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Flurbiprofen alone and in combination with alfuzosin for the management of lower urinary tract symptoms

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Introduction We aimed to investigate the effectiveness and safety of flurbiprofen, a non–steroidal anti–inflammatory drug with dual cyclooxygenase inhibition, and α–blocker alfuzosin, both alone and in combination with each other for lower urinary tract symptoms suggestive of benign prostatic obstruction (LUTS/BPO).

Material and methods Ninety patients complaining of moderate–to–severe LUTS/BPO were randomly assigned into 3 groups (30 patients each) to receive alfuzosin XL 10 mg, or flurbiprofen SR 200 mg, or combination of alfuzosin XL 10 mg and flurbiprofen SR 200 mg, once daily for 4 weeks. Patients were evaluated using the international prostate symptom score (IPSS) (total and $IPSS_{storage}$, $IPSS_{empty}$ subscores), uroflowmetry (maximum (Q_{max}) and average (Q_{ave}) flow rates) and postvoid residual urine (PVR) both at baseline and following the drug therapy course.

Results There was no difference among the 3 groups regarding age and baseline values of prostate volume, IPSS, $IPSS_{storage}$, $IPSS_{empty}$, Q_{max}, Q_{ave} and PVR ($P > 0.05$). IPSS, $IPSS_{storage}$, $IPSS_{empty}$, and PVR decreased significantly in all the 3 groups after drug therapies ($P < 0.01$). However, Q_{max} and Q_{ave} significantly improved only in the combination group ($P < 0.01$).

Conclusions Addition of flurbiprofen increased the therapeutic effectiveness of alfuzosin by further improving symptoms in patients with LUTS/BPO. Combination therapy also improved urine flow compared to baseline. Monotherapy with flurbiprofen was not superior to alfuzosin.

Key Words: flurbiprofen sodium ‹› nonsteroidal anti–inflammatory agents ‹› prostate ‹› lower urinary tract symptoms

INTRODUCTION

Lower urinary tract symptoms suggestive of benign prostatic obstruction (LUTS/BPO) are highly prevalent conditions worldwide and have a negative impact on patients' quality of life [1, 2]. The primary treatment goal has generally been to alleviate bothersome lower urinary tract symptoms (LUTS) [3]. According to European Urology Guidelines, α–adrenergic blockers can be offered to men with moderate–to–severe LUTS [4]. They can be used isolated or in combination with 5 α–reductase inhibitors as the standard medical treatment for LUTS/BPO. Currently, there are five α–blockers in mainstream use and they all have a similar efficacy. One of the five, alfuzosin, a selective α1–blocker that can be administered at a dose of 10 mg once daily without titration has been shown to provide a significant relief of LUTS, with minimal side–effects [5].

In the last decade, there is accumulating evidence that supposes that inflammation represents the common determinant underlying almost all the age–related health conditions, such as benign prostatic hyperplasia (BPH) [6]. Recent studies strongly suggest that BPH is an immune inflammatory disease [7]. Cytokines produced by inflammatory cells are believed to play essential roles in the development and maintenance of prostate growth by increasing growth factor production and angiogenesis [8, 9, 10]. Nickel et al. demonstrated

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the strong relationship between inflammatory infiltrate levels, international prostate symptom score (IPSS), prostate volume, and BPH progression at the clinical level [11].

Non–steroidal anti–inflammatory drugs (NSAID) inhibit the enzyme cyclooxygenase (COX). This inhibition reduces production of prostaglandins and other mediators of inflammation. They have been widely used to treat pain associated with inflammation in musculoskeletal diseases. One of the most frequently used NSAID in the market, flurbiprofen is a dual COX inhibitor and a member of the phenylalkanoic acid derivative family of NSAID [12]. It is still unclear whether prostaglandins contribute to the pathogenesis of LUTS/BPO. If they have an important role in the etiological mechanisms, treatment with prostaglandin synthesis inhibitors could make sense. Our hypothesis was that flurbiprofen might be useful alone or palliate the efficiency of alfuzosin in the management of LUTS/BPO.

