Comparison of Efficacy Between Oral Morphine Sulphate and Diclofenac Suppository for Analgesia During Transrectal Ultrasound-guided Prostate Biopsy

Hesti Haswir, Rainy Umbas

ABSTRACT

Aim: to prospectively evaluate degree of pain during transrectal ultrasound-guided prostate biopsy after receiving analgesics treatment of oral morphine sulphate compared to suppository sodium diclofenac.

Methods: the study group comprised 60 consecutive men subjects (median age 67.8 years) undergoing transrectal prostate biopsy. They were randomized into two groups; group 1 received oral analgesic of morphine sulphate 10 mg and group 2 received suppository analgesic of sodium diclofenac 100 mg 1 hour before biopsy. Biopsy was taken using a gun biopsy 18 G needle with total 10 biopsies (5 at each lobe). Immediately after the procedure patients were asked to indicate the degree of pain based on visual analogue scale (VAS) from 0 (no pain) to 10 (unbearable pain) scale.

Results: the mean VAS score was 3.83 in oral morphine sulphate group and 4.10 in sodium diclofenac group. According to subdividing of VAS score, low degree of pain was found in 17 patients (56.7%) of morphine sulphate group and in 14 patients (46.7%) of sodium diclofenac group. There was no statistically significant difference in pain between the two groups (P>0.05).

Conclusion: oral analgesic of morphine sulphate 10 mg has the same efficacy with sodium diclofenac suppository 100 mg to decrease pain during transrectal prostate biopsy.

Key words: prostate biopsy, oral analgesia, suppository analgesia, pain.

INTRODUCTION

Transrectal prostate biopsy is a standard diagnostic examination for prostate cancer. Prostate biopsy is performed in patients at outpatient clinic and it is usually carried out without analgesics. Therefore, it may cause pain, uncomfortable feeling, and anxiety. Pain occurs during prostate biopsy is caused by penetrating needle into the prostate capsule through rectal wall which stimulates receptors of sensory nerves in the prostate capsule and parenchyma.1 The major factors associated with low pain tolerance during biopsy procedure are anxiety, increased tone of anal sphincter, and the number of biopsies performed.2,3 Some studies demonstrated a quite significant moderate to severe pain during the biopsy procedure. Approximately 5-90% patients reported uncomfortable feeling or after prostate biopsy using the guiding TRUS and 19% would refuse to have similar procedure without analgesia.2-7

There have been a lot of studies that evaluate the role of analgesics, particularly by giving intratecal lidocaine or periprostatic nerve block, which significantly may decrease pain during prostate biopsy. In Cipto Mangunkusumo Hospital, there have been studies about periprostatic analgesics injection of lidocaine (Alvarino and Umbas, 2003)8 and suppository sodium diclofenac (Afadal and Umbas, 2004) which demonstrated a significant difference in decreasing pain compared to placebo. However, a study that evaluate oral analgesic administration to decrease pain during prostate biopsy procedure compared to suppository sodium diclofenac has not been performed yet. Oral analgesics or tablet is more recommended for treating acute pain due to easier route of administration, no pain, relatively safe and comfortable for the patient. Nevertheless, it should provide an effective analgesia effect.9,12

The aim of this study is to evaluate the degree of pain in patients who have received oral analgesics
treatment of oral morphine sulphate during transrectal ultrasound-guided prostate biopsy compared to suppository sodium diclofenac. We expected that the result of this study may provide an alternative for a less expensive, safe and comfortable analgesics to decrease pain during the transrectal prostate biopsy procedure.

METHODS

This study is a prospective, non-blinding clinical randomized trial that evaluates the effects of decreased pain during transrectal prostate biopsy by giving analgesics treatment of oral morphine sulphate 10 mg compared to suppository sodium diclofenac 100 mg.

The study was conducted at the Department of Urology, Cipto Mangunkusumo Hospital, Jakarta. Prostate biopsy by guiding TRUS method was performed in all subjects from June 2006 to February 2007 after being approved by the Ethical Committee or Institutional Review Board at Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo Hospital. The sample was selected by consecutive sampling, i.e. all of enrolled and eligible subjects. The inclusion criteria were willing to participate as the study subject; a new patient of suspected prostate cancer with Prostate Specific Antigen (PSA) score > 10 ng/mL or PSA score of 4 – 10 ng/mL with Prostate Specific Antigen Density (PSAD) > 0.15 or suspected prostate cancer on digital rectal examination; and underwent 5 prostate biopsies at each lobe (total 10 biopsies). The exclusion criteria were patients who had prostatitis, anal infection, hemmorhoid or anal fissures; and patients who was using analgetic or thrombolytic agents; patients with history of prostate biopsy; and total prostate biopsies more or less than 10. All patients’ history of treatment including history of implantation, heart disease and allergy should be known prior to the biopsy procedure. Patients should continue to take their medicine for their heart or blood pressure condition on the day of biopsy; while aspirin or warfarin should better be stopped for 10 days prior to the biopsy procedure. Fasting was not recommended for the subjects, particularly for patients with diabetes who should better continue their daily food as usual.13,14

