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# Comparative assessment of the efficacy of onabotulinumtoxinA as monotherapy and combined therapy with propiverine in female refractory overactive-bladder syndrome

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ORIGINAL STUDY

# Comparative assessment of the efficacy of onabotulinumtoxinA as monotherapy and combined therapy with propiverine in female refractory overactive-bladder syndrome

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**Abstract**

*Objectives*: **The aim of the study was to compare the efficacy of onabotulinumtoxinA and anticholinergic popeverine in adult females. This is a placebo-controlled study.**

*Introduction*: **The active ingredient, propiverine hydrochloride, blocks muscarinic receptors with a slightly higher affinity for the $M_3$ as compared with the $M_2$ subtype. In addition, it inhibits calcium influx and modulates intracellular calcium in the bladder smooth-muscle cells, which then leads to musculotropic spasmolysis.**

*Patients and methods*: **Between 2015 and 2019, 94 patients received intravesical onabotulinumtoxinA for the treatment of refractory idiopathic detrusor overactivity after its introduction into the Department of Urology of our National Institute of Urology and Nephrology. Of these patients, 37 had more than 4 years of follow-up. Intravesical injection of 200 U of onabotulinumtoxinA (Botox, Allergan, Irvine, California, USA) from August 2015 to June 2019. All patients received Botox injections. The intravesical injections of Botox were performed at 30 different sites of the bladder wall, excluding the trigone. The patients were randomly classified into three groups. Group one received onabotulinumtoxinA only, and group two received onabotulinumtoxinA and propiverine hydrochloride; group three received onabotulinumtoxinA and placebo. Eighty-nine patients completed the study.**

*Results*: **In our study, the decreased urgency-incontinence episodes per 24 h in the GII were significantly greater than in GI and GIII ($P < 0.00001$). The average decrease in the number of urgency-incontinence episodes per 24 h in GI was from 2.57 to 1, in GII from 3.12 to 0.55, and in GIII from 3.42 to 1.28. The average Urgency score decreased from 2.69 to 1.78. Also, the decrease in average Urgency score was from 2.64 to 1.93 when propiverine in GII was added and from 2.31 to 1.91 when placebo was added in GIII. The average cystometric capacity was increased from 240.43 to 329 ml in GI, from 252.64 to 351.83 in GII, and from 231.2 to 317.4 ml in GIII.**

*Conclusion*: **OnabotulinumtoxinA combined therapy with propiverine in female refractory overactive-bladder syndrome is considered as one of the options for a third-line treatment even if the efficacy of onabotulinumtoxinA is insufficient.**

*Keywords:* Detrusor overactivity, OnabotulinumtoxinA, Overactive bladder, Propiverine, Urgency incontinence, Urgency

## 1. Objectives

The aim of this study was to compare the efficacy of onabotulinumtoxinA and anticholinergic popeverine in adult females.

## 2. Introduction

Overactive bladder (OAB) is a deficiency in bladder storage. According to the International Continence Society, it is defined as 'urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology' [1]. OAB varies in the degree of severity and may progress; in many patients, the symptoms can be bothersome and have a negative impact on quality of life (QOL) [2]. In population-based studies, OAB prevalence rates range from 9 to 43% in women in the United States [3–7].

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Female gender, young age, and the presence of OAB-wet were associated with the success in univariate analysis. However, female gender was the only independent factor associated with the success [8]. Several treatment options are available, including bladder and behavioral training, pharmacological treatment, onabotulinumtoxinA, neuromodulation (sacral-nerve stimulation, percutaneous tibial-nerve stimulation), and surgical therapies. Antimuscarinic agents are the second-line treatment and have a more than 70% of success rate. Urothelial dysfunction and abnormalities of sensory-receptor expression or transmitter release in the suburothelial nerves may contribute to OAB, which is refractory to antimuscarinics [9,10].

Since OAB is a symptom-based diagnosis, the QOL impact of the symptoms is a critical aspect of the condition. The degree of bother caused by OAB symptoms directly affects OAB care-seeking, treatment intensity, and satisfaction with treatment.

