

# THE DIFFERENCE OF PAIN PERCEPTION BETWEEN KETOPROFEN SUPPOSITORY AND 1% PERIPROSTATIC LIDOCAINE INJECTION

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## ABSTRACT

**Objective:** To compare the pain control results of ketoprofen suppository and periprostatic injection of lidocaine 1% for prostate biopsy. **Material & Method:** A total of 30 patients who underwent transrectal ultrasound guided prostate biopsy were randomized into 2 groups. Group 1 consisted of 15 patients received 200 mg of ketoprofen suppository. Group 2 received 1% periprostatic lidocaine injection. A visual analog scale was used to assess the pain score during prostate biopsy. Statistical analysis of pain scores was performed using independent t-test and Pearson correlation test. **Results:** The 2 groups were homogenous in age and prostate volume. There was significant difference in pain score among groups 1 and 2 during prostate biopsy (mean VAS  $\pm$  SD  $0,8 \pm 0,8$  and  $4,5 \pm 1,6$  respectively,  $p < 0,0001$ ). There was no significant correlation between pain perception with age ( $p = 0,779$ ), or prostate volume ( $p = 0,389$ ) in both groups. **Conclusion:** Periprostatic lidocaine injection is more effective for decreasing the pain for prostate biopsy compared to ketoprofen suppository.

**Keywords:** Prostate biopsy, pain, transrectal ultrasonography, periprostatic nerve block, visual analog scale.

## ABSTRAK

**Tujuan Penelitian:** Membandingkan persepsi nyeri antara pemberian ketoprofen supositoria dengan injeksi lidokain 1% periprostatika pada TRUS guided prostate biopsy. **Bahan & Cara:** Penelitian ini bersifat prospektif, randomized clinical trial, pada 30 pasien biopsi prostat. Tiga pasien dieksklusi karena hasil pemeriksaan patologi anatomi adenokarsinoma prostat. Pasien dirandomisasi, 13 pasien diberikan ketoprofen 200 mg supositoria (kelompok 1) dan 14 pasien diinjeksi lidokain 1% periprostatika (kelompok 2) sebelum biopsi prostat. Pasien ditanya skala nyeri saat biopsi menggunakan visual analog scale (VAS), kemudian dianalisa statistik dengan t-independent test dan uji korelasi Pearson. **Hasil Penelitian:** Umur dan volume prostat pasien homogen pada kedua kelompok. Injeksi lidokain 1% periprostatika mengurangi nyeri secara signifikan dibandingkan dengan ketoprofen supositoria dengan skala VAS  $\pm$  SD  $0,8 \pm 0,8$  vs  $4,5 \pm 1,6$  dengan  $p < 0,0001$ . Tidak ada hubungan yang signifikan antara persepsi nyeri dengan umur ( $p = 0,779$ ), dan volume prostat ( $p = 0,389$ ) pada kedua kelompok. **Simpulan:** Nyeri biopsi prostat berkurang secara signifikan pada injeksi lidokain 1% periprostatika dibandingkan ketoprofen supositoria, juga tidak didapatkan hubungan antara persepsi nyeri dengan umur dan volume prostat pada biopsi prostat.

**Kata Kunci:** Biopsi prostat, nyeri, transrectal ultrasonography, periprostatic nerve block, visual analog scale.

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## INTRODUCTION

Prostate cancer is the fourth most common malignancy in men,<sup>1</sup> approximately 15% of cancers in men in developed countries and 4% in developing countries.<sup>2</sup> Prostate cancer deaths in the United States are approximately 30,000 cases/year, decreasing 25% over the previous decade. It was

suggested to have correlation with prostate cancer early detection program. The program initially involves examination of prostate specific antigen (PSA) and digital rectal examination.<sup>3,4</sup> In 1989, Hodge introduced the systematic sextant prostate biopsy procedures under guidance of transrectal ultrasonography (TRUS), which later became the procedure of choice and gold standard for the

diagnosis of prostate cancer.<sup>3,4,5</sup>

TRUS guided prostate biopsy procedure is safe and can be performed on an outpatient basis. In the United States about 500,000 TRUS guided prostate biopsies are performed each year. However, this procedure causes discomfort and pain.<sup>3,6</sup> Approximately 65-90% of patients felt pain during the action, and nearly 20% experience significant pain and refused re-biopsy was performed without analgesic/aesthesia.<sup>3,7,8</sup> Six percent patients regard this procedure very painful and must be performed under general anesthesia.<sup>8,9</sup>

