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Effectiveness of trospium chloride and doxazosin mesylate combination in neurogenic bladder patients with spinal cord injury

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ABSTRACT

Objective. The aim of this study was to compare the effects of trospium chloride (TCL) and TCL + doxazosin (DXZ) combination to bladder capacity and residual urine volume (RUV) in spinal cord injury (SCI) patients with neurogenic bladder. ***Methods***. The study included 120 patients with SCI. Urodynamic data of patients were reviewed retrospectively. Changes in maximum cystometric capacity (MCC) as well as RUV were determined in patients using 60-90 mg/day TCL (Group 1, n = 98) or 60-90 mg/day TCL + 4-6 mg/day DXZ (Group 2, n = 22). ***Results***. There was statistically significant increase in both MCC and RUV values in both groups. There was no statistical difference in MCC and RUV values in Group 1 and Group 2 (p=0.111 and p=0.664, respectively). There was a significant weak negative correlation between duration of injury and MCC values (r = 0,185; p=0.043), meaning as the duration of injury increased, MCC decreased. There was no statistically significant correlation between medication usage duration with MCC and RUV (r = -0.129; p=0.159 and r = -0.68; p=0.462, respectively). ***Conclusions***. Anticholinergic treatment is currently the mainstay conservative treatment of neurogenic detrusor overactivity. The impact of alfa blockers on neurogenic bladder has been less well evaluated. We consider that, adding DXZ to TCL has no additional benefit to increase bladder capacity and reduce RUV. Further studies are needed to determine the location of DXZ treatment in SCI patients with neurogenic bladder.

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Keywords: spinal cord injury, neurogenic bladder, doksazosin mesylate, trospium chloride

Introduction

In suprasacral spinal cord injuries (SCI), the sacral and pontine micturition centers are separated, and reflex voiding is initiated by an involuntary detrusor contraction rather than relaxation of the external urethral sphincter. Urologic complications are associated with increasing bladder pressures [1]. Neurogenic bladder (NB), which occurs in 70-84% of patients with SCI, is a high-risk factor for renal dysfunction and at the same time reduces quality of life [2, 3]. Therefore, NB treatment should be

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managed appropriately in order to improve quality of life and preserve renal function. The 2006 Consortium for Spinal Cord Medicine Clinical Practice Guidelines on Bladder Management has identified three main goals for the management of bladder treatment in patients with SCI. Preservation of the upper urinary tract, minimization of lower urinary tract complications, and compatibility with the patient's lifestyle [4]. Treatment of NB if not managed appropriately, life threatening complications may occur such as vesicoureteral reflux, urinary tract infections, nephrolithiasis, hydronephrosis and renal failure. Conservative treatment is the first choice in almost all cases and will continue to be the primary choice in the majority of NB patients. Anticholinergics are the first-line choice for treating neurogenic detrusor overactivity. The mode of action of anticholinergic drugs is not clear. However, it is believed that drugs reduce detrusor overactivity and block muscarinic receptors, resulting in resistance to parasympathetic stimulation. This action results in improved bladder compliance and reduced symptoms of overactive bladder [5]. Alpha adrenergic receptors have been identified in the proximal urethra, prostate, and bladder neck. Alpha-blockers have been found to lower urethral resistance and improve voiding. Alpha-blockers seem to be effective for decreasing bladder outlet resistance, residual urine volume (RUV), and autonomic dysreflexia [4]. Doxazosin (DXZ) is an alpha-1 adrenergic blocker and contributes to the treatment of NB due to SCI by performing the above effects. Trospium chloride (TCL), is a quaternary amine with a low oil-to-water partition coefficient, poor absorption from the gastrointestinal tract with low bioavailability and poor central nervous system penetration [6]. The aim of this study was to compare the effects of TCL and TCL + DXZ combination to bladder capacity and RUV in SCI patients with NB.

