

Peer Review File

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Reviewer A

The authors present a study looking for the efficacy of medication for overactive bladder symptoms in a single institution for 70 patients. The outcomes were IPSS, OABSS, nocturia >2 , and urgency episode before and after medication.

Overall, the paper was written concisely with a good methodology to evaluate the efficacy of medication to treat PD patients with storage symptoms. I would recommend publication after addressing some issues enumerated below:

General comments

Abstract

- In the Result, It would be better to show IPSS-s than IPSS because the objective of this study is managing overactive bladder symptoms in PD

Introduction

- No specific comments.

Material and Methods

- Why do you exclude patients who have had catheterization? And what is the urodynamic study result in this group?

This study aimed to investigate the medical management of overactive bladder symptoms in patients with Parkinson's disease. Further, most PD patients with urinary retention are willing to have catheterization if oral medicine failed. In the database, 187 patients were excluded from acute urinary retention when they were included. Eight male patients and 2 female patients in the 187 patients had catheterization after urodynamic study due to urinary retention and were further excluded in the study. The eight male patients were managed with tamsulosin + catheterization, and 4 patients of them were successfully got rid of catheterization after Tamsulosin usage. The urodynamic results for those male patients were as following: 3 patients of bladder outlet obstruction, 3 patients of detrusor underactivity, and 2 patients of detrusor overactivity + detrusor underactivity. Two female patients who were managed with intermittent catheterization had stress incontinence + acontractile bladder for urodynamic study.

- In patients who underwent TUR-P and Botox injections, what is the reason for excluding patients? And what is the urodynamic study result in this group? Also, the patient uses Estrogen cream and Antidepressants.

An individualized approach was adopted for the management of urinary dysfunction in the database for the PD patients. However, this study aimed to investigate the medical management of overactive bladder symptoms in those patients. People with Parkinson's disease have low willingness to have surgery for urinary dysfunction.

For the 187 patients in the database, we suggested transurethral resection of the prostate in 24 selected patients with mean age of 65.3 ± 7.6 years (range: 55-75) and median H-Y scale 2 (IQR: 2, 3); however, only 7 patients underwent the surgery during the follow-up period and others denied. The urodynamic results for the 7 patients who underwent TURP were as following: 5 patients of detrusor overactivity + bladder outlet obstruction, 2 patients of bladder outlet obstruction. The urodynamic results for the 5 patients who underwent botulinum toxin A injection were as following: 1 male patient of detrusor overactivity, 3 female patients of detrusor overactivity, and 1 female patient of detrusor overactivity + bladder outlet obstruction.

Three female patients who took antidepressant were excluded because the diagnoses were not OAB, and the urodynamic results were as following: 2 patients of normal, and 1 patient of increased bladder sensation. One female patient who had estrogen cream for outward application was excluded because the diagnosis was paresthesia (hot) around urethral, and the urodynamic result was normal.

- This is a retrospective cohort study. If you use rigid criteria, it will not be generalizability to the general PD patient.

Results

- Is there any demographic data or outcome difference on patients for neurological outpatient clinic, the hospital's neurological outpatient clinic, the urological ward, and the neurological ward? I think this result is not important.

- What is the cause of BOO in 2 female patients? The primary bladder is less common than dysfunctional voiding or pseudo detrusor sphincter dyssynergia. Thus, the patient might not improve after alpha-blocker treatment.

The etiology of urinary dysfunction in PD patients is complex and it is difficult to determine to what extent PD contributes to urinary dysfunction. Pseudo detrusor sphincter dyssynergia, detrusor underactivity and urethral stricture may be the main reasons for dysuria in female PD patients. In the database, the standards of BOO in women were as following: dysuria and $P_{detQ_{max}} > 30$ cmH₂O together with $Q_{max} < 10$ ml/s. However, the discrimination between BOO and DUA in women remains to be a vexing problem because there are not strict urodynamic criteria to establish the differential diagnosis. Urethral meatus stricture was not uncommon in old women. In the database, 6 female patients who had BOO were underwent urethrocystoscopic urethral dilation weekly, and the dysuria was improved in 4 of them. Actually, we tried alpha-blockers in female PD patients for dysuria, and some patients responded to treatment.

