

Investigative Urology

# Value and Safety of Midazolam Anesthesia during Transrectal Ultrasound-Guided Prostate Biopsy

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**Purpose:** Although transrectal ultrasound-guided prostate biopsy is useful for diagnosing prostate cancer, it is a painful procedure. There are many methods for providing pain relief and for treating discomfort during the procedure, but occasionally these are reported to be of limited use. We aimed to evaluate the value and safety of midazolam-induced anesthetic transrectal ultrasound-guided prostate biopsy.

**Materials and Methods:** From August 2008 to December 2009, 104 male patients, who were examined with transrectal ultrasound-guided prostate 12-core biopsy, were randomly assigned to two groups. Group 1 (n=51) received ketorolac (Tarasyn<sup>®</sup>) 30 mg. Group 2 (n=53) was treated with midazolam (Dormicum<sup>®</sup>) 3 mg, which was increased to 5 mg if necessary. Immediately after the procedure, the patients were asked to rate their comfort level by using a 10-point visual analog self-assessment pain scale.

**Results:** The pain scale in group 2 was significantly lower than that in group 1 (p < 0.05). The patients assigned to group 2 experienced no side-effects from midazolam and were more satisfied than the patients in group 1 (p < 0.05).

**Conclusions:** Midazolam anesthesia relieves pain effectively, and the patient's satisfaction is better than with conventional transrectal ultrasound-guided prostate biopsy. Midazolam-induced anesthetic transrectal ultrasound-guided prostate biopsy is useful and safe.

**Key Words:** Biopsy; Midazolam; Pain measurement

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**Article History:**

received 10 December, 2010

accepted 24 February, 2011

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## INTRODUCTION

Transrectal ultrasound-guided prostate biopsy is routinely done to diagnose the absence or presence of malignancy. However, with 10 to 12 prostatic cores now being the standard, the procedure can be painful unless adequate analgesia is provided. Although a wide variety of anesthetic techniques are available for transrectal ultrasound-guided prostate biopsy, including rectal administration of lidocaine gel, periprostatic nerve blocks, intravenous propofol, and narcotic intramuscular premedication, these methods may not optimally prevent or relieve pain.

Midazolam has been the most widely used sedative premedication because of its short half-life, faster onset of se-

dition, and excellent sedative hypnotic effect without any significant 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 easily treated [1-3]. This study was performed to evaluate the value and safety of midazolam anesthesia during transrectal ultrasound-guided prostate biopsy.

## MATERIALS AND METHODS

From August 2008 to December 2009, 104 patients underwent a 12-core prostate biopsy. Of the 104 patients, 51 patients (group 1) were randomly assigned to prostate biopsy with 30 mg of IM ketorolac (Tarasyn<sup>®</sup>) and 53 patients

(group 2) were given 3-5 mg of midazolam IV (Dormicum®). Each subject provided informed consent and this study was approved by our medical center's institutional review board.

The indications for prostate biopsy were an abnormal prostate on digital rectal examination and/or elevated serum prostate-specific antigen (PSA) ≥4 ng/ml. The patients ranged in age from 40 to 86 years (mean, 66.9±9.3 years). Subjects who had previous prostate biopsy, severe cardiovascular disease, pulmonary disease, bleeding hemorrhoids, acute anal fissure, or a history of chronic alcohol or drug abuse were not included in this 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. Anticoagulation or aspirin therapy was stopped 1 week before the biopsy and the patients received a glycerin enema before the procedure.

