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# Comparison of Intrathecal Midazolam and Sufentanil for Postoperative Analgesia

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*Abstract*

**Background:** Intrathecal opioids have many side effects such as nausea/vomiting, pruritus, somnolence and so on. However, intrathecal midazolam has been known to have less side effects. Therefore, we used intrathecal midazolam as an alternative to intrathecal opioids in spinal anesthesia.

**Methods:** Sixty patients, ASA I-II, who were scheduled for elective orthopedic surgery under spinal anesthesia were randomly allocated to one of three groups: In group 1 (control, n = 20), 0.5% bupivacaine was used for spinal anesthesia. In group 2 (sufentanil, n = 20), 0.5% bupivacaine and sufentanil 20㎍ were used. In group 3 (midazolam, n = 20), 0.5% bupivacaine and midazolam 1 mg were used. The onset time to T10, maximum sensory level, duration of analgesia, and side effects were compared.

**Results:** Analgesia in group 2 and 3 were longer than that in group 1 ($P < 0.05$). The incidences of pruritus and somnolence were higher in group 2 ($P < 0.05$).

**Conclusions:** Intrathecal midazolam is a good alternative to intrathecal sufentanil.

**Key Words:** intrathecal midazolam, intrathecal opioids, intrathecal sufentanil, orthopedic surgery.

## BACKGROUND

Bupivacaine has been commonly used for spinal anesthesia. However, its duration is relatively short for postoperative analgesia. Thus, many anesthesiologists prefer to add small amount of opioids to bupivacaine for postoperative analgesia. As known, opioids have many side effects including nausea/vomiting, pruritus, respiratory depression, urinary retention and somnolence.[1,2] And these side effects limit the use of opioids as adjuncts to intrathecal bupivacaine.

Since the early 1980s, intrathecal midazolam has been reported to have an analgesic effect as an alternative to opioids.[3-8] As an adjunct to intrathecal bupivacaine, midazolam has less side effects than opioids do.[3,9] If intrathecal midazolam has an equipotent analgesic effect with intrathecal opioids, it could be a great alternative to intrathecal opioids.

The purpose of this study was to determine the analgesic effect of intrathecal midazolame and its side effects as an alternative to intrathecal sufentanil.

## METHODS

After the study protocol had been approved by the local Ethical Committee, written informed consent was obtained from ASA I-II patients, aged 20-60 years, receiving spinal anesthesia for elective orthopedic surgery on lower extremities.

No patient received premedication. On arrival in operating room, patients were randomly allocated to one of three groups. In the first group (control, n = 20), 0.5% bupivacaine (Marcaine®, AstraZeneca, Sweden)

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was used for spinal anesthesia. In the second group (sufentanil, n = 20), 0.5% bupivacaine and sufentanil (Sufental, Geukdong, South Korea, 50㎍/ml) 10㎍ were used. In the third group (midazolam, n = 20), 0.5% bupivacaine and midazolam (Dormicum®, Roche, Switzerland, 5 mg/ml) 1 mg were used. The amount bupivacaine used was 11 to 14 mg depending on patients' height.

Patients were placed in the lateral position with the limb to be operated on in the dependent position. Dural puncture was performed at the L4-5 interspace using 26-gauge Quincke spinal needle (Spinocan®, B. Braun, Germany) with a midline approach. The needle orifice was turned toward the dependent side. All agents were injected intrathecally over 30 seconds. Then the patients were immediately turned to the supine position.

The parameters assessed in this study were as follows; sex, age, height, weight, the amount of bupivacaine used, time to T10 sensory level, maximum sensory level (checked with a 26 gauge needle at 30 minutes after spinal anesthesia), duration of surgery, time to first self voiding, duration of effective analgesic time from the spinal anesthesia (interval between spinal anesthesia and the time patients required first analgesics), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), heart rate (HR), and other side effects (nausea/vomiting, pruritus, somnolence, headache, dizziness, urinary retention). Any neurological changes, such as motor and sensory deficits, bowel and bladder dysfunction, were also checked before discharge.

Data are expressed as mean ± SD. Statistical analysis was performed using the computer program SPSS 10.0 for windows. One-way analysis of variance (ANOVA) and Fisher's exact test were used for normally distributed parametric data. A $P < 0.05$ was considered statistically significant.

There were no significant differences in patient characteristics (Table 1).

