Southern African Journal of Anaesthesia and Analgesia 2015; 21(2):13-16
http://dx.doi.org/10.1080/22201181.2015.1028216

South Afr J Anaesth Analg
ISSN 2220-1181 EISSN 2220-1173

RESEARCH

Efficacy of intrathecal midazolam versus fentanyl for endoscopic urology surgery[i]

Neerja Bharti[1]*, Yatindra K Batra[1] and Sunder L Negi[1]

[1]*Department of Anesthesia & Intensive Care, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh 160012, India*
**Corresponding author, email*: bhartineerja@yahoo.com

Background: This prospective randomized double-blind study was designed to compare the analgesic efficacy and safety of intrathecal midazolam versus fentanyl as an adjunct to bupivacaine for endoscopic urology surgery.
Methods: Sixty adult ASA grade I–II patients undergoing transurethral resection of prostate or bladder tumor under spinal anesthesia were randomly allocated into three groups. Group B (control group) received 2 ml 0.5% hyperbaric bupivacaine while group BM received midazolam 2 mg and group BF received fentanyl 25 µg along with 2 ml of 0.5% bupivacaine in subarachnoid block. Postoperative analgesia was provided with intravenous diclofenac. The onset and duration of sensory and motor blockade, postoperative pain and the time to 1st rescue analgesia was noted. Patients were observed for hypotension, bradycardia, sedation, respiratory depression, pruritus, and postoperative nausea-vomiting.
Results: The onset times and the duration of motor blockade were comparable among groups while the time to sensory block regression was longer in group BM and group BF as compared to group B ($p < 0.001$).The duration of postoperative analgesia was significantly prolonged in group BM and group BF as compared with group B ($p < 0.001$) while there was no difference between group BM and BF. The incidence of pruritus and vomiting was more in group BF.
Conclusions: Addition of midazolam to intrathecal bupivacaine provides prolonged postoperative analgesia similar to intrathecal fentanyl and appears safe in patients undergoing endoscopic urology surgery.

Keywords: adverse effects, adjuvants-fentanyl, anesthesia-spinal, endoscopic urology surgery, midazolam, postoperative analgesia

Introduction

Spinal anesthesia for endoscopic urology surgery like transurethral resection of the prostate or bladder tumor is a well-established technique. Opioids like morphine and fentanyl are extensively used as an adjunct to local anesthetics in neuraxial blockade to enhance the duration of postoperative analgesia.[1–3] However, worrisome adverse effects like pruritus, urinary retention, postoperative vomiting and respiratory depression limit the use of opioids in such procedures [4,5].

Midazolam produces a synergistic effect on postoperative analgesia when administered intrathecally with bupivacaine.[6–10] Previous reports have shown that administration of intrathecal midazolam with local anesthetics prolongs the duration of spinal anesthesia and produces longer postoperative analgesia after lower abdominal and perianal surgeries.[11–17] None of these studies reported any serious adverse effects in patients receiving intrathecal midazolam. A large cohort study investigating the adverse neurological effects of intrathecal midazolam has also found no association between intrathecal midazolam and neurologic symptoms.[18] However, none of the studies to date compared the efficacy of intrathecal midazolam with fentanyl in endoscopic urology surgeries. Therefore, this prospective randomised double-blind study was planned to compare the analgesic efficacy and safety of intrathecal midazolam with fentanyl as an adjunct to bupivacaine spinal anesthesia in patients undergoing endoscopic urology surgery.

Material and method

After approval from the 'Ethics Review Committee' and written informed consent, 60 adult patients of ASA grade I–II undergoing transurethral resection of prostate or bladder tumor were included. Patients with major organ disease, on chronic use of analgesic medications, having any contraindication to regional anesthesia or known hypersensitivity to the drugs under investigation were excluded. The patients were randomly allocated into three groups: group B (control group) received 2 ml of 0.5% hyperbaric bupivacaine with 0.5 ml normal saline, group BF received 25 µg fentanyl while group BM received 2 mg preservative-free midazolam along with 2 ml of 0.5% hyperbaric bupivacaine in total, a 2.5 ml volume intrathecally in each group. The study drug was prepared by an anesthesiologist not involved in the patient management and data collection.

