Efficacy and safety of methoxyflurane (Penthrox) for pain control during water vapor thermal therapy (Rezūm) for benign prostatic enlargement

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Introduction: *The safety and efficacy of low dose methoxyflurane disposable inhaler (Penthrox) was assessed in this study of men undergoing Rezūm water vapor thermal therapy (WVTT).*

Material and methods: *An open-labeled, single-center study was conducted to demonstrate the safety and efficacy of using methoxyflurane inhaler during a Rezūm procedure. Patients assessed current pain intensity using a 10-point Visual Analog Scale (VAS) of Pain at 4 timepoints including (1) before any medication, (2) initially after insertion of the rigid cystoscope and before any Rezūm treatment, (3) immediately after final injection of Rezūm treatment and (4) at discharge. Patients were asked to fill out the Treatment Satisfaction Questionnaire for Medication (TSQM 1.4) and one question about pain relief at discharge. Treating physician also completed the TSQM 1.4.*

Results: *Ten patients were recruited. Median prostate volume was 53.4 cc (range 24-158 cc). Patients received a median of 10.5 Rezūm injections, with a median procedure time of 4.5 minutes. Median VAS scores were 0, 0.1, 0 (primary efficacy outcome) and 0 (out of scale of 10) at the 4 timepoints, respectively. TSQM scores on effectiveness, side effects, convenience and global median satisfaction rated by patients were respectively 69.4, 100.0, 77.8 and 82.1 (out of scale of 100). Treatment satisfaction on pain relief was rated as 4.0 (very good). There were no observed adverse events.*

Conclusions: *Methoxyflurane inhaler (Penthrox) was low cost, rapid, feasible and easy to administer as a pain management strategy for Rezūm therapy. Further data from a larger comparative study will be conducted.*

Key Words: Rezūm, Penthrox, methoxyflurane inhaler, pain, analgesia, prostates, prostatic hyperplasia

Introduction

Benign prostatic hyperplasia (BPH) is one of the most common urological diseases among men. Based on a recent systematic review and meta-analysis on the global burden, the lifetime prevalence of BPH is 26.2%.[1] The prevalence of histologically diagnosed BPH is 50% in men aged 51 to 60.[2] BPH is characterized by benign overgrowth of prostatic tissue surrounding the urethra, which constricts the urethral opening and results in lower urinary tract symptoms (LUTS) including hesitancy, intermittency, nocturia, incomplete urination, and weak urinary stream. There are different treatment modalities for BPH, including medication and surgery. Minimally invasive surgical therapies (MISTs) such as water vapor thermal therapy (WVTT) or Rezūm for the management of LUTS resulting from BPH have gained a high level of interests over the past few years.

The Rezūm system uses the stored thermal energy in water vapor (steam) to treat the obstructing prostate

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tissue that is causing LUTS. The system uses a radiofrequency generator and transurethral probe to deliver the thermal energy, through convection, in a constant dose of 208 calories (103 °C).[3] Although the Rezūm procedure does not require general anesthesia, intra-procedural pain management with or without sedation is needed for office-based treatment. A variety of analgesia options are available and an optimal pain control protocol has yet to be determined. In the Rezūm II clinical trial, the majority of men received oral sedation and intraurethral anesthetic gel.[4] Other modalities included local peri-prostatic nerve block and intravenous sedation (i.e. propofol).[5] In the quest to find the optimal analgesic to perform this minimally invasive procedure in an office-based setting without the need to use needles, either intravenous or peri-prostatic, we investigated patient-administered inhaled Penthrox (methoxyflurane) for procedural analgesia.

Methoxyflurane belongs to the fluorinated hydrocarbon group that was first originally used as an inhaled anesthetic agent. However, it has shown to have analgesic effects in low and sub-anesthetic doses which can be used for pain control during different procedures including prostate biopsy.[6-8] Low dose methoxyflurane is administered via a portable, disposable, single-use handheld inhaler (Penthrox) by the patient for pain relief. Penthrox is approved in over 55 countries, including throughout Canada, Europe, Middle East, Africa, Asia and Australia. It is currently available in some States within the United States.

Despite the extensive data on the safety of analgesic doses of methoxyflurane, there is no data on its application for office procedures, particularly its use during convective thermal therapy using the Rezūm system in BPH. In order to evaluate the role of Penthrox in the pain control paradigm for the Rezūm procedure, a study was conducted to demonstrate the safety and efficacy in patients undergoing the Rezūm procedure using Penthrox.

