

Midazolam anesthesia during rigid and flexible cystoscopy

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Abstract The objective of this study was to investigate the usefulness and safety of midazolam-induced anesthesia for cystoscopy. From September 2005 to March 2006, 80 patients scheduled for regular outpatient follow-up cystoscopy participated in this study. The patients were randomized and classified according to the cystoscope type and midazolam use as follows: group 1 (10 men and 10 women), flexible cystoscopy + midazolam; group 2 (10 men and 10 women), flexible cystoscopy + no midazolam; group 3 (10 men and 10 women), rigid cystoscopy + midazolam; and group 4 (10 men and 10 women), rigid cystoscopy + no midazolam. Immediately after the procedure, the patients were asked to rate their comfort level using a ten-point visual linear analog self-assessment pain scale. The patients assigned in the midazolam group experienced no side-effects from the midazolam. Blood pressure and pulse rate did not change significantly during the procedure. The degree of pain experienced by group 1 was lower than other groups ($P < 0.05$) and group 4 had a significantly greater pain score than other groups ($P < 0.05$). No difference was evident between group 2 and 3 regarding the pain score. Midazolam anesthesia may relieve pain during rigid and flexible cystoscopy. Our findings suggest that midazolam anesthesia during cystoscopy is useful and safe.

Keywords Cystoscopy · Anesthesia · Midazolam · Pain

Introduction

Although there is a wide variety of anesthetic techniques for cystoscopy, including urethral lubricating jelly alone, intraurethral injection of lidocaine, or narcotic intramuscular premedication, these methods may not optimally relieve pain during cystoscopy. Midazolam has been the most widely used sedative premedication because of its many advantages, such as a short half-life, a faster onset of sedation and an excellent sedative hypnotic effect without any particular side-effects, such as vasculitis. Midazolam is also associated with strong anterograde amnesia and with usage of flumazenil as an antagonist the side effects are treated easily [1–3]. This study was performed to evaluate the usefulness and safety of midazolam anesthesia during cystoscopy.

Materials and methods

From September 2005 to March 2006, 80 patients (40 men and 40 women) scheduled for regular outpatient follow-up cystoscopy participated in this study. The patients ranged in age from 16 to 83 years (mean, 25.9 ± 13.2 years). Subjects who had severe cardiovascular disease, pulmonary disease, chronic alcohol or drug abuse history were not included in the study. We also excluded subjects taking medications such as erythromycin, verapamil, diltiazem, itraconazole and ketoconazole, which can have drug interactions specifically with the benzodiazepine class to which midazolam belongs. Of the 80 patients, 40 each were randomly assigned to rigid or flexible cystoscopy. Ten male and ten female patients were sub-classified according to midazolam use to each of the following groups: group 1, flexible cystoscopy + midazolam; group 2, flexible cystoscopy + no midazolam; group 3, rigid cystoscopy + midazolam; and group 4, rigid cystoscopy + no midazolam. Each subject provided informed consent and this study was approved by our medical center's institutional review board.

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Patients were placed in the dorsolithotomy position with their legs suspended in stirrups. The penis or vagina were prepared with povidone–iodine solution and draped. The same urological surgeon (Yun Seob Song) performed all cystoscopies using a 15 Fr flexible or 17.5 Fr rigid cystoscope. The average procedure time was 2–3 min. In patients randomly assigned to the groups without midazolam (groups 2 and 4), the urologist instilled 2% lidocaine topical jelly into the urethra 5–10 min before rigid or flexible cystoscopy. The patients randomly assigned to the groups with midazolam (groups 1 and 3) were instructed to avoid consuming nicotine, alcohol and caffeinated beverages for at least 12 h prior cystoscopy in order to maximize the likelihood that they would be able to sleep. A nurse intravenously administered midazolam to the subjects at doses of 3–5 mg. The initial intravenous dose was 1 mg (no more than 0.03 mg/kg) given slowly over at least 2 min, titrating to the desired level of sedation. An intravenous dose of 0.02–0.03 mg/kg was repeated at 2-min intervals while the appropriate level of sedation was continually monitored. A total intravenous dose of more than 5 mg was not necessary for all examinations. The sedation scale was measured after a stimulus such as conversing with the patient or shaking the patient awake. The responses were measured and divided according to five stages (“Appendix”). Cystoscopy was performed when the stage was greater than three [4]. After administration of midazolam, the presence of complications or side-effects including apnea, oxygen desaturation, autonomic movement, chest pain, arrhythmia, injection in situ pain and phlebitis were also examined. The subjects were discharged once they fully recovered orientation of time and space with vital signs within the normal range. A nurse monitored the patients. Immediately after the procedure, the patients were asked to rate their comfortable level using a ten-point visual linear analog self-assessment pain scale (“Appendix”) [5]. The distance from the left end of the scale was used for quantification. The left end of the scale was defined as no pain at all and the right end was defined as extremely painful. Recovery from sedation was assessed by the mini-mental state examination (MMSE) by which one point is given for each of the portion underlined, totaling 13 points (“Appendix”) [6]. The MMSE was translated into and cross-culturally validated for the Korean language (K-MMSE) [7].

