

RESEARCH ARTICLE**Update on Prostatic Artery Embolization****Authors****Benjamin Brown, MD, MPH**UNC-Chapel Hill School of Medicine, Benjamin.Brown@unchealth.unc.edu**Diego A. Hipolito Canario, BS**UNC-Chapel Hill School of Medicine, diego_hipolito@med.unc.edu**Rachel Brader, MD**UNC-Chapel Hill Department of Radiology, Rachel.Brader@unchealth.unc.edu**Ari J. Isaacson, MD**UNC-Chapel Hill Department of Radiology, ari_isaacson@med.unc.edu**Abstract**

Background: Prostatic artery embolization (PAE) has emerged as a treatment option in the management of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). Management guidelines addressing PAE remain mixed with recommendations for more long-term trials comparing the procedure to standard therapies.

Materials and Methods: This review presents PAE indications and technical considerations. To evaluate recent updates to the PAE evidence base, a limited literature search of the last 2 years was conducted. Three recent randomized controlled trials (RCTs), comparing PAE to either transurethral resection of the prostate (TURP) or sham procedure, were identified and analyzed.

Results: PAE and TURP performed similarly in significant reductions in international prostate symptoms score (IPSS) and Quality of life (QoL) scoring at 3 and 12 months. The majority of improvement after PAE occurred within a few months, with potentially greater effect in patients with larger prostates and severe symptoms. TURP was generally superior in functional outcomes such as peak urinary flow (Qmax), prostate volume (PV) reduction and post void residual (PVR), although TURP patients underperformed in Qmax improvement in one trial. PAE was superior to sham procedure in all relevant outcomes at 6 months. Overall, complication rates were lower with PAE than with TURP.

Conclusions: PAE and TURP produced similar significant improvements in LUTS. Functional improvements favored TURP while complication rates favored PAE. Clinical improvement after PAE significantly surpassed initial placebo effects of sham procedure. Further comparative studies with longer term follow-up are still needed.

Keywords: Prostate Artery Embolization, Benign Prostatic Hyperplasia, Prostate, Lower Urinary Tract Symptoms, IPSS

1. Introduction

Lower urinary tract symptoms (LUTS) have many causes and are commonly attributed to enlargement of the prostate secondary to benign prostatic hyperplasia (BPH-LUTS). A standard, validated instrument for evaluating LUTS in patients is the International Prostate Symptom Score (IPSS), also known as the American Urological Association (AUA) Symptom Index. IPSS utilizes a 35-point scale, with ≥ 20 points indicating severe symptoms, while 8-19 points, and 1-7 points indicate moderate and mild symptoms respectively. IPSS includes a urinary quality of life scale (QoL), a 0-6 scale ranging from delighted (0) to terrible (6). These patient-reported outcomes are included in most studies evaluating BPH-LUTS interventions, in addition to functional metrics such as peak urinary flow rate (Qmax), post-void residual volume (PVR), prostate volume (PV), and prostate specific antigen (PSA) levels. Evaluation of sexual function with the patient-reported International Index of Erectile Dysfunction (IIEF) is also often included in analyses.

Watchful waiting is appropriate for patients with mild symptoms, whereas moderate-to-severe symptoms (IPSS ≥ 8) should prompt discussion of available treatment options.¹ Initial therapy is typically medical management with α -blockers (e.g. terazosin) and/or 5α -reductase inhibitors (e.g. finasteride). More recently, daily dosage of a phosphodiesterase 5 inhibitor (tadalafil) has also been recommended to treat BPH-LUTS. Interventional therapies are indicated when symptoms are refractory to medication, or if the patient is unwilling or unable to tolerate these medications.² In these cases, according to the AUA, transurethral resection of the prostate (TURP) remains the gold standard,

particularly for moderately sized prostates (30-80 mL).³⁻⁵ TURP leads to IPSS improvements of 70%, or approximately 15-16 points, while QoL improves by 69% or 3-3.5 points.⁶⁻⁹ However, TURP can lead to considerable morbidity including urethral stricture, urinary retention, incontinence, retrograde ejaculation, erectile dysfunction and blood loss requiring transfusion, with trends suggesting higher complication rates in larger prostates.^{7,10} Bipolar TURP (B-TURP), as compared to monopolar-TURP (M-TURP), has lowered morbidity,⁷ and in institutions with this capability, TURP has been used for prostates $>80 \text{ cm}^3$.^{3,5,11-13} Holmium Laser Enucleation of the Prostate (HoLEP) and laparoscopic or robotic prostatectomy are other options for large prostates.^{3,5,14} A range of other minimally invasive surgical techniques (MIST) are generally not recommended for very large prostates ($> 100 \text{ cm}^3$).^{3,5} Clinical efficacy of prostatectomy is on par with TURP with expected IPSS improvements ranging from 12-19 points;^{15,16} however, prostatectomy requires longer hospital stays and produces higher morbidity than TURP, with complications of blood loss, UTI, urethral stricture, and incontinence.^{5,13,17-20}

