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Rezum: a new transurethral water vapour therapy for benign prostatic hyperplasia

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Abstract: Rezum is a minimally invasive transurethral water vapour therapy for benign prostatic enlargement which uses thermal energy for treatment. The short-term results show it to have good outcomes with a potential for outpatient-based treatment preserving sexual function. This review serves to provide an overview of the technique and evaluate its safety and efficacy.

Keywords: Rezum, BPH, Prostate, benign prostatic hyperplasia, minimally invasive surgery, TURP, LUTS, lower urinary tract symptoms

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Introduction

Benign prostatic hyperplasia (BPH) is a common urological condition characterized by progressive increase in the size of the prostate gland. It is a disease of ageing, affecting 40% of men in their 50s and 90% of men over 90 years.[1] In a large proportion of BPH patients, prostate enlargement causes bladder outflow obstruction (BOO), which results in lower urinary tract symptoms (LUTS). LUTS have a significant impact on quality of life (QoL) with symptom progression often correlating with progressive prostatic enlargement.[2–5] Furthermore, there is a considerable socioeconomic burden as it represents the most commonly presenting urological complaint.[2]

The current management algorithm for LUTS caused by BOO secondary to BPH includes conservative approaches (watchful waiting and lifestyle modifications), pharmacotherapy and surgical intervention. However, pharmacotherapy can produce unsatisfactory symptom relief. Furthermore, it can be associated with adverse effects such as postural hypotension, asthenia and reduced sexual function.[5] Surgical intervention remains the mainstay treatment for this clinical problem. While there are a number of options now available including Holmium laser enucleation of the prostate, UroLift and prostate artery embolization,[3] transurethral resection of the prostate (TURP) is still considered the gold standard intervention. However, TURP is not without its own limitations. This includes a high complication rate and retreatment rate of 1–2% per year.[4] Complications include retrograde ejaculation (65%), erectile dysfunction (10%), urethral stricture (7%), urinary tract infection (UTI) (4%), bleeding requiring transfusion (2%) and urinary incontinence (2%).[3–4] Furthermore, it requires the use of general or spinal anaesthesia and carries a mean hospital stay of 2 days.[3,4] In order to improve this, several minimally invasive procedures have been developed with the aim of providing alternative surgical strategies to TURP.[5,6] Among these is the Rezum system (NxThera, Maple Grove, MN, USA), a novel ablative procedure, which has gained increasing attention since receiving United States Food and Drug Administration (US FDA) approval in 2015. This article outlines the evidence for Rezum with the objective of assessing its usefulness through measures of efficacy, safety and durability.

The procedure

In contrast with other minimally invasive procedures that utilise conductive heat transfer, such as transurethral needle ablation or transurethral microwave therapy (TUMT), the mechanism of action for the Rezum system uses the principles of convective heat transfer that exploits the thermodynamic properties of water.[5] The system

comprises a radiofrequency (RF) generator and a single-use transurethral delivery device, which incorporates a standard 4 mm 30-degree cystoscopy lens. With the patient in a lithotomy position, an RF current is applied to an inductive coil heater, producing thermal energy in the form of water vapour. Water vapour is delivered through a retractable vapour needle *via* emitter holes in the transurethral device.[7] 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 tissue, the water vapour then condenses. This phase shift to a liquid state dispenses concentrated energy onto the cell membranes of the target tissue, triggering instant cell necrosis. Overlapping injection sites can be established with repeated applications in order to fully target areas of hypertrophy. Saline flush irrigation is used to both cool the urethra and to promote visualization.[8] The efficacy of the Rezum system has been assessed with gadolinium-enhanced magnetic resonance imaging and histological testing post procedure. Both tests have demonstrated the Rezum system to be successful at producing necrosis in targeted cell tissue while preserving non-treated tissue around the area, as the thermal energy is contained within the zonal boundaries of the prostate.[7,9] Mean reduction of total prostate volume at 6 months post procedure was 28.9%.[7] Anaesthesia and sedation use is varied and used at the discretion of the clinician. Majority of patients received oral sedation only, approximately 1/5 of patients required prostate block and 10–20% required intravenous sedation.[8,10]

