Prostate Artery Embolization: A Minimally Invasive Option for the Treatment of BPH

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Educational Objectives

To understand:

- Epidemiology and pathophysiology of Benign Prostatic Hyperplasia (BPH)
- Origin and current utilization of Prostate Artery Embolization (PAE)
  - Minimally invasive treatment option
- Identification of patients suitable for PAE
- PAE procedural safety and efficacy
Benign Prostatic Hyperplasia (BPH):
- One of the most common health conditions of aging men worldwide
- High histologic prevalence at autopsy
  - 50% in pts <60 yo
  - 90% in pts <85 yo
- At age 70, 40% men symptomatic and by age 75, 50%
- 4.5 million office visits in 2009
- Direct cost of 1.1 billion dollars
BPH Epidemiology

Relationship between histologic hyperplasia, clinical symptomatology (LUTS), benign prostatic enlargement and bladder outlet obstruction.
BPH Pathophysiology

Histopathology:

- Increased number epithelial and stromal cells
  - Molecular etiology of process remains uncertain
  - Due to cellular proliferation or impaired programmed cell death
  - End result is cellular accumulation

- Multifactorial process
  - Androgens
  - Estrogens
  - Stromal-epithelial interaction
  - Growth factors
  - Neurotransmitters
BPH Pathophysiology

Histopathology:

- Hyperplasia
  - Androgens
    - Required for normal cell growth and differentiation
    - But, actively inhibit cell death
    - Prostate continually responds to androgens
  - Aging
    - Development of well-differentiated cells reduced
    - Reduced cell death rate
  - Stromal-epithelial interactions
    - Prostatic stroma induces epithelial cell development

- Inheritable, genetic component
BPH Pathophysiology

Transitional zone surrounding urethra, 5-10% of normal prostate volume, contains glands that undergo benign hyperplasia.
BPH Pathophysiology

Normal Prostate

- Bladder
- Complete emptying of the bladder
- Sphincter apparatus
- Urethra
- Prostate

Prostatic Hypertrophy

- Bladder
- Incomplete emptying of the bladder
- Urine
- Sphincter apparatus
- Urethra
- Enlargement of the Prostate
BPH Pathophysiology

Lower Urinary Tract Symptoms (LUTS):

- **Voiding / Obstructive**
  - Hesitancy
  - Straining
  - Prolonged voiding or weak flow
  - Terminal dribbling
  - Retention
  - Overflow incontinence

- **Storage / Irritative**
  - Frequency or nocturia
  - Urgency
  - Urge incontinence

Untreated BPH → urinary retention, recurrent UTI’s, hydronephrosis and renal failure
BPH Pathophysiology

International Prostate Symptom Score (IPSS):

- 0-7 = Mild
- 8-19 = Moderate
- 20-35 = Severe

QOL Score

- 0 = Delighted
- 6 = Terrible
BPH Treatment

Treatment options:

- Watchful waiting
  - “Self management” – restrict evening fluid, ETOH, and caffeine

- Medical therapy
  - $\alpha_1$-adrenergic blockers
    - reduce smooth muscle tone in bladder neck and prostate to $\downarrow$ BOO
    - dizziness and orthostatic hypotension, possible retrograde ejaculation
  - $5\alpha$-reductase inhibitors
    - inhibit conversion of testosterone to dihydrotestosterone, a more potent androgen
    - cause apoptosis of prostatic epithelial cells $\rightarrow$ volume reduction
    - sexual dysfunction
BPH Treatment

Treatment options:

- Medical therapy
  - antimuscarinic drugs
    - reduces bladder smooth muscle contraction
    - dry mouth, constipation and voiding difficulty
  - phosphodiesterase \(_{5}\) inhibitors
    - decrease smooth muscle tone and contraction in bladder, prostate and penile tissues
    - contraindicated in pts using nitrates
Treatment options:

- Traditional surgical interventions, “Gold Standard”
  - TURP and prostatectomy
    - Peri-operative morbidity, incontinence and erectile dysfunction
- Minimally invasive surgical therapies (MIST)
  - Transurethral incision of the prostate (TUIP)
    - If smaller gland, <30mL
  - Thermo-ablative strategies
    - Transurethral microwave therapy
    - Transurethral evaporation of the prostate
    - Transurethral needle ablation
    - Rezum utilizing water vapor
BPH Treatment

