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Review of Current Outcomes of Prostate Artery Embolization to Treat Patients with Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia

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ABSTRACT

The standard management of benign prostatic hyperplasia (BPH) is based on the overall health of the patient, on the severity of the lower urinary tract symptoms (LUTS), and on quality-of-life (QoL) considerations. Voiding difficulties attributable to BPH can be quantified with the American Urological Association Symptom Index score (AUA-SI) or International Prostate Symptom Score (IPSS). Various medications can decrease the severity of voiding symptoms secondary to BPH. Impotence, decreased libido, and ejaculatory disorders are known side effects.

The AUA guidelines indicate that patients with mild LUTS secondary to BPH (AUA-SI score < 8) and patients with moderate or severe symptoms who are not bothered by their LUTS should be managed using a strategy of watchful waiting. If the patient elects interventional therapy and there is sufficient evidence of obstruction, the patient and urologist should discuss the benefits and risks of the various interventions.

Transurethral resection of the prostate (TURP) is the most common interventional treatment, but it can be associated with bleeding, erectile dysfunction, and ejaculatory disorders in up to 10 to 65% of patients. The high prevalence rate of BPH has a tremendous impact on the health and quality of life of men. Increasingly, BPH therapy trends are moving away from the gold standard operation of TURP and toward less invasive pharmacological options and minimally invasive procedures provided in an outpatient setting.

Prostatic artery embolization (PAE) is a new BPH treatment under clinical investigation. PAE is a minimally invasive procedure that blocks the blood flow to the prostate, causing shrinkage of the gland. PAE is performed under local anesthesia as an outpatient procedure. A team of interventional radiologists, diagnostic radiologists, and urologists at the University of Sao Paulo Medical School are pioneers of the procedure, which has been widely reported since 2008. The multi-disciplinary team is encouraged by the data demonstrating PAE is a safe and effective minimally invasive treatment for patients with LUTS.

KEYWORDS: Benign prostate enlargement, benign prostatic hyperplasia, bladder outlet obstruction, transurethral resection of the prostate, prostatic artery embolization, lower urinary tract symptoms

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ACRONYMS AND ABBREVIATIONS

BPE: benign prostate enlargement
BPH: benign prostatic hyperplasia
TURP: transurethral resection of the prostate
PAE: prostatic artery embolization
LUTS: lower urinary tract symptoms
PSA: prostate specific antigen
QoL: quality of life
IPSS: International Prostate Symptoms Score
IIEF: International Index of Erectile Function

INTRODUCTION

Symptomatic benign prostatic hyperplasia (BPH) typically occurs in the beginning of the sixth decade, with more than 40% of men aged 60 and older presenting clinical manifestations [1]. As the world's population ages, the prevalence of BPH is expected to increase, calling for a therapy that reduces and maintains reductions in prostate volume, provides lasting improvements of symptoms, and minimizes the risk for adverse outcomes.

Despite the advances in effective drug treatment and minimally invasive procedures, transurethral resection of the prostate (TURP) remains the treatment of choice when medical management fails [1]. TURP is performed under direct endoscopic visualization with an electrocautery tool to remove prostate tissue. While considered a safe technique with a mortality rate below 0.25%, it is not without adverse events. The most frequent complications are ejaculatory disorders (up to 65%), early urinary incontinence (30 to 40%), acute urinary retention caused by blood clots (2 to 5%), sexual impotence (up to 5%), and the need for blood transfusions (0.4 to 7%). Patients who have undergone TURP require surgical retreatment for lower urinary tract symptoms (LUTS) in 3 to 14.5% of cases [1,2].

Minimally invasive techniques such as transurethral microwave thermotherapy (TUMT) and laser ablations have been developed as alternative treatments for LUTS, but they involve introducing energy into the gland and all require access through the urethra. Complications from these procedures are similar to TURP [1-4].

Patients with a history of TURP or pelvic trauma should not undergo TUMT because of potential alterations in pelvic anatomy. Patients with glands that are smaller than 30 g or a prostatic urethral length of less than 3 cm respond poorly to TUMT, as do patients with glands greater than 100 g and patients with a prominent median lobe. Other contraindications include patients with penile prosthesis, severe urethral stricture disease, artificial urinary sphincter, or American Society of Anesthesiologists (ASA) class group V patients. Patients with pacemakers need clearance from their cardiologists concerning turning their pacemakers off during therapy, and performing TUMT in this group should be approached with apprehension [1-4]. These comorbidities are not considered a contraindication for prostatic artery embolization (PAE).

