

The Role of Oxybutynin Chloride in the Management of Patients with Benign Prostatic Hyperplasia

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Abstract:-

Objectives: To determine the efficacy and tolerability of Oxybutynin chloride in men with benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) in which previous α -blocker therapy had failed.

Materials and Methods: A total of 38 consecutive men with BPH complaining of LUTS in whom a mean of 6.3 months of α -blocker therapy had failed received Oxybutynin (5 mg twice daily orally) for 3 months in addition to the usual α -blocker medication. Primary efficacy end points were American Urological Association symptom score, and mean daytime and nighttime micturition frequency. Secondary end points were the peak urinary flow rate, post-void residual volume, the incidence of urinary retention, and adverse events. Statistical analysis was used when needed.

Results: A total of 33 men (87%) with a mean age of 59 years completed the 3-month trial. Mean 24-hour micturition frequency decreased from 11.2 to 6.5 voids and nocturia decreased from 5.1 to 2.4 episodes nightly. Significant changes in mean American Urological Association symptom scores (-5.31), the peak urinary flow rate (1.8 ml per second) and post-void residual volume (-21 ml) were also observed. Five men (13%) discontinued therapy because of intolerable dry mouth. There were no reports of urinary retention.

Conclusions: Treatment with Oxybutynin in carefully selected men with BPH and moderate LUTS may be a reasonable therapeutic option after failed treatment with α -blockers.

فعالية عقار الأوكسيبوتنين كلورايد في علاج المرضى المصابين بتضخم البروستات الحميد

المستخلص:-

الهدف:

إن هدف الدراسة هو لتحديد فعالية عقار الأوكسيبوتنين كلورايد في معالجة أعراض الجهاز البولي السفلي للمرضى المصابين بتضخم البروستات الحميد بعد فشل العلاج بصادات مستقبلات ألفا.

منهج الدراسة: اشتملت الدراسة على 38 شخص مصابين بتضخم البروستات الحميد ويعانون من أعراض الجهاز البولي السفلي بعد فشل العلاج بصادات مستقبلات ألفا لمدة (6.3 شهر بالمعتل). أعطى المرضى عقار الأوكسيبوتنين كلورايد (5 ملغم مرتين يومياً عن طريق الفم) لمدة 3 أشهر بالإضافة إلى العلاج الأولي بصادات مستقبلات ألفا. اعتمد التقويم الأولي للنتائج على إستبيان الجمعية الأمريكية للجراحة البولية، مع معتل تكرار التبول في الليل و النهار. أما التقويم الثانوي فقد اعتمد على نسبة جريان الإدرار العليا، كمية الإدرار المتبقي في المثانة بعد التبول، عدد حالات حدوث إحتباس الإدرار، بالإضافة إلى الأعراض الجانبية للعلاج.

نتائج الدراسة: 33 شخص (87%) وبمعتل عمري قدره 59 سنة أكملوا الدراسة لمدة 3 أشهر. أدى العلاج إلى تقليل المعتل اليومي لتكرار الإدرار من 11.2 إلى 6.5 في النهار و من 5.1 إلى 2.4 في الليل. كذلك أثبتت الدراسة إلى حدوث تغير ملحوظ في إستبيان الجمعية الأمريكية للجراحة البولية للمرضى بعد العلاج (-5.31)، نسبة جريان الإدرار العليا (1.8 مل بالثانية) و كمية الإدرار المتبقي في المثانة بعد التبول (-21 مل). لم يستطع 5 أشخاص من إكمال فترة الدراسة بسبب عدم تحملهم لتبيس الفم الناتج من العلاج. لم تُسجل حالات لإحتباس الإدرار خلال مدة الدراسة.

الاستنتاج: أثبتت الدراسة فعالية عقار الأوكسيبوتنين كلورايد في علاج أعراض الجهاز البولي السفلي للمرضى المختارين بعناية و المصابين بتضخم البروستات الحميد بعد فشل العلاج بصادات مستقبلات ألفا.

