RESEARCH ARTICLE

Efficacy and Safety of Desmopressin with Anticholinergics in Female Patients with Overactive Bladder

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Abstract

Aims and objectives: The main aims and objectives of this study were to study efficacy, safety, and quality of life with combination anticholinergics and desmopressin compared to anticholinergics alone.

Materials and methods: A total of 92 patients were randomly assigned to two groups. Patients were randomly assigned to receive 5 mg of solifenacin (group I) or 5 mg of solifenacin and 0.2 mg of desmopressin (group II) for 1 month. The patients were followed for 2 weeks to look for undesired side effect and then at 1 month with 3-day voiding diary. IIQ-7 questionnaire score was used to assess changes in voiding symptoms and quality of life.

Results: Out of 42 in group I and 50 in group II, one patient in group I and three patients in group II did not follow and were excluded from the study. Baseline parameters between the two groups were statistically similar. Posttreatment parameters such as mean number of voids in first 8 hours decrease from 5.53 to 3.48 in group I vs 5.7 to 2.13 in group II, *p* valve <0.01. The mean number of urgency episodes in first 8 hours in group I decreased from 4.23 to 3.11 vs 4.68 to 2.29 in group II, *p* valve <0.01. The mean number of nocturnal voids in group I decreased from 3.55 to 2.48 vs 3.35 to 1.34 in group II, *p* valve <0.01. The mean IIQ-7 score in group I decreased from 51.10 to 32.8 vs 54.63 to 18.82 in group II, *p* valve <0.01. Differences were statistically significant. There was statistically insignificant change in serum sodium level posttreatment between group I and group II.

Conclusion: Combination of desmopressin and anticholinergics was more effective and safe than anticholinergics alone in the treatment of female patients with overactive bladder. Therefore, desmopressin combined with anticholinergics could be considered feasible and safe method for relief of symptoms in female patients with overactive bladder. However, larger and long-term studies for proper evaluation are warranted.

Keywords: Anticholinergics, Desmopressin, Overactive bladder, Solefenacin.

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Introduction

The International Continence Society defines overactive bladder (OAB) as symptom syndrome consisting of urinary urgency with or without urge incontinence, usually with frequency and nocturia, if there is no proven infection or other obvious pathology.[1] The finding of involuntary detrusor contractions (detrusor overactivity) during the filling phase of the micturition cycle is considered to play an important role in the pathophysiology of OAB. In females storage, lower urinary tract symptoms (LUTS) has prevalence of around 60% (EPIC Study),[2] and more than 70% of women with OAB have nocturia,[3] and around 40% experience two or more voids every night.[4]

Anticholinergic drugs are first-line drugs for the treatment of OAB; their effectiveness is around 60–70%,[5] but the main issue with these drugs are side effects, such as dry mouth, blurred vision, constipation, and dizziness that effect their compliance.[6]

Desmopressin (synthetic analog of arginine vasopressin) promotes osmotic reabsorption of solute-free water in the collecting tubules of the kidney, and by this mechanism, it decreases urine production, increases its concentration, and increases the time taken to reach functional bladder capacity, thus reducing frequency and urgency and offering symptomatic improvement.

Combination pharmacotherapy, using drugs with different mechanism of action,[7] is not used often for LUTS and number of other conditions. This study evaluates role of combination therapy of solefenacin and desmopressin for OAB.

Materials and Methods

This study was a prospective comparative randomized controlled study conducted in the Department of Gynaecology, GMC, Srinagar, Jammu and Kashmir, India, between May 2019 and April 2020.

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Conflict of interest: None

Eligible patients were females more than 18 years of age with OAB syndrome and who had four or more voids in the first 8 hours of the day excluding the first morning void and more than two nocturnal voids confirmed from successive 3-day voiding diaries completed 2 weeks apart.

Patients with treatable medical conditions leading to OAB, such as urinary tract infections, interstitial cystitis, bladder/urethra stone, diabetes insipidus, myasthenia gravis, significant pelvic organ prolapse, stress urinary incontinence, and hyponatremic patients with OAB were excluded (Tables 1 and 2).

