Prostatic Diseases and Male Voiding Dysfunction

Voiding and Storage Domain-Specific Symptom Score Outcomes After Prostate Artery Embolization for Lower Urinary Tract Symptoms and Urinary Retention

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OBJECTIVE To characterize voiding and storage symptom domain-specific outcomes after prostate artery embolization (PAE) to treat lower urinary tract symptoms (LUTS) or urinary retention caused by benign prostatic hyperplasia (BPH).

METHODS Two hundred forty patients (age = 74.5 ± 8.6 years) underwent PAE between May 2013 and March 2020 at a single center for LUTS (n = 161) or urinary retention (n = 79). Total International Prostate Symptom Score (IPSS-t), voiding domain score (IPSS-v), storage domain score (IPSS-s), and Quality of Life score (QoL) were obtained pre-PAE for LUTS patients (IPSS-t = 21.7 ± 6.2, IPSS-v = 11.9 ± 4.3, IPSS-s = 9.6 ± 3.1, QoL = 4.5 ± 1.2), and post-PAE through 36 months (mean = 22.9 ± 15.2 months) for LUTS and retention patients. Mean relative changes in IPSS-t, IPSS-v, IPSS-s, and QoL were calculated for LUTS patients. Mean voiding or storage component scores were calculated for retention patients.

RESULTS For evaluable LUTS patients (n = 147), IPSS-t showed sustained substantial improvement through 36 months (6.3 ± 4.2-8.6 ± 7.6), as did QoL (1.1 ± 1.1-1.8 ± 1.5). One month after PAE, improvements in IPSS-v (69% ± 29%) were greater than in IPSS-s (46% ± 33%; $P < .000001$), and remained so through 36 months (68% ± 31% vs 53% ± 28%, $P = .004$). Among evaluable retention patients (n = 75), 84% passed voiding trials. Both IPSS-t (6.0 ± 3.9-8.2 ± 6.7) and QoL (0.9 ± 1.2-1.5 ± 1.6) remained low through 36 months. One month after PAE, mean IPSS-v component score (0.9 ± 1.3) was lower than mean IPSS-s component score (1.7 ± 1.4; $P = .003$) and remained so through 24 months (0.9 ± 1.2 vs 1.3 ± 1.1, $P = .02$), with similar trend at 36 months (0.7 ± 1.1 vs 1.1 ± 1.1, $P = .07$).

CONCLUSIONS PAE effectively treated BPH-related LUTS and retention. IPSS-v improved more than IPSS-s in LUTS patients, and remained lower in LUTS and retention patients through 36 months. UROLOGY 00: 1–9, 2021. © 2021 Elsevier Inc.

The International Prostate Symptom Score (IPSS) quantifies lower urinary tract symptoms (LUTS) resulting from bladder outlet obstruction caused by benign prostatic hyperplasia (BPH).[1] The IPSS quantifies seven component symptoms of LUTS that are grouped into voiding and storage symptom domains. Voiding symptoms are experienced during urination: incomplete emptying, intermittency, weak stream, and straining. Storage symptoms are experienced during bladder filling: frequency, urgency, and nocturia. The IPSS is an extensively validated metric that is combined with the Quality of Life score (QoL), cystoscopy, and urodynamic studies to evaluate patients with symptomatic BPH, for both initial assessment and follow-up after treatment.[2] Although by definition the IPSS cannot be used to assess patients in urinary retention, it can be used to follow patients after their retention has been treated.

Most patients with BPH-related LUTS or urinary retention experience both voiding and storage symptoms. For those who fail medical therapy and thus require procedural treatment, transurethral resection of the prostate (TURP) is the gold-standard.[2] While TURP effectively

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decreases the overall symptom burden, it seems to improve voiding symptoms more so than storage symptoms.[3,4] Indeed, Steers et al and Chai et al described an enhanced spinal micturition reflex in rats and humans that developed secondarily to prolonged bladder outlet obstruction, and persisted after relief of such obstruction.[5-7] Additionally, storage symptoms can be caused by conditions distinct from but co-existing with BPH, such as overactive or neurogenic bladder.

Prostate artery embolization (PAE) is another procedure that is also safe and effective for treating LUTS and urinary retention from BPH.[8,9] Embolic infarction causes shrinkage of obstructing hyperplastic prostatic tissue, resulting in substantially improved LUTS or resolution of retention.[8] Although the National Institute for Health and Care Excellence in the United Kingdom has endorsed PAE for treatment of symptomatic BPH, guidelines from the American Urological Association and European Association of Urology continue to recommend further clinical investigation of PAE.[2,10,11] Indeed, while the adenomatous tissue shrinkage seen in PAE would presumably improve symptoms in a fashion similar to transurethral tissue resection, only 2 small studies have reported stratified data for improvements in voiding and storage symptom domain scores after PAE.[12,13] These studies report improvements greater in voiding symptoms than in storage symptoms, with systematic data collection through 12 months but with small sample sizes limiting statistical significance. Only one of these studies cites data beyond 12 months, and neither characterize postembolization symptom score trends for retention patients.[12,13]

This study therefore aims to analyze stratified voiding and storage domain symptom improvements following PAE in a large cohort, including both LUTS and urinary retention patients, with follow up through three years. Changes in prostate gland volume (PGV), post void residual (PVR), and prostate serum antigen (PSA) level are also analyzed.

MATERIALS AND METHODS

Patients

Between May 2013 and March 2020, 240 consecutive patients (age = 74.5 ± 8.6 years, Charlson comorbidity index=3.9 ± 1.8) were treated with PAE at a single center, for LUTS (n = 161) or urinary retention (n = 79, duration of retention = 145 ± 129 days).[14] Data were retrospectively reviewed under an institutional review board-approved protocol. Eligibility for PAE included age >45 years, PGV >40 mL, IPSS >12 and QoL >2 or urinary retention, and contraindication to or failure of medical therapy. For LUTS patients, preprocedure total IPSS (IPSS-t) and QoL scores were obtained, voiding (IPSS-v) and storage (IPSS-s) domain scores were tabulated, and preprocedure PVRs were recorded. For all patients, preprocedure PGVs and PSA levels were obtained when available.