MATERIAL AND METHODS

In the urology clinic of a tertiary care teaching hospital, 90 men aged 40 years or older with moderate–to–severe LUTS/BPO and responding to the inclusion criteria were enrolled in the study. Ninety patients were randomly assigned into three groups of 30 patients each, to receive a once daily dose of alfuzosin XL (extended release) 10 mg (alfuzosin group), or flurbiprofen SR (sustained release) 200 mg (flurbiprofen group), or alfuzosin XL 10 mg plus flurbiprofen SR 200 mg combination drug therapy (combination group) for 4 weeks.

Patients with cardiac or hepatorenal insufficiency, peptic ulcers, gastritis, coagulopathy, neurological disease, diabetes mellitus, active or recurrent urinary tract infection, drug–induced LUTS, bladder stone, cancer or diverticulum, urethral stricture, a history of prostate or pelvic surgery, and the patients currently on α–blocker, anti–inflammatory, 5–α reductase inhibitor, antimuscarinic or any other phytotherapeutic therapies were not included. Patients having a prostate specific antigen (PSA) level over 4 ng/mL and/or a suspicious digital rectal examination finding for prostatic malignancy were offered a prostate biopsy and were not included in the study either. The institutional ethical committee approved our study and all patients provided a written informed consent.

Patients were evaluated at baseline by medical history, validated Turkish version of IPSS (total and $IPSS_{empty}$, $IPSS_{storage}$ subscores), frequency volume chart, physical examination including digital rectal examination, post–void residual (PVR) urine and prostate volumes on ultrasonography (Hitachi EUB–400 with 3.5 MHz abdominal and 6.5 MHz biplanar trans–rectal probes; Hitachi Medical Corp. of America), urinalysis and urine culture (if necessary), serum creatinine, free and total PSA, and maximum (Q_{max}) and average (Q_{ave}) flow rates on uroflowmetry (Medical Measurement Systems (MMS), Ankara, Turkey). Following a 4–week treatment course, patients were re–evaluated by IPSS, uroflowmetry and PVR urine volume and development of adverse drug events were assessed.

Statistical methods

Statistical package for social sciences, version 18.0 (SPSS Inc., Chicago, IL) software was used for the analysis of the results. The data was expressed as the mean ± standard deviation. Kruskal–Wallis, Wilcoxon signed ranks and Mann–Whitney U tests were applied. P values <0.05 were considered significant.

RESULTS

Among the 90 patients included in the study, 78 completed a 4–week drug therapy course. Three patients in flurbiprofen group and one patient each in the other two groups were lost to follow–up. Six patients in flurbiprofen group and one patient in combination group discontinued drug therapy due to gastrointestinal adverse events. As a consequence, there remained 29 patients in the alfuzosin group, 21 patients in the flurbiprofen group and 28 patients in the combination group. No serious adverse events were observed in the remaining 78 patients, except postural hypotension in 5 patients (3 in alfuzosin and 2 in combination groups). Postural hypotension did not prevent those patients from continuation of the therapy.

Mean age was 59.78 ±7.32 (43–79). There were no differences among the 3 groups regarding age and baseline IPSS, $IPSS_{empty}$, $IPSS_{storage}$, prostate volume, PVR and flow measures ($P > 0.05$).

After a 4–week course of drug therapy, IPSS, $IPSS_{empty}$, $IPSS_{storage}$ and PVR decreased significantly in all the 3 groups compared to baseline. However, Q_{max} and Q_{ave} significantly improved only in the combination group (Table 1 and Figure 1).

To evaluate the relative strength of improvement in the different drug therapy regimens, mean percent changes from baseline in variables of the 3 groups were compared. Results are given in the table (Table 2). As seen in the table, the amount of changes from baseline in percentages regarding IPSS and $IPSS_{empty}$ were significantly different among the 3 groups, while regarding Q_{max}, Q_{ave}, PVR and $IPSS_{storage}$ were not ($P > 0.05$). The differ-

ence originated from superiorities of both alfuzosin and combination over flurbiprofen. This is because significant differences were present in alfuzosin *vs* flurbiprofen (P = 0.024 for IPSS and 0.008 for $IPSS_{empty}$ in Mann–Whitney U test), and combination vs flurbiprofen (P = 0.036 for IPSS and 0.037 for $IPSS_{empty}$) comparisons.

