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ORIGINAL ARTICLE

Efficacy and cost analysis of transrectal ultrasound-guided prostate biopsy under monitored anesthesia

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Sedation may result in reduction in pain during transrectal ultrasound (TRUS)-guided prostate biopsies. We aimed to evaluate the efficacy and safety of a combination of propofol and remifentanil infusion during TRUS-guided prostate biopsy and the related increases in health care costs. From January to September 2010, 100 men undergoing a transrectal prostate biopsy were randomized into two groups. In Group 1, 50 patients received a combined infusion of propofol and remifentanil; in Group 2, 50 patients received lidocaine jelly. After TRUS-guided biopsies were performed, pain and patient satisfaction were evaluated by a 10-point visual analog scale (VAS), and a cost-related patient satisfaction questionnaire was completed by all patients. Patients were also asked whether they would be willing to undergo repeat biopsy by the same method. Patients in Group 1 showed a significantly lower VAS score than those in Group 2 (mean VAS score: 0.9±1.1 versus 6.3±2.5; $P<0.001$). In addition, the patient satisfaction scale was significantly higher in Group 1 ($P=0.002$). Although the overall cost was significantly higher in Group 1 ($P=0.006$), patient satisfaction scales considering cost were also higher in this group ($P=0.009$). A combination of propofol and remifentanil is a safe and effective way to decrease patient pain and increase patient satisfaction during TRUS-guided prostate biopsy. Although the costs were higher in the group that received sedation, as expected, the patients exhibited heightened satisfaction and willingness to repeat biopsies by the same method.
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INTRODUCTION

Transrectal ultrasound (TRUS)-guided prostate biopsy has become the standard procedure for diagnosing early prostate cancer.[1] During the last decade, the number of needle biopsy cores taken has increased, as have biopsies in younger patients and repeated biopsies.

Although anesthesia or analgesia has historically not been used in outpatient TRUS-guided biopsies, a significant proportion of patients (65%–90%) still find the procedure uncomfortable.[2,3] Some examples of anesthetics that may be used during TRUS-guided biopsies include intrarectal lidocaine gel, periprostatic nerve blockers, sedation and caudal blockage.[4–6] Peters *et al.*[7] reported the first use of propofol during TRUS-guided biopsies, and observed significantly decreased patient discomfort. However, they performed sextant biopsies in different with current extended biopsy methods, and cost was not considered. Another study reported that midazolam sedation is advantageous during repeat biopsies and extended biopsies are efficacious as well in young patients, abnormally anxious patients, and patients with anal or rectal disease.[5] However, despite multiple studies, there is still no consensus between practitioners regarding standard anesthetic practice for prostate biopsy.

While a previous study reported that the concentration of propofol required for moderate sedation during TRUS-guided biopsy is 1.5 μg ml^{-1}, more extensive studies are necessary to gain a complete picture of ideal sedation parameters.[6] The present prospective, double-blind, randomized study was undertaken to investigate the effects of propofol infusion combined with low-concentration remifentanil in terms of pain score and patient satisfaction during TRUS-guided prostate biopsy. We compared our results to those associated with use of intrarectal lidocaine gel, the standard practice at most centers. To our knowledge, this is the first study to analyze both costs and patient satisfaction according to the cost of these biopsies.

MATERIALS AND METHODS

We performed a prospective, randomized comparative study from January through September 2010. The data were prospectively collected and the study was approved by the Institutional Review Board of Korea University Anam Hospital and informed consent was obtained from the participating patients. Patients received either propofol sedation with reminfentanil (Group 1, $n=50$) or a transrectal lidocaine gel (Group 2, $n=50$). Prostatic biopsy was indicated by

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abnormal prostate on digital rectal examination and/or elevated prostate-specific antigen (PSA) levels (>4 ng ml^{-1}).

Our exclusion criteria included patients with bleeding hemorrhoids, acute anal fissures and prostatitis, congestive heart failure, chronic obstructive pulmonary disease, chronic use of opioid drugs, allergy to propofol, bleeding diathesis and hepatic failure. All patients were evaluated by the American Society of Anesthesiologists Physical Status Classification System (I–III) before procedure.

The patients were given intravenous ceftizoxime (1 g) one day prior to biopsy and continued on this regimen for a total of 2 days. Aspirin and other anticoagulants were discontinued 7 days prior to the procedure. Intravenous isepamicin sulphate (400 mg) and a combination of metronidazole (500 mg) and ceftriaxone (1 g) were given 60 min before the procedure and prophylaxis continued for 2 days after the procedure every 12 h. All patients underwent a 12-core prostatic biopsy under ultrasound guidance using a Hawk 2102 EXL scanner (B-K Medical, Herlev, Denmark), a biplanar 7.5 MHz transrectal probe and an automated biopsy gun with 18-gauge biopsy needles. All procedures were performed by the same urologist. Group 1 patients were placed in the lithotomy position while Group 2 patients were placed in the left lateral decubitus position, and digital rectal examinations were followed by rectal cleaning with Betadine.

