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MIDAZOLAM VS. BUPRENORPHINE: PATIENT CONTROLLED EPIDURAL ANALGESIA FOR POSTOPERATIVE PAIN IN GASTRECTOMY

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ABSTRACT
The purpose of this study was to compare the effects between midazolam and buprenorphine in postoperative patient controlled epidural analgesia. Forty patients aged 30 to 70 years with ASA physical status I or II for gastrectomy were enrolled. After insertion of an epidural catheter, general anesthesia was induced with thiopental, fentanyl, and vecuronium, and maintained with sevoflurane, nitrous oxide in oxygen with intermittent epidural injection of 1.5% lidocaine. At the end of surgery, 0.25% bupivacaine 5 mL + midazolam 3 mg (Midazolam group) or + buprenorphine 0.1 mg (Buprenorphine group) was epidurally injected followed by continuous epidural infusion at 3.3 mL/h for 24 hours with patient controlled analgesia (PCA) of 3 mL (lock out time of 30 minutes). The contents of the infuser were 0.25% bupivacaine 38 mL + midazolam 10 mg (Midazolam group) or 0.25% bupivacaine 39 mL + buprenorphine 0.2 mg (Buprenorphine group) for 12 hours and continued for 24 hours. Intramuscular pentazocine 15 mg was the rescue after PCA. Blood pressure, heart rate, respiratory rate, percutaneous oxygen pressure (SpO_2), visual analog score (VAS) for pain, sedation level, the number of the PCA and pentazocine usage, and nausea and vomiting were monitored for postoperative 24 hours. All parameters measured were not different between the two groups. From these results, epidural PCA with midazolam had similar effects with buprenorphine when used for postoperative analgesia in gastrectomy.

KEYWORDS: Postoperative analgesia, epidural block, patient controlled, analgesia, midazolam, buprenorphine, gastrectomy.

1. INTRODUCTION
It is well known that midazolam, a benzodiazepine, has spinally mediated analgesic effects.[1] We have already reported that epidural midazolam was effective for postoperative analgesia without any significant side effects.[2,3,4] Buprenorphine, a μ opioid partial agonist, is also used for postoperative epidural analgesia.[5,6] However, there is no study to investigate which better is, midazolam or buprenorphine, for postoperative epidural analgesia, especially using patient controlled analgesia. The purpose of this study was to compare the effects and side effects between midazolam and buprenorphine in postoperative patient controlled epidural analgesia.

2. MATERIALS AND METHODS
After the approval of the ethics committee of the hospital and informed consent from the patients, 40 patients aged 30 to 70 years with ASA physical status I or II for gastrectomy were enrolled in this study. Those who had liver, renal, mental, or severe cardiac diseases, who had previous spine surgery, allergy to the agents scheduled to use, or habits of hypnotics or analgesics, and who were obese (body mass index > 30) were excluded from the study.

In the operating room, an epidural catheter was inserted into one of the interspinal space between T7 and T12. General anesthesia was induced with thiopental 5 mg/kg and fentanyl 3-5 μg/kg, then oro-tracheal intubation was facilitated with vecuronium 0.15 mg/kg. Anesthesia was maintained with sevoflurane, nitrous oxide in oxygen, and intermittent epidural injection of 1.5% lidocaine. At the end of surgery, sevoflurane and nitrous oxide was stopped and 0.25% bupivacaine 5 mL + midazolam 3 mg (Midazolam group) or 0.25% bupivacaine 5 mL + buprenorphine 0.1 mg (Buprenorphine group) was epidurally injected followed by continuous epidural infusion with patient controlled analgesia (PCA) at 3.3 mL/h. The balloon infuser (DIB・K-PCA 40mL type, DIB International, Tokyo, Japan), which had a constant flow of 3.3 mL/h with PCA of 3 mL (lock out time of 30 minutes) was used. The contents of the infuser was 0.25% bupivacaine 38 mL + midazolam 10 mg (Midazolam group) or 0.25% bupivacaine 39 mL + buprenorphine 0.2 mg (Buprenorphine group). The infusion and PCA was continued for 24 hours.

Pain was rated by the VAS (visual analogue score, 0 - 10) and when the VAS score was more than 5, PCA was used by a nurse. Fifteen minutes after epidural PCA, when still the VAS score was more than 5, pentazocine 15 mg was intramuscularly administered.

Blood pressure, heart rate, respiratory rate, percutaneous oxygen pressure (SpO_2), VAS score, sedation level accessed by the Ramsay sedation score, the number of the PCA and pentazocine usage, and nausea and vomiting were monitored for postoperative 24 hours.

Data were expressed as mean ± standard deviation or median and range. Statistical analysis was performed with factorial analysis of variance (ANOVA) and chi-square test for demographic data, and repeated measures ANOVA followed by Student-Newman-Keuls test for blood pressure, heart rate, respiratory rate and SpO_2, and the Kruskal Wallis test followed by Mann-Whitney U test for VAS score, sedation score, and the number of analgesics. The p value less than 0.05 was considered to be statistically significant.

3. RESULTS

Demographic data were not different between the groups (Table 1).

