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

Mohammadreza Ebadzadeh, M.D.[1], Rayka Sharifian Amiri, M.D. [2], Arsalan Jalili, Ph.D. [3], Afshin Sarrafinejad, Ph.D. [4], Hamed Zanganeh, M.D. [5], Aliasghar Ketabchi, M.D. [6]

1- Assistant Professor, Department of Urology, Clinical Research Center, Shahid Bahonar Hospital, Kerman University of Medical Sciences, Kerman, Iran

2- Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

3- Department of Stem Cell and Developmental Biology, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran

4- Assistant Professor of Medical Informatics, Medical Informatics Research Center, Institute of Futures Studies in Health. Kerman University of Medical Sciences, Kerman, Iran

5- Medical Practitioner, Kerman University of Medical Sciences, Kerman, Iran

6- Associated Professor of Urology, Physiology Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran (Corresponding author; E-mail: dr.ketabchi@gmail.com)

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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.

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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 incontinency 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

Response to Diclofenac Na	Number	Percent %
Excellent	35	49.3
Improve	28	39.4
Unchanged	8	11.3
N	71	100

Table 2. Comparison of means before and after treatment

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

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 nucturia 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 5AR 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

1. Tikkinen KA, Johnson TM, Tammela TL, Sintonen H, Haukka J, Huhtala H, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol 2010; 57(3):488-98.
2. Bergman AM, Sih AM, Weiss JP. Nocturia: an overview of evaluation and treatment. Bladder 2015; 2(2):e13.
3. Abdel Rahman TT, El Gaafary MM. Nocturia among elderly men living in a rural area in Egypt, and its impact on sleep quality and health-related quality of life. Geriatr Gerontol Int; 14(3):613-9.
4. Patel A, Hasak S, Cassell B, Ciorba MA, Vivio EE, Kumar M, et al. Effects of disturbed sleep on gastrointestinal and somatic pain symptoms in irritable bowel syndrome. Aliment Pharmacol Ther 2016; 44(3):246-58.
5. Abete P, Cherubini A, Di Bari M, Vigorito C, Viviani G, Marchionni N, et al. Does comprehensive geriatric assessment improve the estimate of surgical risk in elderly patients? An Italian multicenter observational study. Am J Surg 2016; 211(1):76-83.
6. Aristide G, Weinstein M, Nair GB. Nocturia in obstructive sleep apnea-hypopnea syndrome: an underappreciated symptom. Current Respiratory Medicine Reviews 2013; 9(3):217-24.
7. Gormley EA, Lightner DJ, Faraday M, Vasavada SP, American Urological Association; Society of Urodynamics, Female Pelvic Medicine. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. J Urol 2015; 193(5):1572-80.
8. Payne CK. Men Have Bladders, Too. In: Potts JM. Men's Health. New York: Springer; 2016. p. 187-205.
9. Corcos J, Mac Diarmid S, Heesakkers J. Overactive Bladder: Practical Management. US: John Wiley & Sons; 2015.
10. Bae WJ, Bae JH, Kim SW, Chung BH, Kim JH, Kim CS, et al. Desmopressin add-on therapy for refractory nocturia in men receiving α-blockers for lower urinary tract symptoms. J Urol 2013; 190(1):180-6.
11. Toyama M, Yamamoto M, Yoshda K, Maeda T, Nakayama T. Poster Session: PS 0149; Neurology: The Impact of Non-Motor Symptoms on Qol in Japanese Patients with Parkinsons Disease: A Cross-Sectional Study. Essentials of Primary Care j. 2014; 2014(1):84.
12. Nimeh T, Alvarez P, Mufarreh N, Lerner LB. Nocturia: current evaluation and treatment for urology. Curr Urol Rep 2015; 16(9):66.

13. Soloway MS, Weiss JP, Wein AJ. Nocturia. Current Urology Reports 2016; 17:77.

14. Nimeh T, Alvarez P, Mufarreh N, Lerner LB. Nocturia: current evaluation and treatment for urology. Curr Urol Rep 2015; 16(9):66.

15. Skokan A, Newman DK. Behavioral Intervention for Lower Urinary Tract Symptoms in Older Adults. In: Guzzo T, Drach G, Wein A. Primer of Geriatric Urology. New York: Springer; 2016.

16. Tai BT, Tai TT, Chang YJ, Huang KH. Factors associated with remission of primary nocturnal enuresis and changes of parental perception towards management strategies: a follow-up study. J Pediatr Urol 2017; 13(1):44.e1-9.

17. Johnson TM 2nd, Vaughan CP, Goode PS, Bliwise DL, Markland AD, Huisingh C, et al. Pilot results from a randomized trial in men comparing alpha-adrenergic antagonist versus behavior and exercise for nocturia and sleep. Clin Ther 2016; pii: S0149-2918(16)30742-1.

