

RELIEF BY BOTULINUM TOXIN OF VOIDING DYSFUNCTION DUE TO BENIGN PROSTATIC HYPERPLASIA: RESULTS OF A RANDOMIZED, PLACEBO-CONTROLLED STUDY

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ABSTRACT

Objectives. To evaluate the therapeutic role of botulinum toxin injection in men with benign prostatic hyperplasia.

Methods. Men with benign prostatic hyperplasia were enrolled in a randomized, placebo-controlled study. After a baseline evaluation, each participant received 4 mL of solution injected into the prostate gland. Patients in the control group received saline solution and patients in the treated group received 200 U of botulinum toxin A. The outcome of each group was evaluated by comparing the symptom scores, serum prostate-specific antigen concentration, prostate volume, postvoid residual urine volume, and peak urinary flow rates.

Results. Thirty consecutive patients were enrolled. No local complications or systemic side effects were observed in any patient. After 2 months, 13 patients in the treated group and 3 in the control group had subjective symptomatic relief ($P = 0.0007$). In patients who received botulinum toxin, the symptom score was reduced by 65% compared with baseline values and the serum prostate-specific antigen concentration by 51% from baseline. In patients who received saline, the symptom score and serum prostate-specific antigen concentration were not significantly changed compared with the baseline values and 1-month values. Follow-up averaged 19.6 ± 3.8 months.

Conclusions. Botulinum toxin injected into the prostate seems to be a promising approach for the treatment of benign prostatic hyperplasia. It is safe, effective, and well-tolerated. Furthermore, it is not related to the patient's willingness to complete treatment. UROLOGY 62: 259–265, 2003. © 2003 Elsevier Inc.

Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate.^{1,2} Symptoms of BPH stem from urethral obstruction and gradual loss of bladder function, which results in incomplete bladder emptying, and can lead to complications, including acute urinary retention.³ More than one half of men in their 60s and as many as 90% of men in their 70s and 80s have some BPH symptoms.⁴

The goal of therapy is to reduce or alleviate lower urinary tract symptoms, to prevent complications, and to minimize the adverse effects of treatment.⁵

Few treatments are without any adverse consequences, and this is particularly so with treatments for BPH, for which a delicate balancing act is needed between the benefits and demerits of the available treatments. Several treatment options are available, including watchful waiting, medical therapy, and surgical procedures.^{1,6,7} Although transurethral resection is an effective treatment for symptomatic BPH, it is by no means perfect. Approximately 15% to 25% of patients who undergo surgery do not have satisfactory long-term outcomes.⁸ An analysis of data found that mortality in the 30 days after transurethral resection for BPH ranged from 0.4% for men aged 65 to 69 years to 1.9% for men aged 80 to 84 years and has fallen in recent years. In observational studies, transurethral resection for BPH was associated with immediate surgical complications in 12% of patients, bleeding requiring intervention in 2%, erectile dysfunction in 14%, retrograde ejaculation in 74%,

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and incontinence in about 5%. Analysis of claims data found a reoperation rate of about 1% annually.⁹

Because of these problems, as well as the desire of patients to avoid surgery whenever possible, there has been much interest in alternative treatments. Recent studies have reported that both finasteride and long-acting α_1 -adrenergic antagonist drugs are safe and effective treatments for BPH.^{3,6,10–12} Although these drugs represent attractive options for men with BPH, they have adverse effects. However, a systematic review found that withdrawals attributed to adverse events were similar for alfuzosin and tamsulosin^{10,12,13}; a higher rate was found with doxazosin and terazosin. Both selective and less-selective α -blockers may be associated with dizziness, asthenia, and postural hypotension, limiting therapy. Furthermore, decreased libido and impotence were more common in men taking finasteride.

Botulinum toxin (BT) blocks acetylcholine release at the neuromuscular junction and in autonomic neurons. It has been extensively used to treat patients with dystonia, pelvic floor disorders, and gustatory or axillary sweating.^{14,15} Furthermore, it has been noted that a weakening of the urethral sphincter muscle by BT injection is followed by pain relief and symptom improvement in patients with voiding dysfunction.^{16–19} Recently, it has been documented that BT injection into the rat prostate induces selective denervation and subsequent atrophy of the gland.²⁰ Therefore, we conducted a study of BT in men with BPH who no longer responded favorably to medication and who refused to undergo surgical treatment.