Second-line treatment with oral or transdermal antimuscarinics or β3-adrenoceptor agonists is not invasive and presents the risk of side effects that primarily compromise QOL. One of the presently prescribed drugs for OAB treatment is propiverine. The active ingredient, propiverine hydrochloride, blocks muscarinic receptors with a slightly higher affinity for the $M_3$ as compared with the $M_2$ subtype. In addition, it inhibits calcium influx and modulates intracellular calcium in the bladder smooth-muscle cells, which then leads to musculotropic spasmolysis. Also, propiverine adding a1-adrenoceptor antagonist was more effective in terms of decreasing difficulty in voiding [11]. Propiverine is unique in having both anticholinergic and calcium-channel-blocking effects [12]. The former effects are known to suppress neurogenic detrusor contraction, while the latter have a direct spasmolytic effect on the bladder, even if the importance of the calcium-antagonistic component for the drug's clinical effects has not been established. Propiverine has no selectivity for muscarinic-receptor subtypes [13]. The efficacy of propiverine appeared more rapidly in women than in men by an unknown mechanism [14].

Propiverine was effective for urgency, frequency, and urgency incontinence, suggesting that it contributes to improving overall OAB symptoms, especially by improving urgency and urgency-incontinence episodes; propiverine may have improved the daily living activities impaired by OAB [15]. However, the ability of propiverine to improve nocturia and the risk of urinary retention remain controversial [16]. Some research reported that patients with previous histories of poor antimuscarinic efficacy had less therapeutic efficacy [17].

Third-line treatment with intradetrusor onabotulinumtoxinA is invasive and presents risks for infection as well as increased post void residual (PVR) and the potential need for self-catheterization, which is not quickly reversible. Unlikely to propiverine, the successful rate of onabotulinumtoxinA injection for OAB ranged from 60% to 80% based on the change on urodynamic parameters or QOL assessment [18,19]. Although this success rate of onabotulinumtoxinA injection for patients with OAB, the improvement in incontinence episodes is 22.9% of treated patients [20].

The goal of the present study was to evaluate the safety and efficacy of onabotulinumtoxinA and propiverine in treating OAB switching from second-line medications, which may resolve some of the current controversies, overuse of these medications in the management of OAB, and urge incontinence. The secondary aims were an overview on their tolerability, safety, and health-related QOL.

## 3. Patients and methods

Between 2015 and 2019, 94 patients received intravesical onabotulinumtoxinA for the treatment of refractory idiopathic detrusor overactivity with or without the addition of propiverine medication after its introduction into the Department of Urology of our National Institute of Urology and Nephrology. Of these patients, 37 had >4 years of follow-up. Intravesical injection of 200 U of onabotulinumtoxinA (Botox, Allergan, Irvine, California, USA) from August 2015 to June 2019. All patients received Botox injection. The intravesical injections of Botox were performed at 30 different sites of the bladder wall, excluding the trigone. The patients were randomly classified into three groups. Group I received onabotulinumtoxinA only, group II received onabotulinumtoxinA and propiverine hydrochloride, and group III received onabotulinumtoxinA and placebo. Eighty-nine patients completed the study.

Thus, 89 patients with 42 months of follow-up were available for evaluation. All patients were resistant to or intolerant of oral antimuscarinic therapy and/or adrenergic β3 agonists for at least 6 months. Detrusor overactivity had been confirmed by urodynamic studies, which was done for all patients.

Eligibility criteria included patients 18 years old and more with refractory OAB symptoms of urgency, frequency, nocturia, and urgency urinary incontinence for at least 6 months with no response

to first- and second-line treatment. Exclusion criteria included polydipsia, nocturnal polyuria, interstitial cystitis/bladder-pain syndrome and narrow-angle glaucoma, impaired gastric emptying, a history of urinary retention, tachyarrhythmias, moderate-to-severe hepatic impairment, and individuals with symptoms related to neurologic conditions. Also, we exclude current use of an indwelling catheter or clean intermittent catheterization, patients with evidence of bladder-outlet obstruction, and impaired bladder compliance.

A careful history, physical exam, and urinalysis were done for every patient. All patients were advised to continue the 1st-line treatment. First-line treatment for OAB is most commonly behavioral modifications or simply educating patients to be more strategic with regard to their fluid-intake habits. We recommend that patients try to moderate their fluids to no more than 4−6 ounces of fluid per hour and limit themselves to no more than one caffeinated beverage per day. In addition, we ask those patients to stop drinking fluids at least 2−3 h prior to bedtime, with the exception of a sip of fluid with medications as needed. In our patients, we followed International Urogynecological Association/International Continence Society joint report [21].