Results

The results are provided in Table 1. Since US FDA approval in 2015 numerous studies on Rezum have been published, including one randomized controlled trial (RCT) with a 36-month follow up, one crossover trial and one pilot trial, with an additional recently published retrospective study post-approval.[8–11] In 2016 a pilot trial by Dixon and colleagues, following up at 24 months demonstrated a mean change of international prostate symptom score (IPSS) from 21.7 to 9.6, a mean improvement of Qmax from 8.3 ml/s to 12 ml/s and a mean change of postvoid residual (PVR) from 78.5 to 62.8 ml.[8] The results from the 5-year RCT, currently with a 3-year follow up, has shown a mean improvement of IPSS of 11 points, a mean Qmax improvement from 9.7 ml/s to 13.2 ml/s and a mean PVR improvement from 81.5 ml to 55.1 ml ($p < 0.001$).[10] The crossover trial has demonstrated a mean improvement of IPSS at 12 months from 19.4 to mean 8.6, a mean Qmax improvement from 10.3 ml/s to 16.2 ml/s and a mean PVR decrease from 101 ml to 83.8 ml ($p < 0.001$).[12] Crossover trials are particularly useful in highlighting outcomes as participants serve as self-controls, so possible placebo effects can therefore be negated. These results point towards a significant improvement in clinical outcomes in all studies including IPSS, Qmax and PVR with $p < 0.001$ as outcome measures, with the greatest improvement seen in IPSS, which every study reported as having a mean improvement of over 10 points. Clinical improvements were seen from as early as 1 month post procedure. Furthermore, no *de novo* cases of ejaculatory dysfunction were reported in any of the selected studies. Retreatment rates varied between 3% and 5%.

In most surgical treatments for BPH, a high incidence of negative impact on ejaculatory function is common. The RCT conducted also measured sexual function, using the International Index of Erectile Function (IIEF-15) and the Male Sexual Health Questionnaire for Ejaculatory Function (MSHQ-EjD) as indicators. Patients who were not sexually active were censored. A study by McVary and colleagues[13] published data specifically on these outcomes using regression analysis to analyse the results from baseline to 1 year. There was no device-related or treatment-related cases of *de novo* erection dysfunction. Notably, the ejaculatory bother score improved by 31% compared with baseline, and 27% achieved minimal clinically important differences in erection function at 1 year.[13] A key strength of convective water vapour thermal therapy, therefore, seems to lie in its ability to preserve sexual function.

Potential further scope for the practical application of the Rezum procedure in nontrial settings has been established by a recent, retrospective study.[11] The study analyses Rezum in 131 patients in the postmarket environment in multiple medical centres. The selection criteria were at the discretion of the urologist. This included patients with varying prostate sizes (13–183 cm), patients who had previously had invasive prostate treatment (including TURP and other minimally invasive treatments) and patients in retention (PVRs ranged from 0 ml to 2000 ml, mean

Table 1. Measured outcomes of Rezum at 12 months.

Authors	Year	*N* = total *n* = Rezum	IPSS (%) reduction	Qmax (%) improvement	PVR (%) reduction	IPSS QoL (%) reduction	IIEF-EF (%) improvement	Complications (related adverse events), *n*		Supported by industry
								Clavien–Dindo I-II	Clavien–Dindo III–V	
McVary and Roehrborn (RCT)[10]	2017	*N* = 201 *n* = 136	53	55	5	52	−1	Dysuria: 16.9% Haematuria: 11.8% Frequency and Urgency: 5.9%	*N* = 3 (2.2%) (urinary retention =1, hospitalization due to nausea and vomiting =1, NOS = 1)	Yes
Dixon and colleagues (pilot)[8]	2016	*N* = 65 *n* = 65	58	55	32	61	11	Urinary retention: 33.8% Dysuria: 21.5% Urgency: 20% UTI (suspected): 20% Haematuria: 13.8% Poor stream: 13.8% Pain/discomfort: 10.8% Nocturia: 7.7% Frequency: 6.2% Fever: 4.6% Dribbling: 3.1% Scrotal pain: 3.1% Incontinence: 1.5%	*N* = 3 (4.6%) (urinary retention = 1, poor stream = 1, urinary frequency = 1)	Yes
Roehrborn and colleagues (crossover)[12]	2017	*N* = 53 *n* = 53	56	53	17	55	18	Dysuria: 18.9% Haematuria: 11.3%	*N* = 3 (5.6%) (bladder neck contracture = 1, bladder stone formation =1, sepsis = 1)	Yes
Darson and colleagues[11]	2017	*N* = 131 *n* = 131	45	51	35	38	n/a	Acute urinary retention: 10.7%	Nil	No

IIEF-EF, international index of erectile function; IPSS, international prostate symptom score; n/a, not applicable; NOS, not otherwise specified; PVR, post-void residual; Qmax, urine flow rate; QoL, quality of life; RCT, randomized controlled trail; UTI, urinary tract infection.

