



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203



Human Journals

Review Article

November 2018 Vol.:13, Issue:4

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Rezum: A New Non Invasive Promise for Benign Prostate Hyperplasia Treatment



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Submission: 22 October 2018

Accepted: 28 October 2018

Published: 30 November 2018



HUMAN JOURNALS

www.ijppr.humanjournals.com

Keywords: BPH, LUTS, MIT, Rezum systems, Thermal ablation, cost-effectiveness.

ABSTRACT

BPH (Benign Prostate Hyperplasia) is a disease commonly seen in elderly males and is a condition of the enlarged prostate that causes voiding difficulties and other LUTS (Lower Urinary Tract Symptoms). Many treatment options are available for treating BPH. Minimally invasive procedures are now being used including RF thermal therapies (Rezum and Prostiva systems) and Prostatic urethral lift. The aim of this review is to show the efficacy and safety of thermal ablation using Rezum system. FDA approved Rezum system in 2015 to treat symptomatic BPH. It has been demonstrated to have substantial, prolonged symptomatic relief, with positive outcomes in IPSS (International prostate symptom score), Q_{max} (maximum urine flow rate), PVR (Post-void residual volume) and QoL (quality of life), without causing erectile and ejaculatory dysfunctions. There is relative cost-effectiveness of Rezum compared to other MIT's and combination drug treatment.

INTRODUCTION

BPH (benign prostate hyperplasia) is a disease common with elderly males. It is a condition of the enlarged prostate that causes voiding difficulties and other LUTS often leading to further bladder and kidney problems. Prevalence of BPH is 25% at 40-49 age group and 80% at 70-79 years of age^[1]. That is the disease progression with increasing of their age.

Many treatment options are available for treating BPH. Watchful waiting is often preferred in those having mild symptoms and should be considered together with bladder training and lifestyle modifications.^[2]

Combination drug therapies are considered as the next option. Generic combinations of drugs are both clinically and cost-effective compared to brand combinations prescribing. But the generic prescription is not followed due to non-availability and distrust of quality^[3]. This often leads to high treatment cost, particularly in cases of longer duration of therapies^[4]. Lack of medication adherence is another problem faced by pharmacological treatment.

Minimally invasive procedures are now being used for avoiding wait full long treatment period and for quick relief from symptoms. They include RF thermal therapies (Rezum and Prostiva systems) and Prostatic urethral lift (pro-life systems). They also have lesser hospital stay than more invasive procedures like green light PVP (Photo-vaporization of Prostate) and TURP (Transurethral Resection of Prostate). The aim of this review is to show the efficacy and safety of new minimally invasive procedure of thermal ablation using Rezum system.

Developments of MIT's are mainly done for an OP procedure, no need for anesthesia, minimizing post-procedure complications together with clinical efficacy. This has lead to the development of needle insertion and ablation techniques using water vapor, radio frequencies together with mechanical interventions like Uro Lift technology.

High energy radiofrequency thermal therapy procedures include Rezum system and Prostiva system and are now being used for minimally invasive treatments. A study by James C Ulchaker and Melissa S Martinson shows improved I-PSS scores and QoL by Rezum and is much less expensive and might be a preferred choice in managing BPH for a health care system seeking to contain cost^[4].



Figure: 1; Rezum System generator and transurethral delivery device.

Rezum System

Thermal therapy is used to treat various diseases such as menorrhagia, cancer, and benign prostate hyperplasia. Rezum is a thermal therapy used for the treatment of BPH and can be performed in a clinic or out-patient setting. FDA approved Rezum system in 2015 to treat symptomatic BPH. Rezum is a safe and effective minimally invasive treatment that relieves lower urinary tract symptoms caused by BPH.

Rezum uses the stored thermal energy in form of water vapor (steam) to treat the extra prostate tissue that is causing symptoms such as frequency, urgency, irregular flow, weak stream, straining and getting up at night to urinate.

