European Journal of Molecular & Clinical Medicine (EJMCM)
ISSN: 2515-8260 Volume 09, Issue 03, 2022

Original research article

A Prospective Study of the Pattern of Antispasmodic Drug use in Urological Disorders with Detrusor Overactivity

Dr. Kaushal Kumar[1], Dr. Dinesh Kumar Das[2], Dr. Ajit Singh[3]

[1] Senior Resident, Department of Urology, PMCH Patna

[2] Associate prof., Department of Urology, PMCH Patna

[3] Prof., Department of Urology, PMCH Patna

Corresponding Author: Dr. Kaushal Kumar

Abstract

Background: Detrusor overactivity (DO) characterized by urgency, frequency, with or without urge incontinence occurs as manifestation of various urological disorders like over active bladder (OAB), neurogenic bladder, infection or inflammation of thelower urinary tract, resulting in adverse impact on quality of life. The antispasmodics are selected, depending on various factors like age, co-morbid conditions, tolerability and acceptability. Antimuscarinic antispasmodic agents are commonly used. With no universal consensus on antispasmodic choice, and few systemic studies reported in the Indian literature regarding pattern of antispasmodic use in bladder overactivity, comparison of their efficacy and tolerability.
Methodology: A prospective observational cohort study was done in 120 subjects with symptoms of detrusor overactivity attending outpatient department of Urology in Patna medical college and Hospital, patna Study duration of two years.. The various study groups under DO included OAB, neurogenic bladder and OAB with urinary tract infection. The pattern and criteria for antispasmodic drug selection were noted. Their efficacy was assessed in terms of symptom improvement using OABSS, ICIQ-SF and VAS score along withassessment of tolerability and patient acceptability of antispasmodics.
Conclusion: Various antimuscarinic antispasmodics commonly used in DO are equal in efficacy, tolerability and patient acceptability. Flavoxate being the most preferred antispasmodic in subjects with associated lower UTI.
Keywords: Urinary antispasmodics, Detrusor overactivity, Overactive bladder.

Introduction

Detrusor overactivity is an urodynamic disorder with involuntary rise indetrusor pressure during the filling of the bladder, characterized by urgency, frequency with or without urge incontinence. This results in collection of various unpleasant physical, psychological and social embarrassment leading to isolation, lossof confidence, depression, the avoidance of one's sexual partner with adverse impact on quality of life. It may occur as a manifestation of various urological disorders like OAB, neurogenic bladder, infection or inflammation of lower urinary tract, following pelvic surgeries, catheterization, etc. **Non-pharmacological** measures for subjective and symptomatic improvementare aimed at lifestyle modification mainly fluid and

diet modification like reduction orelimination of caffeinated and alcoholic beverages, weight loss, behavioral therapy like bladder training with pelvic floor muscle exercises. The **pharmacological measures** involves use of various antispasmodics with prominent action on the urogenital system which mainly include antimuscarinic agents. The antimuscarinic agents specially approved for this purpose include flavoxate, oxybutynin, trospium, tolterodine, fesoterodine, darifenacin, solifenacin, propaverine, collectively referred as urinary antispasmodics, which differ in theirreceptor subtype selectivity and pharmacokinetics. They are almost similar in their efficacy but differ in their tolerability and side effect profile**.** Apart from antimuscarinic agents there are several other class of drugs like mirabegron, a β3 agonist, α1 antagonists like tamsulosin, siladosin, alfazosin which are approved for the treatment of bladder overactivity. Antidepressants like tricyclic antidepressants particularly imipramine and duloxetine an SNRI, have shown significant improvement in OAB symptoms. They decrease bladder contractility and increase bladder outlet resistance, hence useful for facilitating urine storage. Botulinum neurotoxins (BoNT) is extensively studied as alternatives to antimuscarinic in OAB and neurogenic bladder. BoNT -A, has been FDA approved for the use in patients who do not tolerate or refractory to antimuscarinic drugs. The choice of drugs depends mainly on the age, presence of co-morbid conditions, duration of action, the tolerability of the medication, its cost and availability. Despite many researches there is no universal agreement regarding the standard guidelines on the widely prevalent detrusor overactivity especially in elderly people. As there is paucity of information regarding the same in our Indian population the pattern of antispasmodics use in bladder overactivity, their relative efficacy and tolerability, this study may be of help to generate useful information and to formulate appropriate guidelines regarding the drug use.

Objectives

To determine the pattern of antispasmodic drug prescribing for subjects withdetrusor overactivity due to OAB, Neurogenic bladder or other causes, To evaluate the efficacy of drugs in symptomatic improvement, To assess their tolerability and patient acceptability.

