Early Results from a United States Trial of Prostatic Artery Embolization in the Treatment of Benign Prostatic Hyperplasia

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ABSTRACT

Purpose: To report early findings from a prospective United States clinical trial to evaluate the efficacy and safety of prostatic artery embolization (PAE) for benign prostatic hyperplasia (BPH).

Materials and Methods: From January 2012 to March 2013, 72 patients were screened and 20 patients underwent treatment. Patients were evaluated at baseline and selected intervals (1, 3, and 6 mo) for the following efficacy variables: American Urological Association (AUA) symptom score, quality of life (QOL)–related symptoms, International Index of Erectile Function score, peak urine flow rate, and prostate volume (on magnetic resonance imaging at 6 mo). Complications were monitored and reported per Society of Interventional Radiology guidelines.

Results: Embolization was technically successful in 18 of 20 patients (90%); bilateral PAE was successful in 18 of 19 (95%). Unsuccessful embolizations were secondary to atherosclerotic occlusion of prostatic arteries. Clinical success was seen in 95% of patients (19 of 20) at 1 month, with average AUA symptom score improvements of 10.8 points at 1 month ($P < .0001$), 12.1 points at 3 months ($P = .0003$), and 9.8 points at 6 months ($P = .06$). QOL improved at 1 month (1.9 points; $P = .0002$), 3 months (1.9 points; $P = .003$), and 6 months (2.6 points; $P = .007$). Sexual function improved by 34% at 1 month ($P = .11$), 5% at 3 months ($P = .72$), and 16% at 6 months ($P = .19$). Prostate volume at 6 months had decreased 18% ($n = 5$; $P = .05$). No minor or major complications were reported.

Conclusions: Early results from this clinical trial indicate that PAE offers a safe and efficacious treatment option for men with BPH.

ABBREVIATIONS

AUA = American Urological Association, BPH = benign prostatic hyperplasia, IIEF = International Index of Erectile Function, PAE = prostatic artery embolization, QOL = quality of life, TURP = transurethral resection of the prostate

Benign prostatic hyperplasia (BPH) affects more than 15 million men in the United States, with an annual health care cost of more than $3 billion (1,2). By 60 years of age, the prevalence of BPH is greater than 50%, and, by 85 years of age, the prevalence is as high as 90% (3). BPH significantly alters quality of life (QOL), interferes with normal daily activities and sleep patterns, and manifests primarily with lower urinary tract symptoms, which consist of urinary frequency and urgency, nocturia, decreased and intermittent force of stream, and the sensation of incomplete bladder emptying. Complications of longstanding BPH include urinary calculi, infection, neurogenic bladder, and complete bladder outlet obstruction.

Therapeutic options for patients with mild or moderate-grade symptoms include watchful waiting and medical or surgical therapy. Although long-term medical
therapy can be effective, it is limited by significant side effects such as dizziness, orthostatic hypotension, erectile dysfunction, and decreased libido. Often, medical therapy cannot be maintained for long periods of time because of compliance, cost, significant drug interactions, and, ultimately, lack of efficacy.

Investigators (4,5) have been seeking less invasive and durable therapies for BPH-related symptoms; one of the newest approaches has been prostatic artery embolization (PAE). Pisco et al (6) initially studied PAE in 15 human patients in Portugal, demonstrating technical success in 14 (92%), with good short-term clinical results and minimal adverse effects. PAE was shown to provide improvement in urinary flow rates, prostate volume, and QOL. In a follow-up study (7), Pisco et al demonstrated technical success rates of 97% with PAE, with 86 of 89 patients treated. Short- and intermediate-term results were also impressive, with patients who received smaller embolic particles (mean 100-μm and 200-μm polyvinyl alcohol) exhibiting longer-term symptom improvement. In a study of 255 patients treated over a 36-month period (8), Pisco et al showed cumulative clinical success rates of 81.9%, 80.7%, 77.9%, 75.2%, 72.0%, 72.0%, 72.0%, and 72.0% at 1, 3, 6, 12, 18, 24, 30, and 36 months, respectively.

The purpose of the present study is to report early findings from a prospective physician-initiated United States clinical trial to evaluate the efficacy and safety of PAE in the treatment of BPH.

**MATERIALS AND METHODS**

From January 2012 to March 2013, 72 patients were screened at a single center for eligibility to participate, with 20 patients (mean age, 66.6 y; range, 57–81 y) enrolled thus far in the trial. Institutional review board approved enrollment is for between 30 and 45 patients, and is ongoing. Patients were excluded for the following reasons: elected alternate surgical therapy (n = 3), diagnosed with non-BPH-related symptoms (n = 5), chose watchful waiting (n = 10), prostate cancer (n = 1), declined embolization procedure (n = 17), or did not complete preprocedure tests (n = 16). All patients enrolled in this institutional review board-approved trial signed written informed consent, and the study was compliant with the Health Insurance Portability and Accountability Act. The primary outcome of this study is to measure the reduction in lower urinary tract symptoms from baseline to 1, 3, 6, and 12 months in men undergoing PAE. The inclusion criteria were age greater than 50 years, lower urinary tract symptoms believed to be secondary to bladder outlet obstruction from BPH, AUA symptom score of at least 8, and the ability to give informed consent. Exclusion criteria included bleeding diathesis, renal insufficiency (creatinine level > 1.6 mg/dL), neurologic disease believed to affect the bladder or history of neurogenic or chronically decompensated bladder, known prostate cancer, active bladder cancer (≤ 2 y), prostate-specific antigen level greater than 4.0 ng/dL (unless biopsy findings were negative or biopsy was declined), and acute urinary retention.