In injection techniques, our team uses onabotulinumtoxinA, which is a 900-kD albumin protein, by Allergan Pharmaceuticals. A rigid 21-French injection cystourethroscopy (Karl Storz, Germany) was utilized with injection 25-gag needle (5.0 Fr./35 cm, tip length 4 mm). We considered that 200 U was reconstituted with 0.9% normal saline to a dosage of 10 units/ml. The BoNT/A was injected into intradetrusor muscle supratrigonally in aliquots of 1 ml, delivering ten units at each injection site, creating a 'wheal' under the bladder mucosa, and demonstrating successful success of submucosal injection. In our practice, a rigid cystoscope with an injectable setup is utilized. Injections are generally started in the midline just above the interureteric ridge and then, moving to the right, and injections are performed at 0.5-cm intervals to the level of the bladder sidewall and then back to the midline at the site of the initial injection, now moving to the left. Once the initial row is completed, the surgeon moves upward 0.5−1 cm and starts another row left and right. A total of anywhere from 20 injections may be performed.

Consistently, in our practice, patients taking anticholinergic medications are asked to stay on their current regimen for 5 days post treatment before discontinuing these drugs. Subjective symptoms and objective findings were assessed by the OABSS, Urgency Severity Scale questionnaire, bladder diary, micturition volume per micturition, incontinence episodes per 24, and International Consultation on Incontinence Questionnaire-urinary incontinence the short form. Also, all patients were assessed urodynamically for PVR urine, cystometric capacity, detrusor contractions, and intravesical pressure. Ultrasound examination was also utilized to evaluate PVR urine. About 15 mg of immediate-release propiverine twice daily was used as antimuscarinic with botox injection in the GII group. Nonblinded placebo twice daily was used with botox injection in the GIII group. Those in the placebo group were given two placebo pills that contained 500 mg of proprietary-food phytomaterial.

### 3.1. Statistical methods

Standard computer program SPSS for Windows, release 13.0 (SPSS Inc., USA), was used for data entry and analysis. All numeric variables were expressed as mean ± standard deviation (SD), or median and interquartile range. The relationship between categorical variables was done by Mann−Whitney test for nonparametric variables.

Wilcoxon signed-rank tests were used to compare multiple readings of the same variables. $\chi^2$ test was used to compare the frequency of qualitative variables among the different groups. For all tests, including Mann−Whitney $U$ test, a probability ($P$) less than 0.05 ($P < 0.05$) was considered significant.

## 4. Results

Recently, in August 2011, Food and Drug Administration-approved Botox for the treatment of NDO, specifically 'urinary incontinence due to detrusor overactivity associated with a neurological disease and refractory to oral medication' [22]. In total, 89 patients continue the study. Three patients discontinued the medication, and two patients did not continue the study. The median age of 89 patients was 53, 52, and 94.3 years in group I, group II, and III, respectively. No significant difference was observed in age (mean ± standard deviation) between the three groups. Regarding the mean age, distribution in group I was 48.26, in group II was 46, and in group III was 49 years (95% confidence) (Mann−Whitney $U$).

Median-day frequency was 9,11 and 11 in group I, group II, and group III at the start of the study and changed to 5,6 and 6 (95% confidence) (Mann−Whitney $U = 323.5$). There was no significant change in day frequency pre- and postoperative in three groups (Sig = 0.204). Forty five (65%) had

*Table 1. Comparison of preoperative and postoperative day frequency in the three groups.*

| Frequency | Preoperative | | | Postoperative | | |
|---|---|---|---|---|---|---|
| | GI | GII | GIII | GI | GII | GIII |
| Median | 9 | 11 | 11 | 5 | 6 | 6 |
| Interquartile range (IQR) | 5 | 5 | 5 | 1 | 7 | 4 |
| Mann–Whitney *U* | 342 | | | 285 | | |
| Asymp. Sig. (2-tailed) | 0.799 not significant | | | 0.204 not significant | | |

frequency more than seven times per day 18/23 in GI (78%), 23/31 in GII (74%), and 28/35 (80%) in GIII. In 48 months, follow-up revealed that 6 cases had frequency eight times or more per day in GI (26%), 12/31 cases in GII, and 11 in GIII, the day frequency more than seven times per day was significant (95% confidence) (Mann–Whitney $U = 322$) (Sig = 0.024) (Table 1).