PAE is being evaluated as an alternative treatment for LUTS due to BPH. Clinical studies are ongoing to assess the outcomes and advantages of PAE. Results indicate that PAE can provide symptom relief through prostate-size reduction. There is a growing body of literature and data presented at scientific meetings supporting PAE as a safe and effective alternative for treating BPH when medical management fails [5-9].

Embolization of the prostatic artery has been used for decades to treat prostate bleeding after TURP or biopsy [10-15]. DeMeritt and colleagues reported the early clinical observation of prostate volume reduction after embolization for persistent hematuria in 2000. A 76-year-old man with a history of moderately symptomatic BPH developed acute urinary retention and was treated with transurethral catheter drainage for 2 weeks, after which he presented with severe gross hematuria, which failed to respond to multiple attempts at conventional therapy. The patient's condition was successfully managed with super-selective transarterial embolization using polyvinyl alcohol particles (PVA). The patient stopped bleeding immediately after embolization, and his voiding significantly improved after the procedure. At 12 months after treatment, prostate reduction was almost 40% [16].

Similarly, embolization of the uterine arteries was originally used to treat heavy bleeding after childbirth. Embolization of fibroids was also done presurgically to decrease blood loss during myomectomy, after which it was recognized that many patients had spontaneous resolution of their fibroid symptoms and no longer required the surgery. From these observations, uterine fibroid embolization (UFE) was developed as a minimally invasive treatment for symptomatic fibroids. Embosphere Microspheres (Merit Medical Systems, Inc., Utah) were the first embolic cleared by the FDA for the indication of treating symptomatic uterine fibroid tumors. In a recent commentary on the potential value of PAE compared to TURP for BPH, Mauro indicated that PAE, not unlike UFE for fibroids, could be a minimally invasive alternative to TURP and current minimally invasive procedures [17]. At the same time, he underscored the need for more data on the procedure to assess the efficacy, durability, and adverse event rates compared to these treatments. Carnevale et al. and Pisco et al. have both published results from performing PAE using techniques similar to those used for fibroid embolization [5-8].

METHODS

Prostatic artery embolization is a promising, minimally invasive alternative procedure for BPH, which has been shown to be safe and effective in both animal models and clinical trials. Until the recent clinical investigations, PAE was used principally to control massive hemorrhage after prostatectomy or prostate biopsy. In publications and scientific presentations, Carnevale and colleagues have reported successful PAE outcomes of LUTS symptom improvement and patient quality of life, prostate volume reduction averaging 30%, and low rates of adverse events [5-7]. Pisco et al. have reported similar outcomes [7].

Benign prostatic hyperplasia treatment with PAE requires a trained interventional radiologist because of the prostatic vascular anatomy. The normal human prostate is composed of a combination of glandular, fibromuscular (stromal), and smooth-muscle cells. Benign prostatic hyperplasia is due to a

proliferation of glandular elements, stromal elements, or both, resulting in the formation of large, discrete nodules in the periurethral region of the prostate. The blood supply to the prostate arises from the anterior branch of the internal iliac artery, mainly by the inferior vesicle artery, which subsequently branches into the urethral and capsular vessels. Minor prostatic vessels also arise from the internal pudendal, obturator, umbilical, and middle hemorrhoidal arteries.

Initially, the blood supply to the prostate is mapped by angiography of the iliac vessels and the prostate arteries. Microcatheters are used for super-selective catheterization of the right and left inferior vesicle arteries. Embolization of arteries supplying the prostate is performed with a microcatheter to deliver microspheres or PVA particles. The PAE procedure takes an average of 2 hours to perform.

The main challenge of PAE is navigating within the narrow, tortuous, often atherosclerotic vessels, which can make visualization and super-selective catheterization of the inferior vesical arteries and the anatomical variations of the prostate arteries difficult.

Potential complications can arise from mistargeted embolizations, resulting in infarction of the bladder, rectum, or genitals. These complications can be avoided by using a microcatheter and calibrated microspheres for a predictable embolization.

PAE can be indicated in patients with small or large prostates and does not manipulate the urethra, thereby avoiding urethral stenosis. Severe comorbidities such as heart disease, atherosclerosis, penile prosthesis, severe urethral stricture, artificial urinary sphincter, or ASA class group V are not contraindications for PAE. Embolization can be repeated in the future, if necessary, and if it does not achieve the desired clinical outcome, it can be converted to prostatectomy. This procedure has been shown to be safe, effective, and with a low rate of complications. In addition, the overall cost of the procedure seems to be lower than other surgical therapies.