In Figure 3, there is no (C)urgency and (D) urge incontinence. And in many OAB

studies (Kelleher C, Hakimi Z, Zur R, Siddiqui E, Maman K, Aballéa S, Nazir J, Chapple C. Efficacy and Tolerability of Mirabegron Compared with Antimuscarinic Monotherapy or Combination Therapies for Overactive Bladder: A Systematic Review and Network Meta-analysis. *Eur Urol.* 2018 Sep;74(3):324-333. doi: 10.1016/j.eururo.2018.03.020. Epub 2018 Apr 23. PMID: 29699858.), the outcome could be Mean change from baseline in the number of micturition episodes/24 h, Mean change from baseline in the number of UUI episodes/24 h, Number of patients with zero incontinence episodes, or 100% reduction in incontinence episodes, Number of patients with 50% reduction in mean number of incontinence episodes, Mean change from baseline in the number of incontinence episodes/24 h. Why do you use zero incontinence episodes?

-We changed the Fig captions to Fig. 3a-d, and Fig3c, 3d were about urgency and urge incontinence, respectively. Mean change from baseline in the number of micturition episodes/24 h, UUI episodes/24 h, and zero incontinence/24 h are commonly analyzed from voiding diary. However, it is difficult for a PD patient to perform a 3-day voiding diary in the daily practice. At the beginning of the study, we tried to have patients keep a voiding diary, however, we found that few patients were able to stick to it, and eventually we cancelled the voiding diary.

Discussion

Miscellaneous

- In Figure 1. Idiopathic PD patients who had urinary dysfunction

We rectified “dysfunction” to “dysfunction”.

Reviewer B

This is a well executed retrospective cohort study from a single institution evaluating the medical management of lower urinary tract symptoms in patients with Parkinson's disease using Tamsulosin and/or Tolterodine.

There are some issues that need to be addressed with the manuscript:

1. The inclusion and exclusion criteria are not well described in the methods section.

Figure 1 is confusing with two separate areas showing exclusions (n=83 and n=34)

- these should be combined or shown in a more logical sequence.

-We combined the two parts of exclusions (n=83 and n=34) as suggestion.

2. Figure 2 and 3 captions indicate there is c) and d) but the actual figure does not include these items.

-We rectified the Fig captions to Fig. 2a-d and Fig. 3a-d.

3. The caption in figure 2 does not make sense: what is the difference between OAB symptoms and "urinary severity".

We changed the Fig 2 caption “Improvement of overactive bladder symptoms according to the (A) IPSS and (B) OABSS, and improvement in urinary severity

according to the IPSS (C) and OABSS (D)” to “Improvement of overactive bladder symptoms according to the IPSS (a, c) and OABSS (b, d)”.

4. There needs to be more limitations indicated in the discussion section. Other limitations of the study include: Small sample size, heterogeneous population based on gender and urodynamic findings, therefore heterogenous treatment patterns.

We added the limitations in Line 224-225 as suggestion: “This study has some limitations: small sample size, heterogeneous population based on gender and urodynamic findings, therefore heterogenous treatment patterns”.

5. The first sentence of the discussion is non-sensical: OAB symptoms cause more distress due to motor disorders in PD patients.

In Line 224-225, we changed the sentence “OAB symptoms cause more distress due to motor disorders in PD patients” to “OAB symptoms deteriorate the quality of life in PD patients and the management is challenging”.

6. The authors should comment on the use of urodynamics before treatment in this patient population: Is this common practice in their hospital and did this approach to medical management provide any benefit over empirical treatment. In most health systems I suspect medical treatment for LUTs happens empirically and when symptoms are refractory then urodynamics is used to guide further treatment.