Review of Literature

The urinary bladder, is a unique organ in the pelvis of the human body with complex neural innervations having dual function of storage and periodic elimination of the urine. An empty bladder is tetrahedral in shape with an anterior apex, aposterior base, an inferior neck, a superior surface and two inferolateral surfaces with four borders- two lateral, one anterior, one posterior border.[1] A full bladder is ovoid inshape with an apex, a neck and two surfaces anterior and posterior, and can be palpated abdominally when the bladder is full, and also in case of infants and children as the pelvis in them is shallow.[1,2] In males, the urinary bladder lies between the rectum and pubic symphysis andin females, it lies between the rectum and uterus/vagina. Anterioinferiorly and laterally, the bladder is surrounded by retropubic and perivesical fat and connective tissue which is termed as the space of Retzius.[1,3] the urinary bladder is divided into two parts: a body/fundus which lies above the ureteral orifices, and a base consisting of trigoneand bladder neck.[5] The trigone is a smooth triangular region of urinary bladder formedby the two ureteric orifices and the internal urethral orifice. The bladder neck is 3 to 4 cm behind the pubic symphysis which is composed of detrusor muscle interlaced with pelvic floor muscles. A layer of smooth muscle that surrounds the bladder neck is known as the internal-urethral sphincter. In females, the base of the bladder and urethra rest on the anterior wall of the vagina and the internal-urethral sphincter is not as well developed.[3] The bladder wall consists of three layers: mucosa, detrusor, and adventitia. Regulation of micturition involves various mechanisms at the level of cortical, subcortical, brain stem, spinal cord and urinary bladder.[4] Bladder-sphincteric complex involve three mixed sensory and motor

nerves (hypogastric, pelvic, and pudendal nerves) innervating the LUT. The hypogastric nerve carries sympathetic fibres, the pelvic nerve carries the parasympathetic fibres both under involuntary control, and the pudendal nerve carries the somatic nervous system innervations to the LUT which is under voluntary control.[2,4] During the bladder filling phase, supraspinal centers produce inhibition of the pontine micturition center (PMC), which results in activation of thoracolumbar sympathetic outflow simultaneously suppressing the sacral parasympathetic outflow tothe LUT , cause excitatory outflow through the pudendal nerve to produce external urethral sphincter contraction. The spinal neurons located in the dorsal commissure, superficial dorsal horn and parasympathetic nucleus are involved in the regulation of micturition. Glutamate serves as excitatory neurotransmitter while glycine and γ-aminobutyric acid (GABA) are inhibitory neurotransmitters at the spinal level.[5,7] Various mechanisms involving receptors, neurotransmitters and hormonal functions at the level of the urinary bladder, for both storage and voiding of urine. Muscarinic mechanisms: out of five muscarinic receptor subtypes, pharmacologicaly M_1, M_2, M_3 receptors are found on the urinary bladder. Although M2 receptors are predominant, M_3 receptors mediate cholinergic contractions.[6] Stimulation of M_3 receptors by ACh leads to activation phospholipase C, resulting in hydrolysis ofionositol triphosphate (IP3), and release of intracellular calcium and also transmembrane influx of calcium through L-type of calcium chanel is known to occur together contributing to detrusor smooth muscle contractions.[6,7] Prostanoids- prostaglandin (PG)I_2, PGE_2, $PGF_{2\alpha}$ and thromboxane A_2 in decreasing order of potency are known to contract human detrusor by specific receptors on the cell membrane.[5,7] Endothelins (ET)- ET_1, ET_2, ET_3 are known to play role in controlling bladder smooth muscle tone, bladder wall remodeling in pathologic conditions and regulation of local blood flow. Increase in ET_1 expression is noted in Bladder outlet obstruction with detrusor overactivity.[5,7] It can be defined as an urodynamic disorder with involuntary rise in detrusor pressure during the filling of the bladder, characterized by urgency, frequency with or without urge incontinence.[8,9] Urgency is symptom comprised of sudden and compelling desire to pass urine which is otherwise difficult to defer. Frequency has conventionally been considered as voiding >= 8 times per 24hours. Night time frequency/Nocturia is one or more voids per night as defined by international continence society (ICS), Urge Incontinence is involuntary leakage of urine accompanied or immediately preceded by urgency.[11] Neurogenic hypothesis states that DO arises from generalized, nerve mediated excitation of the detrusor muscle. The mechanisms that are believed to be involved are damage to the brain resulting in DO by reducing suprapontine inhibition, damage to axons in the spinal cord resulting in the expression of primitive spinal bladder reflexes, synaptic plasticity leading to reorganization of sacral activity with newreflexes emerging which are triggered by C-fiber bladder afferent neurons and lastly sensitization of the peripheral afferent neurons in the bladder which can trigger DO. Myogenic hypothesis suggests that overactive detrusor contractions result froma combination of an increased spontaneous excitation within smooth muscle of the bladder and enhanced propogation of this activity to affect an excessive proportion of the bladder wall. Patchy denervation and upregulation of membrane receptors with altered membrane potential in the bladder smooth muscle is observed.[19,16] Based on the EPIC study, overall OAB prevalence is 11.8% (10.8% in men and 12.8% in women) in general population using ICS definitions.[19,20] In Asia, the prevalence of OAB is reported at 53.1%.[10] Men were shown to have higer prevalence of OAB dry and woman had higher prevalence of OAB wet[13]. Incidence increaseswith increasing age.[13,14,15] Pathophysiology is not clearly understood, several hypothesis and mechanismsare attributed to its manifestation including neurogenic and myogenic hypothesis of DO. Autonomous bladder hypothesis suggesting the overactivity due to inappropriate activation or modulation of phasic activity has been recently proposed.[10] Urothelium and suburothelium acting as barrier, is recently known to detectthe