LUTS cohort patients were then excluded for technical failure (unilateral or no embolization; n = 8), interval development of bladder or prostate cancer (n = 4), loss to follow-up (n = 1), or unrelated death before follow-up (n = 1). For IPSS domain score analysis, additional patients (n = 10) with insufficient preprocedure IPSS component score data were excluded. Retention cohort patients were similarly excluded for technical failure (n = 3) or unrelated death before follow-up (n = 1). For IPSS domain score analysis, 8 retention patients who failed voiding trials and 19 patients with sustained successful voiding but no postprocedure IPSS data (due to dementia, unrelated death, or loss to follow-up after voiding trial) were further excluded. Thus, 137 LUTS patients and 48 retention patients were ultimately studied for IPSS domain score analysis. Some data from these patients were previously reported, however novel IPSS domain score data, longer follow-up, and additional patients are included in this study.[15-17]

Procedure

As described elsewhere, patients with urinary tract infections were given 2-7 days of antibiotic prior to PAE.[15-17] 237 procedures were performed using moderate sedation (midazolam IV, fentanyl IV) and ketorolac IV. Three procedures were performed under general anesthesia per patient preference, due to anxiety or difficulty with laying supine. All procedures were performed by a single operator.[15-17] Arterial access was obtained via a 6F femoral (n = 213) or radial (n = 27) arterial sheath, per operator preference. Both internal iliac arteries were in turn selected with a 5F angiographic catheter. The prostatic arteries were then subselected using an end-hole microcatheter (2.1F Maestro or 2.4F SwiftNinja by Merit Medical, South Jordan, UT) or balloon-occlusion microcatheter (2.2F Sniper by Embolx, Sunnyvale, CA). As balloon-occlusion microcatheter use in PAE has previously been shown to have no impact on embolic parameters or clinical outcomes, microcatheter selection was not considered an experimental variable.[17,18] Cone-beam CT angiography was performed to delineate prostatic arterial anatomy and to identify non-target vessel anastomoses. When necessary, nontarget vessels were protected by coil-embolization blockade (Tornado by Cook Medical, Bloomington, IN or Concerto by Medtronic, Minneapolis, MN). Two hundred micrograms nitroglycerin were then injected into each prostatic artery, followed by embolization to stasis with 100-300 μm trisacryl gelatin spherical particles (Embosphere by Merit Medical Systems, South Jordan, UT). Larger 300-500 μm particles were used when collateral vessels raised concern for possible nontarget embolization (31/137 LUTS patients, 8/48 retention patients). Finally, hemostasis was obtained with a 6F Angio-Seal device (femoral) or a TR Band (radial) (Terumo Medical Corporation, Somerset, NJ). Post-procedure medications were prescribed as reported elsewhere.[15-17]

Follow-up

Follow-up IPSS data were obtained at 1, 3, 6, 12, 24, and 36 months after PAE. PVRs and PGVs were measured by transabdominal ultrasound from 3 months onward. PSA levels were measured 1 year after PAE. Retention patients underwent voiding trials at 1 month. Catheters were removed if voiding efficiency ([voided volume/(voided volume + PVR)] * 100%) was ≥60%, otherwise a second voiding trial was attempted 2 months after PAE. BPH medication cessation was encouraged if patients had sustained IPSS-t improvement into the mild range (0-7) with PVR < 200 mL. Anticholinergic medications or dietary/lifestyle modifications to further treat residual storage symptoms were routinely encouraged, but not quantified for this study. Due to rolling accrual of patients, progressively fewer patients were eligible for follow-up at each timepoint (Table 1). Thirty-day adverse events were reported for all 240 patients using Clavien-Dindo classification.[19]

Data Analysis

For LUTS patients, differences between absolute preprocedure and postprocedure IPSS-t, IPSS-v, IPSS-s, and QoL values at each timepoint through 36 months were analyzed using paired Wilcoxon signed rank tests. Comparisons between relative postprocedure changes in IPSS-v and IPSS-s were made at each timepoint through 36 months using 2-tailed paired Student t-tests. By definition, comparisons to preprocedure IPSS or QoL values could not be made for retention patients. Furthermore, because the IPSS-v domain score (range 0-20) is composed of 4 component scores while the IPSS-s domain score (range 0-15) is composed of 3 component scores, comparisons between absolute postprocedure IPSS-v and IPSS-s scores could not be made. Therefore, comparisons between mean postprocedure IPSS-v and postprocedure IPSS-s component scores were made at each timepoint through 36 months using 2-tailed paired Student t-tests. PGV values (for LUTS and retention patients) and PVR values (for LUTS patients) were compared to preprocedure baselines at each timepoint through 24 months using 2-tailed paired Student t-tests. Pre-embolization and 1-year follow-up PSA levels were also so-compared. All statistical analyses were performed using R (The R Foundation for Statistical Computing, Version 4.0.0, 2020). $P < .05$ was considered statistically significant.

RESULTS

LUTS Patients

One hundred forty-seven LUTS patients (mean PGV = 126 ± 74 mL) underwent technically successful PAE and returned for follow-up. Among them, 116 (78.9%) had sustained clinical success with IPSS-t reduced to the mild range (0-7) at last follow-up (mean = 600 ± 348 days). Thirteen (8.8%) had initial improvement to mild range followed by return of symptoms to the moderate (n = 8) or severe (n = 5) range, and 18 (12.3%) never reported IPSS-t improvement into the mild range. IPSS-t improved from 21.7 ± 6.2 preprocedurally to values between 8.6 ± 7.6 and 6.3 ± 4.2 through 36 months follow-up ($P < .00002$ throughout; Fig. 1A, Table 1A). QoL improved from 4.5 ± 1.2