KEY WORDS: Prostatic hyperplasia, Oxybutynin chloride, Lower urinary tract symptoms (LUTS)

Introduction:-

Benign prostatic hyperplasia (BPH) is a common condition generally associated with aging. Based on autopsy findings, Berry et al^[1] estimated the prevalence of symptomatic BPH was 43% in 50 to 59 year-old, 70% in 61 to 70-year-old and 82% in 71 to 80-year-old men.^[1] BPH often causes bladder outlet obstruction (BOO) and it commonly results in lower urinary tract symptoms (LUTS).^[2] LUTS have adverse effects on health related quality of life, including interference with daily activities and decreased psychological well-being, which worsen with symptom severity. LUTS include overactive bladder (OAB) symptoms, e.g. frequency, urgency and incontinence, and voiding (or obstructive) symptoms, e.g. dribbling, hesitancy, a weak stream and incomplete emptying.^[3]

Although voiding symptoms are more prevalent in men with BPH and BOO, OAB symptoms are generally more bothersome and, thus, they represent an important target in the management of BPH and BOO.^[4] Frequency, urgency and urge incontinence have been attributed to detrusor overactivity (DO), which reportedly occurs in 40% to 70% of patients with BOO.^[5, 6] BOO induced DO may result from ischemia,^[7] cholinergic detrusor denervation,^[8] increased detrusor collagen content^[9] or changes in the electrical properties of detrusor smooth muscle cells.^[10] Previous studies have shown that BPH associated LUTS can be best alleviated by transurethral resection of the prostate (TURP). However, because of the expense of TURP and the development of pharmacotherapies for BPH, the frequency of TURP procedures has decreased.^[11] Today uroselective $\alpha 1$ -adrenoreceptor antagonists, e.g. tamsulosin and alfuzosin, are often chosen as initial therapy for symptomatic BPH. These agents promote relaxation of the bladder neck and prostate smooth muscle and, thus, they decrease bladder outlet resistance.^[12] However, the low density of detrusor α -receptors may preclude the direct effects of α -blockers on detrusor contractility^[13] and α -blockers have demonstrated limited success for OAB symptoms.^[14] The 5 α - reductase inhibitors, e.g. finasteride and dutasteride, inhibit the conversion of testosterone to the more potent

androgen 5 α -dihydrotestosterone and they are also used to treat BPH symptoms. The decrease in 5 α -dihydrotestosterone by these agents induces epithelial apoptosis and atrophy, and reduces prostate size.^[12] However, endocrine changes mediated by 5 α -reductase inhibitors are unlikely to attenuate DO and related OAB symptoms. Furthermore, some studies suggest that selective $\alpha 1$ -adrenoreceptor antagonists and 5 α -reductase inhibitors are associated with an increased incidence of ejaculatory dysfunction.^[15] The development of new therapies for male LUTS should minimize sexual side effects and avoid urinary retention, for which patients with BPH are at high risk.^[16] Muscarinic receptor antagonists such as Oxybutynin are widely used to treat OAB symptoms but the potential role of antimuscarinics for LUTS secondary to BPH has not been explored extensively. We assessed the efficacy and tolerability of Oxybutynin for LUTS in men with BPH who did not respond to treatment with α -blockers.

Patients and Methods:-

This prospective study was conducted at Baghdad Medical City during the period from the 1st of May 2006 to the end of January 2007. Enrolled men were 50 years or older with an American Urological Association (AUA)^[17] symptom score between 8 and 19 (moderate symptoms), a maximum urinary flow rate (Qmax) of 4 to 15 ml per second and avoided volume of at least 150 ml. Prostatic enlargement was confirmed by digital examination and ultrasound examination and prostate specific antigen (PSA) levels were recorded in each patient. The exclusion criteria were previous surgical intervention for BPH, previous treatment with a 5 α -reductase inhibitor or muscarinic receptor antagonist, or serum PSA greater than 10 ng/ml. Patients received 5 mg Oxybutynin chloride two times daily orally for 3 months in addition to the usual α -blocker medication. Patient micturition diaries were evaluated at baseline, after 1, and 3 months of Oxybutynin therapy. Primary outcomes were the 3-month change in AUA symptom score and

urinary frequency during the daytime and nighttime hour.