Materials and methods

Population

This was an open-labeled, single-center study (Clinicaltrials.gov: NCT04029012). The study was approved by Advarra IRB and the protocol approval number of Advarra IRB is Pro00037484. Written informed consent of patients was obtained from all participants following a detailed explanation of the procedures that they may undergo before participating into the study. Enrollment criteria included men 18 years of age or above who had elected for Rezūm for the management of their BPH and had no contra-indication on using Penthrox. Subjects with any of the following conditions were excluded from using Penthrox: (1) ongoing use of analgesic agents for chronic pain, (2) concomitant use of nephrotoxic agents, (3) INR > 4, (4) use of Penthrox within the previous 3 months, (5) known allergy to Lorazepam, Percocet (oxycodone and acetaminophen)/ Oxycodone, or lidocaine gel, (6) known personal or familial hypersensitivity to Penthrox or other halogenated anesthetics, (7) clinically significant respiratory depression, cardiovascular instability, renal or hepatic impairment, (8) an altered level of consciousness, due to any cause, including head injury, drugs, or alcohol, (9) known or genetically susceptible to malignant hyperthermia or a history of severe adverse reactions in either patient or relatives, and (10) history of liver dysfunction after previous Penthrox use or other halogenated anesthetics. Baseline medical history including prostate volume and International Prostate Symptom Score (IPSS) and IPSS Quality of Life (QoL) were collected as standard of care. A total of 10 subjects were recruited in this study.

Standard medical analgesia

Based upon the Rezūm II pivotal study,[4] the same standard medical therapy was used as a baseline form of analgesia. For ethical reasons patients had to receive some form of minimum analgesia, whereby, based on the Rezūm II study, average Visual Analogue Score (VAS) pain scores ranges between 5/10 (at device insertion) to 6.4/10 (immediately after treatment).[4] Standard medical analgesia included oral anxiolytic and analgesia including oral lorazepam and oral Percocet (oxycodone and acetaminophen) were given 1 hour before and intra-urethral lidocaine gel (Xylocaine) was given 30 minutes before the procedure.

Penthrox administration

Penthrox is a portable, lightweight, non-invasive inhaler for self-administration. Each subject started using Penthrox 5 minutes before procedure, and continuously breathed through the inhaler during the procedure.

Measurement methods

Pain intensity was measured using the validated Visual Analog Scale (VAS) of Pain on the current pain intensity at the following four timepoints: (1) before any oral analgesia was given, (2) initially after insertion of the rigid cystoscope into the bladder and before any treatment or stimulation was applied, (3) immediately after final injection of Rezūm treatment (primary efficacy outcome), (4) at discharge. Subjects were asked

to recall the maximum pain intensity during procedure at discharge as well. The scale of VAS was from 0 (no pain) to 10 (maximum pain).

Global medication performance using Treatment Satisfaction Questionnaire for Medication (TSQM 1.4) was rated by both treating physician and subject.[9] The self-report TSQM questionnaire, which was licensed by IQVIA,[9] consists of 14 items in four scales: effectiveness (TSQM effectiveness), side effects (TSQM side effects), convenience (TSQM convenience), and global satisfaction (TSQM global satisfaction). This English language questionnaire has validity and reliability in Canada, where this study was conducted. Scores range from 0 (extremely dissatisfied) to 100 (extremely satisfied) and were clustered into four groups: 0-25 (not satisfied), 26-50 (not satisfied or dissatisfied), 51-75 (satisfied), and 76-100 (very satisfied).

Additionally, each subject rated one treatment satisfaction question on pain relief by the Penthrox. Other parameters such as the baseline BPH condition, vitals and details of Rezūm procedure, and adverse event were also documented as standard of care. It is through these validated questionnaires and recording of adverse events that we were able to assess safety and efficacy of Penthrox use in Rezūm therapy.

Statistical analysis

For the primary efficacy outcome, a change on the VAS of 30% between two timepoints of an assessment is regarded as being clinically significant.[10]

The baseline demographic and drug administration date were presented as median and range. Other efficacy outcomes were presented as percentage, median and range. The primary safety endpoint was the percentage of adverse events. Due to the small sample size, the statistics were performed using Excel.

Results

Baseline subject demographic data is listed in Table 1. The median age of the participants was 72.0 years old. Prostate volume ranged from 24-158 cc with a median volume of 53.4 cc. At baseline, 4 out of 10 men had urinary retention before. Median IPSS score was 26 and IPSS QoL score was 5. A median number of 10.5 injections of Rezūm were given, and the median duration of procedure was 4 minutes 39 seconds.

