Midazolam versus Neostigmineadding to Lidocaine in Post Operation Pain in Colporrhaphy Surgery in Spinal Anesthesia

Alireza Kamali; M.D.[1], Maryam Shokrpour; M.D.[2], Khatereh Vatanpour; M.D.[3], Majid Golestani Eraghi; M.D.[4]

1 Department of Anesthesiology, Arak University of Medical Sciences, Arak Iran.
2 Department of Gynecology, Arak University of Medical Sciences, Arak, Iran.
3 Student of Arak University of Medical Sciences, Arak, Iran.
4 Resident of anesthesiology, University of Medical Sciences, Arak, Iran

Received October 2011, Revised and accepted in January 2012

Abstract

Objective: To compare the effect of intrathecal midazolam versus neostigmine added to lidocaine on the duration of sensory block and the duration of postoperative pain relief in women undergoing colporaphy in spinal anesthesia.

Materials and methods: In this double blind clinical trial we evaluated 60women (ASA) I,II that were candidate to elective colporaphy. The patients were randomly divided in three groups ,first group(midazolam group)received hyperbaric lidocaine and 1mg midazolam(0.5cc),second group (neostigmine group) received hyperbaric lidocaine and 50µg midazolam(0.5cc) and third group were considered as control and received hyperbaric lidocaine plus normal saline(0.5cc).VAS pain score 4,12 and 24 hours after surgery and duration of analgesia in tree groups were compared.

Results: The duration of sensory block in the midazolam group was 98.4±18.2minuts, 74.5±32.6 in neostigmine and 64.5±9.9 in control group and difference between three groups was significant (p=0.001). Postoperative pain scores in midazolam group was 1.5±1.3, in neostigmine group was 2.4±1.6 and in control group was 3.5±2.7 and difference between three groups was significant (P=0.009).

Conclusion: Midazolam & neostigmine added to lidocaine 5% prolonged postoperative analgesia in colporrhaphy surgery in spinal anesthesia but midazolam was more effective than neostigmine.

Keywords: midazolam &Neostygmine , Spinal anesthesia, analgesia, colporrhaphy

Introduction

Spinal anesthesia using local anesthetics has been broadly applied in lower limbs and lower abdominal operations. Postoperative pain is the most important cause of unintended hospital admissions following spinal anesthesia and a major source of dissatisfaction with perioperative outcome (1-2).A diver's class of intrathecal agents such as ketamine, clonidine, opioids and neostigmine are often added to enhance the duration of spinal anesthesia and reduce pain after surgeries. However, applying these agents are limited owing to adverse effects such as respiratory depression, hemodynamic instability, pruritis, urinary retention, nystagmus, and severe nausea and vomiting (3-6).It is well known that intrathecal midazolam create antinociception and potentiate the effect of local anesthetic without having remarkable side

Correspondence:
Maryam shokrpour,
E–mail: Maryam_shokrpour@yahoo.com

effects (7).Moreover, other studies showed intrathecal midazolam is safe (8)and when combined with other intrathecal agents, improves postoperative recovery and increased painless period in patients under surgery (9). On the other hand some studies divulged that intrathecal neostigmine is adjunctive spinal analgesic in very small doses (10).

Hence we conducted this study to compare the intrathecal midazolam plus lidocaine with neostigmine added to lidocaine and their effect on the duration of sensory block and the duration of postoperative pain relief in patients undergoing colporrhaphy surgery.

Materials and methods

In this double blind clinical trial we evaluated 60women aged 30-50, class American Society of Anesthesiologists (ASA) I,II that were candidate to elective colporaphy. The study protocol was approved by ethical committee of Arak university of medical sciences. Furthermore study protocol was explained for patients and informed written consent was taken from the patients. Patients with contraindications to regional anesthesia or sensitivity to study drugs and who were on chronic analgesic therapy were excluded from the study. Patients