## RESULTS

There were no significant differences in the amount

**Table 1.** Demographic Data

| Group | Sex (M/F) | Age (yr) | Height (cm) | Weight (kg) |
|---|---|---|---|---|
| 1 (n = 20) | 15/5 | 38.7 ± 11.9 | 167.8 ± 7.3 | 65.3 ± 10.9 |
| 2 (n = 20) | 15/5 | 42.5 ± 12.3 | 168.9 ± 9.4 | 68.7 ± 10.2 |
| 3 (n = 20) | 15/5 | 42.5 ± 9.0 | 170.0 ± 5.2 | 68.3 ± 8.7 |

Values are mean ± SD. There were no significant differences among groups. Group 1: control group, Group 2: sufentanil group, Group 3: midazolam group.

**Table 2.** Spinal Anesthesia Data

| Group | Used bupivacaine (mg) | Time to T10 (min) | Maximum level | Duration of surgery (min) | Time to first self-voiding (min) |
|---|---|---|---|---|---|
| 1 (n = 20) | 12.6 ± 1.0 | 4.6 ± 1.7 | 7.6 ± 2.3 | 75.3 ± 29.3 | 501.0 ± 180.0 |
| 2 (n = 20) | 12.6 ± 1.4 | 5.4 ± 2.8 | 6.3 ± 2.0 | 76.0 ± 22.9 | 533.4 ± 158.4 |
| 3 (n = 20) | 12.3 ± 1.2 | 4.6 ± 2.7 | 6.9 ± 2.1 | 74.7 ± 42.9 | 455.5 ± 138.0 |

Values are mean ± SD. There were no significant differences among groups. Group 1: control group, Group 2: sufentanil group, Group 3: midazolam group.

**Table 3.** Hemodynamic Changes

| | Group | Base line | 30AS | 60AS | 90AS |
|---|---|---|---|---|---|
| SAP (mmHg) | 1 | 144.7 ± 21.4 | 127.6 ± 20.1 | 129.6 ± 17.0 | 130.3 ± 17.5 |
| | 2 | 143.7 ± 15.4 | 131.8 ± 18.0 | 129.2 ± 15.7 | 129.5 ± 18.2 |
| | 3 | 140.0 ± 18.0 | 127.4 ± 14.7 | 127.7 ± 15.3 | 129.2 ± 12.2 |
| DAP (mmHg) | 1 | 82.5 ± 16.3 | 72.1 ± 12.8 | 75.3 ± 14.0 | 80.8 ± 11.0 |
| | 2 | 84.3 ± 11.7 | 73.5 ± 13.3 | 72.0 ± 11.2 | 73.1 ± 13.4 |
| | 3 | 83.4 ± 12.2 | 76.9 ± 11.9 | 75.2 ± 13.0 | 79.5 ± 13.2 |
| HR (beats/min) | 1 | 72.7 ± 12.4 | 61.0 ± 10.7 | 63.0 ± 16.9 | 68.0 ± 10.1 |
| | 2 | 73.0 ± 13.3 | 65.0 ± 12.2 | 60.6 ± 10.7 | 63.3 ± 9.4 |
| | 3 | 79.2 ± 15.4 | 68.8 ± 10.6 | 75.2 ± 8.7 | 60.9 ± 8.0 |

Values are mean ± SD. There were no significant differences among groups. Group 1: control group, Group 2: sufentanil group, Group 3: midazolam group. 30AS: 30 minutes after spinal anesthesia, 60AS: 60 minutes after spinal anesthesia, 90AS: 90 minutes after spinal anesthesia, SAP: systolic arterial pressure, DAP: diastolic arterial pressure, HR: heart rate.

**Table 4.** Side Effects

| Side effect | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| Nausea/vomiting | 3 | 4 | 4 |
| Pruritus | 0 | 9* | 0 |
| Somnolence | 0 | 6* | 1 |
| Headache | 2 | 1 | 2 |
| Dizziness | 2 | 2 | 2 |
| Urinary retention | 20 | 20 | 20 |

Values are number of patients. Group 1: control group, Group 2: sufentanil group, Group 3: midazolam group. *: $P < 0.05$ compared with group 1 and 3.

of bupivacaine, time to T10, maximum sensory levels, the duration of surgery and time to first episode of self-voiding (Table 2).

