Prostatic Artery Embolization and its Efficacy in the Reduction of Nocturia

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Abstract

Introduction: Nocturia is a major problem in men with lower urinary tract symptoms (LUTS) and Benign Prostatic Hyperplasia (BPH). Transurethral resection of the prostate (TURP) and photoselective vaporization (PVP) have been shown to reduce nocturnal frequency in 32.2% of patients by 0.8 to 1.0 episodes per night, though they carry the risk of operative morbidity. We report on the efficacy of prostatic artery embolization (PAE) in the reduction of nocturia.

Materials & Methods: IRB-approved retrospective study was performed of sixty-eight PAE patients performed in two U.S. centers (Site 1 n=40, Site 2 n=28). American Urological Association symptom index (AUA-SI), quality of life-related symptoms (QoL), nocturnal frequency were evaluated at baseline and at one and three-months. A paired t-test was performed to assess significance.

Results: Baseline demographics demonstrated mean age 64.5 years, AUA-SI 23.9, QoL 4.8, PV 80.6 cc, and Nocturnal Frequency 3.3 episodes. 54.4% (25/46) of patients reported improvement in nocturnal frequency at 1 month and 73.7 % (28/38) at 3 months. Absolute reduction of 0.82 and 1.56 episodes per night were reported at 1 and 3 months ($p<0.0001$). AUA-SI decreased by 10.0 and 13.4 points at 1 and 3 months ($p<0.0001$). Quality of Life improved by 2.1 and 2.8 points at 1 and 3 months ($p<0.0001$). Ten minor self-limiting complications were observed. No major complications were reported.

Conclusions: PAE significantly reduced nocturnal frequency in more than 70% of patients at 3 months.

Keywords: Benign prostate hyperplasia; prostatic artery embolization; nocturia.

1. Introduction

Benign prostatic hyperplasia (BPH) is the most common benign neoplasm in men, prevalent in over half of men by age 60 and up to 90% of men by age 85 (1). Lower urinary tract symptoms (LUTS) are common complaints in BPH, and consist of incomplete voiding, frequency, urgency, weak stream and nocturia (also referred to as nocturnal frequency); symptoms that can significantly affect ones quality of life (QOL).

The negative impact of nocturia on QOL is largely related to diminished sleep quality, which can result in diurnal fatigue, decreased concentration, lower work performance, depression, and cardiovascular morbidity (2). As nocturia is not unique to BPH, underlying pathophysiology may be broken down into the following categories: 1) Global polyuria, a continuous overproduction of urine defined as > 40ml/kg in a 24 hour period, 2) nocturnal polyuria or nocturnal urine overproduction, 3) decreased nocturnal bladder capacity 4) sleep disorders, and 5) mixed etiologies (3).

Surgical treatments of BPH by TURP and PVP have been shown to decrease nocturnal frequency by 0.8 to 1 episodes per night; however these procedures carry a relatively high operative morbidity (6,7). Recently, prostate artery embolization has become an attractive treatment option for BPH due to its minimally invasive nature, ability to be performed in the outpatient setting under moderate sedation, and relatively low side effect profile and complication rate compared to surgical options. Several studies have shown that PAE is a safe and effective option in the treatment of BPH, with similar clinical benefits compared to other surgical options in glands of varying sizes (8,9,10,11). Further, unlike TURP, there does not appear to be an upper limit of prostate size that can be effectively treated (12). Given the potential advantages of PAE over traditional surgical options and challenges in treating nocturia, this study was aimed at assessing the efficacy of PAE in reducing nocturnal frequency.