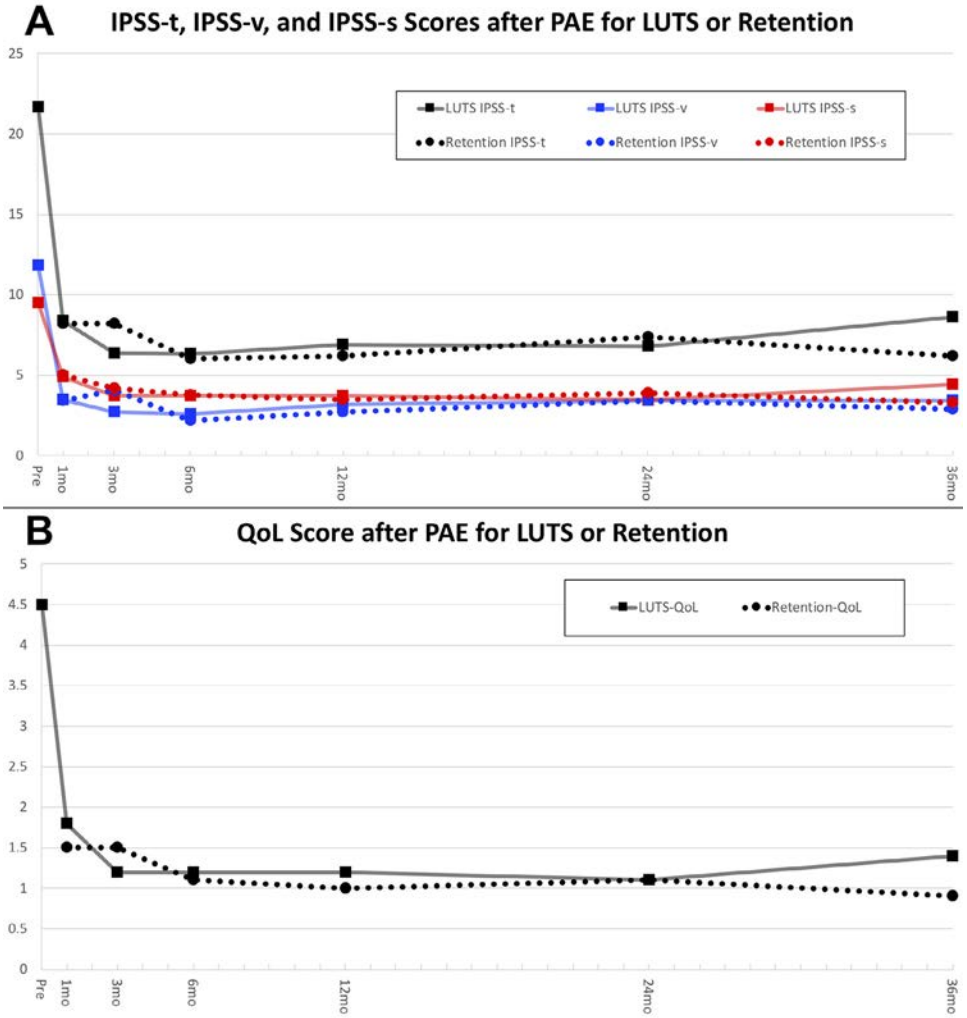

Figure 1. IPSS-t improved substantially and in a sustained fashion after PAE for LUTS. No differences in IPSS-t were found between LUTS and retention patients through 36 months (black plots, Fig. 1A). Furthermore, IPSS-v and IPSS-s both improved substantially and in a sustained fashion after PAE for LUTS. There were no differences between LUTS and retention patients in either IPSS-v or IPSS-s after PAE through 36 months (blue and red plots, Fig. 1A). Similarly, QoL improved substantially and in a sustained fashion after PAE for LUTS, with no differences in QoL found between LUTS and retention patients through 36 months (Fig. 1B). (Color version available online.)

Table 1. Pre-embolization baseline and postembolization values for IPSS-t, IPSS-v, IPSS-s, QoL, PGV, and PVR

TABLE 1A		Pre-Embolization	1 Month n=122 (83%)	1 Month Decrease	3 Month n=105 (71%)	3 Month Decrease	6 Month n=108 (77%)	6 Month Decrease	12 Month n=96 (83%)	12 Month Decrease	24 Month n=54 (71%)	24 Month Decrease	36 Month n=32 (84%)	36 Month Decrease
All Included LUTS Patients (n=147)	IPSS-t	21.7 ± 6.2	8.4 ± 6.1	61% ± 26%	6.4 ± 4.5	70% ± 20%	6.3 ± 4.2	67% ± 23%	6.9 ± 5.4	67% ± 29%	6.8 ± 5.0	69% ± 22%	8.6 ± 7.6	62% ± 27%
	QoL	4.5 ± 1.2	1.8 ± 1.5	59% ± 31%	1.2 ± 1.1	72% ± 26%	1.2 ± 1.2	71% ± 28%	1.2 ± 1.1	72% ± 25%	1.1 ± 1.1	72% ± 30%	1.4 ± 1.4	69% ± 25%
	PGV (mL)	125 ± 73	-	-	74 ± 40	-	76 ± 48	-	73 ± 42	-	73 ± 39	-	-	-
	PVR (mL)	188 ± 197	-	-	109 ± 179	-	98 ± 159	-	103 ± 229	-	71 ± 79	-	-	-
TABLE 1B		Pre-Embolization	1 Month n=36 (54%)		3 Month n=43 (65%)		6 Month n=42 (67%)		12 Month n=41 (72%)		24 Month n=27 (64%)		36 Month n=19 (79%)	
All Included Retention Patients with Catheters Removed (n=63)	IPSS-t	-	8.2 ± 5.0		8.2 ± 6.7		6.0 ± 3.9		6.2 ± 4.8		7.4 ± 5.9		6.2 ± 5.0	
	QoL	-	1.5 ± 1.2		1.5 ± 1.6		1.1 ± 1.1		1.0 ± 1.1		1.1 ± 1.2		0.9 ± 1.2	
	PGV (mL)	162 ± 103	-		78 ± 49		71 ± 44		73 ± 43		100 ± 83		-	
	PVR (mL)	-	-		178 ± 223		141 ± 196		164 ± 203		156 ± 159		-	
TABLE 1C		Pre-Embolization	1 Month n=114 (83%)	1 Month Decrease	3 Month n=97 (71%)	3 Month Decrease	6 Month n=93 (70%)	6 Month Decrease	12 Month n=79 (75%)	12 Month Decrease	24 Month n=46 (68%)	24 Month Decrease	36 Month n=23 (74%)	36 Month Decrease
LUTS Patients with IPSS Data (n=137)	IPSS-v	11.9 ± 4.3	3.5 ± 3.6	69% ± 29%	2.6 ± 3.7	77% ± 23%	2.6 ± 2.4	75% ± 25%	3.3 ± 3.5	70% ± 36%	3.3 ± 3.2	73% ± 25%	3.8 ± 4.2	68% ± 31%
	IPSS-s	9.8 ± 3.1	5.0 ± 3.3	46% ± 33%	3.7 ± 2.5	59% ± 27%	3.7 ± 2.8	55% ± 35%	3.8 ± 2.6	58% ± 35%	3.6 ± 2.3	59% ± 27%	4.4 ± 2.5	53% ± 28%
	Incomplete Emptying	3.2 ± 1.6	1.0 ± 1.2	68% ± 38%	0.9 ± 1.1	76% ± 30%	0.7 ± 0.9	75% ± 33%	1.0 ± 1.2	66% ± 53%	1.0 ± 1.3	70% ± 38%	1.2 ± 1.3	63% ± 38%
	Intermittency	3.1 ± 1.4	1.0 ± 1.2	69% ± 34%	0.8 ± 1.1	74% ± 34%	0.7 ± 0.9	75% ± 36%	0.8 ± 1.1	73% ± 37%	0.8 ± 1.2	76% ± 31%	1.0 ± 1.6	67% ± 44%
	Straining	2.1 ± 1.6	0.4 ± 0.8	75% ± 54%	0.2 ± 0.5	91% ± 22%	0.2 ± 0.6	83% ± 52%	0.3 ± 0.7	85% ± 30%	0.3 ± 0.5	85% ± 26%	0.5 ± 0.8	81% ± 30%
	Weak Stream	3.5 ± 1.3	1.1 ± 1.2	65% ± 39%	0.8 ± 1.0	75% ± 30%	1.0 ± 1.0	68% ± 33%	1.2 ± 1.4	59% ± 55%	1.2 ± 1.4	66% ± 40%	1.1 ± 1.4	67% ± 40%
	Frequency	3.4 ± 1.3	1.6 ± 1.4	53% ± 42%	1.2 ± 1.1	66% ± 33%	1.2 ± 1.2	59% ± 42%	1.1 ± 1.1	66% ± 42%	1.1 ± 1.0	63% ± 40%	1.4 ± 1.1	54% ± 44%
	Urgency	3.1 ± 1.5	1.4 ±1.4	54% ± 49%	1.1 ± 1.1	63% ± 34%	1.0 ± 1.2	61% ± 53%	1.1 ± 1.1	58% ± 57%	0.9 ± 0.8	69% ± 31%	1.4 ± 1.3	54% ± 47%
	Nocturia	3.1 ± 1.2	2.0 ± 1.2	33% ± 35%	1.4 ± 1.0	51% ± 30%	1.5 ± 1.0	45% ± 39%	1.5 ± 1.1	49% ± 32%	1.5 ± 1.1	47% ± 34%	1.6 ± 1.0	50% ± 31%
TABLE 1D		Pre-Embolization	1 Month n=29 (60%)		3 Month n=33 (69%)		6 Month n=30 (65%)		12 Month n=25 (63%)		24 Month n=18 (58%)		36 Month n=13 (72%)	
Retention Patients with IPSS Data (n=48)	Mean IPSS-v Component Score	-	0.9 ± 1.3		1.0 ± 1.5		0.5 ± 0.9		0.7 ± 1.0		0.9 ± 1.2		0.7 ± 1.1	
	Mean IPSS-s Component Score	-	1.7 ± 1.4		1.4 ± 1.3		1.3 ± 1.2		1.2 ± 1.3		1.3 ± 1.1		1.1 ± 1.1	
	Incomplete Emptying	-	1.0 ± 1.3		0.9 ± 1.2		0.7 ± 1.1		0.8 ± 1.1		0.9 ± 1.2		0.6 ± 1.0	
	Intermittency	-	1.0 ± 1.3		0.8 ± 1.4		0.4 ± 0.7		0.7 ± 1.2		0.8 ± 1.2		0.6 ± 1.1	
	Straining	-	0.5 ± 1.1		0.5 ± 1.1		0.2 ± 0.4		0.3 ± 0.5		0.6 ± 1.3		0.4 ± 0.8	
	Weak Stream	-	1.1 ± 1.3		1.3 ± 1.6		0.9 ± 1.2		0.8 ± 1.0		1.2 ± 1.2		1.3 ± 1.3	
	Frequency	-	1.6 ± 1.4		0.9 ± 1.1		1.0 ± 1.2		0.9 ± 1.3		1.5 ± 1.0		1.2 ± 1.3	
	Urgency	-	1.7 ± 1.7		1.4 ± 1.6		1.2 ± 1.4		1.0 ± 1.3		0.9 ± 1.2		0.6 ± 0.8	
	Nocturia	-	1.8 ± 1.2		1.5 ± 1.0		1.6 ± 1.0		1.6 ± 1.2		1.5 ± 1.1		1.5 ± 1.3	

