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Title: Rezūm therapy for ≥ 80 ml benign prostatic enlargement: a large, multi-center cohort study

Running Head: Rezum for ≥ 80 ml

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Conflict of Interest declaration
Dr. Dean Elterman, Dr. Kevin C. Zorn, Dr. Naeem Bhojan and Dr. Bilal Chughtai are Consultants & Investigators of Boston Scientific. Mr. Christopher Vannabouathong has not conflict of interest to declare.

Abstract

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Objective: The purpose of this study was to evaluate the efficacy and safety of Rezūm therapy in benign prostatic hyperplasia (BPH) patients with prostates ≥ 80 ml.

Methods: A prospective registry was established at two high-volume Canadian centers. Patients had baseline medical history documented, and uroflowmetry and questionnaires recorded over 12 months.

Results: 83 patients (median age: 69.2 years, IQR 63.2, 74.8) with a prostate size ≥ 80 ml were included. Median prostate volume was 100.0 ml (IQR 88.5, 115.0) and 65% had a median lobe. 21 patients had prior urinary retention. Median number of injections was 13 (IQR 11, 15). Median catheterization length was 9 days (IQR 7, 14). IPSS improved by 24%, 57%, and 59% at 1, 3, and 12 months, respectively ($p<0.001$). QoL scores improved by 27%, 56%, and 70% at these same timepoints ($p<0.001$). Qmax improved by 55% at 3 months ($p=0.002$) and 59% at 12 months, and PVR improved by 58% at 3 months ($p=0.006$). BPHII scores improved by 57% at 3 months and 71% at 12 months. IIEF-15 scores improved by 15% at 6 months, and MSHQ-EjD function scores improved by 22.4% at 1 month. 3 (3.6%) men observed reduced/anejaculation. No Clavien-Dindo events ≥ Grade III occurred.

Conclusion: This study demonstrates for the first-time safety and efficacy of Rezum in large glands >80mL. IPSS improved by 59% and QoL improved by 70% at 12 months. Objective maximum flow measures improved at 12 months by 59%, while erectile and ejaculatory function remained preserved.

Keywords: Benign prostatic hyperplasia, Large gland, Lower urinary tract, Rezūm, Water vapour thermal therapy

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a urologic condition characterized by a progressive increase in prostate size [1, 2]. Patients with BPH will eventually develop lower urinary tract symptoms (LUTS), and it has been found that healthcare costs attributed to BPH are among the top 10 most prominent and costly diseases in men older than 50 years [3, 4]. A subset of these patients have large volume prostates, defined as glands ≥ 80 millilitres (ml), which are considered more difficult to treat compared to patients with smaller prostate glands [5-7]. Generally speaking, there are numerous treatment options available for BPH patients, including conservative and pharmacological therapies, in-office procedures, and traditional surgeries such as transurethral resection of the prostate (TURP); however, recommendations for those with large glands are limited to invasive interventions (i.e., open prostatectomy) that are associated with long hospital stays and catheterization durations, and a high risk of complications [1, 5, 7-10].

In recent years, a novel, minimally-invasive procedure was introduced for the management of BPH, the Rezūm System (Boston Scientific Company Inc., Marlborough, MA, USA), which harnesses thermal energy stored in water vapour to cause time-delayed ablation of prostatic tissue [1, 4]. The Rezūm System was approved by the Food and Drug Administration (FDA) in 2015 based on the results of the pivotal trial (NCT01912339). This was a randomized trial that allocated 197 men with prostates ranging between 30-80 mL to either Rezūm therapy or control. Outcomes demonstrated that Rezūm therapy provided clinical improvements by 1 month and durable improvements in BPH symptoms [4, 11]. Support for Rezūm therapy was also published by the National Institute for Health and Care Excellence (NICE) in June 2020 [12, 13].

Major guidelines, namely the American Urological Association (AUA), European Association of Urology (EAU), and Canadian Urological Association (CUA), have included Rezūm therapy in their most recent recommendations [1, 8, 10, 14]. The EAU guidelines state that additional randomized controlled trials (RCTs) of the Rezūm System against a reference technique are still needed before offering any recommendation [8]. On the other hand, the AUA and CUA now consider water vapour therapy as an alternative treatment option that may be offered to BPH patients with LUTS and a prostate volume < 80 ml and those men wishing to preserve antegrade ejaculatory function. However, they currently offer no recommendation with regards to Rezūm therapy for those with large glands [10, 14]. Early research on this particular topic has so far demonstrated promising results [5, 6]. The objective of this study was to evaluate the efficacy and safety of Rezūm therapy in patients with large volume prostates from a cohort of BPH patients enrolled in a real-world study.