chemical, thermal and mechanical stimuli in the bladder as afferent functionthereby releasing the chemical mediators responsible for smooth muscle contraction inthe bladder.[16]

Material and methods

This prospective observational study was done to assess the pattern ofantispasmodic drug use in various urological disorders with detrusor overactivity, along with the comparison of their efficacy, tolerability and patient acceptability. Study subjects included patients with symptoms of bladder overactivity, such as frequency, nocturia, urgency with or without urge incontinence irrespective of the cause, in Patna medical college and Hospital Patna, Bihar. Study duration of Two years. Purposive sampling, involving 120 patients with symptoms of overactive bladder in PMCH, Patna Centre were included.

Inclusion criteria

Subjects of either gender>18years of age, with symptoms of bladder overactivitysuch as frequency, nocturia, urgency with or without urge incontinence. Willingness to give written informed consent.

Exclusion criteria

Subjects with BPH, Subjects with known or suspected prostatic carcinoma, Subjects with gynaecological disorders, Subjects with anatomical abnormality in the urogenital tract, Subjects with serious heart disease(NYHA Class iii or iv).

After obtaining approval and clearance from the institutional ethical committee, 120 subjects presenting with symptoms of bladder overactivity, such as frequency,nocturia, urgency with or without urge incontinence, irrespective of the cause were included for the present study. After fully explaining the study procedure, written informed consent was obtained from all the subjects. The demographic data, personal history, present and past medical history, drug history, and family history, subject's medical records if available was also scrutinized to obtain any relevant were recorded. All the subjects underwent a thorough physical examination, the nutritional status, general health, presence of any medical illness or co- morbid conditions were assessed. The tolerability was assessed by monitoring side effects reported by the subjects. The side effects were graded as **mild (**no functional impairment**), moderate (**some functional impairment**),** or **severe(** significant functional impairment). The causality was assessed by Naranjo's casuality grading.

Results

Table 1: Age distribution of study subjects(n=120)

Age in years	n	%
18-20	3	2.5
21-30	25	20.8
31-40	22	18.3
41-50	16	13.3
51-60	23	19.2
61-70	26	21.7
>70	5	4.2
Total	**120**	**100.0**

Mean age ± SD: 46.8 ± 16.7years

summarizes the demographic characteristics of age of 120 subjects enrolled in the study.

The mean age was 46.8 years.

Table 2: Gender distribution of study subjects(n=120)

Gender	n	%
Male	49	40.8
Female	71	59.2
Total	120	100.0

summarizes the demographic characteristics for gender of 120 subjects enrolled in thestudy.

Table 3: Causes of Detrusor overactivity(DO)(n=120)

Causes of DO	n	%
OAB	81	67.5
Neurogenic bladder	2	1.7
OAB with UTI	37	30.8
Total	**120**	**100.0**

summarizes the various causes of detrusor overactivity in the study subjects.
Majority of the subjects belonged to OAB (67.5%).

Table 4: Prescription pattern in neurogenic bladder(n=2)

Antispasmodics	n	%
Solifenacin	1	50
Darifenacin	1	50
Total	**2**	**100**

summarizes the prescription pattern in study subjects with neurogenic bladder.

