Efficacy and Safety of Rezūm System Water Vapor Treatment for Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia

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OBJECTIVE To assess 1-year efficacy and safety data from pilot trials of the Rezūm System water vapor to treat lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH).

MATERIALS AND METHODS A total of 65 men with symptoms of moderate to severe BPH were enrolled in pilot studies at centers in the Dominican Republic, the Czech Republic, and Sweden. Each patient was treated with transurethral delivery of sterile water vapor (steam). International Prostate Symptom Score (IPSS), peak urinary flow (Qmax), quality of life (QoL), postvoid residual, International Index of Erectile Function, and prostate-specific antigen were evaluated at 1 week and 1, 3, 6, and 12 months post-treatment. Safety was also assessed.

RESULTS Statistically significant clinical improvements at 1, 3, 6, and 12 months were reported for IPSS (decreased by 6.8, 13.4, 13.1, and 12.5 points, respectively) and Qmax (increased by 2.0, 4.7, 4.3, and 4.6 mL/sec, respectively). At 12 months, these results equated to a 56% improvement in IPSS ($P < .001$) and an 87% improvement in Qmax ($P < .001$). QoL also improved at 12 months with a 61% improvement. Sexual function was maintained. Most of the adverse events (AEs) were related to endoscopic instrumentation and were of short duration. One case of urinary retention was classified as a procedure/device-related serious AE.

CONCLUSION The Rezūm System provides effective relief of LUTS associated with BPH at 1 year. The procedure is safe with an acceptable side effect profile. UROLOGY 86: 1042–1047, 2015. © 2015 Elsevier Inc.

In the United States, the number of men with symptomatic benign prostatic hyperplasia (BPH) who require treatment is projected to increase to 10.3 million by 2020.[1] Treatment options include watchful waiting, medical therapy, and both surgical and nonsurgical interventional procedures. One of the most common surgical approaches is transurethral resection of the prostate (TURP), which is associated with a mean 14.8-point improvement in International Prostate Symptom Score (IPSS) at 1 year but has reported perioperative complications including ejaculatory dysfunction (65%), erectile dysfunction (10%), urethral strictures (7%), and urinary incontinence (3%).[2,3] For men who do not want to undergo surgery, a range of medical therapies can be considered. In the past 20 years, less invasive treatments have been introduced including prostatic urethral lift (PUL), transurethral microwave therapy (TUMT), and transurethral needle ablation (TUNA), of which the latter 2 rely on conductive heat transfer to ablate tissue. However, their adoption has been variable because of patient selection issues, durability, and retreatment rates.[4] In addition, further clinical evidence with longer follow-up is required for the newer therapies.[4]

The Rezūm System (NxThera Inc., Maple Grove, MN) uses Convective Water Vapor Energy to deliver targeted, precise thermal treatments of sterile water vapor into the prostate. Radiofrequency power is used to create thermal energy in the form of water vapor, which is injected at slightly above interstitial pressure and rapidly disperses convectively through the cellular interstices. As the water vapor interacts with body temperature tissue, the water vapor condenses, transferring concentrated energy (540 cal/mL H_2O) onto the exterior of the tissue cell

