Comparison of midazolam versus midazolam and buprenorphine as an adjuvant to intrathecal bupivacaine for post operative analgesia in lower abdominal surgeries

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ABSTRACT

Background: Intrathecal Midazolam, apart from its own analgesic and sedative effect, potentiate the analgesic effect of Bupivacaine.[1] Addition of Buprenorphine to Midazolam might have an additive analgesic effect and thus may be helpful in reducing the dose of individual drug given alone for the same degree of analgesia.

Aim: To compare the analgesic efficacy and safety profile of midazolam and midazolam and buprenorphine as an adjuvant with intrathecal bupivacaine for post operative analgesia.

Methods: Sixty patients aged 20-60 years, of either sex, weighing 40-70 kg, measuring >145 cm in height, of ASA status I /II scheduled for lower abdominal surgeries were randomized in to two Groups. **Group I (n=30)** received preservative free Midazolam 1mg (0.2ml),0.5ml Normal Saline added to Inj.Bupivacaine hyperbaric 0.5% 3.2 ml intrathecally. **Group II (n=30)** received preservative free Midazolam 1 mg (0.2ml), Buprenorphine 150 µg (0.5ml) with Bupivacaine hyperbaric 0.5% 3.2 ml intrathecally. Statistical analysis was performed using T- Test and a value of $P<0.05$ was considered significant.

Results: In Group I, mean duration of pain free period was 5.63 ± 0.96 hrs while in Group II, it was 24.24 ± 2.13 hrs, which was statistically highly significant ($p <0.001$).

Conclusion: Addition of Buprenorphine to Midazolam with intrathecal Bupivacaine prolongs the duration of postoperative analgesia with minimal side effects.

Keywords: post-operative analgesia, intra thecal midazolam, buprenorphine, bupivacaine

INTRODUCTION

Various studies have shown that intrathecal midazolam produces prolongation of spinal anaesthesia and reduces the requirement of postoperative analgesics and now there is considerable evidence that midazolam given intrathecally produces antinociceptive effect.[1]

If a patient is to receive spinal anaesthesia, with intrathecal local anaesthetic agents, addition of another intrathecal drug that will produce prolongation of analgesia is a logical choice. Predictably, thus a number of adjuvants have added to intrathecal local anaesthetic drugs like Opioids, Clonidine, Benzodiazepines and Ketamine etc.[2,3,4,5] Buprenorphine an opioid has high lipid solubility and high affinity for opioid receptor.[6] Midazolam is a short acting, potent, water soluble benzodiazepine[7].It has been used for potentiating the analgesic effect of local anaesthetic induced neuraxial blockade.

Therefore we conducted a prospective, double blind study to compare the efficicacy of intrathecal Midazolam to Midazolam, Buprenorphine and Bupivacaine on quality of spinal anaesthesia and postoperative analgesia.

METHODS

After obtaining approval from the Institutional Ethics Committee and informed written consent, this prospective randomized double blind study was carried out in the Department of Anaesthesiology Govt. Medical College and Sir. T. Hospital Bhavnagar. Sixty patients aged 20-60 years, of either sex, weighing 40-70 kg, measuring >145 cm in height, of ASA status I and II scheduled for lower abdominal surgeries were included in our study.

Patients having contraindication to regional anaesthesia, opioid dependence, history of drug allergy and abuse and any major systemic illness were excluded from the study. After detail preanaesthetic evaluation, routine and specific investigations, each patient was informed regarding nature, purpose of the study and visual analogue score(0- no pain , 10 – maximum pain). Preoperative adequate fasting hours (6-8 hours) were confirmed and baseline vital parameters were recorded.

Patients were randomly allocated into two Groups. **Group I (n=30)** received preservative free Midazolam 1mg (0.2ml) with 0.5ml Normal Salineand Bupivacaine hyperbaric 0.5% 3.2 ml intrathecally. **Group II (n=30)** received preservative free Midazolam 1 mg (0.2ml) with Buprenorphine 150 µg (0.5ml) and Bupivacaine hyperbaric 0.5% 3.2 ml intrathecally.

Multipara monitor was attached for monitoring of vitals. Peripheral venous access was secured on nondominant hand with 18G canula and preloading with Inj. Ringer Lactate 10-15 ml/kg was initiated. The mixture of drugs according to assigned group was injected intrathecally in a double blind manner.

