The Effect Of Intrathecal Midazolam 2.5 mg With Hyperbaric Bupivacaine On Postoperative Pain Relief In Patients Undergoing Orthopedic Surgery

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Abstract

In this prospective, randomized, double- blind study, we investigated the postoperative analgesic efficacy of intrathecal midazolam 2.5mg as an adjunct to bupivacaine for spinal anesthesia in 80 patients undergoing lower limb orthopedic surgery. Patients were allocated randomly to 2 groups: Group B received 3.5 ml hyperbaric bupivacaine 0.5% plus 0.5 ml saline intrathecally; group BM received 3.5 ml bupivacaine plus 0.5 ml midazolam (5 mg/ml). Mean duration of postoperative analgesia was 258±37 min in group B compared with 412±57min in group BM ($p< 0.001$). Supplemental analgesic dose requirement with diclofenac were significantly less in group BM (2.17 ± 0.50) compared with group B (3.00 ± 0.39) ($p< 0.001$). Time to onset of sensory analgesia, maximum level of sensory block, time to reach it, and time to two segment regression were comparable. We conclude that intrathecal midazolam 2.5mg provided moderate prolongation of postoperative analgesia when used as an adjunct to bupivacaine.

Support was from Institutional source

INTRODUCTION

Regional anesthetic techniques provide an excellent means for managing postoperative pain following orthopedic procedures. Spinal anesthesia with bupivacaine is administered routinely for lower limb surgery[1] and provides effective analgesia in the early postoperative period. Various adjuvants have been added to spinal local anesthetic to prolong postoperative analgesia. Intrathecal morphine provides effective postoperative analgesia but is associated with adverse effects such as itching, nausea, urinary retention, sedation, ileus and life-threatening respiratory depression.[2] Other adjuvants such as clonidine and ketamine have also been administered but none have become established in regular clinical use because of their adverse effects.[3]

Intrathecal midazolam has been reported to have antinoceptive action. [4] Evidence indicates that intrathecal midazolam may be useful in the treatment of somatic pain [5], [6], [7]. The optimum dose of intrathecal midazolam for postoperative analgesia is not identified. In previous studies midazolam has been administered in the dose of 1mg and 2mg intrathecally. [3], [8], [9] Up to 6 mg per day of midazolam has been used safely as an intrathecal infusion for relief of chronic refractory pain. [10] In this prospective, randomized, double-blind study, we evaluated the analgesic efficacy of a combination of intrathecal midazolam and bupivacaine and compared it with bupivacaine alone in patients undergoing lower limb orthopedic surgery.

MATERIALS AND METHODS

After approval by the hospital ethics committee and obtaining written informed consent, 80 patients (ASA class I and II), aged 20 to 50 years, scheduled to undergo elective lower limb orthopedic surgery (internal fixation of femur) were included in this prospective, randomized, double-blind trial.

Patients were excluded from the study if there was a contraindication to regional anesthesia, known sensitivity to study drugs, or were on chronic analgesic therapy. Visual analogue scale (VAS-consisting of 100 mm line with 0 = no pain and 100 = worst possible pain) was explained to all patients during the preoperative visit. No premedication was administered.

Patients were randomly allocated to one of two groups:

Group B (n = 40) received 3.5 ml hyperbaric bupivacaine 0.5% plus 0.5 ml saline 0.9% intrathecally; group BM (n = 40) received 3.5 ml hyperbaric bupivacaine 0.5% plus 0.5 ml preservative free midazolam (5 mg/ml). Active and placebo solutions were prepared by a second anesthesiologist otherwise uninvolved with the case. The anesthesiologist performing the block and postoperative assessments was blinded to the solution administered.

Monitoring was established with electrocardiography, pulse oximetry and non-invasive blood pressure measuring device. A 16 gauge intravenous canula was sited and a preload of 10 ml/kg of lactated Ringer's solution was administered. Dural puncture was performed at the lumbar 3-4 inter space in the sitting position using a 25G spinal needle. The patients were immediately placed in the supine position after intrathecal administration of the study drugs.