After the informed consent had been obtained, the subjects received antibiotic, i.e. 500 mg ciprofloxacin and suppository analgesic (Sodium-diclofenac 100 mg) with oral placebo tablet or oral analgesic tablet (10 mg morphine sulphate) with placebo suppository. After an hour, prostate biopsy was performed using a gun biopsy 18G needle (US Biopsy MCN 1820-T) with 5 biopsies at each lobe (total 10 biopsies) by guiding TRUS method. The degree of pain was immediately determined by the patients after the procedure had been completed and patients were asked to indicate the degree of pain based on visual analogue scale (VAS) from 0 (no pain) to 10 (unbearable pain) scale.

Data were processed by using SPSS 10.0 program. The quantitative and qualitative data analyses were performed by using student t-test independent and Kruskall-Wallis test respectively that provided comparison between two groups. P < 0.05 was considered as significant.

RESULTS

From June 2006 to February 2007, there were 60 subjects whose prostate biopsies had fulfilled the inclusion criteria. The median age was 67.8 years (ranged 52 – 87 years). The characteristics of subjects in both study groups are shown on table 1. The match test revealed that there was no significant difference between both study groups regarding variables of age, prostate volume and PSA score (P > 0.05). The mean V AS score was 3.83 in oral morphine sulphate group with minimal score 1 and maximal score 10; while the mean V AS score was 4.10 in sodium diclofenac group, with minimal score of 1 and maximal score 8. (Table 2) There was no significant difference in V AS score between both study groups (P > 0.05). According to subdividing of pain score, i.e. low degree of pain (VAS score 1-3), moderate degree of pain (VAS score 4-7) and severe degree of pain (VAS score 8-10), the low, moderate and

<table>
<thead>
<tr>
<th>Variables</th>
<th>Morphine sulphate (n =30)</th>
<th>Sodium-diclofenac (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>67.67 (53 – 82)</td>
<td>68.10 (52 – 87)</td>
<td>0.843</td>
</tr>
<tr>
<td>Volume of prostate (cc)</td>
<td>53.82</td>
<td>53.29</td>
<td>0.956</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>49.62 (1.71 – 390)</td>
<td>72.89 (1.87 – 858)</td>
<td>0.527</td>
</tr>
</tbody>
</table>
severe degree of pain were found 56.7%, 36.7% and 6.7% respectively in morphine sulphate group. In sodium diclofenac group, there were 46.7% low degree of pain, 50% moderate pain and 3.3% severe pain. (Table 3). There was no significant difference in pain between two groups ($P > 0.05$).

DISCUSSION

Some studies demonstrated that approximately 10-90% patients who have undergone prostate biopsy without analgesia have moderate to severe pain of VAS score > 5.2,6,7,15,16 A study reported that approximately 19% patients will refuse re-biopsy procedures if it is performed without analgesia or anesthesia.17 A study by Tjahyo and Umbas in 2003 at Cipto Mangunkusumo Hospital reported that 77.5% patients who had prostate biopsy without analgesia would experience moderate to severe pain.18 While the study by Alvarino and Umbas in 2003 at Cipto Mangunkusumo Hospital reported mean VAS score of 5.7 ± 1.7 in patients who received placebo during the prostate biopsy procedure.8

The prostate innervation consists of parasympathetic nerves derived from pelvic splanchnic nerve through pelvic plexus and symphatetic nerve originated from hypogastric nerves through the pelvic plexus. Such neurovascular prostate tissues are located between prostate and rectum on lateral side of prostate. There are two areas of prostate innervation as subdivisions of such neurovascular tissues, i.e. superior pedicles and inferior pedicles. Superior pedicles begin at the level of prostate bottom, which then are subdivided, distributed and penetrate the prostate capsule before entering the parenchyma of approximately 80% of glands. Inferior pedicles begin at the apex across the capsule in the Denonvilliers’ fascia adjacent to membranous part of the urethra and rectourethra muscles, before being subdivided and penetrates into small parts of apical capsule at the midline.19 Pain that occurs during prostate biopsy is caused by needle that penetrates prostate capsule through rectal wall and stimulates receptors of sensory nerves in the prostate capsule and parenchyma.1

In addition to pain, anxiety is also frequently found in patients who will have prostate biopsy procedure and the most worried patient usually will have more severe pain symptom.16 In some patients, biopsy procedure should even be stopped due to unbearable pain for the patient. Major factors associated with low pain tolerance during biopsy procedure are anxiety, increased tone of anal sphincter and the number of biopsy performed.2,3 Today, analgesic administration during prostate biopsy has become a routine procedure. Various analgesic/anesthetics that have been reported include intrarectal local anesthetics, oral or intratecal analgesics, periprostatic nerve block and intravenous or inhalation anesthesia.

