Midazolam as an adjuvant to intrathecal lignocaine: A prospective randomized control study

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ABSTRACT

Context: Unfortunately in the past decade, phenomenon of transient neurologic symptoms (TNS) cast doubts on the use of lignocaine for spinal anesthesia. Intrathecal midazolam has been proved to have its role in relieving neuropathic pain. We attempted to study the role of midazolam as an adjuvant to intrathecal lignocaine. **Aims:** The primary objective of the study was to evaluate the effect of intrathecal midazolam as an adjuvant to spinal lignocaine in terms of quality and duration of spinal sensory blockade. The secondary objectives are to study the effect on hemodynamics and the incidence of TNS. **Settings and Design:** A prospective randomized control double-blinded study in American Society of Anesthesiology I and II surgical population. **Materials and Methods:** Hundred healthy adult patients scheduled for elective infraumbilical surgery were randomly assigned to group A patients received spinal anesthesia with 1.5 ml of 5% lignocaine heavy with 0.4 ml of 0.9% saline and group B (control group) received spinal anesthesia with 1.5 ml of 5% heavy lignocaine with 0.4 ml of preservative-free 0.5% midazolam. **Statistical Analysis Used:** *Z* test for study parameters and analysis of variance was used for hemodynamic parameters in the same group. $P < 0.05$ was considered statistically significant. **Results:** Midazolam resulted in improved quality of sensory blockade in terms of early onset, increased duration of effective analgesia, and delayed two segment regression time and also decreases the incidence of TNS with intrathecal lignocaine. **Conclusions:** Midazolam is an effective adjuvant to intrathecal lignocaine.

Key words: *Analgesia, lidocaine, midazolam*

INTRODUCTION

Spinal anesthesia with lignocaine heavy has been popular for short surgical procedures as it has predictable onset and provides dense sensory and motor block of moderate duration. The choice is based on a record of more than several decades of its safe use. Unfortunately, in the past decade, some reports of neurotoxicity have cast doubts on the use of lignocaine for spinal anesthesia.[1-3] This phenomenon of transient neurologic symptoms (TNS) may be associated with all local anesthetics, but it is 79 times higher following lignocaine than with bupivacaine.[4] The etiology of TNS remains unclear and unproven[5] as well as the reason why after nearly a century of use, it is only now being recognized as an adverse effect of spinal anesthesia.[6]

However, the growing number of outpatient procedures combined with rapid discharge criteria has brought attention to lidocaine for intrathecal regional anesthesia. This study has been carried out in this part of the world where intrathecal lignocaine is still being considered as a safe anesthetic mode by the anesthesia care providers. In view of the uncertainty surrounding, the use of spinal lignocaine the present study was undertaken. The primary objective of the study was to evaluate the effect of intrathecal midazolam as an adjuvant to spinal lignocaine in terms of quality and duration of spinal sensory blockade. The secondary objectives are to study the effect on hemodynamics due to intrathecal midazolam and the incidence of TNS.

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MATERIALS AND METHODS

After Institutional Ethical Committee approval and informed patient consent, 100 healthy adults of American

Society of Anesthesiology grade I and II scheduled for infra umbilical elective surgeries were enrolled for these prospective randomized controlled study. The sample size of 50 in each group based on statistical power analysis is arrived from previous studies. We have employed sample size of 80% power and an alpha error of 5% to detect a 20% change in terms of our primary goal. Apart from the usual contraindications for spinal anesthesia, exclusion criteria includes pregnant patients, surgeries demanding lithotomy position, anticipated early ambulation, prior history of neuropathies, prolonged duration of surgery >2 h, obesity with body mass index >35 and age >65.