With the patients in the left lateral decubitus position, a digital rectal examination was performed and the rectum was cleaned with a Betadine gauze pack. The urologist performed all prostate biopsies under ultrasound guidance by using a Medison SA-6000 machine with a 6.5 MHz biplane transrectal probe during longitudinal scanning by using an automated biopsy gun with a disposable 18 gauge biopsy needle. A Betadine pack was kept for approximately 6 hours at the end of the procedure. The patients in group 2 were instructed to avoid consuming nicotine, alcohol, and caffeinated beverages for at least 12 hours before prostatic

biopsy to maximize the likelihood that they would be able to fall asleep. A nurse intravenously administered midazolam to the subjects at doses of 3 to 5 mg. The initial intravenous dose was 3 mg (no more than 0.05 mg/kg) given slowly over at least 2 min, with titration to the desired level of sedation. An intravenous dose of 0.02 to 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 required for any examinations. At the end of the procedure, we gave an intravenous injection of flumazenil to facilitate rapid recovery from sedation.

The sedation scale was measured after stimulating the patient (i.e., conversing with the patient or shaking the patient awake). The responses were measured and divided according to 5 stages (Table 1). Prostate biopsy was performed when the stage was greater than 3 [4]. After administration of midazolam, the presence of complications or side-effects to include apnea, oxygen desaturation, autonomic movement, chest pain, arrhythmia, injection in situ pain, and phlebitis were also assessed. The subjects were discharged once they fully recovered orientation of time and space in the setting of normal vital signs. Immediately after the procedure, the patients were asked to rate their comfort level by using a 10-point visual linear analog self-assessment pain scale (Fig. 1) [5]. The degree of pain was interpreted as none (0), mild (1-3), moderate (4-6), severe (7-9), and intolerable (10), accordingly. They were also asked whether their pain control method was satisfactory and whether they would be willing to undergo a repeat biopsy.

Recovery from sedation was assessed by using the Mini-

**TABLE 1.** Sedation responses of patients with midazolam-induced anesthetic prostate biopsy by sedation scale

	Sedation scale	No. of patients
No response to shaking	1	0
Responds only to shaking	2	6
Responds only to name call loudly	3	47
Lethargic response to name spoken in a normal tone	4	0
Responds readily to name spoken in a normal tone	5	0
Total		53



**FIG. 1.** Pain score was evaluated with a visual analog scale. A patient is asked to rate his pain on a scale of 1-10. Rating of 1 represents mild discomfort from time to time, and a 10 is so severe that a trip to the emergency room for relief is required. The degree of pain was interpreted as none (0), mild (1-3), moderate (4-6), severe (7-9), and intolerable (10).

**TABLE 2.** Recovery test before and after prostate biopsy with the scale of the Mini Mental State Examination

Category	Possible points	Description
Orientation to time	5	From broadest to most narrow. Orientation to time has been correlated with future decline.
Orientation to place	5	From broadest to most narrow. This is sometimes narrowed down to streets, and sometimes to floor.
Registration	3	Repeating named prompts
Attention and calculation	5	Serial sevens, or spelling "W-O-R-L-D" backwards. It has been suggested that serial sevens may be more appropriate in a population where English is not the first language.
Recall	3	Registration recall
Language	2	Name a pencil and a watch
Repetition	1	Speaking back a phrase
Complex commands	6	Varies. Can involve drawing figure shown.

Mental State Examination (MMSE) (Table 2) [6]. The MMSE was translated into and cross-culturally validated for the Korean language (K-MMSE) [7]. The survey responses were coded and analyzed by using descriptive statistics, which are reported as medians with 5-95th percentiles. The statistical analysis was carried out by using the Student's t-test or the paired t-test. Statistical significance was defined as a p-value less than 0.05. The statistical analyses were performed by using SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA).

