Prominent Complaint: a Guide to Medical Therapy of Overactive Bladder Syndrome in Older Women

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Abstract- To evaluate Overactive bladder (OAB) with detrusor overactivity (DOA) following oxybutynin or tolterodine treatment in recommended doses at a four-week course. A total of 100 Iranian women 45 years or older with urgency that also showed idiopathic detrusor overactivity (IDO) in the filling phase of their cystometry were included in the current study. In this double-blinded trial two parallel groups were randomized by using two kinds of the antimuscarinic drugs for a four- week course [oxybutinin 5mg, t.d.s. or Tolterodin 2mg, b.i.d.] in the same packages. Data were collected from three-day frequency volume chart (FVC) one month before and after the treatment course. The effectiveness of each drug was compared using the paired, samples t-test. Patients' improvement regarding urinary urgency, frequency and urge incontinence after treatment in both groups was seen, but mean improvements in the terms of urgency and urge incontinence were larger in patients who were treated by oxybutynin. Night-time frequency was shown to be improved by a significantly larger score by tolterodine. Discontinuation of treatment due to adverse events had no significant difference in two groups. Four-week treatment with oxybutynin was better than tolterodine IR in improving urgency and urge incontinence, but there were not statistically significant difference between them. In planning a course of treatment especially in the elderly, the difference in the group of symptoms that reduce patients' quality of life should be considered. Physicians should consider the patient's prominent symptom in selection of anti-muscarinic drugs for the treatment of overactive bladder syndrome especially in elderly patients.

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Introduction

Oxybutynin and tolterodine are two highly effective anticholinergic drugs suitable for treatment of overactive bladder (OAB) syndrome. Each drug has a different specificity to bladder muscarinic receptors; thus different adverse effect profiles should be considered. Additionally different individuals experience the symptoms of OAB and the adverse effect to different extents. Therefore quality of life is affected differently in the patients with OAB. Previous findings supported similar efficacy of both drugs in different types and doses of improvement of symptoms of OAB, but to reduce the adverse side effects tolterodine was recommended and oxybutynin may minimize treatment costs (1-8). Determining the lowest therapeutic dose of the drugs helps selecting different preparations regarding the prominent symptom, cost, and adverse effects. This study was designed to determine the effectiveness of oxybutynin (5 mg IR tablet t.d.s.) vs. tolterodine (2 mg IR table b.i.d.) in the treatment of the OAB.

Materials and Methods

This randomized, double-blind, parallel-group trial was conducted in the women's clinic of Imam Hospital affiliated with the Tehran University of Medical Sciences, Tehran, Iran. The study design was reviewed and approved by Research and Ethics Committee office of the university. A total of 100 female outpatients aged ≥45 years with documented overactive bladder syndrome defined as urinary frequency >or=8 micturations /24 hours plus urge incontinence (>or=5

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episodes/week)] who show idiopathic detrusor overactivity (IDO) in the filling cystometry were randomized to receive oral treatment with oxybutynine hydrochloride tablet (5 mg, Iran Daru Co., Iran) every 8 hours or tolterodine tablet (2mg, Loghman Co., Iran) twice daily for four weeks. The study included all eligible patients from February 2011 till February 2012. A three-day frequency volume chart (FVC) was obtained before and after the treatment course. Subjective and objective symptoms were assessed one month before and after treatment.

The effectiveness of each drug was compared using the paired samples t-test.

Results

Total of 100 women with the age of 53 ± 12 years (mean ± SD) were included. Mean subjective daytime and night-time frequency, urgency, and urge urinary incontinence decreased after treatment in both groups. On a three-day frequency volume chart, after treatment with oxybutynin the daytime and the nighttime frequency of patients decreased 22% (P=0.000) and 17.6% (P=0.035) respectively. In tolterodine group, the daytime and the night-time frequency of patients decreased 16.4 % (P=0.000) and 24.3% (P=0.006), respectively.

The evaluation of urinary urgency showed a significant decrease in both groups. The urinary urgency and nocturnal urinary urgency were decreased by 58.8% (P=0.008) and 39.7% (P=0.001), respectively in oxybutynin group and 41.8% (P=0.000) and 39.1% (P=0.001), respectively in tolterodine group. There was a significant decrease in episodes of incontinence with oxybutynin (46.7%; P=0.001) also a significant decrease in patients treated with tolterodine (39.7%; P=0.002).

In this study, the treatment discontinuation rate due to adverse events was not significantly different in two groups (6% and 8% in oxybutynin and tolterodine group, respectively, P= 0.82). Dry mouth was the most common side-effect in both groups (30% in oxybutynin group and 26% in the tolterodine group).

Discussion

Anticholinergics are the mainstay of pharmacotherapy for OAB. Evidence for their efficacy is mostly derived from short-term phase III randomized drug trials (9).