The segmental sensory level of anaesthesia was assessed by the patients' response to pinprick and motor block was assessed by using modified Bromage scale. Sedation score was graded as per Chernik scale.[8] Haemodynamic parameters, respiratory rate, and level of sedation were monitored immediately after spinal anaesthesia, every 5 minutes for 30 minutes, then at 30 minutes interval till the end of surgery.

On completion of surgery patients were shifted to Post anaesthesia care unit. Intravenous fluids were continued, pain score, vital parameters and sedation score were recorded every half hourly upto 4 hours, 1 hourly upto 8 hour, 2 hourly upto 12 hour and 4 hourly upto 24 hour. Any side effects were also recorded and treated accordingly.

Residual motor block and Residual sensory block was monitored and it's wearing off time (Bromage scale 0 and regression of sensation to pin prick to S_1 dermatom respectively) was noted.

Inj. Diclofenac Sodium 75 mg was given intramuscularly as a rescue analgesic when patient's VAS score reached ≥4. Time of administration of first analgesic was noted. Duration of pain relief was taken as time from onset of subarachnoid block to time of administration of rescue analgesic.

Statistical Analysis:

All data were analyzed statically using T- test and a value of $P<0.05$ was considered significant. The data's were presented as Mean ± SD and percentage.

RESULTS

There were no significant differences between the two groups in demographic data and duration of surgery. Also, there was no significant difference in systolic and diastolic blood pressure and SpO_2 in both the groups. Group II patients had lower pulse rate and respiratory rate compared to Group I, but none had respiratory depression. The sedation was higher in Group II. Adverse effects like pruritus, urinary retention and nausea was higher in Group II.

Duration of sensory block was higher in Group II (323.26±30.17 min) compared to Group I (281.73±49.56 min) which is highly significant

(p<0.05). Duration of motor block was comparable between the two Groups.

Duration of analgesia was assessed by VAS score. Inj. Diclofenac Sodium 75 mg intramuscularly was given as rescue analgesic when patient's VAS score reached ≥4. Mean duration of analgesia was 5.63 ± 0.96 hrs in Group I, while in Group II, it was 24.24 ± 2.13 hrs. The differences showed statistically highly significant (p <0.001). The two groups were compared for sensory and motor blockade and duration of analgesia.

Table. 1. Analgesic Profile

Blockade	GROUP 1	GROUP 2	P value
Sensory (min)	281.73±49.56	323.26±30.17	<0.005(S)
Motor (min)	251.16±47.46	267.23±28.72	>0.05(N.S)
Duration of analgesia (hrs)	5.63 ± 0.96	24.24 ± 2.13	<0.001(S)

S- significant, N.S – not significant

Table. 2. Duration of pain free period (hours)

	GROUP I	GROUP II
TOTAL NO. OF PATIENTS	30	30
RANGE	3.10-7.05	18.2-27.4
MEAN SD (HOURS)	5.63 ± 0.96	24.24 ± 2.13
P<0.001#		

- Highly Significant

Table. 3. Requirement of rescue analgesic

TIME OF IM INJECTION	GROUP 1		GROUP 2	
	NO. OF PTS.	%	NO. OF PTS.	%
3 to 3.9 hr.	2	7	0	0
4 to 4.9 hr	2	7	0	0
5 to 5.9 hr	11	36	0	0
6 to 6.9 hr	12	40	0	0
7 to 7.9 hr	3	0	0	0
8 to 9.9 hr	0	0	0	0
10 to 11.9 hr	0	0	0	0
12 to 15.9 hr	0	0	0	0
16 to 19.9 hr	0	0	1	4
20 to 23.9 hr	0	0	9	30
>24 hr	0	0	20	64
Total	30	100	30	100

Table. 4. Post operative complications

Complications	GROUP I (No. of patients)	GROUP II (No. of patients)
Nausea	2 (7.2%)	2 (7.2%)
Vomiting	0	0
Bradycardia	0	0
Hypotension	0	1 (3.6%)
Shivering	6 (20%)	4 (13.3%)
Respiratory Depression	0	0
Pruritus	0	10 (33.3%)
Headache	1 (3.6%)	0

