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Original Research Article

Effect of addition of intrathecal midazolam to 0.5% hyperbaric bupivacaine to prolong the post-operative analgesia in lower abdominal surgeries

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ABSTRACT

Background: Bupivacaine when used alone produces analgesia for 2.5 to 3 hours, making it unsuitable in cases where the duration of surgery is longer and in cases which require further analgesia during post-operative period. Present study is intended to evaluate the effect of addition of intrathecal midazolam to bupivacaine to prolong the post-operative analgesia.
Methods: Present clinical study was conducted in Kamineni Institute of Medical Sciences, Narketpally, Nalgonda District, Andhra Pradesh, India. After obtaining approval from institutional ethical committee, present clinical study was undertaken to evaluate the effects of addition of intrathecal midazolam to bupivacaine 0.5% (heavy). The study was conducted on 60 patients undergoing lower abdominal surgeries.
Results: Mean onset of analgesia was 190.5 with SD 21.3 in group-C whereas in group-M, mean onset of analgesia was 185.3 with SD 26.81. Mean difference between the groups not showing statistical significance. In the present study the Maximum height of sensory blockade in control and midazolam group was T7 (T6-T8) compared to T7 (T6-T8) midazolam group. Mean duration of sensory blockade was 130.4 with SD 36.36 in group-C whereas in group-M, mean duration of sensory blockade was 191.9 with SD 36.4. Mean difference between the groups showing statistical significance. Mean duration of motor blockade was 176.3 with SD 23.7 in group-C whereas in group-M, mean duration of motor blockade was 208.1 with SD 18.21. Mean difference between the groups showing statistical significance.
Conclusions: Midazolam is a useful adjuvant to bupivacaine in subarachnoid block. Intrathecal midazolam combined with intrathecal bupivacaine produces a longer and more effective anaesthesia and analgesia. It also prolongs post-operative analgesia without increasing adverse effects.

Keywords: Hyperbaric Bupivacaine, Intrathecal midazolam, Lower abdominal surgeries, Post-operative analgesia

INTRODUCTION

The simplicity of the technique of spinal anesthesia and its reliability has made it one of the preferred techniques to carry out a surgical procedure. Bupivacaine when used alone produces analgesia for 2.5 to 3 hours, making it unsuitable in cases where the duration of surgery is longer and in cases which require further analgesia during post-operative period.

One of the methods of providing postoperative analgesia is by prolonging the duration of intrathecal bupivacaine by additives such as opioids, clonidine, ketamine etc. However, each drug has its limitations.[1-3] Discovery of

benzodiazepine receptors in spinal cord triggered the use of intrathecal midazolam for analgesia.[4] Midazolam exerts an indirect effect on pain transmission downstream from its expected effects on benzodiazepine-GAMA aminobutyric acid (GABA) A receptors Kohno T et al, demonstrated that midazolam augmented GABA-mediated responses in substantia gelatinosa neurons from rat spinal cord, an effect that would increase inhibitory neurotransmission.[5-7]

The midazolam effects are also linked with a non-m, possibly kappa opioid pathway. Rattan AK et al, have shown that the in vivo antinociceptive effects of intrathecal midazolam can be reversed by the opioid antagonist naloxone, indicating the involvement of opioid receptors at spinal delta-receptors.[8] Several studies have shown that intrathecal midazolam produces a dose dependent modulation of spinal nociceptive processing and is not associated with neurotoxicity, respiratory depression or sedation.[9-12]

Present study is intended to evaluate the effect of addition of intrathecal midazolam to bupivacaine to prolong the post-operative analgesia.

Aim of this study was based on to evaluate the effect of addition of intrathecal midazolam to 0.5% hyperbaric bupivacaine to prolong the post-operative analgesia in lower abdominal surgeries.

The objectives of this study were to compare onset of sensory block, to compare duration of sensory block, to compare duration of motor blockade, to compare duration of post-operative analgesia, to compare side effects.