Table 5: Causality assessment of adverse drug reaction(ADR)

Naranjo's causality grading of ADR	n	%
Definite	3	6
Probable	41	82
possible	6	12
doubtful	0	0
TOTAL	**50**	**100**

summarises the causality assessment of adverse drug reaction by Naranjo's causalitygrading of ADR.

Table 6: Assessment of patient acceptability

Patient acceptability grade*	n	%
Mild satisfaction	8	6.67
Moderate satisfaction	35	29.17
Well satisfied	77	64.17
Total	**120**	**100.00**

*based on a questionnaire from previous study.[17]

Majority of the study subjects(64.17%) were well satisfied at the end of the study period
Discussion
In the present prospective observational cohort study, pattern of antispasmodic drug use in various urological disorders with detrusor overactivity was observed, the criteria for drug selection, their efficacy. Thepercentage of the subjects in the age group of 18-20 years were 2.5%, 21-30 years were 22.8%, 31-40 years were 18.3%, 41-50 years were 13.3%, 51-60years were 19.2%, 61-70 years were 21.7%, age greater than 70years were 4.2% respectively. Majority of the subjects (21.7%) were in the age group of 61-70 years reflecting the higher incidence of detrusor overactivity in this age group(figure4). Mean age of the subjects was

46.8 ± 16.7 years which was similar to previous study.[18] The percentage of female subjects were 59.2% which was slightly higher when compared to the percentage of male subjects which were 40.8%.The presence of seventy one female subjects with symptoms of detrusor overactivity shows more prevalence in females, due to under develo The lifestyle history has been summarized for per day intake of water, alcohol status, smoking, caffeinated beverages in table 6(a), 6(b), 6(c) and 6(d) respectively. Majority of the study subjects 58(48.3%) had the water intake <1L per day followed by 55(44.8%) subjects with 1-2L of water intake per day and 7(5.8%)subjects had daily water intake of 2.1-3L. Majority of subjects restricted fluid intake similar to previous ,ped internal urethral sphincter. This is similar to thefindings of previous studies.[11,10,13] summarizes the overall prescription pattern ofantispasmodic in DO. Majority of the study subjects 54(45%) were prescribed solifenacin, followed in the descending order by darifenacin 26(21.7%), flavoxate 21(17.5%), tolterodine 15(12.5%), trospium 3(2.5%) and oxybutynin 1(0.8%) being least commonly used. Similar to previous study solifenacin and darifenacin were most commonly prescribed and formed the preferred choice of drug as antispasmodics in subjects with DO.[13] At week 2, mean night frequency symptom score of group receiving flavoxate was nil when compared with tolterodine (0.26±0.46) which was of high statistical significance (p value <0.01). This was followed by in the descending order of decline in mean night frequency symptom score by the following groups darifenacin (0.26±0.53), solifenacin (0.407±0.59) and trospium (1.67±1.15) (p value: <0.01). At week 3, mean night frequency symptom score of group receiving flavoxate continued to be nil when compared with tolterodine (0.06±0.26) which was of statistical significance(p value<0.05), followed by solifenacin (0.11±0.32), darifenacin (0.15±0.46),and trospium (1.33±1.53) in the descending order of decline in symptoms (p<0.05). At week 4, at the end of the study period the decline with flavoxate, tolterodine was nil when compared with solifenacin (0.03±0.19) which was of high statistical significance(P<0.001). Followed by darifenacin (0.15±0.46) and trospium (1±1) in the descending order of decline in symptoms (p value<0.001). At baseline, the group receiving trospium (2.33±4.04) had highest mean ICIQ-SF score which was statistically significant (p value <0.05) compared to other groups darifenacin (1.15±2.18) and solifenacin (0.43±1.43), in the descending order of mean ICIQ-SF symptom score. At week 1, the group receiving the solifenacin (0.32±1.17) had the lowest mean ICIQ-SF symptom score decline which was statistically significant (p value <0.05) compared to darifenacin (0.96±1.91) followed by trospium (2.33±4.04) decline in descending order. At week 2, the group receiving the solifenacin (0.20±0.88) had the lowest mean ICIQ-SF symptom score decline which was not statistically significant(p value >0.05) compared to darifenacin (0.58±1.47) and trospium (2.0±3.46) decline. At week 3, the group receiving the solifenacin (0.16±0.69) had the lowest mean ICIQ-SF symptom score decline which was not statistically significant(p value >0.05) compared to darifenacin (0.34±1.29) and trospium (1.67±2.89) decline in descending order. shows the mean VAS score change from baseline to week4 for the symptoms of dysuria and bladder area pain. At baseline, subjects receiving flavoxate had maximum mean VAS score (3.19±2.44) which was of high statistical significance (p value<0.001) compared to solifenacin(1.44±2.52), darifenacin (0.92±2.17) and tolterodine (1.07±2.25) in the descending order of mean VAS score. At week 1, among the group receiving flavoxate (0.143±0.4) had lower mean VAS score which was not statiscally significant (p value >0.05) when compared with other groups, darifenacin (0.15±0.61), tolterodine (0.2±0.77), solifenacin (0.37±0.91), in the descending order. At week 2, the mean VAS score was nil among the group receiving tolterodine which was statistically not significant (p value >0.05) when compared with other groups receiving solifenacin (0.019±0.136), darifenacin (0.07±0.27),and flavoxate (0.095±0.301)in the descending order of decline. The limitations of the present study were limited number of study subjects with each group derived, subjective symptom scoring could be influenced by other variable factors, limited period of