Treatment options:
- Minimally invasive surgical therapies (MIST)
  - Mechanical approaches
    - UroLift®
    - Intraprostatic stents

Placement of non-absorbable monofilament sutures into the prostatic urethra through to the lateral lobes with traction, to increase diameter of the urethral channel.
Prostate Artery Embolization

Percutaneous, image-guided, highly selective catheter-directed embolization of bilateral prostatic arteries

Significant reduction in prostatic blood flow → cessation of hemorrhage & tissue ischemia → inflammatory rxn with cytotoxic edema and leukocytic infiltration

Initial swelling subsides → gland size reduction, decreased tissue density and cystic change

Decreased pressure in prostatic urethra and improved LUTS due to BPH
PAE Origin

Performed as salvage therapy for vascular injury and hemorrhage s/p prostate biopsy, TURP or open prostatectomy
Case Report: 76 yo M with heart disease, prosthetic valve, and prostate volume of 305mL p/w acute urinary retention and hematuria requiring transfusion due to BPH. Sx’s refractory to medical and interstitial laser tx so b/l PAE with PVA. Hematuria stopped and at 12 months LUTS significantly improved with 40% reduction in prostate volume and no change in sexual function.
Preliminary and midterm results of PAE in 2 pts with acute urinary retention due to BPH:
67 yo M voided PPD #15 s/p b/l PAE and remained catheter free with 50% reduction in gland size at 18 months. At 30 months, IPSS score 1 and QoL score 0.
68 yo M s/p unilateral PAE, catheter out PPD #10 and at 18 months, 20% reduction in gland size.
2011: Feasibility of PAE in 15pts with BPH refractory to medical tx. Mean f/u 8 months, IPSS $\downarrow$ 6.5, QoL $\downarrow$ mean 1.14, and prostatic volume $\downarrow$ 27%. One complication of bladder wall ischemia.

2013: Prospective study of 255 pts with BPH and mod-sev LUTS refractory to 6 months medical tx. Technical success in 98% pts, clinical success rate of 72% at 36 months.
PAE Origin

Merit Medical's Embosphere® Microspheres Receive FDA 513(f)(2) (de novo) Classification for Prostatic Artery Embolization Indication

SOUTH JORDAN, Utah, June 22, 2017 (GLOBE NEWSWIRE) -- Merit Medical Systems, Inc. (NASDAQ:MMSI), a leading manufacturer and marketer of proprietary disposable devices used in interventional, diagnostic and therapeutic procedures, particularly in cardiology, radiology and endoscopy, today announced that it has received 513(f)(2) (de novo) classification from the FDA to expand indication for Merit’s Embosphere® Microspheres. The indication now includes prostatic artery embolization (PAE) for symptomatic benign prostatic hyperplasia (BPH).

“Merit’s Embosphere is the first embolic agent to receive FDA 513(f)(2) classification for prostatic artery embolization, providing a non-surgical treatment option for millions of men who suffer from BPH,” said Fred P. Lampropoulos, Merit’s Chairman and Chief Executive Officer.

BPH is an enlarged prostatic gland and can cause lower urinary tract symptoms for more than half of all men in their 60s and as many as 90% of men over age 70.¹ The PAE procedure is performed through a tiny incision in the patient’s upper thigh or wrist, and uses Embosphere Microspheres to occlude the prostatic arteries, reducing their blood supply and causing the prostate to shrink and improve symptoms.

Minimally invasive, outpatient treatment option for men with hematuria and/or LUTS due to BPH
PAE Indications

Patient selection:

- Non-surgical candidates
  - Refusal of surgery
  - Medical co-morbidities
  - Prostate gland size, greater than 100-150 mL’s
- Failure of medical therapy
  - Refractory symptoms despite drug regimen
  - Limited compliance or refusal due to side-effects
  - Contraindication to medical therapy
PAE Indications

Patient selection:
- **LUTS**
  - IPSS >12 -18 and/or QoL score ≥3
- Prostate volume > 40cm$^3$
  - “Larger the better”
- **Urodynamics**
  - Qmax <12-15 mL/s
  - Acute urinary retention
- **Catheter dependent pts**
  - Foley or suprapubic tube
- **Hematuria**
  - Inability to tolerate anticoagulation
PAE Contraindications

Ineligible Patients:
- LUTS not due to BPH
- Active infection
  - Chronic UTI
  - Prostatitis
- Prior pelvic radiation
- Renal failure
  - CO₂ as alternative to contrast material
- Neurogenic bladder
Pre-Procedure Work-Up

Interventional Radiology Consultation:
- H&P
- Review of LUTS and/or hematuria
- Evaluation of Cr, coagulation parameters, etc.

