The Effect of Diclofenac Sodium on Nocturia Caused by Benign Prostatic Hyperplasia

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Abstract

Background: Nocturia is a common cause of night awakenings which bothers many patients with urinary tract diseases. NSAIDs can improve nocturia by decreasing urine production and modify the altered neural pathways between bladder and CNS. The aim of this study was to evaluate the efficacy of NSAID in the treatment of nocturia secondary to BPH. Seventy-one patients complaining of BPH with LUTS that was prominent with nocturia entered this study.

Methods: Between January 2013 and March 2014, 71 men aged 50-85, complaining of BPH with LUTS that was prominent with nocturia (voiding more than 2 times at night) entered this prospective study. All patients received 100 mg Diclofenac Na suppository for 30 days at night (9pm). The main outcomes included night-time frequency; IPSS, prostate volume and PSA were recorded before and after study. Statistical analysis was performed using the paired t-test, Pearson’s correlation and Wilcoxon rank test.

Results: In our study, 88.7% of patients had an acceptable response to Diclofenac Na. Prostate size showed a significant reduction after one month treatment with diclofenac Na. There were no serious adverse effects.

Conclusion: In our study Diclofenac Na can improve symptoms of BPH and can be used for the treatment of nocturia secondary to BPH.

Introduction

Nocturia is a condition in which a person wakes up during the night to urinate and it may disturb his/her sleep (1, 2). Nocturia can decrease the quality of life by disturbing the night sleep affecting the mental status and somatic health system (3, 4). On the other hand, it can increase the mortality and morbidity (5, 6). According to the international continence society (ICS), nocturia has complex symptoms which involve urinary urgency with or without urgency incontinence and frequency. Also, the symptom of overactive bladder (OAB) is another important issue (7-9). The etiology of nocturia is not completely clear, but there are conditions which are related to this symptom (10,11). Some of these conditions include benign prostatic hyperplasia, overactive bladder, nocturnal polyuria,
obstructive sleep apnea, anxiety and behavioral factors as well as excessive fluid intake before bedtime (12-17). Nocturia is a bothersome symptom (18). About 22% of aged men between 60 to 69 years and one-third of them between 70 to 85 years have nocturia as the main symptom of BPH (19-22). The main symptom of BPH in some patients is nocturia and an urologist often treats patients with two modalities including conservative treatment and surgical intervention (23, 24). Some pharmacologic approaches include alpha blockers, 5-alpha-reductase inhibitors and anti-muscarinic bladder relaxant (25, 26). Recent researches show that non-steroidal-anti-inflammatory drugs can be effective for patients with nocturia (27, 28). The main pathogenesis of BPH includes lymphocytic infiltration and chronic inflammation that are related to COX2 expression (27). NSAIDs can improve symptoms of BPH by the inhibition of COX2 and BPH1 cell growth line. In addition, NSAIDs can improve nocturia by decreasing urine production and modifying altered neural pathways between bladder and CNS (29,30). This study aimed to evaluate the efficacy of NSAID (Diclofenac Na, 100mg, Suppository) in the treatment of nocturia as a symptom of BPH.

Material and Method

Between January 2013 and March 2014, 71 men aged 50-85, complaining of BPH with LUTS that was prominent with nocturia (more than 2 nights voiding) entered this prospective study. This study was approved by the Ethics Committee of Kerman University of Medical Sciences (Ethical code: KA.93.615). The international prostate symptom score (IPSS) of 8 or more and the prostate volume of more than 30cc in ultrasonography were considered as the inclusion criteria. Patients with renal, hepatic or cardiac failure, anorectal disease or lung disorder were excluded from the study. Moreover, diabetes mellitus, diabetes insipidus, primary polydipsia, allergy to NSAIDs, peptic ulcer disease and severe BPH that indicated a surgical intervention were other exclusion criteria. The purposes of the study were explained to all patients and informed consent was granted. All patients received 100 mg Diclofenac Na suppository for 30 days at night (9 pm). The main outcomes included night-time frequency, IPSS, prostate volume and PSA were recorded before and after the study. Patients’ response were categorized into three groups excellent (nocturia disappeared or decreased by >2 void/night), improved (nocturia decreased by <2 void/night), unchanged. Statistical analysis was performed using the paired t-test, Pearson’s correlation and Wilcoxon rank test. P<0.05 was regarded as the level of significance.

Result

In this study, 35 (49.3%) out of 71 patients had an excellent response to Diclofenac Na treatments. Twenty-eight (39.4%) out of 71 patients had an improvement and 8 patients (11.3%) out of 71 patients had no changes. In this regard, 88.7% of patients had an acceptable response to Diclofenac Na (Table 1).

The mean number of nocturia episodes decreased from 3.54 ± 0.65 times/night to 2.11 ± 0.80 times/night (P= 0.000) (Table 2). The mean of IPSS decreased after the study significantly (Table 2). There were only 13 patients with reported PSA before and after the study. There were no significant changes in PSA level (P=0.077) (Table 2). Fifty-six out of 71 patients had an appropriate cooperation for prostate ultrasound. Prostate size showed a statistically significant reduction from 41.65 ± 14.59 ml to 38.69 ± 14.50 ml after one month of treatment with diclofenac Na (Table 2). There were no serious adverse effects in our study.
Table 1. Response of BPH patients to diclofenac sodium

<table>
<thead>
<tr>
<th>Response to Diclofenac Na</th>
<th>Number</th>
<th>Percent %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>35</td>
<td>49.3</td>
</tr>
<tr>
<td>Improve</td>
<td>28</td>
<td>39.4</td>
</tr>
<tr>
<td>Unchanged</td>
<td>8</td>
<td>11.3</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td><strong>71</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