The durations of effective analgesic time in group 2 (438.3 ± 112.6 minutes) and 3 (320.0 ± 236.0 minutes) were longer than that in group 1 (260.6 ± 65.0 minutes)($P < 0.05$), and that in group 2 was longer than that in group 3 ($P < 0.05$).

There were no significant differences in hemodynamic changes (Table 3).

Pruritus and somnolence were more frequent in group 2 ($P < 0.05$)(Table 4).

There was no neurologic deficit on discharge.

## DISCUSSION

We found that intrathecal midazolam has prolonged analgesic effect compared with control group. But, analgesia was not longer than that in sufentanil group. Though 2 mg of intrathecal midazolam in human subjects was reported to be safe,[6,10] we used 1 mg of midazolam, because we worried about the possibility of neurotoxicity induced by midazolam. If we used 2 mg of midazolam, the analgesic effect would be longer.[9]

Many anesthesiologists use the small amount of sufentanil in spinal anesthesia for postoperative analgesia. Adequate amount of sufentanil for addition to local anesthetics in spinal anesthesia is 5-10㎍.[11] Sufentanil < 2.5㎍ has a little analgesic effect and sufentanil > 10㎍ increases its analgesic effect but not in proportion to the amount of sufentanil.[12] In our study, we used 10㎍ sufentanil according to the previous report.[11]

Intrathecal opioids have an analgesic effect by inhibiting A-delta and C nerve fibers related to pain transmission. But side effects such as pruritus, nausea, vomiting and respiratory depression appear in proportion to the amount of administration of opioids.[13] In our study, pruritus and somnolence also appear sig-

nificantly in group 2 (sufentanil group). Another side effects such as nausea and vomiting etc in group 2 were not different from those in group 1 (control group) and 3 (midazolam group). Yegin et al.[14] reported 2 mg of intrathecal midazolam induced somnolence. But we couldn't find the increased incidence of somnolence in group 3 compared to group 1 and 2. We assumes that somnolence doesn't occur with 1 mg of intrathecal midazolam.

Since the early 1980s, intrathecal midazolam has been introduced as an alternative to intrathecal opioids to reduce the side effects of intrathecal opioids.[3-8] Intrathecal midazolam has been known to have less side effects such as respiratory depression, nausea, vomiting, urinary retention and pruritus.[3,9] In our study, the side effects in group 3 (midazolam group) were also less than those in group 2 (sufentanil group).

The mechanism of intrathecal midazolam as an analgesic has been demonstrated recently. Delta-selective antagonist, naltrindole, inhibits the antinociceptive effect of intrathecal midazolam. It suggests that intrathecal midazolam may act at delta receptors on spinal cord.[15] Other authors proved intrathecal midazolam acts at kappa and delta receptors both, but not at mu receptors. They observed midazolam acted at kappa receptors dominantly, and the effect of midazolam was weakly active at delta receptors. The effect of intrathecal midazolam could be also prevented by a selective kappa antagonist.[16] Other possible mechanism for antinociception by intrathecal midazolam is that intrathecal midazolam acts on GABAergic transmission in spinal cord. Kohno et al.[17] examined it with adult rat spinal cords. They demonstrated that intrathecal midazolam augmented both the duration of GABA-mediated synaptic current and the amplitude of GABA-induced current by acting on the GABA(A)-benzodiazepine receptor in substantia gelatinosa neurons; this would increase the inhibitory GABAergic transmission.

But, the possibility of neurotoxicty induced by intrathecal midazolam is the most concerned matter. Fortunately, animal studies have shown that intrathecal midazolam has no toxic effect.[18] Johansen et al.[18] examined it with sheep. Sheep received intrathecal midazolam 5-15 mg at a rate of 125㎍/hour for 43 days. They concluded that midazolam 5-15 mg/day were not toxic in sheep. In human studies,[6] 2 mg of midazolam also didn't show any damage to nerve. In our study, there was also no neurotoxcity observed.

In conclusion, the duration of postoperative analgesia in group 2 (sufentanil group) and 3 (midazolam group) was longer than that in group 1 (control group). The frequencies of pruritus and somnolence in group 1 (control group) and 3 (midazolam group) were fewer than that in group 2 (sufentanil). It suggests that the intrathecal midazolam could be an alternative to intrathecal sufentanil for postoperative analgesia in spinal anesthesia.

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