American Urological Association (AUA)

Patient's Name		Not At All	Less Than 1 Time in 5	Less Than Half the Time	About Half the Time	More Than Half the Time	Almost Always	Your Score
Date of Birth	Date Completed							
1. Incomplete emptying								
Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?		0	1	2	3	4	5	
2. Frequency								
Over the past month, how often have you had to urinate again less than two hours after you finished urinating?		0	1	2	3	4	5	
3. Intermittency								
Over the past month, how often have you found you stopped and started again several times when you urinated?		0	1	2	3	4	5	
4. Urgency								
Over the past month, how often have you found it difficult to postpone urination?		0	1	2	3	4	5	
5. Weak stream								
Over the past month, how often have you had a weak urinary stream?		0	1	2	3	4	5	
6. Straining								
Over the past month, how often have you had to push or strain to begin urination?		0	1	2	3	4	5	
		None	1 Time	2 Times	3 Times	4 Times	5 Times or More	
7. Nocturia								
Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?		0	1	2	3	4	5	

The nocturnal period was defined as the time that the patient intended to fall asleep until the time that the patient intended to awaken. Secondary outcomes were the incidence of urinary retention, and changes in Qmax and post-void residual (PVR) volume, which were measured by standard uroflowmetry and catheterization techniques. The AUA symptom score was also divided into obstructive (items 1, 3, 5, and 6) and storage symptoms (items 2, 4,

and 7) to determine whether Oxybutynin had a greater effect on either type of symptom. AEs were recorded throughout the study.

Statistical analyses were performed using SPSS software, version 9.0 for Windows (SPSS, Chicago, Illinois, USA). A P-value of less than 0.05 was considered significant. End point values after 1, and 3 months of treatment were compared to baseline values using the Student *t* test.

Table (1): Changes in AUA symptom score, Q max, and PVR volume after Oxybutynin therapy.

	Mean AUA Score \pm SD	Mean Q _{max} \pm SD (ml/Sec)	Mean PVR \pm SD (ml)
Baseline	15.4 \pm 1.7	9.7 \pm 2.6	83 \pm 2.5
1 Month	10.6 \pm 2.3	11.3 \pm 2.3	72 \pm 3.3
3 Months	10.1 \pm 2.1	11.5 \pm 2.1	62 \pm 3.9
Net Change	- 5.3	1.8	- 21
P value	< 0.001	<0.01	< 0.02

Results:-

Of the 38 included patients, 33 (87%) completed the 3-month study. The mean age of included patients was 59 years (range 50 to 77) and the mean duration of previous failed α -blocker therapy was 6.3 months. The α -blockers – used previously by patients – included terazosin in 25 patients, doxazosin in 5, and alfuzosin in 5, and tamsulosin in 3 patients. Mean baseline PSA was 3.7 ng/ml.

Urinary frequency decreased from 11.2 to 6.5 micturition daily ($p < 0.02$) and nocturia episodes decreased from 5.1 to 2.4 nightly ($p < 0.01$). The changes in the mean AUA symptom score ($- 5.3$, $p < 0.001$), Qmax (1.8 ml per second, $p < 0.01$) and PVR volume (-21 ml, $p < 0.02$) after 3 months of Oxybutynin treatment were statistically significant. Total AUA symptom scores were significantly decreased after only 1 month of treatment ($- 4.8$, $p < 0.03$). (Table 1).

Mean scores for storage and voiding symptoms were also significantly decreased after 3 months of treatment with Oxybutynin ($p < 0.02$, $p < 0.03$). Figures 1 and 2 respectively.

Five men (13%) discontinued Oxybutynin therapy because of intolerable dry mouth. There were no occurrences of urinary retention.

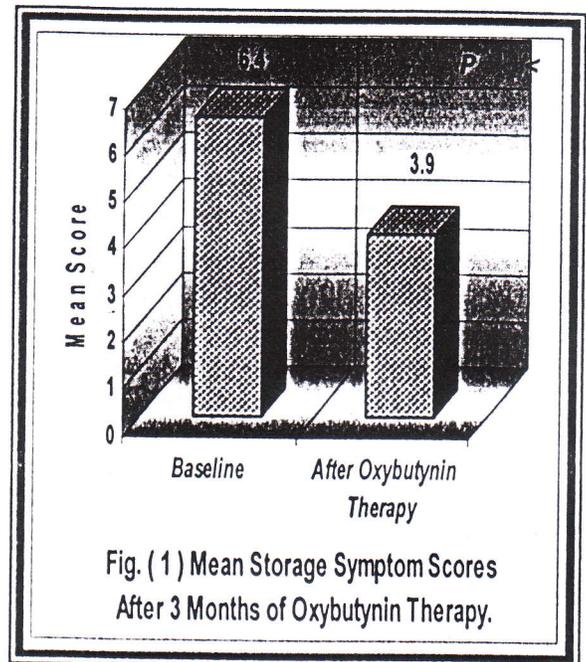


Fig. (1) Mean Storage Symptom Scores After 3 Months of Oxybutynin Therapy.

