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Comparison of postoperative pain relief by using intrathecal midazolam added to bupivacaine and buprenorphine

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Abstract
Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Inadequate pain control, apart from being inhumane, may result in increased morbidity or mortality.
Aims and Objectives: To study the postoperative pain relief by intrathecal midazolam added to bupivacaine and buprenorphine.
Methodology: This was a cross-sectional double-blinded comparative study carried out at our institute. The patients of age between 18 to 60 yrs. with ASA I and ASA II to be posted for surgery under spinal anaesthesia were enrolled to either Group A or B. Group A (n=45) patients received 15 mg hyperbaric bupivacaine and 75 mcg. Buprenorphine or Group B: (n=45) who received 15 mg hyperbaric bupivacaine and 75 mcg buprenorphine with additional Inj. Midazolam 2 mg (0.4 ml). The data was entered to excel sheets and analysed unpaired t-test, chi-square test calculated by SPSS 19 version software.
Result: We observed that the demographic data was comparable. The duration of post-operative analgesia was significantly higher in Group B as compared to Group A i.e.11.18 ± 2.31 hrs. And 8.67± 3.27 hrs respectively. The VAS score at 10 hours post operatively was significantly lesser in the Group B as compared to Group A i.e. 4.23±1.94 and 6.93± 2.19 (t=6.19, df=88, p<0.001) respectively.
Conclusion: The addition of midazolam to bupivacaine and buprenorphine significantly improved the post –operative analgesia.

Keywords: intrathecal midazolam, buprenorphine, VAS (visual analogue scale), postop analgesia

1. Introduction
Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Inadequate pain control, apart from being inhumane, may result in increased morbidity or mortality [1, 2]. It is a major symptom in many medical conditions, and can interfere with a person's quality of life and general functioning. The main purpose of perioperative pain control is providing an adequate comfort level and acceptable side effects for patients. Effective postoperative analgesia improves patients' outcome as observed by early ambulation, decrease in side effects, and reduce the incidence of postoperative chronic pain [3, 4]. Many additives are suggested in view of increasing the efficacy and duration of spinal analgesia in postoperative period. Many Opioid drugs are also used intrathecally [5]. Among all, Buprenorphine is known to have analgesic property when injected intrathecally [6, 7, 8, 9]. It was also used epidurally for purpose of analgesia [10].
Similarly, midazolam a water-soluble benzodiazepine primarily used as sedative was tested intrathecally for its antinociceptive action since decades [11]. Its mechanism of action was well explained in vivo and vitro i.e in human and animal as well as microscopic pharmacological studies [12, 13]. Also its safety profile for neurotoxicity after intrathecal administration was tasted by various animal and human studies [23, 25]. Hence this study was undertaken to compare the effect of addition of both Midazolam and buprenorphine to bupivacaine for intrathecal use for spinal anaesthesia with safe doses suggested by various studies for its postoperative analgesia [14].

2. Materials and Methods
This was a cross-sectional double blinded comparative study carried out at Department of Anaesthesiology at Indira Gandhi Government Medical College Nagpur during the two-year period of postgraduation in patients of age 18 yrs. to 60 yrs. with ASA I and ASA II, undergoing various lower abdominal surgeries posted under spinal anaesthesia were included into the study. Total 90 patients were enrolled after taking written consent and each patient explained the procedure. Out of them, 45 enrolled to Group A: (n=45) 15 mg hyperbaric Bupivacaine and 75 mcg. Buprenorphine remaining 45 to Group B: (n=45) who received 15 mg hyperbaric Bupivacaine, 75 mcg. Buprenorphine and 2mg (0.4 ml) Midazolam preservative free intrathecally randomly in double blinded manner. The information from patients like age, sex, duration of post-operative analgesia recorded from time of spinal to demand of rescue analgesic by patient. Pain was assessed by VAS (Visual Analogue Scale). Degree of motor block was assessed by Modified Bromage scale (MBS) at 2, 5, 10 and 15 min as 1= complete motor block, 2= almost complete motor block (able to move feet only), 3= able to move knees, 4= able to raise the legs but unable to keep them raised, 5= no detectable weakness of hip flexion, 6= no weakness at all.