METHODS

Present clinical study was conducted in Kamineni Institute of Medical Sciences, Narketpally, Nalgonda District, Andhra Pradesh, India. After obtaining approval from institutional ethical committee, present clinical study was undertaken to evaluate the effects of addition of intrathecal midazolam to bupivacaine 0.5% (heavy). The study was conducted on 60 patients undergoing lower abdominal surgeries from January 2012 to February 2013. Patients were reassured about the technique and an informed consent was obtained. All the patients were explained about the procedure of spinal anesthesia, the aim, essence and parameters of the study to gain their co- operation.

Inclusion criteria

- Age: 18 to 60 years of either gender, ASA grade I and II.

Exclusion criteria

- ASA grade III and above, neurological problems, Allergy to study drug, patients undergoing caesarian section, patients with coagulation disorders, unco-operative patients, emergency surgeries.

For every patient, after a thorough clinical examination and routine laboratory investigations, a written and informed consent was obtained, both for conduct of study as well as administration of spinal anesthesia.

All patients were kept nil by mouth from midnight before surgery and Tab alprazolam (0.01mg/kg) was administered at bedtime the day before surgery.

All the patients were re-examined, assessed and weighed pre-operatively on the day of surgery. Nil per oral status (for 6 hours) was confirmed. Intravenous access was established with a 18G Intravenous cannula and pre-loading was done with 15ml/kg lactated ringer's solution. Before performing, spinal anesthesia, anesthesia machine, with accessories as well as with equipment's and drugs, including emergency drugs were checked for an efficient use. Also monitoring equipment's like pulse oximeter, NIBP and ECG monitors were checked and applied to each patient on arrival to the operating room.

All the patients were randomly allocated into two groups using computer generated random numbers by simple randomization technique.

- Group C: control group,
- Group M: midazolam group.

Under all aseptic precautions, in lateral position with midline approach a lumbar puncture was done with a 23G spinal needle and after free flow of CSF, 3.5ml of 0.5% hyperbaric bupivacaine plus 2mg (preservative free) midazolam in study group and 3.5ml of 0.5% hyperbaric bupivacaine plus 0.4ml of 0.9% saline in control group was given.

No sedative or analgesic drug was given during the study period. Intensity of motor blockade was evaluated according to Bromage scale.

Grade criteria

- I: Free movement of the legs and feet,
- II: Just able to flex knees with free movement of feet,
- III: Unable to flex knees, but with free movement,
- IV: Unable to move legs or feet,

Onset of sensory block

Time taken from time of sub arachnoid block to achievement of T10 sensory blockade.

Duration of analgesia

Duration was assessed by time taken from onset of subarachnoid block to time of administration of rescue analgesic.

Duration of sensory block

Time of regression of analgesia was determined as the point at which the upheld level of sensory anesthesia receded by 2 segments.

Duration of motor blockade

Duration of motor blockade was taken as the time required for the patients to be able to move legs or feet (Bromage score-'4') after administration of spinal anesthesia.

Pulse rate, blood pressure, respiratory rate, oxygen saturation was monitored and recorded at every 15 minutes interval.

Level of sedation was assessed by modified Wilson sedation scale

- Oriented; eyes may be closed but can respond to verbal command,
- Drowsy; eyes may be closed, arousable only to command,
- Arousable to mild physical stimulation (earlobe tug),
- Unrousable to mild physical stimulation.

Post operatively patients were examined at 2 hours interval till the administration of first rescue analgesic to evaluate the duration of post-operative pain relief and for complications if any, like nausea, vomiting, itching and respiratory depression.

Statistical analysis

Data were entered in MS Excel and analyzed in SPSS V22. Descriptive statistics were represented with percentages, mean, SD. Independent t-test and chi-square test were applied to find significance.

RESULTS

Mean age in group-C was 41 with SD 15.69 whereas in group-M, mean and SD were 39.46 and 13.50. The mean difference between the groups not showed statistical significance.

