COMPARISON OF OXYBUTYNIN AND TOLTERODINE IN TREATMENT OF DETRUSOR OVERACTIVITY ASSOCIATED WITH UPPER MOTOR NEURON LESIONS, BASED ON CHANGES IN URODYNAMIC PARAMETERS

Sumeera Matee[1], Mahmood Ahmad[1], Muhammad Farooq[2], Saeed Bin Ayaz[2], Noreen Akhtar[3]
[1]Armed Forces Institute of Rehabilitation Medicine, Rawalpindi, Punjab, Pakistan.
[2]Combined Military Hospital, Okara, Punjab, Pakistan.
[3]Combined Military Hospital, Abbottabad, Khyber Pakhtunkhwa, Pakistan.

Correspondence to: *Dr. Saeed Bin Ayaz, Consultant Physical Medicine and Rehabilitation, Combined Military Hospital, Okara, Pakistan. Email:saeedbinayaz@gmail.com*
Date of Submission: *August 15, 2015* ***Date of Revision:*** *September 29, 2015* ***Date of Acceptance:*** *October 15, 2015*

ABSTRACT

Objectives: To compare efficacy of oxybutynin and tolterodine in managing Detrusor Overactivity (DO) in Pakistani patients with different upper motor neuron lesions. **Methods:** A randomized controlled trial was carried out at Armed Forces Institute of Rehabilitation Medicine, Rawalpindi from January to August 2015 including individuals with a diagnosis of DO as a result of upper motor neuron lesions. Maximal detrusor pressure (MDP) and maximal cystometric capacity (MCC) were measured at baseline and at four months post-treatment. Group-A was treated with tolterodine and group-B with oxybutynin. **Results:** A total of 60 individuals (mean age: 43.9 ± 15 years) were included. Majority (83.3%) were male and had spinal cord injury as the commonest etiology (56.7%). Group-A had a mean pre-treatment MCC of 188.3 ± 48.2 ml, and a mean post-treatment MCC of 281.5 ± 49.1 ml ($p< 0.001$). The mean pre-treatment MDP was 83.6 ± 9.5 cm of H2O, and the mean post-treatment value was 40.9 ± 10.2 cm of H2O ($p< 0.001$). Group-B had a mean pre-treatment MCC of 209.8 ± 60.5 ml, and mean post-treatment MCC of 308.7 ± 65 ml ($p< 0.001$). The mean pre-treatment MDP was 80.7 ± 10.6 cm of H2O, and the mean post-treatment value was 40.7 ± 10.1 cm of H2O ($p< 0.001$). The difference in mean reduction in MCC and MDP produced by tolterodine and oxybutynin was statistically insignificant. **Conclusions:** Both oxybutynin and tolterodine showed similar efficacy in the treatment of DO based on measurable urodynamic outcomes.

Key Words: Detrusor overactivity, oxybutynin, Pakistan, tolterodine, upper motor neuron lesions

BACKGROUND

Upper motor neuron (UMN) injury can result from a large number of conditions which are quite common in the population. The conditions which lead to UMN lesions include cerebrovascular accidents, traumatic brain injury, Parkinson's disease, multiple sclerosis and suprasacral spinal cord injury, etc. Detrusor overactivity (DO) is one of the deleterious consequences of many upper motor neuron lesions. DO is underdiagnosed and commonly untreated. The problem is further compounded by complications like vesicoureteric reflux, hydronephrosis, nephropathy, urinary tract infections, urolithiasis, chronic kidney disease and even malignancy.[1] This deteriorates the quality of life of the patient not only due to medical complications but also because of the ensuing depression and social stigmatization thus creating hindrance in early achievement of rehabilitation goals. At the same time, the complications put an extra burden on the healthcare system. This is the reason why treatment of bladder dysfunction is an important pillar in the management of upper motor neuron lesions. Bladder management in UMN lesions focuses on carefully diagnosing the underlying bladder disorder and its targeted treatment. The treatment of DO can be undertaken on clinical grounds but it is beneficial to quantify the defect on objective parameters like the urodynamic study because it helps in monitoring the response to treatment and in gathering data for future follow up. The aim of bladder management in DO is to improve the bladder capacity and decrease the detrusor contractions in order to enable clean intermittent catheterization (CIC) by the patient. This can be achieved by various modalities including pharmacotherapy as well as surgical options. Pharmacotherapy is the most commonly used first line treatment because of non-invasiveness, efficacy and ease of use. The drug options include anticholinergics/ antimuscarinics, tricyclics, intravesical instillation of capsaicin or lignocaine and botulinum injections to the detrusor muscle. Anti-muscarinic agents are the backbone of pharmacological treatment for DO.[2,3] These agents are used to abolish detrusor contractions in order