The subjects were randomly assigned to two groups A and B. Randomization is by sealed envelope technique group A patients received spinal anesthesia with 1.5 ml of 5% lignocaine heavy along with 0.4 ml of 0.9% saline and group B (control group)received spinal anesthesia with 1.5 ml of 5% heavy lignocaine with 0.4 ml of preservative free 0.5% midazolam. Preloading was done with 500 ml of lactated Ringer's solution before the spinal block to all patients. Lumbar puncture was performed in the lateral position using 27 gauge Quincke spinal needle positioned midline at L3-4 interspace. Injection was given over 30s after free flow of cerebrospinal fluid was ensured. The patient was immediately turned to the supine position. The anesthetist who performed the subarachnoid block as well as the observer collecting the data were blinded.

Blood pressure(BP), pulse rate, electrocardiogram, and SpO_2 were monitored continuously. Any complication or adverse effects in the form of hypotension, bradycardia (fall of 20% of baseline value), nausea, vomiting, chest discomfort, pruritus, shivering, and respiratory depression (fall in SpO_2 below 90%) were noted and treated accordingly.

The primary study parameters are the time for the onset of sensory block, two segment regression, and duration of effective analgesia. Onset of sensory block was measured by checking for loss of sensation to cold stimuli every 15s after the patient is shifted to the supine position at the level of the umbilicus. The sensory level achieved after 20 min is taken as maximum sensory level. Following which the time for two segment regression of sensory block is checked at 5 min interval. Degree of motor block was noted using Bromage scale after 20 min of onset of block. Visual analog scale was used for pain measurement. Duration of effective analgesia was defined as the duration till the patient has a pain sore of 3 and above.

All the patients were followed-up to seven postoperative days for the occurrence of headache, backache, paresthesia, burning pain in thighs, buttocks or legs, etc. Every day, all the patients were categorically asked leading questions regarding paresthesia, radiating pain in legs, buttocks or thighs or any other neurological symptoms which is suggestive of TNS by the same anesthesiologist who is blinded. The symptomatic patients are evaluated by a blinded neurophysician.

For statistical analysis, *Z* test was used for comparison between the groups and one-way analysis of variance was used for hemodynamic parameters in the same group. $P < 0.05$ was considered statistically significant. Data were presented as mean ± standard deviation.

RESULTS

Table 1 shows the patient characteristics of the groups. There was no significant difference in patient's age, sex, weight, type or duration of operation among the groups. The time for the onset of the sensory analgesia level was significantly less in group B ($P < 0.05$). Time for two segment regression of sensory block was significantly prolonged in group B as compared to group A as also the duration of effective is more prolonged than group B [Table 2].

Table 3 shows the comparison of hemodynamic parameters in both the groups which shows that there is statistically significant change in the mean heart rate, systolic BP, and diastolic BP between the preoperative and intraoperative readings, while there is no statistically significant change observed between the preoperative and postoperative values.

Comparing the incidence of probable TNS, there were eight cases who complained symptoms suggestive of TNS in group A and there is no incidence in group B. Of the eight cases, six patients were for inguinal herniorrhaphy, six of them were of age group of 4555 years and two are of female gender. All developed symptoms suggestive of

Table 1: Patient characteristics

Patient characteristics	Group A	Group B	*P*
Age	34.34±6.15	33.18±7.05	0.1
Height	161.20±6.64	161.14±7.11	0.2
Weight	56.44±5.61	56.7±5.59	0.4
Sex (male/female)	21/9	20/10	
Duration of surgery	59.62±13.04	58.42±84	0.2

Table 2: Comparison of study parameters

Study parameters	Group A	Group B	*P*
Onset of analgesia	4.9±0.66	4.56±0.7	0.04
Two segment regression	59.8±7.6	79.3±5.1	0.04
Duration of effective analgesia	188.4±37.6	296.4±24.87	0.001