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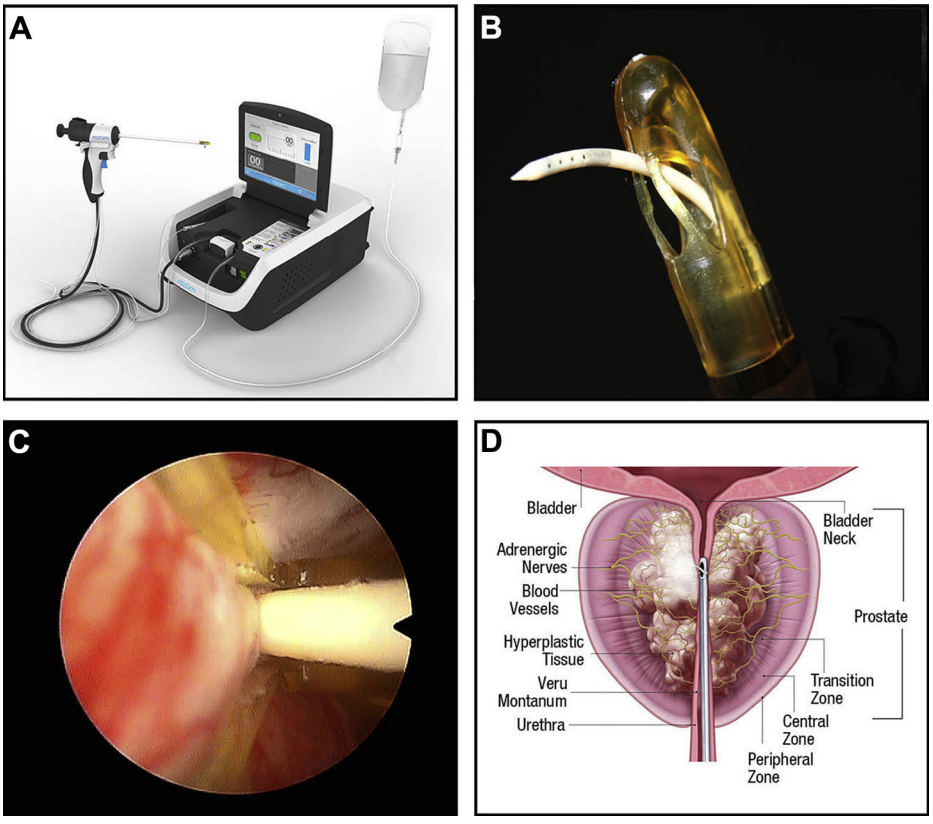

Figure 1. **(A)** Rezūm System generator and transurethral delivery device. The generator delivers RF power into the delivery device, where sterile water is converted into water vapor. **(B)** The tip of the delivery device contains an 18-gauge PEEK needle where 12 small holes allow for water vapor to be circumferentially emitted. **(C)** Transurethrally, the needle is deployed at 90° into the prostatic tissue where **(D)** water vapor is dispersed. Typically, 1 to 3 injections of water vapor are delivered into each lateral lobe, and 1 to 2 injections into a median lobe, if present. RF, radiofrequency; PEEK, polyether ether ketone.

membranes in the treatment area, thereby causing cell death and creating areas of necrosis.[5,6] The zonal anatomy of the prostate[7,8] results in treatments being restricted to the defined targeted areas. The delivery of thermal energy via convection used in water vapor energy differs from conduction of electromagnetic thermal energy (radiofrequency or microwave), which involves the time-dependent transmission of heat through nonmoving material from the area of higher temperature to lower temperature.[5] Previous Rezūm clinical studies have shown large areas of necrosis within the obstructing adenoma produced by injections of water vapor, each of which is completed in less than 10 seconds.[9]

We report here on the 1-year efficacy and safety of the Rezūm System in small-scale pilot studies involving men with lower urinary tract symptoms (LUTS) due to BPH.

MATERIALS AND METHODS

A series of nonrandomized pilot studies were conducted at health centers in the Dominican Republic, the Czech Republic, and Sweden to evaluate the efficacy and safety of the Rezūm System in men with LUTS due to BPH. Sixty-five consented men were enrolled in ethics committee—approved studies, with the first 20 patients treated in the Dominican Republic, the next 18 in the Czech Republic, and the final 27 in Sweden. Each patient was diagnosed with LUTS and met the inclusion criteria, which were the same in each location. Inclusion criteria included the following: age ≥45 years; IPSS ≥15; peak urinary flow (Qmax) ≤15 mL/sec; postvoid residual (PVR) <300 mL; and prostate volume, 20-120 mL.

The Rezūm System included a generator and a single-use transurethral water vapor delivery device that incorporated a standard rigid 30° cystoscope lens (Fig. 1), which allowed the procedure to be performed under direct visualization. Hand-held controls in the device were used to deliver vapor through a polyether ether ketone 18-gauge needle and saline flush for visualization and to cool the urethra during treatments. With the patients in a lithotomy position, the water vapor delivery device was inserted into the urethra. The vapor needle was deployed under direct visualization into the transition zone of the prostate at a fixed depth of 10 mm and water vapor was delivered through 12 small emitter holes spaced around the polyether ether ketone needle at 120° intervals, allowing for the circumferential dispersion of water vapor into the tissue. The sterile water vapor was delivered in injections averaging 9 seconds (range, 7-10 seconds) duration into the tissue commencing approximately 1 cm from the bladder neck at the 3- and 9-o'clock positions. Additional injections of vapor were delivered every 0.5-1.0 cm from the initial injection site caudally

down the length of the prostatic urethra to the proximal edge of the verumontanum. When present, the median lobe was treated with 1-3 injections. The total number of water vapor injections in each lobe of the prostate was determined by the size of the adenoma and length of the prostatic urethra.