Mechanism of Action

Developed by NxThera, Rezum is a minimally invasive therapy in the U.S. it uses the natural thermal energy, to treat the enlarged prostate tissues. This new model is based on a thermophysical property of liquid and rate of blood perfusion model. In this method, radio frequency (RF) energy is applied to water droplets to produce vapor (steam). The water vapor is injected into the prostate tissue that is blocking the flow of urine from the bladder, when the vapor comes in contact with the tissue it condenses and turns back to water, releasing the energy stored in the vapor into the cell membranes results in damage of cell causing cell death. Over the next few weeks, the body's natural healing response eliminates the treated tissue, shrinking the prostate. The removal of extra tissue causes the urethra to opens and thereby reducing BPH

symptoms and improving the patient's quality of life. Studies have shown that the Rezum treatment allows men to retain sexual function.



Figure: 2; *The tip of the delivery device contains an 18-gauge PEEK needle where 12 small holes allow for water vapor to be circumferentially emitted.*

Principle

The principles of RF-generated water vapor thermal energy are based on the thermodynamic properties of water and the use of convective versus conductive heat transfer to ablate tissue. Convection is the movement of a heated gas or liquid within a defined space whereas conduction is the transfer of heat through a nonmoving material from the area of higher temperature to lower temperature.

In Rezum System transurethral thermal therapy utilizes RF to generate wet thermal energy in the form of water vapor and it generates vapor by application of radiofrequency energy to create heat via electromagnetic induction in the handle of the delivery device.

A PEEK (polyether ether ketone) needle is smoothly and rapidly deployed under direct visualization into the obstructive regions of the transition zone and the steam is delivered into the tissue from an array of vapor emitter holes spaced 120 degrees circumferentially around the tip of the needle. Each injection of steam is for approximately 9 seconds. Steam fills a defined space between the cells as the vapor (103°C) disperses through the tissue, its phase shifts from vapor to liquid immediately upon injection into the tissue, releasing and delivering 208 calories of thermal energy in 9 seconds. The target tissue temperature reaches about 70°C resulting in irreversible and instantaneous cell death, creating a roughly spherical ablative lesion. Because vapor has mass and is physically less dense it travels through the interstices between cells.

No thermal effects have been shown to occur outside of the prostate or in the peripheral zone when the transition zone (TZ) is targeted. The number of injections in each prostate is determined by the size of the adenoma and length of the prostatic urethra. In addition, because the vapor is wet thermal energy, there is no charring, desiccation, or carbonization of the treated tissue, while tissue ablation involving conductive heat transfer (TUNA- Transurethral needle ablation or TUMT- Transurethral Microwave Therapy) induces molecular agitation. Most common adverse effects are dysuria, haematuria, haemospermia and UTI [5].

Procedure

The mechanism of action for the Rezum system uses the principles of convective heat transfer that exploits the thermodynamic properties of water. The system comprises a radio frequency (RF) generator and a single-use transurethral delivery device containing 4 mm 30-degree cystoscopy lens. RF current is applied to an inductive coil heater, producing thermal energy in the form of water vapor. Water vapor is delivered through a retractable vapor needle *via* emitter holes in the transurethral device^[6]. This is done in 9-second bursts to the transition zone of the prostate, where, *via* convection, it diffuses evenly throughout the target tissue. The depth of the needle penetrating is approximately 10 mm.

Upon contact with body-temperature of tissue, the water vapor then condenses. This phase shifts to a liquid state from vapor state and results in cell necrosis^[7, 8]. Saline flush irrigation is used to both cool the urethra and to promote visualization^[9]. The efficacy of the Rezum system has been assessed with gadolinium-enhanced magnetic resonance imaging and histological testing post procedure. Both tests have demonstrated that the Rezum system was successful at producing necrosis in targeted cell tissue while preserving non-treated tissue around the area. The procedure can be performed in an office or ambulatory outpatient with minimal transient Perioperative side effects^[10].

Advantages

Firstly, it has been demonstrated to have substantial, prolonged symptomatic relief. The most extensive data were collected for a period of 36 months, and patients in these studies were shown to have sustained positive outcomes in IPSS, Q_{max} , PVR, and QoL^[11]. Moreover, these improvements in LUTS and urinary flow come without impacting their erectile and ejaculatory function typically associated with TURP^[12]. There have been no de novo cases of ejaculatory dysfunction reported in the data so far reported^[9,13]. Another significant benefit is that it can be

performed as a day case procedure in an outpatient setting. It has predominantly been performed under sedation. In contrast with many other novel BPH therapies, Rezum is able to target and treat the prostatic median lobe.