Prostatic artery embolization (PAE) is a minimally invasive option for BPH-LUTS. The procedure is usually performed under moderate sedation by an interventional radiologist (IR) using fluoroscopy. Microcatheter cannulation of the prostatic arteries (PA) is achieved through either femoral or radial artery access. Proper location is assessed with angiography, and embolization is performed by slowly injecting dilute embolic particles, with size and type dependent on provider preference. When possible, bilateral embolization is more effective at reducing PV and improving

symptoms, when compared to unilateral treatment.²¹ Improvement after embolization is attributed to ischemic necrosis, apoptosis, a possible reduction in adrenergic receptors, and changes in prostate innervation that lead to reduced smooth muscle tone.^{22,23}

Current evidence points to favorable outcomes and low complication rates for PAE.^{6,24,25} Two previous randomized controlled trials (RCTs) comparing PAE to TURP found significant improvements from baseline to one year in IPSS, QoL, Qmax, and PVR in all groups. Comparisons of effect magnitudes and complication rates yielded mixed results.^{26,27} Proper patient selection remains a subject of investigation, but criteria is often similar to that of TURP.²² Patients generally are excluded from PAE if they have a urethral stricture, active UTI or prostatitis, renal insufficiency, large bladder diverticula or stones, a neurogenic bladder, or other neurologic disorder affecting bladder function. Advanced atherosclerosis may also preclude treatment with PAE.^{22,28} As described, prostate volume is a factor when deciding between invasive therapy options, and > 40mL is generally recommend for PAE.²² Larger prostates (>80 mL) also respond well to PAE,^{13,29-31} a potential advantage of PAE over alternative MIST with similar safety profiles. Those with surgical co-morbidities, wishing to preserve sexual function, with indwelling catheters, those on anti-coagulation or those with hematuria of prostatic origin.¹³

1.1 Guidelines

The National Institute for Health and Care Excellence (NICE) in the United Kingdom supports the use of PAE in the management of BPH-LUTS.³² The United

States Food and Drug and Administration (FDA) has included PAE as an indication of use for two different embolic microspheres. Conversely, current AUA guidelines recommend against PAE outside of a clinical trial, citing a lack of consistent, high quality evidence.³ More standardized trials were recommended, including comparisons of PAE to sham procedures to control for placebo effects.³³ The most recent multi-society consensus statement released by the Society of Interventional Radiology (SIR) recognizes the short and mid-term safety and efficacy of PAE, supporting its use in appropriately selected patients. With this support comes recognition that long term outcomes are lacking, and that further trials comparing PAE to other therapies, including MIST, are needed.¹³

2. Methods

A limited review was performed, assessing the literature for updates to the evidence that informed the aforementioned guidelines and recommendations. A search of PubMed, Embase and the Cochrane databases was conducted using the search terms “Prostate Artery Embolization OR PAE.” Included publications were limited to English-language, randomized controlled trials (RCTs) containing PAE as a comparison group. Three RCTs were ultimately selected for review, two comparing PAE to TURP and one comparing PAE to sham procedure.³⁴⁻³⁶ One other RCT was found, but was not in the English language and therefore was not included.³⁷ Multiple registered clinical trials were also noted, highlighting efforts to build the PAE evidence base.

3. Study Design

Two recent RCTs comparing TURP and PAE included patients with moderate to severe LUTS (IPSS \geq 8, QoL \geq 3), in whom TURP would otherwise be indicated.^{34,36} Abt et al. randomized 103 patients \geq 40 y.o. with PV of 25-80 mL to either M-TURP or PAE in a non-inferiority comparison IPSS improvement from baseline to 3 months. Authors pre-defined a margin of 3 IPSS points, which had been characterized elsewhere as slight symptomatic improvement. After exclusions, 48 PAE and 51 TURP patients were included in the analysis. Insausti et al. randomized 61 patients $>$ 60 y.o. to either PAE or TURP in a non-inferiority comparison of change from baseline in Qmax at one year (margin: -

0.5mL/s). Change in IPSS at one year was dubbed a co-primary outcome. Data were also collected at 3 and 6 months. After a number of different exclusions, including for PV $>$ 100mL, 45 patients were analyzed (23 undergoing PAE and 22 undergoing TURP).

