INTRATHECAL MIDAZOLAM PROLONGS THE ANALGESIC EFFECTS OF SPINAL BLOCKADE WITH LIDOCAINE FOR PERINEAL OPERATION

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Abstract- Intrathecal administration of midazolam has been reported to have antinociceptive action, and to be an effective analgesic agent. In this prospective double-blind study we aimed to evaluate the postoperative effects of intrathecal midazolam with lidocaine following perineal operation. Forty patients were randomly allocated to two groups: 20 patients in the control group received 2 ml of 5% heavy lidocaine plus 0.4 ml of 0.9% saline intrathecally; 20 patients in the midazolam group received 2 ml of 5% heavy lidocaine plus 0.4 ml of 0.5% midazolam. Duration of analgesia was significantly greater in the midazolam group (7 ± 1 hours) compared to the control group (1.5 ± 0.5 hours).

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Key words: Anesthetic techniques, lidocaine, benzodiazepine, intrathecal midazolam

INTRODUCTION

Wang *et al.* reported the first intrathecal administration of opioid in patients in 1979, and achieved a prolonged analgesia (1). However, opioid-induced side effects, such as respiratory depression, nausea, vomiting, urinary retention, and pruritus, limit their use (2). But since the early 1980s, intrathecal administration of midazolam has been reported to have antinociceptive action, and to be an effective analgesic agent in animals, and humans (3). After perineal operations, many patients require parenteral, oral opioids, and nonsteroid anti-inflammatory drugs (NSAIDs) for analgesia.

The purpose of our study was to assess the analgesic effects of intrathecal midazolam as an adjunct to intrathecal lidocaine after perineal operation.

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MATERIALS AND METHODS

In this study, 40 patients (ASA Class I-II) who were admitted for perineal operation between January 1999, and May 2001 underwent study & observation. The group included 20 men, and 20 women aged from 25 to 65 years. All patients filled written informed consent, and local ethics committee approved the research. Those who had a contraindication to regional anesthesia or opioid tolerance were excluded. The patients were premedicated with diazepam 5 mg orally, 60 minutes before coming to the operation room. After preloading with 500 ml of intravenous 0.9% salt solution, spinal anesthesia was performed on patients in the sitting position under aseptic conditions at the L_4-L_5 interspace. The intrathecal space was located with a 25 gauge needle (Portex UK) and subarachnoid placement was confirmed by free flow of cerebrospinal fluid. Twenty patients in the control group received 2 ml of 5% heavy lidocaine, and 0.4 ml of 0.9% saline intrathecally. Twenty patients in the midazolam group received 2 ml of 5% heavy lidocaine, and 2 mg of midazolam in 0.4 ml (5 mg/ml) intrathecally.

Hyperbaric midazolam solution (Dornicom, Hoffman-La Roche, Basle, Switzerland), with the specific gravity of 1006 contains midazolam hydrochloride without preservative.

After intrathecal drug injection, all patients of the two groups were kept in the sitting position for 5 minutes, tested for sensory loss, and then placed in the surgical position.

During surgery, patients were monitored with electrocardioscopy, pulse oximetry, and non invasive measurement of arterial pressure and heart rate.

After surgery, all patients were admitted to surgical ward for 24 hours. We instructed patients to ask for one Acetaminophen Codeine tablet (500 mg acetaminophen and 8 mg codeine phosphate) every 4 hours in case of pain. No other analgesic was allowed during the 24 hours after surgery.

Analgesic time (pain-free period) from the beginning of intrathecal anesthesia and total consumption of analgesics in the 24 hours after surgery were assessed in our study. Before discharge all patients were checked for neurological changes such as, motor and sensory deficits, bowel and bladder dysfunction together with hypotension and bradycardia. The anesthesiologist who performed intrathecal anesthesia was not involved in the assessment of patients and the observer was blinded in data collection. Statistical analysis was performed by using SPSS for windows version 10. Data were analyzed using Fisher exact and student *t* test. The 0.05 probability value was adopted as statistically significant for all tests.

RESULTS

There were not significant differences between the two groups in patient characteristics, and duration of surgery (Table 1). Analgesic time in midazolam group (7 ± 1 hours) was significantly longer than that in the control group (1.5 ± 0.5 hours) ($P < 0.05$).

The number of oral analgesic administration required in 24 hours after surgery in midazolam group was significantly less than that in the control group (2 ± 1 vs. 5 ± 1, $P < 0.05$) (Table 2).

In all patients, there were not any episodes of bradycardia, hypotension, urinary retention, and neurological deficits at the time of discharge from hospital.

Table 1. Patient characteristics and duration*

Characteristic	Control group	LMI group
Male	10	10
Female	10	10
Age (year)	45 (± 20)	45 (± 20)
Surgery (minute)	45(± 15)	45(± 15)

Abbreviation: LMI, lidocaine plus intrathecal midazolam.
* Data are given as mean (SD) or number.

DISCUSSION

In this study, we found that the analgesic effect of intrathecal lidocaine was potentiated by intrathecal midazolam. The addition of 2 mg of intrathecal midazolam prolonged the postoperative analgesic effect of lidocaine (7 ± 1 hours), and patients used less analgesic drugs in the first 24 hours after surgery.

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 (4). In 1987, Goodchild reported benzodiazepines-pines analgesic effect especially of intrathecal midazolam in rats and humans (5-7). 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 (3, 8).

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 caesarean section (9, 10).

Table 2. Postoperative analgesia results*

Result	Control group	LMI group
Time to first medication (hour)	1.5 (± 0.5)	7 (± 1)†
Number of oral medication administrations in 24 hours	5 (± 1)	2 (± 1)†

Abbreviation: LMI, lidocaine plus intrathecal midazolam.
* Data are given as mean (SD).
† $P < 0.05$ compared with the control group.

A single intrathecal injection of 2 mg midazolam produced significant analgesia for 2 months in patients with chronic low back pain without side effects such as pruritus, vomiting, urinary retention respiratory depression, hypotension, bradycardia, and motor block (4).

In conclusion, the use of opioid in intrathecal anesthesia induces postoperative analgesia with some side effects such as respiratory depression, nausea, vomiting, urinary retention, and pruritus. In our study, intrathecal midazolam increased the analgesic effect of spinal blockade with lidocaine without side effects induced by intrathecal opioid as mentioned above.

Conflict of interests

The authors declare that they have no competing interests.

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