MATERIAL AND METHODS

The study was conducted at Department of Surgery of the University Hospital Agostino Gemelli, Rome. The institutional review board approved the protocol for this double-blind, placebo-controlled study.

RECRUITMENT AND BASELINE EVALUATION

Men 50 to 80 years of age who had symptomatic BPH were enrolled. All patients underwent a digital rectal examination. The symptoms were assessed with the American Urological Association (AUA) index,^{21,22} which assess the occurrence of seven BPH symptoms, each scored on a scale from 0 (absent) to 5 (severe). The total score reflects the overall severity of BPH (1 to 7, mild; 8 to 19, moderate; and 20 to 35, severe). In addition, uroflowmetry was performed with a Urodyne 1000 uroflowmeter (Dantec Medical), and the postvoid residual urinary volume was determined ultrasonographically.²³ Serum concentrations of prostate-specific antigen (PSA) were measured, and transrectal ultrasonography was performed to determine the prostate volume.⁹ Prostate biopsies were performed if clinically indicated.

CRITERIA FOR ELIGIBILITY AND EXCLUSION

The inclusion criteria were as follows: moderate-to-severe symptoms of urinary obstruction as determined by the AUA

score, mean peak urinary flow rate of no more than 15 mL/s with a voided volume of 150 mL or more, and an enlarged prostate gland on digital rectal examination.

Patients with neurogenic voiding disorders, prostate or bladder cancer, or a serum PSA level of 10 ng/mL or more, or who had undergone surgery were excluded from the study. Patients previously treated with BT were also excluded.

STUDY DESIGN

Eligible patients were enrolled from January to December 2000. Randomization was performed after informed consent was obtained. The randomization schedule was generated by computer. Allocations were sealed in opaque, numbered envelopes that were opened after collection of the baseline data. The randomization data were not available to the investigators. The code was broken at 2 months when the patients had completed the first part of the trial. At the 1 and 2-month follow-up visits, one examiner, unaware of the treatment assignment, evaluated the outcome. The outcome of each group was evaluated by comparing the AUA scores, serum PSA levels, prostate volumes, postvoid residual volumes, and peak urinary flow rates.

The primary endpoint was evaluation of symptomatic improvement after treatment, as measured by the AUA score and peak urinary flow rates. The secondary endpoint was the evaluation of prostate volume, serum PSA level, and postvoid residual urinary volume.

Each of the participants received 4 mL of solution injected into the prostate, divided into two injections of equal volume (2 mL) into each lobe of the gland. With the patient lying on the left side, a 22-gauge spinal needle (0.7 × 90-mm Yale spinal needle, Becton-Dickinson, Spain) was inserted in the perineum in the anterior midline approximately 1.5 to 2.0 cm from the anus. The injection sites were visualized using transrectal ultrasonography. Neither sedation nor local anesthesia was used during the procedure. Patients in the control group received saline solution only, and patients in the treated group received 200 U of BT (Botox, Allergan).

FOLLOW-UP

Patients underwent the same evaluations at 1 and 2 months after treatment as were performed at baseline, regardless of their treatment and outcome. At each visit, the patients were asked whether they wanted to stay in the study. If not, they were offered medical therapy or surgical resection. If symptoms persisted at 2 months, the examiner (who remained unaware of the patients' treatment assignments) could decide to retreat the patient. The retreated patients always received BT (200 U); they were then evaluated with the same protocol.

STATISTICAL ANALYSIS

All statistical analyses were obtained using Statistics for Windows (Statsoft). The results are expressed as the mean $\pm$ standard deviation. Differences between data were compared using the Student *t* test. The clinical outcomes of the two groups were compared using Fisher's test. All *P* values were two tailed. *P* < 0.05 was considered to indicate statistical significance.

