International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 08, 2020
ISSN: 1475-7192

Can pyridostigmine improve lower urinary tract symptoms and bladder function in patients with potentially-weak bladder contractility?

[1]Ahmed A. Essa

Abstract

Materials and methods

A total of 60 patients with high urinary bladder volumes and significant urinary symptoms were included in this study. Patients were considered to have weak detrusor contractility (potentially suitable for pyridostigmine therapy) if they had clinical history of poor stream and/or subjective feeling of incomplete bladder emptying, confirmed by significant post-void residual urine (PVR) on ultrasound (Mindray DC30 hospital type), in the absence of clinically significant mechanical bladder outflow tract obstruction.
Patients included were older patients with high bladder capacity and high PVR with persistent obstructive-like symptoms, such as females with high PVR with no urethral stricture or pelvic organ prolapse and males with high PVR on alpha blockers or those who failed to void after TURP and prostatectomy or did not show satisfactory symptomatic improvement or decrease in PVR after surgery.
Baseline bladder volumes, both pre-void and post-void, were recorded and the measurements were repeated after 2 weeks of oral pyridostigmine 60 mg 3 times per day. Ultrasound measurements were obtained by a single experienced operator.
Those attending urological clinic in Al-Noman Teaching Hospital and Privet clinic.A written consent was obtained from all patients participating in this study after explaining to them the important and purpose of the study, emphasized that such study could not harm them, with ensure them about complete confidentiality of information sought and will not be used other than research purpose. Patients were provided with a direct phone number to call in case of any bothersome adverse effects during pyridostigmine therapy.

Results

A total of 60 patients aged 40 to 65 years (mean 61.1 years, 41.7% females) included in this study, there was a significant overall decrease in PVR and significant improvement in voiding symptoms after 2 weeks of pyridostigmine therapy (mean PVR before treatment, 290.23± cc…and after treatment, 81.1±c ..p <.0000001 and for symptom score before treatment 18.5± and after treatment 13.9± … P<0.0001 and for bladder volume before

[1] University teacher in department of surgery, Collage of Medicine, Al-Iraqia University, Baghdad, Iraq.

Received: 03 Apr 2019 | Revised: 21 May 2020 | Accepted: 12 Jun 2020

treatment 349.93± and after treatment 302.48± ...p <0,003)
In only 4 patients (6.7%) there was no appreciable change in voiding symptoms or PVR on ultrasound. All patients tolerated the drug well without the need to discontinue the medication or reduce the dose during the 2 week period of the study.

Conclusion

Pyridostigmine is an effective and well-tolerated therapeutic option for patients with weak detrusor contractility. Further studies are needed to confirm the long-term benefit of pyridostigmine in a larger patient population.

Keywords: *Pyridostigmine, PVR, urological clinic*

I. Introduction

The definition of detrusor underactivity in 2002 by the International Continence Society is stated as a "detrusor contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span". While this is a widely accepted definition, it requires an invasive and expensive urodynamic study that cannot be done for every patient. Therefore, a more practical working definition for the “underactive bladder” was suggested by a group of experts in 2015, stated as “a symptom complex suggestive of detrusor underactivity and is usually characterized by prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling, and a slow stream. Since the symptoms of underactive bladder and bladder outlet obstruction are clinically- indistinguishable, exclusion of clinically obvious lower urinary tract obstruction together with significant postvoid residual on ultrasound can be used to provisionally diagnose a potential underactive bladder with reasonable confidence in the absence of confirmatory urodynamic study.

The largest published study reporting the prevalence of urodynamically-defined detrusor underactivity in patients over 65 years with lower urinary tract symptoms and no significant neurological or anatomical disorders, showed a prevalence of 40.2% in men and 13.3% in women. The prevalence was even higher in smaller studies which did not exclude patients with neurological conditions, reporting a prevalence of up to 48% in men and 12% in women. All studies showed a much higher incidence of underactive bladder in males compared to females, at least partially related to prostatic disease and bladder outlet obstruction in elderly males.

The etiology of underactive bladder is multifactorial. The causative factors are summarized in a recent review by Osman et al. as illustrated in Table 1.