The patients received 5 mg diazepam orally at night before surgery. On arrival in the operation theatre, an infusion of normal saline 15 ml/kg/hr was started. Standard monitoring of five-lead electrocardiography, non-invasive blood pressure and pulse oximetry was instituted. Spinal anesthesia was performed at L3–4 intervertebral space with a 25-G Quincke needle with patients in right lateral position. Once free flow of cerebrospinal fluid was obtained, the study drug was injected at the rate of approximately 0.2 ml per second. The assessment of sensory blockade was performed by pin-prick sensation at every 2 min until maximum level was achieved, and every 15 min interval during postoperative period until regression of block to S2 segment. The motor blockade was assessed at the same intervals using a modified Bromage scale (0 = no paralysis, 1 = unable to raise extended leg, 2 = unable to flex knee, 3 = unable to flex ankle). The onset and duration of sensory and motor blockade were recorded. The patients received oxygen 6 l/min via a face mask during surgery. Intravenous fluids (crystalloids, colloids or blood) were administered for maintenance and according to the surgical blood loss. Heart rate, blood pressure and oxygen saturation (SpO_2) were recorded at baseline, after intrathecal injection and then every 5 min until the end of surgical procedure.

Hypotension (mean arterial pressure < 25% of baseline) and bradycardia (heart rate < 40 beats/min) were treated with intravenous ephedrine 5 mg and atropine 0.5 mg respectively.

The patients were observed in the post anesthesia care unit for vitals and block characteristics by an anesthesiologist blinded to the group assignment. Postoperative pain was assessed by verbal rating pain scale (0–10, 0 = no pain and 10 = worst imaginable pain) at 1 h intervals till requirement of supplementary analgesia. Rescue analgesia was provided with intravenous diclofenac1.5 mg/kg when the VRS was recorded 4 or more. The duration of postoperative analgesia i.e. time from intrathecal injection till administration of first rescue analgesia (primary outcome) was recorded. The level of sedation was assessed every hour for 6 h postoperatively by 4-point categorical scoring system [19] (0 = awake, 1 = sleeping comfortably, easily arousable on verbal command, 2 = deep sleep but arousable by physical stimulus, 3 = deep sleep, difficult to arouse). Any adverse effects like bradycardia, hypotension, respiratory depression, pruritus, headache and postoperative nausea-vomiting (PONV) were recorded. Symptomatic pruritus (frequent or generalized itching) was treated by intravenous diphenhydramine 0.2 mg/kg. Patients were discharged home after administration of first rescue analgesia once they were fully awake, pain free and having no residual sensory or motor blockade, and followed up for 7 days. They were contacted daily by telephone and examined after one week for any neurological complication.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 15). Data was presented as mean and standard deviation (SD) or numbers with percentage. Continuously distributed data variables were analyzed using one-way analysis of variance with *post hoc* test while categorical data (peak sensory level, side effects) were analyzed using the Chi-square test. The non-parametric data were compared using Mann–Whitney *U*-test or Kruskal–Wallis test followed by the Dunnett test for *post hoc* multiple comparisons. A *p*-value of <0.05 was considered statistically significant. Sample size was calculated on the basis of previous studies for detecting clinically significant difference of 30% in duration of analgesia, assuming a power of 80% and a significance level of 5%.

Results

Patients' characteristics and the duration of surgery were similar among groups. There was no significant difference among groups regarding the type and duration of surgery (Table 1). The onset times of sensory and motor blockade were also comparable. The regression of sensory blockade to S2 segment was significantly prolonged in the fentanyl and midazolam groups as compared to the bupivacaine only group (Table 2). However, the duration of complete recovery of motor blockade was comparable between the groups. The duration of postoperative analgesia was also significantly prolonged in the fentanyl and midazolam groups as compared to the bupivacaine only group ($p < 0.001$), while there was no statistical difference between the fentanyl and midazolam groups (Table 2).The pain scores were higher in the bupivacaine only group during 4–6 postoperative hours as compared to the other two groups ($p < 0.01$).