Mean nocturia was 2.6, 2.8, and 2.2 in GI, GII, and GIII as basic, but it changed post management to 2.4, 2.8, and 2.3 (Mann–Whitney $U = 317.5$). Mean micturition number was 12.7, 13.3, and 12.6 in group I, group II, and group III as basic, but it changed post management to 8.1, 10, and 8.7 (Mann–Whitney $U = 320$). The mean urgency score was 2.7, 2.6, and 2.5 in group I, group II, and group III as basic, but it changed post management to 1.7, 1.9, and 2.1 (Mann–Whitney $U = 347$). Mean incontinence episodes were 2.5, 3.1, and 3.4 in group I, group II, and group III as basic, but they changed post management to 1, 0.5, and 1.2 (Mann–Whitney $U = 23.5$). Mean cystometric capacity was 240.4, 252.6, and 231.2 ml in group I, group II, and group III as basic, but it changed post management to 329, 351.8, and 317.4 ml, respectively (Mann–Whitney $U = 253.5$). Mean preoperative detrusor-contraction number was 4, 3.1, and 3 in group I, group II, and group III as basic, but it changed post management to 2.7, 1.35, and 2.66, respectively (Mann–Whitney $U = 214$).

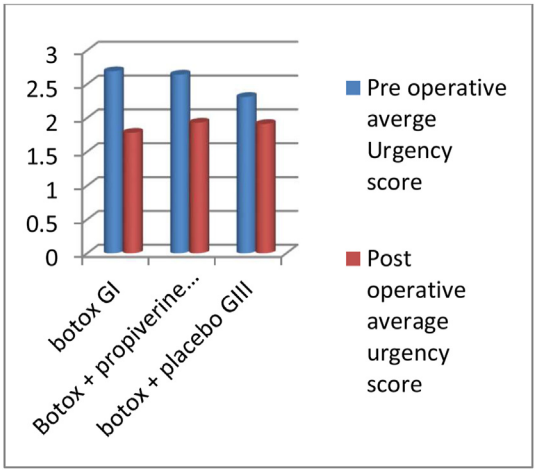


*Fig. 1. Distribution of preoperative and postoperative urgency score in the three groups.*

Urgency-incontinence episodes occurred preoperatively in 7 patients in GI (18 episodes/week), in 6 patients of GII (25 episodes/week), and seven patients in GIII (24 episodes/week). Postoperative follow-up revealed that episodes occurred in 7 patients in GI (7 episodes/week), in 8 patients of GII (5 episodes/week), and seven patients in GIII (9 episodes/week). No significant change occurred in episodes in relation to the number of patients ($P = 0.527$) (Table 2) and a change of $P$ from 0.613 to 0.189 in Table 3 (Fig. 1).

There were significant changes in postoperative urgency-incontinence episodes between GI and GII where the marked improvement occurred in GII ($P = 0.032$) (Tables 3 and 4).

There was no significant change in postoperative urgency-incontinence episodes between GI and GIII (Fig. 2).

There was a significant change in postoperative urgency-incontinence episodes between GII and GIII, where the marked improvement occurred in

*Table 2. Change in average urgency score.*

| | Botox GI | Botox + propiverine GII | Botox + placebo GIII |
|---|---|---|---|
| Preoperative average urgency score | 2.69 | 2.64 | 2.31 |
| Postoperative average urgency score | 1.78 | 1.93 | 1.91 |
| Significance | $P = 0.527$ (not sig.) | | |

*Table 3. Comparison of urgency-incontinence episode cases in ranks of GI and GII.*

| | GI 23 | | GII 31 | | Total number in | | Sig. | Sig. |
|---|---|---|---|---|---|---|---|---|
| | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| Patients with episodes | 7 | 6 | 8 | 5 | 13 | 13 | 0.613 Not sig. | 0.189 Not sig. |
| No. of episodes | 18 | 7 | 25 | 5 | 43 | 12 | 0.452 Not sig. | 0.032 sig. |

Post, postoperative; Pre, preoperative.