Nash (1996) pioneered the use of 1% lidocaine injection into the prostate nerve bundles to reduce pain during prostate biopsy,<sup>5</sup> and found a significant decrease in pain compared to patients without lidocaine injection.<sup>10</sup> Another method using diclofenac suppositories, which has local and general analgesic effect with low complications. There are significant differences in the patients who were given with diclofenac suppository on prostate biopsy, where only 4 patients with a score of visual analog scale (VAS) > 5 and 11 patients received placebo.<sup>11</sup>

Periprostatic nerve block (PNB) with 1% lidocaine injection anesthesia is the technique most frequently performed and is considered as the gold standard.<sup>8,12</sup> A study of 90 patients found an average pain score of 1,51 on the injection of lidocaine 1% compared to 3,98 in the control group.<sup>7</sup> Another study comparing the provision of intrarectal lidocaine jelly found differences in the average pain score in lidocaine injection 2,4 vs 3,7.<sup>3</sup> About 93% had only mild pain on periprostatic injection of 1% lidocaine. Whereas, in patients without anesthesia, 55% felt the pain significantly, even 10% required sedation.<sup>13</sup> Other researchers revealed average pain score of 2,6 in periprostatic lidocaine injection.<sup>14</sup>

Approximately 84% of patients with injection of lidocaine 1% had VAS scores < 5,9 of 50 patients, only 1 patient felt pain in this procedure.<sup>15</sup>

In Dr. Soetomo Hospital Surabaya, to reduce pain during TRUS guided prostate biopsy, we used ketoprofen suppositories 200 mg/rectal.

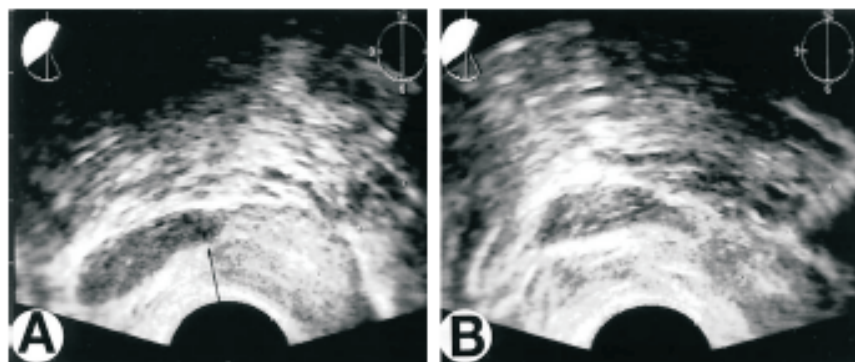
## OBJECTIVE

To determine differences in pain perception between ketoprofen suppositories with periprostatic 1% lidocaine injection in TRUS guided prostate biopsy using VAS scores.

## MATERIAL & METHOD

This study was a prospective randomized clinical trial. Study sample were BPH LUTS patients in Dr. Soetomo Hospital Surabaya with TRUS guided prostate biopsy indication. Inclusion criteria were suspicion prostate malignancy with PSA > 4 ng/ml, PSAD > 0,15; digital rectal examination revealed hard, nodular, or asymmetrical prostate; lesions found on TRUS prostate were hypo- or hyperechoic. The exclusion criteria were patients who had previous prostate biopsy, prostate cancer, prostatitis, rectal infections, hemorrhoids, anal fissure, blindness or cataracts; currently using analgesics or anticoagulant/antiplatelet, allergy to lidocaine and ketoprofen.