In most patients, 12 core prostate biopsies were performed, including six parasagittal and six laterally targeted biopsies covering the base, mid zones and apexes. A Betadine pack was used for approximately 5 min at the end of the procedure.

In Group 1, propofol infusion was performed by an attending anesthetist using a target-controlled infusion (TCI) system (Diprifusor, Fresenius Vial SA, Brézins, France).[8,9] Based on the age and weight of the patient, the TCI system calculates the initial bolus dose of propofol and the subsequent infusion rate required to achieve and maintain a desired target plasma concentration using a three-compartment pharmacokinetic model. After the desired level of sedation was achieved, the target-controlled concentration of propofol and remifentanil was titrated by the anesthetist in increments of 0.1 μg ml^{-1} to maintain the predetermined level of sedation. In Group 2, 10 ml of 2% lidocaine gel were applied to the rectum 1 min prior to the procedure.

Pain severity for the procedure was assessed by VAS according to the following scale: 0, no pain; 1–3, mild pain; 4–6, moderate pain; 7–10, severe pain. All patients were asked about pain within 1 h immediately after the procedure. The primary end point was efficacy as evaluated by a decreased VAS score in monitored anesthesia care (MAC) group compared to that of lidocaine jelly group. The secondary end point was patient satisfaction including cost analysis. Patient satisfaction and cost-related satisfaction questionnaires were also completed by all patients respectively (both having four grades: score 1, unsatisfactory; score 2, somewhat unsatisfactory; score 3, satisfactory; score 4, highly satisfactory). Cost analyses were performed with patient consent. Overall cost and anesthetic-related cost analyses were performed. Anesthetic-related cost included not only anesthesiologist fee and drugs' cost but also the preprocedural blood test, urine analysis test, chest radiography and electrocardiography.

All costs are reported in 2010 Korean won (KW; 2010 exchange rate US$1=KW1200). Differences in the age, body mass index, volume of the prostate, PSA levels and cost analysis were analyzed by unpaired *t*-test. The difference in VAS between the two groups and patient satisfaction scales were analyzed by Mann–Whitney *U* test. In addition, Pearson's chi-square test was used to compare frequency and complications. The *P* value was accepted as significant when it was less than 0.05. All analysis was performed using SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

There were no significant differences between Groups 1 and 2 in patient demographic data (**Table 1**). **Table 2** shows the pain scores experienced by patients during the procedure.

Thirty-five patients (35%) were diagnosed with prostate cancer; 18 patients in Group 1 (36%), and 17 in Group 2 (34%). There was no significant difference in cancer prevalence between the two groups ($P>0.05$).

The mean pain scores and patient satisfaction scale scores are shown in **Table 2**. The mean VAS scores of patients undergoing prostate biopsies were significantly lower in Group 1 (0.90 versus 6.30) than those in Group 2 ($P=0.001$). The overall patient satisfaction scores were significantly higher in Group 1 (3.23 versus 2.43) than those in Group 2 ($P=0.002$). In addition, VAS scores exceeding 4 (moderate-to-severe discomfort) were detected in 0% and 83% of patients in Groups 1 and 2, respectively.

Overall patient satisfaction scores considering cost were significantly higher in Group 1 than those in Group 2, and overall cost was also higher in Group 1 by approximately 203 000 KW (about $169; **Table 3**).

There were only minor complications, such as mild hematuria, mild hematochezia and hemospermia. Sixteen patients had gross hematuria, 13 patients had rectal bleeding and 9 patients had urinary tract infection. All patients recovered with conservative management; no patient required hospitalization due to complications including sepsis. There were no significant differences in the complication rates between the two groups. There were only two cases of mild upper airway obstruction, both of which were immediately resolved with oropharyngeal airways (**Table 4**). None of the patients required hospital admission. None of the patients experienced motor blockade. All patients in both groups were able to walk without assistance immediately after the procedure.