Table 2. Comparison of means before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of nocturia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before study</td>
<td>71</td>
<td>3.54</td>
<td>0.65</td>
<td>T = 15.99</td>
</tr>
<tr>
<td>After study</td>
<td>71</td>
<td>2.11</td>
<td>0.89</td>
<td>df = 70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = 0.000</td>
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<tr>
<td><strong>IPSS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before study</td>
<td>71</td>
<td>15.11</td>
<td>3.53</td>
<td>Negative rank = 67</td>
</tr>
<tr>
<td>After study</td>
<td>71</td>
<td>12.95</td>
<td>3.29</td>
<td>Positive rank = 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ties = 4</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Wilcoxon rank Z test = -7.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = 0.000</td>
</tr>
<tr>
<td><strong>Prostate volume (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before study</td>
<td>71</td>
<td>41.65</td>
<td>14.59</td>
<td>T = 3.82</td>
</tr>
<tr>
<td>After study</td>
<td>71</td>
<td>38.68</td>
<td>14.50</td>
<td>df = 55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = 0.000</td>
</tr>
<tr>
<td><strong>PSA level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before study</td>
<td>13</td>
<td>2.53</td>
<td>2.00</td>
<td>T = 1.93</td>
</tr>
<tr>
<td>After study</td>
<td>13</td>
<td>2.16</td>
<td>1.87</td>
<td>df = 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = 0.077</td>
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**Discussion**

Nocturia, the most common symptom of BPH, is a main reason of interrupted sleep in old ages. This condition has a negative effect on the quality of life. Nocturia can decrease productivity at work and cause economic burdens (33, 34, 54). Several important treatments are available for the reduction of LUTs due to BPH and the positive response of patients with nocturia as a main symptom of BPH is about 50 percent (35, 36). The effect of NSAIDs for the treatment of nocturia in patients in which their symptoms are uncontrolled or poorly controlled is recently mentioned. The effect of NSAIDs on LUTS can be related to five different mechanisms (37, 38). First, NSAIDs block COX-1 and COX-2 enzymes which convert arachidonic acid to prostaglandins (39, 40). In other words, prostaglandins cause vasodilatation of the afferent arterioles. Glomerular filtration rate and the amount of urine are decreased due to the reduction of prostaglandin synthesis by COX-2 inhibitors (41, 42). Second, one of the common pathogenesis of BPH is chronic inflammation. NSAIDs decrease LUTS by their anti-inflammatory properties (43, 44).
Third, it decreases the tone of detrusor muscles by the suppression of PGF (45); thereby reducing the desire of void. Fourth, suppression of afferent or efferent nerve pass ways may affect the central nervous system and increase the threshold of the sense of urination. Last, it may regulate the sleep cycle and induce a proper sleep (46, 47).

In 2016, Marshal et al. studied the Current Levels of Evidence and Recommendations from the International Consultation on Male Lower Urinary Tract Symptoms. The evidence review and consensus recommendations were made in the areas of epidemiology, pathophysiology, assessment, and treatment. Their review presented a condensed summary of the International Consultations on Urological Diseases—Société International d’Urologie evaluation of nocturia, which offers contemporaneous expert consensus on this topic, with an assessment algorithm emphasizing the potential contribution of systemic conditions to the symptom (48). Sutcliffe et al. in 2012 evaluated the effect of NSAIDs on the risk of benign prostatic hyperplasia related outcomes and nocturia in a cancer screening trial. They investigated the relationship between the use of NSAID and the incidence of benign prostatic hyperplasia (BPH)-related outcomes and nocturia in the light of accumulating evidence suggesting a role for inflammation in BPH/LUTS development. The findings obtained in the study did not support a protective role for recent NSAID use in BPH/LUTS development (49). In 2016, Tyagi et al. studied the nocturnal polyuria in older women with urge urinary incontinence, the Role of Sleep Quality, Time in Bed, and Medications Used. Since nocturnal polyuria (NP) is a major contributor, they examined factors associated with NP in a group of people to identify those possibly amenable to intervention. They concluded that BMI, use of ACE-I/ARB, time in bed and DUS are independently associated with NP in older women with UUI, and are potentially modifiable. These findings also confirm the association between sleep and NP (50). Miller et al. studied the nocturia work productivity and activity impairment compared with other common chronic diseases. They characterized the burden of nocturia by comparing published data from patients with nocturia with data from patients with any of 12 other common chronic conditions, specifically focusing on its impact on work productivity and activity impairment. They concluded that the overall work productivity impairment as a result of nocturia is substantial and was found to be similar to impairment observed as a result of several other more frequently researched common chronic diseases (51). Flamiatos studied the Cyclooxygenase2 (COX2) inhibition for prostate cancer chemoprevention as a double blind randomized study of pre prostatectomy celecoxib or placebo. In their study, patients with localized prostate cancer were randomized to receive either celecoxib 400 mg twice daily or placebo for 4 weeks before RP. The rate of apoptosis and the level of prostaglandins and androgen receptors were estimated in specimens. They concluded that Celecoxib had no effect on apoptosis, prostaglandins or AR levels in cancerous or benign prostate tissues. Their findings revealed that using drugs as chemoprevention agents had a limited application in patients with localized prostate cancer (52). Also, in molecular scale, Liu et al. in 2016 studied the opposing effects of cyclooxygenase-2 (COX-2) on estrogen receptor β (ERβ) response to 5α-reductase inhibition in prostate epithelial cells. They uncovered the signaling pathways in BPH-derived prostate epithelial cells (BPH-1) that were impacted by 5αR inhibition (53).
Conclusion

After using the diclofenac Na for a month, the prostate size showed a statistically significant reduction. There were no serious adverse effects in our study. Diclofenac NA can improve symptoms of BPH and can be used for the treatment of nocturia secondary to BPH.

References


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