Comparison of solifenacin and fesoterodine in treatment of overactive bladder

Önder Ercan, MD, Bülent Köstü, MD, Murat Bakacak, MD, Yusuf Aytaç-Tohma, MD, Bora Çoşkun, MD, Fazıl Avcı, MD, Erkan Efe, MD.

ABSTRACT

الأهداف: لمقارنة استخدام سوليفيناسين و فيسوتيرودين في علاج فرط نشاط المثانة (OAB).

الطريقة: أجريت هذه الدراسة المستقبلية في المرضى الذين شخصت إصابتهم OAB والذين حضر لقسم أمراض النساء والتوليد وجراحة المسالك البولية، كلية الطب، جامعة سوتشوإمام كهرمان، كهرمان، تركيا خلال الفترة ما بين أكتوبر 2013م وأغسطس 2014م. قُسم المرضى إلى مجموعتين. المجموعة 1 (n = 60) تلقت 5 ملغ سوليفيناسين يومياً، في حين تلقت المجموعة 2 (n = 59) 4 ملغ فيسوتيرودين يومياً. وسجلت نتائج أعراض جميع المرضى OAB باستخدام (OABSS) في الأسابيع 0 و 4 و 12. بالإضافة إلى ذلك، تم تقييم تكاليف العلاج والآثار الجانبية للأدوية.

النتائج: تم تحديد OABSS (درجة 1) على النحو التالي: 9.5 ± 2.8 المجموعة 1 و 10.7 ± 1.8 المجموعة 2 في الأسبوع 0؛ 2.2 ± 1.2 (المجموعة 1) و 2.4 ± 1.3 (المجموعة 2) في الأسبوع 4 (النتيجة 2)؛ و 1.3 ± 0.5 المجموعة 1 و 1.3 ± 0.6 المجموعة 2 في الأسبوع 12 (3 نقاط). وبالإضافة إلى ذلك، لا يوجد اختلاف إحصائي كبير بين درجات (p = 0.062 (درجة 1)، p = 0.464 (درجة 2)، و p = 0.527 (درجة 3). كان معدل التوقف عن الدواء بسبب آثارها الجانبية 0 (0%) عن المجموعة 1، و 6 (10.2%) عن المجموعة 2. وكانت التغيرات داخل المجموعة في النتائج 2–1، 3–1، و 3–2 القيم ذات دلالة إحصائية في كل من المجموعتين (p ⩽ 0.001).

الخاتمة: لا يوجد فرق كبير بين OABSS من هذين النوعين من الأدوية. ومع ذلك، كان التوقف عن استخدام الأدوية بسبب الآثار الجانبية أكثر تواتراً في فيسوتيرودين.

Objectives: To compare the use of solifenacin and fesoterodine in treatment of overactive bladder (OAB).

Methods: This prospective study was conducted on patients diagnosed with OAB who presenting to the Department of Obstetrics and Gynecology and Urology, School of Medicine, Kahramanmaraş Sütçü İmam University, Kahramanmaraş, Turkey between October 2013 and August 2014. Patients were randomized into 2 groups. Group 1 (n=60) received 5 mg solifenacin per day, while Group 2 (n=59) received 4 mg fesoterodine per day. All the patients' OAB symptom scores (OABSS) in weeks 0, 4, and 12 were recorded. In addition, treatment costs and side effects of the drugs were evaluated.

Results: Average OABSS (score 1) was determined as: 9.5 ± 2.8 for Group 1 and 10.7 ± 1.8 for Group 2 at week 0; 2.2 ± 1.2 (Group 1) and 2.4 ± 1.3 (Group 2) at week 4 (score 2); and 1.3 ± 0.5 for Group 1 and 1.3 ± 0.6 for Group 2 at week 12 (score 3). In addition, no statistically significant difference was found between the scores (p=0.062 (score 1), p=0.464 (score 2), and p=0.527 (score 3). The discontinuation rate of medication due to its side effects was 0 (0%) for Group 1, and 6 (10.2%) for Group 2. Intragroup changes in the scores 1-2, 1-3, and 2-3 values was statistically significant in both groups (p<0.001).

Conclusion: No significant difference was found between the OABSS of these 2 drugs. However, discontinuation of drugs due to side effects was more frequent in fesoterodine.

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From the Departments of Obstetrics and Gynecology (Ercan, Köstü, Bakacak), Urology (Efe), School of Medicine, Kahramanmaraş Sütçü Imam University, Kahramanmaraş, and the Department of Obstetrics and Gynecology (Aytaç-Tohma), Konya Hospital, Baskent University, Konya, and the Department of Obstetrics and Gynecology (Çoşkun), Etlik Zübeyde Hanım Women's Health Teaching and Research Hospital, Ankara, and the Department of Obstetrics and Gynecology (Avcı), Patnos State Hospital, Ağrı, Turkey.