The survey responses were coded and analyzed using descriptive statistics, which are reported as the median with the 5th–95th percentiles. The statistical analysis was carried out using the Kruskal–Wallis test or the Wilcoxon signed ranks test. A 5% level of significance was used throughout, and all statistical tests were two-sided. The statistical analyses were performed using the commercially available program, SPSS 10.0 (SPSS, Inc., Chicago, IL, USA).

Results

There were no significant differences in age among the groups. We did not detect the aforementioned side-effects of midazolam in patients randomized to the midazolam groups. Mild headache and nausea were noted in some patients but spontaneously disappeared without treatment. In this study, we did not use an intravenous injection of flumazenil, the antidote for midazolam for the rapid recovery of consciousness and orientation. Blood pressure and pulse rate did not change significantly during the procedure. All changes in blood pressure and pulse rate were below 20% of baseline value and no patients were treated due to changes in vital signs. The differences in the MMSE were statistically significant ($P < 0.05$). The results are shown in Table 1.

Figure 1 shows the values recorded on the visual analog pain scales by the four groups. The degree of pain experienced by group 1 was lower than other groups ($P < 0.05$). Group 4 exhibited significantly higher pain scores than did other groups ($P < 0.05$). No difference was evident between groups 2 and 3 with regard to the pain score. The degree of pain was comparable in male and female patients.

Discussion

Urethral pain during cystoscopy and anticipating anxiety about the pain may be a cause of incomplete cystoscopic examinations or patient’s refusal to undergo a cystoscopic examination. Although the application of local anesthesia and lubrication is effective, pain may not be optimally relieved during cystoscopy in some patients.

Midazolam, a kind of benzodiazepine, is a water-soluble benzodiazepine with a short half-life. Midazolam provides sedation/anesthetic effects but not analgesic effects. The major advantages of midazolam over diazepam include shorter duration of action, profound anterograde amnesia and better local tolerance such as less burning on injection and lack of postoperative phlebitis [3, 8, 9]. Midazolam has a high affinity for the benzodiazepine receptor in the central nervous system, with in vitro data demonstrating that it has

Table 1 Patient monitoring during midazolam anesthesia

	Baseline	Cystoscopy
Systolic pressure (mmHg)	120.0 (120.0–164.8)	120.0 (110–160.0)
Diastolic pressure (mmHg)	80.0 (70.5–99.7)	80.0 (65.3–90.0)
Pulse rate (per min)	80.0 (57.2–90.0)	80.0 (60.0–90.0)
MMSE scale	29.0 (25.0–30.0)	27.0 (14.2–30.0)

Data are presented as the medians (5th–95th percentiles)