18. Shekarchi B, Zamani M. Nocturia: a bothersome urological symptom in the elderly. Clin Interv Aging 2016; 11:1463-65.

19. Ertel P, Adalig B, Demircan I, Lartey B, Manyak MJ. Understanding patient and physician perceptions of benign prostatic hyperplasia in Asia Pacific, Latin America and the Commonwealth of Independent States: the prostate research on behaviour and education (PROBE) II survey. Int J Clin Pract 2016; 70(10):870-80.

20. Fukuta F, Masumori N. Natural History of Lower Urinary Tract Symptoms Secondary to BPH. Current Bladder Dysfunction Reports 2013; 8(2):166-73.

21. Cantrell MA, Baye J, Vouri SM. Tadalafil: a phosphodiesterase-5 inhibitor for benign prostatic hyperplasia. Pharmacotherapy 2013; 33(6):639-49.

22. Lee YJ, Jeong SJ, Byun SS, Lee JJ, Han JW, Kim KW. Prevalence and correlates of nocturia in community-dwelling older men: results from the korean longitudinal study on health and aging. Korean J Urol 2012; 53(4):263-7.

23. Han J, Sukumar S, Bakker CJ, Ebell MH, Dahm P. Desmopressin for Treating Nocturia in Men with Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia. US: John Wiley & Sons; 2016.

24. Cornu JN, Abrams P, Chapple CR, Dmochowski RR, Lemack GE, Michel MC, et al. A contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management—a systematic review and meta-analysis. Eur Urol 2012; 62(5):877-90.

25. Cantlay A, Ni Raghallaigh H. Benign prostatic hyperplasia. InnovAiT 2015; 8(4):238-45.

26. Sharifi SH, Mokarrar MH, Khaledi F, Yamini-Sharif R, Lashay A, Soltani MH. Does sildenafil enhance the effect of tamsulosin in relieving acute urinary retention? Int Braz J Urol 2014; 40(3):373-8.

27. Wilson JC, Murray LJ, Hughes CM, Black A, Anderson LA. Non-steroidal anti-inflammatory drug and aspirin use and the risk of head and neck cancer. Br J Cancer 2013; 108(5):1178-81.

28. Ishiguro H, Kawahara T. Nonsteroidal anti-inflammatory drugs and prostatic diseases. Biomed Res Int 2014; 2014:436123.

29. Mungadi IA, Mbibu HN, Eltahawy E, Abdulwahab-Ahmed A. Manual of Medical Treatment in Urology. New Delhi: Jaypee Brothers Medical Pub; 2013.

30. Kahokehr A, Vather R, Nixon A, Hill AG. Non-steroidal anti-inflammatory drugs for lower urinary tract symptoms in benign prostatic hyperplasia:

systematic review and meta-analysis of randomized controlled trials. BJU Int 2013; 111(2):304-11.

31. Sirab N, Robert G, Fasolo V, Descazeaud A, Vacherot F, de la Taille A, et al. Lipidosterolic extract of Serenoa repens modulates the expression of inflammation related-genes in benign prostatic hyperplasia epithelial and stromal cells. Int J Mol Sci 2013; 14(7):14301-20.

32. De Nunzio C, Presicce F, Tubaro A. Inflammatory mediators in the development and progression of benign prostatic hyperplasia. Nat Rev Urol 2016; 13(10):613-26.

33. Duffy JF, Scheuermaier K, Loughlin KR. Age-related sleep disruption and reduction in the circadian rhythm of urine output: contribution to nocturia? Curr Aging Sci 2016; 9(1):34-43.

34. Shao IH, Wu CC, Hsu HS, Chang SC, Wang HH, Chuang HC, et al. The effect of nocturia on sleep quality and daytime function in patients with lower urinary tract symptoms: a cross-sectional study. Clin Interv Aging 2016; 11:879-85.

35. Kim SH, Ho JN, Jin H, Lee SC, Lee SE, Hong SK, et al. Upregulated expression of BCL2, MCM7, and CCNE1 indicate cisplatin-resistance in the set of two human bladder cancer cell lines: T24 cisplatin sensitive and T24R2 cisplatin resistant bladder cancer cell lines. Investig Clin Urol 2016; 57(1):63-72.

36. Yeo JK, Choi H, Bae JH, Kim JH, Yang SO, Oh CY, et al. Korean clinical practice guideline for benign prostatic hyperplasia. Investig Clin Urol 2016; 57(1):30-44.