Table 1 Etiology of Detrusor Underactivity

Type	Possible causes
Idiopathic	Normal aging*
	Unknown cause in younger patients*
Neurogenic	Diabetes
	Parkinson disease
	Multisystem atrophy
	Multiple sclerosis
	lumbar disc hernia/spinal cord injury/congenital
	Guillain-Barré syndrome
Myogenic	Bladder outlet obstruction*
	Diabetes*
Iatrogenic	Pelvic surgery
	Radical prostatectomy
	Radical hysterectomy
	Anterior/abdominoperineal resection

* Likely major etiological factors

To have good bladder smooth muscle contraction its needs intact efferent neural function, intact neuromuscular junction function, and intact post-junctional excitation-contraction coupling events. Drugs that act by stimulating the excitatory neurotransmitter (acetylcholine) actions at the detrusor neuromuscular junction may be logically helpful to alleviate bladder under activity. These drugs include muscarinic agonists, such as bethanechol and carbachol, and cholinesterase inhibitors such as distigmine, pyridostigmine and neostigmine. The principle of bladder muscle contraction needed to void occur through stimulation of muscarinic M3 receptos. Griffin et al showed that acetylcholine contracts the bladder by binding to muscarinic M3 receptors on the detrusor, leading to Ca^{2+} influx via voltage-gated Ca^{2+} channels. Cholinergic-dependent contractions of the bladder are known to be mediated by

stimulation of muscarinic receptors . The M2 and M3 subtypes are the most abundant in bladder tissue, however in most species M3 receptors are predominantly responsible for muscle contraction. In this study we focused on stimulating efferent neurons to increase bladder contraction using pyridostigmine, an old drug getting a new interest as a promising approach to manage the underactive bladder. Pyridostigmine, an acetyl cholinesterase inhibitor, increases acetylcholine at the neuromuscular junction.

II. Materials and methods

A total of 60 patients with high urinary bladder volumes and significant urinary symptoms were included in this study. Patients were considered to have weak detrusor contractility (potentially suitable for pyridostigmine therapy) if they had clinical history of poor stream and/or subjective feeling of incomplete bladder emptying, confirmed by significant post-void residual urine (PVR) on ultrasound (Mindray DC30 hospital type), in the absence of clinically significant mechanical bladder outflow tract obstruction.
Patients included were older patients with high bladder capacity and high PVR with persistent obstructive-like symptoms, such as females with high PVR with no urethral stricture or pelvic organ prolapse and males with high PVR on alpha blockers or those who failed to void after TURP and prostatectomy or did not show satisfactory symptomatic improvement or decrease in PVR after surgery.
Baseline bladder volumes, both pre-void and post-void, were recorded and the measurements were repeated after 2 weeks of oral pyridostigmine 60 mg 3 times per day. Ultrasound measurements were obtained by a single experienced operator.
Those attending urological clinic in Al-Noman Teaching Hospital and Privet clinic. Written consent was obtained from all patients participating in this study after explaining to them the important and purpose of the study, emphasized that such study could not harm them, with ensure them about complete confidentiality of information sought and will not be used other than research purpose.
Patients were provided with a direct phone number to call in case of any bothersome adverse effects during pyridostigmine therapy.

The AUA symptoms score, PVR values and bladder volumes were compared the study group before and after the use of pyridostigmine Student paired-samples t-test using SPSS version 25.

III. Results

A total of 60 patients aged 40 to 65 years (mean 61.1 years, 41.7% females) included in this study, there was a significant overall decrease in PVR and significant improvement in voiding symptoms after 2 weeks of pyridostigmine therapy (mean PVR before treatment, 290.23± cc…and after treatment, 81.1±c ..p <.0000001 (as mentioned in table 3) and for symptom score before treatment 18.5± and after treatment 13.9± … P<0.0001 as mentioned in table 4) and for bladder volume before treatment 349.93± and after treatment 302.48± …p <0,003 as mentioned in table 2)

Received: 03 Apr 2019 | Revised: 21 May 2020 | Accepted: 12 Jun 2020

In only 4 patients (6.7%) there was no appreciable change in voiding symptoms or PVR on ultrasound. All patients tolerated the drug well without the need to discontinue the medication or reduce the dose during the 2 week period of the study.