Imaging Evaluation:
- Transrectal US or Prostate MRI
  - Determine size
- Optional pre-procedure CTA
  - Sublingual NTG with monitoring by Radiology Nursing staff
  - Determine arterial supply of prostate gland
  - 3D reformatted images for pre-procedural planning
Pre-Procedure Work-Up

Urologic Evaluation:
- Overall eligibility
  - Initial referral to Interventional Radiology
- PSA
  - If abnormal, cancer workup to be performed
- Urodynamic testing
- Medical therapy optimization

TEAM APPROACH to achieve best results for each individual patient
PAE Procedure

Pre-Procedural/Intra-procedural Care:

- Same-day, outpatient procedure
- Antibiotic prophylaxis
  - Cipro IV 400mg
- Anti-inflammatory prophylaxis
  - Dexamethasone 8mg IV
- Conscious sedation
  - Versed and Fentanyl
  - Intra-procedural Toradol, 30mg IV
- Foley catheter placement
  - Removed post-procedure if not catheter dependent
PAE Procedure

Vascular access
PAE Procedure

Super-selective arterial catheterization
PAE Procedure

Super-selective arterial catheterization
PAE Procedure

Super-selective arterial catheterization

Complex pelvic arterial anatomy & collateral arterial arcades supplying bladder, rectum and penis
PAE Procedure

Particle embolization +/- coil embolization
Emboshperes® microspheres composed of trisacryl monomer and porcine gelatin

Highly consistent sphere size

Reliability of vascular occlusion level – Stop blood flow at level of pre-capillary arterioles

Smooth hydrophilic surface
PAE Procedure

Procedural outcome

Constricted Urethra from Enlarged Prostate

Post-Embolization Prostate
PAE Procedure

Post-procedural care:

- Post-PAE Syndrome x 3-5 days
  - Pelvic burning
  - Dysuria
  - Increased urinary frequency

- Pharmacologic management
  - Cipro BID for 7 days
  - Medrol DosePak
  - Motrin prn
  - Pyridium prn
90 yo M with h/o hematuria and multiple prior episodes of urinary retention; IPSS 30 and QoL 6
Patient Example #2

84 yo M in acute urinary retention and with a left common iliac artery aneurysm; 147 mL gland
Patient Example #2

In 5 weeks,
147 mL to 102 mL
Patient Example #3

91 yo M with h/o urinary retention due to BPH; IPSS 27

Initial gland volume 221 mL, at approx 3 months 120 mL
Clinical Outcomes

Short- to Midterm Safety and Efficacy of Prostatic Artery Embolization: A Systematic Review

Ziga Cizman, MD, MPH, Ari Isaacson, MD, and Charles Burke, MD

http://dx.doi.org/10.1016/j.jvir.2016.04.015

ABSTRACT

**Purpose:** To review the available safety and efficacy data for prostatic artery embolization (PAE) in the treatment of benign prostatic hyperplasia (BPH).

**Materials and Methods:** PubMed was searched for publications that included PAE for the treatment of BPH through May 2015. Two independent reviewers determined the appropriateness for inclusion of each article and compiled data by using pooled weighted means and standard deviations.

**Results:** The literature search identified 161 articles, of which 7 studies, with a total of 562 patients, met all inclusion/exclusion criteria. PAEs were performed bilaterally in 85% of patients, unilaterally in 12%, and unsuccessfully in 3%. International Prostate Symptom Score decreased from 24.51 ± 6.12 at baseline to 10.42 ± 5.39 at 6 months. Quality of life score decreased from 4.76 ± 0.98 at baseline to 2.51 ± 1.13 at 6 months. Peak urinary flow rate increased from 8.41 mL/s ± 2.63 at baseline to 15.44 mL/s ± 5.64 at 6 months. Postvoid residual measurement decreased from 105.94 mL ± 76.77 at baseline to 39.57 mL ± 15 at 6 months. Prostate-specific antigen level decreased from 4.79 ng/mL ± 5.42 at baseline to 3.16 ng/mL ± 1.5 at 6 months. None of these parameters showed clinically significant changes from 6 months to 12 months. Total prostate volume decreased from 96.56 cm³ ± 35.47 at baseline to 46.73 cm³ ± 20.51 at 12 months. There were 200 minor complications and 1 major complication.