At the discretion of the treating physicians, the therapies in this study were performed under intravenous sedation (n = 14) or oral medications such as anxiolytic and nonsteroidal anti-inflammatories (n = 51). Intravenous sedation was administered at the first 2 sites only. In Sweden, patients received oral medications only.

The treatment dosimetry and approach varied slightly from the first patients in the Dominican Republic to the final patient group in Sweden during these pilot studies. The first variation was small adjustments in the amount of water vapor (energy) delivered in each treatment. The first 15 patients in the trial were treated using between 190 and 289 calories per injection, with approximately 0.3-0.5 mL of sterile water vapor utilized per injection. For subsequent procedures, the energy level determined to deliver sufficient lesion size was stabilized at approximately 208 calories, using 0.4 mL of sterile water. The duration of water vapor injection treatments also varied during these trials. In the first 15 patients, the water vapor injections ranged from 7 to 10 seconds. After these initial 15 patients, the duration of the water vapor injections to deliver 208 calories was determined to be optimal at 9 seconds. In addition, the water vapor delivery device was slightly modified several times over the course of these studies to improve the quality and consistency of the water vapor delivered. Collectively, these modifications to the Rezūm System resulted in water vapor treatments which were ultimately delivered uniformly at approximately 103°C with a consistent energy dose of 208 calories.

After the procedure, gadolinium-enhanced magnetic resonance imaging (MRI) was performed on 59 of the 65 patients at each of the 1 week and 1, 3, 6, and 12 months post-treatment evaluations. The evaluation of the treatments using these MRIs provided information which allowed modifications to be made to dosimetry, device design, and procedure approach, including optimization of device placement. It was noted that because of the dispersion of water vapor circumferentially from the needle, delivering vapor treatments 1 cm distal from the bladder neck allowed sufficient thermal energy to be delivered at the bladder neck itself. In the course of the study, the procedural approach was modified to deliver contiguous necrotic lesions parallel to the slope of the urethra.

Follow-up assessments were conducted at 1 week and 1, 3, 6, and 12 months post-treatment to determine the efficacy and safety of the procedure. Qmax, quality of life (QoL), PVR, and prostate-specific antigen (PSA) were evaluated at each time point. IPSS and the International Index of Erectile Function (IIEF) questionnaire were reported at 1, 3, 6, and 12 months. Adverse events (AEs) and serious adverse events (SAEs) were documented.

Descriptive statistics were used for baseline and follow-up study parameters. Data are presented as mean ± standard deviation, means, and 95% confidence intervals or n (%). For efficacy outcome, a paired *t* test was used to evaluate the change from baseline for each measure. A *P* value <.05 indicated statistical significance.

RESULTS

Baseline patient characteristics are shown in Table 1. The mean number of injections into the lateral lobes was 4.6 (range, 2-9 injections). In addition, 14 (22%) patients had median lobes, which were treated with a mean of 1.8 injections (range, 1-3 injections). Seven (11%) patients did not finish the 12-month studies; 3 were lost to follow-up, 2 relocated, and another 2 had failing health (prostate cancer in one at 6 months resulting in a radical prostatectomy). Two (3%) of the early patients proceeded to TURP at 1- and 6-month assessment points, respectively.

Table 1. Baseline patient characteristics

Variable	Mean (SD)
Age, y	66.6 (7.7)
BMI	26.1 (3.4)
PSA, ng/mL	3.9 (4.2)
TRUS volume, mL	48.8 (20.7)
IPSS	21.6 (5.5)
QoL score	4.3 (1.1)
Qmax mL/sec	7.9 (3.2)
PVR, mL	92.4 (77.3)
Ethnicity	n (%)
Caucasian	46 (70.8)
Black or African origin	2 (3.1)
Hispanic or Latino	17 (26.2)

BMI, body mass index; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; PVR, postvoid residual urine; SD, standard deviation; TRUS, transrectal ultrasound; Qmax, maximum flow rate; QoL, quality of life.