DISCUSSION

A recent histological study showed that almost half of prostatectomy specimens of patients who underwent BPH surgery were predominantly associated with chronic inflammation [13]. In an older study, Kohnen et al. reported the incidence of inflammation

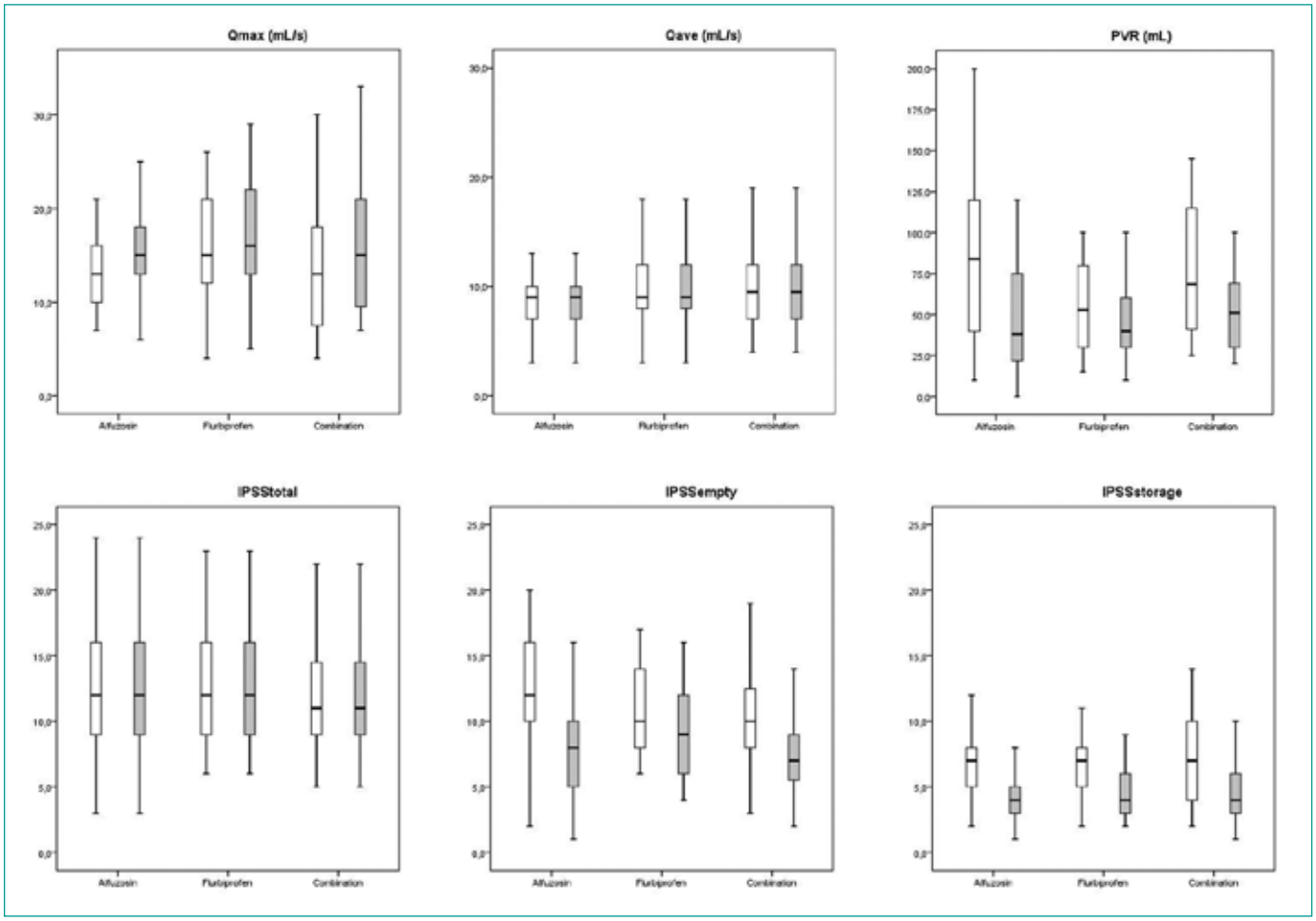

Figure 1. *The view of the results in graphical format (before and after each drug therapy with box-and-whisker plots). White and gray bars represent the baseline and post-therapy values, respectively.*