Baseline characteristics of participants, reflecting these differences in patient selection, are summarized in Table 1. The average age of participants in Insausti et al. was 71.8 and 72.4 years old for the TURP and PAE groups respectively, and respective average PV was 62.8 and 60.0 mL. The 99 patients analyzed by Abt et al., however, were younger, at average age of 66.1 and 65.7 years old respectively, and had smaller prostates, with respective PV of 52.1 and 51.2 mL.

	Abt et al.		Insausti et al.		Pisco et al. §	
	PAE	TURP	PAE	TURP	PAE	SHAM
Age (yrs.)	65.7 (9.3)	66.1 (9.8)	72.4 (6.2)	71.8 (5.5)	64 (59.0-67.5)	64 (60-68.5)
PV (mL)	52.8 (32.0)	56.5 (31.1)	60.0 (21.6)	62.8 (23.8)	68.5 (58.0-103.5)	66.5 (50.0-101.5)
IPSS	19.38 (6.37)	17.59 (6.17)	25.8 (4.64)	26.0 (7.29)	25.5 (22.5-29.0)	27.5 (24.0-30.5)
QoL	4.00*	4.24*	4.5 (1.04)	4.7 (1.09)	4.0 (4.0-5.0)	4.5 (4.0-5.0)
Qmax (mL/s)	7.47*	7.25*	7.7 (2.0)	7.0 (2.5)	7.90 (5.55-10.2)	7.30 (4.90-9.40)
PVR (mL)	168.5*	230.7*	34.5 (65)	54.7 (251)	119 (72-155)	106 (60-178)

Data are listed as mean (standard deviation) unless stated otherwise. PV = prostate volume; IPSS = International Prostate Symptom Score; QoL = IPSS related quality of life; Qmax = peak urinary flow rate; PVR = post void residual urine volume.

*Standard deviations were not listed for these values.

§Data for this trial were given as median (interquartile ranges).

In their comparison of PAE to sham procedure, Pisco et al. included patients \geq 45 y.o. with severe symptoms (IPSS \geq 20) who had completed at least a 6-month course of α -blocker therapy.³⁵ PV was restricted to $>$ 40 cm³ without an upper limit. The mean age of the 77 subject study population was 63.8 years, with an average PV of 79.5 cm³ on

transrectal ultrasound (81.3 cm³ on MRI). Exclusion criteria was similar to the other RCTs, but also added hypersensitivity to Tamsulosin, given the trial's protocol to continue the medication until symptomatic improvement for ethical reasons. To participate, subjects who had taken the 5- α reductase inhibitors underwent a specified

washout period, replacing the medication with either tamsulosin, alfuzosin, or silodosin. A patient was only randomized to either PAE or sham if catheterization of the origin of the prostatic arteries confirmed that the anatomy was the same as on previous CT-angiography and that at least one prostatic artery could be appropriately accessed.

3.1 Procedural comparisons and considerations

Abt et al. had one experienced interventional radiologist (IR) perform all PAE procedures whereas in Insausti et al. and Pisco et al., the procedures were performed by multiple IRs with varying years of experience. Femoral approach was used in all PAE procedures. Abt et al. compared PAE to M-TURP whereas Insausti et al. used B-TURP. Both TURP procedures were conducted under either spinal or general anesthesia following standard technique, with post-procedural placement of a 3-way 20F urinary catheter for continuous irrigation for 1-2 days. The sham procedure in Pisco et al. was identical to PAE, but after the prostatic arteries were catheterized, no embolic was injected. Investigators attempted to maintain blinding by waiting a few minutes prior to removing the catheter.

Perioperative medication management varied among the studies. In both TURP comparative studies, TURP patients discontinued BPH medications the day of the procedure, whereas PAE patients remained on their medications for 2 and 4 weeks in Abt et al. and Insausti et al., respectively. This was presumably for the assumed slower efficacy of PAE. Pisco et al.

continued each patient on 0.4 mg tamsulosin post-procedurally for ethical reasons. Medication was stopped after IPSS and QoL improvement, defined as a change of more than 3 and 1 points, respectively. For antibiotic prophylaxis, Ciprofloxacin 500 mg twice daily was given to both groups in Abt et al. and the sham trial for 3 and 7 days respectively. In contrast, patients in the PAE group of Insausti et al. received 7 days of Ciprofloxacin, while those in the TURP group received ceftriaxone perioperatively, and then were given ciprofloxacin with urinary catheter removal.