Fig. 1. Changes in mean sedation score

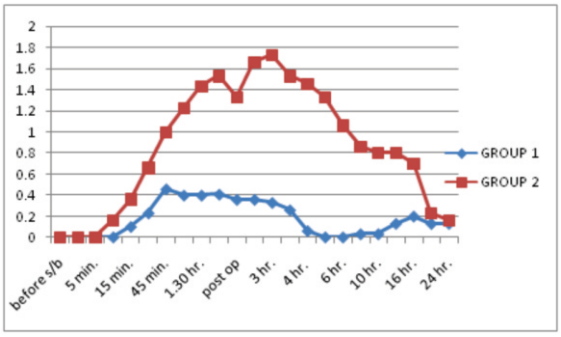
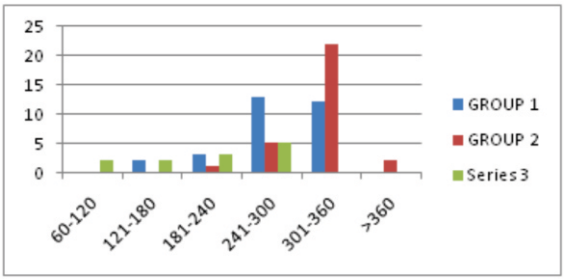


Fig. 2. Duration sensory blockade



DISCUSSION

Postoperative pain has commonly been managed with im/ iv opioid analgesics alone or in combination with conventional NSAIDS, but they are associated with adverse effects so there clinical utility is limited.[9]

Nowadays the advantage of combined pharmacological approaches for postoperative pain relief is emphasised. Breakthrough in analgesic effect of intrathecal opioid and other drugs like benzodiazepines has led to the use of

combination of drugs.[2,10] Intra-thecal administration of combination of drugs targeting different spinal cord receptors, provides prolonged and superior quality of analgesia in relatively small doses compared to individual drugs. Prolonging the duration of postoperative analgesia by adding adjunct like opioids, clonidine, benzodiazepine and ketamine etc to intrathecal local anaesthetic drugs is practiced.[2,3,4,5] The advent of opioid receptors and naturally occurring opioid like substances in CNS started new era in pain control. Buprenorphine an opioid has high lipid solubility and high affinity for opioid receptors. Its analgesic effect primarily affects pain perception while leaving motor, sympathetic and other sensory modalities essentially intact.

Spinal anaesthesia is a popular technique for lower abdominal surgeries. Though it provides effective analgesia in initial postoperative period, the effect is very short lasting and additional analgesics are required. Use of potent opioid like buprenorphine has been less satisfactory owing to side effects.

Off late it has been shown that administration of midazolam by central neuraxial route produces significant segmental nociception. Also, that addition of Midazolam to opioids intrathecally potentiates the action of opioids. Midazolam is short acting, potent, water soluble benzodiazepine and has been used for potentiating the analgesic effect of local anaesthetic induced neuraxial blockade.[4] Spinal analgesic effect of midazoliam is mediated by benzodiazepine-GABA receptor complex which abaundantly present in the dorsal horn of spinal cord with high density found in lamina II of dorsal horn ganglia[1]. Midazolam also acts on kappa or delta opioid receptors which are also present in substantia gelatinosa of spinal cord. Analgesic efficacy of intrathecal benzodiazepines may be attributed, in part, to direct interaction with kappa opioid receptors. Midazolam in addition, is also weakly active at delta opioid receptors[11].

Hemodynamic (Systolic and diastolic blood pressure, SpO_2) remained stable and comparable in both the groups ($p>0.05$). Postoperatively, Group II patients had statistically significant lower pulse rate and respiratory rate than Group I ($p<0.05$). The data was compared with study of F.R. Shah, A.R. Halbe, C.S. Goodchill[12] for patients undergoing minor and intermediate lower abdominal surgeries.

Group I patients had mean duration of pain free period of 5.63 ± 0.96 hrs and in Group II it was 24.24 ± 2.13 hrs, the difference is statistically highly significant ($p<0.001$) in favour of Group II. However , another study noted the duration of analgesia to be 9.24±2.57 hours in control group (Bupivacaine 5% H + Buprenorphine 150 mcg) & 21 ± 12.69 hours in study group (Bupivacaine 5% H + Buprenorphine 150 mcg + Midazolam 2 mg).[7]

In the present study, no patient in either group was excessively sedated. All patients were calm, sleeping comfortably and responding to verbal commands. However, Group II patients had higher incidence of nausea, vomiting, pruritus and urinary retention.

CONCLUSION

Addition of Buprenorphine to Midazolam and Bupivacaine intrathecally prolongs the duration of postoperative analgesia and allow calm, sedated but arousable patients without the risk of respiratory depression with stable hemodynamics and minimal side effects.

AUTHOR NOTE

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