Different patients experience symptoms of OAB (frequency, urgency, urge incontinence) to different extents. These findings suggest selecting the drug that most effectively improves the prominent complaints influencing the quality of life in patients with OAB especially elderly (1,2). Therefore, researches are being conducted on different types and the lowest therapeutic dose of anticholinergic drugs. The choice of agent for an individual patient depends on the cost, dosing frequency, drug-drug interactions, potential side effects, and co-morbid conditions that may increase adverse effects of drug.

Although it acts on all types, tolterodine is more commonly known to act on M2 and M3 subtypes of muscarinic receptors (10). In comparison to oxybutynin (M3 and M1 selective, but more so in the parotid than in the bladder), tolterodine is claimed to have fewer side effects as it targets the bladder more than other organs (10).

Treatment with oxybutynin and tolterodine (either immediate-release or extended-release tablets) has shown a similar efficacy in improving urination diary variables in patients with overactive bladder (7,8,11,12).

Previous studies showed the discontinuation rates caused by adverse events were similar between the two formulations. Discontinuation rates for extended-release agents were slightly lower compared with short-acting agents. However, extended-release (ER) preparations are more expensive than the others (12).

There is no compelling evidence that one agent is safer than another. In addition to efficacy and adverse effects, cost and the effect on the most prominent symptom have essential roles in choosing the appropriate treatment. Extended-release (ER) preparations are more expensive but better tolerated than the immediate release (12).

There is a trend for detecting the lowest therapeutic dose of anticholinergic drugs in the treatment of OAB in elderly because of 32% reported rate of using other drugs with anticholinergic effects which leads to cumulative adverse effects (13). Therefore, especially in older patients, antimuscarinics should be started at the lowest possible dose and titrated as needed.

There were not statistically significant differences between the different doses of oxybutynin and tolterodin [(5 vs. 10 mg ER tablet of oxybutynin) (4,12) , (3 x 5mg IR tablet of oxybutynin vs. 2 x 2mg IR tablet of tolterodin) (7,8,12) and (2 x 2 mg IR tablet vs. 4mg ER of tolterodin) (11,12)].

Multiple drug trials indicate that antimuscarinic efficacy increases for up to four weeks, suggesting that clinicians should avoid escalating the dose or abandoning therapy too soon (7-12).

More severe and frequent dry mouth episodes were seen in whom took oxybutynin immediate-release (IR) compared to other preparations (11). In this study 3 x 5mg IR tablet of oxybutynin was used, and significant improvement in frequency, urgency and urge incontinence episodes were seen.

Thus determining the lowest therapeutic dose of the drugs is mandatory in treatment designation with different preparations regarding cost effectiveness and decreased adverse effects. This recommended dose of oxybutynin (3 x 5mg IR tablet) is associated with similar therapeutic effect and fewer adverse effects especially dry mouth, and may thus be preferable.

In this study, the adverse events resulted in discontinuation of treatment were similar in two groups. This result is in contrast with some other studies concerning tolterodine to have fewer adverse effects in comparison to oxybutynin (7,12). Different age groups under study and ethnic disparities may interpret the distinction. In another study conducted on the same ethnic group dispensing the age limitation of patients, no differences were shown between two groups in terms of symptom cure (13).

OAB presents with various symptoms. Urgency in 54% and urge incontinence in 36% of patients with OAB are reported (14). In present study improvements in urinary urgency, frequency and urge incontinence after treatment were seen in both groups. Improvement score in patients treated by oxybutynin was larger especially in terms of urgency and urge incontinence. Therefore, patients suffering from OAB with the chief complaint of urgency or urge incontinence oxybutynin regimen could be more beneficial, whereas night-time frequency was shown to be improved by a significantly larger score by tolterodine. Accordingly, for elderly patients in whom the most troublesome complaint is nocturnal frequency and the disturbed sleep pattern prescription of tolterodine is suggested. Mostly the studies have implemented that applying FVCs of ≥3 days can be used to monitor therapeutic outcomes of drugs in OAB (15). Present data were collected from micturition diaries of three days recorded by the patients who were educated by a gynecologic resident.

The limitations of the current study are small sample size, short follow-up duration, and the subjective nature of follow-up. However, subjective (i.e., patient-reported) outcome measures are most relevant to clinical practice. Follow-up was short but averaged three months. Sample size was small, but this is a single-center study, and all patients were managed by a uniform management protocol that avoids the variation in practices observed in multicenter studies. In addition, the present study was not industry-supported.

In conclusion, to save the patient's quality of life physicians should consider the patients' prominent symptom in selecting antimuscarinic drugs in the treatment of overactive bladder syndrome especially in elderly patients.

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