

TREATMENT WITH OXYBUTYNIN, IMPRAMINE AND DOXAZOSIN IN PATIENTS WITH REFRACTORY DETRUSOR OVERACTIVITY: RESULTS AND SIDE EFFECTS

Hypothesis / aims of study:

Patients with DO have a negative impact on quality of life, often changing their daily habits, thus leading to stress and anxiety. Its prevalence is estimated at between 2.4% to 18.6% of the general population. Treatment of choice for DO is with antimuscarinic drugs, but approximately 30% of patients treated with monotherapy of antimuscarinic persist with DO requiring new treatment options. Alpha blockers have action on various adrenoceptor (AR) in the lower urinary tract, with more relevance on AR alpha-1a and alpha-1d, the first found near bladder neck and the second in detrusor muscle, reducing urinary and irritative symptoms. Tricyclic antidepressants allow bladder relaxation and increase urethral resistance to urinary flow, although not known its exact mechanism of action. The goal of the study was to assess whether the association of antimuscarinic, alpha-blocker and tricyclic antidepressants increases success in treatment of refractory detrusor overactivity patients who have failed to treatment with isolated antimuscarinic drug.

Study design, materials and methods:

Patients diagnosed with refractory DO, previously treated with antimuscarinic drugs, were selected to participate in this study. Previous oxybutynin dose administered was 15mg per day, divided into three intakes during 24hours. Inclusion criteria were having failed to previous treatment, absence of urinary tract infection or glaucoma. Patients who had been submitted to bladder or prostate surgery, have a sacral route stimulator in place, is on active treatment with any kind of bladder instilled drug, had been submitted to radiotherapy affecting bladder or any pelvic surgery were excluded from study. Patient's evaluation consisted of clinical history and examination, three day daily urinary chart, bladder questionnaire on overactivity - OAB - V8 and uodynamic (UD) assessment. Before starting the study patients remained 30 days without using any antimuscarinic drug. Assessment of daily urinary chart, OAB questionnaire - V8 and UD were repeated after two months of treatment. Protocol drug treatment doses were 4mg of Doxazosin at night, 10mg of Oxybutynin divided into two intakes and 25mg of Imipramine in the morning. The criteria for improvement or cure of patients were objectively evaluated by UD, being defined as presence of one DIC or less. Side effects and tolerability were evaluated after treatment by visual scale. The level of significance adopted for the statistical tests was 5% ($p < 0.05$).

Results:

A total of 27 patients completed the study. Distribution of neurological disorders comprise spinal cord trauma, meningocoele, encephalitis, myelitis and multiple sclerosis. Comparing daily urinary chart before and after treatment we found a significant increase on bladder capacity and decrease on urgency and urge Incontinence as well as of frequency (Table 1).

	Pre treatment	Post treatment	
Urgency	85%	32%	$p < 0,001$
Losses	78%	48%	$p = 0,052$
Frequency	9	6	$p < 0,001$
Interval	3	4	$p = 0,011$
Medium volume	100mL	200mL	$p = 0,007$

Table 1: Daily urinary chart variables - pre and post treatment.

After 60 days, objective data from UD revealed that the median MBC ranged from 200 to 300mL ($p < 0001$), with triple treatment. The same trend was observed with the other UD variables as can be seen in Table 2. The subjective symptoms assessment was obtained with the use of the questionnaire OAB - v8 (for symptoms of overactive bladder), and we found a direct correlation between scores of the questionnaire and symptoms. It obtained a median pre-treatment of 25 points, then going after the triple treatment for a median of 17 ($p < 0.01$). Among side effects, 2 patients did not complete the visual scale of 0 to 10, while the rest of sample showed as main complaints dry mouth and constipation (40% for each complaint). The average score for these complaints was 5.16 and 3.08, respectively. The other complaints such as blurred vision, fatigue, dizziness and hypotension were made sporadically and always with low scores (less than 1), not being of great impact for patients. There was no abandonment of treatment due to side effects.

	Median pre treatment	Median post treatment	
Compliance (mL/cmH ₂ O)	6	20	$P < 0,001$
Amplitude IDC (cmH ₂ O)	64	40	$P < 0,001$
Number of IDC	5	2	$P < 0,001$
MBC (mL)	200	300	$P < 0,001$

Table 2: UD variables, pre and post treatment.

Interpretation of results:

The sample consists of adults and children, patients with and without neurological damage, in program of self clean intermittent catheterism and with spontaneous micturition. The reason for such wide inclusion criteria is justified by the restricted number of refractory patients. It has been shown improvement in clinical and UD parameters as response to treatment with double dose of anticholinergic (from maximum manufacturer's recommended), with no prohibitive side effects, improving symptoms and quality of life of patients (1). Similar results in the improvement of the UD parameters were obtained with the use of Trospium. In our study a similar response was found, with the use of triple therapy, improving on UD variables (table 2) and the scores of the questionnaire OAB - v8. However these figures may not be widespread in view of the limited number of the sample. By combining oxybutynin and tricyclic antidepressant, the aim is to extend the outbreaks to anticholinergic block since they associate the peripheral action of oxybutynin to the central action of the tricyclic, without increasing the side effects at same proportion. Studies show that the stimulation of alpha receptor facilitates the release of more acetylcholine. Thus the use of alpha blocker reduces the concentration of acetylcholine, leading to improvement of symptoms without the need to increase the direct anticholinergic dose (2). By making

use of triple therapy we observed good response to treatment, which allows us to observe in practice that the association of alpha-blockers reduces the need of direct anticholinergic medication. The increase in micturition interval shows to be significant, with relatively small gain (one hour), however we should bear in mind the presence of 37% of the sample in program of self clean intermittent catheterism, ever 6 hours, which limits having higher interval improvement. On the urgency, it causes great influence on patients daily activities and work. Carried out the analysis of data related to urgency and losses, we found similar to literature with improvement of the two variables, $p < 0.01$ $p = 0.02$, respectively. In like manner had improved nocturia with the reduction in episodes ($p = 0.021$). As in Western Europe, but in a slower curve, the proportion of older people in developing countries like Brazil, increases over time. The possibility of a conservative management of this condition, allowing to postpone or decline the need of an invasive therapy are important issues when analyzing the positive results obtained. Analyzing side effects from this series, when comparing the results to studies that have made use of oxybutynin immediate release, we found lower side effects rates than the ones specified by literature - may reach up to 93% (3). Although the triple therapy presents a moderate rate of dry mouth and constipation, the improves on clinical picture and quality of life takes the patient to be more tolerant with these side effects, being highly motivated to keep the use of the combination of drugs.

Concluding message:

Triple therapy may be an effective alternative in treatment of patients with refractory detrusor overactivity, being a choice of low cost, with potential good results and tolerability, easy to be employed. However more studies are necessary to achieve more consistent data on the matter.

References

Neurourology and Urodynamic (2006) 25: 441-445.
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 World J Urol (2001) 19: 319-323.

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<i>What were the subjects in the study?</i>	HUMAN
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