Efficacy outcomes are shown in Table 2. The principal measure of clinical success was change in IPSS from baseline, and statistically significant reductions were noted after 1 month and maintained through 12 months (P <.001). At 12 months, the mean change was an improvement of −12.5 (56%). Significant increases were reported in Qmax from 1 month through to 12 months (P <.001); the mean change at 12 months was an improvement of +4.6 (87%). QoL also improved significantly from 1 week through to 12 months (P <.001). At 12 months, the mean change was an improvement of −2.7 (61%). Improvement in PVR occurred from 1 week but was only significant at 1 month (P = .037), 3 months (P = .004), and 12 months (P = .014). At 12 months, the mean change was an improvement of −29 (12%). IIEF scores did not change significantly from 1 to 12 months. A temporary increase in PSA level was reported at 1 week (mean increase of 680%) and 1 month (mean increase of 87%) but returned to baseline values by 3 months.

There were no unanticipated adverse device effects in the 125 AEs reported by 45 patients. Clavien Dindo Grades are shown in Table 3. The 3 Grade IIIb events relate to a single patient (poor stream, frequency, and urinary retention). Urinary retention was defined as inadequate voiding as determined by the physician and classed as an AE if duration was >24 hours. Seventy-five percent of these AEs occurred within the first 30 days after procedure and were typically of short duration. A total of 12 SAEs were reported in 10 patients, one of which was procedure/device related. This case of Clavien Dindo Grade IIIb urinary retention occurred at 33 days

Table 2. Efficacy outcome

Variable	Follow-up Point				
	1 wk	1 mo	3 mo	6 mo	12 mo
IPSS					
N (paired values)		64	62	62	58
Baseline		21.6 (5.5)	21.7 (5.5)	21.6 (5.6)	21.7 (5.7)
Follow-up		14.8 (8.4)	8.3 (5.8)	8.5 (7.0)	9.2 (6.5)
Change		−6.8 (10.0)	−13.4 (7.6)	−13.1 (8.6)	−12.5 (7.6)
Mean % change (95% CI)		−28 (−38 to 17)	−60 (−68 to 52)	−59 (−68 to 49)	−56 (−64 to 48)
P value		<.001	<.001	<.001	<.001
Qmax (mL/sec)					
N (paired values)	61	63	61	60	56
Baseline	8.1 (3.1)	7.9 (3.2)	8.1 (3.2)	8.0 (3.1)	8.2 (3.3)
Follow-up	7.6 (3.9)	9.9 (3.9)	12.8 (6.4)	12.3 (5.3)	12.8 (6.3)
Change	−0.5 (4.2)	2.0 (4.5)	4.7 (6.4)	4.3 (5.5)	4.6 (6.5)
Mean % change (95% CI)	10 (−12 to 31)	54 (25 to 83)	85 (52 to 118)	78 (49 to 107)	87 (51 to 124)
P value	.332	<.001	<.001	<.001	<.001
QoL					
N (paired values)	64	64	62	62	58
Baseline	4.3 (1.1)	4.3 (1.1)	4.3 (1.1)	4.3 (1.1)	4.4 (1.1)
Follow-up	3.6 (1.8)	2.9 (1.8)	1.5 (1.4)	1.6 (1.6)	1.7 (1.4)
Change	−0.8 (1.8)	−1.5 (2.0)	−2.8 (1.6)	−2.7 (2.0)	−2.7 (1.6)
Mean % change (95% CI)	−16 (−27 to 6)	−30 (−41 to 20)	−64 (−71 to 56)	−59 (−71 to 47)	−61 (−69 to 53)
P value	<.001	<.001	<.001	<.001	<.001
PVR (mL)					
N (paired values)	61	62	60	58	54
Baseline	90.7 (77.9)	92.1 (77.9)	89.5 (77.3)	87.3 (74.2)	92.0 (79.1)
Follow-up	117.4 (125.2)	67.1 (64.4)	59.6 (66.4)	65.9 (88.5)	63.1 (72.2)
Change	26.7 (131.1)	−25.0 (92.3)	−29.9 (78.0)	−21.4 (88.3)	−28.9 (83.2)
Mean % change (95% CI)	88 (17 to 159)	21 (−24 to 65)	−20 (−41 to 1)	3 (−38 to 44)	−12 (−38 to 14)
P value	.117	.037	.004	.071	.014
IIEF					
N (paired values)		52	54	53	52
Baseline		32.9 (25.7)	32.5 (25.2)	33.9 (25.5)	33.4 (25.1)
Follow-up		29.2 (24.7)	38.6 (24.3)	40.2 (25.0)	38.4 (24.5)
Change		−3.7 (21.3)	6.1 (21.3)	6.3 (17.6)	5.0 (17.3)
Mean % change (95% CI)		34 (−9 to 77)	90 (36 to 144)	79 (32 to 126)	72 (23 to 121)
P value		.216	.040	.012	.041
PSA (ng/mL)					
N (paired values)	42	26	61	61	58
Baseline	3.9 (4.2)	4.7 (4.7)	4.0 (4.3)	4.0 (4.3)	4.0 (4.4)
Follow-up	20.2 (20.1)	6.4 (5.4)	4.2 (4.6)	4.4 (4.9)	4.7 (6.0)
Change	16.3 (18.3)	1.7 (3.8)	0.2 (2.8)	0.4 (3.4)	0.7 (4.0)
Mean % change (95% CI)	680 (447 to 913)	87 (27 to 147)	22 (−13 to 56)	35 (−9 to 79)	34 (2 to 66)
P value	<.001	.036	.660	.357	.159