There was no difference in heart rate and blood pressure among groups. No episode of hypotension or bradycardia was recorded. Although the patients receiving intrathecal midazolam were sleepy during intraoperative period, they were easily arousable. No episode of hypoxia or respiratory depression was recorded. Four patients in the fentanyl group and two in the control group had postoperative vomiting, while only one in the midazolam group experienced this complication. The difference was not statistically significant. Six patients (30%) complained of pruritus in the fentanyl group while none in others ($p < 0.01$). Two of these patients developed severe pruritus and required diphenhydramine. None of the patients complained of postural headache or any neurological deficit.

Table 1: Demographic data and surgical duration

	Group B (*n* = 20)	Group BM (*n* = 20)	Group BF (*n* = 20)
Age (yr)	57.8 ± 9.2	50.8 ± 13.1	53.9 ± 12.8
Weight (kg)	57.3 ± 9.5	63.6 ± 9.5	62.1 ± 4.1
Gender (M:F)	16:4	17:3	18:2
ASA (I:II)	18:2	15:5	16:4
Duration of surgery (min)	67.7 ± 18.6	53.4 ± 13.1	76.4 ± 21
Type of surgery			
TURP	6	9	7
TURBT	14	11	13

Notes: Data presented as mean ± SD or number of patients, Group B: only bupivacaine, Group BM: bupivacaine plus midazolam, Group BF: bupivacaine plus fentanyl, TURP = transurethral resection of prostate, TURBT = transurethral resection of bladder tumor.

Table 2: Block characteristics and postoperative analgesia

	Group B (*n* = 20)	Group BM (*n* = 20)	Group BF (*n* = 20)
Onset sensory (min)	8.1 ± 0.7	6.8 ± 0.8	7.6 ± 0.5
Onset motor (min)	6.82 ± 0.9	7.73 ± 0.6	8.33 ± 0.7
Duration sensory (min)	166.5 ± 14.9	217.4 ± 15.7*	198.8 ± 16.5*
Duration motor (min)	132.1 ± 11.6	139.9 ± 12.8	145.4 ± 10.9
Duration of analgesia (min)	197.8 ± 16.8	284.2 ± 18.2*	272.4 ± 15.6*

Notes: Data presented as mean ± SD, Group B: only bupivacaine, Group BM: bupivacaine plus midazolam, Group BF: bupivacaine plus fentanyl.
*$p < 0.001$, compared to Group B.

Discussion

This study demonstrated increased duration of sensory blockade and postoperative analgesia after subarachnoid injection of midazolam or fentanyl to hyperbaric 0.5% bupivacaine in patients undergoing endoscopic urology surgery. The analgesic effect of intrathecal midazolam was comparable to intrathecal fentanyl, with lesser incidence of pruritus in the midazolam group. The administration of intrathecal midazolam, 2 mg, did not appear to increase the occurrence of neurologic symptoms, although numbers in each group were small.

Previous studies demonstrated a dose-dependent effect of intrathecal midazolam on postoperative analgesia. Kim et al.[14] found that the addition of 1 or 2 mg of midazolam to intrathecal bupivacaine provided analgesia of approximately 2 and 4.5 h, respectively. In another study Prakash et al.[9] demonstrated that 2 mg of intrathecal midazolam, when used as an adjunct to bupivacaine in patients undergoing caesarean delivery, could provide a moderate prolongation of postoperative analgesia with decreased incidence of postoperative nausea and vomiting. Others also observed that intrathecal midazolam produced significant postoperative pain relief in patients undergoing lower abdominal and perineal surgeries.[12,13,15,17]

Midazolam produces spinally mediated analgesia that is different in quality from that produced by the μ-opioid agonist fentanyl. The analgesic effects of intrathecal midazolam have been proposed to be due to its intrathecal spinal receptor interactions affecting the type A gamma-aminobutyric acid receptors.[20] It has also been suggested that intrathecal midazolam is involved in the release of an endogenous opioid acting at spinal delta receptors.[21]

Yegin et al.[1] reported that addition of 25 μg fentanyl to 18 mg hyperbaric ropivacaine for spinal anesthesia in patients undergoing transurethral resection of the prostate provided postoperative analgesia of approximately 3.5 h; 4 out of 15 patients in fentanyl group had pruritus. Though, the analgesic efficacy of intrathecal fentanyl has not been compared with intrathecal midazolam in normal patients, a recent study demonstrated that addition of 1 mg intrathecal midazolam to bupivacaine produces much longer duration of anesthesia (140 min) as compared with 25 μg intrathecal fentanyl (107 min) in opium abusers undergoing lower limb orthopedic surgery.[22] Another study, comparing intrathecal midazolam with clonidine, reported that 2 mg intrathecal midazolam provided superior analgesia than 30 μg clonidine with fewer adverse effects in patients undergoing lower abdominal surgeries.[23]