Table 1. *Comparison of baseline and post–therapy variables of the three groups*

Variables	Alfuzosin			Flurbiprofen			Combination		
	Baseline	Post-therapy	*P	Baseline	Post-therapy	*P	Baseline	Post-therapy	*P
Q_{max} (mL/s)	14.7 ±6.6	15.3 ±5.8	0.26	15.6 ±6.3	16.8 ±7.0	0.22	14.0 ±7.6	16.9 ±8.4	<0.001
Q_{ave} (mL/s)	8.5 ±3.9	8.8 ±3.5	0.26	8.9 ±3.7	10.0 ±3.8	0.17	8.9 ±4.0	9.9 ±4.2	<0.001
PVR (mL)	97.8 ±84.5	71.7 ±92.1	0.002	81.1 ±86.2	45.7 ±25.4	0.006	95.4 ±80.1	59.9 ±47.0	<0.001
IPSS	19.0 ±4.5	12.4 ±5.3	<0.001	17.3 ±4.8	13.4 ±5.4	<0.001	17.8 ±5.9	11.9 ±4.6	<0.001
$IPSS_{empty}$	12.1 ±4.2	8.1 ±3.7	<0.001	10.8 ±3.2	9.0 ±3.6	0.002	10.4 ±3.7	7.4 ±3.4	<0.001
$IPSS_{storage}$	6.9 ±2.5	4.2 ±1.8	<0.001	6.5 ±2.3	4.4 ±2.1	<0.001	7.5 ±3.6	4.5 ±2.2	<0.001

*Wilcoxon signed ranks test

Table 2. *Comparison of mean percent changes from baseline of the groups*

Variables	Alfuzosin	Flurbiprofen	Combination	*P
Q_{max} (mL/s)	11.29% ±44.31	14.37% ±35.16	29.98% ±50.93	0.151
Q_{ave} (mL/s)	11.16% ±49.14	10.79% ±42.13	26.80% ±42.11	0.135
PVR (mL)	-21.79% ±58.04	-18.58% ±50.03	-24.08% ±85.23	0.270
IPSS	-33.12% ±12.48	-22.91% ±20.90	-36.75% ±19.28	0.040
$IPSS_{empty}$	-29.02% ±18.36	-17.42% ±19.65	-33.53% ±18.51	0.018
$IPSS_{storage}$	-30.76% ±39.86	-30.40% ±25.23	-35.81% ±21.73	0.590

*Kruskal-Wallis test

as high as 98.1% in surgically resected hyperplastic prostates [14]. Not only in the pathogenesis of BPH, but also in the progression of the disease, role of prostatic inflammation is growingly supported by clinical and experimental studies [9, 10, 15, 16]. Furthermore, prostatic inflammation has been found to be associated with higher IPSS and symptom progression in BPH patients by data analysis of the large clinical study "reduction by dutasteride of prostate cancer events" also known as REDUCE [11]. These results have paved the way for LUTS/BPO treatment trials with anti−inflammatory agents.

Clinical studies are not yet as abundant as experimental studies on this subject. There are only a few clinical studies evaluating the use of NSAID for LUTS in literature [17]. Improved treatment outcomes for nocturia were achieved with celecoxib monotherapy [18]. Rofecoxib monotherapy and combination of rofecoxib and 5α−reductase inhibitor finasterid were evaluated in patients with LUTS/BPO [19]. Tenoxicam plus α−adrenergic antagonist doxazosin, celecoxib plus doxazosin and meloxicam plus another α−adrenergic antagonist tamsulosin were the other combinations investigated [20, 21, 22].