to permit voiding by CIC. Antimuscarinics have been considered the gold standard of treatment for many decades but are well-known for their side effects presenting as dry mouth, constipation and tachycardia. Oxybutynin is the most commonly used drug in this class and can be used orally and/ or intravesically.[4] Tolterodine is another commonly used antimuscarinic agent and has lesser incidence of side effects than oxybutynin in usual doses.[5] Recently, many newer drugs with better tolerability have been added to the arsenal against DO.[6] In Pakistan, most patients are unable to afford the newer agents. The mainstay of treatment for DO remains either oxybutynin or tolterodine, out of which oxybutynin is the cheaper choice.[7] International studies have proved that both these drugs have a comparable efficacy in dealing with DO.[8,9,10] No study has been conducted in our indigenous population to address this issue so far, using objective and measurable outcomes like improvement in urodynamic parameters. This issue has been addressed in the present study which aims to gather reproducible data on the subject.

MATERIALS AND METHODS

It was a single blinded randomized controlled trial carried out at Armed Forces Institute of Rehabilitation Medicine, Rawalpindi from January 2015 to August 2015. We included individuals belonging to both genders fitting in the age group of 18-60 years with a diagnosis of DO as a result of upper motor neuron lesions. We had chosen the above mentioned age limit to lessen the influence of confounding factors in geriatric and pediatric population. Above 60 years, the females are likely to have stress incontinence and males are prone to develop lower urinary tract symptoms due to prostatic disease. Likewise, the urodynamic parameters in the pediatric population are different than adults. Patients having conditions other than DO that might have led to urinary incontinence or urgency e.g. urinary tract infection, prostatic hypertrophy or utero-vaginal prolapse were excluded from the study. Smokers and women who were pregnant or breast feeding their children were also placed in the exclusion group. After approval from the hospital ethics committee, prospective candidates for enrollment were evaluated thoroughly to meet the inclusion criteria. Patient's informed consent for participation was taken after explaining the objectives and benefits of the study. The patients who were enrolled underwent baseline urodynamic studies using PICO SMART Urodynamics System (PICO SMART, Menfis Division, MEDICA S.p.A., Bologna, Italy) to quantify maximal detrusor pressure (MDP) and maximal cystometric capacity (MCC). MDP is the pressure created by bladder wall forces. It is a component of intravesical pressure and is calculated by subtracting abdominal pressure from intravesical pressure. It was measured in cm of H2O. MCC is the volume at which the patient feels that he/she can no longer delay micturition. It was measured in ml. The patients were consecutively divided into two study groups i.e. Group A and B. Group A was treated with oral tolterodine (Detrusitol, Pfizer Laboratories, Karachi, Pakistan) 2 mg twelve hourly [11] and group B received oral oxybutynin (Taivor, Raazee Therapeutics, Lahore, Pakistan) 3 mg eight hourly.[12] The urodynamic parameters assessed at baseline were repeated after four weeks. The data were endorsed for each patient in a written proforma. The data were analyzed with the help of statistical program Statistical Package for Social sciences (SPSS) version 19.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were calculated for both qualitative and quantitative variables. For qualitative variables like gender and primary diagnosis of UMN lesion, frequencies and percentages were calculated and for quantitative variables like age, MDP and MCC, means and standard deviations were calculated. Paired-samples t-test was applied to statistically analyze the effect of both therapeutic modalities in either study groups. The mean reduction in MCC and MDP between two groups were compared using independent-samples t-test. A p-value < 0.05 was considered significant.