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Address correspondence and reprint request to: Dr. Yusuf Aytaç-Tohma, Atlantis City Blokları, İnci Blok, Kat: 1 No: 6 Batıkent, Ankara 06010, Turkey. E-mail: aytactohma@hotmail.com

Overactive bladder (OAB) has been defined by the International Continence Society as urgency, frequency, and nocturia no matter whether it is urge incontinence or not, and as a condition, in which other pathological and metabolic factors that may cause those situations are excluded.[1] While 85% of OAB patients were diagnosed with urge incontinence, 90% of them have urgency, frequency, and nocturia.[2] In the United States, OAB affects approximately 33 million people.[3] Prevalence of this disorder in the over 18-year-olds general population in Europe is similar in men and women, at a rate of 11.8%.[4] The prevalence of OAB increases with aging in both genders, and this rate is approximately 30% in women over the age of 65.[5] Overactive bladder causes significant impairment in an individuals' physical, social, emotional, and sexual functions. Therefore, its treatment is quite important, as it reduces the quality of life for patients.[6] Various methods for treatment of OAB is used, such as behavior training, medical, and surgical treatment. In the pharmacological treatment of OAB, particularly anticholinergics (solifenacin, tolterodine, fesoterodine, trospium, darifenacin, propantheline), Ca channel blockers, antidepressants (duloxetine, imipramine), α-adrenergic receptor antagonists (doxazosin, prazosin, tamsulosin, terazosin) β-adrenergic receptor agonists (mirabegron, albuterol, terbutaline), cyclooxygenase (COX inhibitors) (indomethacin, flurbiprofen) toxin and mix effective drugs (oxybutynin, propiverine, baclofen, and so forth) are used.[7,8] While there are a lot of studies in the literature, which compare the effectiveness of drugs in the treatment of OAB, there is no study, which examines solifenacin and fesoterodine that are relatively new drugs. Although a study comparing solifenacin and tolterodine, which is the active metabolite of fesoterodine was published in 2014, there is no study in the literature, which compares solifenacin and fesoterodine.[9] Taking effect through substantially and rapidly converting into active metabolite 5-hydroxymethyl tolterodine (5-HMT) by nonspecific esterase, fesoterodine was approved by the European Medicines Agency in 2007.[10,11] On the other hand, solifenacin which has a greater selectivity for the bladder M3 receptor, and is distinguished with the ability of long-term effectiveness, and reducing urge attacks was approved by the European Medicines Agency in 2004.[12,13] In this study, we aim to compare the effectiveness of these 2 drugs in the treatment of OAB, the use of which has started in recent years.

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Methods. The study protocol has been prospectively prepared and submitted to, and approved by the Local Ethics Committee in Kahramanmaraş, Turkey. This work was undertaken and conforms with the provisions of the Helsinki Declaration. Patients who presented to the Department of Obstetrics and Gynecology and Urology at the School of Medicine, Kahramanmaraş Sütçü İmam University, Kahramanmaraş, Turkey between October 2013 and August 2014 with disorder of urinary incontinence, and with frequency of urination of ≥8/day and urgency of ≥1/day, and diagnosed with OAB were included in the study. Patients using alpha blockers or 5-alpha reductase inhibitors, or having used them in the previous 2 months, those who experienced pelvic surgery (hysterectomy, suspended operations, and so forth), and received OAB treatment with antimuscarinics within the previous 3 months, and have been through co-morbidities, such as neurogenic bladder, diabetes, and those with the history of acute urinary retention, predominant stress urinary incontinence, and pelvic organ prolapse that require catheterization, or those who experienced lower urinary tract surgery within the last 6 months were excluded from the study. At the beginning of the study, patients who met the inclusion criteria were randomly divided into 2 groups using a web-based randomization software (www.randimizer.org). Our power value for an effect size of 0.88 calculated with α=0.05, n=60 (Group 1), n=59 (Group 2) was found as 0.99 (99%) in the post power analysis carried out when the total number of the patients reached to 119, the study was terminated due to the number of samples was considered sufficient statistically. With the diagnosis of OAB, Group 1 (n=60) received 5 mg solifenacin per day while Group 2 (n=59) received 4 mg fesoterodine per day. All patients' OAB symptom scores (OABSS) for the beginning week (0), week 4, and week 12 were recorded. The maximum score for intraday frequency was 2, night frequency was 3, urgency was 5, and urgency incontinence was 5.[14] Besides the side-effects that occurred in both groups, the rate of discontinuation of the treatment were recorded. Finally, monthly drug costs were calculated for both groups. After the study, follow-ups of patient's who left treatment due to side effects were continued in our clinic.

