



Evaluation of transurethral GreenLight laser-selective vaporization for refractory overactive bladder in women

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Background: Refractory overactive bladder (OAB) in women is a common yet challenging condition for which traditional treatments have been unsatisfactory. This study aimed to evaluate the efficacy and safety of transurethral bladder mucosal GreenLight laser-selective vaporization for treating refractory OAB in women.

Methods: The female patients with refractory OAB who were admitted to the Department of Urology, Shandong Provincial Hospital Affiliated to Shandong First Medical University between May 2022 and July 2023 were examined retrospectively in this study. Transurethral bladder mucosal GreenLight laser-selective vaporization was used to treat the patients, and the perioperative and postoperative parameters were reviewed and compared. Bladder mucosa was examined by immunohistochemical staining to explore the expressions of TRPV1, P2X3, tumor necrosis factor alpha (TNF- α), and interleukin 6 (IL-6) before and after treatments.

Results: Surgeries were performed successfully for all 32 patients in 57.38 \pm 11.22 minutes with minimal intraoperative bleeding. Twelve weeks post-surgery, there was a significant decrease ($P<0.05$) in the patients' Overactive Bladder Symptom Score (OABSS), 3-day bladder diary (daytime frequency, nocturia, urgency, and urgency incontinence), and Overactive Bladder questionnaire Short Form (OAB-qSF) score. After treatments, both first desire to void (FDV) and maximum bladder pressure capacity (MCBC) increased significantly ($P<0.05$). The immunohistochemical analysis revealed that the GreenLight laser significantly reduced the expressions of TRPV1, P2X3, TNF- α , and IL-6 in the bladder mucosa ($P<0.05$). No severe complications were observed after interventions.

Conclusions: For female patients with refractory OAB who have shown poor response to conventional treatment approaches, transurethral bladder mucosal GreenLight laser-selective vaporization may represent a promising alternative treatment option.

Keywords: Refractory overactive bladder (OAB); GreenLight laser; bladder mucosa; Overactive Bladder Symptom Score (OABSS)

Submitted Feb 01, 2024. Accepted for publication May 16, 2024. Published online Jul 15, 2024.

doi: 10.21037/tau-24-67

View this article at: <https://dx.doi.org/10.21037/tau-24-67>

Introduction

Overactive bladder (OAB) is defined as the presence of increased nocturia, frequency, and urgency in the urine, with or without urinary acute incontinence, and urodynamics that may be characterized by detrusor of bladder hyperactivity, provided that a urinary tract infection or other obvious pathology is ruled out (1). Several studies (2,3) have reported that OAB prevalence is 16.9–17.4% in women. Nowadays, anticholinergic medications such as tolterodine and solifenacin, as well as behavioral therapies like bladder training, constitute the primary clinical treatments for OAB (4). While pharmaceutical treatments are generally effective, several side effects and patient compliance issues prevent a subset of patients from receiving ongoing treatment (5).

Refractory OAB is defined as inadequate symptomatic remission after an extended behavioral training regimen or failure after 6–12 weeks of anticholinergic drug treatment (including the onset of intolerable side effects or insufficient symptomatic remission) (6). For some patients with refractory OAB, intramural bladder injections of botulinum toxin type A (BoNTA), sacral neuromodulation (SNM), and percutaneous tibial nerve stimulation (PTNS) may be beneficial (7). However, the efficacy of these treatments is not definitive, and the symptoms of OAB severely impact the patient's quality of life.

As a vast urologic center, over the past 12 years, we have conducted approximately 5,000 GreenLight laser photoselective vaporization (PV) treatments, with 4,500 cases involving photoselective vaporization of the prostate (PVP) and nearly 500 involving PV for urethral stricture. The utilization of laser systems for PV dates back to their initial introduction in 1998, beginning with the GreenLight KTP laser (80 W) (8), progressing to the GreenLight HPS laser (120 W), and culminating in the latest iteration known as the GreenLight XPS lasers (180 W). The GreenLight laser generator emits a pulsed laser beam characterized by a wavelength of 532 nm, a pulse width ranging from 100 to 120 ns, a frequency of 13 kHz, and a laser beam area that varies between 0.2 and 0.5 mm², with a specific size contingent upon the distance between the fiber tip and the tissue surface (9).

