93

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COMBINATION OF A CHOLINERGIC DRUG AND AN ALPHA-BLOCKER IS MORE EFFECTIVE THAN MONOTHERAPY FOR THE TREATMENT OF VOIDING DIFFICULTY IN PATIENTS WITH UNDERACTIVE DETRUSOR

Aims of Study

Cholinergic drugs such as bethanechol chloride and distigmine bromide have been considered to enhance detrusor contractility and promote bladder emptying in patients with underactive bladders. Oral administration of bethanechol and distigmine has been empirically used for underactive bladder dysfunction in the hope of reducing residual urine, but it has not been well standardized for long term therapy and its effect has been questioned. In some placebo-controlled double-blind studies, cholinergic drugs have been shown to be ineffective(1), but recently, oral bethanechol (25 mg q.i.d.) showed a significant reduction of residual volume and an increase of Qmax compared to placebo(2).Recently, alpha-blockers have been reported to be effective for the treatment of voiding dysfunction in patients with neurogenic bladder by reducing urethral resistance during voiding(3). A combination of a cholinergic drug and an alpha-blocker has also been reported to be effective in improving urination by enhancing detrusor contractility and lowering urethral resistance in patients with underactive bladder(4). However, whether the combination therapy is better than the monotherapy with a cholinergic drug or alpha-blocker has yet to be proven. The aim of the present study is to compare the effectiveness of a cholinergic drug, an alpha-blocker and a combination treatment for underactive voiding dysfunction.

Methods

A total of 119 patients with underactive detrusor were entered into a single-blinded randomized controlled study. After the pretreatment observation period of one week, patients were randomly assigned to three groups: the cholinergic group consisting of 40 patients taking cholinergic drugs such as bethanechol chloride (20 mg t.i.d.) or distigmine bromide (5 mg t.i.d.), the alpha-blocker group consisting of 38 patients taking urapidil (30 mg b.i.d.) and the combination group of 41 patients taking both a cholinergic drug and an alpha-blocker. The effectiveness of each therapy was assessed at 4 weeks after the therapy. Urinary symptom scores were assessed by the International Prostate Symptom Score (IPSS). This score was evaluated as a total score, storage symptom scores and voiding symptom scores. Urinary flow rates and postvoid residual urine volume were evaluated at the end of the observation period and after the therapy. Postvoid residual urine volume (ml) and the rate of residual urine (residual urine volume / (residual urine volume + voided volume) $\times$ 100 % were measured.

Results

The total IPSS decreased significantly after the therapy in the alpha-blocker and the combination groups (both $p < 0.0001$) when compared to the baseline values, but did not decrease significantly in the cholinergic group. The sum of the storage symptom scores decreased significantly in the alpha-blocker and the combination group ($p = 0.0068$ and $p = 0.0031$, respectively), but not in the cholinergic group. The sum of the voiding symptom scores decreased significantly in all groups ($p = 0.0116$, $p < 0.0001$ and $p < 0.0001$, respectively). There were significant differences with regard to the sum of IPSS between the cholinergic vs. the alpha-blocker group ($p = 0.0008$), and the cholinergic vs. the combination group ($p = 0.0033$), in favor of the latter, respectively. The average and maximum flow rates did not increase significantly after the monotherapy with either the cholinergic drug or the alpha-blocker, but they were significantly increased after the combination therapy as compared to baseline values ($p=0.0033$ and $p=0.0004$, respectively). There was a significant inter-group difference between the combination therapy and cholinergic group with regard to maximum flow rate ($p=0.0457$).

In the cholinergic group, the postvoid residual urine volume did not decrease significantly ($p=0.1928$), but the rate of residual urine decreased significantly ($p = 0.0005$) after the therapy. The postvoid residual and the rate decreased significantly after the therapy in both

the alpha-blocker group (p=0.0043 and p=0.0176, respectively) and the combination therapy group (p=0.0008 and p=0.0001, respectively). In females, average and maximum flow rates increased significantly in the alpha-blocker and combination groups, but not significantly in the cholinergic group. Postvoid residual urine volume and the rate of residual decreased significantly in all groups for all female patients. On the contrary in males, average and maximum flow rates increased significantly in the cholinergic and the combination groups, but they did not change in the alpha-blocker group. Postvoid residual urine volume and the rate of residual decreased marginally significantly in the male combination group.

Mild adverse events were observed in 3 of the cholinergic group patients (diarrhea in 1 and abdominal pain in 2 patients), and in 3 of the combination treatment group (diarrhea in 1 and dizziness in 2 patients). The dizziness in the combination group occurred after the daily dose of urapidil was increased to 60 mg, but therapy could be continued after decreasing the dose to 30 mg. In all groups there were no significant variations detected in the systolic or diastolic blood pressure, or the pulse rate, after the therapy was initiated. There was no clear decrease in blood pressure noted in the patients who showed adverse events.

	Cholinergic Group	Alpha-blocker Group	Combination Group
Total IPSS			
Pre-treatment	16.00±6.73	13.37±6.05	15.54±6.37
Post-treatment	14.83±7.80	8.55 ±5.38	10.90±6.88
Intra-group difference	p = 0.1241	p = 0.0001	p = 0.0001
Total storage symptom scores			
Pre-treatment	4.88±2.95	4.26±2.90	5.05±3.05
Post-treatment	4.90±3.35	3.45 ±2.62	3.93±2.65
Intra-group difference	p = 0.9530	p = 0.0068	p = 0.0088
Total voiding symptom scores			
Pre-treatment	11.08±5.59	9.11±4.37	10.49±5.52
Post-treatment	9.73±6.4	5.11 ±4.12	6.98±5.83
Intra-group difference	p = 0.0116	p = 0.0001	p = 0.0001
Average Flow Rates	(ml/sec)		
Pre-treatment	4.21±2.15	353±2.26	4.42±2.36
Post-treatment	4.96±2.50	4.25±3.03	6.52±4.94
Intra-group difference	p=0.0738	P=0.1095	p = 0.0033
Maximum Flow Rates	(ml/sec)		
Pre-treatment	8.63±3.96	8.53±5.07	9.56±5.99
Post-treatment	9.53±4.37	9.6±5.76	12.68±8.08
Intra-group difference	p=0.2323	p=2805	p = 0.0004
Postvoid Residual Volume	(ml)		
Pre-treatment	144.8±118.0	166.1±147.2	162.3±108.3
Post-treatment	122.3±134.6	134.6±123.7	103.9±109.3
Intra-group difference	p=0.1928	p=0.0043	p = 0.0008
Rate of Residual Urine (%)			
Pre-treatment	51.64±27.40	46.99±28.02	54.95±25.88
Post-treatment	35.74±27.82	38.48±8.57	33.20±27.73
Intra-group difference	p=0.0005	p=0.0176	p = 0.0001

Conclusions

Combination therapy with a cholinergic drug and an alpha-blocker appears to be more useful than monotherapy for the treatment of underactive detrusor.

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