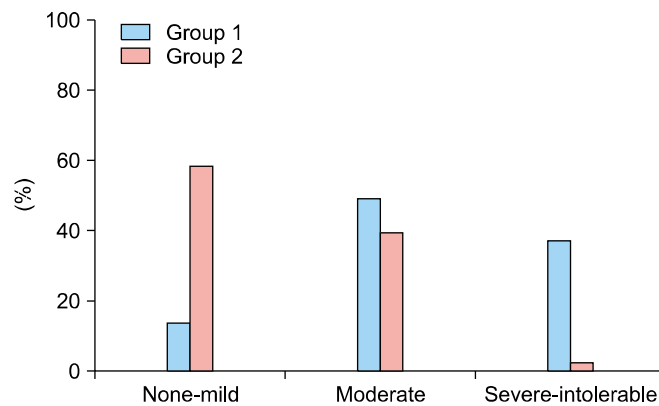
**RESULTS**

There were no significant differences in age, weight, body mass index, PSA, or prostate volume among the groups (Table 3). The differences in the pain scores were statistically significant ( $p < 0.05$ ). In group 1, none or mild degrees of discomfort were expressed by 7 (13.7%) cases and severe or intolerable discomfort by 19 (37.2%), respectively. In group 2, none or mild degrees of discomfort were reported by 31 (58.5%) cases, whereas severe or intolerable discomfort occurred in only 1 (1.8%) patient (Fig. 2). In group 1, satisfaction with the pain control methods was noted in 11 (21.5%) cases and willingness to undergo a repeat biopsy by using the same pain control measures was noted in 10 (19.6%) cases. Satisfaction and willingness were higher in group 2 than in group 1 (75.5% and 60.3%, respectively,  $p <$

**TABLE 3.** Characteristics of the patients

Mean±SD	Group 1 (n=51)	Group 2 (n=53)	p-value
Age (yr)	67.1±9.3	66.4±9.2	> 0.05
Weight (kg)	64.9±10.1	67.4±8.2	> 0.05
Body mass index (kg/m <sup>2</sup> )	24.3±2.7	23.7±3.3	> 0.05
Prostate-specific antigen (ng/ml)	48.9±111.8	21.4±280.6	> 0.05
Prostate volume (cc)	41.4±15.8	44.5±21.8	> 0.05

Group 1: ketorolac group, Group 2: midazolam-induced anesthetic group



**FIG. 2.** Distribution of the cases in each group in regard to the degree of discomfort.

0.05) (Fig. 3).

The mean midazolam usage dose was 3.94 mg, and the mean time from injection to sedation was 5.1 minutes. We did not detect the aforementioned side-effects of midazolam in patients randomly assigned to the midazolam groups. Mild headache (4 patients), nausea (3), paradoxical rage (1), and transient delirium (1) were noted but spontaneously disappeared without treatment. All changes in blood pressure and pulse rate were below 20% of baseline values, and no patients were treated owing to changes in vital signs. The differences in the MMSE score were not statistically significant ( $p > 0.05$ ) (Table 4).

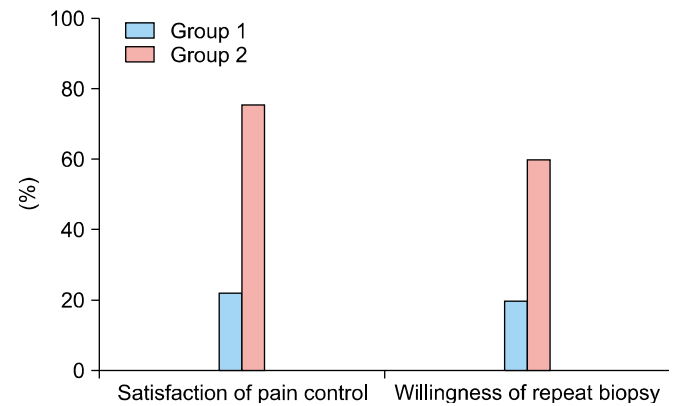
**DISCUSSION**

Transrectal ultrasound-guided prostate biopsy is generally performed on an outpatient basis given its low complication rates and minimal to no need for anesthesia. However, a considerable degree of patient discomfort has been reported in the literature [8,9]. Pain during prostate biopsy and the anticipating anxiety regarding the procedure may cause unfavorable results or may influence a patient's decision to undergo a repeat biopsy. Although the application of local anesthesia is somewhat effective, pain may not be optimally relieved during prostate biopsy in some patients.