In our clinical practice, GreenLight laser vaporization has demonstrated positive outcomes in the treatment of refractory OAB. In the present study, the potential of GreenLight laser vaporization as a treatment for refractory OAB was investigated, and the underlying therapeutic mechanism was examined, with our experience being shared. We present this article in accordance with the STROBE reporting checklist (available at <https://tau.amegroups.com/article/view/10.21037/tau-24-67/rc>).

Methods

Data collection

This retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University (No. 2023-549) and individual consent for this retrospective analysis was waived.

The data of female patients with refractory OAB in the Department of Urology, Shandong Provincial Hospital Affiliated to Shandong First Medical University from May 2022 to July 2023 were reviewed. This study included female OAB patients who were unable to tolerate more than one anticholinergic medication or had shown no response after three months of treatment, as well as those who had not achieved the anticipated effects with SNM, PTNS, or intramural bladder injections of BoNTA. The following exclusion criteria were applied: combination of mental illnesses or severe physical disease; combination of bladder outlet obstruction; combination of urinary tract

Highlight box

Key findings

- For female patients with refractory overactive bladder (OAB) who have shown poor response to conventional treatment approaches, transurethral bladder mucosal GreenLight laser-selective vaporization may represent a promising alternative treatment option.

What is known and what is new?

- The etiology and pathogenesis of refractory OAB may be associated with chronic bladder inflammation and urothelial dysfunction.
- The improvement of symptoms in female patients with refractory OAB may be attributed to the suppression of inflammatory factors and sensory receptor expression by GreenLight laser.

What is the implication, and what should change now?

- The finding demonstrates the high potential of transurethral bladder mucosal GreenLight laser-selective vaporization as a treatment option in female patients with refractory OAB.
- The exploration of the etiology of refractory OAB is increased to ensure the effectiveness of surgical treatment.

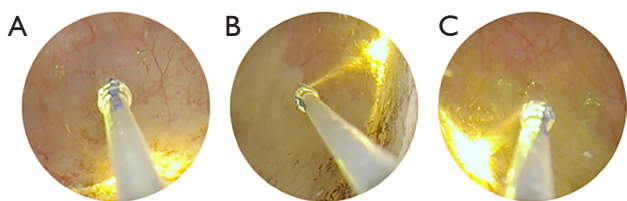


Figure 1 GreenLight laser surgery procedure. (A) Trigone of the bladder. (B) Left lateral wall of the bladder. (C) Right lateral wall of the bladder.

infection, stones, and other urological diseases; previous genitourinary surgery within three months; pregnancy or intention to become pregnant during the study; ultrasound demonstrated that the amount of post-voiding residual urine was >100 mL; with severe liver, kidney, cardiovascular, or pulmonary disorders; individuals who have undergone brain tumor surgery, suffered spinal cord injuries, and have been diagnosed with neurological conditions such as multiple sclerosis, Alzheimer's disease, stroke, and Parkinson's disease; individuals who were unable to tolerate the therapeutic procedures involved in the research.

Study design

Before surgery, patients were assessed using the Overactive Bladder Symptom Score (OABSS) (10), the 3-day bladder diary (11) (daytime frequency, nocturia, urgency, and urgency incontinence), the urodynamics [first desire to void (FDV), maximum bladder pressure capacity (MCBC)], the Overactive Bladder questionnaire Short Form (OAB-qSF) score, and the cystoscopy to obtain bladder mucosal tissue. The necessary cardiac and pulmonary function tests were completed.

At 12 weeks postoperatively, patients were assessed by OABSS (10), 3-day bladder diary (11), urodynamics, and OAB-qSF score, and bladder mucosal tissue was collected by cystoscopy.

Perioperative characteristics, such as operating time, perioperative bleeding, catheterization time, and hospital stay, were evaluated for the patients. The incidence rates of complications, including bleeding, infection, urinary fistula, and bladder contracture, were recorded.

