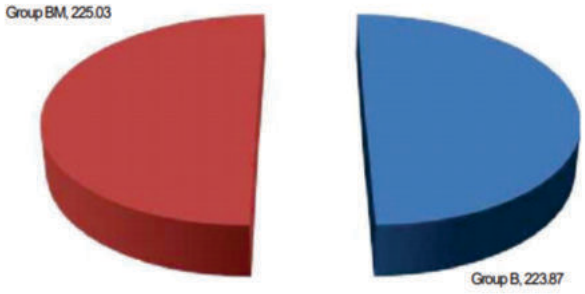
Sensory Block Characteristics:

The onset of sensory block in group- BM was 165.76 seconds, and in group-B was 189.30 seconds.The difference between the two groups was statistically highly significant (Pvalue<0.05).



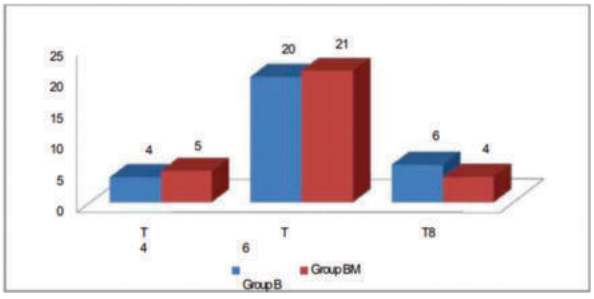
Motor Block Characteristic

Onset of motor blockade (in seconds) in either groups The time of onset of motor block in group-BM was 225.03 seconds as compared to 223.87 seconds in group-B. There was no statistically significant difference in onset of motor block between two groups.



Time To Achieve Maximum Sensory Block

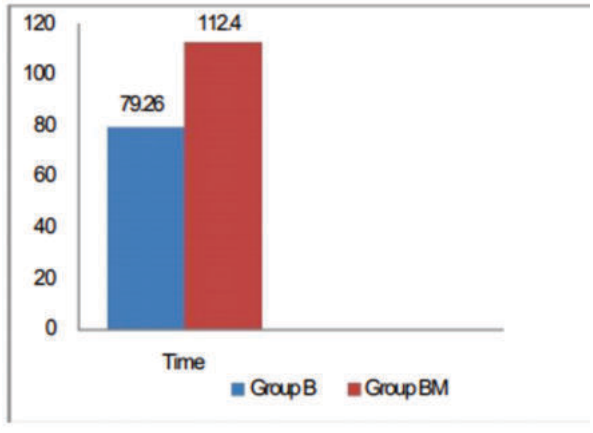
The level of sensory block was from T4-T8. The result showed no significant difference between the two groups. Time to achieve maximum sensory level was 406.50 seconds in group-BM compared to group-B where it was 476.20 seconds. P value was 0.00005 and statistically significant.



Two dermatomal segments regression of sensory level (minutes):
Time to two segment regression in group-BM was 112.4 minutes and in group -B was 26 minutes. There was statistically significant difference between two groups(p-value<0.05).

Time to regression of sensory level to L2 dermatome in group-BM was 169.1minutes, compared to 145.03minutes in group-B. The difference between the two groups in regression time was statistically significant.

The time of first request of analgesics by the patients in group-BM was 296.0 minutes, where as it was 146.53 minutes in group-B patients. The difference between the two groups was statistically highly significant.



Regression of Bromage scale from 3 to 0) was 174.90 minutes in group-BM, compared to 175.90 minutes in group-B patients. The time difference between the two groups for complete motor recovery was statistically insignificant.

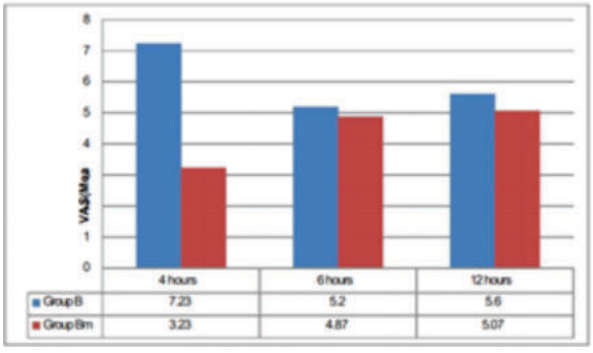
In post-operative period visual Analogue scores for pain at 4, 6 and 12hours were recorded for first 12 hours after surgery.