observation and follow-up. The comparison of DO among groups of different etiopathological causes with their different concomitant medications could have influenced the efficacy outcome. The non-pharmacological measures in the management of DO could have been considered.

Conclusion

The overall drug prescribing pattern in the present study were in the following**,** descending order: solifenacin, darifenacin, flavoxate, tolterodine, trospium and oxybutynin, The main criteria for antispasmodic drug selection was lesser side effects with better tolerability, All the groups of antispasmodics were equally efficacious in relieving thesymptoms.

References

1. Chung BI, Sommer G, Brooks JD. Anatomy of the lower urinary tract and male genitalia. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-walsh Urology. 10th ed. USA: Elsevier; 2012. p.33-70.
2. Yueng CK. Non-neuropathic dysfunction of lower urinary tract in children. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell- Walsh Urology. 10th ed. USA: Elsevier;2012.p.3411-3430..
3. Hickling DR, Sun TT, WU XR. Anatomy and physiology of the urinary tract:Relation to host defense and microbial infection. Microbiol spectr 2015;3(4):1-29.
4. Dorsher PT, Mcintosh PM. Neurogenic Bladder. Advances in Urology 2012: 1-16.
5. Yoshimura N, Chancellor MB. Physiology and the pharmacology of the bladder and urethra. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh Urology. 10th ed. USA: Elsevier; 2012. p.1786-1833.
6. Andersson K, Arner A. urinary bladder contraction and relaxation: physiology and pathophysiology. The American physiological society 2004; 84: 935-986.
7. Fowler CJ, Griffiths D, De groat WC. The neuronal control of micturition. Naturereviews neuroscience 2008;9(6): 1-28.
8. Foon R, Toozs-Hobson P. Detrusor overactivity obstetrics, gyanecology and reproductive medicine 2007;17(9):255-260.
9. Drake M, Abrams P. Overactive Bladder. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh Urology. 10th ed. USA: Elsevier;2012.p.1947-1957.
10. Ubee SS, Manikandan R, Singh G. medical management of overactive bladder. Indian journal of urology 2010;26(2):270-278.
11. Corcos J, Przydacz M, Campeau L et al.CUA guidelines on adult overactive bladder. Canadian urological association journal2017;11(5):E142-173.
12. De groat WC. A neurologic basis for the over active bladder. Urology 1997;50:36-52.
13. Jayarajan J, Radomski SB. Pharmacotherapy of overactive bladder in adults:a reviewof efficacy, tolerability, and quality of life. Research and reports in urology2014;6:1-16.
14. Bragg R, Hebel D, Vouri SM, Pilick JM. Mirabegron: A beta-3 agonist foroveractive bladder. The journal of American society of consultant pharmacist 2014;29(12):823-837.
15. Tomeszewski J. postmenopausal overactive bladder. Prz menopauzalny 2014;13(6):313-329.
16. Osman NI, Chapple CR. Overactive bladder syndrome:current pathophysiological concepts and therapeutic approaches. Arab journal of urology2013;11:313-318
17. Cartwright R, Cardozo L. Transdermal Oxybutynin; sticking to the facts. European association of urology.2007; 907-914.
18. Watanabe M, Yamanishi T, Honda M, Sakakibara R, Uchiyama T, Yoshida KI.
19. Efficacy of extended-release tolterodine for the treatment of neurogenic detrusor

overactivity and/or low compliance bladder. International Journal of Urology2010; 17:931-936.
20. Koff SA. Estimating bladder capacity in children. Urology 1983.XXI(3):248.
21. Burnstock G. Purinergic signaling in the urinary tract in health and disease.Springer2014; 10:103-155.