MMSE mini-mental state examination

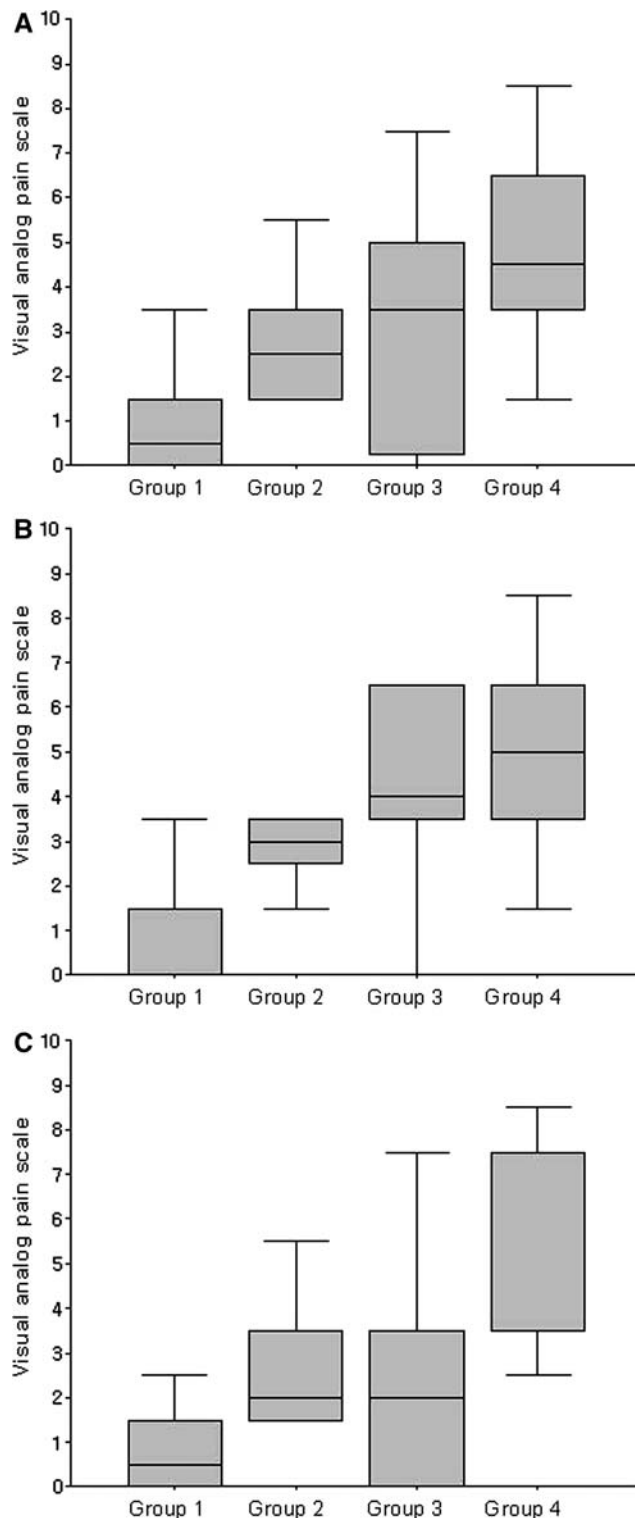


Fig. 1 Visual analog pain scales in total (a), male (b) and female (c) patients

approximately twice the affinity of diazepam [10, 11]. The amino acid neurotransmitter gamma-aminobutyric acid (GABA) must be present for the benzodiazepine to elicit a response [12] and benzodiazepines enhance the inhibitory

action of GABA [13]. The actions of benzodiazepines do not involve the synthesis, release, or altered metabolism of GABA but rather potentiate the inhibitory actions of GABA by augmenting the flow of chloride ions through ion channels. The increased flux of chloride ions into the cell decreases the ability of the cell to initiate an action potential [14].

Midazolam is a sedative drug with amnesic properties. Retrograde amnesia is a valued property since decreased recall considerably enhances patient tolerance and acceptance of surgical and diagnostic procedures. Previous studies have found that anterograde, but not retrograde amnesia can be demonstrated with midazolam [15–17]. Thus, retrograde amnesia has not been conclusively demonstrated. However, midazolam produces the immediate onset of anterograde amnesia in patients [18]. This may be useful in preventing the explicit recall of perioperative events.

In this study, midazolam anesthesia relieved pain during both rigid and flexible cystoscopy. In addition, there was no difference in pain perception between patients undergoing conventional flexible cystoscopy and rigid cystoscopy during midazolam-induced sedation. However, while a reduced pain score was identified after midazolam anesthesia, it is unclear whether midazolam anesthesia reduces pain in all patients. Since pain scores in patients undergoing cystoscopy during midazolam-induced sedation show marked variability, the statistically significant difference in our study may not be clinically important.

Outpatient flexible cystoscopy is the gold standard procedure used to follow patients with superficial bladder tumors [19, 20]. However, routine use of flexible cystoscopy in all patients is not feasible because of its lack of availability and high cost (\$ 25,000) compared with rigid cystoscopy (\$ 9,000) for urologists working at private clinics since only approximately 50 flexible cystoscopies are available in Korea. However, the use of midazolam anesthesia may increase the cost of cystoscopy. In the present study, the total cost per procedure was higher (from \$ 6.64 to \$ 16.60) for the midazolam anesthesia group. The additional cost for midazolam-induced anesthesia under health insurance coverage is shown in Table 2.

If there is no difference in pain perception between the two procedures, patients can be evaluated more easily, especially by physicians who do not have easy access to flexible cystoscopy. In the present study, although the difference in the MMSE was statistically significant after the midazolam anesthesia, it was not clinically significant. The side-effects of midazolam administration have been found in some patients [4, 21, 22]. However, in the present study, no patients had to be treated for side-effects after midazolam anesthesia. Our study indicates that midazolam anesthesia during cystoscopy is well tolerated and is associated with no or minimal discomfort.