Animal Studies

The first animal study to evaluate the feasibility and safety of PAE was conducted in a canine model and reported by Faintuch et al. [18] The study demonstrated the promising potential of PAE to decrease prostate volume and urethral stenosis due to BPH. The success rate for identification and selective catheterization of the prostatic arteries was 100%. Initial computed tomography (CT) showed good distribution of spheres in the embolized territory (hemi-prostate or prostate), with no evidence of non-targeted embolization. Clinical follow-up did not show evidence of fever, infection, decreased appetite, or access site complications. One animal (bilateral PAE) required a single, straight bladder catheterization for urinary retention on the second day after embolization, and 3 days of NSAID therapy. Imaging done during the 1-month follow-up showed decreased perfusion, cavitary necrosis, and 40% prostate volume reduction. There was excellent radiologic-pathologic correlation during histopathological examination.

Subsequently, Sun et al. evaluated the technical feasibility and safety of transcatheter arterial embolization (TAE) of the prostate in 16 healthy pigs [19]. Embolization of the prostate was technically successful in all animals, without complications. The mean prostate volume after embolization was significantly ($p < 0.001$) reduced compared to the mean prostate volume for the group control. There was no significant difference ($p = 0.328$) in sexual or erectile function between the 2 groups. Most recently, Jeon et al. evaluated the feasibility of prostate embolization for reducing the volume in hormone-induced canine prostate hyperplasia in a study with 9 beagle dogs [20]. They demonstrated the feasibility for reducing prostate volume without serious complication using arterial embolization.

Clinical Investigations

Carnevale et al. published preliminary results of PAE from a proof-of-concept study of 2 men with indwelling catheters for acute urinary retention due to BPH [5]. Both patients were initially managed with selective alpha-blockers without success, and stopped taking medication 1 month before PAE. Patients were evaluated using the IPSS, digital rectal examination, urodynamic testing, prostate biopsy, transrectal ultrasound (US), and magnetic resonance imaging (MRI) before PAE. Malignancy and any other cause of voiding dysfunction such as neurogenic bladder obstruction were excluded. The procedure was performed under local anesthesia, and embolization of the prostatic arteries was done with a microcatheter and 300 to 500 μm microspheres. One patient had bilateral PAE and the other unilateral PAE. They urinated spontaneously after removal of the urethral catheter 15 and 10 days after the procedure, respectively. The urine stream increased with time, with reduction of the post-void residual urine volume. At the 6-month follow-up, prostate reduction determined by US and MRI was 39.7% and 47.8%, respectively, for bilateral PAE. For the patient with unilateral PAE, prostate reduction was 25.5% and 27.8%, respectively.

Midterm evaluation of PAE at 18 months demonstrated that post-void residual volume remained normal and stable in the patient with bilateral embolization. In the patient with unilateral embolization, however, the post-void residual volume increased (68 to 200 ml), as did the size of the prostate. Carnevale and colleagues postulated that unilateral PAE is an effective procedure to reduce prostate size, but bilateral PAE might provide better long-term prostate reduction and LUTS

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relief [6].

From this proof-of-concept investigation, Carnevale and colleagues conducted a Phase 2 study of 11 men with acute urinary retention due to BPH, who were on the waitlist for surgery [17]. Embolizations were performed with local anesthesia in the men who had failed previous treatment with selective alpha-blockers and were being managed by indwelling urethral catheters. Patients were discharged in less than 24 hours [8]. Urologists referred all patients in the study. The mean age was 68.5 years (range: 59 to 78 years). Prostate size ranged from 30 to 90 grams. Men with prostate cancer, stenosis of the urethra, detrusor failure, neurogenic bladder, previous treatment for BPH, and creatinine greater than 2.0 g/dL were excluded from the study. Prior to the procedure, all patients received 1 g per day of ciprofloxacin, and this was continued for 7 days post-procedure. Bilateral embolization was possible in 75% (9 of 12 procedures), and unilateral procedures were performed in 3 cases (3 of 12). One patient was embolized bilaterally twice but did not have clinical success (defined as catheter removal) and was referred to TURP. Less bleeding was observed during TURP because of the PAE before surgery. Clinical success (catheter removal and symptom improvement) was 91% (10 of 11 patients). The 10 successful patients urinated spontaneously post-embolization after catheter removal 4 to 25 days (mean: 12.1 days) post-PAE.