Surgical procedure

At our center, all operations were performed by Y.Z. who was skilled with all generations of GreenLight laser systems and

was well beyond the learning curve of surgical techniques. All procedures were carried out under general anesthesia. The GreenLight XPS laser system, which incorporated side-firing laser fibers called Flare, was procured from the Realton Corporation in Beijing, China. The 30 W was the coagulation power, while 80 W was the evaporation power. Isotonic saline at room temperature was employed as the flushing agent. For GreenLight laser vaporization, the side-emitting laser fiber's tip was directed toward the lesion sites, including the lesions of follicular hyperplasia and congestive edema on the trigone of the urinary bladder and lateral wall. At the distance of two fiber caps (width =3.6 mm) from the bladder mucosa, the slow sweep was conducted at a rate of 4 millimeters per second (4 mm/sec), vaporizing the trigone, lesion sites, and the surrounding 2 cm, vaporizing to the submucosa (Figure 1A-1C). Throughout the procedure, the patient's bladder was observed for excessive filling, and if necessary, the surgery was paused to allow the bladder to empty an additional isotonic saline solution. After the procedure, an F18 three-way Foley catheter was inserted.

Immunohistochemical staining

To demonstrate the histological changes of bladder mucosa provoked by the GreenLight laser, the immunohistochemical staining of bladder mucosal tissues was performed. Bladder mucosa was removed from the trigone of the urinary bladder and the inflammatory lesion site using biopsy forceps during the cystoscopy performed before the surgery and 12 weeks following the surgery.

All samples were embedded in paraffin (8002-742, Shandong Dongyang Chemical Co., Ltd., China) after being fixed for at least 24 hours in 4% paraformaldehyde. Immunohistochemical staining was performed using the avidin-biotin-peroxidase method (ab64212, Abcam, Cambridge, MA, USA) with TRPV1 antibody (CSB-PA822774LA01HU, CUSABIO, Houston, TX, USA), P2X3 antibody (17843-1-AP, Proteintech, Rosemont, IL, USA), tumor necrosis factor alpha (TNF- α) antibody (17590-1-AP, Proteintech, Rosemont, IL, USA), and interleukin 6 (IL-6) antibody (21865-1-AP, Proteintech, Rosemont, IL, USA).

Expression was examined under the light microscope (Olympus, Tokyo, Japan). Cells were deemed positive if the bladder mucosa had brownish-yellow granules and the staining intensity exceeded the background nonspecific staining. Each sample was examined in triplicate with three high-power fields counted at 400 \times magnification at each

Table 1 Patients' general characteristics

Characteristic	Values
Age (years)	57.88±6.53
BMI (kg/m ²)	24.29±2.81
Education	
Primary	5 (15.6)
High school	10 (31.3)
> High school	17 (53.1)
Smoking	
Yes	6 (18.8)
No	26 (81.2)
Alcohol drinking	
Yes	4 (12.5)
No	28 (87.5)
Vaginal delivery	
0	0 (0.0)
1–3	24 (75.0)
>3	8 (25.0)
Daily water intake (mL)	
500–1,000	23 (71.9)
1,001–1,500	8 (25.0)
1,501–2,000	1 (3.1)

Data are presented as n (%) or mean ± SD. BMI, body mass index; SD, standard deviation.

section. Using ImageJ v1.53h, the positive expressions of TRPV1, P2X3, TNF- α , and IL-6 were analyzed, and the average optical density (AOD) value was used to determine the expressions' intensity.

Statistical analysis

IBM SPSS Statistics (version 27.0, SPSS Inc., Armonk, NY, USA) was used for statistical analysis. To examine parameter differences between baseline and 12 weeks postoperatively, normally distributed data were expressed as mean ± standard deviation (SD) using the Student's *t*-test; skew data were described as median (interquartile range) using the Wilcoxon signed rank-sum test. At $P < 0.05$, statistical significance was established.