Duration Of Analgesia:

The time to first pain medication in group-BM was 296.0 minutes, where as in group-B was 246.53 minutes. Total number of times analgesics required in the first 12 hours after surgery in group-BM was 1.33 and in group-B were 1.67.

Time to first pain medication was significantly longer in group-BM, compared to Group-B ($p < 0.05$ and statistically significant.

Visual Analogue scores at different time intervals Duration of analgesia: The time to first pain medication in group-BM was 296.0 minutes, where as in group-B was 246.53 minutes. Total number of times analgesics required in the first 12 hours after surgery in group-BM was 1.33 and in group-B were 1.67.



Time to first pain medication was significantly longer in group-BM, compared to Group-B ($p < 0.05$ and statistically significant.

Intraoperative sedation scores between the two groups:
Intraoperative sedation scores were 0 in 22 patients in group-B and 4 patients in group-BM. 8 patients in group-B and 20 patients in group-BM had a sedation score of 1. Six patients in group-BM had a sedation score of 2 and none of the patients in group-B.

There was no significant difference in the incidence of side effects between two groups. Postoperatively, the patients were monitored for the first six hours after surgery to assess any abnormalities in heart rate, blood pressure, oxygen saturation and level of sedation. All the patients in both groups were haemodynamically stable and wide awake.

DISCUSSION

Spinal anaesthesia is the most commonly used regional technique. Local anaesthetics commonly used for this purpose have various side effects and have less duration of analgesia. In order to minimize these side effects and to maximize analgesia, many adjuvants have been used along with local anaesthetics. There is a need for an adjuvant which increases the duration of analgesia without increasing the duration of motor blockade, thus prolonging post operative analgesia, reducing post operative analgesic requirements, facilitating early ambulation, reducing the hospital stay of the patient. Of all the agents used intrathecal midazolam almost meets the above requirements. The principal mechanism by which intrathecal midazolam provides analgesia is through the GABA-Benzodiazepine system in the spinal cord and there is ample evidence to show the GABA receptors in the spinal cord are involved in nociceptive mechanisms. This prospective study was conducted to compare intrathecal bupivacaine and bupivacaine with midazolam in lower abdominal and lower limb surgeries. The patients were selected at random, to avoid any kind of bias and to allow comparability of results obtained. This was a double blinded controlled study where neither the patient nor the observer who recorded the parameters were aware of the group allocation and the drug received.

Patient characteristics across the groups: The patients studied across the group did not vary much with respect to age, sex or height. In both groups female patients were significantly larger in number than the male patients. The types of surgeries performed were almost identical in both the groups.

Perioperative cardiovascular parameters: In the present study, the incidence of hypotension was almost equal in both groups with 4 patients had a fall in blood pressure in group-B and 5 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.

Goodchild CS, Noble J in 1987, Bahar M and et al. 1997, Batra Y.K and et al. in 1999 and Bharti N and et al. in 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 2.0 mg of midazolam along with bupivacaine causes no gross hemodynamic disturbances.

Onset of sensory blockade:

In the present study the onset of sensory blockade in group-BM was 165.76 seconds compared to 189.30 seconds in group-B which is statistically highly significant. It shows that addition of midazolam to local anaesthetic .enhances the onset of sensory block.

Yegin A and et al. 2004 have found in their study that addition of 2mg of midazolam to hyperbaric bupivacaine in spinal anaesthesia 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 blockade in different studies. Though it is statistically significant in our study it does not have any clinical implications.

Onset and duration of motor blockade:

In this study the degree of motor block was assessed using modified Bromage score. In the present study, the onset of motor blockade in group-B was 223.87 seconds compared to 225.03 seconds in group-BM, which is statistically insignificant ($P > 0.05$). Similarly the duration of motor block in group-B was 175.90 minutes compared to 174.90 minutes in group-BM, which is statistically insignificant ($p > 0.05$). There is no significant difference in onset and duration of motor block between two groups.

A study done by Shadangi et al.in 2011 concluded that the addition of preservative free midazolam to bupivacaine intrathecally resulted in prolonged postoperative analgesia without increasing the motor block, which is correlated to the present study.