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METHODS

Study subjects

A prospective registry was established at two high-volume centers. The subgroup of BPH patients who received Rezūm water vapor therapy at these institutions and had prostates ≥ 80 ml were included in this study.

Treatment procedure

Rezūm water vapor therapy was performed as previously described [4, 15, 16]. This system includes a generator containing a radiofrequency power supply, system controls, and a single-use transurethral delivery device that incorporates a standard 4 mm, 30-degree endoscopic cystoscopy lens. Water vapour thermal energy, created by the radiofrequency current against an inductive coil heater in the device handle, is delivered via a retractable needle and saline flush. The water vapour is delivered for 9 seconds, retracted, and then administered to another treatment site at the surgeon's discretion. The goal is to create contiguous, overlapping lesions running parallel to the natural slope of the urethra. The intervention is customized to the shape and location of the gland, including treatment of the median lobe.

Assessments

All patients had baseline medical and BPH history documented, along with uroflowmetry outcomes (i.e., peak urinary flow [Qmax] and post-void residual volume [PVR]). All patients in this cohort with large prostate volumes were assessed preoperatively by transrectal ultrasound
(TRUS) performed by a radiologist. Patients completed the following validated questionnaires at one, three, six, and 12 months following the procedure:

- The International Prostate Symptom Score (IPSS) and IPSS Quality of Life (QoL) subscale [17]
- The International Index of Erectile Function (IIEF-15) [18]
- The Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD) function and bother domains [19]
- The Benign Prostatic Hyperplasia Impact Index (BPHII) [20]

Adverse events were monitored during study follow-up.

Statistical methods

Cohort characteristics and assessments were summarized using descriptive statistics. To compare the change in each outcome from baseline to follow up at 1, 3, 6 and 12 months, each patient's change from baseline was calculated. The change from baseline was summarized using the mean, standard deviation, and percent change. Analyses included only patients who had both baseline and follow up assessment values; patients missing either were excluded. To evaluate if the change from baseline was statistically significant, the Wilcoxon

signed-rank test was used for each outcome at each time point. Statistical analyses were conducted using R version 3.6.0, and a p-value of less than 0.05 was considered to be statistically significant.

RESULTS

Subject demographics

A total of 83 subjects (median age 69.2 years, IQR 63.2, 74.8) were treated with Rezūm from April 2019 to December 2020 (**Table 1**). All were performed in the outpatient office setting using a combination of anesthesia, with 63.9% using IV sedation local TRUS anesthesia, 12% spinal anesthesia, 19.3% prostate block, 62.7% lidocaine gel, and 7.2% Penthrox™. The median prostate volume was 100.0 mL (IQR 88.5, 115.0 mL). 65% of subjects had a median lobe and 25% had a prior episode of urinary retention. Six patients were in retention at time of Rezum procedure. The median number of injections was 13 (IQR 11, 15) and the median duration of procedure was 5.5 minutes (IQR 4.9, 6.6 minutes). Postoperatively, the median duration of catheterization was 9 days (IQR 7, 14 days). An initial failed voiding trial occurred in 12 patients who were re-catheterized. At 1-month post-procedure, all patients were voiding spontaneously.

IPSS

IPSS scores reduced from baseline by 24%, 57%, 59%, and 59% at one, three, six, and 12 months, respectively (**Figure 1a**). Similarly, IPSS QoL scores also improved from baseline by 27%, 56%, 68%, and 70% at one, three, six, and 12 months, respectively (**Figure 1b**).

Uroflowmetry

Qmax improved from baseline by 38%, 55%, 67%, and 59% at one, three, six, and 12 months, respectively (**Figure 2a**). PVR values also improved from baseline at each of these timepoints, by 54%, 58%, 69% and 62%, respectively (**Figure 2b**).

IIEF-15, MSHQ-EjD, & BPHII

IIEF-15 scores improved by 15% at six months (**Figure 3a**). MSHQ-EjD function scores improved by 22% at 1 month, and no significant changes were seen in the MSHQ-EjD bother items over 12 months (**Figure 3b**). Lastly, BPHII scores improved from baseline by 57%, 75%, and 71% at three, six, and 12 months, respectively.

All results were listed on Table 2.

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Safety

The procedure was well-tolerated by patients over the course of the study. No grade ≥ III Clavien-Dindo events occurred. Twelve men required re-catheterization (failed TOV). Three patients reported reduced/anejaculation. Two patients had Greenlight within 1 year after Rezum.