Table 2 Additional cost for midazolam-induced anesthesia under the health insurance coverage

	At admission	At office
Midazolam	\$ 0.25	\$ 0.63
Intravenous injection fee	\$ 0.31	\$ 0.78
Percutaneous blood O ₂ saturation monitoring	\$ 0.90	\$ 2.24
ECG monitoring	\$ 2.28	\$ 5.70
Blood pressure monitoring	\$ 2.90	\$ 7.25
Recovery room	None	None
Extra-personnel	None	None
Total costs	\$ 6.64	\$ 16.60

Appendix

1. Sedation scale

Alert (0)

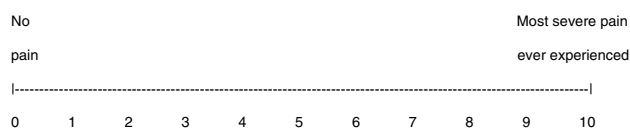
Drowsy, partial lid closure (1)

Eyes closed, responding to verbal command (2)

Unresponsive to verbal command, but responsive to pain (3)

Unresponsive (4).

2. Visual analog pain scale



3. Recovery test (mini mental state examination)

Orientation for time (five points): what is the (year) (month) (date) (day) (season)?

Attention and calculation (five points): Serial 7's. One point for each correct. Stop after five answer.

Language (three points): follow a three-stage command:

Take a paper in your right hand, fold it in half, and put it on the floor.

One point is given for each portion with a total of 13 points.

References

- Ross WA (1989) Premedication for upper gastrointestinal endoscopy. *Gastrointest Endosc* 35:120
- Whitwam JG, Al-Khudhairi D, McCloy RF (1983) Comparison of midazolam and diazepam in doses of comparable potency during gastroscopy. *Br J Anaesth* 55:773
- Hanno PM, Wein AJ (1983) Anesthetic techniques for cystoscopy in men. *J Urol* 130:1070
- Forrest P, Galletly DC (1987) Comparison of propofol and antag-onised midazolam anaesthesia for day-case surgery. *Anaesth Intensive Care* 15:394
- Johnson EW (2001) Visual analog scale (VAS). *Am J Phys Med Rehabil* 80:717
- Folstein MF, Folstein SE, McHugh PR (1975) Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12:189
- Kang YW, Na DL, Hahn SH (1997) Validity study on the Korean mini-mental state examination (K-MMSE) in dementia patients. *Korean J Neurol Assoc* 15:300
- Gerecke M (1983) Chemical structure and properties of midazo-lam compared with other benzodiazepines. *Br J Clin Pharmacol* 16(Suppl 1):11S
- Pieri L (1983) Preclinical pharmacology of midazolam. *Br J Clin Pharmacol* 16(Suppl 1):17S
- Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ (1985) Midazo-lam: pharmacology and uses. *Anesthesiology* 62:3104
- Kanto JH (1985) Midazolam: the first water-soluble benzodiaze-pine. Pharmacology, pharmacokinetics and efficacy in insomnia and anesthesia. *Pharmacotherapy* 5:138
- Amrein R, Hetzel W (1991) Pharmacology of drugs frequently used in ICUs: midazolam and flumazenil. *Intensive Care Med* 17(Suppl 1):S1
- Greenblatt DJ, Shader RI, Abernethy DR (1983) Drug therapy. Current status of benzodiazepines. *N Eng J Med* 309:410
- Study RE, Barker JL (1982) Cellular mechanisms of benzodiaze-pine action. *JAMA* 247:2147
- Dundee JW, Wilson DB (1980) Amnesic action of midazolam. *Anaesthesia* 35:459
- Koht A, Moss JI (1997) Does midazolam cause retrograde amne-sia, and can flumazenil reverse that amnesia? *Anesth Analg* 85:211
- Twersky RS, Hartung J, Berger BJ, McClain J, Beaton C (1993) Midazolam enhances anterograde but not retrograde amnesia in pediatric patients. *Anesthesiology* 78:51
- Bulach R, Myles PS, Russnak M (2005) Double-blind randomized controlled trial to determine extent of amnesia with midazolam given immediately before general anaesthesia. *Br J Anaesth* 94:300
- Herr HW (1990) Outpatient flexible cystoscopy and fulguration of recurrent superficial bladder tumors. Outpatient flexible cystos-copy and fulguration of recurrent superficial bladder tumors. *J Urol* 144:1365
- Herr HW, Schneider M (2001) Outpatient flexible cystoscopy in men: a randomized study of patient tolerance. *J Urol* 165:1971
- Forster A, Gardaz JP, Suter PM, Gemperle M (1980) I.V. midazo-lam as an induction agent for anaesthesia a study in volunteers. *Br J Anaesth* 52:907
- Ginsberg GG, Lewis JH, Gallagher JE, Fleischer DE, al-Kawas FH, Nguyen CC, Mundt DJ, Benjamin SB (1992) Diazepam versus midazolam for colonoscopy: a prospective evaluation of predicted versus actual dosing requirements. *Gastrointest Endosc* 38:651