Efficacy variables of AUA symptom score, QOL, International Index of Erectile Function (IIEF) score, peak urine flow rate, and prostate volume on magnetic resonance (MR) imaging were assessed at baseline and at 6 months following the procedure (Table). AUA score, QOL, IIEF score, and adverse event monitoring were performed at all visits, including 1, 3, and 6 months. Follow-up is planned at 12 and 24 months as well. All patients were evaluated by a urologist and offered other therapeutic options. Patients were allowed to choose between PAE and other available therapies, including transurethral resection of the prostate (TURP), photoselective vaporization, and transurethral microwave therapy.

**Embolization Technique**

Patients received 30 mg ketorolac (Roche, Basel, Switzerland) and 500 mg ciprofloxacin (Bayer, Wayne, New Jersey) immediately before the procedure, with a second dose before discharge. Ciprofloxacin was prescribed for 3 days postoperatively, along with oral ibuprofen 600 mg and 200 mg phenazopyridine (Warner Chilcott, Rockaway, New Jersey) three times daily. No additional analgesic agents were given for pain. The procedure was performed with moderate sedation, with patients receiving midazolam (Westward, Eatontown, New Jersey) and fentanyl (Hospira, Lake Forest, Illinois).

| Table . Baseline Efficacy Values per Treatment Cohort |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Variable                                      | 1 Mo (n = 19)                                  | 3 Mo (n = 13)                                  | 6 Mo (n = 5)                                  |
| Age (y)                                       | Mean ± SD 66.5 ± 6.84 57–81                   | Mean ± SD 68.9 ± 6.58 61–81                   | Mean ± SD 71.0 ± 6.28 63–80                   |
| AUA symptom score                            | 24.1 ± 5.25 14–35                             | 24.1 ± 4.59 14–30                             | 21.8 ± 5.02 14–28                             |
| QOL score                                     | 5.79 ± 1.08 4–7                               | 5.61 ± 1.12 4–7                               | 5.80 ± 1.10 5–7                               |
| IIEF score                                    | 13.4 ± 6.90 3–30                              | 13.0 ± 7.75 3–30                              | 11.2 ± 7.40 6–24                              |
| Prostate volume (cm³)                         | 82.7 ± 62.0 28–274                             | 66.4 ± 38.1 28–177                            | 56.7 ± 18.1 28–76                             |
| Peak urine flow (mL/s)                        | 8.64 ± 4.40 4–23                               | 9.26 ± 4.87 4–23                              | 7.40 ± 2.30 4–10                              |

AUA = American Urological Association, IIEF = International Index of Erectile Function, QOL = quality of life.
Angiography was performed with a unilateral femoral approach in all patients. Selective hypogastric artery digital subtraction angiography was performed in the anterior–posterior view and ipsilateral 30° oblique/10° craniocaudal view (Fig 1a). Angiography with contrast medium (Visipaque; GE Healthcare, Princeton, New Jersey) was performed in each projection to identify and map the prostatic arteries. The prostatic arteries were selected with a 2.4-F microcatheter (Renegade STC; Boston Scientific, Natick, Massachusetts), and digital subtraction angiography was performed in the anterior–posterior projection (Fig 1b). Cone-beam
computed tomography (CT) was performed with a 4–6-
second delay after hand-injection of 2–3 mL iodinated
contrast agent to evaluate for sites of nontarget embo-
lization (Fig 1c). Embolization was performed with
spherical embolic agents (100–400-μm Embozene;
CeloNova, San Antonio, Texas) to an endpoint of
near-stasis (Fig 1d). The same technique was used to
perform embolization of the right prostatic artery. A
closure device was used in all patients (StarClose SE;
Abbott Laboratories, Abbott Park, Illinois). The emboli-
zation was considered technically successful if bilateral
embolization was performed. Patients were assessed for
pain with a visual analog scale immediately after the
procedure and before discharge. Clinical success was
defined as a greater than 3-point improvement in AUA
symptom score.

Statistical Analysis
For this preliminary analysis, repeated-measures analysis
of variance was used to evaluate AUA symptom
improvement and QOL at 1 and 3 months. AUA
symptom and QOL scores at each of the three time
points were normally distributed (Shapiro–Wilk W test),
so a parametric statistical technique was used to produce
the reported P values. Symptom scores and quality
scores are reported as means with 95% confidence
intervals. A P value of .05 or lower was considered to
indicate statistical significance. AUA symptom score
reduction of at least 3 points was considered to indicate
a clinically significant improvement. All analyses were
conducted by using SAS software (version 9.2; SAS
Institute, Cary, North Carolina).