In group-C, male and females were 96.7% and 3.3% respectively whereas in group-M, male and females were 90% and 10%. Gender difference was not showing statistical significance.

Mean weight in group-C was 53.63 with SD 7.95 whereas in group-M, mean and SD were 54.96 and 7.30. The mean difference between the groups not showed statistical significance.

SBP, DBP, HR, RR were not showing any statistical significance between the groups at base, 15, 30, 45, 60, 75, 90, 105 and 120.

Table1: Comparison of onset of analgesia, duration of analgesia, sensory blockade, motor blockade between the groups.

Parameter	Group C (n=30)	Group M (n=30)	P-value
Onset of analgesia	190.50±21.30	185.33±26.81	0.41
Duration of analgesia	195.56±36.29	318.93±38.24	<0.001
Duration of sensory blockade	130.40±36.36	191.90±36.40	<0.001
Duration of motor blockade (min)	176.30±23.70	208.10±18.21	<0.001

From Table 1, mean onset of analgesia was 190.5 with SD 21.3 in group-C whereas in group-M, Mean onset of analgesia was 185.3 with SD 26.81. Mean difference between the groups not showing statistical significance.

Mean duration of sensory blockade was 130.4 with SD 36.36 in group-C whereas in group-M, mean duration of sensory blockade was 191.9 with SD 36.4. Mean difference between the groups showing statistical significance.

Mean duration of motor blockade was 176.3 with SD 23.7 in group-C whereas in group-M, mean duration of motor blockade was 208.1 with SD 18.21. Mean difference between the groups showing statistical significance.

Mean duration of analgesia was 195.56 with SD 36.29 in group-C whereas in group-M, mean duration of analgesia was 318.93 with SD 38.24. Mean difference between the groups showing statistical significance.

Table 2: Comparison of maximum height of sensory blockade, sedation and complications between the groups.

Sedation	Group C (n=30)	Group M (n=30)	P-value
Maximum height of sensory blockade (segments)	T7 (T6-T8)	T7 (T6-T8)	-
Patients having sedation	0 (0.0%)	8 (26.66%)	0.002
Complication			
Nausea	4 (13.3%)	4 (13.3%)	1
Urinary retention	5 (16.6%)	4 (13.3%)	0.72

From Table 2, in the present study the maximum height of sensory blockade in control and midazolam group was T7 (T6-T8) compared to T7 (T6-T8) midazolam group.

No patient was having sedation in group-C whereas in group-M, sedation was present in 26.7% of the patients. Sedation was showing statistical significance between the groups.

There were 4 (13.3%) and 4 (13.3%) in control and midazolam group respectively had nausea. 5 (16.6%) and 4 (13.3%) in control and midazolam group respectively had urinary retention.

DISCUSSION

Onset of sensory blockade

In the present study the onset of sensory blockade in control group was 190.50±21.30 seconds compared to 185.33±26.81 seconds in midazolam group

The mean time of onset of sensory blockade is comparable with Agrawal N et al, (186 and 180 sec) and Gupta A et al, (180 and 174 sec).[13,14] Yegin A et al, have found in their study that addition of 2mg of midazolam to hyperbaric bupivacaine in spinal anesthesia does not delay onset of sensory compared to hyperbaric bupivacaine alone in patients undergoing perianal surgery.[15] From the above study it can be seen that there is no quickening in the onset of sensory blockade up on addition of intrathecal midazolam to bupivacaine.

Maximum height of sensory blockade

In the present study the maximum height of sensory blockade in control and midazolam group was T7 (T6-T8) compared to T7 (T6-T8) midazolam group. The maximum height of sensory blockade is comparable with Lee JM et al, Hi YJ et al, wherein the control group was T8(T4-T10) and midazolam group was T8(T2-T10) respectively.[16] In Gupta A et al, in control group it was T7(T6-T8) and midazolam group was T7 (T6-T8) respectively.[14]

Duration of sensory blockade

In the present study, the two-segment regression of sensory blockade in control group was 130.40±36.36 minutes compared to 191.90±36.40 minutes in midazolam group. The mean duration of sensory blockade is increased in midazolam group.