Time of first request of analgesics In the present study, the time of first request of analgesics in group-B was 146.53 minutes compared to 296.0 minutes in group-BM which is statistically highly significant.

Prakash et al. evaluated the efficacy of two doses(1mg,2mg). Intrathecal midazolam with bupivacaine in patients undergoing caesarean section. They concluded that intrathecal midazolam 2mg provided a moderate prolongation of post operative analgesia. Shadangi et al. in 2011 concluded that addition of intrathecal preservative free midazolam to bupivacaine resulted in prolonged post operative analgesia without prolonging the motor block. Thus we can conclude that intrathecal midazolam along with bupivacaine prolongs the duration of analgesia thus prolonging the time of first request of supplemental analgesics in the post operative period.

Visual Analogue Score:

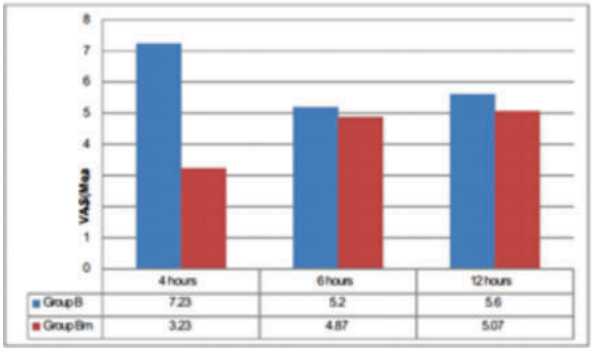
In this study Visual Analogue Score at first pain medication was 7.23 in group-B compared to 4.87 in group-BM. This is similar to the study done by Aikta Gupta et al.51 where the Visual Analogue Score was shorter in group-BM. In the present study, there is significant reduction in the visual Analogue score of the patients in group-BM in comparison with higher VAS in group-B recorded at 4 hours, 6 hours and 12 hours of spinal anaesthesia.

Valentine J.M. J and et al.31 in 1996, Sen A and et al.41 in 2001, Bharti N and et al 44 in 2003, Amr M and et al.9 in 2003 found significantly decreased frequency of postoperative analgesic intake in those receiving intrathecal midazolam. In our study, less number of analgesics were given in group-BM compared to group-B. The present study is correlated with the study done by Aikta Gupta et al.51 also found that supplemental analgesic dose requirement with diclofenac was significantly less in group-BM compared to group-B.

Hence we conclude that intrathecal midazolam augments onset of action , prolongs the duration of analgesia of the intrathecal bupivacaine and also enhances the analgesic effect of drugs used along with it.

Level of sedation:
In this study the sedation scores are '0' (wide awake), in 22 patients in group-B compared to 4 patients in group-BM. 20 patients in group-BM had a sedation score of '1'(sleeping comfortably), compared to 8 patients in group-B. 6 patients in group-BM had a sedation score of 2 and none in group-B. Sedation score of 3 (deep sleep unarousable) are not observed in both groups.

Adverse Effects:
In the present study, 5 patients had hypotension, 2 patients had shivering and 3 patients had nausea vomiting in group-BM compared to 4 patients of hypotension, 3 patients of shivering and 2 patients of nausea vomiting in group-B. This signifies that adverse effects are minimal with intrathecal midazolam.



Erdine S and et al. in 1999 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 and et al. in 1996, Sen A and et al.41 in 2001, Bharti N and et al.44 in 2003, Shah FR and et al.43 in 2003, Amr M and et al.9 in 2003, Tucker AP and et al.45 in 2004, Yegin A and et al.47 in 2004 found no adverse neurological symptoms in those received intrathecal midazolam. They also found that intrathecal midazolam has mild sedative and antiemetic effects.

CONCLUSION

On the basis of the study, the addition of 2mg preservative free midazolam to 0.5% hyperbaric bupivacaine for subarachnoid block in lower abdominal and lower limb surgeries prolongs the duration of effective analgesia as compared to bupivacaine alone and delays the need for post operative analgesic requirements. Intrathecal midazolam in a dose of 2 mg does not have any clinically significant effects on perioperative haemodynamics Advantages are: Excellent surgical anaesthesia. Longer duration of analgesia. Comfortable sedation. Reduced post operative analgesic requirement. Rapid motor recovery. Minimal side effects.

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