RESULTS
Embolization was technically successful in 18 of 20
patients (90%). One technically unsuccessful embolization
was secondary to atherosclerotic occlusion of the bilateral
prostatic arteries and another was secondary to unilateral
atherosclerotic occlusion. Follow-up was discontinued in
a different patient after 1 month as a result of a diagnosis
of recurrent colon carcinoma. Nineteen patients were
discharged on the same day as the procedure and one
patient was observed overnight because the procedure
was completed in the evening. Mean fluoroscopy time was
30.2 minutes (range, 11.5–63.9 min; 10 frames
per second), with an average dose–area product of
55,923 μGy·cm² (range, 5,689–339,676 μGy·cm²). Aver-
age procedure time was 72 minutes (range, 41–177 min).
Clinical success at 1 month was seen in 95% of
patients (18 of 19), with a mean 10.8-point AUA
symptom score improvement (P < .0001) and 1.9-point
QOL improvement (P = .0002; Fig 2). Erectile function,
as measured by IIEF, improved on average from 12.9 to
10.9 (P = .02). For the cohort with at least 3 months of
follow-up (n = 13), there was a mean reduction in AUA
symptom score of 12.1 points (P = .0003), and QOL
improved by 1.9 points (P = .003; Fig 3). At 6 months,
mean AUA improvement was 9.8 points (n = 5, P = .06), and QOL improved by 2.6 points (P = .007). Sexual function improved, although not significantly, by 34% at 1 month (P = .11), 5% at 3 months (P = .72), and 16% at 6 months (P = .19). Prostate volume (Figs 4, 5) in patients with at least 6 months of follow-up (n = 5) decreased by an average of 18% (mean, 8.7 cm³; 95% confidence interval, 0.09–17.4 cm³).

Complications were classified according to the Society of Interventional Radiology classification system (9). No minor or major complications were reported. No patients experienced periprocedural pain; all patients were discharged with a visual analog scale pain score of 0 of 10. A total of 42% of patients (eight of 19) did experience transient (< 72 h) increase in urinary frequency within the first 3 days after PAE. Three of the 19 patients (16%) experienced self-limited (ie, < 4 wk) hematospermia, and one patient experienced diarrhea, which resolved in less than 24 hours.
DISCUSSION

Early results from the present prospective pilot study on PAE demonstrate that the procedure is effective in significantly reducing the lower urinary tract symptoms related to BPH. On average, efficacy scores improved 12 points within 3 months from baseline. When compared with the results of multiple clinical trials of medical therapy, PAE demonstrates twice the average AUA score improvement compared with medical therapy alone (1). PAE demonstrates similar improvements in efficacy scores compared with other surgical and minimally invasive therapies, such as microwave and transurethral laser therapy (10).

The present results also suggest that PAE is a safe procedure, without significant increases in morbidity or mortality. Compared with TURP, early safety results of PAE are also promising. Whereas TURP has well documented complication rates of 5%–15% (11), studies of PAE (5,7,8) have demonstrated a lack of complications associated with transurethral therapies, including bleeding, sexual dysfunction, incontinence, and dilutional hyponatremia. In one series (6), there was one reported case of nontarget embolization causing bladder ischemia among more than 300 procedures. The present study used cone-beam CT before embolization, which may offer improved safety; however, further study may be needed to define its exact role in PAE.

The present study is limited by its lack of long-term follow-up; however, continued follow-up is ongoing, and patients will be assessed for 2 years after embolization.

At present, the optimal type of embolic agent, spherical or nonspherical, is unknown. Results from a randomized trial (12) that used nonspherical embolic particles concluded that there was no significant difference in efficacy between smaller and larger particles; however, prostate volume decreased more with the use of smaller particles. It is interesting to note, however, that, in the present study, which used spherical embolic agents (Embozene; CeloNova), no associated postprocedural pain was reported. In contrast, results from Pisco et al (8) indicated that pain was experienced in 24% of patients who were treated with nonspherical embolic agents, despite receiving preprocedural (2 d) and postprocedural (7 d) naproxen in addition to ketorolac.

Overall, the early results from the present United States trial are encouraging that PAE offers a safe and efficacious treatment option for men with lower urinary tract symptoms related to BPH. Future study to refine techniques to improve safety, perhaps with cone-beam CT, would also be useful. Further studies, including evaluation of varying techniques that may affect clinical outcome and comparative studies with standard therapeutic options, are planned.

ACKNOWLEDGMENTS

The authors acknowledge the staff at the Cardiovascular and Interventional Radiology Department at Inova Alexandria Hospital for their continued dedication to excellence and research, including Jennifer L. Hedden, PA, Michelle Ponturo, ACNP, Sarah Pollach, NP, and Lauren McDermott, PA.

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