Table 2 lists the details of the treatment given. Oral lorazepam and Percocet were given on average 1 hour 20 minutes before procedure. Lidocaine gel was applied inside the urethra. The median time from Lidocaine gel application to procedure was 51 minutes, and median time from Penthrox inhalation to cystoscopy was 6 minutes.

Table 3 lists the details of the outcomes. Median VAS scores were 0, 0.1, 0 (primary efficacy outcome) and 0 (out of scale of 10) at the 4 timepoints, respectively. TSQM scores on effectiveness, side effects, convenience and global median satisfaction rated by patients were respectively 69.4, 100.0, 77.8 and 82.1 (out of scale of 100). Treatment satisfaction on pain relief was rated as 4.0 (very good). There were no reported adverse events during the study.

TABLE 1. **Cohort characteristics**

Mean age (years)	72.0 (52.4-78.3)
Prostate volume (mL)	53.4 cc (24-158 cc)
History of BPH	Less than 5 years: n = 3 5-7 years: n = 4 8-10 years: n = 2 More than 10 years: n = 1
History of urinary retention	Yes: n = 4 No: n = 6
IPSS (n = 7)	26 (22-31)
IPSS QoL	5 (4-6)
Mean procedure	4 minutes 39 seconds (range: 1 minutes time (min) 32 seconds – 7 minutes 35 seconds)
Total treatment injections	10.5 (5-21)

Continuous variables are reported as median (range)
BPH = benign prostatic hyperplasia; IPSS = International Prostate Symptom Score; QoL = quality of life

TABLE 2. **Drug administration**

Drug	**Median time to Rezūm cystoscopy (range)**
Lorazepam (1 mg, n = 4; 2 mg, n = 6)	1 h 19 min (45 min-2 h)
Percocet, n = 10	1 h 19 min (45 min-2 h)
Lidocaine gel	51 min (25 min-1 h 35 min)
Methoxyflurane (Penthrox)	6 min (5 min-15 min)

TABLE 3. **Treatment outcomes**

Outcome	Median (range)
VAS	
Before any drug	0 (0-0)
After scope insertion and before Rezūm	0.1 (0-7)
After last Rezūm injection (primary outcome)	0 (0-6)
At discharge	0 (0-5)
Recall max (additional data beyond protocol)	3 (0-10)
TSQM, by patient	
Effectiveness	69.4 (61.1-100)
Side effect	100 (62.5-100)
Convenience	77.8 (55.6-100)
Global satisfaction	82.1 (50.0-100)
Treatment satisfaction on pain relief, by patient	4 (3-5)
TSQM, by physician	
Effectiveness	100 (83.3-100)
Side effect	100 (100-100)
Convenience	100 (83.3-100)
Global satisfaction	100 (78.6-100)

VAS = Visual Analogue Score
TSQM = Treatment Satisfaction Questionnaire for Medication

Most noteworthy results

Penthrox is a self-administered methoxyflurane inhaler for pain control with rapid onset on action.

This study showed that Penthrox on top of standard oral anxiolytic and analgesia is an easy pain management option for Rezūm therapy.

Both physician and patients were highly satisfied with using Penthrox during Rezūm therapy.

There were no reported adverse events during the study.

Discussion

Penthrox is self-administered by the patient, has a rapid onset of action (within approximately 4 minutes or 6–10 inhalations), its effects are quickly reversed (within 3-20 minutes after inhalation stops) and there are no reported drug interactions at analgesic doses.[11-13] These characteristics make Penthrox suitable for use as a sole agent, or as a bridging agent to other analgesia. One inhaler provides 25-30 minutes of analgesia with continuous inhalation.[13,14] Low-dose methoxyflurane analgesia has a well-established safety profile: no respiratory depression or clinically significant effects on vital signs have been reported and adverse events are usually transient and self-limited.[13-16]

The pivotal Rezūm II clinical trial included 197 subjects who were randomized 2:1 to treatment (n = 136) and rigid cystoscopy placebo (n = 61).[6] The total number of water vapor injections averaged 4.5 ± 1.9 and when a median lobe was present, added another 1.6 injections on average. Investigators were allowed to use varying pain and anxiety management option based upon their clinical judgment and standard of practice. In the study 68.9% of subjects received oral sedation only, 20.9% received a prostate block, and 10.2% received intravenous conscious sedation.