Methods

One hundred and twenty patients (94 male, 26 female) who were on rehabilitation program in our hospital with the diagnosis of SCI with NB were studied retrospectively. After retrospective screening, patients at spinal shock period; patients who underwent urodynamic study before; patients with previous lower urinary system disease, individuals with NB due to other causes (diabetes mellitus, previous stroke or brain injury, other neurologic diseases etc.), patients with SCI out of lesion level, brain injury and pelvic trauma accompanying to SCI and previously used pharmacological agents for the urinary bladder such as anticholinergics, alpha-blockers, baclofen and injections were not included in the study. The study protocol was approved by the ethical committee of our institution. Patients were assessed based on the results of two consecutive urodynamic tests with a time interval of no more than 2 months. The patients were divided into two groups using only TCL 60-90 mg/day (Group 1, n = 98) and TCL 60-90 mg/day + DXZ 4-6 mg/day (Group 2, n = 22). Changes in maximum cystometric capacity (MCC) as well as RUV of patients were determined in both groups. For urodynamic testing, a computer-assisted urodynamic unit (Libra + MMS, Enschede, The Netherlands) was used in all patients. The bladder was filled and the intravesical pressure was recorded via a sterile transurethral double-lumened 8 F catheter. Sterile saline solution at body temperature was used as a filling medium, and the bladder was filled at a rate of 50 ml/min. MCC was defined as a patient experienced sensation that would normally lead to immediate evacuation of the bladder, the volume at the time as intravesical pressure was above 40 cmH20 and the volume at the time as the beginning of voiding without control [7].

Statistical Analysis

The statistical analysis was performed using SPSS-15.0 and level of statistical significance was defined as $p < 0.05$. Descriptive statistics, paired-samples t test, Pearson correlation test and independent-samples t test were used.

Results

Mean age of the patients was 34.95 ± 13.61 years, mean duration of injury was 13.17 ± 30.49 months and medication usage duration was 2.57 ± 1.93 months. In Table 1, demographic properties of the patients and in Table 2, both groups' MCC and RUV levels were shown. There was no significant difference between groups in terms of duration of injury, age and medication usage duration. There was statistically significant increase in both MCC and RUV values in both groups. There was no statistical difference in MCC and RUV in Group 1 and Group 2 (MCC: 148 ml vs. 83 ml; $p = 0.111$ and RUV: 141 ml vs. 122 ml; $p = 0.664$). There was a significant weak negative

Table 1. Characteristics of the groups

Characteristics		Group 1 (n = 98)	Group 2 (n = 22)	*p*
Age (year)		34.5 ± 13.3	36.6 ± 14.93	0.510
Sex	**Female**	23 (23.5%)	3 (13.6%)	0.420
	Male	75 (76.5%)	19 (86.4%)	
Neurological level	**Cervical**	10 (10.2%)	1 (4.5%)	0.371
	Thoracic	66 (67.3%)	13 (59.1%)	
	Lumbar	22 (22.5%)	8 (36.4%)	
Etiology	**Gun injury**	9 (9.2%)	1 (4.5%)	0.108
	Traffic accident	39 (39.8%)	5 (22.7%)	
	Falling	36 (36.7%)	8 (36.4%)	
	Others	14 (14.3%)	8 (36.4%)	
Duration of injury (month)		12.95 ± 3.39	16.50 ± 35.73	0.633

Data are shown as mean ± standard deviation or number (percent).

correlation between duration of injury and MCC values before treatment in both groups (r = 0.185; *p*=0.043), meaning as the duration of injury increased, MCC decreased. There was no meaningful correlation between medication usage duration with MCC and RUV in both groups (r = -0.129; *p* = 0.159 and r=-0.68; *p* = 0.462, respectively).

Discussion

Neurogenic lower urinary tract dysfunction (NLUTD) is an important cause of morbidity and mortality among SCI patients [8]. The condition is known to be life threatening if not properly managed. There are three main goals for the management of bladder treatment in patients with SCI. Preservation of the upper urinary tract, minimization of lower urinary tract complications, and compatibility with the patient's lifestyle [4]. Urodynamic testing will be necessary in many patients to gain more complete diagnosis of how the neurogenic dysfunction has changed the function of different components in the lower urinary tract and their interaction [9]. Drugs are often used in patients with neurogenic bladder. They aim at decreasing detrusor activity, increasing bladder capacity and/or increasing/decreasing bladder outlet resistance [9]. Anticholinergic treatment is the first-line therapy for neurogenic detrusor overactivity. This treatment works by blocking cholinergic transmission at muscarinic receptors. Anticholinergic agents have similar efficacy; however, they have different side effect and tolerability profiles that depend on their muscarinic receptor selectivity and the rate of drug distribution. Several studies have shown that anticholinergic treatment increases bladder capacity, reduces bladder pressure, and improves compliance and quality of life [10]. TCL is a quaternary ammonium derivative with mainly antimuscarinic actions, its effectiveness and safety was confirmed by meta-analysis. It does not break the blood–brain barrier. Central nervous system side effects are therefore not expected [9]. Alpha-blockers are a nonsurgical method to treat detrusor sphincter dyssynergia and low bladder pressure during voiding. Alpha adrenergic receptors have been identified in the proximal urethra, prostate, and bladder neck. Alpha adrenergic blockers have been found to lower urethral