2. Materials and Methods

After Institutional Review Board approval was obtained for a retrospective chart review at two separate institutions, the electronic medical records were used to identify all patients who underwent PAE from May to August 2015. The study was compliant with the Health Insurance Portability and Accountability Act. Data from sixty-eight consecutive patients, 40 from Site 1 and 28 from Site 2, with moderate or severe grade symptoms from BPH underwent PAE were used. Patients were evaluated at baseline and routine clinical follow-up after embolization was performed at 1 and 3 months with American Urological Association symptom index (AUA-SI) including quality of life-related symptoms (QoL). Episodes of nocturia were obtained as a component of the AUA-SI. The embolization was considered technically successful if bilateral embolization was performed. Clinical success was defined as either: a greater-than-3 point improvement in AUA-SI at 1-month and 3-month follow-up, catheter independence in patients with urinary retention, or cessation of medication as defined by the American Urologic Management of Benign Prostatic Hyperplasia (13). Complications were reported according to the Society of Interventional Radiology Complications Classification System (14).

2.1 Embolization Technique

Patients received 30 mg Ketorolac intravenously (Roche Laboratories, Basel, Switzerland) and 500 mg ciprofloxacin per oral route (Bayer Pharmaceuticals, Wayne, NJ) immediately prior to the procedure, and a second dose prior to discharge. The procedure was performed with moderate

sedation, with patients receiving Midazolam (West-ward Pharmaceuticals, Eatontonwn, NJ) and Fentanyl (Hospira Inc., Lake Forest, IL). Ciprofloxacin was prescribed for 5 days post-procedurally along with an Ibuprofen 600 mg orally three times daily, as well as 200 mg Phenazopyridine orally three times daily (Warner Chilcott, Rockaway, NJ). No additional analgesics were given for pain.

Angiography (Visipaque, GE Healthcare Inc., Princeton, NJ) was performed with a unilateral femoral approach in 55 patients and left radial approach in 13 patients per the interventionalist's discrection. Selective hypogastric artery digital subtraction angiography (DSA) (Siemens Artis Zee Siemens Medical Solutions, Forchheim, Germany) was performed in the ipsilateral 30-degree oblique view. Angiography was performed in each projection to identify and map the prostatic arteries (Figure 1).