Time to onset of analgesia at the dorsum of foot, maximum level of sensory block and the time required to achieve it were noted. The observations were assessed by loss of sharp sensation to pinprick with a short-beveled needle at 2 min intervals for 15 min after intrathecal injection and subsequently at 10 min intervals intraoperatively. Time to two segment regression of analgesia was recorded. The level of sedation, oxygen saturation, respiratory rate, and blood pressure were recorded every 10 min during the surgery. The level of sedation was assessed every hour for six hours following arrival in the recovery room by using the sedation score described by Chernik et al [11] (wide awake = 0; sleeping comfortably, responding to verbal commands = 1; deep sleep, but arousable = 2; deep sleep, not arousable = 3). Postoperatively, in addition to the above, VAS score was noted at 4, 6, 12 and 24 h from the institution of block.

Rescue analgesia was administered when VAS score was ? 4 with 1 mg/kg diclofenac sodium intramuscularly. If satisfactory analgesia was not achieved, 1 mg/kg tramadol was administered intravenously. Time to first analgesic (time between intrathecal injection and first administration of rescue analgesic) and the total number of analgesic doses required in the first 24 h postoperatively were recorded.

Duration of motor block, time to first micturition, side effects (nausea, vomiting, shivering, urinary retention), neurological deficits and post dural puncture headache were recorded.

Statistical Analysis: Data was analyzed on Stata version 5.0 (1997). Parametric and nonparametric observations were analyzed using two sample test, Mann- Whitney test or Chi-square test, as appropriate. $P < 0.05$ was considered as statistically significant.

RESULTS

The two groups of patients were comparable with respect to age, height, sex and type of surgery distribution ($p > 0.05$) (Table 1). No statistically significant differences were observed in heart rate, arterial blood pressure, respiratory rate, and oxygen saturation between the two groups, both intraoperatively as well as postoperatively.

Figure 1

Table 1: Patient characteristics and duration of surgery

	Group B	Group BM
Age (yr)	34.9 ± 8.5	36.4 ±8.8
Height (cm)	160.6 ±5.7	162.5 ± 5.8
Sex (M: F)	32 : 8	33 : 7
Duration of surgery (min)	142.9 ± 31.9	146.4 ± 29.7

Values are mean ± SD.

Time to onset of sensory analgesia, maximum level of sensory block, time to reach it, and time to two segment regression were not statistically significant between the two groups; $p > 0.05$ (Table 2).

Figure 2

Table 2: Characteristics of spinal blockade.

	Group B	Group BM	p value
Onset of sensory analgesia (min)	3.0 ± 0.7	2.9 ± 0.7	0.750
Maximum sensory level (thoracic dermatome)	T7 (T6-T8)	T7 (T6-T8)	-
Time to achieve maximum sensory level (min)	9.8 ± 0.9	9.6 ± 1.0	0.19
Time to two segment regression (min)	108.8 ± 14.7	107.4 ± 15.3	0.68

Values are mean ± SD

Mean time to first administration of rescue analgesia with diclofenac sodium 1mg/kg was 258.3 ± 37.4 min in group B and 412.1 ± 57.3 min in group BM (Table 3). The duration of analgesia in group B was significantly shorter than that in group BM; $p < 0.001$. (Table 3).

Figure 3

Table 3: Time to rescue analgesia, and post operative analgesic requirement in 24 h.

	Group B	Group BM	p value
Time to rescue analgesic (min)	258.3 ± 37.4	412.1 ± 57.3	0.001
24h diclofenac dose requirement (n)	3.0 ± 0.4	2.2 ± 0.5	0.001
24h tramadol dose requirement (n)	3	1	0.01

Values are mean ± SD

Patients in group B required significantly greater number of doses of rescue analgesia (3.0 ± 0.4) compared with group BM (2.2 ± 0.5); $p < 0.001$. Three patients in group B and one patient in group BM required additional analgesia with tramadol (Table 3). Mean visual analogue scores at 4, 6, 12 and 24 h postoperatively are shown in Table 4.

Figure 4

Table 4: Post operative visual analogue scores at various time points.

	Group B	Group BM	p value
4 hours	5.78 ± 1.40	3.0 ± 0.96	0.001
6 hours	3.55 ± 1.06	5.20 ± 1.41	0.001
12 hours	3.93 ± 1.40	3.35 ± 1.56	0.08
24 hours	3.40 ± 1.08	2.87 ± 1.01	0.06

Values are mean ± SD

Figure 5

Table 5: Intraoperative sedation scores.