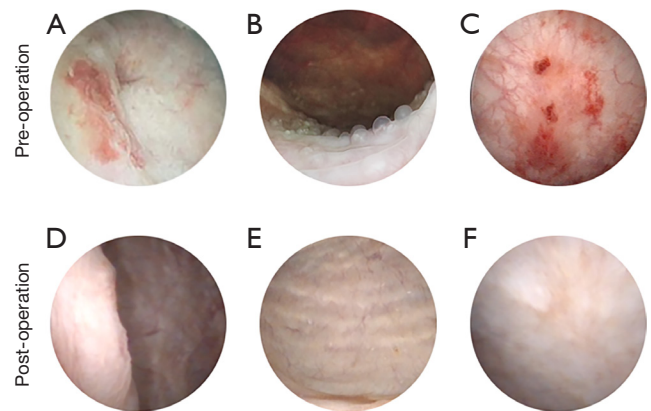


Figure 2 The representative photographs by cystoscope of patients with refractory OAB before and after treatment. (A-C) Preoperative bladder mucosa. (D-F) Postoperative bladder mucosa. OAB, overactive bladder.

Results

Patients' general characteristics

Thirty-two patients were included in this study, all successfully followed up. Twelve of them had hypertension, four had coronary heart disease, and four had type II diabetes mellitus with hypertension. Before surgery, the above conditions were controlled to normal levels. Their average age was 57.88±6.53 years (*Table 1*).

All procedures of GreenLight laser surgeries were successful with an operation time of 57.38±11.22 min, 6.88±2.12 mL of intraoperative bleeding, catheterization time of 2.88±0.94 days, and hospital stay duration time of 3.88±1.07 days. Complications were rare, with only 3 patients (9.4%) experiencing urinary tract infections, all successfully resolved through antibiotic therapy. No severe complications occurred.

Cystoscopy

Follicular hyperplasia in 13 patients (40.6%) and congestive edema in 19 patients (59.4%) were observed during preoperative cystoscopy. Of the cases, 14 (43.8%) had lesions exclusively in the trigone of the urinary bladder, 8 (25%) in the trigone and lateral wall, 7 (21.9%) in the trigone and bladder neck, and 3 (9.4%) in the trigone and the mucosa adjacent to the ureter's opening (*Figure 2A-2C*).

Postoperative cystoscopy examination revealed the

Table 2 OABSS at baseline and 12 weeks follow-up

OABSS	Baseline	12 weeks	P value
Total scores	9.13±1.74	6.97±1.60	<0.001
Daytime frequency	2 [1]	1 [0]	0.02
Nocturia	3 [1]	2 [1]	0.01
Urgency	2.5 [1]	2 [2]	<0.001
Urgency incontinence	3 [1.75]	2 [0.75]	0.004

Data are presented as mean ± standard deviation or median [interquartile range]. OABSS, Overactive Bladder Symptom Score.

Table 3 Three-day bladder diary at baseline and 12 weeks follow-up

3-day bladder diary	Baseline	12 weeks	P value
Daytime frequency	13.13±1.76	9.89±1.93	<0.001
Nocturia	2.33 [1.33]	1.67 [1.25]	0.02
Urgency	2.17 [1.33]	1.67 [1]	<0.001
Urgency incontinence	2.33 [1]	1.33 [1.58]	<0.001

Data are presented as mean ± standard deviation or median [interquartile range].

Table 4 OAB-qSF score and the urodynamic level at baseline and 12 weeks follow-up

Variable	Baseline	12 weeks	P value
OAB-qSF	71.19±6.62	43.38±6.48	<0.001
FDV (mL)	118.50±13.26	179.38±14.21	<0.001
MCBC (mL)	207.19±18.19	312.56±26.82	<0.001

Data are presented as mean ± standard deviation. OAB-qSF, Overactive Bladder questionnaire Short Form; FDV, first desire to void; MCBC, maximum bladder pressure capacity.

lesions' noticeable reduction and complete disappearance (Figure 2D-2F).

Therapeutic effect

OABSS

The evaluation data for the OABSS parameters are displayed in Table 2. Compared to the baseline, total scores (9.13±1.74 vs. 6.97±1.60, $P<0.001$), daytime frequency {2 [1] vs. 1 [0], $P=0.02$ }, nocturia {3 [1] vs. 2 [1], $P=0.01$ }, urgency {2.5 [1] vs. 2 [2], $P<0.001$ }, and urinary incontinence {3 [1.75] vs. 2 [0.75], $P=0.004$ } showed significant improvements at

follow-up (12 weeks).