DISCUSSION

TRUS-guided prostate biopsy is considered to be a simple and accurate method for diagnosing prostate cancer. In patients with elevated serum PSA level and/or an abnormal-feeling prostate on exam, TRUS-guided prostatic biopsy is routinely performed to diagnose the presence or absence of malignancy.[10] Recently, the performance of multiple-core prostatic biopsies has become standard practice, and repeat biopsies are often performed despite initial negative histology. There is a general consensus regarding the necessity of some form of anesthesia during TRUS-guided prostate biopsy due to preoperative pain and/or discomfort.[7,11,12]

The most common methods for alleviating discomfort during TRUS-guided biopsy are intrarectal gel or periprostatic injection.[13,14] Periprostatic nerve blocks have been reported to be effective for the reduction in discomfort, but may have limited ability to reduce

Table 1 Patient characteristics and biopsy results

	Group 1 (n=*50*)	*Group 2* (n=*50*)	P *value*
Mean age (year)	63.57	63.30	0.890
Mean BMI	24.71	24.54	0.486
Mean prostate volume (ml)	39.96	38.26	0.374
Mean PSA (ng ml^{-1})	10.12	7.99	0.137

Abbreviations: BMI, body mass index; PSA, prostate-specific antigen.

Table 2 Patient VAS score and satisfaction scales

	Group 1	*Group 2*	P *value*
VAS scores (mean±s.d.)	0.90±1.09	6.30±2.48	0.001
Patient satisfaction scales (mean±s.d.)	3.23±0.73	2.43±1.10	0.002
Moderate-to-severe pain (*n*, %)	0 (0%)	42 (83.3%)	<0.001

Abbreviation: VAS, visual analog scale.
Moderate-to-severe pain: VAS ⩾4.

Table 4 Complication rates (%)

Complication	*Group 1 (%)*	*Group 2 (%)*	P *value*
Hematuria	7 (14%)	9 (18%)	0.585
Hemospermia	4 (8%)	2 (4%)	0.400
UTI	4 (0%)	5 (10%)	0.727
Fever	0 (0%)	2 (4%)	0.153
Rectal bleeding	5 (10%)	8 (16%)	0.372
Total	20 (40%)	26 (52%)	0.229

Abbreviation: UTI, urinary tract infection.

pain.[15,16] In addition, nerve blocks do not reduce pain during the insertion of ultrasound probes, and are even associated with increases in pain during repeated needle punctures.[17]

Peters *et al.*[7] first reported the use of propofol during prostate biopsy in 2001, but subsequent reports related to this form of sedation did not appear until 2005. This is largely due to the fact that prostate biopsies are considered minor outpatient procedures, as well as the high cost of sedation.[18] However, taking 10–12 prostatic cores is becoming standard practice and repeat or saturation biopsies are increasing in frequency. Due to the popularity of PSA screening, younger patients who present with elevated anal tonus are likely to undergo more extensive and repeated TRUS-guided biopsies, and there has been an increase in interest of using sedation or caudal blocks. Cesur *et al.*[6] reported that 'walking' caudal analgesia is an effective method, and suggested that it results in perianal analgesia and anal sphincter relaxation. However, they admitted that caudal injection was an additional procedure that caused extra discomfort. Shrimali *et al.*[10] reported that the use of midazolam was both simple and resulted in excellent analgesic effects. In a separate study, researchers also reported that midazolam was an effective alternative for increasing patient comfort during TRUS-guided prostate biopsy, especially in clinical situations including patient anxiety, young age, repeat biopsies or inflammatory anal diseases.[5]

MAC refers to monitoring of a patient receiving local anesthesia, or to administration of supplemental drugs to patients undergoing diagnostic or therapeutic procedures for comfort, safety and/or satisfaction.[19] Midazolam is widely used for MAC. Besides its hypnotic and amnestic effects, it also has an anxiolytic effect, although it does not have analgesic properties. In addition, the context-sensitive half time of midazolam is longer than that of propofol and remifentanil, indicating that recovery times after midazolam infusion can prolong even if the time of drug infusion is the same as propofol and/or remifentanil.[20]

Sedation by propofol infusion has advantages over midazolam bolus and intermittent administration. First, the duration of sedation can be controlled due to the fast metabolism of propofol. Second, the degree of sedation can be controlled easily by increasing or decreasing the infusion rate. In many previous studies, midazolam was administered not by continuous infusion but by bolus administration. However, during bolus administration, midazolam can cause insufficient sedation so that patients awaken or feel discomfort during medical procedures probably due to pharmacokinetic differences from other sedatives.[21] To overcome this problem, we used propofol with a TCI system. In fact, propofol infusion is the most commonly used sedation technique in many medical procedures.[22–24]

Although propofol infusion combined with remifentanil can cause respiratory depression, MAC requires observation of respiratory function and hemodynamic stability because benzodiazepine, propofol and opioids can all result in respiratory and cardiovascular depression.[24] In MAC patients, we used remifentanil as a TCI for analgesia and synergism with propofol.[25] All patients were under the constant vigilance of an anesthesiologist during procedures, and there were only two cases of upper airway obstruction, both of which were immediately resolved with oropharyngeal airways so that hypoxemia or desaturation did not occur.