Disadvantages

Rezum does not collect tissue specimens; therefore, it lacks the ability to ascertain incidental cases of prostate cancer. Patient with urinary retention and large prostate burdens potentially would not be eligible, excluding a significant section of the patient population.

Table: 1; Advantages and Disadvantages of Rezum system

ADVANTAGES	DISADVANTAGES
<ul style="list-style-type: none"> • <i>Cost-effective</i> 	<ul style="list-style-type: none"> ▪ <i>Not suitable for the large prostate size (>120 ccs)</i>
<ul style="list-style-type: none"> • <i>Out-patient procedure</i> 	<ul style="list-style-type: none"> • <i>Exclusion criteria- Urinary retention</i>
<ul style="list-style-type: none"> • <i>The strong short-term safety profile</i> 	<ul style="list-style-type: none"> • <i>Not suitable for a patient with recurrent UTI</i>
<ul style="list-style-type: none"> • <i>Time for the procedure – short</i> 	<ul style="list-style-type: none"> • <i>Only limited reports available</i>
<ul style="list-style-type: none"> • <i>Good improvement in subjective and objective outcome measures: ipss and qol</i> 	<ul style="list-style-type: none"> • <i>Not suitable for patients if the prior invasive procedure for treatment of prostate or prior radiation on prostate</i>
<ul style="list-style-type: none"> • <i>No reports of erectile dysfunction</i> 	<ul style="list-style-type: none"> • <i>Require catheterization in some cases</i>
<ul style="list-style-type: none"> • <i>Can be preferred for obstruction in the median lobe.</i> 	
<ul style="list-style-type: none"> • <i>Can only be performed under anesthesia</i> 	
<p><i>IPSS, International Prostate Symptom Score; QoL, Quality of life; UTI, urinary tract infection</i></p>	

Complications

The most common adverse events are dysuria, haematuria, haemospermia, symptoms of urgency and UTIs and resolve within a few weeks. In a pilot trial done by Dixon and colleagues reported a patient with three grade 3b AEs wherein a patient had persistent LUTS symptoms with the poor stream, frequency and urinary retention recorded as separate events; in this case, the patient opted for TURP procedure at 42 days^[9]. A crossover trial found that two patients suffered three serious procedure-related AEs collectively, including one patient who developed

urosepsis post cystoscopy and on a patient who suffered from bladder calculi and bladder neck contracture^[14]. Finally, a published RCT by McVary and colleagues in 2016 recorded two treatment subjects having serious AEs: one patient had *de novo* extended urinary retention, a second patient was admitted to the hospital overnight for observation due to nausea and vomiting after taking alprazolam^[15].

Safety, Efficacy, and Tolerability

A study conducted by Christopher et al. showed that the Rezum system is an effective treatment for LUTS secondary to BPH. Rezum had shown clinically and statistically, improvement in LUTS within 1 month and at 12 months IPSS improved by 12.5 points, improvement in PVR occurred from 1 week but was only significant at 1 month, 3 months and 12 months and improvement in Q_{max} occurred by 4.6 mL/second. A temporary increase in PSA level was reported at 1 week and 1 month but returned to baseline values by 3 months. The outcome at 6 months is comparable to that reported by other minimally invasive therapies. QoL improvements were reported from 1 week and were maintained out to 12 months and at 6 months there was a significant reduction in prostate volume by 28.9%.^[16]

The safety of the Rezum System was confirmed in this study. A number of the AEs reported were due to the endoscopic procedures such as dysuria which occurred in 50% of patients following cystoscopy, in addition 37% had a change in urinary frequency and 19% had haematuria. It appeared that erectile function was not adversely affected by Rezum therapy.

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 more efficient as compared with the energy delivered by the conductive ablation devices.^[16]

Table:2; Adverse Events reported for the Rezum Pivotal Clinical Trial were mild to moderate in severity and resolved within 3 weeks.