**TABLE 4.** Comparison of parameters between before and after midazolam injection

	Group 2 (n=53)		p-value
	Pre-I	Post-I	
BP (mean±SD)			
Systolic	120±18.8	116±18.5	< 0.05
Diastolic	82±11.7	76±10.5	> 0.05
PR (mean±SD)	73±10.1	73±10.4	> 0.05
MMSE	26.04±2.36	25.95±2.0	> 0.05*

Group 2: midazolam-induced anesthetic group, BP: blood pressure (mmHg), PR: pulse rate, Pre-I: before midazolam injection, Post-I: after midazolam injection, MMSE: Mini-Mental State Examination



**FIG. 3.** Comparison of the groups for mean pain scale and satisfaction percentil.

Given the general consensus regarding the need for some form of anesthesia, establishment of standard methods during transrectal ultrasound-guided prostate biopsy has been prompted.

Midazolam is a water-soluble benzodiazepine with a short half-life. Midazolam provides sedation/anesthetic effects but without any analgesic effects. The major advantages of midazolam over diazepam include a shorter duration of action, profound anterograde amnesia, and better local tolerance, such as less burning on injection and lack of postoperative phlebitis [3,10,11]. Midazolam has a high affinity for the benzodiazepine receptor in the central nervous system, with *in vitro* data demonstrating that it has approximately twice the affinity of diazepam [12,13]. The amino acid neurotransmitter gamma-aminobutyric acid (GABA) must be present for the benzodiazepine to elicit a response and for benzodiazepines enhance the inhibitory action of GABA [14,15]. 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 [16]. Midazolam is a sedative drug with amnesic properties. Previous studies have found that anterograde, but not retrograde, amnesia can be demonstrated with midazolam [17-19]. However, midazolam produces the immediate onset of anterograde amnesia in patients [20]. This may be useful in preventing the explicit recall of perioperative events. Because the onset of and the recovery from sedation is rapid and the risk of respiratory and cardiovascular depression is less for midazolam in comparison with the other agents used for sedation, it is the preferred agent for intervention procedures [12]. In addition, it can safely be used in patients suffering from coronary artery disease or hypertension [21].

In this study, the patients who received midazolam had both significantly less pain than did the ketorolac group and more satisfied pain control. Also, 32 patients (60.3%) in the midazolam group were willing to undergo a future biopsy if required. The mean pain score in group 1, which received ketorolac, was 6.7, which is within the range of moderate to severe discomfort. The mean score of 2.7 calculated for group 2 was within the range of a mild degree of discomfort. Prostate biopsy has now become common with the increased use of PSA, and more biopsy cores are taken to increase the cancer detection rate. It has been reported that rectal administration of lidocaine has no impact on the tolerance of prostatic biopsy [22]. Although a periprostatic nerve block has been widely reported to be highly efficient, it is worthy to note that no significant difference or only borderline improvement in pain scores was detected in several recent studies, which suggests that pain relief with periprostatic nerve block is not as effective as previously suggested [23,24]. Irani and colleagues also reported that there was ineffective pain control, with 19% not agreeing to undergo prostate re-biopsy without some form of anes-

thetia [25]. There is no doubt that it is of great importance to establish a method of anesthesia that would improve patient tolerance to the procedure. In turn, improved pain control will likely increase patient agreement for re-biopsy when needed for cancer detection.

The administration of midazolam and the routine non-invasive monitoring was performed by an anesthesiologist in several studies [26,27]. In our study, blood pressure and pulse rate did not change significantly during the procedure and no patients had respiratory depression or hypotension. Based on our experience, it is not necessary to have monitoring performed by an anesthesiologist. However, monitoring should be performed by an appropriately trained nurse or physician.