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DISCUSSION

The purpose of this study was to evaluate the efficacy and safety of Rezūm therapy in patients with BPH and large volume prostates in a real-world setting. A total of 83 patients, with a median prostate volume of 100.0 mL (IQR 88.5, 115.0 mL), were treated with Rezūm. The median procedure time was 5.5 minutes (IQR: 4.9, 6.6 minutes), and patients demonstrated early and sustained improvements according to the IPSS, IPSS QoL, BPHII, and uroflowmetry outcomes over 12 months. More specifically, the IPSS, Qmax, and PVR improved by 59%, 59%, and 62%, respectively, over this time frame, which is similar to the results seen in the pivotal Rezūm trial [4]. The median catheterization length was 9 days (IQR 7, 14 days). No patients had a grade ≥ III Clavien-Dindo event, though 12 men required recatheterization. After a secondary voiding trial occurring between 7-14 days, all patients were spontaneously voiding by 1-month post-procedure. There were three cases of anejaculation and two cases of reintervention with Greenlight. Overall, Rezūm therapy was shown to be a safe, effective, and quick procedure for patients with large prostate glands.

FDA approval of the Rezūm System was based on the results of the randomized trial by McVary et al. (2016); however, unlike the current investigation, McVary et al. (2016) only included BPH patients with prostate volumes between 30 to 80 ml [4, 11]. Also, as noted previously, Rezūm therapy is currently only recommended for BPH patients with prostate volumes < 80 mL based upon the inclusion criteria of the aforementioned pivotal study, highlighting the need for additional research in those with large glands [10, 14]. Though the current evidence base on this particular topic is limited, results are indeed promising. Bole et al. published the first report on the use of Rezūm on BPH patients with prostates > 80 ml, which demonstrated that patients with large glands (n = 47) had comparable outcomes to those with small glands (n = 135) in terms of symptomatic and objective improvement in voiding parameters at three months [5]. Additionally, another recent study by Garden et al. on 204 men with BPH (36 with prostates ≥ 80 mL) also concluded that Rezūm therapy provided short-term symptomatic relief and improved voiding function that were similar between small and large gland patients [6]. Though both studies support the consideration of Rezūm therapy for BPH patients with large glands, they both also emphasized the need for more studies with long-term outcomes.

In terms of study limitations, there was no comparator intervention, so it is unclear how the Rezūm System performs against other treatment options for BPH patients with large glands.

Secondly, as treatment allocation was known by both the patient and treating physician, outcomes assessment was unblinded; however, in addition to patient-reported outcome measures, more objective uroflowmetry outcomes (i.e., Qmax and PVR) were also measured, which also demonstrated early and sustained improvements from baseline. Finally, missing data required that complete case analyses had to be done to compare changes in outcomes from baseline. A strength of this study was that it demonstrated that Rezūm therapy is safe and effective in a real-world setting for a particular indication defined using an objective criterion (i.e., a prostate volume ≥ 80 ml). This confirms what has been previously stated in the literature that the treatment may be indicated for any BPH patient, regardless of prostate volume [5, 6]. Additionally, this study evaluated the efficacy of Rezūm using established outcome measures that have previously been validated in this particular patient population [17-20]. Improvements in these measures occurred as early as one month and up to 12 months following surgery.

CONCLUSION

While Rezum has been studied in prostates 30-80mL in volume, this study demonstrates for the first-time safety and efficacy in large glands >80mL. We can conclude that men may avoid more invasive surgeries typically used for large glands and instead opt for a quick, office-based minimally invasive treatment. Future research might involve comparative studies to other large gland modalities and longer-term follow-up.

Conflict of Interest declaration

Dr. Dean Elterman, Dr. Kevin C. Zorn, Dr. Naeem Bhojan and Dr. Bilal Chughtai are Consultants & Investigators of Boston Scientific. Mr. Christopher Vannabouathong has no conflict of interest to declare.