4. Results

4.1 IPSS and QoL

Major symptomatic and functional outcomes from each trial are listed in Table 2 for comparison. Abt et al. demonstrated similar reductions in IPSS scoring for PAE (-9.23) and TURP (-10.77) at 3 months. A direct comparison of change from baseline (difference of 1.54 points) was not statistically significant ($p=0.31$). However, non-inferiority at a margin of < 3 points could not be demonstrated, attributable to high variation in individual outcomes (95% CI: -1.45 to 4.52; one sided $p=0.17$). A subsequent analysis of covariance (ANCOVA), adjusting for difference in baseline symptoms, also failed to show PAE non-inferiority with a mean difference of 2.87 points, further favoring TURP ($p=0.46$). QoL improvements were not statistically different between TURP and PAE (-2.33 vs. -2.69; $p = 0.015$) at 3 months.

Table 2: Comparison of Symptomatic and Functional Outcomes									
Variable	Abt et al.			Insausti et al.			Pisco et al.		
	(3-month endpoint)			(12-month endpoint)			(6-month endpoint)		
	PAE	TURP	<i>p</i>	PAE	TURP	<i>p</i>	PAE	SHAM	<i>p</i>
IPSS	-9.23	-10.77*	0.46	-21.0	-18.2	0.08	-17.1	-5.03 ^a	<0.001
QoL	-2.33	-2.69*	0.15 ^a	-3.78	-3.09	0.002	-3.0	-1.03	<0.001 ^a
PV (mL)	-12.17	-30.27	< 0.001 ^a	-20.5	-44.7	< 0.001	-17.6	-0.06	0.002 ^d
Qmax (mL/s)	5.19	15.34	< 0.001 ^a	6.14	9.65	0.86 ^b	6.82	2.80	0.005 ^d
PVR (mL)	-86.36	-199.98	0.003 ^a	-20.2	-44.7	0.67 ^c	-59.9	8.63	0.03 ^d

All values listed are mean change from baseline except PVR for Insausti et al. which lists median change values. Unless otherwise noted, *p* values result from ANCOVA analyses of changes from baseline, adjusted for baseline measurements.

^a Two-sided t-test

^b One sided test at significance level 0.025

^c Mann-Whitney U test

^d ANCOVA analysis with Bonferroni correction for multiple comparisons

In Insausti et al., IPSS improvement at 12 months favored PAE (-21.0 points) over TURP (-18.2 points) by 3.04 points, although this was not statistically significant (*p*=0.080). Both PAE and TURP led to clinically significant improvements in QoL, decreasing by -3.78 and -3.09 points, respectively. PAE showed statistical superiority with an adjusted between group difference of 0.92 (95% CI: 0.34-1.49; *p*=0.002).

Pisco et al. reported a 6-month IPSS improvement of 17.1 in the PAE group compared to 5.03 in the sham group. ANCOVA analysis, controlling for baseline IPSS, yielded a difference of 13.2 points (95% CI: 10.2 – 16.2; *p*<0.0001). Mean IPSS at 6 months was 8.75 in the PAE group and 21.9 in the sham group, meaning that, on average severe LUTS persisted after sham procedure out to 6 months. QoL demonstrated a similar pattern, decreasing from baseline by 3.0 for PAE and 1.03 for sham procedure respectively (*P*<0.0001). Mean QoL scoring differed by 2.13 at 6 months (*p* <0.0001). Controlling for Tamsulosin use did not change results of the

coprimary outcomes. Subsequently, 38/40 sham patients then underwent PAE in the exact same manner as the original group, with similar average procedure time, fluoroscopy time, and radiation exposure. Follow up occurred at 7, 9 and 12 months in this group, and at 12 months for the original PAE group. Within the original sham group, statistically significant improvements in all efficacy variables were found at the one-year endpoint (except in IIEF). Between group t-test comparisons with the original PAE group showed no statistically significant difference for any efficacy variables at 12 months. Unadjusted mean improvements in IPSS at the one year from baseline were -16.9 and -18.3 for the PAE and original sham groups, respectively (*p*=0.066). For the sham group 27% (5.0 points) of the total improvement occurred prior to the PAE procedure. Unadjusted mean improvements in QoL from baseline to one year were -3.02 for PAE and -3.05 for the original sham group. Similar to IPSS, 33% of the overall change occurred prior to PAE. These results suggest a not insignificant initial placebo effect, but the majority of clinical improvement occurred after the actual procedure.