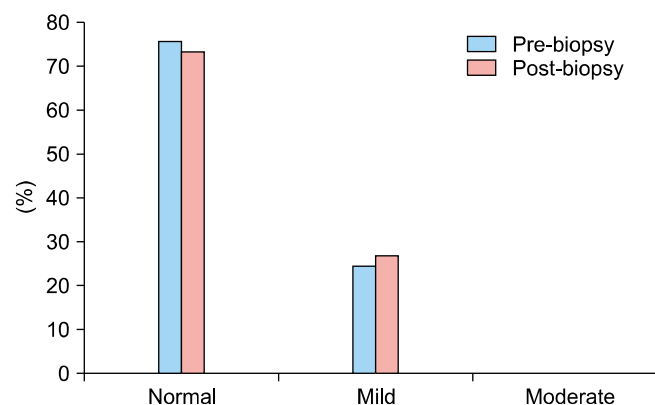
The use of midazolam anesthesia may increase the procedure costs associated with a prostate biopsy. In the present study, the total cost per procedure was higher (\$5.14) for the midazolam anesthesia group, but the majority of the cost was covered by Korean health insurance. The additional cost for midazolam-induced anesthesia under health insurance coverage is shown in Table 5.

Overall, 40 patients had a baseline MMSE score of  $\geq 25$  (normal), 13 had an MMSE score of 21-24 (mild), and no patients had an MMSE score of  $\leq 20$  (moderate to severe). After prostate biopsy, an MMSE score of  $\geq 25$  was found in 39 patients, an MMSE score of 21-24 was found in 14 patients, and an MMSE score of  $\leq 20$  was not found (Fig. 4). The difference in the MMSE score was not significant after

**TABLE 5.** Additional cost for midazolam-induced anesthesia under health insurance coverage

Midazolam	\$0.20
O <sub>2</sub> saturation monitoring	\$1.07
Intravenous injection fee	\$0.21
ECG monitoring	\$1.73
Blood pressure monitoring	\$1.93
Total cost	\$5.14

ECG: electrocardiogram



**FIG. 4.** Distribution of the cases in regard to the degree of cognition Mini-Mental State Examination (MMSE).

the midazolam anesthesia and there was no cognitive change to moderate or severe (score below 20). Side effects of midazolam administration have been seen in some patients [28,29]. However, no patients in this study had to be treated for side effects after midazolam anesthesia. Our study indicates that midazolam anesthesia during prostate biopsy is well tolerated and is associated with no or minimal discomfort.

## CONCLUSIONS

The use of midazolam is a very simple technique that provides adequate analgesia during transrectal ultrasound-guided prostate biopsy. In addition, patient satisfaction is improved during conventional transrectal ultrasound-guided prostate biopsy. The use of midazolam is non-invasive and free of any local complications or systemic side effects. Midazolam reduced pain sensation significantly. Midazolam-induced anesthetic transrectal ultrasound-guided prostate biopsy is a safe and useful method.

## Conflicts of Interest

The authors have nothing to disclose.