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Table 1. Baseline characteristics (83 subjects)

5ARI, 5-alpha reductase inhibitor; BPH, benign prostatic hyperplasia; BPHII, Benign Prostatic Hyperplasia Impact Index; IIEF-15, International Index of Erectile Function; IPSS, International Prostate Symptom Score; MSQH-EjD, Male Sexual Health Questionnaire for Ejaculatory Dysfunction; PAE, prostatic artery embolization; PSA, prostate specific antigen; PVR, post-void residual volume; Qmax, peak urinary flow; QoL, quality of life; SD, standard deviation; TUIP, transurethral incision of the prostate; TUNA, transurethral needle ablation; TURP, transurethral resection of the prostate

Table 2. Changes in outcomes from baseline to 12 months

Qmax, peak urinary flow; PVR, post-void residual volume; SD, standard deviation
IPSS, International Prostate Symptom Score (scores of severity of BPH symptoms; 0 - 7 = mildly symptomatic; 8 - 19 = moderately symptomatic; 20 - 35 = severely symptomatic);
IPSS QoL, International Prostate Symptom Score Quality of Life (score ranges from 0-6 where lower scores are indicative of better QoL)
BPHII, Benign Prostatic Hyperplasia Impact Index (score ranges from 0-13 where higher scores are indicative of higher impact on life by BPH symptom)
IIEF-15, International Index of Erectile Function (score ranges from 6-75 where lower scores are indicative of erection problems on sex life);
*MSQH-EjD function, Male Sexual Health Questionnaire for Ejaculatory Dysfunction function (score ranges from 0-15 where lower scores are indicative of poor e*jaculatory function)
MSQH-EjD bother, Male Sexual Health Questionnaire for Ejaculatory Dysfunction bother (score ranges from 0-5 where higher scores are indicative of high bothersome)

Fig. 1 a) IPSS and b) IPSS QoL scores (95% CI) over time
International Index of Erectile Function; IPSS, International Prostate Symptom Score; QoL, quality of life

Fig. 2 a) Qmax and b) PVR values (95% CI) over time
PVR, post-void residual volume; Qmax, peak urinary flow

Fig. 3 a) IIEF-15 and b) MSHQ-EjD scores (95% CI) over time
IIEF-15, International Index of Erectile Function; MSQH-EjD, Male Sexual Health Questionnaire for Ejaculatory Dysfunction

Table M. Baseline characteristics (83 subjects)

Characteristic	**Median (IQR), Mean (SD) or n (%)**
Age, years [Median (IQR)]	69.2 (63.2, 74.8)
Prostate volume, mL [Median (IQR)]	100.0 (88.5, 115.0)
PSA, ug/L [Median (IQR)]	4.8 (3.3, 7.7)

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Characteristic	**Median (IQR), Mean (SD) or n (%)**
Median lobe	54 (65%)
Duration of BPH	
<5 years	24 (29%)
5-7 years	25 (30%)
8-10 years	15 (18%)
>10 years	19 (23%)
Previous BPH surgery	
TURP	2 (2%)
Urolift	2 (2%)
PAE	2 (2%)
Rezūm	1 (1%)
TUIP	1 (1%)
Current BPH medication	
Alpha-blocker	61 (73%)
5ARI	24 (29%)
Cialis/Viagra	14 (17%)
None	16 (19%)
Medical history	
Hypertension	23 (28%)
Dyslipidemia	18 (22%)
Diabetes	7 (8%)
Kidney/bladder stone	7 (8%)
History of urinary retention	21 (25%)
Operative characteristics	
Anesthesia	
Propofol	53 (64%)
Lidocaine gel	52 (63%)
Prostate block	16 (19%)
Spinal	10 (12%)
	6 (7%)
Penthrox/methoxyflurane	8 (10%)
Pain medication/anxiolytic	3 (4%)
Acetaminophen	3 (4%)
Percocet	1 (1%)
Ativan/Lorazepam	
Midazolam	
Number of injections [Median (IQR)]	13 (11, 15)
Saline volume, mL [Median (IQR)]	415.0 (356.2, 531.8)
Duration of procedure, minutes [Median (IQR)]	5.5 (4.9, 6.8)

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Characteristic	Median (IQR), Mean (SD) or n (%)
Planned duration of catheter, days [Median (IQR)]	9 (7, 14)
Postoperative medications	
Antibiotics	82 (99%)
Stool softener	55 (66%)
Pain medications	54 (65%)
Anti-inflammatories	37 (45%)
Bladder	21 (25%)
Alpha-blocker	16 (19%)
Uroflowmetry [Mean (SD)]	
Qmax, mL/sec	8.0 (4.5)
PVR, mL	183.7 (176.3)
Clinical outcome scales [Mean (SD)]	
IPSS	21.9 (7.3)
IPSS QoL	4.3 (1.2)
IIEF-15	40.7 (21.0)
MSQH-EjD function	8.5 (3.5)
MSHQ-EjD bother	1.8 (1.5)
BPHII	6.7 (2.9)