Sodium diclofenac is a derivate of benzene acetic acid, i.e. an non-steroid anti-inflammatory (NSAID) agents, which has central or peripheral anti-inflammatory, analgesic and antipyretic effect. Mechanism of action of sodium diclofenac, as other NSAID drugs, has not been fully understood. However, it is assumed to be associated with inhibition of prostaglandin synthesis. Prostaglandin is formed as a response to trauma or disease through cyclooxygenase enzymes which causes
pain, edema and inflammation. Combination of sodium diclofenac and other NSAID is not recommended because there is no evidence of synergic advantages. Suppository agents are contraindicated in anal/rectal inflammation and patients with history of anal/rectal bleeding.20,21

The analgesia effect of morphine is caused by its ability to inhibit ascending transmission of nociceptive information from spinal cord and pain control from midbrain to spinal cord. Morphine mechanism of action is similar to endorphine in opioid receptors at brain and spinal cord which will inhibit pain transmission sent by nerves to the brain. Therefore, although the cause of pain is still present, but the quality of pain felt will be reduced. In addition to analgesia effect, morphine also has sedation and anxiolytic effect, which may reduce anxiety or uncomfortable feeling. Slow-released oral morphine is available, therefore the drug can be titrated for administration as an analgesic in minimal invasive urologic procedure are including morphine sulphate in the transurethral microwave thermotherapy (TUMT), which is given 2 hours prior to procedures with dose of 20 - 40 mg per oral.24-27

A study by Haq et al28 indicated VAS score of 2.8 for administration of 100 mg sodium diclofenac suppository; while the study by Afdal and Umbas reported VAS score of 3.22 (2004, data have not been published). In this study the mean value of VAS score was higher i.e. 4.10 in 100 mg suppository sodium diclofenac group with 16 patients (53.3%) included in moderate and severe pain score. In the study by Afdal and Umbas, mean of total biopsy number was 9.37 (6 to 12 biopsies); while in this study, total number of biopsy was 10. This may affect the degree of pain score, therefore this study reveals a relative higher VAS score. In the 10 mg oral morphine sulphate group, the mean VAS score was 3.83 with 13 patients (43.4%) with moderate to severe degree of pain. The statistics reveals no significant difference of VAS score (P = 0.599) between two groups although there is a lower VAS score in 10 mg oral morphine sulphate group (VAS 3.83) compared to 100 mg sodium diclofenac suppository group (VAS 4.10). Thus, there is no significant difference in degree of pain (P=0.668) between the two groups, although there is a higher number of patients included in low degree of pain in 10 mg morphine sulphate group (56.7%) compared to 100 mg sodium diclofenac group (46.7%).

Adverse effects of 10 mg oral morphine sulphate were found in 3 subjects, i.e. nausea and vomiting in 1 subject and drowsiness in 2 subjects. Patient who takes morphine sulphate is suggested not to drive or operate machine because this drug may cause drowsiness or lethargy. Patients with severe lung disease, congestive heart failure, gastrointestinal disorder, defect in liver or kidney function; and patients who are addicted to opiate should not received morphine sulphate.

CONCLUSION

This study is the first study that compares morphine sulphate and sodium diclofenac for analgesia in prostate biopsy. Morphine sulphate 10 mg per oral provides similar analgesia effect to sodium diclofenac 100 mg suppository in transrectal prostate biopsy procedure using the guiding TRUS. In general, single dose 10 mg morphine sulphate can be well tolerated without resulting in any significant adverse effect in most patients. Limitation of this study is that we only conducted evaluation on degree of pain and adverse effect of drug immediately after the biopsy procedures and we did not perfom further follow up after the patient had been discharged or followed few days after the biopsy. Further studies with a larger number of samples and longer follow up period are necessary to evaluate the adverse effect of oral morphine sulphate, particularly in elderly who tends to be more sensitive to the adverse effect of morphine sulphate, considering that most patients who have prostate biopsy are more than 60 years of age.

REFERENCES