Three-day bladder diary

The data from the 3-day bladder diary are displayed in Table 3. At the 12-week follow-up, there were notable improvements observed in the daytime frequency (13.13±1.76 vs. 9.89±1.93, $P<0.001$), nocturia {2.33 [1.33] vs. 1.67 [1.25], $P=0.02$ }, urgency {2.17 [1.33] vs. 1.67 [1], $P<0.001$ }, and urgency incontinence {2.33 [1] vs. 1.33 [1.58], $P<0.001$ } when compared to the baseline.

OAB-qSF and urodynamics

The data changes of OAB-qSF and urodynamics are shown in Table 4. At 12 weeks of follow-up, the OAB-qSF score (71.19±6.62 vs. 43.38±6.48, $P<0.001$) exhibited a significant decrease compared to the baseline, indicating improvement. On the other hand, both the FDV (118.50±13.26 vs. 179.38±14.21, $P<0.001$) and MCBC (207.19±18.19 vs. 312.56±26.82, $P<0.001$) showed a substantial increase from the baseline, suggesting a notable enhancement.

Immunohistochemical staining

To investigate the pathophysiological changes of the bladder mucosa after vaporization, some inflammatory factors and sensory receptors, including TRPV1, P2X3, TNF- α , and IL-6, were stained by immunohistochemical staining (Figure 3A).

Figure 3B shows the average optical density of inflammatory factors and sensory receptors in patients' bladder mucosal tissues before and after surgery. Compared to before treatment, the expressions of TRPV1 ($P<0.001$), P2X3 ($P<0.001$), TNF- α ($P<0.001$), and IL-6 ($P<0.001$) in the bladder mucosa showed a significant decrease after treatment.

Discussion

Refractory OAB is a common yet challenging disorder. Patients have undergone both behavioral therapy and medication therapy. However, approximately 40% of patients either do not achieve the expected therapeutic effects or are utterly intolerant to the treatment (12). It has been demonstrated that OAB significantly reduces quality of life and can lead to sleep disturbances and a decline in sexual function (2). In this study, due to male patients being more susceptible to etiological factors such as prostate disease or excessive alcohol consumption, female patients were selected