*Table 4. Comparison of urgency-incontinence episode cases in ranks of GI and GIII.*

| | GI 23 | | GIII 35 | | Total no. in both groups | | Sig. | Sig. |
|---|---|---|---|---|---|---|---|---|
| | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| With episodes | 7 | 6 | 7 | 6 | 13 | 13 | 0.259 (not sig.) | 0.456 (not sig.) |
| No episodes | 18 | 7 | 25 | 9 | 43 | 13 | 0.154 (not significant) | 0.127 (not significant) |

Post, postoperative; Pre, preoperative.

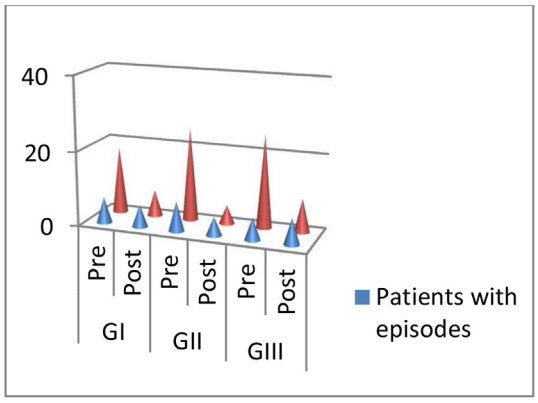


*Fig. 2. Distribution of the preoperative and postoperative number of incontinence episodes.*

GII ($P = 0.041$) (Table 5). Urgency-incontinence episodes' variable study revealed that there were no significant changes in episodes in comparison with other variables in three groups postoperatively (Mann–Whitney Exact Sig. = 0.189).

The median micturition number is significantly decreased ($P = 0.036$) in GII (botox injection with propiverive) than GI (botox injection) (Table 6). Also, there was a slight decrease in micturition number between GII and GIII, which was insignificant ($P = 0.132$).

Also, the median post-treatment detrusor-contraction number is significantly decreased ($P = 0.002$) in GIII (Botox injection with propiverine) than GI (Botox injection) (Table 7).

Although the median post-treatment detrusor-contraction number is significantly decreased ($P = 0.002$) in GIII (Botox injection) than GI (Botox injection), there was significant variation between them in the pretreatment stage ($P = 0.004$) (Table 7).

No significant changes in other variables such as Urgency score median and urgency-incontinence episodes were noticed.

Comparison of all variables in the pretreatment stage showed no significant changes, but there were significant changes in post-treatment median detrusor-contraction number ($P = 0.05$), cystometric capacity ($P = 0$), and urgency-incontinence episodes ($P = 0.046$) (Table 8).

Wilcoxon Signed Rank Test preoperative and postoperative variables in GII.

Wilcoxon Signed Rank Test GII (Table 9) revealed significant changes in pre- and postoperative variables, including frequency ($P = 000$), micturition

*Table 5. Comparison of urgency-incontinence episode cases in ranks of GII and GIII.*

| | GII 31 | | GIII 35 | | Total number in both groups | | Sig. | Sig. |
|---|---|---|---|---|---|---|---|---|
| | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| Patients with episodes | 8 | 5 | 6 | 7 | 14 | 12 | 0.259 (not sig. | 0.456 (not sig. |
| Number of episodes | 25 | 5 | 25 | 9 | 30 | 14 | 0.326 (not sig.) | 0.041 (sig.) |

Post, postoperative; Pre, preoperative.

*Table 6. Comparison of variables in GI and GII.*

| Parameters | Pretreatment | | *P* value | Posttreatment | | *P* value |
|---|---|---|---|---|---|---|
| | GI | GII | | GI | GII | |
| Frequency, median (IQR) | 9.00 (5) | 11.00 (5) | 0.799 | 5.00 (1) | 6.00 (7) | 0.204 |
| Nocturia, median (IQR) | 2.00 (3) | 3.00 (2) | 0.486 | 2.00 (2) | 3.00 (2) | 0.232 |
| Micturition number, median (IQR) | 11.00 (7) | 13.00 (6) | 0.521 | 8.00 (4) | 10.00 (4) | 0.036 |
| Urgency score, median (IQR) | 3.00 (2) | 3.00 (2) | 0.863 | 2.00 (1) | 2.00 (2) | 0.527 |
| Urgency-incontinence episodes, median (IQR) | 3.00 (1) | 3.00 (4) | 0.587 | 1 | 0.50 (1) | 0.109 |
| Cystometric capacity, median (IQR) | 237.00 (41) | 326.00 (42) | 0.071 | 237.00 (41) | 367.00 (60) | 0.005 |
| Detrusor contraction number, median (IQR) | 4.00 (5) | 3.00 (5) | 0.011 | 3.00 (1) | 1.00 (1) | 0 |
| PVR, median (IQR) | 12.00 (6) | 13.00 (5) | 0.062 | 7.00 (2) | 10.00 (8) | 0.015 |

PVR, post void residual.