5ARI, 5-alpha reductase inhibitor; BPH, benign prostatic hyperplasia; BPHII, Benign Prostatic Hyperplasia Impact Index; IIEF-15, International Index of Erectile Function; IPSS, International Prostate Symptom Score; MSQH-EjD, Male Sexual Health Questionnaire for Ejaculatory Dysfunction; PAE, prostatic artery embolization; PSA, prostate specific antigen; PVR, post-void residual volume; Qmax, peak urinary flow; QoL, quality of life; SD, standard deviation; TUIP, transurethral incision of the prostate; TUNA, transurethral needle ablation; TURP, transurethral resection of the prostate

Table 2. Changes in outcomes from baseline to 12 months

	Baseline	1 month	3 months	6 months	12 months
Qmax, mL/sec					
Number analyzed	71	29	24	11	2
Absolute, mean (SD)	8.0 (4.5)	12.0 (5.6)	14.3 (6.2)	15.5 (8.2)	19.9 (3.0)
Change, mean (SD)		3.3 (7.1)	5.1 (6.8)	6.2 (8.3)	7.4 (5.2)
% change, mean		38.2%	54.7%	66.8%	58.8%
P-Value		0.01	0.002	0.031	0.5
PVR, mL					
Number analyzed	68	27	22	10	6
		81.7 (72.5)	69.8 (62.6)	48.8 (54.2)	95.3 (90.4)

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	Baseline	1 month	3 months	6 months	12 months
Absolute, mean (SD)	183.7 (176.3)	-97.6 (132.4)	-96.1 (141.6)	-107.4 (176.3)	-153.3 (135.6)
Change, mean (SD)		-54.4%	-57.9%	-68.8%	-61.7%
% change, mean		<0.001	0.006	0.049	0.063
P-Value					
IPSS					
Number analyzed	76	55	47	32	21
Absolute, mean (SD)	21.9 (7.3)	15.8 (7.3)	9.0 (5.4)	8.4 (5.9)	8.4 (5.4)
Change, mean (SD)		-5.1 (7.8)	-11.8 (7.0)	-12.1 (7.1)	-12.2 (7.7)
% change, mean		-24.3%	-56.7%	-58.9%	-59.1%
P-Value		<0.001	<0.001	<0.001	<0.001
IPSS QoL					
Number analyzed	76	55	47	32	21
Absolute, mean (SD)	4.2 (1.2)	3.1 (1.7)	1.8 (1.3)	1.4 (1.3)	1.4 (1.2)
Change, mean (SD)		-1.1 (2.0)	-2.4 (1.6)	-2.9 (1.6)	-3.1 (1.4)
% change, mean		-27.0%	-56.3%	-67.9%	-69.5%
P-Value		<0.001	<0.001	<0.001	<0.001
IIEF-15					
Number analyzed	64	25	28	19	15
Absolute, mean (SD)	40.7 (21.0)	45.6 (20.9)	52.2 (17.9)	58.3 (15.7)	57.1 (17.6)
Change, mean (SD)		-2.0 (15.6)	3.6 (10.8)	7.8 (11.8)	5.1 (13.1)
% change, mean		-4.1%	7.4%	15.4%	9.7%
P-Value		0.8	0.081	0.015	0.18
MSQH-EjD function					
Number analyzed	50	25	30	18	15
Absolute, mean (SD)	8.5 (3.5)	10.3 (4.3)	9.3 (4.4)	9.9 (4.4)	10.1 (4.0)
Change, mean (SD)		1.9 (4.0)	0.1 (4.4)	0.4 (3.8)	-0.1 (3.3)
		22.4%	1.4%	4.7%	-1.3%
		0.039	0.7	0.6	0.9

	Baseline	1 month	3 months	6 months	12 months
% change, mean					
P-Value					
MSQH-EjD bother					
Number analyzed	50	25	30	18	15
Absolute, mean (SD)	1.8 (1.5)	1.6 (1.3)	1.7 (1.4)	1.7 (1.5)	1.3 (1.3)
Change, mean (SD)		-0.4 (1.9)	-0.1 (2.0)	-0.1 (2.0)	-0.1 (1.5)
% change, mean		-18.8%	-5.7%	-3.2%	-4.8%
P-Value		0.2	0.9	0.8	1
BPHII					
Number analyzed	59	45	38	26	19
Absolute, mean (SD)	6.7 (2.9)	6.4 (3.4)	2.8 (2.4)	1.8 (2.3)	1.8 (2.2)
Change, mean (SD)		0.0 (3.5)	-3.7 (3.0)	-5.2 (2.7)	-4.5 (3.0)
% change, mean		-0.7%	-56.7%	-74.7%	-71.0%
P-Value		0.9	<0.001	<0.001	<0.001