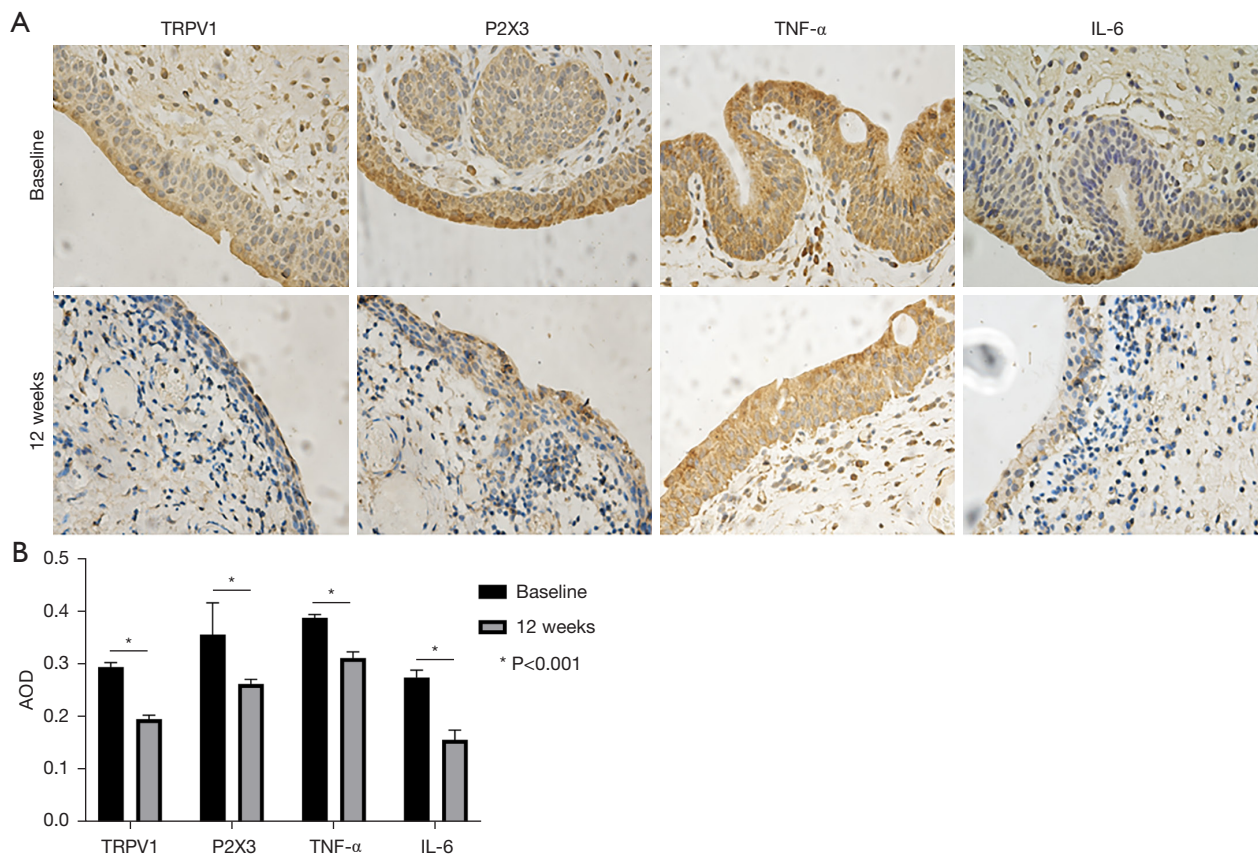


Figure 3 Expressions and comparisons of inflammatory factors and sensory receptors in bladder mucosa tissues before and after treatment. (A) The expressions of TRPV1, P2X3, TNF- α , and IL-6 in patients' bladder mucosal tissues were stained by immunohistochemical staining before and at 12 weeks after treatment. Representative histological images are shown at 400 \times magnification. (B) Average optical density value of inflammatory factors and sensory receptors before and after treatment were presented in the bar chart. TNF, tumor necrosis factor; IL-6, interleukin 6; AOD, average optical density.

as the subjects of our research. Additionally, we found a higher prevalence of female patients with refractory OAB at our center, where their anxiety was more severe.

There are multiple treatment modalities available for refractory OAB. The preferred choice is combination drug therapy. However, in a prospective study (13), only 24% of the patients continued the combination for up to 1 year. Reasons for discontinuing the combination included adverse effects (21.7%) and ineffectiveness (54.3%). Other treatment options include intramural bladder injections of BoNTA, SNM, and PTNS. These treatment options require long-term persistence by patients, and the treatment outcomes are unsatisfactory, with only about 2% of patients opting for these treatments (14). Therefore, refractory OAB remains a persistent challenge for both patients and urologists.

The etiology and pathogenesis of refractory OAB are still unclear but may be associated with chronic bladder inflammation and urothelial dysfunction (15). The study has found that the severity of chronic bladder inflammation is significantly higher in OAB patients than in normal tissues (16). Our study result also supports this phenomenon. TNF- α and IL-6 are mainly produced by monocytes and macrophages, and their expressions play an essential regulatory role in immune responses such as inflammation (17,18). In our study, we selected these two inflammatory factors for detection and found that they were highly expressed in the bladder mucosa of patients. The study (19) has shown that repeated inflammatory stimuli can lead to bladder dorsal root ganglia neuron enlargement, resulting in a decreased activation threshold of bladder afferent nerves.