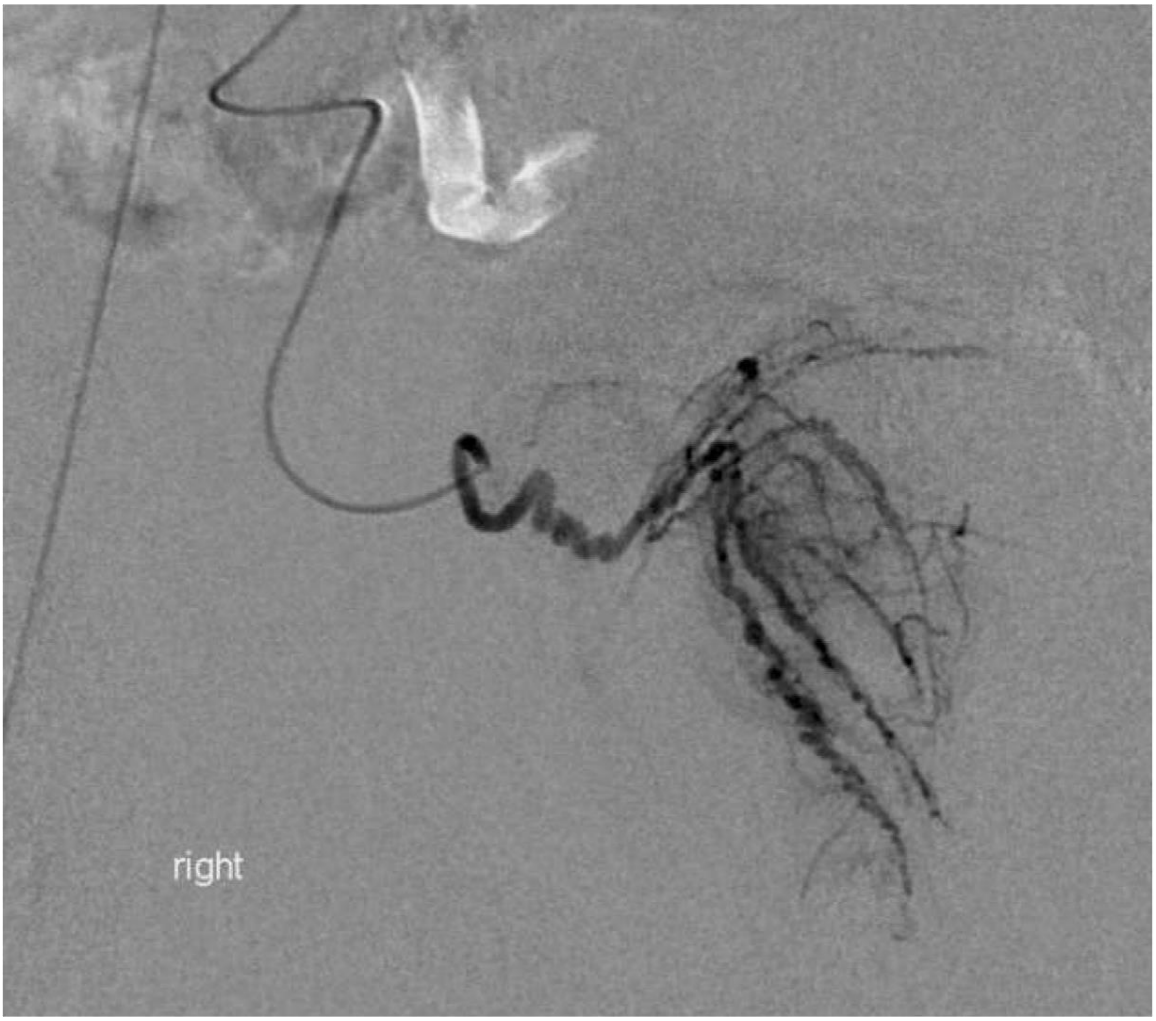


Fig. 1: Angiography demonstrating selection of the prostatic artery.

The prostatic arteries were selected with a 2.4 french microcatheter (Direxion, Boston Scientific, Natick, MA) and digital subtraction angiography (DSA) was performed in the anterior-posterior projection. Cone beam computed tomography (CBCT) was performed with a 4-6 second delay after hand-injection of 2-3 cc iodinated contrast to evaluate for sites of non-target embolization at the discretion of the operator. Bilateral embolization was performed with spherical embolic agents (Range 100-400 micron Embozene, CeloNova, San Antonio, TX; or Embospheres 100-500 micron range Merit Medical, South Jordan, UT) to complete stasis. Gelatin sponge 'slurry' (Gelfoam®, Pharmacia and Upjohn Company, Kalamazoo, MI) was used an adjunct to achieve complete stasis of the proximal prostatic artery.

2.2 Statistical Analysis:

Independent t-test analysis was used to assess for statistical differences of baseline demographics between patients at the different institutions. Paired t-test analysis was used to assess for longitudinal changes in individual patient AUA-SI, QoL, and episodes of nocturia from baseline to 1 and 3 months. A $p \leq 0.05$ value was considered statistically significant. Symptom scores, nocturnal frequency and quality scores are reported as means with 95% confidence intervals. AUA-SI symptom score reduction ≥3 was considered to indicate clinical success. All analyses were conducted using IBM SPSS Statistics (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

3. Results

Baseline demographics of 68 patients demonstrated mean age of 64.5 years, prostate volume of 80.6cc, AUA-SI of 23.9, QoL of 4.8, and nocturia frequency of 3.3 episodes per night (Table 1). Independent t-test demonstrated no significant difference between patient baseline demographics.

Table 1. Baseline Demographics	
Age years (mean)	64.5
AUA-SI	23.9
QOL	4.8
Nocturia Frequency	3.3
Prostate Volume (cc)	80.6

Technical success, as defined by bilateral embolization, was achieved in 100% of patients. All patients were discharged to their home from IR recovery within less than six hours post-procedure. Ten patients experienced self-limiting minor complications as follows: small groin hematoma, transient prostatitis, urinary incontinence, hematospermia, hematuria, epididymo-orchitis, erectile dysfunction, and acute urinary retention. No major complications were observed.