Qmax, peak urinary flow; PVR, post-void residual volume; SD, standard deviation
IPSS, International Prostate Symptom Score (scores of severity of BPH symptoms; 0 - 7 = mildly symptomatic; 8 - 19 = moderately symptomatic; 20 - 35 = severely symptomatic);
IPSS QoL, International Prostate Symptom Score Quality of Life (score ranges from 0-6 where lower scores are indicative of better QoL)
BPHII, Benign Prostatic Hyperplasia Impact Index (score ranges from 0-13 where higher scores are indicative of higher impact on life by BPH symptom)
IIEF-15, International Index of Erectile Function (score ranges from 6-75 where lower scores are indicative of erection problems on sex life);
*MSQH-EjD function, Male Sexual Health Questionnaire for Ejaculatory Dysfunction function (score ranges from 0-15 where lower scores are indicative of poor e*jaculatory function)
MSQH-EjD bother, Male Sexual Health Questionnaire for Ejaculatory Dysfunction bother (score ranges from 0-5 where higher scores are indicative of high bothersome)

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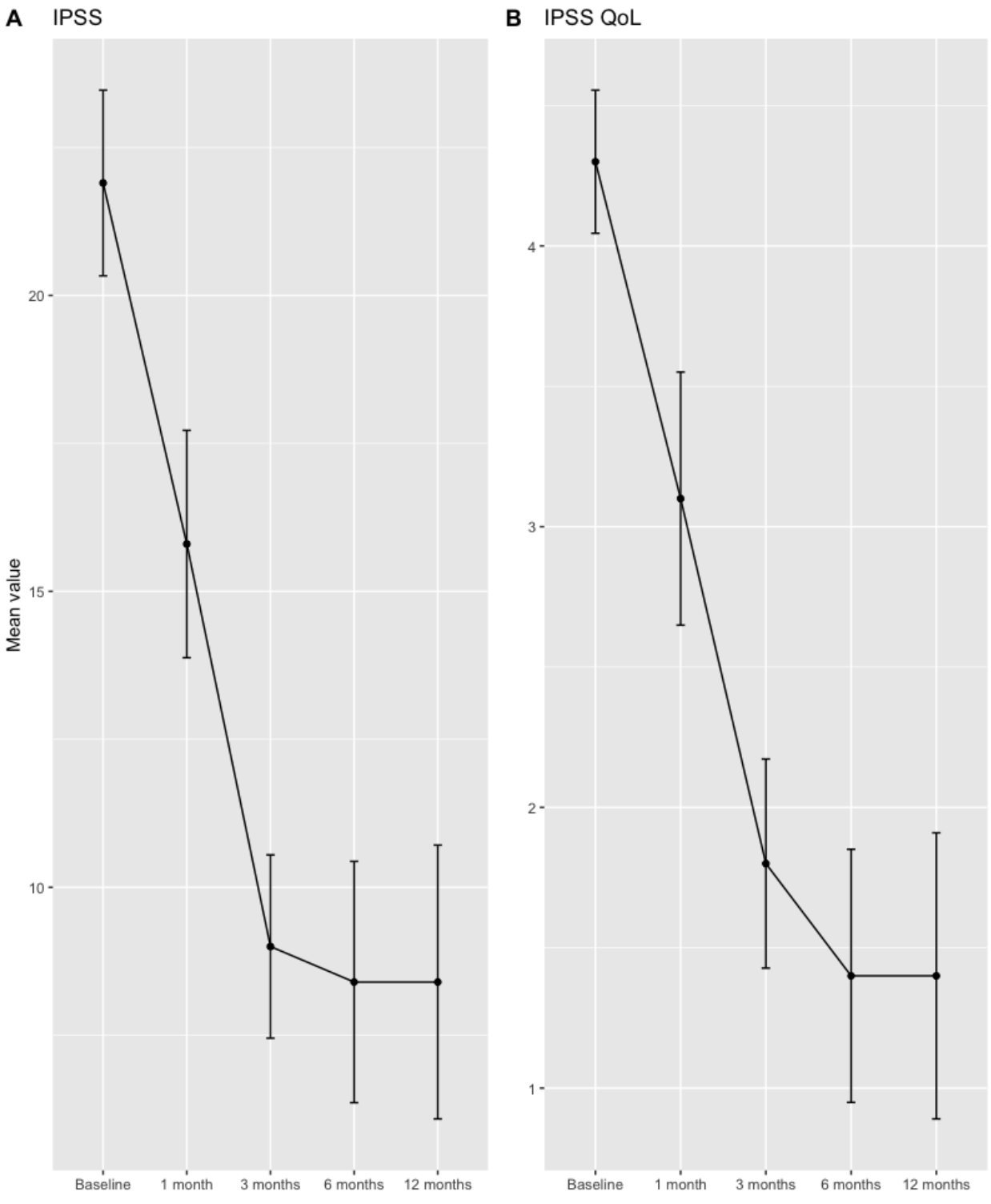