4.2 Functional outcomes

TURP was more effective at improving Qmax (15.34 vs. 5.19 mL/s; $p < 0.001$), PVR (-199.98 vs. -86.36 mL; $p = 0.003$) and prostate volume (-30.27 mL vs. -12.17 mL; $p < 0.001$) at 3 months in Abt et al. A co-primary outcome in Insausti et al., Qmax improved by 6.14 mL/s after PA and by 9.65 mL/s after TURP, an adjusted improvement difference of 3.31 mL/s, in favor of TURP. The results did not permit determination of PAE non-inferiority at the pre-established 0.5 mL/s margin (95% CI -1.84 vs. 8.46; one sided $P=0.862$). Insausti et al. also found TURP to be superior in mean PV reduction (-44.7 cm³ vs. -20.5 cm³ ($p < 0.001$)). Median PVR reduction similarly favored TURP (-44.7 cm³ vs. -20.2 cm³), although this was not statistically significant ($p = 0.667$), given high outcome variability.

At 6 months, PAE was superior to sham at improving Qmax (6.82 vs. 2.80 mL/s); adjusted difference of 4.22 mL/s ($p = 0.005$). Mean PVR decreased in PAE patients by -59.9 mL while increasing after sham procedure by 8.63 mL (adjusted mean difference -60.6 ($p=0.03$)). PV decreased on average by -0.06 cm³ after sham procedure vs. -17.6 cm³ after PAE (adjusted mean difference -16.8 cm³ (95% $p=0.002$)). Insausti et al. found TURP to be superior in mean PSA reduction (-2.71 ng/mL vs. -0.72 ng/mL; $p = 0.013$), while Pisco et al. reported PAE to be superior to sham procedure (-1.52 ng/dL vs. -0.02 ng/dL; $p=0.01$).

4.3 Hospitalization and procedure time

Bilateral (vs. unilateral) PAE was performed in 75% of patients in Abt et al., 100% of patients in Insausti et al., and in

92.5% of the patients in the sham comparison trial. Abt et al. reported significantly longer procedure time for PAE over TURP (122.2 vs 69.5 min.; $p < 0.001$), but significantly shorter average hospital stay (2.2 vs. 4.2 days; $p=0.001$). PAE also demonstrated significantly shorter catheter indwelling time (1.3 vs 3.3 days; $p=0.001$). Insausti et al. similarly reported longer procedure time for PAE (138.7 vs 70.2 min.; $p < 0.001$). Median procedure time for PAE in the sham trial was shorter than the other trials at 75 min. (IQR:60-90 min.). The sham procedure had a median length of 30 min. (IQR: 30-45 min.).

Mean fluoroscopy time was similar for PAE in the two TURP comparison trials at 50.8 (SD: 17.5) and 58.0 (SD:20.8) minutes. Median fluoroscopy time for PAE procedures in the sham trial was shorter at 15.0 min (IQR: 12.0-24.8). Despite this shorter fluoroscopy time, the median radiation exposure to patients was 201.5 Gy/cm² (IQR: 130.0-335.6), higher than the average exposure reported by Abt et al. 176.5 \pm 101.2 Gy/cm²). Insausti et al. reported the highest average exposure at 228.0 \pm 61.6 Gy/cm²

5. Complications and Adverse Events

Each included study used the Clavien-Dindo classification of adverse events (AEs). Abt et al. found fewer AEs after PAE vs. TURP (36 vs. 70; $p= 0.003$), with the discrepancy attributed to fewer patients in the PAE group having multiple complications (16.7% vs. 45.1%; $P= 0.005$). All complications were limited to grades I-III. Despite an overall similar distribution between groups, TURP showed a higher rate of major AEs (grade III) at 11.3% compared to 5.4% after PAE. Insausti et al. also

reported fewer AEs in PAE patients (15) than in TURP patients (47), $p < 0.001$. There was one major complication in the TURP group, a urethral stricture successfully treated with dilation, with all remaining AEs being grade I or II. The overall distribution of AEs did not differ between groups ($p=1.47$). Common adverse events after TURP in both studies included retrograde ejaculation, mild hematuria, UTI, irritation/pain/discomfort and erectile dysfunction. Urinary retention, pain and discomfort, and UTI were among the more common complications after PAE.