Statistical analysis was performed using the Statistical Package for Social Sciences version 20 (IBM Corporation, Armonk, NY, USA). Quantitative data were expressed as mean ± SD (standard deviation) in tables. In analyzing data, the values of average, frequency, and SD were identified. To demonstrate the differences between the 2 groups, Student-t and Mann-Whitney U test was used. Matched t-test was applied to determine the change in OABSS values. Data were analyzed with 95% confidence interval and statistical significance was determined at $p>0.05$. Post power analysis was performed in order to determine the sufficient number of patients that will be enrolled in the study.

Results. Sixty patients in Group 1 and 59 patients in Group 2 were included in the study. The average age of patients was determined as 58.9 for Group 1, and 58.1 for Group 2. The average age of both groups was similar ($p=0.759$). In Group 1, 45% of women and 44% of women in Group 2 were aged 65 years and above. Participants involved in both groups consisted of patients in the similar age range ($p=0.919$). Demographic characteristics of patients are given in **Table 1**. No statistical significant difference was observed in OABSS values of the groups at 0, 4, and 12 weeks (**Table 2**). In addition, the score of these groups for week 0 (score 1), 4 (score 2), and 12 (score 3) was evaluated. Changes in the intragroup scores 1-2, 1-3, and 2-3 values was statistically significant in both groups ($p<0.001$) (**Table 3**). During the study period, dry mouth was observed in 3 (Group 1), and 8 (Group 2) patients. Constipation was observed in 1.7% in Group 1, and 5.1% in Group 2. The total number of patients with complaints was 4 in Group 1, and 11 in Group 2. The discontinuation of drugs due to side effects was of 0 in Group 1, and 6 in Group 2, and it was significantly more common in Group 2 ($p=0.013$) (**Table 4**). The monthly drug costs of patients who received solifenacin and fesoterodine were determined as US$21 in Group 1, and US$34 in Group 2.

Table 1 - Demographic characteristics of the groups.

Characteristics	Group 1 Solifenacin	Group 2 Fesoterodine	*P*-value
Age, years*	58.9 ± 11.5	58.1 ± 10.2	0.759
Gravidity†	3 (5-1)	3 (6-1)	0.856
Parity†	2 (4-1)	3 (4-1)	0.244
Body mass index, kg/m² *	27.4 ± 5.1	26.8 ± 7.4	0.659
Duration of onset of OAB symptoms, months*	16 ± 5	18 ± 4	0.722

*mean ± standard deviation, †median range (maximum-minimum).
OAB - overactive bladder

Table 2 - The OABSS of the group according to weeks.

Weeks	Group 1 Solifenacin	Group 2 Fesoterodine	*P*-value
0	9.5 ± 2.8	10.7 ± 1.8	0.062
4	2.2 ± 1.2	2.4 ± 1.3	0.464
12	1.3 ± 0.5	1.3 ± 0.6	0.527

OABSS - over active bladder symptom scores

Table 3 - Difference within 2 groups in terms of the values of score 1-2, 1-3, and 2-3.

Scores	Group 1 Solifenacin	*P*-value, Group 1	Group 2 Fesoterodine	*P*-value Group 2
Score 1-Score 2	9.5±2.8 / 2.2±1.2	<0.001	10.7±1.8 / 2.4±1.3	<0.001
Score 1-Score 3	9.5±2.8 / 1.3±0.5	<0.001	10.7±1.8 / 1.3±0.6	<0.001
Score 2-Score 3	2.2±1.2 / 1.3±0.5	<0.001	2.4±1.3 / 1.3±0.6	<0.001

Score 1 - 0 week over active bladder symptom scores (OABSS), Score 2 - 4 week OABSS, Score 3 - 12 week OABSS

Table 4 - Incidence of drug-related side effects in both groups.

Side effects	Group 1 Solifenacin	Group 2 Fesoterodine	*P*-value
Dry mouth	3 (5.0)	8 (13.6)	0.186
Constipation	1 (1.7)	3 (5.1)	0.256
Total	4 (6.7)	11 (18.6)	0.144
Drug stop	0 (0.0)	6 (10.2)	0.013

Discussion. Storage and urination function of the bladder depends on the interaction between parasympathetic, sympathetic, physical, and sensory nerves.[15] Parasympathetic nerves trigger the contraction of the bladder detrusor muscle through stimulation of M2 and M3 muscarinic receptors by acetylcholine, and of purinergic receptors (P2X1) by adenosine triphosphate, and it also relax the urethral smooth muscles by nitric oxide action. When compared with M3 receptors (20%) in the bladder, the M2 receptors (80%) have more expression. However, it was shown that the detrusor contraction is substantially carried out through the M3 receptor.[7] The major M3 subtype that mediates for bladder contractions is also included in the salivary gland, stomach smooth muscle, and ciliary and iris sphincter muscles, and the blockade of this receptor results in anti-cholinergic side-effects, such as dry mouth, constipation, and blurred vision.