Table 3: Comparison of hemodynamic parameters

Parameter	Group A					Group B				
	Preoperative	Intraoperative	*P*	Postoperative	*P*	Preoperative	Intraoperative	*P*	Postoperative	*P*
Mean systolic BP	121.6±6.05	118±5.44	0.02	121.8±6.09	0.20	126.4±8.28	119.8±7.06	0.05	126.4±8.1	0.24
Mean diastolic BP	77.6±6.68	76.2±6.09	0.03	77.8±6.02	0.1	81.0±7.6	79±7.28	0.02	80±7.32	0.2
Mean heart rate	79.5±6.68	83.5±6.86	0.04	79.2±5.67	0.08	80.5±6.5	86.2±5.87	0.05	79.9±5.79	0.10

BP: Blood pressure

TNS within the first 48 h after spinal blockade. All the eight cases were observed for 1-week, and they were treated with tablet gabapentin 1000 mg OD for 4 days with the expert help of neurophysician and all of them were relieved of symptoms and discharged.

DISCUSSION

In this study, we found that the analgesic effect of intrathecal lidocaine was potentiated by addition of intrathecal midazolam as an adjuvant. The addition of 2 mg of midazolam to intrathecal lignocaine improved the quality of sensory blockade by giving a quicker onset, prolonged time for two segment regression and prolonged duration of effective analgesia.[7-10] *In vitro* autoradiography has shown that there is a high density of benzodiazepine (GABA-A) receptors in lamina II of the dorsal horn in the human spinal cord.[11] In 1987, good child reported benzodiazepines analgesic effect especially of intrathecal midazolam in rats and humans.[12-14] The delta-selective opioid antagonist, naltrindole, suppresses the antinociceptive effect of intrathecal midazolam, suggesting that intrathecal midazolam is involved in the release of endogenous opioid acting at spinal delta receptors.[15] The analgesic effect of intrathecal midazolam was segmental without alteration in sympathetic tone. Midazolam has been demonstrated to be effective against visceral pain in rabbits subjected to intestinal distension, and in humans after cesarean section.[9,16] A single intrathecal injection of 2 mg midazolam produced significant analgesia for 2 months in patients with chronic low back pain.[17]

In terms of the secondary goals of the study, the hemodynamics responses due to the addition of midazolam are similar to the control group.

In terms of the incidence of the symptoms suggestive of TNS, our finding suggests that intrathecal midazolam may be protective against the development of TNS. The patients were categorically asked leading questions regarding paresthesia, radiating pain in legs, buttocks, or thighs or any other neurological symptoms. Certainly, none of the risk factors that increase the likelihood of TNS were present in our patients except the drug, 5% heavy lignocaine. The risk factors being long duration surgery, lithotomy or arthroscopic position, obesity, early mobilization, etc.[18] The surgeries were of moderate duration (50-65 min) done in the supine position. No patient was mobilized before 24 h (which is a routine in our surgical wards). Freedman *et al*.[3] performed a 14-month large scale epidemiological study at 15 medical centers. Their findings suggested a profound risk for developing TNS in patients having received intrathecal lidocaine compared to those receiving bupivacaine or tetracaine. Incidences as high as 36% have been reported. We observed around 16% incidence of symptoms suggestive of TNS.

Previous studies have proved the efficacy of intrathecal midazolam with or without epidural methylprednisolone for management of postherpetic neuralgia involving lumbosacral dermatomes.[19] Intrathecal midazolam has been shown earlier to be effective in the treatment of neuralgic pain, and hence, we explain the absence of symptoms suggestive of TNS in the midazolam group.

The advantage of our study is the continuous follow-up of all the patients for 7 days in the postoperative ward itself, all the patients are interviewed personally by the anesthesiologist, and also the symptomatic patients are evaluated by a neurophysician. These advantages are lacking in other studies related with TNS. Telephone interviews are not the optimal source of data collection and weaken a study significantly. Finally, a patient may be more apt to report pain if directly asked about that specific pain.

The limitations of our study are that the incidence of TNS is a secondary goal, and the sample size may not be sufficient to detect effect change in the incidence of TNS among the two groups.