The research was conducted in January to March 2011 with a sample size of 30 patients, each 15 patients per group. Two patients of group 1 and group 2 were excluded because of the anatomic pathology of prostate adenocarcinoma. The night before the biopsy, the patients were given enemas. Before the procedure, prophylactic antibiotics were provided. Randomization was done for the



**Figure 1.** Transrectal ultrasound of prostate and seminal vesicles. A) Arrows indicate the injection of lidocaine, B) After injection of the seminal vesicles are lifted and separated from the perirectal fat.<sup>3</sup>

allocation of groups 1 and 2. The position of the patient was left lateral decubitus. Group 1 was given with 200 mg ketoprofen suppositories per rectal, one hour later prostate biopsies were performed. Group 2 was given local injection of periprostatic 1% lidocaine at the lateral area of the junction of the seminal vesicles and prostate base using a 22G spinal needle and a length of 7 inches by 7 MHz TRUS guidance with sagittal cuts (Fig. 1). The injection is appropriate if seminal vesicles are lifted and separated from rectal wall or perirectal fat. Five minutes later we performed a prostate biopsy with 10-core technique using 18G biopsy needle. After the biopsy, the patients determined the degree of pain that is felt on the score. Interpretation of the pain was as follows: score 0 no pain, 1-3 mild pain, 4-7 moderate pain, and 8-10 severe pain.

Data distribution normality test was performed with Kolmogorov-Smirnov test. Data analysis were followed by independent t-test, with

the degree of significance of  $p < 0,05$ . For correlation test we used Pearson test.

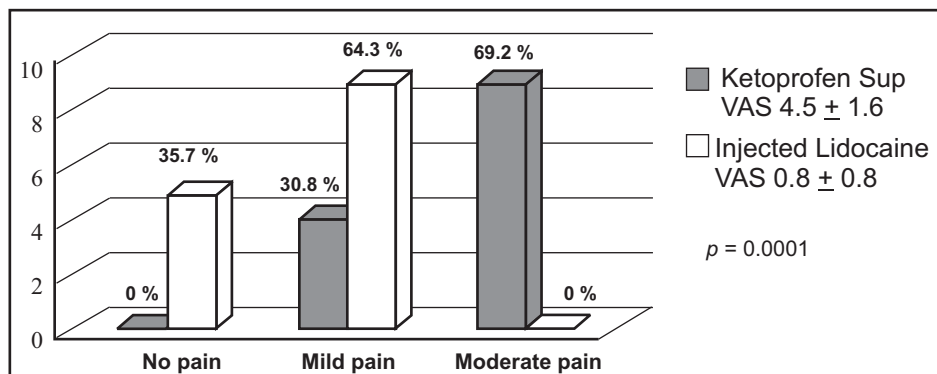
## RESULTS

Based on the test for normality of data distribution by Kolmogorov-Smirnov test, obtained the distribution of age ( $p = 0,378$ ) and prostate volume (0,244) of patients were normal or homogeneous in both study groups (Table 1).

Evaluation of patient perception of pain during a prostate biopsy is shown in Figure 2. In group 1, the VAS value was  $4,5 \pm 1,6$ . While in the second group, the VAS was  $0,8 \pm 0,8$ . In group 1, as many as 9 patients (69,2%) felt moderate pain and 4 patients (30,8%) mild pain. Whereas in group 2, a total of 5 patients (35,7%) had no pain and 9 patients (64,3%) only mild pain. Statistical tests with independent t-test revealed  $p < 0,0001$ , indicating significant difference between the two groups in

**Table 1.** Characteristics of the study sample.

Variables	Group		Value <i>P</i>
	Ketoprofen n = 13 (%)	Lidocaine n = 14 (%)	
Age (year)			
Range	50 – 80	51 – 78	0,378
Mean $\pm$ SD	63,5 $\pm$ 8,5	66,1 $\pm$ 7,0	
Volume prostate (cc)			
Range	22,1 – 86,4	21,5 – 127,4	0,244
Mean $\pm$ SD	37,6 $\pm$ 17,7	48,9 $\pm$ 29,6	