Table 2. MCC and RUV comparison in both medication groups

	Before Treatment	After Treatment	*p*
Group 1 (n = 98)			
MCC (ml)	244.32 ± 144.83	393.30 ± 206.38	0.000
RUV (ml)	191.52 ± 148.40	332.8 ± 238.17	0.000
Group 2 (n = 22)			
MCC (ml)	271.90 ± 135.66	355.31 ± 127.09	0.001
RUV (ml)	155.00 ± 118.60	277.13 ± 187.84	0.005

Data are shown as mean ± standard deviation. MCC = maximum cystometric capasity, RUV = residual urine volume

resistance and improve voiding. Though earlier adrenergic blockers were less urologic-specific, they were commonly used for medical treatment of lower urinary tract dysfunction in individuals with SCI [11]. More specific adrenergic blockers (against alpha 1-A adrenergic receptors) are now being used to treat lower urinary tract dysfunction associated with high urethral resistance in individuals with SCI [12]. Understanding the risks, benefits, and contraindications of the different alpha-blockers will help the individual with SCI make an informed decision on the type of bladder management to be tried [4]. In 1994, Swierzerwski *et al.* [13] studied the effect of terazosin on bladder compliance in 12 spinal cord injured patients with poor bladder compliance and they found that improvement in compliance was statistically and clinically significant. After this result, they suggested that terazosin may have an effect on alpha receptors in the detrusor muscle or central effects and that improved compliance is not due to decreased outlet resistance [13]. In addition, in 1996, Yasuda *et al.* [14] studied a placebo controlled double blind trial with 136 patients with NB. They gave to patients' placebo, 30 mg or 60 mg urapadil (an alpha blocker) for 4 weeks and they found that the highest dose group showed a statistically significant decrease in urodynamic detrusor overactivity. Our study basically designed with the possible beneficial effects of alpha blockers on the NB in the direction of the above-mentioned mechanisms and studies. In our study TCL was used as an anticholinergic agent and DXZ as an alpha-blocker. Patients were divided into 2 groups as TCL 60-90 mg/day users and TCL 60-90 mg/day + DXZ 4-6 mg/day users. By separating these groups, we aimed to investigate whether DXZ may have any therapeutic effect on MCC and RUV values in addition to TCL in the direction of the above-mentioned alpha-blocker action mechanisms. At the end of our study, we found a significant increase both MCC and RUV values in both groups after treatment. However, despite the increase in MCC and RUV values, there was no statistical difference between Group 1 and Group 2 in terms of these values. In 1991, Stöhrer et al. [15] studied the urodynamic effects of TCL on SCI patients with NB and they found that TCL improved MCC. In accordance with the study of the Stöhrer *et al.* [15], we found a significant increase in MCC in both groups. So, we agree with Stöhrer *et al.* [15] that TCL has increased the MCC values. However, Groen *et al.* [2] suggested that alpha blockers seem to be effective for decreasing bladder outlet resistance, RUV and autonomic dysreflexia in neurourological patients, but we did not find a significant decrease in RUV values in Group 2. Although theoretically sharing the proposal with alpha blockers in Groen *et al.*'s study [2], we have not observed any improvement in the RUV values in our study. Administration of anticholinergic agent simultaneously may embower the RUV decreasing effect of alpha blocker in our study. However, we believe that our study is important as it gives information about anticholinergic and alpha blocker combination therapy in SCI patients with neurogenic bladder.

The Limitations of the Study

The rates of bladder filling during the urodynamic test of the patients included in the study were 50 ml / min. in our retrospective study. Although this filling rate is the upper limit of medium fill cystometry, it may provoke detrusor overactivity in SCI patients with overactive detrusors. Choosing individualized filling rate (body weight-kg / 4) would be more suitable.

Conclusions

In this study we have detected that, adding DXZ to TCL had no additional benefit to increase bladder capacity and reduce RUV. Further studies are needed to determine the location of DXZ treatment in SCI patients with NB.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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