In terms of the future prospects, intrathecal addition of midazolam to lignocaine as an adjuvant may have advantages of decreasing the incidence of TNS and can be the resurgence of the most effective and short acting spinal local anesthetic which is ideal for the growing outpatient anesthesia.

REFERENCES

1. Schneider M, Ettlin T, Kaufmann M, Schumacher P, Urwyler A, Hampl K, *et al.* Transient neurologic toxicity after hyperbaric subarachnoid anesthesia with 5% lidocaine. Anesth Analg 1993;76:1154-7.

2. Hampl KF, Schneider MC, Ummenhofer W, Drewe J. Transient neurologic symptoms after spinal anesthesia. Anesth Analg 1995;81:1148-53.
3. Freedman JM, Li DK, Drasner K, Jaskela MC, Larsen B, Wi S. Transient neurologic symptoms after spinal anesthesia: An epidemiologic study of 1,863 patients. Anesthesiology 1998;89:633-41.
4. Karovits J, Scott H. Minor sequelae of central neural block. In: Adams AP, Coshman JN, editors. Recent Advances in Anesthesia and Analgesia. 21st ed. London: Churchill Livingstone; 2000. p. 197.
5. Pollock JE. Neurotoxicity of local anesthetics. Curr Anesthesiol Rep 2000;2:10-5.
6. Mc Donald SB, Neal JM. Spinal anesthesia in the ambulatory setting. Curr Anesthesiol Rep 2001;1:33-7.
7. Kim MH, Lee YM. Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy. Br J Anesth 2001;86:77-9.
8. Bharti N, Madan R, Mohanty PR, Kaul HL. Intrathecal midazolam added to bupivacaine improves the duration and quality of spinal anesthesia. Acta Anesthesiol Scand 2003;47:1101-5.
9. Sen A, Rudra A, Sarkar SK, Biswas B. Intrathecal midazolam for postoperative pain relief in caesarean section delivery. J Indian Med Assoc 2001;99:683-4.
10. Jahangiri B, Jahangiri R. Intrathecal midazolam prolongs the analgesic effects of spinal blockade with lidocaine for perineal operation. Acta Med Iran 2006;44:354.
11. Faull RL, Villiger JW. Benzodiazepine receptors in the human spinal cord: A detailed anatomical and pharmacological study. Neuroscience 1986;17:791-802.
12. Goodchild CS, Serrao JM. Intrathecal midazolam in the rat: Evidence for spinally-mediated analgesia. Br J Anesth 1987;59:1563-70.
13. Goodchild CS, Noble J. The effects of intrathecal midazolam on sympathetic nervous system reflexes in man — A pilot study. Br J Clin Pharmacol 1987;23:279-85.
14. Bahar M, Cohen ML, Grinshpon Y, Chanimov M. Spinal anesthesia with midazolam in the rat. Can J Anesth 1997;44:208-15.
15. Goodchild CS, Guo Z, Musgreave A, Gent JP. Antinociception by intrathecal midazolam involves endogenous neurotransmitters acting at spinal cord delta opioid receptors. Br J Anesth 1996;77:758-63.
16. Crawford ME, Jensen FM, Toftdahl DB, Madsen JB. Direct spinal effect of intrathecal and extradural midazolam on visceral noxious stimulation in rabbits. Br J Anesth 1993;70:642-6.
17. Serrao JM, Marks RL, Morley SJ, Goodchild CS. Intrathecal midazolam for the treatment of chronic mechanical low back pain: A controlled comparison with epidural steroid in a pilot study. Pain 1992;48:5-12.
18. Wallace P. Transient neurologic symptoms: Lidocaine hurting for attention. Internet J Anesthesiol.2007;17:21.
19. Dureja GP, Usmani H, Khan M, Tahseen M, Jamal A. Efficacy of intrathecal midazolam with or without epidural methylprednisolone for management of post-herpetic neuralgia involving lumbosacral dermatomes. Pain Physician 2010;13:213-21.

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