Were received with oral diazepam (0.3 mg/kg)1 and ranitidine (ampoule, sina pharmacy Co. , Tehran-Iran 3 mg/kg) two the night before surgery. In the operating room, standard monitors (electrocardiogram, non-invasive blood pressure and pulse oximeter) was attached to the patient, and baseline vitals were recorded. An 18G intravenous line was secured and preloaded with Ringer's lactate 10 mL/kg3. The patients were randomly divided in three groups as follow: first group: received hyperbaric lidocaine (ampoule, Abureyhan pharmacy Co., Tehran – Iran) and 1mg midazolam (ampoule, Abureyhan pharmacy Co., Tehran – Iran), second group received hyperbaric lidocaine and 50µg neostigmine (ampoule, Tamin pharmacy Co., Rasht – Iran) and third group were considered as control and received hyperbaric lidocaine plus normal saline (0.5cc).

The anesthetics were administered intrathecal in lateral position in L3–4 or L4–5 space with a 25-gauze spinal needle. The study solution, prepared by another researcher who was not involved in the patient's care, was injected through the spinal needle over a period of ten seconds with no barbotage. After injecting the drug, the patient was turned to supine position, and the onset

time (defined as the time interval between the completion of intrathecal drug injection to the onset of complete loss of pinprick sensation at T8), level of sensory block (defined as the highest dermatomal level of sensory blockade by pinprick testing), time to achieve maximum sensory block level, duration of sensory block (defined as the time interval from completion of intrathecal drug injection and 2-segment regression of sensory block by pinprick method), duration of motor block (defined as the time taken from onset of complete motor block, score 3 to complete recovery of motor block, score 0) and time for rescue analgesia (defined as the time interval between administration of intrathecal drug to the time of administration of first rescue analgesia) were noted. Pain was weighed using the Visual Analogue Score(VAS) (0: no pain, 10: maximum pain). Pulse rate and blood pressure were monitored every five minutes in intraoperative and every ten minutes subsequently till 2-segment regression of block. Hypotension (> 20% decrease in systolic blood pressure from baseline) was managed with intravenous fluid (20 mL/kg).

Intraoperative rescue analgesia was administered with fentanyl (1 µg/kg, intravenously) (ampoule, Abureyhan pharmacy Co., Tehran – Iran), when required. If the pain was not relieved, the patient was given general anesthesia and excluded from the study. Postoperatively, rescue analgesic medication with diclofenac sodium suppository (1.5 mg/kg) (Dr Aabidi pharmacy Co., Tehran – Iran) was administered, if VAS was found to be ≥ 4. The level of sensory anesthesia was recorded at two-minute intervals for 15 minutes after completion of intrathecal injection, and every ten minutes thereafter. Motor block was assessed by the Bromage score (0: no motor loss, 1: inability to flex the hip, 2: inability to flex the knee joint, 3: inability to flex the ankle) at one-minute intervals until complete motor blockade occurred. Onset of motor block was defined as time taken from injection of drug to development of complete motor block (Bromage score3). The level of sedation of the patients was assessed by the Ramsay sedation score (1: anxious, agitated and restlessness, 2: oriented and cooperative, 3: responds to command only, 4: brisk response to loud voice and light glabellas tap, 5: sluggish to no response to light glabellas tap or loud auditory stimulus, 6: no response even to pain). All patients were followed up after surgery for up to 24 hours (4h.12h, 24h) for any behavioral side effects as confusion, dizziness,

nystagmus, nausea, vomiting or any neurological complications like pain or numbness in the leg.

Data were analyzed using the SPSS version 16.00.Student's *t*-test was used for comparing the three groups, while the chi-square test was used to analyze categorical data. P-value < 0.05was considered to be statistically significant.

Results

We evaluated 60 patients mean age 46.5±8.51 (three groups, 20 patients /group). Patients before study were properly matched and difference between groups regarding age was not significant. All patients had successful spinal anesthesia, and none required general anesthesia.