Table 2 comparison between bladder volume pre- and post- Mestinone usage.

Bladder volume	Pre- Mestinone			Post-Mestinone			Significance*	
	No.	Mean ± SD	St. error of mean	No.	Mean ± SD	St. error of mean	Mean differences	95% CI
Bladder Volume	60	349.93 ± 189.923	24.519	60	302.48 ± 166.198	21.456	47.450	16.961-77.939
t: 3.114, df: 59, P= 0.003								

Table 3 Comparison of PVR in pre- and post- Mestinone usage.

Post Void residual volume	Pre- Mestinone			Post-Mestinone			Significance*	
	No.	Mean ± SD	St. error of mean	No.	Mean ± SD	St. error of mean	Mean differences	95% CI
PVR	60	209.23 ± 144.047	18.596	60	83.43 ± 93.047	12.012	125.800	91.692- 159.908
t: 7.380, df: 59, P= 0.000								

Table 4 Comparison of symptoms score in pre- and post- Mestinone usage

AUA score	Pre- Mestinone			Post-Mestinone			Significance*	
	No.	Mean ± SD	St. error of mean	No.	Mean ± SD	St. error mean	Mean ofdifferences	95% CI
Symptoms score	60	18.52 2.783	±0.359	60	13.92 ± 3.832	0.495	4.600	3.920- 5.280
t: 13.543, df: 59, P= 0.000								

IV. Discussion

Bladder under activity or Bladder poor contractility is Detrusor underactivity is defined as "a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span" in the standardization of terminology of lower urinary tract function proposed by the International Continence Society (ICS) Subcommittee.

Patient considers to have weak detrusor contraction if his Post void residual urine more than 50 and he is straining, with Q max less than 10 and maximum detrusor pressure less than 20 cm H2O.

Due to unavailability of urodynamic study we included in this study patients with obstructive symptoms in IPSS (weak stream , incomplete emptying , straining) and patient with high post void residual urine after exclusion of obstructive symptoms or in another terms patient who not responding for alpha blocker drugs alone, and also depending on older age, large capacity bladder.

In this study using mono therapy muscarinic agonist found to have statistical significant decrease in bladder volume and PVR after 2 weeks of pyridostigmine therapy (349.9 ± 189.9 ml vs 302.5 ± 166.2 ml for bladder volume, p = 0.0028, and 209.2 ± 144.0 ml vs 83.4 ± 93.0 ml for PVR, p < .0001, respectively). A significant improvement in voiding symptoms was also noted by 56 (93.3%) of study patients (p <0.0001)

In only 4 patients (6.7%) there was no appreciable change in voiding symptoms or decrease PVR on ultrasound

Suggestive management to bladder under activity depend on stimulation of afferent (sensory) pathway, or activation of the motor pathway in micturition reflux, or relaxation of the external sphincter.9 For this reason in this study using Mestinone (Pyridostigmine 60mg 3 times daily) working on afferent pathway through stimulation M3 (muscarnic) receptors to stimulate detrusor muscle to contract . We used in this study the Symptoms score (IPPS) and PVR as marker or mounting tole for the function of bladder as it is used by Ahmed A et al in their mini-review research done at 2016 and as used by Oelke M et al in addition to IPSS and uroflowmetry and pressure flow study.

Cholinergic receptors are found not only in the detrusor, but also in the smooth muscles of the bladder base and the urethra. Although the presence of the muscarinic receptor is less in the urethra than in the bladder, small contractile effects of cholinergic drugs on the urethra have been suggested.

studies proved that longitudinal smooth muscle of urethra connected to the longitudinal layers of detrusor clarifying the possible role of opening bladder neck and shortening of urethra during voiding, on the other hand the circular smooth muscle of urethra not connected to circular layers of detrusor possibly share in urethral closure and be more sensitive to noradrenalin than acetylcholine.1012 For this reason, the cholinergic stimulation to the longitudinal muscle of the urethra may facilitate micturition, but stimulation to the circular muscle may oppose the micturition by increasing the bladder outlet resistance. Although cholinergic stimulation elicits a greater response from the longitudinal muscles of the urethra than from the circular muscles, it may also elicit a response in the circular muscles especially in pathological states

the dose of Pyridostigmine 60mg 3 times daily used by Tatsuya Yamamoto et al

The present study demonstrated that IPSS (total IPSS, total storage and voiding symptoms), and postvoid residual urine improved significantly after cholinergic therapy compared to baseline values.