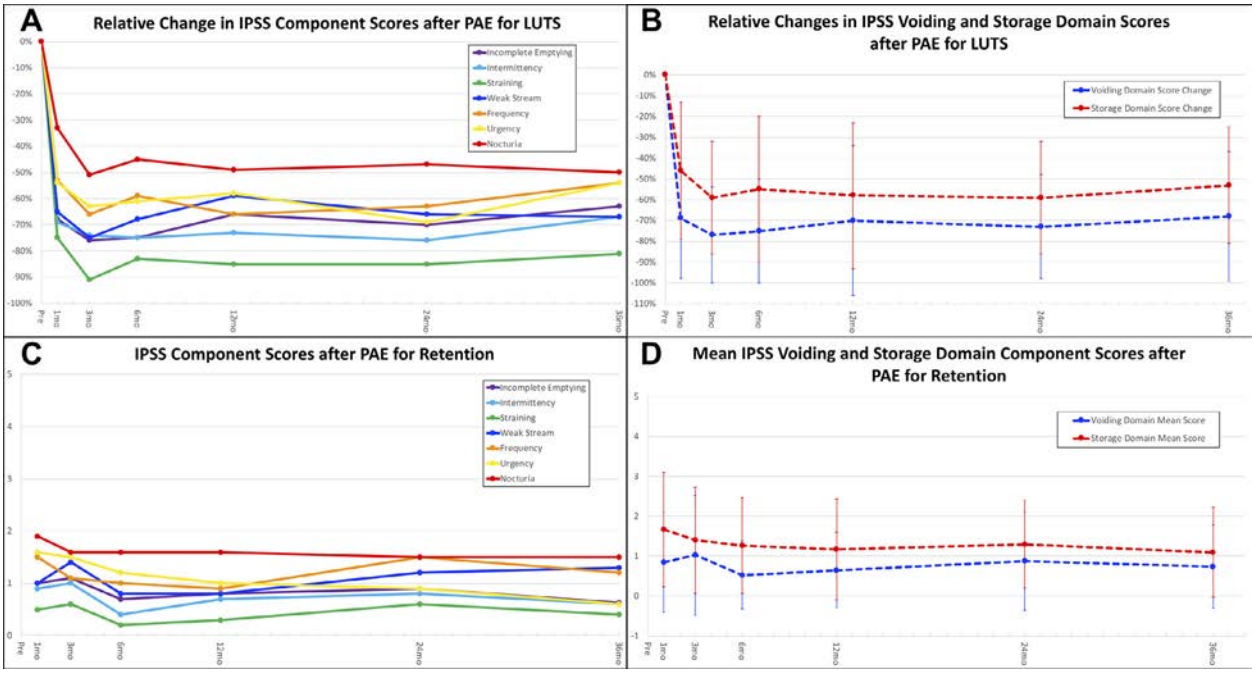

Figure 2. IPSS component, voiding domain, and storage domain scores following PAE for LUTS or retention. Individual IPSS component scores are shown following PAE for LUTS (Fig. 2A) or retention (Fig. 2C). Relative changes in IPSS-v and IPSS-s domain scores following PAE for LUTS are shown in Fig. 2B, with IPSS-v improved more than IPSS-s through 36 months. Mean IPSS-v and IPSS-s component scores following PAE for retention are shown in Fig. 2D, with mean IPSS-v component scores lower than mean IPSS-s component scores through 36 months. (Color version available online.)

preprocedurally to values between 1.8 ± 1.5 and 1.1 ± 1.1 through 36 months ($P < .00002$ throughout; Fig. 1B, Table 1A).