37. Weiss JP, Blaivas JG, Blanker MH, Bliwise DL, Dmochowski RR, Drake M, et al. The New England Research Institutes, Inc. (NERI) Nocturia Advisory Conference 2012: focus on outcomes of therapy. BJU Int 2013; 111(5):700-16.

38. Smith A, Wein A. Current pharmacotherapy of nocturia. Expert Opin Pharmacother 2013; 14(7):885-94.

39. Zurier RB. Prostaglandins, leukotrienes, and Related Compounds. In: Mackay IR, Rose NR, Diamond B, Davidson A. Encyclopedia of Medical Immunology. New York: Springer; 2014.

40. Akasaka H, Ruan KH. Identification of the two-phase mechanism of arachidonic acid regulating inflammatory prostaglandin E2 biosynthesis by targeting COX-2 and mPGES-1. Arch Biochem Biophys 2016; 603:29-37.

41. Mederle K, Meurer M, Castrop H, Höcherl K. Inhibition of COX-1 attenuates the formation of thromboxane A2 and ameliorates the acute decrease in glomerular filtration rate in endotoxemic mice. Am J Physiol Renal Physiol 2015; 309(4):F332-40.

42. Gordish KL, Beierwaltes WH. Resveratrol induces acute endothelium-dependent renal vasodilation mediated through nitric oxide and reactive oxygen species scavenging. Am J Physiol Renal Physiol; 306(5):F542-50.

43. Kahokehr A, Vather R, Nixon A, Hill AG. Non-steroidal anti-inflammatory drugs for lower urinary tract symptoms in benign prostatic hyperplasia: systematic review and meta-analysis of randomized controlled trials. BJU Int 2013; 111(2):304-11.

44. Torkko KC, Wilson RS, Smith EE, Kusek JW, van Bokhoven A, Lucia MS. Prostate biopsy markers of inflammation are associated with risk of clinical progression of benign prostatic hyperplasia: findings from the MTOPS study. The Journal of urology 2015; 194(2):454-61.

45. Hypolite JA, Lei Q, Chang S, Zderic SA, Butler S, Wein AJ, et al. Spontaneous and evoked contractions are regulated by PKC-mediated signaling in detrusor smooth muscle: involvement

of BK channels. Am J Physiol Renal Physiol 2013; 304(5):F451-62.

46. Hofer MJ, Campbell IL. Immunoinflammatory diseases of the central nervous system–the tale of two cytokines. Br J Pharmacol 2016; 173(4):716-28.

47. Coomans CP, Geerling JJ, van den Berg SA, van Diepen HC, Garcia-Tardón N, Thomas A, et al. The insulin sensitizing effect of topiramate involves KATP channel activation in the central nervous system. Br J Pharmacol 2013; 170(4):908-18.

48. Marshall SD, Raskolnikov D, Blanker MH, Hashim H, Kupelian V, Tikkinen KA, et al. Nocturia: current levels of evidence and recommendations from the international consultation on male lower urinary tract symptoms. Urology; 85(6):1291-9.

49. Sutcliffe S, Grubb Iii RL, Platz EA, Ragard LR, Riley TL, Kazin SS, et al. Non-steroidal anti-inflammatory drug use and the risk of benign prostatic hyperplasia-related outcomes and nocturia in the prostate, lung, colorectal, and ovarian cancer screening trial. BJU Int 2012; 110(7):1050-9.

50. Tyagi S, Perera S, Clarkson BD, Tadic SD, Resnick NM. Nocturnal polyuria in older women with urge urinary incontinence: role of sleep quality, time in bed, and medications used. J Urol 2016; 197(3 Pt 1):753-8.

51. Miller PS, Hill H, Andersson FL. Nocturia work productivity and activity impairment compared with other common chronic diseases. Pharmacoeconomics 2016; 34(12):1277-97.

52. Flamiatos JF, Beer TM, Graff JN, Eilers KM, Tian W, Sekhon HS, et al. Cyclooxygenase-2 (COX-2) inhibition for prostate cancer chemoprevention: double-blind randomised study of pre-prostatectomy celecoxib or placebo. BJU Int 2017; 119(5):709-16.

53. Liu TT, Grubisha MJ, Frahm KA, Wendell SG, Liu J, Ricke WA, et al. Opposing Effects of Cyclooxygenase-2 (COX-2) on Estrogen Receptor β (ERβ) response to 5α-reductase inhibition in prostate epithelial cells. J Biol Chem 2016; 291(28):14747-60.

54. Ketabchi AA, Ketabchi M, Barkam M. The Effect of Modified TURP (M-TURP) in Intra and Postoperative Complications. *Nephrourol Mon.* 2013; 5(2):758–761. doi:10.5812/numonthly.6607