RESULTS

A total of 60 patients suffering from UMN pathology attributed to various clinical conditions, regardless of age and gender, were included in the study. Fifty patients (83.3%) were male and ten (16.7%) were female. Mean age of the patients was 43.9 ± 15 years with a range of 13-72 years. The cause of upper motor neuron lesion was spinal cord injury in 56.7% (n=34) of the patients followed by cerebrovascular accident (23.3%,n=14), Parkinson's disease (5%,n=3), cerebral palsy (5%, n=3), spinal tuberculosis (5%,n=3), acquired brain injury (3.3%,n=2) and spinal cord tumors (1.7%, n=1) (Figure-1). Mean pre-treatment MCC was 199.1 ± 55.5 ml, and the mean post-treatment MCC was 295.1 ± 59 ml. Mean pretreatment MDP was 82.1 ± 10.2 cm of H2O, and the mean post-treatment value was 40.8 ± 10.1 cm of H2O.

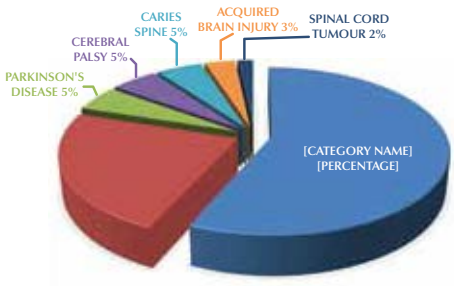

Figure-1: Figure showing relative percentages of different primary etiologies for upper motor neuron lesion in the sample

Twenty-six males and 4 females (n=30) were in group A. Rest of the 24 males and 6 females (n=30), were in group B. Group A had a mean pre-treatment MCC of 188.3 ± 48.2 ml, and a mean post-treatment MCC of 281.5 ± 49.1 ml. (Table-1) The mean pretreatment MDP was 83.6 ± 9.5 cm of H2O, and the mean post-treatment value was 40.9 ± 10.2 cm of H2O. Group B had a mean pre-treatment MCC of 209.8 ± 60.5 ml, and mean post-treatment MCC of 308.7 ± 65 ml. The mean pretreatment MDP was 80.7 ± 10.6 cm of H2O, and the mean post-treatment value was 40.7 ± 10.1 cm of H2O.(Table-1)

	Pretreatment mean MCC*	Post-treatment mean MCC	Mean reduction in MCC with P-value	Pretreatment mean MDP*	Post-treatment mean MDP	Mean reduction in MDP with P-value
Tolterodine	188.3 ± 48.2	MCC of 281.5 ± 49.1	93.2 ± 18.6, p < 0.001	83.6 ± 9.5	40.9 ± 10.2	42.7 ± 3.9, p < 0.001
Oxybutynin	209.8 ± 60.5	308.7 ± 65	98.9 ± 26.7, p < 0.001	80.7 ± 10.6	40.7 ± 10.1	40 ± 10.6, p < 0.001

*MCC: Maximalcystometric capacity
**MDP:Maximaldetrusor pressure
Table-1:Table showing comparison of the effect of oxybutynin and tolterodineonmaximal cystometric capacity and maximaldetrusor pressure

Each drug significantly reduced MCC and MDP in its group (p< 0.001, p< 0.001, p< 0.001 and p< 0.001 respectively). The mean reduction in MCC produced by tolterodine (93.2 ± 18.6) was less than that produced by oxybutynin (98.9 ± 26.7) but did not satisfy the statistical tests for significance (p=0.179). Similarly, the mean reduction in MDP produced by tolterodine (42.7 ± 3.9) was more than that produced by oxybutynin (40 ± 10.6) but could not reach a statistically significant value (p= 0.068).