In Abt et al., post-operative pain was reported more commonly among PAE patients (relative risk 1.76; $p=0.03$). Severe, $\geq 6/10$ pain was reported in 9 PAE patients and only 2 TURP patients; $p=0.06$. However, this pain quickly resolved within 12-24 hrs. post-procedure. PAE patients in Insausti et al. reported lower average pain levels at discharge (0.5 vs 2.6; $p < 0.001$) and at one month (0.2 vs. 2.6; $P < 0.001$). These findings may have contributed to higher patient satisfaction (scale 0-100) for PAE compared to TURP at discharge (88.3 vs. 75.0; $p=0.005$) and at one month (88.9 vs. 65.9; $p < 0.001$).

Abt et al. found a high rate of ejaculatory disorders in the PAE (14/25; 56%) and TURP groups (21/25; 84%; $p=0.06$) although this was not further defined. IIEF scoring declined minimally in both groups, favoring PAE, but was not statistically different (-1.84 vs. -0.98; $p=0.53$). One PAE patient reported de novo erectile dysfunction. In Insausti et al, 5/22 (22.7%) TURP patients and 1/23 (4.3%) PAE patients reported erectile dysfunction. IIEF scoring was not assessed given that many participants lacked relationships, attributed to their older age. Radiodermatitis, rectal

ischemia, bladder wall ischemia, puncture site hematoma, and post-embolization syndrome were rare post-PAE complications affecting single patients.

In Pisco et al., 16 AEs occurred in 14 (35%) PAE patients whereas 17 AEs occurred in 13 (32.5%) patients after sham procedure. Another 13 AEs occurred after PAE in 11 patients who subsequently underwent the PAE after the first 6 months. Of the complications occurring after PAE, 86.2% were grade I, 10.3% were grade II, and one (3.4%) was grade IIIa. This most severe complication consisted of expelled prostate fragments causing hematuria and acute urinary retention that was then treated by TURP with complete recovery. Hematuria and hemospermia were more common complications after PAE, and four inguinal hematomas were also isolated to this group. Bruising was the most common complication in the sham group. No patients in the sham group complained of pain either during the procedure or afterwards. Among PAE patients, two complained of pain at discharge (3-5 hrs. post procedure), and two complained of pain the following morning. PAE and sham did not differ in a marginal improvement of IIEF ($p=0.29$).

6. Discussion

PAE is increasingly accepted as an alternative treatment for BPH-LUTS, achieving FDA approval and inclusion in certain national guidelines. When these guidelines were constructed, existing comparative studies of PAE were subject to criticism for their methodological limitations, and therefore further high-quality trials were suggested in order to promote universal acceptance.³³ Although PAE demonstrates

promising efficacy, outcomes reporting and follow up periods have been inconsistent.²⁴ PAE may reduce severe morbidity when compared to standard treatments; however, analyses of overall complication rates present conflicting evidence.^{14,38} This review detailed three recent trials in the growing PAE evidence base, aiming to address shortcomings through direct comparisons to standard treatments, investigation of placebo effects, and reporting of adverse events.

In comparisons of PAE to TURP, both Abt et al. and Insausti et al. found significant and similar IPSS improvements at 3 and 12 months, respectively. The 12-month IPSS improvements after PAE in Insausti et al. were higher than previously reported (-21 points vs. -16.0-16.5 points).^{39,40} A meta-analysis by Uflacker et al., has estimated an average 12-month IPSS improvement (-20.39) in line with this study's findings, but greater than reported in previous comparative trials.^{14,24} The IPSS improvement after PAE in Insausti et al. was largely in the first 3 months, with a -21.6-point reduction at this time point, compared to a -9.23-point improvement in Abt. et al. within the same period. The larger average PV in Insausti et al., may have been contributory, consistent with previous findings.^{31,41} More severe symptoms also leaves greater opportunity for improvement, and Insausti et al. had a higher average baseline IPSS in the PAE group (26.6 vs. 19.6 in Abt et al.). A higher rate of bilateral PAE procedures in Insausti et al. (100% vs. 75% in Abt et al.), and a superior volume reduction at 3 months in the PAE group (-19.9 vs. -12.17 cm³ in Abt et al.), likely also influenced results.²¹ Furthermore, results in Pisco et al. support the relative rapid effect of PAE in those with severe symptoms, with almost 100% of post-procedural IPSS improvement (and 83% of

QoL improvement) occurring within one month. Baseline factors may also help explain the above average 12 month IPSS improvement in Insausti et al.'s TURP group (18.2 vs. an expected 15-16 points).^{6,9} Compared to PAE, his group experienced slower IPSS change, with a reduction of only -14.4 points (out of -18.2 total) in the first 3 months. Post-surgical irritation and a higher rate of complications may lead to slower symptomatic improvement after TURP.