Table 2. Advantages and disadvantages of Rezum.

Advantages	Disadvantages
• Can be performed under sedation only • Day case procedure • Strong short-term safety profile • No reports of *de novo* sexual dysfunction • Suitable for patients with an obstructing median lobe • Short procedure time • Good improvement in subjective and objective outcome measures: IPSS, QoL, Qmax and PVR • Cost effective	• Limited long-term data available • Patients with urinary retention excluded • Not suitable for patients with history of recurrent urinary tract infections • Not suitable for large prostate size (>120 cc) • Not suitable for patients if prior invasive procedure for treatment of prostate or prior radiation on prostate • >50% patients require catheter post procedure

IPSS, international prostate symptom score; PVR, post-residual volume; Qmax, urine flow rate; QoL, quality of life.

216.6 ml). The findings of this retrospective study are in line with the outcomes from both RCT, crossover and pilot studies. At 12 months, the mean IPSS from a baseline of 19.5 was reduced by an average of 9.4 points. This suggests significant symptomatic relief of LUTS symptoms. The use and subsequent success of the Rezum procedure in such a varied cohort that is not limited by prostate size, urinary retention or previous procedures highlights further potential uses of Rezum that might fill a niche in the current arsenal of BPH treatment methods. However, more data collected over a longer period would be required to demonstrate reproducible results.

Advantages

The Rezum procedure has a number of advantages (Table 2). 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, Qmax, PVR and QoL.[14] Moreover, these improvements in LUTS and urinary flow come without impacting their erectile and ejaculatory function typically associated with TURP.[15] There have been no de novo cases of ejaculatory dysfunction reported in the data so far reported.[8,10] Gupta and colleagues[16] have shown that compared with standard medical therapies, Rezum had significantly better outcomes for QoL, IPSS and prostate volume. Compared with finasteride monotherapy, Rezum had significantly improved Qmax, however this was not replicated in comparison with doxazosin monotherapy or dual therapy. Longer-term follow up is needed to ensure the durability and replicability of the results seen in trial studies so far.

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,[8] negating the need for a general anaesthetic. However, as the Rezum procedure is planned on rigid cystoscopy, which in the United Kingdom (UK) is predominately carried out under general anaesthesia, the success of day case Rezum procedures in clinical settings in the UK is yet to be established.

Furthermore, there is a short resection time (average of 8 min) of Rezum, potentially limiting the window in which adverse events can occur,[7] while maximising the number of procedures that can be undertaken. In contrast with many other novel BPH therapies, Rezum is able to target and treat the prostatic median lobe. This expands the potential patient cohort eligible for this procedure.[14] In theory, there are no anatomical restrictions for Rezum and in the future it is anticipated there will be evidence to support its application for larger prostate burdens. The current recommended cut-off of 120 cc is a reflection of surgeon and study experience to date.

Disadvantages

It is evident that the Rezum system has many strengths that endorse its use. Despite this, it is not without its disadvantages. A significant benefit of TURP is its use in incidental identification of prostate cancer, with positive detection on 4.1–16.7% of TURP specimens.[17] In contrast, Rezum does not collect tissue specimens; therefore, it lacks the ability to ascertain incidental cases of prostate cancer. Furthermore, the nature of the exclusion criteria limits the number of patients who qualify for the procedure. Patients with

Table 3. Selection criteria used in studies.

Inclusion criteria	Exclusion criteria
• >45 years with symptomatic BPH • IPSS 13 or greater • Qmax between 5 ml and15 ml per second • Prostate volume <120 cc	• Prior invasive prostate intervention/surgery • PVR > 300 ml • PSA > 2.5 ng/ml • Recurrent/active urinary tract infection

BPH, benign prostatic hyperplasia; IPSS, international prostate symptom score; PVR, post-residual volume; PSA, prostate-specific antigen.

urinary retention and large prostate burdens potentially would not be eligible, excluding a significant section of patient population.

Catheterization post procedure is at the discretion of the clinician. In a pilot trial by Dixon and colleagues,[8] 55% of patients were catheterized prior to discharge plus an additional 17% requiring catheterization post discharge, with an average duration of catheter use of 4.1 days. Of note, many of the sites involved in this trial adopted default position of catheter placement.