CI, confidence interval; IIEF, International Index of Erectile Function; other abbreviations as in Table 1.

post-treatment, persisted, and resulted in the subject electing to undergo a TURP procedure at 42 days.

Overall, 36 patients were catheterized immediately after procedure or before release. Of these, 15 were at the discretion of the physician, 14 because of inadequate voiding as determined by physician, 6 because of hematuria, and 1 because of dysuria. The catheter remained in place for an average of 5.6 days (range, 1.0-29.1 days). The patient who was catheterized for 29 days requested a prolonged catheter time as he was traveling out of the country. An additional 11 patients were catheterized after release: 10 were due to urinary retention and 1 patient due to him traveling. For these men, catheter time averaged 4.3 days (range, 0.3-17.0 days).

COMMENT

The initial studies with the Rezūm System evaluated the histologic effects of the device following treatment of patients who were previously scheduled to undergo an open prostate adenectomy.[9] Results showed thermal ablation in the transition zone as well as a distinct

Table 3. Safety outcome—Clavien Dindo grade of device and procedure-related events

Adverse Event	Number of Events	Number of Patients (%)	Clavien Dindo Grade					
			Grade I	Grade II	Grade IIIa	Grade IIIb	Grade IV	Grade V
Urinary retention	25	22 (33.8)	24	0	0	1	0	0
Dysuria	14	14 (21.5)	14	0	0	0	0	0
Urinary urgency	14	13 (20)	14	0	0	0	0	0
UTI—suspected	13	13 (20)	1	12	0	0	0	0
Hematuria	10	9 (13.8)	10	0	0	0	0	0
Poor stream	9	9 (13.8)	8	0	0	1	0	0
Painful urination	7	7 (10.8)	7	0	0	0	0	0
Nocturia	6	5 (7.7)	6	0	0	0	0	0
Urinary frequency	5	4 (6.2)	4	0	0	1	0	0
Urethral secretion—without hematuria or stones	3	3 (4.6)	3	0	0	0	0	0
Fever	3	3 (4.6)	3	0	0	0	0	0
Urinary incontinence—urge	2	1 (1.5)	2	0	0	0	0	0
Terminal dribbling	2	2 (3.1)	2	0	0	0	0	0
Scrotal pain/discomfort	2	2 (3.1)	2	0	0	0	0	0
Urinary incontinence—not specified	1	1 (1.5)	1	0	0	0	0	0
UTI—prophylaxis	1	1 (1.5)	0	1	0	0	0	0
Prostatic urethral injury	1	1 (1.5)	1	0	0	0	0	0
Bladder spasms	1	1 (1.5)	1	0	0	0	0	0
Epididimytis	1	1 (1.5)	0	1	0	0	0	0
Prostatic cyst de novo	1	1 (1.5)	1	0	0	0	0	0
Hesitancy	1	1 (1.5)	1	0	0	0	0	0
Gross hematuria with clots and retention	1	1 (1.5)	1	0	0	0	0	0
Perineum pain/discomfort	1	1 (1.5)	1	0	0	0	0	0
Pelvic pain/discomfort	1	1 (1.5)	1	0	0	0	0	0
Total	125	45 (69.2)	108	14	0	3	0	0