RESULTS

Forty-two consecutive outpatients were assessed for eligibility. Of them, 8 patients did not meet the inclusion criteria and 4 patients refused to participate. Thus, 30 patients were randomized: 15 received BT and 15 placebo. No differences were found at baseline between the two groups

TABLE I. Baseline characteristics and results at 1 and 2-month evaluation in the 30 patients with BPH

Characteristic	BT Group	Control Group
Patients (n)	15	15
Age (yr)	69.4 ± 4.9	68.2 ± 3.9
Baseline		
AUA symptoms score	23.2 ± 4.1	23.3 ± 3.9
Serum PSA (ng/mL)	3.7 ± 0.9	3.5 ± 1.0
Prostate volume (mL)	52.6 ± 10.6	52.3 ± 10.0
Peak urinary flow (mL/s)	8.1 ± 2.2	8.8 ± 2.5
Residual urinary volume (mL)	126.3 ± 38.3	118.0 ± 39.7
1-mo evaluation		
AUA symptoms score	10.6 ± 1.7	23.4 ± 3.5
Serum PSA (ng/mL)	2.1 ± 0.7	3.4 ± 0.8
Prostate volume (mL)	23.8 ± 6.2	50.5 ± 8.1
Peak urinary flow (mL/s)	14.9 ± 2.1	8.8 ± 2.3
Residual urinary volume (mL)	49.6 ± 13.4	116.7 ± 33.1
2-mo evaluation		
AUA symptoms score	8.0 ± 1.6	23.3 ± 3.3
Serum PSA (ng/mL)	1.8 ± 0.7	3.4 ± 0.8
Prostate volume (mL)	16.8 ± 7.8	50.3 ± 7.9
Peak urinary flow (mL/s)	15.4 ± 1.7	8.7 ± 2.3
Residual urinary volume (mL)	21.0 ± 16.2	116.7 ± 31.0

KEY: BPH = benign prostatic hyperplasia; BT = botulinum toxin; AUA = American Urological Association; PSA = prostate-specific antigen.

Data presented as the mean ± SD; all patients were included in all evaluations.

(Table I). No complications during the procedure were observed in any patient.

ONE-MONTH EVALUATION

Urinary incontinence was not observed in any patient from either group. No local complications or systemic side effects were reported. Two patients in the control group and 11 in the treated group had subjective symptomatic relief ($P = 0.001$). In the BT patients, compared with baseline values, the AUA score was reduced by 54% ($P = 0.00001$) and the serum PSA level by 42% ($P = 0.00006$). In patients who received saline, the AUA score ($P = 0.9$) and serum PSA level ($P = 0.8$) were not significantly changed from the baseline values and were significantly different statistically from the values in the treated patients.

In the treated patients, compared with the baseline values, the prostate volume and postvoid residual urine volume were reduced by 54% ($P = 0.00001$) and 60% ($P = 0.00001$), respectively. The mean peak urinary flow rate increased from 8.1 ± 2.1 to 14.9 ± 2.1 mL/s ($P = 0.00001$). In patients who received saline, these values were not significantly different from the baseline values (prostate volume, $P = 0.6$; peak urinary flow rate, $P = 0.9$; postvoid residual volume, $P = 0.9$) and were significantly different from the values in the treated patients.

TWO-MONTH EVALUATION

No urinary incontinence or systemic side effects were reported at the 2-month visit. Thirteen patients in the treated group and 3 in the control group had subjective symptomatic relief ($P = 0.0007$). In the BT patients, the AUA score was reduced by 65% ($P = 0.00001$) compared with the baseline values and varied from the 1-month values ($P = 0.0001$). In the same patients, the serum PSA level was reduced by 51% ($P = 0.00001$) from baseline and did not vary from the 1-month value ($P = 0.2$). In the control group, the AUA score and serum PSA level were not significantly different statistically compared with the baseline values (AUA score, $P = 1.0$; PSA, $P = 0.7$) and 1-month values (AUA score, $P = 0.9$; PSA, $P = 0.9$). These values were significantly different statistically from the values in the treated patients.

In the treated patients, compared with the baseline values, the prostate volume and postvoid residual urine volume were reduced by 68% ($P = 0.00001$) and 83% ($P = 0.00001$), respectively. The mean peak urinary flow rate was significantly increased from the baseline value ($P = 0.00001$) and did not vary from the 1-month value ($P = 0.4$). In the control group, these values were not significantly different compared with the baseline and 1-month values. They were significantly different statistically from the values in the treated patients.