There is a lack of long-term follow up; currently, there is only one RCT providing data for a period up to 36 months as part of a 5-year trial.[10] It can be argued that further evidence and longer-term data are required to demonstrate that the benefits provided by Rezum can be sustained. Furthermore, all evidence collected to date has been sponsored by NxThera (Maple Grove, MN, USA), which is a potential be a conflict of interest.

Patient selection and procedure planning

As for all surgical procedures, patient selection is paramount. Not every patient with BPH are candidates for Rezum therapy (Table 3). However, in contrast with some other procedures, patients with median lobe obstruction are eligible to receive Rezum therapy. Critical factors that preclude patients from receiving Rezum therapy include previous surgical/radiation treatment involving the prostate, a history of urinary retention and patients with a large prostate burden (>120 cc). Prior to surgery, in order to determine areas of prostate enlargement, patients undergo flexible cystoscopy. It potentially also provides an opportunity to assess the patient's tolerance to rigid cystoscopy while awake. Obtaining an ultrasound scan to assess prostate volume is also useful.[14]

Complications

The majority of reported complications have been minor in nature (Clavien I–II). The most common adverse events are dysuria, haematuria, hematospermia, symptoms of urgency and UTIs.[18] These typically resolve within a few weeks. There have been no reported complications at medium-term follow up and no reports of *de novo* erectile dysfunction.[8,10,18]

However, the analysed data highlighted the presence of more serious adverse events (AEs). In their pilot trial, Dixon and colleagues reported a patient with three grade 3b AEs wherein a patient had persistent LUTS symptoms with poor stream, frequency and urinary retention recorded as separate events; in this case, the patient opted for TURP procedure at 42 days.[8] A crossover trial found that two patients suffered three serious procedure related AEs collectively, including one patient who developed urosepsis post cystoscopy and on patient who suffered with bladder calculi and bladder neck contracture.[12] 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 hospital overnight for observation due to nausea and vomiting after taking alprazolam.[19]

Cost

Currently, there are no available European studies providing cost-analysis data assessing cost effectiveness. Given its ambulatory status, potential cost-saving benefits may be expected due to decreased length of hospital stay. A cost-effectiveness analysis report comparing therapies for LUTS symptoms has been conducted in the US, comparing direct upfront cost and factoring in cost of retreatment and treatment for AEs in relation to relative success rates (using IPSS data collected over 2 years) of each therapy.[20] Although

estimated costs in the US are not directly comparable with those in Europe, this study suggests Rezum to be both a cost-effective and clinically effective treatment for BPH.[20] Although it does not provide as greater relief of symptoms as TURP, it has the benefits of incurring fewer upfront costs and AEs proving less costly overall, while maintaining good clinically efficacy.[20] Interestingly, it was shown to be less costly and with fewer side effects than other minimally invasive therapies such as UroLift.[20] Further prospective studies should include assessment of cost effectiveness of Rezum in comparison with other minimally invasive treatments, including cost of procedure, treatment of AEs, potential retreatment costs and patient lost work days.[21,22]

Further considerations and research

The Rezum system is an exciting and novel minimally invasive therapy for treating BPH, which thus far has demonstrated strong evidence of clinical effectiveness with a potential wide scope of use with limited drawbacks. However, it is important to consider limitations in the current literature when assessing this novel treatment.

Previous trials have been supported or sponsored by NxThera (the producers of Rezum) which may represent a potential conflict of interest. So far outcomes up to 3 years have been recorded, this is as part of a 5-year RCT currently ongoing. Long-term outcomes are currently awaited so it is difficult to comment on the long-term efficacy of Rezum as a treatment for BPH and whether there will be continued success in relief of LUTS symptoms. A reduction in prostate volume was noted, although no logical explanation on lack of substantial reduction in PVR was noted, which needs to be explored in the future studies.

Further evidence in a nontrial setting is needed in order to confirm the effectiveness of Rezum in real-world applications and also to provide additional support of findings published in a retrospective trial indicating the potential use of Rezum in patients with a large prostate burden and in urinary retention.[11]

Conclusion

The Rezum procedure is a novel minimally invasive therapy for treating BPH. So far, data from available studies point towards good clinical outcomes with a short-term risk of self-limiting minor complications. Its application has demonstrated clinical effectiveness and possesses specific benefits that distinguish it among other treatments. It is applicable to outpatient setting, is effective in preserving sexual function and is versatile in its ability to treat a variety of prostate gland morphologies.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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