Sedation score	Group B	Group BM
0	23 (57.5)	25 (62.5)
1	17(42.5)	15 (37.5)
2	0	0
3	0	0

Values are numbers (per cent)

lntraoperative and postoperative sedation scores were comparable between the two groups (Table 5).The incidence of emesis, shivering and post dural puncture headache was not statistically different between the groups.

DISCUSSION

Our results confirm the efficacy of intrathecal midazolam in post-operative pain control. The addition of midazolam to intrathecal bupivacaine increased the duration of analgesia compared with bupivacaine alone. Previous pre-clinical studies have demonstrated the potential role of spinal benzodiazepine receptors in segmental anti-nociceptive action of intrathecal midazolam.[12, 13] Goodchild and Noble [5] conducted early clinical trials in humans. Intrathecal midazolam has been found to be an effective treatment for chronic mechanical low back pain.[14] The analgesic efficacy of epidural and caudal midazolam in combination with local anesthetics has been assessed for postoperative pain relief in both adults [15] and in children.[16]

The present study was carried out to evaluate the efficacy, duration of action and adverse effects, if any, of 2.5 mg midazolam when given with 0.5% bupivacaine by intrathecal route for postoperative analgesia in patients undergoing elective lower limb orthopedic surgery. Time of onset of sensory block, maximum level of block and time taken for maximum cephalic spread were not affected after addition of midazolam to bupivacaine as compared with bupivacaine alone. Similar results have been reported by Batra et al. [3] In our study, the mean time to two segment regression of sensory block was comparable in the two groups. This is in contrast to that reported by Batra et al [3] who found that there was a statistically significant difference between midazolam and bupivacaine groups.

The addition of midazolam 2.5 mg intrathecally prolonged the duration of spinal analgesia to 6.8 hours in our study. Kim & Lee [8] evaluated the postoperative analgesic effects of intrathecal midazolam with bupivacaine following hemorrhoidectomy. The addition of 1 or 2 mg of intrathecal midazolam prolonged the postoperative analgesic effect of bupivacaine by 2 hr and 4.5 hr, respectively, compared with controls. In addition, midazolam treated groups used less analgesic in the first 24 hour after surgery. Their results suggest a dose- dependent effect of intrathecal midazolam.[8]

Valentine et al[9] assessed intrathecal midazolam for use as a postoperative analgesic when given alone and in conjunction with intrathecal diamorphine in patients scheduled for Cesarean section. Bupivacaine with midazolam showed better analgesia than bupivacaine alone at 1 hr.

Intrathecal midazolam 2 mg improved the quality and duration of postoperative pain relief afforded by intrathecal

buprenorphine and bupivacaine.[17] Batra et al[3] reported an increased duration of postoperative analgesia with intrathecal midazolam 2mg and bupivacaine in 30 patients undergoing knee arthroscopy. All patients received rescue analgesia in the control group at a mean duration of 258 ± 46.8 min whereas only one patient in midazolam-bupivacaine group required supplemental analgesia within this period.3 Intrathecal midazolam 2mg provided a moderate prolongation of postoperative analgesia when used as an adjunct to bupivacaine in patients undergoing Cesarean delivery.[18] In addition, intrathecal midazolam, 1mg and 2mg, decreased postoperative nausea and vomiting.[18]

Sedation was not observed in any patient. Previous studies have similarly not observed sedation in patients following administration of intrathecal midazolam.[3, 14]Sedation has been reported with higher doses of epidural midazolam (75-100 µg). [19]

The postoperative supplemental analgesic requirement was significantly less in the bupivacaine – midazolam group compared with bupivacaine group. Other workers have similarly reported that patients who received intrathecal or epidural midazolam required less analgesic medication in 24 hours postoperatively. [8, 9, 15, 16]

A serious risk of intrathecal administration of any drug is its neurotoxicity. Studies in animals have revealed no neurotoxic effects, [12, 20, 21] though two other studies [22, 23] observed signs of neurotoxicity. No clinical signs of neurotoxicity in humans have yet been reported. [5, 8, 14]In a cohort study investigating safety in 547 patients, administration of intrathecal midazolam 2mg did not increase the occurrence of neurologic symptoms. [24]

In conclusion, post operative analgesia was prolonged with intrathecal midazolam 2.5 mg when used as an adjunct to bupivacaine as evidenced by significantly longer time to first rescue analgesia and lower VAS scores. There were no adverse effects.

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