The duration of sensory blockade is illustrated in table 1. As assessed by kruskal-wallis test the duration was 98.4±18.2 minutes in the midazolam group , 74.5±32.6 in neostigmine and 64.5±9.9 in control group and difference between three groups was significant (p=0.001).The Mean number of diclofenac sodium suppository consumption in 24h post operation was 2, 05±0.94 in neostigmine group, 1.6±0.68 in midazolam group and 4.4± 1.4 in control group and difference between three groups was significant (P=0.001). Mean arterial pressure before anesthesia in all patients was 80.90 ±5.0 and difference between three groups was not significant (P= 0.06). Postoperative pain scores in midazolam group was 1.5±1.3, in neostigmine group was 2.4±1.6 and in control group was 3.5±2.7 and difference between three groups was significant as shown in table 2 (P=0.009). Pain scores 4 and 12 hours after operation in 3 studied groups are illustrated in table 3 and 4 respectively.

Table 1: Duration of sensory blockade after operation and the number of diclofenac suppositories used in three studied groups

	n	Mean	SD
Duration of anesthesia (minutes)			
Midazolam	20	98.4500	18.25398
Neostigmin	20	74.5500	32.62785
Control	20	64.5500	9.96560
total	60	79.1833	26.22619
Diclofenac suppositories used (n)	20	1.6000	0.68056
	20	2.0500	0.94451
	20	4.4000	1.46539
	60	2.6833	1.63118

Table 2: Pain score in recovery ward

	Mean± SD	P value*
midazolam	1.5± 1.3	
neostigmin	2.4±1/6	P=0.009
control	3.5±2.7	

* by Kruskal- Wallis test

Table 3: Pain score 4 hours after operation

	Mean± SD	P value*
midazolam	5.8±1.6	
neostigmin	6.7±1.4	0.07
control	6.1±2.3	

* by ANOVA

Table 4: Pain score 12 hours after operation

	Mean± SD	P value*
midazolam	2.3±1.5	
neostigmin	3.1±1.1	0.001
control	4.05±1.6	

* by ANOVA

Discussion

Several studies have revealed intrathecal midazolam have analgesic properties and when adding to intrathecal local anesthetics, potentiates the effects of these agents (11-14).Some of these studies indicated that intrathecal midazolam released an endogenous opioid acting at spinal delta receptors(15) .Therefore, adding intrathecal midazolam may potentiate the antinociceptive effect of morphine-like agents(12) .In a comparative study Shadangi et all used 2 mg midazolam as an additive to bupivacaine for intrathecal administration and reported that addition of preservative-free midazolam to bupivacaine intrathecally prolonged the postoperative analgesia without increasing motor block(16).Furthermore Son et al in a study on 40 women (ASA I,II) under cesarean surgery showed intrathecal midazolam added to lidocaine 0.05% is more effective in post operation pain control than lidocaine 0.05% alone(17).

In this trial we divulged the duration of sensory blockade in the midazolam group significantly was more than neostigmine and control groups' .Moreover post operation analgesic consumption in midazolam group significantly was lower than control and neostigmine groups. Furthermore we did not detect any adverse effect in our patients in 24 h postoperation in three groups. Previous studies agree that 1–2 mg intrathecal midazolam is safe and effectual (12-15)and one study on patients under cesarean section exposed intrathecal midazolam 2 mg

moderately prolonged postoperative analgesia as compared to 1 mg when used as an adjunct to bupivacaine(18).

We designated postoperative pain scores were lower in patients who received

intrathecal midazolam in addition to lidocaine than patients received neostigmine and control group. In line with our results ,Bharti et al, reported the postoperative pain scores were lower in patients who received intrathecal midazolam (1 mg) with bupivacaine(19).Moreover in agreement to our results

Prakash et al.administered intrathecal bupivacaine along with midazolam in either 1-mg or 2-mg doses and specified the duration of postoperative analgesia was significantly prolonged with the addition of intrathecal midazolam and that the effect was dose-dependent (18).

We did not observe any complication in postoperative period, in line with our study; Tucker et al evaluated and followed up a large group of patients (574 cases) for one month for a wide range of symptoms related to neurotoxicity who received intrathecal midazolam. They revealed occurrence of neurological symptoms did not increase when they administrated up to 2 mg intrathecal midazolam (7). However, in contrast to our results two studies indicated the duration of motor blockade was more prolong in the midazolam group compared with the control group (14, 19).