MOST COMMON DEVICE AND/ OR PROCEDURE RELATED ADVERSE EVENTS	TREATMENT SUBJECTS (N= 136)	RESOLVED
Dysuria	24 (16.9%)	23
Hematuria	16 (11.8%)	16
Hematochezia	10 (7.4%)	9
Urinary frequency	8 (5.9%)	6
Urinary urgency	8 (5.9%)	5
Total events (#patients, %)	151 (55, 40.4%)	124

Cost-effectiveness

The treatment options for BPH are:

- Therapy with a combination of prescription drugs (ComboRx) which include an alpha-blocker (Tamsulosin or doxazosin) and 5 α reductase inhibitor (Finasteride, Dutasteride)
- Minimally Invasive Therapies
 - Rezum System (a radio frequency [RF] thermal therapy procedure)
 - Prostiva RF Therapy System (an RF thermal therapy procedure)
 - UroLift System (prostatic urethral lift)
- Surgical therapies
 - TURP (Transurethral Resection of Prostate)
 - Green light laser photo-vaporization of the prostate

Most of the surgical invasive procedures such as TURP and Greenlight have greater symptomatic relief but the postoperative patients may experience a higher incidence of incontinence, stricture, stenosis, and UTI. Treatments with ComboRx are least expensive,

showed less symptomatic improvement and had a higher rate of erectile dysfunction. The generic ComboRx is least expensive compared to branded ComboRx.

The two minimally invasive RF energy-generated thermal therapies, Prostiva and Rezum, were similar; they were intermediate in costs and effects when compared to Greenlight PVP and TURP. They have IPSS reductions of 25% less than TURP (16-point IPSS reduction) however the ICERs were considerably higher for TURP and Greenlight PVP. A comparison of the two RF thermal therapies, Rezum and Prostiva, shows Rezum to be slightly more expensive time and more effective, indicating that the costs are unlikely to differ much, but offering strong evidence of a point that difference occurs ineffectiveness. The UroLift procedure costs about \$3,500 more than a Rezum procedure on average. It is more expensive and less effective, therefore the Rezum procedure dominates. The Rezum therapy is more costly than generic ComboRx but comparing both simulations Rezum is more effective. So it can be concluded that Rezum and Prostiva are the next frontier therapies. ^[17]

Rezum vs TURP

In fact, medical therapy usually preferred for patients with mild to moderate voiding symptoms and TURP is preferred as the most commonly used surgical option and is the standard option for severe BPH for the improvement in urinary function. TURP may be associated with perioperative morbidities directly related to prostate volume and surgically high-risk patients with associated comorbidity, including pacemakers, and anticoagulant and platelet anti-aggregate medications. TURP and Green light PVP remain the most costly alternatives today and typically are reserved for treatment of moderate-to-severe LUTS or larger prostates.

Comparatively, the rates of AEs including incontinence, UTI, erectile dysfunction and bladder neck contracture, for these surgical procedures are significant, again contributing to more discomfort for the patients and costs to patients. The new MIT - RF Rezum thermal therapy (FDA clearance 2015) has given rise to therapies that provide durable relief of urinary symptoms over at least 2 years of follow-up with IPSS improvements nearly approaching those of TURP and Green light PVP for patients with moderate-to-severe LUTS/ BPH.

Rezum vs UroLift

Comparing Urolift and Rezum, their effectiveness is supported by well-controlled studies. Currently, these technologies serve as a bridge between medical management and surgical

options due to demonstrated tolerability, safety and effectiveness, and cost savings. However, Rezum is much less expensive and might be a preferred choice in a health care system seeking to contain costs. UroLift costs more and provides slightly less relief than Rezum. The re-treatment rate for Rezum is about 4% over 2 years compared with about 7.5% to UroLift. In the UroLift procedure patients had a fivefold or greater rate of return of symptoms.

Rezum vs Prostiva

The Rezum System uses the convective delivery of stored thermal energy via steam water vapor created with RF electromagnetic energy, rather than the application of RF energy directly to prostate tissue with the Prostiva System which relies on the conductive delivery of heat thermal energy through the tissue. [17]

SUMMARY

The convective transmission of the stored thermal energy of water vapor to ablate prostate tissue with the Rezum System holds promise as a treatment for LUTS related to BPH. So far, data from available studies point towards good clinical outcomes for BPH and preserving sexual function. They are cost-effective, safe and efficacious treatment strategy with better improvement in IPSS and QoL and has an only short-term risk of self-limiting minor complications. This flexibility of treatment makes the procedure to be used within a broad range of patients, including those with median lobes. It is applicable to the outpatient setting, for its versatility in its ability to treat a variety of prostate gland morphologies.

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