We agree the suggestion, and added “Most OAB patients benefit from empiric therapy. It is advisable to manage refractory/complex urinary dysfunction under the guidance of urodynamics in PD patients, which allows objective discrimination of the underlying bladder and voiding disorder. However, urodynamics were performed in all the patients in this study, and the reason was that PD patients were prospectively recruited from those who underwent urodynamic evaluation in our urodynamic center” in Line 186-191. We also deleted “Urodynamic evaluation provides an objective assessment of bladder–urethral function and is helpful for determining the therapeutic schedule, especially to assess if antimuscarinic drugs should be applied in patients with voiding symptoms” following Line 202.

Reviewer C

I commend the authors on performing a study for OAB in a difficult to treat patient population especially given the sparse data in the literature. It is reassuring that medical therapy is effective to improve symptoms in most of these patients.

1. Lines 65-67: I would recommend rephrasing this sentence. I would not consider alpha-1 blockers commonly being used with antimuscarinics in male patients with irritative voiding symptoms. While it is an option, I do not consider this common practice. Would recommend to remove the word "commonly" or may state common alpha blocker usage without combination with antimuscarinics.

We remove the word "commonly" in Line 65.

2. Recommend including a hypothesis and the reason for such hypothesis in the introduction.

We modified the sentence in Line 66-69 “However, few studies have specifically evaluated these agents in PD patients with OAB symptoms 2. The aim of this study was to investigate the management of OAB symptoms in PD patients treated with tolterodine and/or tamsulosin” to “However, few studies have comprehensively examined the features and management of OAB symptoms specifically in PD patients, such as urinary symptoms, bladder-urethral function, management schedule and remained symptoms after treatment. The aim of this study was to investigate the management of OAB symptoms in PD patients treated with tolterodine and/or tamsulosin in our daily work”.

3. Line 170-171: Remove "obviously"

We remove the word " obviously " in Line 170-171.

4. Methods describe treatment is based on 3 general groupings (DO with low risk of retention, obstructive symptoms primarily found, both components). However, the majority of patients got monotherapy with tamsulosin for males and tolterodine for females. It seems that these treatment groupings were not necessarily followed. I believe that an interesting question is which of these groupings respond the best to medical therapy; however, 11 of the male patients did not receive tolterodine despite presence of DO.

We agree with the reviewer’s suggestion. However, as mentioned in the article, the therapeutic schedule was chosen by the urologists who performed the urodynamic evaluation with an individual approach. The concern of urinary retention constrains antimuscarinics usage in PD patients with BOO + DO or DUA + DO. The 3-week follow-up was short in the study. Actually, we add antimuscarinics in some PD patients with OAB symptoms if initial treatment with alpha-blockers was ineffective in our daily practice.

5. Can results be provided for improvement in OABss and IPSS based on the treatment groupings (DO with low risk of retention, obstructive symptoms primarily found, both components) similar to results in figure 2? May be included in the text or as a figure.

We added a Figure 4 in <Results>< Improvement of OAB symptoms> in line 176-177: Further analysis showed OAB in the male patients was improved with tamsulosin alone or tolterodine + tamsulosin (Fig. 4a-c).

6. Please add low sample size as a limitation. Also add that a limitation is the inconsistent usage of medications based on the indication (for instance, methods state combination therapy is supposed to be used for males with both DO and obstruction on urodynamics, but 11 of these patients only received tamsulosin).

Line 235-236: This study has some limitations: small sample size, heterogeneous

population based on gender and urodynamic findings, therefore heterogenous treatment patterns. We also explained the inconsistent usage of medications based on the indication for men in Line 209-212: However, the side effect of urinary retention constrains antimuscarinics usage in men with BOO and DUA. The results of urodynamic evaluation exacerbated concerns about the usage of tolterodine in men in this study. 24 (85.7%) male patients had BOO or DUA.

7. Please elaborate on data from other studies regarding efficacy of treatments for OAB in PD in discussion section (Lines 218-222). How effective is tamsulosin and/or tolterodine compared to other therapies?

We searched Pubmed and no suitable literature was found for LUTS management in PD patients with tolterodine or tamsulosin. We added the reply in in Line 216-218: Currently, no specific well-designed PD studies have reported on the clinical use of tolterodine or tamsulosin for OAB symptoms.