Our study encountered some limitations. Firstly, our study was not sufficiently powered to remark conclusively on the adverse effects in the three groups. Secondly, the relatively small sample size in this review limits the ability to generalize the result of our survey .therefore a larger study is necessary that is adequately powered to study the side effect profile of intrathecal midazolam.

In conclusion, the addition of midazolam & neostigmineto lidocaine 5% prolonged postoperative analgesia in colporrhaphy surgery in spinal anesthesia but midazolam was more effective than neostigmine.

References

1. Anaesthesia, Ronald D Miller. 5th Edn; Churchill Livingstone Philadelphia 2000: 2816.
2. Hawksworth C, Serpell M. Intrathecal anaesthesia with ketamine. Reg Anesth Pain Med 1998; 23:283-8.
3. Lauretti GR, Reis MP, Prado WA, Klamt JG. Dose response study of intrathecal morphine versus intrathecal neostigmine, their combination, or placebo for postoperative analgesia in patients undergoing anterior and posterior vaginoplasty. Anesth and Analg 1996; 82: 1182-7.
4. Lauretti GR, de Oliveira R, Perez MV, Paccola CA. Postoperative analgesia by intraarticular and epidural neostigmine following knee surgery. J Clin Anesth 2000;12:444-8.
5. Batra YK, Arya VK, Mahajan R, Chari P. Dose response study of caudal neostigmine for postoperative analgesia in paedatric patients undergoing genitourinary surgery . Paediatric Anaesth 2003; 13: 515-21.
6. Lauretti GR, De Olivera R, Reis MP, Juliâo MC, Pereira NL. Study of three different doses of epidural neostigmine coadministered with lidocaine for postoperative analgesia. Anesthesiology 1999;90: 1534-8.
7. Tucker AP, Lai C, Nadeson R, Goodchild CS. Intrathecal midazolam I: a cohort study investigating safety. AnesthAnalg 2004; 98:1512-20.
8. Wu YW, Shiau JM, Hong CC, Hung CP, Lu HF, Tseng CC. Intrathecal midazolam combined with low-dose bupivacaine improves postoperative recovery in diabetic mellitus patients undergoing foot debridement. Acta Anaesthesiol Taiwan 2005; 43:129-34.
9. Ho KM, Ismail H. use of inthrathecal midazolam to improve perioperative analgesia : a meta - analysis . Anesth Intensive care 2008; 36: 365-73.
10. Lauretti GR, Hood DD, Eisenach JC, Pfeifer BL. A multi-center study of intrathecal neostigmine for analgesia following vaginal hysterectomy. Anesthesiology 1998; 89:913-8.
11. Nishiyama T, Hanaoka K. Midazolam can potentate the analgesic effects of intrathecal bupivacaine on thermal- or inflammatory induced pain. Anesth Analg 2003; 96:1386-91.
12. Boussofara M, Carlès M, Raucoules-Aimé M, Sellam MR, Horn JL. Effects of intrathecal midazolam on postoperative analgesia when added to a bupivacaine-clonidine mixture. Reg Anesth Pain Med 2006; 31:501-5.
13. Edwards M, Serrao JM, Gent JP, Goodchild CS. On the mechanism by which midazolam causes spinally mediated analgesia. Anesthesiology 1990; 73:273-7.
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.
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 Anaesth 1996;77:758-63.
16. Shadangi BK, Garg R, Pandey R, Das T. Effects of intrathecal midazolam in spinal anaesthesia: a prospective randomized case control study. Singapore Med J 2011; 52: 432-5
17. 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, 686.
18. Prakash S, Joshi N, Gogia AR, Prakash S, Singh R. Analgesic efficacy of two doses of intrathecal midazolam with bupivacaine in patients undergoing cesarean delivery. Reg Anesth Pain Med 2006; 31:221-6.
19. Bharti N, Madan R, Mohanty PR, Kaul HL. Intrathecal midazolam added to bupivacaine improves the duration and quality of spinal anaesthesia. Acta Anaesthesiol Scand 2003; 47:1101-5.