***MCC:** maximal cystometric capacity
****MDP:** Maximal detrusor pressure
Table-1: Table showing comparison of the effect of oxybutynin and tolterodine on maximal cystometric capacity and maximal detrusor pressure

DISCUSSION

DO is commonly seen in patients with UMN lesions as evidenced by various community and hospital based surveys. The complications relating to this disorder are also quite frequent in this population which can be averted to some extent by the use of appropriate modalities. For these patients the care of the bladder is an essential component of any rehabilitation program. In practice, balancing between efficacy and side effects is a challenge. Moreover, cost effectiveness is a major determinant in choosing the appropriate drugs especially in poor countries. A lot of studies have been conducted to determine the safety and efficacy of antimuscarinic agents that are the cornerstone of treatment in patients with both neurogenic and non-neurogenic DO. We also tried to find out the difference in efficacy of commonly available antimuscarinic agents available in Pakistan while targeting Pakistani population. We found that, though both tolterodine and oxybutynin were effective in reducing MDP and MCC, there was no significant difference in the magnitude of effect produced by both drugs. Madhuvrata P et al. embarked upon a study to compare the two drugs in question in our study. They concentrated on bladder leakage episodes in 24 hours and patients' perception of improvement in quality of life. Their results were similar to ours in that both the drugs caused significant but comparable improvements in subjective parameters. [13] In a double blind, multicenter study carried out to compare relative effectiveness of tolterodine (4 mg daily), transdermal oxybutynin and placebo [14], no significant differences were seen in the outcome parameters between the two drugs. However, both were significantly more effective than placebo in reducing incontinence episodes (75% vs 50%) both P < 0.05 vs placebo. In the Overactive Bladder: Performance of Extended Release Agents (OPERA) trial, a comparison was made between extended release oxybutynin (OXY-ER, 10 mg) and tolterodine(TOL-ER, 4 mg). With both these drugs, comparable results were obtained regarding control of incontinence. However oxybutynin was found to had a greater impact on the total micturition frequency per week (28.4 vs 25.2; P = 0.003) as well as overall dry rate (23% vs 16.8%; P = 0.03).[15] Many studies have established a superiority of tolterodine over oxybutynin in side effects' profile. This has led to more compliance with tolterodine therapy and fewer dropouts. The side effect profile was found to be much better especially with dryness of mouth and cognitive impairment. This is because tolterodine has been documented to have 8-fold less affinity to the muscarinic receptors at the parotid gland in radioligand binding.[16, 17, 18] We under took this study because of the high burden of this disorder in the outdoor and as well as the indoor in our Institute. We searched but did not find a single indigenous study on this topic using urodynamic parameters as the gauge to determine efficacy. Our study was carried out to try to address this issue. We, the physicians in the third world, more than our counterparts in the developed world, have to balance the efficacy of a drug against its cost. Oxybutynin is a relatively cheaper drug and therefore is more easily available to our patients. Based on the volume of literature in favor of comparable effectiveness of oxybutynin and tolterodine, we chose the null hypothesis to be the expected outcome on urodynamic parameters. As hypothesized, our results revealed no significant difference in the relative effectiveness of these two drugs. Therefore our study validates the results of previous studies as mentioned above. This has helped us to be more confident in prescribing this drug without feeling the guilt of withholding a potentially better drug

because of financial constraints. The study had a shortcoming. A long term follow up was required to determine the relative frequency of long term treatment failures and dropouts amongst the two groups which could not be carried out properly because of time limitation.

CONCLUSIONS

Both oxybutynin and tolterodine showed similar efficacy in the treatment of DO based on measurable urodynamic outcomes. The improvements in the urodynamic parameters were significant with both these drugs, so their regular use in appropriate patients is justified. Our study was the first of its kind in Pakistan. As mentioned earlier, the database available on DO is not of a very high quality, therefore there is a need to continue research on this subject to further elucidate the differences in response to treatment, if any, amongst the various causes of neurogenic bladder.

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Conflict of Interest: The Author declares no conflict of interest.
Funding Disclosure: Nil

Author's Contribution:
Dr. Sumeera Matee: Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review
Dr. Mahmood Ahmad: Manuscript writing, manuscript review
Dr. Muhammad Farooq: Manuscript review
Dr. Saeed Bin Ayaz: Data analysis, manuscript writing, manuscript review
Dr. Noreen Akhter: Study concept and design, manuscriptreview