Among the 137 LUTS patients with available IPSS component score data, all 7 IPSS component scores showed substantial improvement relative to preprocedure baseline through 36 months (Fig. 2A, Table 1C). When component scores were grouped into voiding (IPSS-v) and storage (IPSS-s) domain scores, IPSS-v improved more robustly than IPSS-s at all follow-up timepoints (Fig. 2B). Relative to preprocedure baselines, domain score reductions were IPSS-v = 69% ± 29% vs IPSS-s = 46% ± 33% at 1 month ($P < .000001$); IPSS-v = 77% ± 23% vs IPSS-s = 59% ± 27% at 3 months ($P < .000001$); IPSS-v = 75% ± 25% vs IPSS-s = 55% ± 35% at 6 months ($P < .000001$); IPSS-v = 70% ± 36% vs IPSS-s = 58% ± 35% at 12 months ($P = .0006$); IPSS-v = 73% ± 25% vs IPSS-s = 59% ± 27% at 24 months ($P = .0001$); and IPSS-v = 68% ± 31% vs IPSS-s = 53% ± 28% at 36 months ($P = .004$; Table 1C).

Retention Patients

Among the 75 retention patients (mean PGV = 161 ± 103 mL) who underwent technically successful PAE and subsequent voiding trial, 63 (84.0%) voided successfully and remained catheter-free as of last follow-up (mean = 611 ± 388 days), while 4 (5.3%) converted to or decreased supplemental self-catheterization, and 8 (10.7%) failed voiding trials. Among the 63 patients who passed voiding trials, 48 patients provided quantifiable follow-up IPSS component score data. They reported post-procedure IPSS-t values (range = 8.2 ± 6.7-6.0 ± 3.9) and QoL scores (range = 1.5 ± 1.6-0.9 ± 1.2) that were low within 3 months after treatment, and sustained in the mild range through 36 months of follow-up (Fig. 1A, Table 1B).

Similar to LUTS patients, successfully treated retention patients reported mean IPSS-v component scores lower than mean IPSS-s component scores at all follow-up timepoints (Fig. 2C and D, Table 1D), although at 36 months this difference fell just short of statistical significance. Their mean component scores were IPSS-v = 0.9 ± 1.3 vs IPSS-s = 1.7 ± 1.4 at 1 month ($P = .003$); IPSS-v = 1.0 ± 1.5 vs IPSS-s = 1.4 ± 1.3 at 3 months ($P = .02$); IPSS-v = 0.5 ± 0.9 vs IPSS-s = 1.3 ± 1.2 at 6 months ($P = .00002$); IPSS-v = 0.7 ± 1.0 vs IPSS-s = 1.2 ± 1.3 at 12 months ($P = .004$); IPSS-v = 0.9 ± 1.2 vs IPSS-s = 1.3 ± 1.1 at 24 months ($P = .02$); and IPSS-v = 0.7 ± 1.1 vs IPSS-s = 1.1 ± 1.1 at 36 months ($P = 0.07$; Table 1D).

Comparisons Between LUTS and Retention Patients

Importantly, postembolization IPSS-t and QoL values did not differ between LUTS and retention patients at any follow-up timepoint through 36 months ($P > .05$ throughout; Fig. 1, Table 1A and B), nor did absolute IPSS-v or IPSS-s domain scores ($P > .05$ throughout; Fig. 1, Table 1C and D). Pretreatment PGVs in retention patients were greater than in LUTS patients (161 ± 103mL vs 126 ± 74mL, $P = .007$), but both groups experienced parallel substantial PGV reductions by 3 months ($P = .0002$ and $P < .000001$, respectively) and sustained through 24 months (Fig. 3, Table 1A and B). LUTS patients experienced substantial reductions in PVR by 3 months (188 ± 197 mL down to 109 ± 179 mL, $P = .00001$) that were sustained through 24 months (Fig. 3, Table 1A). Retention patients who successfully passed voiding trials after PAE had mean PVR of 178 ± 223 mL, which was maintained through 24 months but was higher than that of LUTS patients (Fig. 3, Table 1B). PSA levels dropped after PAE from 6.3 ± 7.0 ng/mL to 2.6 ±

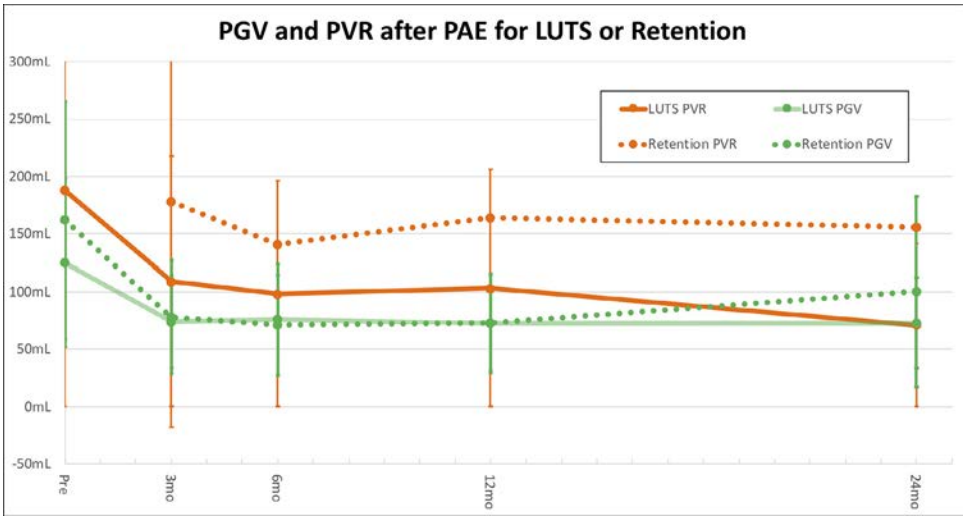

Figure 3. PGV and PVR following PAE for LUTS or retention. Both LUTS and retention patients showed substantial reductions in PGV, maintained through 24 months. Additionally, PVR was reduced substantially after PAE in LUTS patients and sustained through 24 months, and was consistently lower than PVR for retention patients. (Color version available online.)