Sedation was assessed by using Ramsey sedation score as 0= none (alert patient), 1= Mild (sleepy patient but easily arousable), 2= Moderate (drowsy patient but arousable), and 3= Severe (difficult to arouse). Hypotension (fall in BP by > 30%) was treated with increase in IV infusion and Inj. Mephenteramine 5-7.5 mg IV in titrated doses. Bradycardia (Pulse rate < 60 beats/min) was treated with Inj. Atropine 0.6 mg IV. Oxygen (2 lit/min) was supplemented by face mask when SpO_2 falls below 93%. Postoperatively all patients were monitored for complications like nausea, vomiting, shivering, sedation, bradycardia, hypotension, urinary retention, and respiratory depression. Also following parameters were noted.

1. Time of intrathecal injection of drug, time of onset of blockade and highest level of sensory block achieved and its time.
2. Level of motor block with modified Bromage scale.
3. Intraoperative sedation score.
4. Duration of surgery.
5. Total duration of effective analgesia.
6. VAS score

The data was entered to excel sheets and analysed unpaired t-test =, chi-square test calculated by SPSS 19 version software.

Results

Table 1: Distribution of the patients as per the age and sex

	Group A (n=45)	Group B (n=45)	p-value
Average age	43.78±3.65	44.17±2.39	t=0.93, df=88,p>0.05
Sex			X^2=0.42, df=1, p>0.05
Male	25	28	
Female	20	17	

The average age in Group A was 43.78±3.65 Yrs. was comparable with 44.17±2.39 Yrs. in Group B (t=0.93, DF=88, p>0.05), the male to Female ratio was 1.25 and 1.64 was comparable (X^2=0.42, DF=1, p>0.05)

Table 2: Sedation score

Sedation Score	Group A (Control)	Group B(Study)	P value
0	31	33	0.843
1	19	17	
2	0	0	
3	0	0	

Sedation was less in both groups.

Table 3: Quality of sensory and motor block

Score	Sensory			Motor		
	Group A (Control)	Group B (Study)	P value	Group A (Control)	Group B (Study)	P value
1 Excellent	13 (26%)	26 (52%)	0.001	9 (18%)	25 (50%)	0.001
2 Satisfactory	25 (50%)	24 (48%)		31 (62%)	24 (48%)	
3 Fair / Inadequate	11 (22%)	0		7 (14%)	1 (2%)	
4 Poor	1 (2%)	0		3 (6%)	0	

The quality of sensory block was adequate (scores 1 and 2) noted in 76% of patients of group A whereas it was noted in almost 100% of patients in group B. 11% of patients from Group A had fair to inadequate block and 2% had poor block which has to be supplemented with Inj. Ketamine 0.5 mg/kg IV. There was highly significant statistical difference (P value 0.001) of quality of sensory block in group A and B. In group A excellent to satisfactory motor block (expressed by surgeons) was noted in 80% of patients whereas it was seen in 98% of patients f group B. This difference was highly significant statistically (P value 0.001).

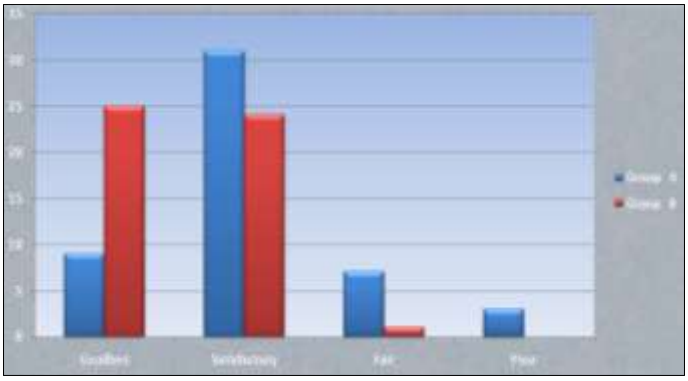

Fig 1: Quality of sensory blockade

Table 4: Intraoperative complications

Intra-operative complications	Control Group		Study group	
	N	%	N	%
Bradycardia	1	2	2	4
Hypotension	2	4	2	4
Shivering	4	8	3	6
Respiratory depression	0	0	0	0

Intraoperative problems were minimal and easily treatable without risking the patient's life. On the contrary patients were calm and cooperative also surgical conditions were good and satisfactory.