*Table 7. Comparison of variables in GI and GIII ranks.*

| Parameters | Pretreatment | | *P* value | Posttreatment | | *P* value |
|---|---|---|---|---|---|---|
| | GI | GIII | | GI | GIII | |
| Frequency, median (IQR) | 9.00 (5) | 11.00 (5) | 0.786 | 5.00 (1) | 6.00 (4) | 0.097 |
| Nocturia, median (IQR) | 2.00 (3) | 2.00 (5) | 0.714 | 2.00 (2) | 2.00 (1) | 0.659 |
| Micturition number, median (IQR) | 11.00 (7) | 13.00 (6) | 0.835 | 8.00 (4) | 9.00 (4) | 0.287 |
| Urgency score, median (IQR) | 3.00 (2) | 3.00 (3) | 0.575 | 2.00 (1) | 2.00 (2) | 0.202 |
| Urgency incontinence episodes, median (IQR) | 3.00 (1) | 3.00 (3) | 0.195 | 1 | 1.00 (1) | 0.389 |
| Cystometric capacity, mean (SD) | 237.00 (41) | 254.00 (101) | 0.880 | 237.00 (41) | 324.00 (69) | 0.404 |
| Detrusor contraction number, median (IQR) | 4.00 (5) | 3.00 (35) | 0.004 | 3.00 (2) | 2.00 (1) | 0.002 |
| PVR urine, median (IQR) | 12.00 (6) | 14.00 (5) | 0.025 | 7.00 (2) | 6.00 (3) | 0.142 |

PVR, post void residual.

*Table 8. Comparison of variables in GII and GIII ranks.*

| Parameters | Pretreatment | | *P* value | Posttreatment | | *P* value |
|---|---|---|---|---|---|---|
| | GII | GIII | | GII | GIII | |
| Frequency, median (IQR) | 11.00 (5) | 11.00 (5) | 0.959 | 6.00 (7) | 6.00 (4) | 0.609 |
| Nocturia, median (IQR) | 3.00 (2) | 2.00 (5) | 0.143 | 3.00 (2) | 2.00 (1) | 0.219 |
| Micturition number, median (IQR) | 13.00 (6) | 13.00 (6) | 0.623 | 10.00 (4) | 9.00 (4) | 0.132 |
| Urgency score, median (IQR) | 3.00 (2) | 3.00 (3) | 0.660 | 2.00 (2) | 2.00 (2) | 0.514 |
| Urgency incontinence episodes, median (IQR) | 3.00 (4) | 3.00 (3) | 0.680 | 0.50 (1) | 1.00 (1) | 0.046 |
| Cystometric capacity, mean (SD) | 326.00 (42) | 254.00 (101) | 0.102 | 367.00 (60) | 324.00 (69) | 0 |
| Detrusor contraction number, median (IQR) | 3.00 (5) | 3.00 (35) | 0.879 | 1.00 (1) | 2.00 (1) | 0.051 |
| PVR urine, median (IQR) | 13.00 (5) | 14.00 (5) | 0.072 | 10.00 (8) | 6.00 (3) | 0.254 |

PVR, post void residual.

*Table 9. Wilcoxon signed-rank test preoperative and postoperative variables in GII rank.*

| | Frequency after | Nocturia after | Micturition no. after | Urgscr score after | Incont. epi after | Capacity after | Continent patient no. after |
|---|---|---|---|---|---|---|---|
| | Frequency before | Nocturia before | Micturition no. before | Urgscr score before | Incont. epi before | Capacity after Capacity before | Continent patient no. before |
| Sig. | 0[a] | 0.705[a] | 0.000[a] | 0[a] | 0.018[a] | 0[b] | 0[a] |

[a] Based on positive ranks.
[b] Based on negative ranks.

number ($P = 000$), Urgency score ($P = 000$), cystometric capacity ($P = 000$), PVR urine ($P = 000$), detrusor-contraction number ($P = 000$), and NE ($P = 000$).