Patients were randomly divided into two groups. Patients in group I received 5 mg of solifenacin, and patients in group II received 5 mg of solifenacin and 0.2 mg of desmopressin for 1

Table 1: Baseline line parameters of patients in two groups

Patient parameter	*Group I*	*Group II*	*p value*
No. of patients	41	47	
Age [mean with standard deviation (SD)]	55.41 ± 8.6	56.52 ± 6.7	0.507
No. of voids in first 8 hours (mean and SD)	5.53 ± 1.14	5.70 ± 0.83	0.435
No. of urgency episodes in first 8 hours (mean and SD)	4.23 ± 0.78	4.68 ± 0.99	0.832
Nocturnal voids (mean and SD)	3.55 ± 0.82	3.35 ± 0.99	0.502
Serum sodium levels (mean and SD) in mg/dL	138.9 ± 2.47	139.3 ± 2.87	0.905
IIQ-7 score (mean and SD)	51.10 ± 7.51	54.63 ± 5.96	0.712

Table 2: Posttreatment parameters of patients in two groups

Parameters	*Group I*	*Group II*	*p valve*
No. of voids in first 8 hours (mean and SD)	3.48 ± 0.6	2.13 ± 0.48	<0.01
No. of urgency episodes in first 8 hours (mean and SD)	3.11 ± 0.73	2.29 ± 0.54	<0.01
Nocturnal voids (mean and SD)	2.48 ± 0.50	1.34 ± 0.78	<0.01
Serum sodium levels (mean and SD) mg/dL	137.4 ± 2.5	135.9 ±2.11	0.092
IIQ-7 score (mean and SD)	32.80 ± 5.70	18.82 ± 4.06	<0.01

month after taking proper informed consent. Patients were advised to take the tablets at bed time. Patients were followed at 2 weeks to look for undesired side effect and then at 1 month.

Aims

The main aims of this study were to study efficacy, safety, and quality of life with combination therapy of solefenacin and desmopressin compared to solefenacin alone.

Methods

Effectiveness of combination therapy was analyzed by decrease in the average number of OAB symptoms (frequency, urgency, and nocturia) and QoL improvement compared to anticholinergics alone. Three-day voiding diary variables were analyzed for efficacy measurement. The Incontinence Impact Questionnaire (IIQ-7) was completed by patients before the start of treatment (baseline) and at 1 month, and change from baseline was assessed. IIQ-7 was given score of 0 to 100.[8] A score of 0 means that the patient was not bothered at all by a particular symptom, and a score of 100 implied the most severely bothered by a particular symptom. Safety assessments, including serum sodium monitoring and adverse event reports, were recorded at baseline and 1 month.

Data Analysis

Data were analyzed using SPSS ver. 15.0. Statistical tests like Student *t*-test, and univariate logistic regression were used for statistical analysis of results, and a p value < 0.01 was considered statistically significant.

Results

A total of 92 patients were randomly assigned to 2 groups. Group I and group II had 42 and 50 patients, respectively. One patient from group I and three patients from group II did not follow and hence were excluded from our study

Baseline Line Parameters of Patients in Two Groups

Age

The mean age of patients in group I was 55.41 with range from 28 to 70 years, while in group II, the mean age was 56.52 with range from 36 to 66 years. Difference was statistically insignificant, p value 0.507.

Number of Voids in First 8 Hours

The mean number of voids in first 8 hours in group I was 5.53 with range from 3 to 8 voids, while in group II, the mean number of voids in first 8 hours was 5.7 with range from 3 to 9. The differences were statistically insignificant, p value 0.435.

Number of Urgency Episodes in First 8 Hours

The mean number of urgency episodes in group I were 4.23, with range from 3 to 7, while in group II, the mean number of voids in first 8 hours were 4.68 with range from 3 to 6. Differences were statistically insignificant, p value 0.832.

Nocturnal Voids

The mean number of nocturnal voids in group I was 3.55 with range from 2 to 5, while in group II the mean number of nocturnal voids was 3.35 with range from 2 to 6. Differences were statistically insignificant, p value 0.502.

Serum Sodium Concentration in mg/dL

The mean serum sodium concentration in group I was 138.9 mg/dL with range from 136 to 145 mg/dL, while in group II the mean serum sodium concentration was 139.3 mg/dL with range from 135 to 144 mg/dL. The two groups were statistically similar, p value 0.905.

IIQ-7 Score

The mean IIQ-7 score in group I was 51.1 with range from 45 to 65, while in group II the mean score was 54.63 with range from 40 to 70. The two groups were statistically similar, p value 0.71.

Posttreatment Parameters of Patients in Two Groups

Number of Voids in First 8 Hours

The mean number of void in first 8 hours after receiving treatment in group I was 3.48 with range from 2 to 5, while the mean number of voids in first 8 hours in group II after receiving treatment was 2.13 with range from 1 to 3; the difference was statistically significant, p value < 0.01.