3.0 ng/mL in LUTS patients (n = 68), and from 9.9 ± 9.0 ng/mL to 2.8 ± 2.2 ng/mL (n = 16) in retention patients (P = .00002, P = .006, respectively).

Predictors of Technical or Clinical Success, and Adverse Events

Among all 240 patients studied, there were no obvious differences in technical success rates related to the method of arterial access (radial, n = 27 versus femoral, n = 213) or in clinical success rates related to gland size (<80 mL, n = 44 vs >80 mL, n = 196), nor was there any obvious predictor of voiding trial success in retention patients. LUTS patients with PGV > 80 mL showed a trend toward more pronounced IPSS improvements compared to patients with PGV < 80 mL, and patients of age ≥90 year failed voiding trials more frequently. However, this study was not powered sufficiently to objectively evaluate these trends.

Within 30 days of PAE, there were 39 self-limited Grade-1 events (16% of patients) requiring no further management (Supplemental Table 1). There were 28 Grade-2 events (12% of patients), including urinary tract infection (n = 12) or catheter-associated urinary tract infection (n = 10) requiring oral antibiotic, medication reaction requiring oral therapy (n = 2), lower extremity deep vein thrombosis requiring anticoagulation (n = 2), presumed bladder ischemia requiring additional pain medication (n = 1), and penile skin ischemia managed conservatively (n = 1) (Supplemental Table 1). There were two Grade-5 unrelated deaths (1% of patients) caused by fungemia in an immunocompromised patient and warfarin toxicity.

DISCUSSION

As in prior studies, PAE was effective in treating BPH-related LUTS and urinary retention.[9,15,16,20] After embolization, symptoms remained stable in essentially the mild range through 36 months of follow-up. Substantial reductions in PGV and PVR were maintained through 24 months of follow-up. However, the salient findings of this study were that after embolization, (1) voiding symptom domain scores improved proportionately more and remained lower than storage symptom domain scores for LUTS patients, and (2) voiding symptom domain scores remained lower than storage symptom domain scores in retention patients. These differences were significant through 36 months in LUTS patients, and through 24 months in retention patients with a similar trend at 36 months just short of statistical significance (likely owing to smaller sample size). The differentials between voiding and storage symptom domain score improvements may have been more pronounced if residual post-treatment storage symptoms had not been further treated by anticholinergic medications and dietary/lifestyle modifications.

Voiding symptoms have been shown to similarly improve more so than storage symptoms in LUTS patients after TURP.[3,4] This similarity supports the hypothesis that both PAE and TURP work in a similar fashion by reducing obstructive adenomatous tissue (via tissue necrosis with embolization or tissue resection with TURP). Voiding domain symptoms which are more closely related to obstruction would be expected to improve with such treatments more so than storage domain symptoms, which can also be caused by separate bladder pathologies that can contribute to abnormal detrusor activity.[21] Indeed, the findings that storage domain symptoms improved less and remained worse than voiding domain symptoms through three years after PAE corroborate a similar phenomenon observed by Steers et al and Chai et al. They showed that despite successful relief of bladder outlet obstruction, altered innervation governing bladder function can remain, manifesting as persistent storage symptoms.[5-7]

These results for LUTS patients also corroborate findings from previous smaller PAE studies. Lin et al showed a trend toward greater improvement in voiding symptoms

in 37 patients treated with PAE, reaching statistical significance at 6 months.[12] Maclean et al also showed greater improvement in voiding symptoms in 43 patients following PAE, with statistical significance found at 3 and 12 months.[13] The current report demonstrates statistical significance at all timepoints through 36 months, which may be due to larger sample sizes and to the more pronounced improvements in IPSS-v observed. For example, at 3 months Lin et al showed improvements in IPSS-v by 66.0% and IPSS-s by 54.4%, and Maclean et al described improvements in IPSS-v by 65.0% and IPSS-s by 54.5%. However, IPSS-v improved by 77% and IPSS-s improved by 59% at 3 months in the present study. The variation in symptomatic improvements observed among these studies could be related to choice of embolic agent (300-500 μm trisacryl gelatin spherical particles use by Lin et al, non-spherical PVA or 400 μm spherical hydrogel microspheres used by Maclean et al, or predominantly 100-300 μm trisacryl gelatin spherical particles used in this study). Variations in pre-embolization IPSS-t and PGV among these studies (IPSS-t = 16.5 $\pm$ 7.2 and PGV = 91.6 $\pm$ 36.9mL for Lin et al, IPSS-t = 23.0 $\pm$ 5.8 and PGV = 88.7 $\pm$ 37.2mL for Mclean et al, IPSS-t = 21.7 $\pm$ 6.2 and PGV = 125 $\pm$ 73 mL for LUTS patients in this study) may have also contributed to variations in magnitudes of improvement. Indeed, more robust improvements in LUTS after PAE have been reported in larger gland sizes.[22]

Evaluation of symptomatic improvement after PAE for retention patients is more challenging due to the absence of pre-procedural IPSS and post-void residual data. However, both LUTS and retention patients in this study were found to have (1) similar likelihoods of clinical success (78.9% of LUTS achieving mild-range symptoms and 84.0% of retention patients remaining catheter-free); (2) similar absolute postprocedure IPSS-t, IPSS-v, IPSS-s, and QoL scores through 36 months; (3) similarly lower postembolization IPSS-v domain scores compared to IPSS-s domain scores; and (4) similar magnitudes of PGV reduction sustained through 24 months and PSA reduction at 12 months. Baseline PGV and PSA levels for retention patients were greater, and postembolization PVRs remained higher for retention patients through 24 months, albeit in the setting of low symptom scores. This constellation of findings in retention patients suggests more advanced pre-embolization BPH, manifesting as longer-standing bladder outlet obstruction with possible concomitant decreased bladder sensation and contraction. Overall, these direct comparisons of outcomes between LUTS and retention patients treated with PAE could prove useful when counseling urinary retention patients who are considering PAE as a treatment option.

Limitations of this study are mainly due to its single-arm, single-center, retrospective design. No comparison to standard-of-care surgical intervention was made. However, most subjects were nonindex patients who were not surgical candidates because of large gland size or medical comorbidities. Quantitative pre- and postprocedure uroflowmetry data to corroborate subjective IPSS data with objective urine flow measurements were unavailable. Urodynamic studies were performed only in select cases when the diagnosis of bladder outlet obstruction was in question. Incomplete follow-up among elderly patients or those with poor outcomes may have imparted responder bias in this study's results. Lastly, PGV and PVR measurements were obtained by trans-abdominal ultrasound and were therefore subject to operator variability.