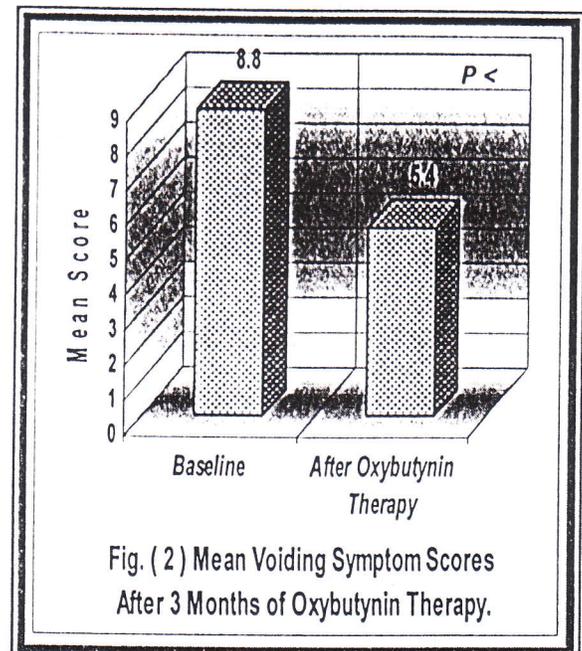


Fig. (2) Mean Voiding Symptom Scores After 3 Months of Oxybutynin Therapy.

Discussion:-

The impact of continuing growth of the elderly population BPH and other age associated conditions have emerged as major public health issues. Although voiding symptoms are the most prevalent LUTS secondary to BPH, studies have

demonstrated that OAB symptoms are the most bothersome and they negatively impact health related quality of life. In an international study of men with LUTS, voiding symptoms accounted for the 5 most frequent symptoms but OAB symptoms accounted for 4 of the 5 most bothersome symptoms.^[4] Thus, controlling OAB symptoms without aggravating voiding symptoms has become an important therapeutic goal in the management of BPH induced LUTS.

The results of this study demonstrate that Oxybutynin decreased OAB and voiding symptoms in men with BPH in whom α -blocker therapy failed. The incidence of AEs was low and urinary retention did not occur in any Oxybutynin treated men. The increases in Qmax and decreases in PVR observed with Oxybutynin treatment further support a low risk of urinary retention. These results are consistent with previous findings in men with BPH and BOO that suggest the inhibitory effect of antimuscarinics agents on detrusor muscle contraction is unlikely to aggravate voiding difficulties in men with OAB symptoms and possible BOO.^[18] To our knowledge, the current study is the first in Iraq to assess the efficacy and safety of Oxybutynin in men with BPH who had not experienced relief from LUTS with α -blocker therapy.

Although the reasons for the failed efficacy of α -blockers in this population are not well established, it is possible that some patients had idiopathic OAB in the absence of BOO. Because α -blockers may not have direct effects on detrusor contractility, the efficacy of Oxybutynin treatment in these men may be attributable only to increased detrusor stability. Decreased detrusor contractions may increase bladder volume at voiding, leading to the observed improvements in hesitancy and intermittency.

The prevalence estimates of BOO in men with LUTS have approached 70%.^[5] Furthermore, the prevalence of DO in men with BPH/LUTS has been estimated to be between 40% and 70%.^[5,6] The current results demonstrate that Oxybutynin was effective for male LUTS and suggest that expensive cystometric and urodynamic diagnostic

techniques used to confirm DO and BOO may not be necessary to effectively treat LUTS. Combination therapies using anticholinergics and α -blockers have also demonstrated promise for symptomatic BOO and DO in male populations.^[14,18]

Conclusions & Recommendations:-

The results suggest that treatment with Oxybutynin in carefully selected men with BPH and moderate LUTS may be a reasonable therapeutic option after failed treatment with α -blockers. To more eventually institute a role for muscarinic receptor antagonists in the treatment of LUTS secondary to BPH, randomized and placebo controlled trials should be performed using urodynamic evaluation and enrolling larger numbers of men for longer treatment periods.

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