## REFERENCES

- Ross WA. Premedication for upper gastrointestinal endoscopy. *Gastrointest Endosc* 1989;35:120-6.
- Whitwam JG, Al-Khudhairi D, McCloy RF. Comparison of midazolam and diazepam in doses of comparable potency during gastroscopy. *Br J Anaesth* 1983;55:773-7.
- Hanno PM, Wein AJ. Anesthetic techniques for cystoscopy in men. *J Urol* 1983;130:1070-2.
- Forrest P, Galletly DC. Comparison of propofol and antagonised midazolam anaesthesia for day-case surgery. *Anaesth Intensive Care* 1987;15:394-401.
- Johnson EW. Visual analog scale (VAS). *Am J Phys Med Rehabil* 2001;80:717.
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-98.
- Kang Y, Na DL, Hahn S. Validity study on the Korean mini-mental state examination (K-MMSE) in dementia patients. *J Korean Neurol Assoc* 1997;15:300-7.
- Collins GN, Lloyd SN, Hehir M, McKelvie GB. Multiple transrectal ultrasound-guided prostatic biopsies--true morbidity and patient acceptance. *Br J Urol* 1993;71:460-3.
- Djavan B, Waldert M, Zlotta A, Dobronski P, Seitz C, Remzi M, et al. Safety and morbidity of first and repeat transrectal ultrasound guided prostate needle biopsies: results of a prospective European prostate cancer detection study. *J Urol* 2001;166:856-60.
- Gerecke M. Chemical structure and properties of midazolam compared with other benzodiazepines. *Br J Clin Pharmacol* 1983;16(Suppl 1):11S-6.
- Pieri L. Preclinical pharmacology of midazolam. *Br J Clin Pharmacol* 1983;16(Suppl 1):17S-27.
- Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. *Anesthesiology* 1985;62:310-24.
- Kanto JH. Midazolam: the first water-soluble benzodiazepine. *Pharmacology, pharmacokinetics and efficacy in insomnia and anesthesia. Pharmacotherapy* 1985;5:138-55.
- Amrein R, Hetzel W. Pharmacology of drugs frequently used in ICUs: midazolam and flumazenil. *Intensive Care Med* 1991;17(Suppl 1):S1-10.
- Greenblatt DJ, Shader RI, Abernethy DR. Drug therapy. Current status of benzodiazepines. *N Engl J Med* 1983;309:410-6.
- Study RE, Barker JL. Cellular mechanisms of benzodiazepine action. *JAMA* 1982;247:2147-51.
- Dundee JW, Wilson DB. Amnesic action of midazolam. *Anaesthesia* 1980;35:459-61.
- Koht A, Moss JI. Does midazolam cause retrograde amnesia, and can flumazenil reverse that amnesia? *Anesth Analg* 1997;85:211-2.
- Twersky RS, Hartung J, Berger BJ, McClain J, Beaton C. Midazolam enhances anterograde but not retrograde amnesia in pediatric patients. *Anesthesiology* 1993;78:51-5.
- Bulach R, Myles PS, Russnak M. Double-blind randomized controlled trial to determine extent of amnesia with midazolam given immediately before general anaesthesia. *Br J Anaesth* 2005;94:300-5.
- Lauven PM, Kulka PJ. Anaesthesia techniques for midazolam and flumazenil--an overview. *Acta Anaesthesiol Scand Suppl* 1990;92:84-9.
- Desgrandchamps F, Meria P, Irani J, Desgrippes A, Teillac P, Le Duc A. The rectal administration of lidocaine gel and tolerance of transrectal ultrasonography-guided biopsy of the prostate: a prospective randomized placebo-controlled study. *BJU Int* 1999;83:1007-9.
- Wu CL, Carter HB, Naqibuddin M, Fleisher LA. Effect of local anesthetics on patient recovery after transrectal biopsy. *Urology* 2001;57:925-9.
- Leibovici D, Zisman A, Siegel YI, Sella A, Kleinmann J, Lindner A. Local anaesthesia for prostate biopsy by periprostatic lidocaine injection: a double-blind placebo controlled study. *J Urol* 2002;167:563-5.
- Irani J, Fournier F, Bon D, Gremmo E, Dóre B, Aubert J. Patient tolerance of transrectal ultrasound-guided biopsy of the prostate. *Br J Urol* 1997;79:608-10.
- Turgut AT, Ergun E, Koşar U, Koşar P, Ozcan A. Sedation as an alternative method to lessen patient discomfort due to transrectal ultrasonography-guided prostate biopsy. *Eur J Radiol* 2006;57:148-53.
- Peters JL, Thompson AC, McNicholas TA, Hines JE, Hanbury DC, Boustead GB. Increased patient satisfaction from transrectal ultrasonography and biopsy under sedation. *BJU Int* 2001;87:827-30.
- Forster A, Gardaz JP, Suter PM, Gemperle M. I.V. midazolam as an induction agent for anaesthesia a study in volunteers. *Br J Anaesth* 1980;52:907-11.
- Ginsberg GG, Lewis JH, Gallagher JE, Fleischer DE, al-Kawas FH, Nguyen CC, et al. Diazepam versus midazolam for colonoscopy: a prospective evaluation of predicted versus actual dosing requirements. *Gastrointest Endosc* 1992;38:651-6.