Intrathecal midazolam did not affect the duration of motor blockade in the present study. Although a few studies have reported prolongation of motor blockade after intrathecal midazolam,[12,14] a meta-analysis aiming to evaluate the effectiveness and side-effects of intrathecal midazolam in the perioperative setting reported that intrathecal midazolam did not affect the duration of motor blockade.[24] The incidence of neurological symptoms after intrathecal midazolam was uncommon (1.8%) and did not differ from placebo (odds ratio 1.20, 95% CI 0.22 to 6.68, $p = 0.84$).[24] We did not find any neurological adverse effect in any group of patients.

Although previous studies [12,14,24] have reported a decreased incidence of PONV with the use of intrathecal midazolam, we did not find any significant difference in PONV among groups. This may be because our study was not adequately powered for PONV. However, the incidence of pruritus was significantly less in midazolam group as compared to fentanyl group. We could not asses the incidence of urinary retention, because most of our patients were catheterised.

In conclusion, the addition of midazolam to intrathecal bupivacaine provides similar potentiating of analgesia as intrathecal fentanyl and appears safe in patients undergoing endoscopic urology surgery. Therefore intrathecal midazolam can be used as an adjuvant to local anesthetics if fentanyl is not available or contraindicated. However, a larger, multicenter study is required to prove its efficacy and safety in various procedures.

Funding — No financial support has been granted from any funding agency.

Conflict of interests — No conflict of interest.

Note

(i) The study has been presented at "9th Congress of SAARC Association of Anesthesiologists" at Bangalore, Karnataka, India, 2011.

References

1. Yegin A, Sanli S, Hadimioglu N, et al. Intrathecal fentanyl added to hyperbaric ropivacaine for transurethral resection of the prostate. Acta Anaesthesiol Scand. 2005;49:401–5. http://dx.doi.org/10.1111/aas.2005.49.issue-3
2. Otokwala JG, Fyneface-Ogan S, Mato CN. Comparative effects of single shot low dose spinal bupivacaine only and bupivacaine with fentanyl on labour outcome. Niger J Med. 2013;22:279–85.
3. Bozdogan Ozyilkan N, Kocum A, Sener M, et al. Comparison of intrathecal levobupivacaine combined with sufentanil, fentanyl, or placebo for elective caesarean section: a prospective, randomized, double-blind, controlled study. Curr Ther Res Clin Exp. 2013;75:64–70. http://dx.doi.org/10.1016/j.curtheres.2013.09.003
4. Wong CA, Scavone BM, Slavenas JP, et al. Efficacy and side effect profile of varying doses of intrathecal fentanyl added to bupivacaine for labor analgesia. Int J Obstet Anesth. 2004;13:19–24. http://dx.doi.org/10.1016/S0959-289X(03)00106-7
5. Raffaeli W, Marconi G, Fanelli G, et al. Opioid-related side-effects after intrathecal morphine. Eur J Anaesthesiol. 2006;23:605–10. http://dx.doi.org/10.1017/S026502150600038X
6. Nishiyama T, Hanaoka K. Midazolam can potentiate the analgesic effects of intrathecal bupivacaine on thermal- or inflammatory-induced pain. Anesth Analg. 2003;96:1386–91. http://dx.doi.org/10.1213/01.ANE.0000057606.82135.7D
7. Gupta A, Prakash S, Deshpande S, et al. The effect of intrathecal midazolam 2.5 mg with hyperbaric bupivacaine on postoperative pain relief in patients undergoing orthopaedic surgry. Internet J Anesthesiol. 2007;14:11.
8. Agrawal N, Usmani A, Sehgal R, et al. Effects of intrathecal midazolam bupivacaine combination on postoperative analgesia. Indian J Anaesth. 2005;49:37–9.
9. Prakash S, Joshi N, Gogia AR, et al. Analgesic efficacy of two doses of intrathecal midazolam with bupivacaine in patients undergoing cesarean delivery. Reg Anesth Pain Med. 2006;31:221–6. http://dx.doi.org/10.1097/00115550-200605000-00008
10. Karbasfrushan A, Farhadi K, Amini-Saman J, et al. Effect of intrathecal midazolam in the severity of pain in cesarean section: a randomized controlled trail. Iran Red Crescent Med J. 2012;14:276–82.
11. Sanad H, Abdelsalam T, Hamada M, et al. Effects of adding magnesium sulphate, midazolam or ketamine to hyperbaric bupivacaine for spinal anaesthesia in lower abdominal and lower extremity surgery. Ain Shams J Anesthesiol. 2010;3:43–52.
12. Chattopadhyay A, Maitra S, Sen S, et al. A study to compare the analgesic efficacy of intrathecal bupivacaine alone with intrathecal bupivacaine midazolam combination in patients undergoing elective infraumbilical surgery. Anesthesiol Res Pract. 2013;2013: 567134. doi: 10.1155/2013/567134.
13. Bharti N, Madan R, Mohanty PR, et al. Intrathecal midazolam added to bupivacaine improves the duration and quality of spinal anaesthesia.