At one-month follow-up, 25/46 (54.3%) patients who completed the AUA-SI form reported improvement in their nocturia frequency with a mean reduction of 0.82 episodes per night from baseline (mean 2.48 episodes/night; standard deviation 1.2; $p<0.0001$). At three-month follow-up, 28/38 (73.7%) patients who completed the AUA-SI form reported improvement of their nocturia frequency with a mean reduction of 1.56 episodes per night from baseline (mean 1.74 episodes/night; standard deviation 1.0; $p<0.0001$) (Table 2).

Table 2. Nocturia Follow-Up					
	Baseline	One Month	p-value	Three Months	p-value
Nocturia Frequency (episodes/night)	3.3	2.5	<0.0001	1.7	<0.0001
Nocturia mean change (episodes/night)		0.82	<0.0001	1.56	<0.0001

AUA-SI decreased from 23.9 at baseline to 14.0 ($p<0.0001$) and 10.4 ($p<0.0001$) at one and three-month follow-up, respectively. QoL also improved from 4.8 at baseline to 2.7 ($p<0.0001$) and 2.0 ($p<0.0001$) at one and three-month follow-up, respectively (Table 3).

Table 3. Overall Follow-Up							
	Baseline	One Month			Three Months		
			STDEV	p-value		STDEV	p-value
AUA-SI (mean)	23.9	14.0	8.26	<0.0001	10.4	7.30	<0.0001
QOL (mean)	4.8	2.7	1.70	<0.0001	2	1.75	<0.0001
Nocturia Frequency (mean episodes/night)	3.3	2.5	1.23	<0.0001	1.7	0.98	<0.0001

Clinical success, as defined by a reduction in score of ≥ 3 from baseline, was seen in 48/52 (92.3%) of patients who followed-up at one month and 38/45 (84.4%) or patients who followed-up at three months.

4. Discussion

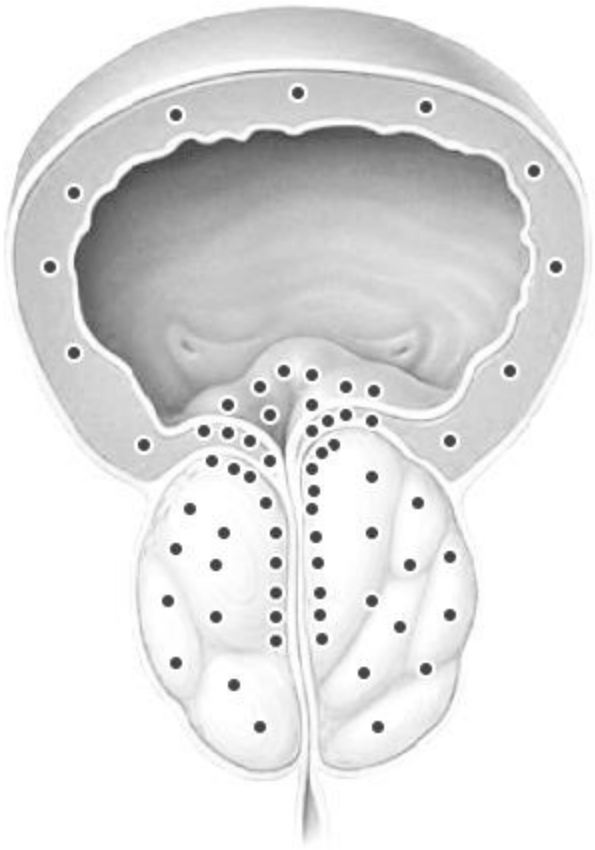
Emerging evidence on the safety and efficacy of PAE for BPH-related symptoms is ongoing, however, there is a lack of focus in the literature on PAE as it relates specifically to nocturia. The etiology of nocturia is multifactorial, and in patients with BPH, the exact causative mechanism is still being elucidated. In the setting of reduced filling capacity, a sequela of BPH, the bladder is overwhelmed by the amount of urine entering at night and cannot accommodate the nocturnal urinary volume. It has benn postulated that in addition to decreased bladder capacity from anatomical compression, there is increased sympathetic nerve activity of the bladder, prostate and urethra, which may elevate the tonicity of the bladder and cause a functional decreased bladder capacity (4). Nocturia is the least specific symptom of BPH and is, unfortunately, the symptom least responsive to BPH therapies (5). This may in part be due to the wide array of etiologies for nocturia, as well as incomplete knowledge of how neuromuscular signals may contribute to nocturia in the setting of BPH.

