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Evaluation of analgesic efficacy and safety of intrathecal midazolam as an adjuvant to bupivacaine

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Abstract

Background: Subarachnoid block (SAB) is the commonest mode of anaesthesia for the lower limb and lower abdominal surgeries. The main disadvantage of SAB is its limited duration of action. To overcome this limitation various adjuvants are added to spinal local anaesthetics. In this present study we evaluated the efficacy and safety of midazolam as an adjuvant to intrathecal bupivacaine for lower limb and lower abdominal surgeries.

Methods: 60 patients of either sex in the age group of 20 to 50 years belonging to ASA class 1 or 2 scheduled for elective/emergency lower abdominal or lower limb surgeries were enrolled for the study and randomly divided in to two groups. Group C (control group) received 3ml of 0.5% (heavy) bupivacaine + 0.4ml of normal saline (0.9%) and Group M (study group) received 3ml of 0.5% (heavy) bupivacaine + 0.4 ml (2mg) of midazolam in SAB. Heart rate, blood pressure, respiratory rate, onset of sensory and motor blockade, visual analogous scale (VAS) at different time intervals postoperatively, duration of analgesia and duration of motor blockade were recorded.

Result: In both the groups onset of sensory and motor blockade were comparable (P>0.05). Mean VAS at different time interval during postoperative period was significantly lower in group M (P<0.001) than group C. The duration of postoperative analgesia (P <0.001) and the duration of motor blockade (P<0.01) was significantly prolonged in group M as compared to group C.

Conclusion: Midazolam as an adjuvant to intrathecal bupivacaine significantly prolongs the duration of postoperative analgesia without any side effect.

Keywords: SAB, midazolam, intrathecal, postoperative analgesia

Introduction

Subarachnoid block (SAB) is the commonest mode of anaesthesia for the lower limb and lower abdominal surgeries. It provides effective analgesia in initial postoperative period. But, main disadvantage of SAB is its limited duration of action. To overcome this limitation various adjuvants like opioids, ketamine, clonidine, midazolam [1, 2, 3]. Etc. have been added to spinal local anaesthetic agents. Opioids are the commonest adjuvants used for prolongation of analgesia, but these are associated with various side effects like itching, sedation, urinary retention, nausea- vomiting and respiratory depression [4].

Benzodiazepine receptors are present throughout the nervous system including spinal cord [5]. Anti-nociceptive effect of intrathecally administered midazolam is through GABA receptors which are abundantly present in lamina 2 of dorsal horn ganglia of the spinal cord [5]. Intrathecal midazolam also causes the release of endogenous opioid acting at spinal delta receptor [6].

In the present study we evaluated the efficacy and safety of midazolam as an adjuvant to intrathecal bupivacaine for lower limb and lower abdominal surgeries and compared it to bupivacaine alone.

Material & methods

After ethics committee approval, 60 ASA class 1 or 2 patients of either sex comprising of age group 20 - 50 years scheduled for elective or emergency lower limb or lower abdominal surgery were recruited for the study. Patients who were unwilling to participate in the study, suffering from peripheral neuropathy, bleeding diathesis, inflammation or infection at the site of injection, spine deformity and patients having history of chronic drug intake like analgesics, benzodiazepines, MAO inhibitors and tricyclic antidepressants were excluded from the study.

Selected patients were randomized by using a computer generated random number table into two groups comprising of thirty patients each. Patients in group C received 3 ml of 0.5% hyperbaric bupivacaine + 0.4 ml of normal saline (0.9%) while group M received 3 ml of 0.5% hyperbaric bupivacaine + 0.4ml (2 mg) of preservative free midazolam.

The drugs were prepared by the second anaesthesiologist who was not involved in the study. The anaesthesiologist who performed the block and postoperative assessment was blinded to the drug administered. Time to attain sensory level (absence of response to pin prick) upto T10 and motor block upto modified bromage grade 3 were recorded. Baseline vital Parameters (heart rate, blood pressure and respiratory rate) were recorded. After SAB vital parameters were recorded at every 5 minutes till 30 minutes and then at 15 minutes interval

till the end of surgery. After surgery vital parameters were recorded hourly till the supplementary analgesia was given. Intra-operative sedation score was also recorded by a blinded observer after 30 minutes of SAB (0-wide awake, 1- sleeping comfortably but responding to verbal commands, 2- deep sleep but arousable, 3- deep sleep non arousable). Postoperative analgesia was assessed with VAS at every 30 minutes interval till the VAS >40 at this time supplementary analgesia was administered. Any intra-operative and post-operative complications were also recorded.

Statistical analysis

All data were entered in the excel sheet, and then into SPSS and subjected to statistical analysis. Student's t test and y2 analysis were performed in appropriate situations and 'P' value < 0.05 was taken as significant.

Result

Table1. Shows demographic parameters. The mean age in group C was 34.93+7.36 years and in group M 36.43+7.39 years (p>0.05) which is statistically not- significant. In group C number of male and female patients were equal, that is 15 (50%) each. While in group M majority 17 (56.67%) were male and 13 (43.33%) patients were female. Majority of patients in both the groups were of ASA class 1. The mean duration of surgery was 76.67+19.40 minutes in group C, while in group M it was 78.33+18.63 minutes (p>0.05) which was also statistically not-significant.

Table 1

	Group C (n=30)	Group M(n=30)
Age in years (mean+ SD)	34.93+7.36	36.43+7.39
M/F	15/15	17/13
ASA class 1/2	16/14	18/12
Duration of surgery Minutes + SD)	76.67+19.40	78.33+18.63

Table 2 shows the vital parameters. The difference in the Baseline vital parameters recorded preoperatively in both the groups was not significant statistically (p> 0.05). Intraoperative variation in vital parameters (heart rate, systolic blood pressure and respiratory rate) at different time interval from the baseline and difference in both the groups was statistically insignificant (p>0.05). We also did not find any significant respiratory depression in both the groups.