The duration of sensory blockade is comparable with Lee JM et al, Hi YJ et al,(139.00 min and 206.70min), Yun MJ et al,(117.00 and 169.20 min) and Prakash S et al, (126.00 and 182.00 min).[16-18] Observed that intrathecal midazolam increases the duration of sensory blockade.

Duration of motor blockade

In the present study, the duration of motor blockade in control group was 176.30±23.70 minutes compared to 208.10±18.21 minutes in midazolam group. The mean duration of motor blockade is increased in midazolam group. The mean durations of motor blockade are comparable with Bharati N et al, (180 min and 225 min) and Lee JM et al, Hi YJ et al, (118.30 min and 179.70 min).[16,19] This shows that addition of midazolam increases the motor blockade provided by bupivacaine.

Duration of analgesia

In the present study, the duration of analgesia in control group was 195.56±36.29 minutes compared to 318.93±38.24 minutes in midazolam group. The mean duration of analgesia is increased in midazolam group.

The mean duration of analgesia is comparable with Bhattacharya D et al, (210.00 min and 300 min) and Prakash S et al, (228 min and 366 min), Kim MH et al, found significantly greater time for first rescue analgesic in the midazolam group in patients undergoing haemorrhoidectomy.[18,20,21] Yegin A et al, and in 2004 studied the effect of intrathecal midazolam and hyperbaric bupivacaine in comparison to hyperbaric bupivacaine alone and found significantly longer time until the first dose of additional analgesic requirement in midazolam group.[15] Bharti N et al, found prolonged duration of postoperative pain relief in midazolam group.[19]

Thus, authors can observe that intrathecal midazolam along with bupivacaine prolongs the duration of analgesia thus prolonging the first request of supplemental analgesics in the post-operative period. Agrawal N et al, described this increase in postoperative analgesia due to antinociceptive effects mediated via benzodiazepine/GABA-A receptor complex which are abundantly present in lamina II of dorsal horn ganglia of spinal cord.[13] Bharati N et al, added that Intrathecal midazolam probably also causes release of an endogenous opioid acting at spinal delta receptor.[19] Its nociceptive effects have been suppressed by the delta selective opioid antagonist nalitrindole.

Sedation

Number of patients with sedation are increased in study group. Four patients had grade 1 and four patients had grade 2 sedation score in midazolam group and none in control group. Total of eight patients had sedation in midazolam group when compared to none in control group the number of patients experiencing sedation is increased in midazolam group.

The number of patients having sedation in midazolam group was comparable with Yegin A et al, (five patients had sedation)(22.7%).[15] According to Yun MJ et al, The sedative effect of intrathecal midazolam seemed to be slower than intravenous midazolam.[17] The mechanism of sedative effect of intrathecal midazolam was not defined but the cephalad spread in the cerebro-spinal fluid or systemic absorption may contribute.

Postoperative complications

Out of 30 patients in each group, 4(13.3%) and 4(13.3%) in control and midazolam group respectively had nausea.

The occurrence of nausea was comparable with Lee JM et al, Hi YJ et al, 1 (6.6%) and 1(6.6%) and Bharati N et al, (2003) 3 (15%) and 2 (13%).[16,19] Out of 30 patients in each group, 5 (16.6%) and 4 (13.3%) in control and midazolam group respectively had urinary retention. The results were comparable between both the groups. The occurrence of urinary retention was comparable with Lee JM et al, Hi Ju et al, 3 (20%) and 3 (20%).[16]

Limitations of this study was based on the however study with larger samples is required to confirm the above findings.

CONCLUSION

Midazolam is a useful adjuvant to bupivacaine in subarachnoid block. Intrathecal midazolam combined with intrathecal bupivacaine produces a longer and more effective anesthesia and analgesia. It also prolongs post-operative analgesia without increasing adverse effects.

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