Table 1. Demographic data

	Midazolam	Buprenorphine
Age (years)	56 ± 13	60 ± 9
Gender (Male/Female)	12/8	14/6
Height (cm)	161 ± 15	159 ± 8
Body weight (kg)	62 ± 10	60 ± 12
Duration of surgery (min)	226 ± 34	209 ± 41

Mean ± standard deviation

Blood pressure decreased significantly after surgery, especially until 6 hours, compared to the value at the end of surgery in both groups, but no differences were seen between the two groups (Data were not shown). Heart rate, respiratory rate and SpO_2 did not change during the study period and were not different between the groups (Data were not shown.).

VAS score (Table 2), sedation score (Table 3), and the numbers of PCA and pentazocine administration (Table 4) were not different between the groups.

Table 2. Postoperative pain (VAS score)

Time	0	0.5	1	2	4	6	12	18	24
Midazolam	4 (2-6)	4 (2-5)	4 (2-6)	5 (3-7)	5 (3-6)	5 (3-7)	4 (2-6)	4 (2-5)	5 (2-6)
Buprenorphine	5 (3-7)	4 (2-5)	4 (3-6)	4 (2-6)	4 (3-6)	5 (3-6)	5 (4-7)	5 (4-7)	4 (3-7)

Median and range are shown. Pain was rating as 0 (no pain) to 10 (maximum pain).

Table 3. Sedation score

Time	0	0.5	1	2	4	6	12	18	24
Midazolam	3.5 (2-5)	3.5 (2-5)	4 (3-5)	4 (3-5)	3.5 (2-5)	4 (3-5)	3 (2-5)	3 (2-5)	3.5 (3-5)
Buprenorphine	3 (2-5)	3 (2-5)	3.5 (3-5)	4 (3-5)	4 (3-5)	3.5 (2-5)	3 (2-5)	3.5 (2-5)	3 (2-5)

Median and range are shown.Ramsay sedation score was used as follows, 1; Anxious, agitated, restless, 2; Cooperative, oriented, tranquil, 3; Responsive to commands only, 4; Brisk response to light glabellar tap or loud auditory stimulus, 5; Sluggish response to light glabellar tap or loud auditory stimulus, 6; No response to light glabellar tap or loud auditory. Stimulus.

Table 4. PCA and pentazocine administration

	Midazolam	Buprenorphine
PCA	4 (2-8)	5 (2-9)
Pentazocine	2 (0-6)	3 (0-6)

Median and range (in the parenthesis) in postoperative 24 hours are shown. PCA, patient controlled analgesia.

As side effects, nausea and vomit happened in 2 patients in the Midazolam group, and 3 patients in the Buprenorphine group, itching was seen in one patient in the Buprenorphine group, and no patients in both groups had headache and other side effects considered to be due to epidural analgesia.

4. DISCUSSION

The present study showed that epidural PCA using midazolam and buprenorphine had similar postoperative analgesia and side effects in gastrectomy.

Spinal benzodiazepine receptors had a role in analgesia,[7] and intrathecal midazolam also acts on the spinal delta receptors to release endogenous opioid.[8] Midazolam 10 to 20 mg added to continuous epidural bupivacaine for 12 hours gave better postoperative analgesia with amnesia and sedation than bupivacaine alone without increasing side effects.[2] Therefore, we chose 10 mg for 12 hours in this study. Increasing the dose of continuous epidural bupivacaine in combination with midazolam increased not only analgesic but also sedative effects.[3] The present study used PCA in addition to continuous infusion, therefore, we used 0.25% bupivacaine to avoid over sedation.[3] The present study had no control group, therefore we could not know sedative effects of midazolam. Midazolam is reported to decrease postoperative nausea and vomit.[9] Kim et al.[10] showed that midazolam added to epidural PCA with fentanyl and ropivacaine decreased postoperative nausea without any differences in pain and other side effects after gastrectomy. The present study showed lower rate of postoperative nausea and vomit, while we could not say midazolam decreased nausea and vomit because of no control groups.

Mitsuhata et al.[11] reported that 0.7 mg buprenorphine in 24 hours with 0.25% bupivacaine could decrease postoperative pain at rest in abdominal surgery. Epidural single administration of 0.25% bupivacaine 8 mL + buprenorphine 0.1mg followed by PCA with buprenorphine 20 μg and 0.1% bupivacaine without continuous infusion was effective for postoperative pain in gynecological surgery.[5] Wajima et al.[6] used almost the same dose of buprenorphine as the present study for continuous epidural administration with 2% lidocaine and reported that high dose lidocaine was better than low dose lidocaine for postoperative analgesia in gastrectomy or cholecystectomy when combined with buprenorphine.

Epidural buprenorphine was reported to provide better postoperative analgesia with few side effects in comparison with μ agonist such as morphine or fentanyl,[12] while Cohen et al.[13] showed that epidural PCA with buprenorphine had no benefits compared to fentanyl. We did not have the fentanyl group, therefore, we could not compare fentanyl and buprenorphine.

There is no study to compare epidural PCA with midazolam and buprenorphine for postoperative analgesia. However, the protocol of the present study showed that both were similarly effective without any significant side effects. We used each only one dose and one infusion rate, therefore, comparison of some different doses and infusion rates should be further investigated.

5. CONCLUSION

Midazolam had similar effects as buprenorphine when used as an adjuvant to 0.25% bupivacaine in postoperative epidural patient controlled analgesia.

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