TABLE II. Results at 6 and 12-month evaluations in 17 patients who received botulinum toxin

Characteristic	6-mo Evaluation	12-mo Evaluation
AUA symptoms score	9.1 ± 3	8.9 ± 3.2
Serum PSA (ng/mL)	2.1 ± 1.1	2.3 ± 1.4
Prostate volume (mL)	21 ± 7.1	20.5 ± 8
Peak urinary flow (mL/s)	14.6 ± 4.1	15 ± 2.9
Residual urinary volume (mL)	24.2 ± 17	24 ± 18

*Abbreviations as in Table I.
Data presented as the mean ± SD; all patients were included in all evaluations.*

FOLLOW-UP AND LONG-TERM OUTCOME

A rescue treatment was proposed to the 14 patients who had reported no symptomatic improvement; 10 refused and underwent medical or surgical therapy. The other 4 patients, all of whom had received saline, each received 200 U of BT, as described. Two months after the injections, the AUA score had decreased from 24 ± 2.9 to 11 ± 3.1 points ($P = 0.0009$), the serum PSA level from 3.9 ± 0.6 to 2.1 ± 0.9 ng/mL ($P = 0.01$), the prostate volume from 49.3 ± 10.7 to 24.1 ± 5.3 mL ($P = 0.005$), and postvoid residual volume from 115 ± 27.1 to 50 ± 6.4 mL ($P = 0.003$). Also, the mean peak urinary flow rate increased from 9 ± 2.1 to 15 ± 0.7 mL/s ($P = 0.001$).

All 17 patients who received BT injections were periodically evaluated. The follow-up period averaged 19.6 ± 3.8 months. No complications or side effects were reported during the follow-up period. Six and twelve months after BT injections, the patients underwent the same evaluations performed at baseline (Table II).

COMMENT

BPH management is currently in transition.^{4,5,7} Although surgery will continue to be widely used, medical therapies are assuming increasing importance, owing to the desire of patients to avoid surgery whenever possible. A pilot study on the impact of a program to aid in decision-making about BPH showed a 40% decrease in the surgery rate in American patients.²⁴ However, the goal of therapy is to relieve lower urinary tract symptoms. For this reason, the efficacy of any treatment for symptomatic BPH is determined primarily on the basis of the decrement in the patient's symptoms and improvement in the urinary flow rate.^{25,26} In the present study, to assess symptoms, the AUA index was used. To obtain objective information about a patient's ability to urinate, the peak urinary flow rate, a more specific BPH indicator than the mean rate, was measured.

Recently, it has been documented that aim of treatment depends on the severity of the BPH

symptoms.^{2,7} In these guidelines, a watchful waiting policy was recommended for patients with mild symptoms, medical treatment for mild to moderate symptoms, and surgery for patients for whom medication or conservative management failed and who have moderate to severe symptoms, and/or BPH complications.

When the available treatment for this disorder was surgery, management was straightforward. With the advent of drug therapy, it became necessary to know more about the pathophysiology of BPH before one could predict the response to treatment. It has been suggested that BPH had two components: a static component that is related to prostatic enlargement and a dynamic component that reflects the degree of contraction of smooth muscle within the gland. The onset of disease also involves hormonal and growth factors and aging, and the pathologic features are heterogeneous, because the ratio of smooth muscle to epithelium can vary in individual patients. There is, therefore, reasonable evidence to support the concept that origin of BPH could be rooted in neural dysregulation of the prostate and alterations in local neuropeptides.²⁷ In view of this heterogeneity, it is clear that no one type of drug therapy would be expected to be effective in all men with BPH.

Drugs to treat BPH fall into two main categories: drugs that relax smooth muscle within the prostate and drugs that inhibit the formation of the intracellular androgen. Both treatments improve lower urinary tract symptoms and were effective in patients with BPH.^{3,6,10,11} However, both alpha-blockers and finasteride may be associated with adverse events, limiting therapy.

The results of this study demonstrate that BT can be used to treat BPH. The BT benefit was evident within 1 month after the treatment, and it continued throughout the follow-up period. Decreases in the AUA symptom score and improvement in the peak urinary flow rate were observed after BT injections. At the 2-month evaluation, compared with the baseline values, the AUA score was reduced by 65% and the mean peak urinary flow rate

had increased significantly. In the control group, these values had not changed significantly compared with baseline and differed from the values in the treated patients. We have also documented that BT induces a decrease in the mean postvoid residual urinary volume (at the 2-month evaluation, ultrasonography did not show a postvoid residual volume in 6 patients) and a reduction in the prostate volume, as documented by both ultrasonography and reduced serum PSA levels.