This seems to be good choice to use cholinergic drugs alone or in combined with alpha blockers to treat voiding dysfunction in those patients with symptoms suggesting detrusor underactivity as it is reported by Tanaka et al. Thus Pyridostigmine alone can be active agent after removing bladder obstruction either by TURP or alpha blockers.

V. CONCLUSIONS:

Pyridostigmine is an effective and well-tolerated therapeutic option for patients with weak detrusor contractility. Further studies are needed to confirm the long-term benefit of pyridostigmine in a larger patient population.

Received: 03 Apr 2019 | Revised: 21 May 2020 | Accepted: 12 Jun 2020

References

1. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: Report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn. 2002;21:167–78.
2. Chapple CR, et al. The Underactive Bladder: A New Clinical Concept? Eur Urol (2015), http://dx.doi.org/10.1016/j.eururo.2015.02.030
3. Aldamanhori R., Chapple CR. Underactive bladder, detrusor underactivity, definition, symptoms, epidemiology, etiopathogenesis, and risk factors. Curr Opin Urol 2017, 27:293–299. doi:10.1097/MOU.0000000000000381
4. Jeong SJ, Kim HJ, Lee YJ, Lee JK, Lee BK, Choo YM, Oh JJ, Lee SC, Jeong CW, Yoon CY, Hong SK, Byun SS, Lee SE. Prevalence and Clinical Features of Detrusor Underactivity among Elderly with Lower Urinary Tract Symptoms: A Comparison between Men and Women. Korean J Urol. 2012 May;53(5):342-348. https://doi.org/10.4111/kju.2012.53.5.342
5. Abarbanel J., Esther-Lee Marcus E.L. Impaired Detrusor Contractility in Community-Dwelling Elderly Presenting with Lower Urinary Tract Symptoms. Urology 2007;69,3:436-440. doi:10.1016/j.urology.2006.11.019.
6. Osman, Nadir I. et al. Detrusor Underactivity and the Underactive Bladder: A New Clinical Entity? A Review of Current Terminology, Definitions, Epidemiology, Aetiology, and Diagnosis. European Urology. 2012;65,2:389–398.
7. Barendrecht MM, Oelke M, Laguna MP, Michel MC. Is the use of parasympathomimetics for treating an underactive urinary bladder evidence-based? BJU Int. 2007;99:749–752
8. Giglio D1, Tobin G: Muscarinic receptor subtypes in the lower urinary tract.: Pharmacology. 2009;83(5):259-69. doi: 10.1159/000209255. Epub 2009 Mar 19.
9. Caoimhin S. Griffin, Keith D. Thornbury, Mark A. Hollywood, and Gerard P. Sergeant: Muscarinic receptor-induced contractions of the detrusor are impaired in TRPC4 deficient mice: Sci Rep. 2018; 8: 9264.Published online 2018 Jun 18. doi: 10.1038/s41598-018-27617-5
10. Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. Physiol Rev. 2004;84:935–86. doi: 10.1152/physrev.00038.2003.
11. Chai TC, Kudze T. New therapeutic directions to treat underactive bladder. Investig Clin Urol. 2017 Dec;58(Suppl 2):S99-S106. https://doi.org/10.4111/icu.2017.58.S2.S99
12. Manini ML1, Camilleri M2, Grothe R3, Di Lorenzo C :Application of Pyridostigmine in Pediatric Gastrointestinal Motility Disorders: A Case Series. Paediatr Drugs. 2018 Apr;20(2):173-180. doi: 10.1007/s40272-017-0277-6.
13. Abrams P, Cardozo L, Fall M et al. The standardisation of terminology of lower urinary tract function: Report from the standardisation sub-committee of the Interna- tional Continence Society. Neurourol. Urodyn. 2002; 21: 167–78.

Received: 03 Apr 2019 | Revised: 21 May 2020 | Accepted: 12 Jun 2020