TABLE 4. **Comparison of Rezūm II study and Penthrox pilot study**

		Rezūm II study[4]	**Penthrox pilot study**
Number of patients received Rezūm treatment		136	10
Average number of Rezūm injection	Mean ± SD Range	4.5 ± 1.9	11 injections 5-21
VAS after insertion of the Rezūm delivery device before any Rezūm treatment	Mean ± SD Range	5.0 ± 2.7	1.4 ± 2.4 0-7
VAS immediately following Rezūm treatment	Mean ± SD Range	6.4 ± 2.6	1.3 ± 2.1 0-6
VAS at discharge	Mean ± SD Range	2.9 ± 2.7	0.9 ± 1.8 (range: 0-5) 0-5

VAS = Visual Analogue Score

Procedural pain VAS was collected twice, initially after insertion of the Rezūm delivery device (5.0 ± 2.7) or rigid cystoscope (4.9 ± 2.8) out of scale of 10, before any treatment of stimulation (same as VAS time point #2 in this Penthrox study) and immediately following the treatment (same as VAS time point #3 in this Penthrox study). At this latter timepoint, pain VAS increased in the Rezūm group to 6.4 ± 2.6, while in control subjects scores decreased to 3.8 ± 2.8 ($p < 0.0001$). Finally at discharge (same as VAS time point #4 in this Penthrox study), pain VAS scores were 2.9 ± 2.7 and 2.1 ± 2.6. In contrast to the aforementioned Rezūm II study, this smaller scale study examined the suitability of Penthrox to provide procedural analgesia for Rezūm. As can be seen in the comparative Table 4, Penthrox consistently provided superior analgesia at all time points compared to the aggregate pain VAS scores in the Rezūm II study.

TSQM 1.4 measures global satisfaction with the performance of a medication. Patients found the effectiveness (median 69.4), side effect (median 100), convenience (median 77.8), and global satisfaction (median 82.1) to be very satisfied with three out of four median scores above 75 (out of 100). Even more so, the physician scores were nearly perfect for effectiveness, side effect, convenience and global satisfaction, with a median value of 100 for all measures, indicating an ease and satisfaction to perform the Rezūm procedure without undue pain to the patient.

Other studies looking at Penthrox include acute pain due to minor trauma in emergency medicine,[11] transrectal prostate biopsy,[6,7] bone marrow biopsy[16] etc. All these studies indicated Penthrox as a well-tolerated, efficacious and rapid-acting analgesic.

There are several notable advantages of MISTs over traditional medical and surgical therapy. In this case, Rezūm offers a one-time, office-based treatment that is superior in symptom improvement (as measured by IPSS) and maximal flow rate compared with medical therapy but with a more favorable sexual dysfunction profile.[17] Additionally, Rezūm has a safer adverse events profile compared to traditional transurethral surgery and can be performed outside of a traditional operating room, reducing the burden of treating BPH with limited resources. Patient comfort during any procedure should be a priority and no less should be expected when employing a MIST. While it has been demonstrated to be technically feasible to perform Rezūm under local anesthesia with intraurethral anesthetic gel and some oral anxiolytic or analgesic, patient comfort levels may not be acceptable.[4,17] Adding intravenous sedation requires personnel, typically an anesthesiologist, to place the intravenous line, administer and monitor the patient. The alternative of a transrectal ultrasound guided peri-prostatic block requires an ultrasound machine, physician expertise with prostate blocks, and carries the small risk of infection as well at the need for antibiotic prophylaxis. Thus, additional personnel, cost, skills and access to additional material/equipment are required. Herein we provide evidence to support a simple, novel, alternative option to provide short-acting analgesia to treat BPH with Rezūm.

We acknowledge the small sample size as a limitation. The statistics used are descriptive in nature and do not include any p values. The goal, however, was a proof-of-principle study to demonstrate that Penthrox could provide safe and effective analgesia for office-based Rezūm therapy. We believe this study creates the foundation for future research in larger cohorts. Additionally, it's unclear how much analgesia is provided by oral Lorazepam and Percocet alone. However, based on the comparison to the Rezūm II study whose composite VAS score which included stronger forms of analgesia (peri-prostatic block and IV sedation) and had VAS scores between 5 to 6.4, we deduce that oral sedation alone probably is insufficient. Lastly, this study included a real-world sample of patients with a wide range of prostate volumes and number of injections. This leads to greater heterogeneity. The mean prostate size of 66.4 cc is larger than the mean prostate size in the Rezūm II pivotal study of 45.8 cc. We hypothesize that a larger prostate requiring more injections of steam over a greater duration of time would result in more pain. However, this study showed a lower VAS pain score in men treated with Penthrox.

Conclusion

Penthrox was a low cost, rapid, feasible and easy to administer pain management strategy for Rezūm therapy. Further studies in larger cohorts will further demonstrate the broader application of Penthrox as a stand-alone analgesic option for men undergoing Rezūm. □

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