Tenoxicam, refecoxib and meloxicam are known as COX−2 inhibitors. To our knowledge, the present study is the first to explore a dual COX (COX−1 and COX−2) inhibitor in LUTS/BPO patients. Both COX−1 and COX−2 have been shown to be expressed in BPH tissues [23]. Activation of COX−1 and COX−2 has been known to increase the levels of prostaglandins and induce angiogenic, antiapoptotic and inflammatory processes [24].

In our study, flurbiprofen monotherapy improved baseline IPSS and PVR, but not flow measures. In the absence of a significant increase in flow measures, if improvement in symptoms was not supported by significant PVR decrease, this result might be referred to as the placebo effect. However, a mean 18.58% ±50.03 PVR decrease was detected in that group. Anti−inflammatory effects of flurbiprofen might have provided this result. The reason for not achieving flow improvement with flurbiprofen monotherapy might have been attributed to the brevity of the 4−week therapy course or paucity of the 200 mg daily dose. We do not know the long−term efficacy of flurbiprofen for LUTS/BPO. Given that its known dose dependant gastrointestinal adverse events and the recommended maximum daily dose of 300 mg for inflammatory arthritis, our 200 mg daily dose seems sufficient for such a chronic condition like LUTS/BPO. In two studies conducted in the 1980s, flurbiprofen 50 mg thrice and four times daily were found beneficial for symptom relief in another chronic urinary condition, idiopathic detrusor instability [25, 26].

Same results were also valid for alfuzosin in our study. While baseline IPSS and PVR significantly improved, Q_{max} and Q_{ave} did not increase in the alfuzosin group unexpectedly. Because alfuzosin has been shown to improve LUTS and urinary flow in short−term studies [27]. We have achieved improvements in symptom scores, but not in flow rates. Although there were mean increases from baseline of 11.29% ±44.31 for Q_{max} and 11.16% ±49.14 for Q_{ave}, these changes were not enough to be significant in our study.

The most striking result of our study was detected in the combination group. Adding flurbiprofen to alfuzosin provided flow increase besides IPSS and PVR improvements in the short−term. Since long−term results of alfuzosin have been corroborated for LUTS/BPO patients [28], we may adapt this result to our daily clinical practice by supporting the long term alfuzosin therapy with an initial 4−week flurbiprofen course.

Considering our data about mean percent changes from baseline, improvements in all variables were higher in combination therapy than in monotherapies. For example, percent increases in combination therapy were more than the sum of two monotherapies in regard to flow rates, but they were not found significant in statistical analysis. However, percent changes in IPSS and $IPSS_{empty}$ were significantly higher in both alfuzosin and combination groups than that in the flurbiprofen group. This result may be referred to the potentiating effect of flurbiprofen in combination therapy on symptomatic improvement especially in voiding symptoms.

We should make mention of treatment−emergent adverse events. Postural hypotension was the most frequent in alfuzosin and combination groups, but

none of our patients discontinued the treatment because of hypotension. We came to this conclusion after considering our patients' subjective declaration about the symptoms of postural hypotension, because a rigorous blood pressure monitoring was not performed in this study. Gastrointestinal adverse events were predominant in flurbiprofen group. A significant proportion of patients (6 of 30, 20%) discontinued the flurbiprofen due to gastric discomfort. Also, the 3 patients who were lost to follow–up in flurbiprofen group might also have resigned from the therapy because of adverse events. Inconsistently with this result, only one patient in the combination group (1 of 30, 3.3%) discontinued drug therapy due to gastrointestinal discomfort of flurbiprofen. Inhibition of COX–1 plays the main role in the pathogenesis of NSAID–associated with gastric discomfort. By inhibiting gastric COX–1, and also impairing specific prostaglandin–dependent defenses which protect the gastric mucosa, flurbiprofen may reduce gastric mucosal blood flow, causing local ischemic injury [29].

CONCLUSIONS

Treatment with the dual COX inhibitor flurbiprofen can symptomatically improve male LUTS. Flurbiprofen in combination with alfuzosin further improves symptoms with significant improvement in uroflowmetry. These results need to be supported by larger studies, but could suggest an active role for these drugs in the treatment of male LUTS.

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