QoL changes followed a similar pattern, with both groups in each trial showing significant improvements from baseline. Again, with a worse baseline QoL (4.5 vs. 4.0), PAE patients in Insausti et al. saw greater improvement overall, (-3.78) and at 3 months (-3.57) than in Abt et al. (-2.33). After TURP, similar 3-month improvements were seen in each study (-2.38 for Insausti et al. and -2.69 for Abt et al.). By the 12-month end point, TURP patients had drawn closer to the PAE group in overall improvement. Although it is assumed that the effects of PAE are less immediate, these findings suggest symptomatic improvements after PAE occur quickly, with the effect more pronounced in larger prostates producing severe symptoms. TURP patients saw similar symptomatic improvement over 12 months, but at a more gradual progression.

A comparison of PAE and a sham procedure has been recommended to address placebo effects.³³ Results from Pisco et al. demonstrated that PAE significantly improved symptoms when compared to sham procedure, suggesting that the effectiveness of PAE itself is far superior than the reported placebo effect. The efficacy of PAE over placebo was further validated by the similar clinical benefit seen at 6 months in both the PAE group and the sham patients who

underwent PAE after the blind period. This study only included those with severe LUTS, with a mandatory wash out of any 5- α reductase inhibitors, both of which may have exaggerated results for the placebo group, PAE group, or both. Average baseline prostate volume was large (81.6 cm³) which may have led to greater effect in the PAE group relative to placebo.^{31,41} The reported difference in 6-month IPSS improvement may be reduced in smaller prostates

Clinically relevant improvements in Qmax were found in both trials for all groups. Insausti et al.'s reported one-year increase in Qmax after TURP (9.69 mL/s) was substantially lower than the 3-month figure reported in Abt et al. (15.34 mL/s), and lower than what has been previously reported.⁷ Although the reason for the sub-optimal performance of Insausti et al.'s TURP group is unclear, it likely contributed to the lack of statistical difference between PAE and TURP in this metric. The superiority of TURP in Qmax improvement, as reported in Abt et al., has been previously corroborated.^{6,26,27} The superiority for TURP in PV reduction found in both studies is also consistent with previous findings. The better performance of TURP in functional outcomes and relative consistency with PAE in symptomatic outcomes can be explained by the poor correlation of functional metrics and subjective LUTS.⁴²

Erectile and ejaculatory function are important concerns for men undergoing BPH treatment. Abt et al. reported relatively high rates of ejaculatory disorders in both groups, but it was unclear how this was specifically assessed. Loss of ejaculation rates after TURP have been reported to be as high as 78% with specifically retrograde ejaculation ranging up to 60-65%.⁴³ Much lower rates of

retrograde ejaculation were reported in Insausti et al., at only 16.7%. Although erectile dysfunction was a complication reported by 23% of TURP patients and 4% of PAE patients in their study, authors in Insausti et al. did not assess IIEF scoring. IIEF did not change meaningfully in either group in Abt et al, with no statistically significant differences between groups, consistent with a previous comparative studies of PAE, M-TURP and B-TURP.^{6,43} Results in Pisco et al. suggest that PAE does not worsen erectile function in comparison to sham.