In this retrospective study, it has been found that PAE resulted in a reduction of nocturnal frequency by 0.85 and 1.4 episodes per night after 1 and 3 months ($p<0.0001$), which is slightly more than 0.8 to 1.0 episodes reported after TURP and PVP (6,7). Additionally, 54.4% of patients reported improvement of nocturnal frequency at 1 month and 73.7% at 3 months. This success rate is considerably higher than the less than 17.9% of patients who reported improvement of nocturia after Tamsulosin and 32.2% after TURP (6**)**. Mean AUA-SI

and QoL scores after PAE were also significantly decreased at 1 and 3 months ($p<0.0001$). This first multi-center US experience demonstrated a reduction of 13 points in IPSS at 3 months which is comparable with surgical therapies, such as TURP (13).

Further, no major complications were reported after PAE in this group. This is crucial when considering approximately 20% of patients experience significant complications following TURP with similar results (15,16). This study suggests PAE is a feasible and attractive option for the treatment of nocturia in the setting of BPH.

In early experience with PAE, it was thought that reduction in prostate volume from ischemia played the predominate role in alleviating LUTS symptoms, however, it has subsequently been found there is not a direct correlation with prostate volume reduction and symptomatic improvement (17). We hypothesize that that the ischemia induced by PAE may lead to necrosis and downregulation of the α1 adrenergic receptors in the prostate, peri-urethral zone, and bladder neck, where they predominate (Figure 2 – black circles illustrate receptors and location of highest concentration).



This in turn would decrease the sympathetic tone of the bladder and prostatic urethra, thereby reducing irritative symptoms such as nocturia and frequency. This is supported by the Medical Therapy of Prostatic Symptoms (MTOPS) trial, where LUTS symptoms were adequately managed by α-blockade alone in patients with LUTS and prostate volumes ranging from 25cc to greater than 40cc (18). In addition, investigators found similar pathologic findings after transurethral needle ablation (19). In this study, prostatic tissue that underwent ablation was found to be necrotic and absent of axonal nerve fibers, compared to those areas without necrosis. The authors concluded that 'denervation of alpha-receptors and/or sensory nerves could explain the clinical effects' of ablation.

Limits of the current study include the retrospective nature, small sample size, difficulty in achieving adequate follow-up, and relatively short-term follow-up. Post void residual and peak urine flow were not assessed with regularity as well, as patients were treated as part of their standard of care. Further, it is possible that a percentage of patients with both 24 hr polyuria and BPH related nocturia could negatively affect outcomes in this study. Future studies may include prospective, randomized comparison of PAE with other surgical options such as PVP and transurethral microwave therapy to help define the role of PAE in the setting of nocturia. A thorough preprocedural clinical history assessing the complex etiology of nocturia should be taken and should be considered in the randomization process. Long term data needs to be collected to assess for the durability of PAE, as it is possible revascularization could limit the long-term therapeutic effect of PAE (12).

In conclusion, PAE has been shown in this study to significantly reduce nocturnal frequency in over 70% of patients at 3 months. Further, it has shown it is well tolerated with high patient satisfaction, minimal self-limiting side effects, and can be performed in an outpatient setting. These findings make PAE an attractive treatment option for patients with nocturia in the setting of BPH.

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