The most frequent symptoms related to PAE were mild pain (perineal, retropubic, and urethral). Opiate medication was not necessary. No major complication was observed. Adverse events were minimal rectal bleeding in 3 patients (25%), diarrhea in 2 patients (16.7%), and a single episode of hematuria in 1 (8.3%) [17]. During the one-month follow-up of the patient who experienced hematuria, an MRI revealed a small defect in the bladder wall due to non-targeted embolization. There were no symptoms other than the single episode of hematuria, and during an MRI at the 3-month follow-up visit the bladder wall appeared normal. No medical treatment was required. The PSA values varied during the first month of follow-up. Before PAE, the mean PSA was 10.1 ng/mL, increased to a mean of 85.6 ng/mL 24 hours after embolization, and it dropped to a mean of 4.3 ng/mL 1 month after the procedure ($p = 0.003$). Imaging follow-up with MRI and US showed a mean average prostate volume reduction of more than 30% after 12 months. Patients had indwelling catheters before intervention, and IPSS declined to 7.1 and 2.2 after 1 month and 1 year, respectively. Erectile function was evaluated using the IIEF score and improved consistently from 1 month to a year. The AUA symptom score and QoL improved from 6 (awful) to 0.25 (delighted) at 1 year.

Pisco and colleagues also studied the safety and potential effectiveness of PAE as an alternative minimally invasive treatment for BPH [7]. In 2011, these investigators published initial results of PAE to treat LUTS due to BPH in 15 patients (ages 62 to 82 years; mean age: 74.1) after failure of medical treatment. Short-term follow-up suggested good symptom control without sexual dysfunction as well as a reduction in prostate volume. Embolization was performed with non-spherical 200μm PVA. Discharge was 4 to 8 hours after the procedure for most patients, with 4 patients discharged the next morning (18 hours later). Unlike the Carnevale patient cohort, the majority of the patients in this published study did not have indwelling bladder catheters, and follow-up ranged from 3 to 12 months. Symptoms measured using the IPSS decreased a mean of 6.5 points, QoL improved 1.14 points, IIEF increased 1.7 points, and peak urinary flow increased 3.85 mL/sec. There was a mean PSA reduction of 2.27 ng/mL and a mean prostate volume decrease of 26.5 mL, as measured by US, and 28.9 mL shown by MRI. There was 1 major complication—an ischemia of the bladder wall treated with surgery—and 4 clinical failures (28.6%).

The initial promising results support the need for a larger study comparing PAE with TURP, the gold standard. Carnevale and colleagues have begun a randomized comparison study of PAE with TURP for reducing symptoms from LUTS due to BPH.

CONCLUSION

Minimally invasive treatments for BPH continue to be part of the therapeutic armamentarium for managing LUTS. However, costs, changes in reimbursement, quality of life, and unanswered questions regarding durability of success have tempered the initial enthusiasm for this class of therapy. Prostatic artery embolization has emerged as a new alternative of treatment for symptomatic patients.

PAE is performed under local anesthesia and can be done as an outpatient procedure. Current reports indicate that LUTS can be controlled even in patients at the end-stage of BPH. PAE does not manipulate the urethra, avoiding urethral stenosis. It can be performed even for large prostates and in patients with urinary retention. This suggests that PAE can be an alternative treatment to TURP or other minimally invasive therapies in the future. In addition, it could be performed before other treatments to reduce the risk of bleeding or to reduce the size of the prostate prior to TURP or laser resection.

A strong understanding of the pelvic vascular anatomy is needed to perform this type of embolization. In addition, inclusion and exclusion criteria using imaging evaluation based on MRI and urodynamic flow are essential. Most important, a collaborative effort between the urologist and interventional radiologist is key. Since the proof-of-concept study in 2008, Carnevale and colleagues have been working as a multidisciplinary group of urologists, diagnostic radiologists, and interventional radiologists for optimum continuity of care.

Prostate embolization has been done for years to control bleeding, with good results, but not as an alternate treatment for BPH. Initial results by Carnevale and colleagues in a selected group of patients suggested BPH can be safely treated by PAE with low rates of side effects and can reduce prostate volume by an average of more than 30 percent. Technical limitations to this technique are tortuous and atherosclerotic vessels, anatomical variations, difficulty visualizing and catheterizing small diameter arteries feeding the prostate, and the potential risk of bladder and rectum ischemia.

As of May 2012, Carnevale and colleagues have treated 40 patients with symptomatic BPH. There are 4 years of follow-up for the first two patients and a minimum of 18 months of data for patients in the phase II study. This patient population has sustained LUTS relief and improved their overall quality of life without symptom recurrence. This data suggests that PAE can be a very effective and safe minimally invasive treatment for patients with symptomatic BPH.