**Figure 2.** VAS differences between groups.

**Table 2.** Correlation between VAS values and age.

Age (years)	VAS (%)			Total
	No pain	Mild pain	Moderate pain	
60	1 (20,0)	2 (40,0)	2 (40,0)	5 (100,0)
61 – 70	4 (22,2)	9 (50,0)	5 (27,8)	18 (100,0)
> 70	0 (0,0)	2 (50,0)	2 (50,0)	4 (100,0)
Total	5 (18,5)	13 (48,1)	9 (33,3)	27 (100,0)

**Table 3.** Correlation between VAS and prostate volume.

Prostate volume (cc)	VAS (%)			Total
	No pain	Mild pain	Moderate pain	
30	4 (44,4)	1 (11,1)	4 (44,4)	9 (100,0)
31 – 40	0 (0,0)	5 (83,3)	1 (16,7)	6 (100,0)
> 40	1 (8,3)	7 (58,3)	4 (33,3)	12 (100,0)
Total	5 (18,5)	13 (48,1)	9 (33,3)	27 (100,0)

VAS values, where the periprostatic injection of lidocaine 1% was better in pain control than ketoprofen suppository on prostate biopsy.

Pearson correlation test was performed to assess the relationship between the perception of pain (VAS) with patients' age, revealing  $p = 0,779$ . This shows no significant correlation between the age of the patient's and their perception of pain in prostate biopsy in both study groups (Table 2). Similarly, no significant correlation was found between the perception of pain with the prostate volume of the patients in both study groups,  $p = 0,389$  (Table 3).

## DISCUSSION

Prostate biopsy is a safe procedure, but patients experience significant pain in this procedure. Pain during TRUS of the prostate biopsy is a remarkable problem, especially when the patients have to undergo repeated biopsies, because the pain can cause the patients to reject such a procedure.<sup>8</sup>

Pain during TRUS guided prostate biopsy procedure may come from two sources, from the TRUS probe insertion and biopsy needle puncture. TRUS probe insertion pain occurs due to the pressure of the probe innervation in the rectum below the dentate line by the inferior rectal branch of the pudendal nerve. Pain results from multiple puncture biopsy needle into the prostate capsule and stroma, innervated by the autonomic branch of NVB between posterolateral prostate and rectum.<sup>6,8,11</sup>

Puncture biopsy needle penetrates through the rectal wall at the lower sensory area above the dentate line, and penetrates the prostate capsule and stroma during biopsy needle penetration. This penetration causes periprostatic nerves stimulate sensory receptors in the prostate capsule.<sup>5,7</sup> Prostatic capsule and stroma contains many autonomic nerve fibers (C-fibers), which carry visceral sensation from spinal cord. Parasympathetic innervation of prostate derives from S2-5 and the sympathetic

innervation of the presacral plexus and hypogaster. The nerve fibers are branched in the prostatic plexus and passes through the vascular pedicle of the prostate at posterolateral base of the prostate at the end of the seminal vesicles between prostate and rectum. So painful because the needle biopsy can be addressed with local anesthetic infiltration into the region of innervation.<sup>3,10,11</sup>

In this study, patients' pain perception was measured by VAS. Degree of pain is difficult to measure because subjective interpretation of results. In the last three decades, VAS has been shown to provide satisfactory results in measuring subjective pain. Due to its sensitivity, VAS has been the best method of measuring the perception of pain or pain treatment.<sup>3</sup> To eliminate the factor of inter-observer variability, the assessment of pain perception using VAS method of prostate biopsy should be performed by the same operator in all patients.<sup>8</sup>

Clinician experience shows that TRUS prostate biopsy cause discomfort and pain, of which 24% of the patients feel moderate-severe pain with  $VAS > 5$ .<sup>16</sup> Research in the Department of Cipto Mangunkusumo, as much as 77,5% of patients with prostate biopsy without anesthesia and analgesia experienced moderate and severe pain, with an average VAS 5.<sup>17</sup>