Table 5: Distribution of the patients as per the duration of post-operative analgesia and VAS score

	Group A (n=45)	Group B (n=45)	p-value
Duration of analgesia (Hours)	8.67± 3.27	11.18 ±2.31	t=8.92, df=88, p<0.001
VAS score at 10 hours post- operatively	6.93± 2.19	4.23±1.94	t=6.19, df=88, p<0.001

The duration of post-operative analgesia was significantly higher in Group B as compared to Group A i.e. 11.18 ±2.31 Hrs. and 8.67± 3.27 respectively. The VAS score at 10 hr. post operatively was significantly lesser in the Group B as compared to Group A i.e. 4.23±1.94 and 6.93± 2.19 (t=6.19, df=88, p<0.001).

4. Discussion

In the recent past, the use of intrathecal adjuvants has gained a lot of acclaim as they prolong the duration of block, there is a better success rate, better patient satisfaction and faster recovery as well as being cost effective. This enables the patients to return to their normal activity more quickly [1, 2]. Opioids have been widely used for providing pain relief postoperatively and their advantages of neuraxial narcotics over systemic narcotics are well established [5]. Buprenorphine is a long acting, highly lipophilic opioid, which has proved to be a promising analgesic, by epidural and

intrathecal route [6, 7, 9, 10]. It is found to be about 25 times more potent than morphine and has a low level of physical dependence. Lanz *et al*, in a study, demonstrate that buprenorphine, when administered intrathecally, produces no adverse reactions and is compatible with CSF. Any method of postoperative analgesia must meet three basic criteria; it must be simple, safe, clinically appropriate and evidence based. The discovery of opioid receptors in the brain and spinal cord started a new era in the field of postoperative analgesia. The first clinical use of opioids was by Wang *et al*. and since then, the use of opioids like buprenorphine was found to be more beneficial as a single intrathecal injection produces pain relief of sufficient duration. Buprenorphine was found to have a mixed agonist-antagonist action. It has a high lipid solubility, high affinity for opioid receptors and has a prolonged duration of action, making it a good choice for intrathecal and peripheral nerve site administration [7, 8].

Midazolam is a short acting, water soluble and potent benzodiazepine with rapid onset of action is mediated through benzodiazepine GABA receptor complex. The major inhibitory neurotransmitter. Binding sites for benzodiazepine receptors have been demonstrated in spinal cord. Highest density of receptors is seen in lamina II of dorsal horn, a region which prominently processes nociceptive information [11, 12] recently many animal and human studies were conducted and demonstrated anti-nociceptive action of midazolam after epidural and intrathecal administration [13]. Effective and safe dose of intrathecal midazolam suggested in various studies is 1-2 mgs [15]. Hence in our study 1 mg intrathecal Midazolam with buprenorphine and Bupivacaine was used to evaluate its effect on onset and quality of blockade. Most importantly duration of analgesia was prolonged without any significant adverse effects. In our study duration of post-operative analgesia was significantly higher in midazolam added group i.e. 11.18 ±2.31 Hrs. than control group 8.67± 3.27 Hrs. Also, the VAS score at 10 hr. post operatively was significantly lesser in the study group as compared to control Group i.e. 4.23±1.94 and 6.93± 2.19 ($t=6.19$, $df=88$, $p<0.001$) respectively.

Our study findings are similar to study conducted by Shah FR as they found that he duration of postoperative analgesia 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 ($P < 0.0001$) [16].

That also lead to less requirement of analgesics in postoperative period as VAS score was less in these group. Similar study findings were reported by N. Bharati. Some patients didn't required analgesics for 36-48 hours postoperatively clearly prolonging of analgesic effect [20]. But this action was not uniform in all patients it may be due to multifactorial nature of cause of pain. Additional advantage of this drug combination intrathecally was is sedation and also comfort level is more among patients and operative conditions were good to surgeon's satisfaction. Also the safety profile of intrathecal midazolam was studied extensively [22, 23, 24]. Perioperative complications were minimal and not life threatening even long-term complications were not observed in follow-up period.

5. Conclusion

It is concluded that addition of midazolam to bupivacaine and buprenorphine significantly improved post-operative analgesia.

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