PAE has a reputation for being a relatively safe procedure with rare major complications.^{13,24} In contrast, a recent meta-analysis found PAE to have higher overall complication rates than other treatments in comparative studies.¹⁴ This finding, however, included data from the controversial RCT by Gao et al., criticized for underreporting TURP complications. In Pisco et al., the large majority of AEs after PAE were limited to minor, class I and II complications. Both TURP comparison studies found statistically fewer adverse events overall as well fewer major complications after PAE. The fact that one study compared PAE to M-TURP and the other to B-TURP likely did not influence clinical outcomes but could have generated differential rates of specific complications such as transurethral (TUR) syndrome or the need for blood transfusion.⁴⁴ TUR syndrome was not reported in either study. Statistically higher blood loss after TURP (M-TURP) was reported by Abt et al., although, at 1.38 g/dL, was arguably not clinically significant. Likewise, after baseline similarity, statistically significant differences in hemoglobin levels were found between groups at one month in Insausti et al., but it was clinically insignificant (0.9 g/dL). Post-

embolization syndrome was reported in only one patient after PAE. Efforts in each study to prevent non-target involvement during PAE by using coil embolization of anastomoses appear to have been effective. Three possible instances occurred: one patient with erectile dysfunction and transient discoloration of the penis, one with rectal ischemia which resolved with conservative management, and patient with limited bladder wall ischemia successfully removed during a transurethral procedure.

Consistent with previous comparative studies, Abt et al. observed TURP to result in longer hospital stays.¹³ This metric was incompletely described by Insausti et al., but was not reported to be statistically significant between groups. Longer procedure times reported for PAE can be attributed to the technical requirements of the procedure, although the average procedure and fluoroscopy times reported in the two TURP studies were longer than in previous randomized trials.¹⁴ Radiation exposure, as assessed by dose area product (DAP) was in line with that previously reported.^{6,45,46} The relatively higher DAP in Insausti et al. may have been influenced by older study patients with more advanced, atherosclerotic disease, increasing technical difficulty, and overall larger prostates necessitating longer time to reach embolization endpoints. This trial produced the only reported case of radiodermatitis. After PAE, 10/48 (20.1%) patients in Abt et al. experienced a post-procedural UTI, while none of the 23 PAE patients in Insausti et al. and only one in Pisco et al. reported this complication. Abt et al. continued antibiotic therapy for a maximum of 3 days after procedure whereas the 7 days allotted in the other trials may have reduced infection rates.

6.1 Limitations

Strengths of the trials included well-performed and described randomization techniques as well as thorough descriptions of the protocols for each procedure. The two TURP comparison trials also pre-registered their protocols with ClinicalTrials.gov. However, similar limitations of previous PAE studies still remained. Follow up was limited to one year, with one trial only lasting 3 months. Long-term evaluation of the sustained effects of PAE, symptom recurrence, and the need for repeat procedure is necessary. Although the presented data suggest rapid onset of benefit, durability of PAE remains in question, whereas evidence supports lasting effects and low long-term complication rate for TURP.⁷ A previous RCT suggested preserved clinical improvement out to 2 years,²⁷ but has been criticized for overstating the benefits of PAE.¹⁴ Abt et al. mention that study follow up will continue for up to five years which, if completed, will provide valuable data. An advantage of PAE, however is that, in the event of symptom recurrence or treatment failure, options for repeat treatment or other approaches remain.¹³

Each study was single center, and relatively small sample sizes were a hinderance. Variability in patient outcomes and higher than expected drop-out rates did not allow authors to demonstrate non-inferiority for PAE in primary outcomes at the pre-established margins. There is still a need for long term, non-inferiority trials comparing PAE to procedural standards that are appropriately powered. Other limitations included the inability to blind patients or clinicians in comparisons of PAE to TURP. Appropriate effort was undertaken to blind patients to PAE or sham procedure in Pisco

et al, however the sham procedures were substantially shorter (median 30 min.) than PAE (median 75 min). For ethical reasons, it is understandable to limit patient harm and reduce radiation exposure in the sham procedure group; however, patients may have deduced groups assignments based on procedure length. Variations in inclusion criteria, such as Pisco et al.'s decision to include those with severe symptoms or Insausti et al.'s inclusion of larger prostates, could limit generalizability of results.

7. Conclusion

PAE has emerged as a safe and effective treatment option for BPH-LUTS. Despite limited literature comparing patient-

reported and functional outcomes after PAE and TURP, the growing evidence on PAE suggests comparable medium-term symptomatic outcomes to the standard of care. Future research directions should continue to investigate the ideal candidates for PAE, optimal size and type of embolic agent, and the technical refinements, such as balloon occlusion strategies, needed to maximize PAE benefit while reducing complications.⁴⁶ Given a treatment failure rate of as high as 15% after 12 months,⁶ large scale trials with long- term follow up are still necessary to investigate the sustained symptomatic improvement of PAE and how often repeat treatment is necessary. Trials directly comparing PAE to other MIST procedures with similar safety profiles should also be conducted.

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