CONCLUSION

PAE is an effective treatment for BPH-related LUTS or urinary retention. Both voiding and storage symptoms improved substantially following PAE. In LUTS patients, voiding symptom scores improved to a greater degree and remained lower than storage symptom scores through 3 years. In retention patients, voiding symptom scores also remained lower than storage symptom scores through 3 years. This is relevant for counseling patients regarding their procedural treatment options for symptomatic BPH, as well as for continuing management of patients' voiding and storage symptoms after undergoing PAE.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2021.02.046.

References

1. Barry MJ, Fowler Jr. FJ, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol*. 1992;148:1549–1557. discussion 1564.
2. Foster HE, Dahm P, Kohler TS, et al. Surgical management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA Guideline Amendment 2019. *J Urol*. 2019;202:592–598.
3. Kang YJ, Kim KH, Seo Y, Lee KS. Effect of transurethral resection of the prostate on storage symptoms in patients with benign prostatic hyperplasia of less than 30 ml. *World J Mens Health*. 2013;31:64–69.
4. Sokhal AK, Sinha RJ, Purkait B, Singh V. Transurethral resection of prostate in benign prostatic enlargement with underactive bladder: A retrospective outcome analysis. *Urol Ann*. 2017;9:131–135.
5. Chai TC, Gemalmaz H, Andersson KE, Tuttle JB, Steers WD. Persistently increased voiding frequency despite relief of bladder outlet obstruction. *J Urol*. 1999;161:1689–1693.
6. Steers WD, De Groat WC. Effect of bladder outlet obstruction on micturition reflex pathways in the rat. *J Urol*. 1988;140:864–871.
7. Chai TC, Gray ML, Steers WD. The incidence of a positive ice water test in bladder outlet obstructed patients: evidence for bladder neural plasticity. *J Urol*. 1998;160:34–38.
8. McWilliams JP, Bilhim TA, Carnevale FC, et al. Society of Interventional Radiology Multisociety Consensus position statement on prostatic artery embolization for treatment of lower urinary tract symptoms attributed to benign prostatic hyperplasia: from the Society of Interventional Radiology, the Cardiovascular and Interventional Radiological Society of Europe, Societe Francaise de Radiologie, and the British Society of Interventional Radiology: Endorsed by the Asia Pacific Society of Cardiovascular and Interventional Radiology, Canadian Association for Interventional Radiology, Chinese College of Interventionalists, Interventional Radiology Society of Australasia, Japanese Society of Interventional

Radiology, and Korean Society of Interventional Radiology. *J Vasc Intervent Radiol*. 2019;30:627–637.
9. Malling B, Roder MA, Brasso K, Forman J, Taudorf M, Lonn L. Prostate artery embolisation for benign prostatic hyperplasia: a systematic review and meta-analysis. *Eur Radiol*. 2019;29:287–298.
10. National Institute for Health and Care Excellence. *Prostate artery embolization for lower urinary tract symptoms caused by benign prostatic hyperplasia. Interventional procedures guidance*. 2018. www.nice.org.uk/guidance/IPG611.
11. Gravas S, Cornu J, Gacci M, et al. Management of non-neurogenic male lower urinary tract symptoms (LUTS). European Association of Urology: Non-Oncology Guidelines. ISBN 978-94-92671-07-3. EAU Guidelines Office, Arnhem, the Netherlands, 2020.
12. Lin YT, Pereira H, Pellerin O, Déan C, Thiounn N, Sapoval M. Four-year impact of voiding and storage symptoms in patients with benign prostatic hyperplasia treated with prostatic artery embolization. *J Vasc Intervent Radiol*. 2020;31:1460–1466.
13. Maclean D, Kong M, Lim J, et al. Does prostate artery embolization (PAE) improve voiding symptoms, storage symptoms, or both? *Cardiovasc Intervent Radiol*. 2020;43:23–28.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
15. Ayyagari R, Powell T, Staib L, et al. Prostatic artery embolization using 100-300 μm trisacryl gelatin microspheres to treat lower urinary tract symptoms attributable to benign prostatic hyperplasia: a single center outcomes analysis with medium-term follow-up. *J Vasc Intervent Radiol*. 2020;31:99–107.
16. Ayyagari R, Powell T, Staib L, et al. Prostatic artery embolization in nonindex benign prostatic hyperplasia patients: single-center outcomes for urinary retention and gross prostatic hematuria. *Urology*. 2020;136:212–217.
17. Ayyagari R, Powell T, Staib L, et al. Case-control comparison of conventional end-hole versus balloon-occlusion microcatheter prostatic artery embolization for treatment of symptomatic benign prostatic hyperplasia. *J Vasc Intervent Radiol*. 2019;30:1459–1470.
18. Bilhim T, Costa NV, Torres D, Pisco J, Carmo S, Oliveira AG. Randomized clinical trial of balloon occlusion versus conventional microcatheter prostatic artery embolization for benign prostatic hyperplasia. *J Vasc Intervent Radiol*. 2019;30:1798–1806.
19. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
20. Bhatia S, Sinha VK, Kava BR, et al. Efficacy of prostatic artery embolization for catheter-dependent patients with large prostate sizes and high comorbidity scores. *J Vasc Intervent Radiol*. 2018;29:78–84.e71.
21. Gacci M, Sebastianelli A, Spatafora P, et al. Best practice in the management of storage symptoms in male lower urinary tract symptoms: a review of the evidence base. *Ther Adv Urol*. 2017;10:79–92.
22. Hacking N, Vigneswaran G, Maclean D. Technical and imaging outcomes from the UK Registry of Prostate Artery Embolization (UK-ROPE) study: focusing on predictors of clinical success. *Cardiovasc Intervent Radiol*. 2019;42:666–676.

EDITORIAL COMMENT

The authors compared voiding and storage symptoms after prostate artery embolization (PAE) for patients with lower urinary tract symptoms (LUTS) and for those with urinary retention.[1] In this study, voiding symptoms improved more than storage symptoms for both groups of patients.

LUTS can be a sign of many conditions other than benign prostate hyperplasia. LUTS may be a presenting feature of prostate cancer, bladder cancer, infection, detrusor overactivity or underactivity and a host of neurological conditions. Even if a patient's symptoms are related to an enlarged prostate, there are many lifestyle management changes that should be considered first. Further, the majority of LUTS can be managed with medications such as alpha blockers, 5-alpha reductase inhibitors, anticholinergics, phosphodiesterase 5 inhibitors, oral desmopressin, or a combination of medications. This is why the European Association of Urology (EAU) guidelines state that the work up of patients with LUTS should be performed by urologists.[2]

The EAU guidelines note that the selection of patients still needs to be better defined, and consider PAE still under investigation.[2] It appears that those with larger prostates and specifically larger central gland volumes do well,[3] as do those with primarily voiding symptoms.[1] Others have suggested that those with intravesical prostatic protrusion do well with PAE.[4] However, this is not uniformly the case, as large middle lobes can still ball-valve and cause obstruction.