Peters *et al.*[7] reported that the use of sedation for TRUS-guided biopsy increases healthcare costs and emphasized the need for cost analysis, although they did not conduct cost analyses themselves. In our investigation, compared with the use of lidocaine jelly, the increased costs of sedation with propofol and remifentanil were minimal at about $169, because the national health insurance corporation covers 80% of the overall cost in Korea. Our results suggest that patient satisfaction is based on the procedure as a whole, including pain and discomfort, and not only by costs, although each patient's insurance system must be considered. Moreover, the willingness to undergo secondary biopsies was significantly higher in Group 1 than that in Group 2, supporting these conclusions.

However, although the individual patient's charge is minimal, the overall health care cost can be increased enormously if a more global consideration is made. So, physician should try to find the guidelines indicating which procedures should be performed under anesthesia because not all patients experience moderate-to-severe degree of pain during the biopsy procedure. Turgut *et al.*[5] reported that sedation has many advantages, in those undergoing repeat biopsies, in cases of extended biopsy protocols, in younger patients, in the more anxious patients and in those with anal or rectal disease such as anal fissure. Therefore, studies to find the risk factors for a painful procedure and guidelines for patient selection should be progressed together in future.

There are some limitations in the present study. First, the authors did not compare the sedation with periprostatic lidocaine block, which now represents the gold standard. It was the major limitation of this study. Most of the recent reports suggested that periprostatic nerve block has an upper hand over periprostatic instillation. However, periprostatic nerve block is not widely used in Korea. It is probably because of the problem that periprostatic nerve block has as follows. Autorino *et al.*[18] reviewed that periprostatic nerve blocks required one or more extra needle punctures and can be associated with a higher incidence of infectious complications. Though Noh *et al.* [4] reported in *Korean Journal of Urology* that the combination of periprostatic nerve block and lidocaine gel instillation showed an excellent performance, it is presumed that trials like this are in their early stage. As the periprostatic nerve block is not yet tried in our hospital either, we compared MAC group with lidocaine jelly group.

Table 3 Comparison of cost and cost-considering satisfaction scale

	Group 1	*Group 2*	P *value*
Overall cost	1104±256	901±209	<0.05
Anesthetic-related cost	256±26	95±0	<0.01
Patients charge	641±186	553±166	<0.05
Patient satisfaction scales considering cost	3.16±0.75	2.53±1.04	<0.01

Data were expressed as Korean won ×103 (mean±s.d.).

However, the periprostatic nerve block is accepted as the gold standard in Western countries and further comparison with periprostatic nerve block group is certainly required to demonstrate the superiority of the MAC anesthesia during TRUS-guided prostate biopsy in the future. Another point we need to take a look at is that the mean VAS score of Group 2 is relatively higher than other study results. Cesur *et al.*[6] found that the VAS score of lidocaine gel group during biopsies was 4 and the mean VAS of control group was 4.7 in the study by Turgut *et al.*[18] In the current study, VAS score of Group 2 was 6.3, which was pretty higher than 4.7. We think that it was because that the VAS score is a considerably subjective evaluation tool. Autorino *et al.*[18] pointed that translating the result regarding pain and discomfort is still subjective and there is no standardized criteria for it. He also said that pain is a complex perceptual experience and still difficult to be quantified. Despite of various kinds of methods of measuring pain, VAS measurement is the most widely used but is still a very subjective tool. It seems that this study also reflected a higher score for actual pain as patients sometimes told so due to the limitation of VAS score. We believe that it was because of patients' intention to ask for painkillers after answering the questions. More objective assessment tool good enough to replace VAS is required to overcome this matter.

There are no standard anesthetic methods for TRUS-guided prostate biopsy, possibly because the procedure is usually performed in an outpatient setting. However, evidence suggests that patient discomfort belies the assumption that biopsy is a minor outpatient procedure.

Combined sedation with propofol and remifentanil was safe and effective for pain control in patients undergoing TRUS-guided prostate biopsy. Although the average cost was higher than standard procedures, patient satisfaction was higher. Further studies are needed to identify the most appropriate anesthetic methods for use in TRUS-guided prostate biopsy, followed by standardization of those methods.

AUTHOR CONTRIBUTIONS

SGK participated in the design of the study, data analysis, interpretation and drafting of the manuscript. BST and SHM helped drafting the manuscript. YHK, SHK, JGL, JJ K and JC helped critical review and approval of article.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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