Fig. 1 a) IPSS and b) IPSS QoL scores (95% CI) over time

International Index of Erectile Function; IPSS, International Prostate Symptom Score; QoL, quality of life

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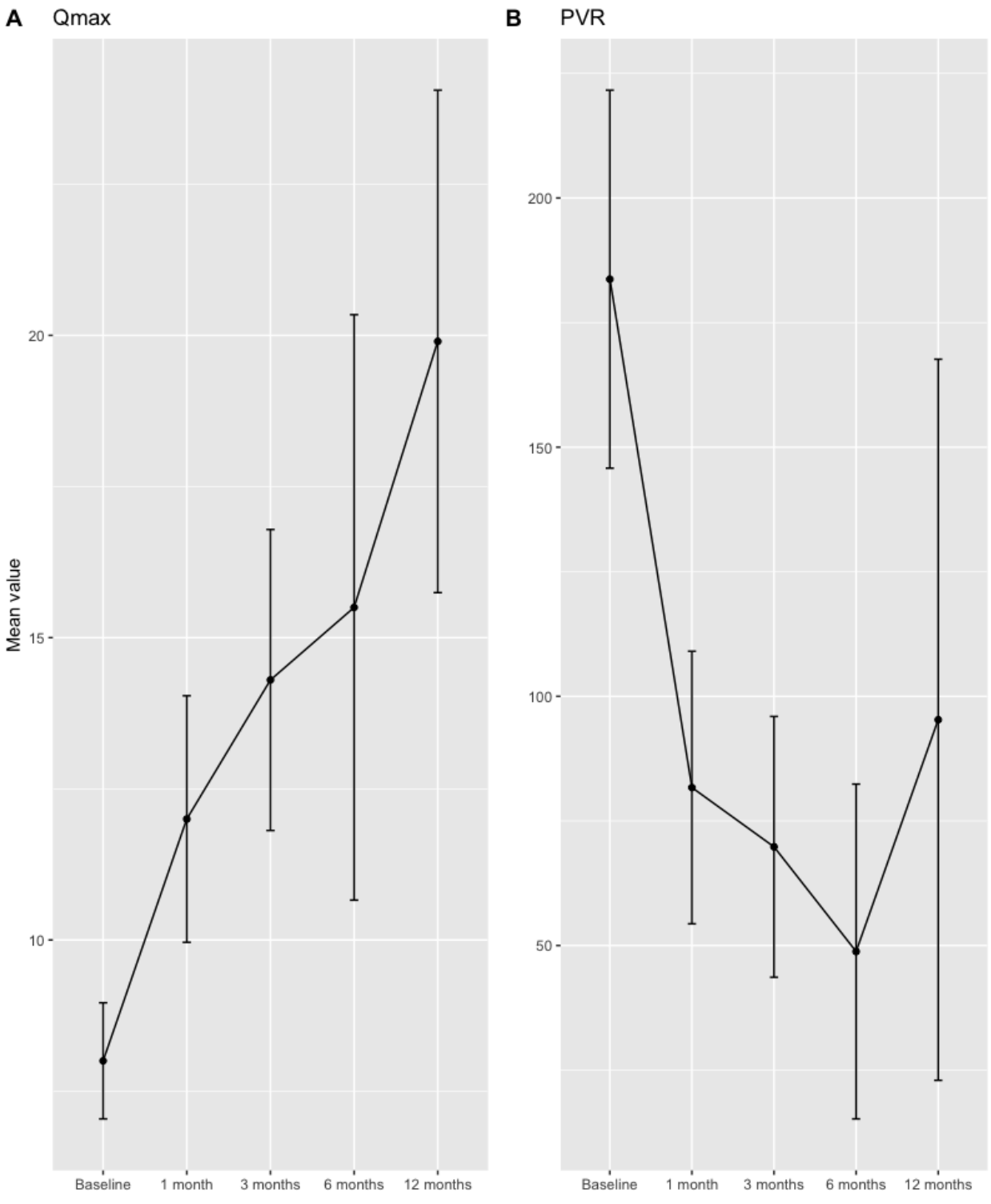