Acta Anaesthesiologica Scandinavica. 2003;47:1101–5. http://dx.doi.org/10.1034/j.1399-6576.2003.00186.x
14. Kim MH, Lee YM. Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy. Br J Anaesth. 2001;86:77–9. http://dx.doi.org/10.1093/bja/86.1.77
15. Yegin A, Sanli S, Dosemeci L, et al. The analgesic and sedative effects of intrathecal midazolam in perianal surgery. Eur J Anaesthesiol. 2004;21:658–62. http://dx.doi.org/10.1097/00003643-200408000-00012
16. Shadangi BK, Garg R, Pandey R, et al. Effects of intrathecal midazolam in spinal anaesthesia: a prospective randomised case control study. Singapore Med J. 2011;52:432–5.
17. Talebi H, Yazdi B, Alizadeh S, et al. Effects of combination of intrathecal lidocaine and two doses of intrathecal midazolam on post-operative pain in patients undergoing herniorrhaphy: a randomized controlled trial. Pak J Biol Sci. 2010;13:1156–60.
18. Tucker AP, Lai C, Nadeson R, et al. Intrathecal midazolam i: a cohort study investigating safety. Anesth Analg. 2004;98:1512–20. http://dx.doi.org/10.1213/01.ANE.0000087075.14589.F5
19. Chen CK, Tan PCS, Phui VE, et al. A comparison of analgesic efficacy between oblique subcostal transversus abdominis plane block and intravenous morphine for laparascopic cholecystectomy. A prospective randomized controlled trial. Korean J Anesthesiol. 2013;64:511–6. http://dx.doi.org/10.4097/kjae.2013.64.6.511
20. Maeda A, Katafuchi T, Oba Y, et al. Enhancement of GABAergic tonic currents by midazolam and noradrenaline in rat substantial gelatinosa neurons *in vitro*. Anesthesiology. 2010;113:429–37. http://dx.doi.org/10.1097/ALN.0b013e3181e19bd4
21. Goodchild CS, Guo Z, Musgreave A, et al. Antinociception by intrathecal midazolam involves endogenous neurotransmitters acting at spinal cord delta opioid receptors. Br J Anaesth. 1996;77:758–63. http://dx.doi.org/10.1093/bja/77.6.758
22. Safari F, Dabbagh A, Sharifnia M. The effect of adjuvant midazolam compared with fentanyl on the duration of spinal anesthesia with 0.5% bupivacaine in opium abusers. Korean J Anesthesiol. 2012;63:521–6. http://dx.doi.org/10.4097/kjae.2012.63.6.521
23. Joshi SA, Subhedar RD, Motghare VM, et al. Comparative evaluation of intrathecal midazolam and low dose clonidine: efficacy, safety and duration of analgesia. A randomized, double blind, prospective clinical trial. Indian J Pharmacol. 2012;44:357–61. http://dx.doi.org/10.4103/0253-7613.96321
24. Ho KM, Ismail H. Use of intrathecal midazolam to improve perioperative analgesia: a meta-analysis. Anaesth Intensive Care. 2008; 36:365–73.

Received: 17-12-2013 Accepted: 15-07-2014