BT exerts its effects on the neuromuscular junction by blockade of acetylcholine. This has led to its use in conditions with muscular overactivity. However, BT is also capable of blocking ganglionic nerve endings at which acetylcholine is the transmitter, but it does not block responses mediated by nitric oxide. This has fueled interest in its use as a treatment for overactive smooth muscles or abnormal activity of glands.

Prostatic growth has been thought to be controlled by endocrine means.^{28,29} However, the abundance of adrenergic and muscarinic receptors suggests that the autonomic nervous system may play a role in the growth and secretory function of the gland.^{29,30} It has also been found that a subtype of muscarinic receptors is present in BPH and was the predominant subtype. It has been proposed that these muscarinic receptors stimulate growth of the human gland.³⁰ It seems conceivable that BT, by blocking these receptors at which acetylcholine is the transmitter, induces denervation and atrophy in the human prostate. We observed that the prostate volume and serum PSA concentration were reduced in treated patients. Furthermore, the use of alpha-adrenergic blockade to treat symptomatic BPH is based on the hypothesis that the disease arises from bladder outlet obstruction and that 40% of the cellular volume of the hyperplastic gland is made up of smooth muscle,²⁹ whose tension is mediated by alpha₁-adrenoceptors. BT may induce smooth muscle relaxation directly or by means of neuronal nitric oxide.

CONCLUSIONS

We found BT injection into the prostate to be a promising approach to the treatment of BPH. It is well-tolerated and should be considered for patients who are at risk of surgery. Furthermore, it is not related to the patient's willingness to complete treatment. Additional investigation of BT treatment is indicated before its general use can be advocated.

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EDITORIAL COMMENT

Within the past decade, a multitude of minimally invasive and medical therapies have been, and are being, developed for the treatment of BPH. This application of BT is one of many, and it is a very novel approach deserving of interest and investigation. However, it is important to note that BPH is a disease whose pathophysiology we are still in the midst of understanding, and its relationship to lower urinary tract symptoms (LUTS) still needs careful examination and investigation. It is well known that not all men with BPH have LUTS and that not all men with LUTS have BPH. However, the initial therapy still consists of an empiric trial of medical therapy. With these concepts stated, it is important to note that this study was a preliminary investigation with a small number of patients and a short follow-up. Additionally, this novel approach was not preceded by at least one more animal model study before this human trial.

Of particular interest is the reduction of prostate size in 2 months from about 49 cm³ to 24 cm³, with an appropriate drop in PSA values as well. The improvements in symptom score and flow rate are also impressive. This suggests that a BT injection into the prostate will produce long-term effects more durable than current medical or minimally invasive office-based thermotherapy treatments. Although the authors posed many hypothetical explanations for its mechanism of action, it would be better to understand its toxic effects before introducing it into the human prostate gland and to perform a more rigorous and worthwhile randomized preliminary study.

The study also did not address several issues. First, immediately after the BT injection, it is not clear whether any patient required catheterization for retention. Second, what was the level of patient discomfort during the injection, and was there any development of postprocedure discomfort, pain, dysuria experienced that was similar to any minimally invasive thermotherapy procedure? Third, because the study was conducted from January to December 2000, why was follow-up

limited to only 2 months? What happened at 3, 6, and 12 months after BT injection? It would be informative to report, even if anecdotally for only 1 or 2 patients, whether these effects (such as a 50% reduction in size and PSA) can be sustained. These improvements in symptoms and flow rate can be considered “resection-like” and seem too good to be true. Of note, one could speculate that these improvements eventually revert back to baseline after the effects of the botox wear off. One would expect this to occur at about 3 to 6 months, as reported for various other botox procedures.

Finally, the widespread application of BT as implied in the article deserves important attention. Currently, this neuromuscular toxin is approved by the Food and Drug Administration only for cosmetic applications. Its application in the urinary tract is clearly investigational. Because BT is easily prescribed and widely available, its “off label” urologic application can be easy to offer as one joins this “fashionable botox” trend in medical care. Therefore, it should be strongly emphasized that cautious examination of its application in the general community is warranted because it is still a neurotoxin with potential and significant life-threatening morbidities. Finally, it is not clear how this therapy or any therapy is not related to a patient's willingness to complete treatment, because follow-up is an equally important facet of any BPH treatment.