To our knowledge, this is the first study to utilize the GreenLight laser to treat refractory OAB. The GreenLight laser operates at a wavelength of 532 nm, with a vaporization depth ranging between 1 and 2 mm. Its energy can be absorbed mainly by hemoglobin, not water (20); the coagulation layer forms on the evaporated tissue. Therefore, it has the advantages of low energy loss, good vaporization, and hemostatic effect. Histological staining in this study showed a decrease in the expression of selected inflammatory factors after vaporization compared to before treatment. As laser energy attenuates with distance from the center of the laser beam, laser therapy can produce a biological activity effect called photobiomodulation (PBM) in surrounding tissues (9). The anti-inflammatory effect is considered one of PBM's most important biological effects (21). The study has shown that PBM anti-inflammatory effects are mediated by mitochondrial cytochrome c on cell mitochondria, regulating the activity of various molecules such as nitric oxide (NO), adenosine triphosphate (ATP), and reactive oxygen species (ROS) (22). In an animal model, PBM was found to reduce inflammation cell migration and lower the concentrations of TNF- α , IL-1 β , and IL-6, ultimately reducing inflammation (23).

Urothelial cells can express sensory receptors, such as TRPV1 and P2X3 (24). The upregulation of P2X3 receptors plays a critical role in mediating sensory input excitation and controlling bladder volume, which is often observed in cases of OAB (19,25). Andersson *et al.* have reported (24) that the sense of urgency is associated with an increased expression of TRPV1 in the mucous membranes of the triangular region of the human bladder, and bladder inflammation sensitizes and enhances sensory receptor function and increases the density of nerve fibers expressing P2X3 and TRPV1. The results of the present study support this theory. In addition, in the present study, tissue staining showed decreased expression of TRPV1 and P2X3 in the bladder mucosa after green laser vaporization. The alleviation of OAB symptoms in patients might be intensely associated with the factors stated above.

As shown in this study, we evaluated patients by OABSS (10), 3-day bladder diary (11), urodynamics, and OAB-qSF score. All these parameters after surgeries were significantly improved at follow-up compared to baseline. These effects might be attributed to the suppression of inflammatory factors and sensory receptor expression by GreenLight laser, including TRPV1, P2X3, TNF- α , and IL-6. In addition, the duration of the operation is really short, and the intraoperative blood loss is minimal,

leading to a significantly reduced length of hospital stay. The complications were rare and tolerable. Therefore, our technology is proved to be effective and safe.

Several limitations should be noted before the conclusion. Firstly, this was a retrospective study with a small sample size and no long-term follow-up, which might introduce bias in the results. Further large-scale, long-term follow-up studies are still needed to validate the findings. Secondly, this study lacked an appropriate control group due to the relative rarity of patients receiving intravesical injections of BoNTA, PTNS, or SNS in clinical practice. Additionally, further in-depth research is required to explore and elucidate the relevant mechanisms.

Conclusions

For female patients with refractory OAB who have shown poor response to conventional treatment approaches, transurethral bladder mucosal GreenLight laser-selective vaporization may represent a promising alternative treatment option. This may be associated with the GreenLight laser's suppression of inflammatory factors and sensory receptor expression. Randomized controlled trials will be required to provide further validation.

Acknowledgments

Funding: This work was supported by the National Natural Science Foundation of China (grant No. 82070782, to H.Z.), the Natural Science Foundation General Project of Shandong Province (No. ZR2023MH346, to X.S.), the National Natural Science Foundation of China (No. 82000306, to F.Y.), the Program for Qilu Health Excellent Young Talents from the Health Commission of Shandong Province, and the Shandong First Medical University (Shandong Academy of Medical Sciences) Youth Science Cultivation Funding Program (No. 202201-060, to X.S.).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://tau.amegroups.com/article/view/10.21037/tau-24-67/rc>

Data Sharing Statement: Available at <https://tau.amegroups.com/article/view/10.21037/tau-24-67/dss>

Peer Review File: Available at <https://tau.amegroups.com/>

[article/view/10.21037/tau-24-67/prf](https://doi.org/10.21037/tau-24-67/prf)

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tau.amegroups.com/article/view/10.21037/tau-24-67/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University (No. 2023-549) and individual consent for this retrospective analysis was waived.

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Cite this article as: Du K, Sun X, Yang F, Qiu Z, Li L, Zhao Y, Zhang H. Evaluation of transurethral GreenLight laser-selective vaporization for refractory overactive bladder in women. *Transl Androl Urol* 2024;13(7):1164-1172. doi: 10.21037/tau-24-67