Number of Urgency Episodes in First 8 Hours

The mean number of urgency episodes in first 8 hours after receiving treatment was 3.11 with range from 2 to 4 in group I. While in group II, the mean number of urgency episodes in first 8 hours was 2.29 with range from 1 to 3. The difference was statistically significant, p value < 0.01.

Nocturnal Voids

The mean number of nocturnal voids of patients in group I was 2.48 with range from 2 to 3, while in group II the mean number of nocturnal voids was 1.34 with range from 0 to 3. The difference was statistically significant, p value < 0.01.

Serum Sodium Levels in mg/dL

The mean serum sodium levels of patients in group I was 137.4 mg/dL with range from 136 to 145 mg/dL, while serum sodium levels of patients in group II was 135.9 with range from 128 to 142 mg/dL. The difference was statistically insignificant, *p* value 0.092.

IIQ-7 Score

The mean IIQ-7 score of patients in group I after treatment was 32.8 with range from 20 to 45, while the mean IIQ-7 score of patients in group II after treatment was 18.82 with range from 15 to 30. The difference was statistically significant, p value < 0.01.

Discussion

An OAB has been defined by The International Continence Society (ICS) as the presence of "urinary urgency, usually accompanied by frequency and nocturia, may or may not be accompanied by urgency urinary incontinence (UUI), in the absence of urinary tract infection or other obvious pathology".[1] OAB syndrome is the diagnosis of exclusion and is a clinical diagnosis defined by the presence of bothersome urinary symptoms. Clinical observations in OAB have been explained by hypothetical concepts. The integrative hypothesis of OAB suggests that a range of triggers can generate localized detrusor contractions that can spread in the bladder wall through various routes of propagation. Consequently, urgency is a result of distortions in the bladder wall, and it is associated with urodynamic DO if the contractions spread to a sufficient proportion of the bladder wall.[9]

After the diagnosis and baseline severity of OAB have been evaluated, initial treatment can be instigated according to the patient's desire for treatment because "cure" is not possible in most of the patients, and the condition is generally progressive. First-line treatment is to use conservative management such as lifestyle modification pelvic floor exercise and bladder training**.** If the patient does not respond to conservative treatment, oral pharmacotherapy is added to conservative treatment. Anticholinergics are the drugs of choice for medical therapy of OAB, but problem with anticholinergic medication is compliance as they are associated with side effects, including dry mouth, constipation, and blurred vision. Desmopressin by promoting osmotic reabsorption of solute-free water in the collecting tubules of the kidney decreases urine production and increases its concentration; hence, it will increase the time taken to reach functional bladder capacity between micturitions, thereby reducing symptoms in OAB and improving symptomatic profile of patient.[10] Combination of anticholinergics with desmopressin has been found in many studies to be more effective than anticholinergics alone.[11] This study was done to assess the efficacy and safety values of combination therapy compared to monotherapy in our setting.

In our study, mean age of patients in group I was 55.41 and in group II 56.52 years.

Han, et al.[11] reported in their study that mean age of patients with OAB was 54.2 $\pm$ 7.3, which corresponds with our study too.

Stewart et al.[12] reported the prevalence of "OAB wet" increases with age from 2.0% in the younger age-group (ages 18–24) to 19.1% older population (ages 65–74).

Effectiveness of treatment was calculated by statistically significant decrease in number of voids in first 8 hours of day, number of urgency episodes in first 8 hours, nocturnal voids as calculated by voiding diary, and IIQ-7 SCORE. We have found statistically significant decrease in all these parameters with combination of anticholinergics with desmopressin compared to anticholinergics alone.

Han et al.[11] reported statistically significant improvement in frequency, urgency episodes, and IIQ-7 score with combination therapy compared to anticholinergics alone.

Rovner et al.[13] reported in their study that combination therapy was similar statistically to monotherapy in reducing nocturia in the overall patient population, but subgroup analyzes confirmed significant clinical benefits of combination therapy in patients with predominantly nocturnal polyurea.

Sand et al.[14] reported desmopressin as a well-tolerated and effective treatment for women with nocturia, and it provides quick and sustainable improvement in nocturia and quality of life.

Safety of treatment was assessed with decrease in sodium concentration (hyponatremia) with combination therapy compared to monotherapy. We do not find statistically significant difference in mean serum sodium levels with combination therapy compared to monotherapy. Two patients developed biochemical evidence of hyponatremia (asymptomatic) at 1 month which was managed conservatively by free water restriction and dietary modification.