Wilcoxon Signed Rank Test GII revealed no significant changes in pre- and postoperative variables, including nocturia ($P = 0.705$) and urgency-incontinence episodes ($P = 0.018$) (Tables 10 and 11).

*Table 10. Wilcoxon signed-rank test preoperative and postoperative placebo rank.*

| | freqA–freqB | NocturiaA–nocturiaB | MicturitionA–micturitionB | UrgscrA–urgscrB | IncontepiA–incontepiB | CapacityA–capacityB | ContrnumbA–contrnumbB |
|---|---|---|---|---|---|---|---|
| Sig. | 0[a] | 0.257[a] | 0[a] | 0[a] | 0.017[a] | 0[b] | 0[a] |

[a] Based on positive ranks.
[b] Based on negative ranks.

*Table 11. Nocturnal enuresis cross-tabulation of placebo variables.*

| | GI | GII | GIII | Total | GI | GII | GIII | Total |
|---|---|---|---|---|---|---|---|---|
| Not present | 16 (69.6%) | 25 (80.6%) | 28 (80.0%) | 69 (77.5%) | 21 (91.3%) | 30 (96.8%) | 30 (85.7%) | 81 (74.4%) |
| Present (% within NE group) | 7 (30.4%) | 6 (19.4%) | 7 (20.0%) | 20 (22.5%) | 2 (8.7%) | 1 (3.2%) | 5 (14.3%) | 8 (25.6%) |
| Total | 23 | 31 | 35 | 89 | 23 | 31 | 35 | 89 |
| $\chi^2$ | 0.568 | | | | 0.292 | | | |

NE, nocturnal enuresis.

Nocturnal enuresis was preoperatively present in 30.4%, 19.4%, and 22.5% in GI, GII, and GII, respectively, in the pretreatment period. Fortunately, there was no significant variation in cross-tabulation of placebo ranks ($P = 0.568$). A decrease in the number of nocturia was also insignificant postoperatively in three groups of placebo ranks where it became 8.7, 3.2, and 14.3% ($P = 0.292$). A decrease in the number of nocturia was also insignificant in post treatment in GII ranks, where 19.4% of nocturia cases became 3.2% ($P = 0.630$). A decrease in the number of nocturia was also insignificant in post treatment in GI ranks, where 30.4% of nocturia cases became 8.7% ($P = 0.630$).

## 5. Discussion

In our research, the median incontinence episodes were insignificantly decreased from 3 to 1 in GI and GIII, respectively. McCammon et al. [23] concluded that there were significant reductions from baseline in UI episodes/day, frequency, nocturia, and micturition number with onabotulinumtoxinA versus placebo at week 12. The decrease of nocturia when treated with botox injection and oral propiverine ($P < 0.0001$, the average decrease was from 2.83 to 1.8) indicated that propiverine spasmolytic properties to detrusor muscle in the presence of Botox were more effective in decreasing the nocturia. Aldrich and Pauls [24] in follow-up of botox injection found that median PVR was 90 ml (min, max: 0, 750 ml), 13 patients required initiation of clean intermittent catheterization (6.3%), 60% ($n = 133$) of the patients did not require intermittent self-catheterization, and 59% reported postoperative urgency.

Our research found that median PVR was 12 and decreased to 7 in GI, 1 (4%) of GI group needed clean intermittent catheterization. We found a significant decrease in urgency score in GI, GII, and GIII, where the Wilcoxon Signed Rank Test was $P = 0$ in pretreatment and post treatment of the three groups. Hsiao et al. [8] concluded that the female gender was the only independent factor associated with the success.

Incontinence Impact scores were significantly lower for onabotulinumtoxinA-treated versus placebo-treated patients at weeks 2−12.

### 5.1. Conclusion

OnabotulinumtoxinA combined therapy with propiverine in female refractory OAB syndrome is considered as one of the options for a third-line treatment even if the efficacy of onabotulinumtoxinA is insufficient.

## Conflicts of interest

There are no conflicts of interest.

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