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®) 30 mg. Group 2 (n=53) was treated with midazolam (Dormicum®) 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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(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) \( \geq 4 \) 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-

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**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               |
| Responds only to shaking                             | 2               |
| Responds only to name call loudly                    | 3               |
| Lethargic response to name spoken in a normal tone   | 4               |
| Responds readily to name spoken in a normal tone     | 5               |
| Total                                                | 53              |

**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.                                   |

**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).
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 < 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.
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 to 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-

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 ≥25 (normal), 13 had an MMSE score of 21-24 (mild), and no patients had an MMSE score of ≤20 (moderate to severe). After prostate biopsy, an MMSE score of ≥25 was found in 39 patients, an MMSE score of 21-24 was found in 14 patients, and an MMSE score of ≤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  |
| O₂ saturation monitoring                | $1.07  |
| Intravenous injection fee               | $0.21  |
| ECG monitoring                          | $1.73  |
| Blood pressure monitoring               | $1.93  |
| **Total cost**                          | **$5.14** |

ECG: electrocardiogram
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.

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