These results are encouraging but concerns still exist regarding the data and trial designs for PAE. As such, the American Urological Association guidelines recommend that PAE only be performed as part of a clinical trial.[5]

Both the EAU guidelines and the UK National Institute for Health and Care Excellence guidelines stress the need for a multidisciplinary approach with both urologists and interventional radiologists.[2,6] All patients considering treatment options for lower urinary tract symptoms should be first evaluated by an urologist. If after an assessment they are deemed to be a good candidate for PAE, then an interventional radiologist trained in the technique of PAE should be consulted.[7] It is this partnership between urology and interventional radiology that provides the best possible patient selection and outcome.

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References

1. Voiding and storage domain-specific symptom score outcomes after prostate artery embolisation for lower urinary tract symptoms and urinary retention. *Urology*. 2021.
2. Gravas S, Cornu JN, Gacci M, et al. *European Association of Urology, Non-Oncology Guidelines*. 2020. ISBN 978-94-92671-07-03.
3. Abt D, Müllhaupt G, Mordasini L, et al. Outcome prediction of prostate artery embolisation: post hoc analysis of a randomized open-label, non-inferiority trial. *BJU Int*. 2019;124:134–144.
4. Boeken T, Di Gaeta A, Moussa N, et al. Association between intravesical prostate protrusion and clinical outcomes in prostatic artery embolisation. *Diagnostic Intervent Imaging*. 2021;102:141–145.
5. Foster HE, Barry MJ, Dahm P, et al. Surgical management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA Guideline. *J Urol*. 2018;200:612.
6. NICE Guidance — Prostate artery embolisation for lower urinary tract symptoms caused by benign prostatic hyperplasia © NICE (2018). Prostate artery embolisation for lower urinary tract symptoms caused by benign prostatic hyperplasia. *BJU Int*. 2018;122:11–12.
7. McWilliams JP, Bilhim TA, Carnevale FC, et al. Society of Interventional Radiology Multisociety Consensus position statement on prostatic artery embolisation for treatment of lower urinary tract symptoms attributed to benign prostatic hyperplasia: from the Society of Interventional Radiology, the Cardiovascular and Interventional Radiological Society of Europe, Société Française de Radiologie, and the British Society of Interventional Radiology. *J Vasc Interv Radiol*. 2019;30:627–637.

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AUTHOR REPLY

We thank the editorial board for publishing our present and prior work on prostatic artery embolization (PAE) for treatment of lower urinary tract symptoms, urinary retention, and gross hematuria attributed to benign prostatic hyperplasia (BPH). We also appreciate the above Editorial Comment and the invitation to respond.

There is a paucity of randomized trial data comparing PAE to transurethral procedures for BPH treatment in index patients. However, numerous published trials have demonstrated PAE's safety and efficacy. A recent trial comparing PAE to sham showed a robust treatment effect with PAE.[1] In another trial comparing PAE to transurethral prostatic resection (TURP) in patients with glands smaller than 80 mL, PAE demonstrated substantial efficacy albeit inferior to TURP, with significantly fewer adverse events.[2] Nevertheless, the American Urological Association (AUA) and European Association of Urology guidelines still recommend that PAE only be performed within a clinical trial with regards to index BPH patients.

There is little debate, however, about the merits of PAE for nonindex BPH patients, with glands too large or comorbidities too severe for surgical BPH procedures.[3] The prompt, effective hemostasis that patients with gross prostatic hematuria experience after PAE is also evident.[3] Furthermore, our PAE publications in this journal demonstrate sustained durability of excellent outcomes in these patients through 36 months.[3] These types of patients are often ideal candidates for PAE because it is an outpatient endovascular procedure performed under minimal sedation regardless of anticoagulation status, and PAE delivers size-independent efficacy with minimal impact on erectile function.

Yet in the USA, these non-index patients are often excluded from the very procedure that offers them the best benefit-to-risk balance, because insurance providers use the AUA's guideline written for *index* BPH patients to deny reimbursement for PAE to *nonindex* BPH patients.[4] As PAE is clearly safe and effective at treating large glands, urinary retention, and gross hematuria, this is contrary to evidence-based medicine.[1-3,5] This is furthermore incongruous with real-life experiences reported from centers throughout the world where urologists who recognize PAE's role routinely refer appropriately selected patients for PAE. It is unclear why urological societal guidelines continue to be worded in a manner that drives the denial of appropriate treatment to patients who are not the focus of such guidelines.

We agree that the evaluation of a patient for treatment of BPH should be performed by a urologist, who assesses a patient's procedural options based on gland size, gland shape, and comorbidities. All patients in our study underwent such evaluation. If PAE is an appropriate option based on the prevailing evidence for PAE given a particular treatment indication, and a capable interventional radiologist is available, it should be incumbent upon the urologist to refer that patient for further discussion about PAE. By recently endorsing the use of PAE in patients appropriately selected through multidisciplinary evaluation, the UK National Institute for Health and Care Excellence moved beyond specialty-specific biases to promote comprehensive, evidence-based procedural treatment of BPH.[5] Patients throughout the world will only benefit when other leading healthcare authorities move to follow this example.

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References

1. Pisco J, Bilhim T, Costa N, et al. Randomised clinical trial of prostatic artery embolisation versus a sham procedure for benign prostatic hyperplasia. *Eur Urol.* 2020;77:354–362.
2. Abt D, Müllhaupt G, Hechelhammer L, et al. Prostatic artery embolization versus transurethral resection of the prostate for benign prostatic hyperplasia: 2-yr outcomes of a randomised, open-label, single-centre trial. *Eur Urol.* 2021.
3. Ayyagari R, Powell T, Staib L, et al. Prostatic artery embolization in non-index benign prostatic hyperplasia patients: single-center outcomes for urinary retention and gross prostatic hematuria. *Urology.* 2020;136:212–217.
4. Foster HE, Barry MJ, Dahm P, et al. Surgical management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA Guideline. *J Urol.* 2018;200:612.
5. NICE guidance - prostate artery embolisation for lower urinary tract symptoms caused by benign prostatic hyperplasia: NICE (2018) prostate artery embolisation for lower urinary tract symptoms caused by benign prostatic hyperplasia. *BJU Int.* 2018;122:11–12.

https://doi.org/10.1016/j.urology.2021.02.048
UROLOGY 00: 8–9, 2021.

https://doi.org/10.1016/j.urology.2021.02.046
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