The OAB is a pathology that significantly affects the quality of life, and also leads to a sense of shame

and anxiety in patients. People can usually take extreme measures to reduce urinary frequency and incontinence attacks, which substantially affect physical health, vitality, social life, emotional state, and functionality.[16]

Various antimuscarinics, such as oxybutynin, propiverine, tolterodine, trospium chloride, fesoterodine, and solifenacin were used in the treatment of OAB, and they have been widely used with their proven effectiveness and stability.[17] The main basis of the use of anticholinergic agents is the blockage of the muscarinic M3 receptors in the bladder smooth muscle.[18] Although there is a clinical utility of anticholinergics for OAB patients, it is not clear, which drug is more effective.[19] There are some works in literature that evaluate the efficacy of fesoterodine and solifenacin, which have become prominent in recent years. In a review article that compared fesoterodine and tolterodine, it has been reported that fesoterodine is superior to tolterodine due to its OAB symptoms. However, the rate of discontinuation of the drug due to side effects is more common in fesoterodine rather than tolterodine.[20] Although in their study for comparison of fesoterodine and tolterodine, Du Beau et al[21] found out that both drugs are similar in terms of efficacy, dry mouth and constipation symptoms were more commonly observed in the fesoterodine group. A study in which placebo and fesoterodine have been compared in patients that gave sub-optimal response to the tolterodine, puts forward that treatment efficacy of fesoterodine is fair, and can be well-tolerated in terms of anticholinergic side effects.[22]

In the literature, 4 mg/day was proposed for fesoterodine as a starting dose, and the maximum dose was reported as 8 mg/day. However, an increase in anticholinergic side effects was observed along with increased doses.[7] In a meta-analysis that included 1805 patients and comparison of solifenacin and tolterodine by Liu et al[9] solifenacin was found to be superior in terms of OAB symptoms. However, constipation was more frequent in those using solifenacin. No statistically significant difference was observed between them in terms of other side effects. In a study that compared solifenacin and oxybutynin, solifenacin has been found to be very effective in terms of OAB symptoms.[23] In another study that compared solifenacin and tolterodine, the efficacy levels of those drugs were found to be similar, and anticholinergic side effects were substantially less common in the solifenacin group.[24] While the initial treatment dose for solifenacin is 5 mg/day, the maximum dose may be increased to 10 mg/day. Although the increase in dose also means an increase in the efficacy of the drug, the side effects, such as dry mouth also substantially increases.[7] However, in the literature, there is no study in which those drugs have been compared. In our study, we examined the efficacy of both drugs within themselves, and with each other.

A significant difference was found between the OABSS values of both drugs at weeks 0, 4, and 12. This demonstrates the effectiveness of both drugs in the treatment of OAB. Furthermore, this significant difference between OABSS values of patients in weeks 4 and 12 shows that the pharmaceutical activity for the first 3 months is proportional to the lifetime of those drugs. This demonstrates the importance of continuation of using drugs (**Table 3**). No significant difference was observed in the OABSS values of both drugs in weeks 0, 4, and 12. These results indicate that these 2 preparations have similar effects (**Table 2**). Due to the side effects of anticholinergic drugs, such as dry mouth, constipation, and blurred vision, the patients do not follow the treatment.[25] In a study based on prescription data in the United Kingdom, the rate of discontinuation of the drugs is ranges between 65% and 86% in 12 months for OAB patients using antimuscarinics.[26] The most common cause of discontinuation of treatment is dryness of the mouth.[27] While evaluating the side effects in our study, it was found out that the discontinuation of drugs due to the side effects was more common in treatment with fesoterodine, while the use of both drugs did not cause a significant difference for patients with dry mouth and constipation symptoms (**Table 4**). Besides, the cost of one-month treatment in our country was determined as US$21 for solifenacin, and S$34 for fesoterodine.

The main points of our study that can be criticized are the relatively small number of cases, and lack of the placebo control group. Furthermore, another limitation of this study was the lack of examinations in various drug doses. The OABSS being a scoring system, which is not recognized in all countries, was another limitation. As a result, while OABSS values of solifenacin and fesoterodine in the treatment of OAB were similar, and the positive effects of both drugs seem to increase with an increase in the duration of treatment. Discontinuation of the drug due to side effects was more frequent in fesoterodine. Therefore, the use of solifenacin for patients with the diagnosis of OAB seems more reasonable. Further studies will be conducted in the future with different doses of solifenacin and fesoterodine in longer treatment periods, and with greater number of patients are needed.

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