Previous data indicated that the PNB method is the best for reducing pain in TRUS prostate biopsy, and most urologists agree PNB is the gold standards for the control of pain in prostate biopsy.<sup>8</sup> PNB can be accepted with the consideration that the area of anesthesia in accordance with the anatomical source of pain, where the source of the pain comes from the prostate capsule and stroma that contains many innervation of autonomic basolateral fibers along the vascular pedicle. Pain can be caused by direct contact between the needle with the nerve to the capsule and prostatic stroma.<sup>18</sup>

In this study, the administration of ketoprofen 200 mg suppository before prostate biopsy demonstrated VAS value of  $4,5 \pm 1,6$  VAS. Whereas, the periprostatic injection of 1% lidocaine



revealed VAS of  $0,8 \pm 0,8$ . Statistical tests by independent t-test showed significant differences in pain perception with  $p < 0,0001$ , where the periprostatic injection of 1% lidocaine produces pain lower than ketoprofen suppository.

In a study comparing 100 mg diclofenac suppository with a placebo, it was shown that diclofenac produces significantly lower pain with a mean of VAS of  $2,8$  vs  $4,9$  on placebo, with  $p < 0,001$ .<sup>11</sup> Other researchers have also reported significant differences in mean VAS diclofenac suppository of  $3,22 \pm 2,09$  and  $5,03 \pm 2,68$  of placebo,  $p$  value =  $0,004$ .<sup>19</sup>

Alavi (2001), who compared VAS in 10 ml periprostatic injection of 1% lidocaine with topical anesthesia with 10 ml of 2% lidocaine jelly in each of 75 patients, reported better pain control in the lidocaine periprostatic injection periprostatika VAS  $2,4 \pm 0,23$  and lidocaine jelly  $3,7 \pm 0,35$  ( $p = 0,00002$ ).<sup>3</sup> In contrast Mallick (2004) did not obtain significant differences between the two, with the periprostatic injection of lidocaine had VAS  $2,0 \pm 3,9$  compared with  $2,6 \pm 3,7$  with lidocaine jelly,  $p = 0,15$ .<sup>20</sup> Nash (2005), who compared periprostatic injection of 1% lidocaine on one side of the prostate and 0,9% NaCl in its contralater in 64 patients, reported a significant difference in VAS  $1,6 \pm 0,9$  in periprostatic lidocaine injection and  $2,9 \pm 1,2$  on placebo ( $p < 0,0001$ ).<sup>10</sup>

Alvarino (2005) compared periprostatic injection of 1% lidocaine with placebo, and reported significant difference in VAS  $2,1 \pm 1,3$  vs  $5,7 \pm 1,7$  compared to placebo with  $p < 0,05$ .<sup>21</sup> Leibovici (2002) also reported significant difference on both the mean VAS 1 : 51 vs 3,98 ( $p = 0,0001$ ).<sup>7</sup> Other researchers found significant differences in mean VAS periprostatic injection of 1% lidocaine  $3,0$  vs  $4,3$  on placebo,  $p < 0,001$ .<sup>9</sup> In 50 patients with a prostate biopsy receiving periprostatic injection of 1% lidocaine, only one patient had significant pain. Ten patients who previously had undergone prostate biopsy without anesthesia, experience a dramatic reduction in pain compared to the previous biopsy.<sup>15</sup> Similarly, Giannarini (2009) reported a VAS at PNB  $1,27 \pm 1,19$  vs  $4,33$  compared with no anesthesia  $2,26$ ;  $p < 0,001$ .<sup>6</sup>

Bingqian (2009) reported that the combined injection of lidocaine 1% of GNP and intraprostatic reduce pain significantly when prostate biopsy with VAS  $2,89 \pm 1,09$  compared to  $3,56 \pm 1,09$  PNB itself. But the GNP itself is still significantly better than the  $4,81 \pm 1,77$  without anesthesia ( $p < 0,0001$ ).<sup>8</sup>