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REPLY BY THE AUTHORS

We read with great interest the Editorial Comment. No experimental or basic data are available to investigate the distribution of BT in the prostate. Doggweiler *et al.*¹ showed that BT injection into the rat prostate gland induces selective denervation and subsequent atrophy of the prostate.

In our study, no patient required catheterization for retention immediately after BT injections. No local complications during the procedure or postinjection systemic side effects were observed in any patient. A recent report highlighted the popularity of BT treatment and the need for the Food and Drug Administration to do a comprehensive and careful review of the risks and benefits before extending its approval of BT for widespread use. Following the discovery that BT inhibits neuromuscular transmission, this powerful poison has become a drug with many indications. One of the most recent achievements in the field is the observation that BT is a treatment for disorders of the gastrointestinal and urinary tracts. Furthermore, controversy exists regarding the safety of BT treatment. Effects are seen at autonomic ganglia where it blocks autonomic transmission acutely, producing autonomic symptoms. A study of 4 patients with botulism found impairment of heart rate and blood pressure responsiveness, as well as neuromuscular transmission. The sympathetic tests normalized earlier than the parasympathetic tests on follow-up. Systemic side effects such as skin and allergic reactions, increased postvoid residual urine volume, muscular weakness, abnormalities on electromyography of distant muscles, and postural hypotension have been reported. Also, BT diffusion is thought to be responsible for the occurrence of heart block after treatment for esophageal achalasia. In an 8-year period, up to 1000 patients with

pelvic, anorectal, and urologic diseases, such as chronic anal fissure, outlet type constipation, anterior rectocele, prostatic pain, and BPH, have been treated with BT at our institution. During this time, none of the patients had systemic complications or severe side effects. To evaluate the safety of this treatment, we have studied 6 patients, from 22 to 62 years old, without detectable cardiovascular or autonomic diseases, who underwent treatment with 150 U (0.75 mL) of BT (Dysport, Ipsen SpA, Milan, Italy) for chronic anal fissure. We used the Ewing protocol at baseline (before BT treatment) and repeated the tests within 96 hours and 30 days after treatment. The Ewing protocol, including measurement of heart rate changes during deep breathing, Valsalva maneuver, and standing up; and blood pressure measurement during handgrip and standing up, was developed to assess the autonomic control of the cardiovascular system and to diagnose autonomic neuropathy. Three of these tests (responses to the Valsalva maneuver, deep breathing, and standing up) are based on the measurement of heart rate changes and are indexes of parasympathetic activity; the other two are indexes of sympathetic activity. To class the severity of damage of the autonomic nervous system, a score (0, normal response; 1, borderline; 2, abnormal) is given to each test. The final score can change from 0/10 to 1/10 (normal pattern), to 2/10 to 4/10 (borderline pattern), to 5/10 to 10/10 (abnormal pattern). Anorectal manometry was performed before and 1 month after BT treatment. None of the patients had a worsening of test scores after the BT injections. In particular, before treatment, a borderline pattern (2/10 score) was found in 4 patients. At the 96-hour evaluation, a borderline pattern (2/10 score) was found in 1 patient. At the 30-day evaluation, all patients who had previously reported an abnormal score no longer had such a score, and a normal pattern (0/10) was found in all treated patients. Given its effectiveness, we believe that BT appears to be a safe treatment. Nevertheless, more research is needed to optimize the dosage and site of injection. These results show that no autonomic cardiovascular adverse effects have resulted from BT injection.²

Follow-up was not limited to only 2 months. Data from the 6 and 12 month evaluations are reported in Table II.

The inclusion criteria in our study were the same criteria used in very important randomized, placebo-controlled trials.^{3,4} In our study, furthermore, randomization was performed after informed consent had been obtained. The randomization schedule was generated by computer, and allocations were sealed in opaque, numbered envelopes that were opened after collection of the baseline data. The outcome of each group was evaluated by comparing the AUA symptom score, serum PSA concentration, prostate volume, residual urine volume, and peak urinary flow rates. The primary endpoint was evaluation of symptomatic improvement after treatment, as measured by means of the AUA symptom score and peak urinary flow rate. The secondary endpoint was evaluation of the prostate volume, serum PSA concentration, and residual urinary volume.

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