UTI, urinary tract infection.

interface between viable and necrotic prostatic parenchyma. A second study involving 15 patients with BPH included an MRI evaluation of lesions produced by the Rezūm System.[9] Mean lesion size was 9.6 mL, and lesions were confined to the transition zone.

The results presented in this study demonstrate that the Rezūm System is an effective treatment for LUTS secondary to BPH. Clinically and statistically significant improvements were observed from 1 month, and at 12 months IPSS improved by 12.5 points and Qmax by 4.6 mL/second. The outcome at 6 months is comparable to that reported by other minimally invasive therapies.[10-15] QoL improvements were reported from 1 week and were maintained out to 12 months. Again, these findings are in line with other minimally invasive therapies.[10-15] Prostate volume changes are reported in a separate paper, and at 6 months demonstrate a 28.9% volume reduction as compared with 1-week magnetic resonance images.[16]

The safety of the Rezūm System was confirmed in the study. A number of the AEs reported were typical of endoscopic procedures and were transient. It has been reported in a community-based study that dysuria can occur in 50% of patients following cystoscopy, in addition to a 37% rate of urinary frequency and 19% gross hematuria.[17] Twelve AEs were classified as SAEs and only one of these was classified as procedure/device related. It appeared that erectile function was not adversely affected by treatment in the manner tested in the study. As postprocedural catheterization was at the physician's discretion, and often accomplished as convenience in the study countries, the rates of catheterization likely do not provide an accurate estimate of the need for post-treatment catheterization. TUMT and TUNA thermal energy treatments involve the use of conductive heat transfer and, thereby, require a greater amount of energy to be delivered over a longer period of time, resulting in coagulative necrosis. Because stored thermal energy within sterile water vapor is convectively dispersed through the interstices of the prostatic tissue, the energy deposited from the condensation of water vapor is inherently more efficient as compared with the energy delivered by the conductive ablation devices.

The Rezūm System uses radiofrequency power to convert sterile water into stored thermal energy in the form of water vapor. When this water vapor is delivered into the tissue using the principles of convective heat transfer, condensation releases the stored thermal energy onto cell membranes, where almost instantly, the membranes are denatured, rendering the cells unviable, followed by necroptosis. One of the limitations of the study was the modifications made to the technique as experience was gained. There were slight modifications in endoscopic

technique arriving at a series of overlapping injections running parallel to the slope of the urethra. In addition, the water vapor delivery device was slightly modified several times over the course of these studies to improve the quality and consistency of the water vapor delivered. The data presented provide valuable insight into the early clinical development of this technology, but there are additional limitations of this report that should be noted. Erectile function was assessed, but a change in ejaculatory function was not captured beyond Q9 in the IIEF. In addition, this study was not designed, powered, or intended to make a definitive assessment of the safety and efficacy of this treatment but rather to validate the principles of convective water vapor therapy in BPH and provide direction for the design and implementation of a multicenter, randomized, sham-controlled pivotal trial which is underway.

CONCLUSION

The convective transfer of the stored thermal energy of water vapor to ablate prostate tissue with the Rezūm System holds promise as a treatment for LUTS related to BPH. Clinical efficacy and safety of the treatment can be achieved up to 12 months. Patients' QoL is improved and erectile function maintained. This flexibility of treatment makes the procedure potentially viable for a broad range of patients, including those with median lobes. Magnetic resonance studies on the effects of the Rezūm System in this group of patients are reported separately.

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