Pain after biopsy is due to the release of mediators, such as cytokines, prostaglandins, and leukotrienes, that cause local pain, edema, and the release of other immune competent cells.<sup>10,11</sup> Ketoprofen is an NSAID of the propionic acid derivative that has effectiveness as a moderate analgesic and anti-inflammatory. Mechanism of action of ketoprofen inhibits the biosynthesis of prostaglandins, substances that sensitizes pain receptors to mechanical and chemical stimulation,<sup>22</sup> by blocking the enzyme cyclooxygenase (COX) that interferes with the conversion of arachidonic acid into prostaglandins, resulting in activation barriers of peripheral nociceptor important in the pathophysiology of pain.<sup>23</sup>

Lidocaine is a strong local anesthetic. Mechanism of action of lidocaine is by changing neuronal signal conduction by blocking Na channels in cell membranes of neurons that are responsible for signal propagation. Thus the membrane of the post-synaptic neurone is not depolarized and fails to deliver action potential. This causes the anesthetic effect not only preventing the transmission of pain signals to the brain, but also thwart the occurrence of pain in the first place.<sup>24</sup>

In this study, we also assessed the correlation between the perception of pain (VAS) and the patient's age, where the Pearson correlation test  $p = 0,779$  showed no significant correlation between the perception of pain by the patient's age at prostate biopsy. Similarly, no significant correlation was found between the perception of pain by the patient's and prostate volume on prostate biopsy, in which the Pearson correlation test showed  $p = 0,389$ .

In males aged  $< 60$  years, 80% felt moderate-severe pain, and  $> 80\%$  of patients age  $> 70$  years of mild pain.<sup>25</sup> Men age  $< 65$  years were more likely to feel pain during prostate biopsy, probably due to anal sphincter that is not capable of relaxation adequately. This corresponds to a negative correlation between age with the sensation and tone of the sphincter. It requires maximum control of the anorectal components in patients with rectal prostate biopsy.<sup>6,8</sup> Local anesthesia in older patients may not be useful, because the anal pain threshold is higher.<sup>8</sup>

On a smaller prostate volume ( $< 48$  ml), there was a significant difference in VAS between the combination of 1% lidocaine injection PNB and intraprostatic ( $2,7 \pm 1,12$ ), PNB ( $3,9 \pm 1,24$ ), with no anesthesia ( $4,5 \pm 1,76$ ),  $p = 0,0001$ . Although there was no difference in prostate volume was higher ( $> 48$  ml),  $p = 0,185$ . Those with age  $< 66$  years also

showed significant difference in VAS between PNB combination and intraprostatic ( $2,5 \pm 0,96$ ), PNB ( $4,1 \pm 1,33$ ), and with no anesthesia ( $4,4 \pm 1,17$ ),  $p < 0,0001$ , although there was no difference in older age,  $p = 0,155$ .<sup>8</sup>

In contrast, Leibovici (2002) reported that age and prostate size did not affect the level of pain, in the study 90 patients with a prostate biopsy 1% lidocaine periprostatic injection and placebo.<sup>7</sup> Similarly, Mallick (2004) reported that age and prostate volume did not affect VAS values of the patients in the provision of lidocaine jelly and 1% lidocaine periprostatic injection.<sup>20</sup>

PNB technique is more advantageous than an perianal-intra-rectal analgesic cream in the prostates with volume  $> 49$  ml, because the cream in perianal-intra-rectal only acts on the level of the anal sphincter and its spread into innervation fibers of the prostate capsule is adequate only in smaller prostate gland. In large prostates we require wider and longer TRUS probe manipulation to obtain good imaging and guiding sampling.<sup>6</sup> Additionally, larger prostates also requires more lidocaine in prostate biopsy.<sup>8</sup>

## CONCLUSION

There was significant differences in pain perception between the administration of ketoprofen suppositories with 1% lidocaine periprostatic injection in TRUS guided prostate biopsy, in which periprostatic injection of 1% lidocaine provided better pain control than ketoprofen suppository. No significant correlation exists between the perception of pain with patients' age and prostate volume on TRUS guided prostate biopsy.

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