REFERENCES

1. Rassweiler, J., D. Teber, et al. (2006). "Complications of transurethral resection of the prostate (TURP)--incidence, management, and prevention." *Eur Urol* 50(5): 969-979; discussion 980. PubMed ; CrossRef

2. Erol, A., K. Cam, et al. (2009). "High power diode laser vaporization of the prostate: preliminary results for benign prostatic hyperplasia." *J Urol* 182(3): 1078-1082. PubMed ; CrossRef

3. Rubenstein, J. and K. T. McVary. (2004). "Transurethral microwave thermotherapy of the prostate (TUMT)."

4. Muruve, N. A. and K. Steinbecker. (2010). "Transurethral needle ablation of the prostate (TUNA)."

5. Carnevale, F. C., A. A. Antunes, et al. (2010). "Prostatic artery embolization as a primary treatment for benign prostatic hyperplasia: preliminary results in two patients." *Cardiovasc Intervent Radiol* 33(2): 355-361. PubMed ; CrossRef

6. Carnevale, F. C., J. M. da Motta-Leal-Filho, et al. (2011). "Midterm follow-up after prostate embolization in two patients with benign prostatic hyperplasia." *Cardiovasc Intervent Radiol* 34(6): 1330-1333. PubMed ; CrossRef

7. Pisco, J. M., L. C. Pinheiro, et al. (2011). "Prostatic arterial embolization to treat benign prostatic hyperplasia." *J Vasc Interv Radiol* 22(1): 11-19; quiz 20. PubMed ; CrossRef

8. Carnevale, F. C. (2011). *How to start with embolization for benign prostatic hyperplasia, Workshop [WS 3203]*. CIRSE.

9. Pinheiro, C., J. M. Pisco, et al. (2011). "Prostatic artery embolization to treat benign prostatic hyperplasia short and medium term outcomes." *J Urol* 185(suppl 4): e908-e909. CrossRef

10. Mitchell, M. E., A. C. Waltman, et al. (1976). "Control of massive prostatic bleeding with angiographic techniques." *J Urol* 115(6): 692-695. PubMed

11. Li, B. C. (1990). "[Internal iliac artery embolization for the control of severe bladder and prostate haemorrhage]." *Zhonghua Wai Ke Za Zhi* 28(4): 220-221, 253. PubMed

12. Michel, F., T. Dubruille, et al. (2002). "Arterial embolization for massive hematuria following transurethral prostatectomy." *J Urol* 168(6): 2550-2551. PubMed

13. Barbieri, A., M. Simonazzi, et al. (2002). "Massive hematuria after transurethral resection of the prostate: management by intra-arterial embolization." *Urol Int* 69(4): 318-320. PubMed ; CrossRef

14. Rastinehad, A. R., D. M. Caplin, et al. (2008). "Selective arterial prostatic embolization (SAPE) for refractory hematuria of prostatic origin." *Urology* 71(2): 181-184. PubMed ; CrossRef

15. Tan, L., S. K. Venkatesh, et al. (2009). "Treatment of a patient with post-TURP hemorrhage using bilateral SAPE." *Nat Rev Urol* 6(12): 680-685. PubMed ; CrossRef

16. DeMeritt, J. S., F. F. Elmasri, et al. (2000). "Relief of benign prostatic hyperplasia-related bladder outlet obstruction after transarterial polyvinyl alcohol prostate embolization." *J Vasc Interv Radiol* 11(6): 767-770. PubMed ; CrossRef

17. Mauro, M. A. (2008). "Can hyperplastic prostate follow uterine fibroids and be managed with transcatheter arterial embolization?" *Radiology* 246(3): 657-658. PubMed ; CrossRef

18. Faintuch, S., E. M. Mostafa, et al. (2008). "Abstract No.14: Prostatic artery embolization as a primary treatment for benign prostatic hyperplasia in a canine model." *J Vasc Interv Radiol* 19(2): S7. CrossRef

19. Sun, F., F. M. Sanchez, et al. (2008). "Benign prostatic hyperplasia: transcatheter arterial embolization as potential treatment--preliminary study in pigs." *Radiology* 246(3): 783-789. PubMed ; CrossRef

20. Jeon, G. S., J. H. Won, et al. (2009). "The effect of transarterial prostate embolization in hormone-induced benign prostatic hyperplasia in dogs: a pilot study." *J Vasc Interv Radiol* 20(3): 384-390. PubMed ; CrossRef