Rembratt et al.[15] reported that desmopressin was well tolerated by most of patients with nocturia without clinically significant hyponatremia. But the risk of hyponatremia increases with increasing age and low baseline serum sodium concentration.

Vande Walle et al.[16] reviewed various studies regarding safety of desmopressin. Based on these findings, it was found that desmopressin is safe and has minor side effects with oral and intranasal formulations.

Conclusion

We conclude that combination of desmopressin with anticholinergics was more effective and safe than anticholinergics alone in the treatment of female patients with OAB. Therefore, we recommend desmopressin combined with anticholinergics could be considered for relief of symptoms in female patients with OAB. However, larger and long-term studies for proper evaluation are warranted.

References

1. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function; report from standardisation sub-committee of international continence society. Neurol Urodynam 2002;21(2):167–178. DOI: 10.1002/nau.10052.
2. Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol 2006;50(6):1306–1314. DOI: 10.1016/j.eururo.2006.09.019discussion 1306-1314.
3. Jeong JY, Kim SJ, Cho HJ, et al. Influence of type of nocturia and lower urinary tract symptoms on therapeutic outcome in women treated with desmopressin. Korean J Urol 2013;54(2):95–99. DOI: 10.4111/kju.2013.54.2.95.
4. Bosch JL, Weiss JP. The prevalence and causes of nocturia. J Urol 2010;184(2):440–446. DOI: 10.1016/j.juro.2010.04.011.
5. Lee KS, Lee YS. Overactive bladder. Korean J Urol 2007;48(12):1191–1208. DOI: 10.4111/kju.2007.48.12.1191.
6. Kelleher CJ, Cardozo LD, Khullar V, et al. A medium-term analysis of the subjective efficacy of treatment for women with detrusor instability and low bladder compliance. Br J Obstet Gynaecol 1997;104(9):988–993. DOI: 10.1111/j.1471-0528.1997.tb12054.x.
7. Abrams P, Kelleher C, Staskin D, et al. Combination treatment with mirabegron and solifenacin in patients with overactive bladder: exploratory responder analyses of efficacy and evaluation of patient-

reported outcomes from a randomized, double-blind, factorial, dose-ranging, phase II study (SYMPHONY). World J Urol 2017;35(5):827–838. DOI: 10.1007/s00345-016-1908-1.
8. Uebersax JS, Wyman JF, Shumaker SA, et al. Short forms to assess life quality and symptom distress for urinary incontinence in women: the incontinence impact questionnaire and the urogenital distress inventory. Contine Prog Women Res Group Neurou Urodyn 1995;14(2):131–139. DOI: 10.1002/nau.1930140206.
9. Drake M, Mills I, Gillespie J, et al. Model of peripheral autonomous modules and a myovesical plexus in normal and overactiver bladder. Lancet 2001;358(9279):401–403. DOI: 10.1016/S0140-6736(01)05549-0.
10. Hashim H, Malmberg L, Graugaard-Jensen C, et al. Desmopressin, as a "designer-drug," in the treatment of overactive bladder syndrome. Neurourol Urodyn 2009;28(1):40–46. DOI: 10.1002/nau.20613.
11. Han YK, Lee WK, Lee SH, et al. Effect of desmopressin with anticholinergics in female patients with overactive bladde. Korean J Urol 2011;52(6):396–400. DOI: 10.4111/kju.2011.52.6.396.
12. Stewart W, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in united states. World J Urol 2003;20(6):327–336. DOI: 10.1007/s00345-002-0301-4.
13. Rovner ES, Raymond K, Andruczyk E, et al. Low-dose desmopressin and tolterodine combination therapy for treating nocturia in women with overactive bladder: a double-blind, randomized, controlled study. Low Urin Tract Symptoms 2017;10(3):221–230. DOI: 10.1111/luts.12169.
14. Sand PK, Dmochowski RR, Reddy J, et al. Efficacy and safety of low dose desmopressin orally disintegrating tablet in womwn with nocturea: results of a multicenter, randomized, double-blind, placebo controlled, parallel group study. J Urol 2013;190(3):958–964. DOI: 10.1016/j.juro.2013.02.037.
15. Rembratt A, Riis A, Norgaard JP. Desmopressin treatment in nocturia; an analysis of risk factors for hyponatremia. Neurourol Urodyn 2006;25(2):105–109. DOI: 10.1002/nau.20168.
16. Vande Walle J, Stockner M, Raes A, et al. Desmopressin 30 years in clinical use: a safety review. Curr Drug Saf 2007;2(3):232–238. DOI: 10.2174/157488607781668891.