Table 2

	Group C			Group M		
	Baseline	**30 minutes**	**60 minutes**	**Baseline**	**30 minutes**	**60 minutes**
Heart rate (/minute)	83.53 + 13.24	81.35+7.60	82.07+7.60	84.27+12.71	81.74+11.5	82.48+6.99
Systolic BP (mmHg)	123+11.03	114.26+9.96	117.06+9.64	122.4+12.43	113.8+9.5	116.8+7.94
Respiratory rate (/minute)	16.73+1.62	16.46+1.43	16.07+1.11	16.47+1.46	16.16+1.07	15.98+0.89

Table 3. Shows the characteristics of spinal blockade. There is no statistically significant difference in the onset of sensory and motor blockade in both the groups. While duration of sensory and motor blockade both are significantly prolonged statistically in midazolam group (group M). Onset of sensory blockade was 184.83+35.10 seconds in group C while in group M 172.83+37.10 seconds (p >0.05). Onset of motor blockade in group C was 302.6+57.83 seconds while in group M 289+57.83 seconds(p>0.05). The duration of analgesia was 210+46.27 minutes in group C while in group M 439.8 +62.54 minutes (P<0.001). Duration of motor blockade was 179+23.83 minutes in group C while in group M 216.4+30.26 minutes (p<0.01).

Table 3

	Group C (n=30)	Group M (n=30)
Onset of sensory blockade (seconds)	184.83+35.10	172.83+37.10
Duration (minutes)	210+46.27	439.8+62.54
Onset of motor blockade (seconds)	302.6+57.83	289+57.83
Duration (minutes)	179+23.83	216.4+30.26

Table 4

Sedation score	Group C (n=30)	Group M (n=30)
0	30	0
1	0	21
2	0	9
3	0	0

Table 4 shows the sedation score of the patients intra-operatively. Better sedation score was obtained in group M as compared to group C.

Table 5 shows that mean VAS score was significantly lower in group M as compared to group C at different time intervals postoperatively, this difference was statistically significant (p<0.001). Despite adequate anaesthetic level, 3 patients of group C complained of some intraoperative discomfort. In group C, 4 patients and in group M, 3 patients had shivering intraoperatively. In group C, 3 patients complained of nausea and vomiting in immediate postoperative period while in group M there were none.

Table 5: VAS score

Duration in hours	Group C	Group M
2	15.83+5.58	5.76+3.95
4	50.86+6.69	9.81+3.47
6	-	25.83+13.9

Discussion

Postoperative pain is a major concern for anaesthesiologists and patients. Various drugs are being added to intrathecal bupivaicane to prolong postoperative analgesias after SAB [1, 2, 3]. Benzodiazepine receptors are present throughout the cental nervous system including the spinal cord. In the spinal cord they are maximally present in the lamina 2 of dorsal horn ganglion. Intrathecally administered midazolam exerts its effects by occupying GABA receptors present in spinal cord [5, 6, 7, 8]. The delta selective opioid antagonist naltrindole suppresses the antinociceptive effects of intrathecal midazolam suggests that intrathecal midazolam also releases

endogenous opioid which acts on delta receptors [6].

For intrathecal use 2mg preservative free midazolam is found to be optimal without any side effects as demonstrated by Tucker & collegues [9]. Kim & Lee [10] suggested that addition of 1 or 2 mg of midazolam intrathecally prolongs the postoperative analgesia by 2 hours and 4.5 hours respectively. Few studies have demonstrated that addition of midazolam provides better analgesia than bupivaicane alone in cesarean section [6, 11, 12]. Batra *et al.* [13] also reported increased duration of postoperative analgesia by addition of 2 mg midazolam to intrathecal bupivacaine in patients undergoing knee arthroscopy. Bharti *et al.* reported prolonged motor blockade in intrathecal midazolam group as compared to control group [14] along with increased duration of analgesia. Our study also shows significant prolongation of postoperative analgesia and motor blockade by addition of midazolam to intrathecal bupivacaine.

Neurotoxicity remains the major concerns for intrathecally administered drugs. Various studies conducted on animals and human have demonstrated that intrathecal midazolam does not shows any signs of neurotoxicity [15, 16, 17, 18]. In our study we also did not find any sign of neurotoxicity in patients postoperatively. Few studies reported that intrathecal or epidural midazolam with bupivaicane provides better sedation and postoperative analgesia than bupivaicane alone [19, 20]. In our study we also noted better sedation scores in the midazolam group than control group without any signs of respiratory depression intraoperatively. Majority of workers who evaluated hemodynamic effect of intrathecal midazolam have found it safe [12, 19, 20] without any significant changes in hemodynamics and respiration. We also found intrathecal midazolam haemodynamically stable. Rudra *et al.* observed that co-administration of midazolam and fentanyl significantly minimize the incidence of nausea and vomiting in early postoperative period [14]. We also noted reduced nausea and vomiting in midazolam group.

Conclusion

Our study demonstrated that addition of midazolam to intrathecal bupivacaine produces good surgical analgesia and extended postoperative analgesia without any significant effect on cardiovascular and respiratory dynamics. This prolonged analgesia is devoid of any significant side effect. Patients also remained more sedated and comfortable throughout the surgical procedure. Extended postoperative analgesia also reduces analgesic requirement in the immediate postoperative period. To conclude midazolam as an adjuvant to intrathecal bupivacaine is a good choice to prolong the postoperative analgesia.

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