Fig. 2 a) Qmax and b) PVR values (95% CI) over time

PVR, post-void residual volume; Qmax, peak urinary flow

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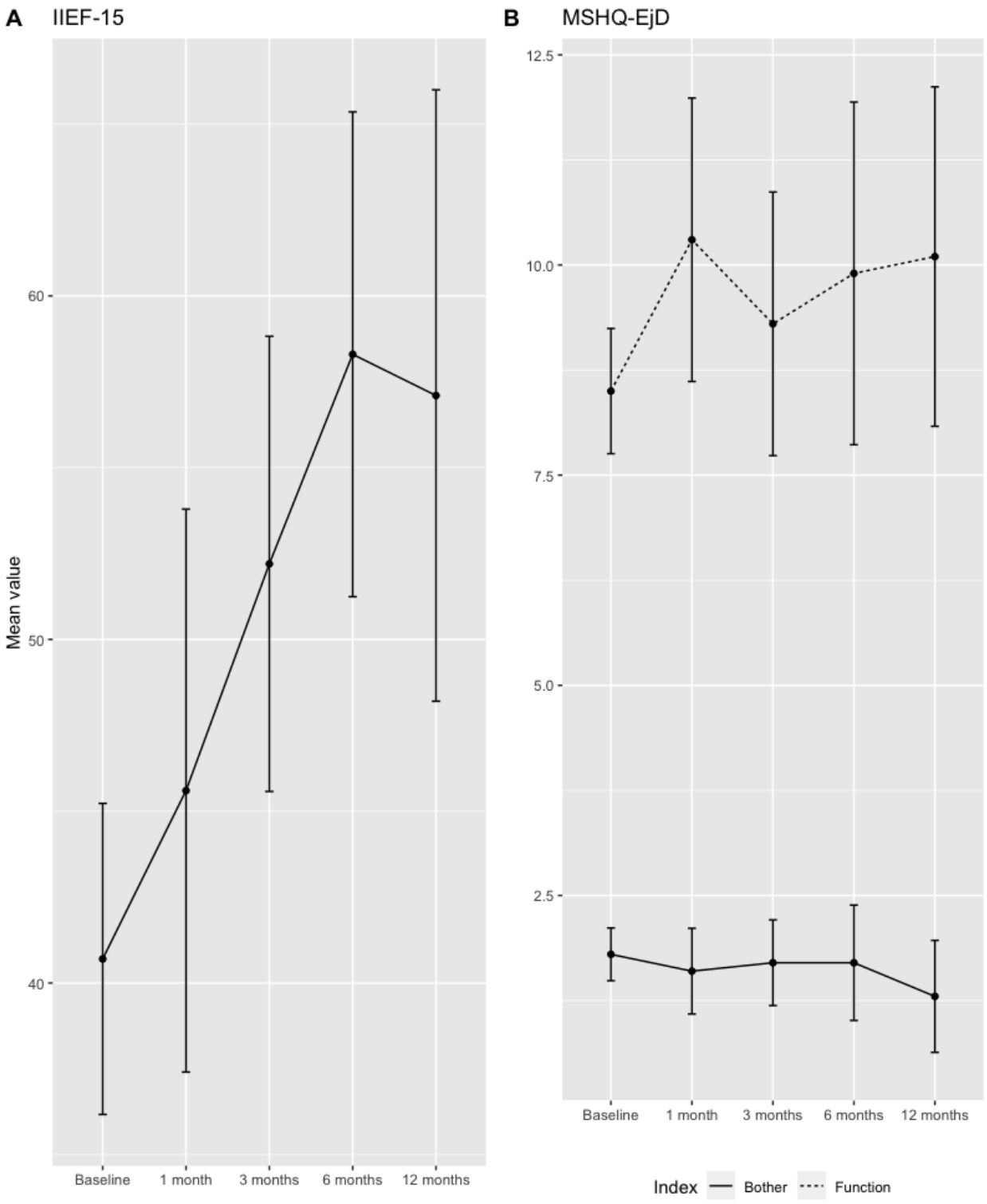

Fig. 3 a) IIEF-15 and b) MSHQ-EjD scores (95% CI) over time
IIEF-15, International Index of Erectile Function; MSQH-EjD, Male Sexual Health Questionnaire for Ejaculatory Dysfunction