**Conclusions:** PAE improves lower urinary tract symptoms caused by BPH, with a favorable short- to midterm safety profile.
Clinical Outcomes

Patient Outcomes:

- Technical success
  - Bilateral embolization performed in 85% pts
  - Unilateral embolization performed in 12% pts
  - Inability to embolize in 3% pts
    - Atherosclerotic disease, vascular occlusion/tortuosity
  - Technical failure rate of 15%

- Post-procedure admission
  - Up to 84% pts discharged within 24 hrs of procedure
  - Average length of stay if admitted, 3 days
Clinical Outcomes

Blood loss requiring transfusion, bladder incontinence and erectile dysfunction NOT reported with PAE

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>46 (8.19)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>25 (4.45)</td>
</tr>
<tr>
<td>Hematospermia</td>
<td>23 (4.09)</td>
</tr>
<tr>
<td>Urethral burning</td>
<td>19 (3.38)</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>17 (3.02)</td>
</tr>
<tr>
<td>UTI*</td>
<td>5 (0.89)</td>
</tr>
<tr>
<td>Balanitis</td>
<td>4 (0.71)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>4 (0.71)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (0.53)</td>
</tr>
<tr>
<td>Dissection</td>
<td>1 (0.18)</td>
</tr>
<tr>
<td>Grade B</td>
<td></td>
</tr>
<tr>
<td>Acute urinary retention</td>
<td>51 (9.07)</td>
</tr>
<tr>
<td>Nontarget embolization</td>
<td>1 (0.18)</td>
</tr>
<tr>
<td>UTI</td>
<td>1 (0.18)</td>
</tr>
<tr>
<td>Grade C</td>
<td>0</td>
</tr>
<tr>
<td>Grade D</td>
<td></td>
</tr>
<tr>
<td>Nontarget embolization</td>
<td>1 (0.18)</td>
</tr>
<tr>
<td>Grade E</td>
<td>0</td>
</tr>
<tr>
<td>Grade F</td>
<td>0</td>
</tr>
</tbody>
</table>

Note—Values in parentheses are percentages. SIR = Society of Interventional Radiology; UTI = urinary tract infection. * Calculation excludes preexisting UTIs (confirmed by culture) found in 14 of 19 patients in the study of Pisco et al (11).
Clinical Outcomes

Clinical results:
- Clinical success in 88% pts
  - 12% clinical failure
    - LUTS medical therapy failure rate, 7.3-17.1%
    - TURP repeat intervention rate at 5 yrs, 8.9-9.7%
    - Equivalent repeat intervention rate at 1 yr for transurethral vaporization, laser resection and thermal ablation
Clinical Outcomes

Clinical results:
- 6 months post PAE
  - Mean IPSS decreased from 25 ± 6 → 10 ± 5
    - At 12 months, 59% reduction
  - QOL Score decreased from 5 ± 1 → 2.5 ± 1
    - At 12 months, 56% reduction
  - Qmax increased from 8 ± 3 → 15 ± 6 mL/s
    - At 12 months, 91% increase
  - PVR decreased from 106 ± 77 → 40 ± 15 mL
  - TPV decreased from 100 ± 35 → 63 ± 28 cm³
    - At 12 months, down to 47 ± 21 cm³
  - No change in IIEF-5 score
    - At 12 months, no change

No reported ejaculatory dysfunction, even at 12 months.
Clinical Outcomes

Long-term results:

- 6 months post PAE
  - Mean IPSS decreased from 25 ± 6 → 10 ± 5
    - At 12 months, 59% reduction
  - QOL Score decreased from 5 ± 1 → 2.5 ± 1
    - At 12 months, 56% reduction
  - Qmax increased from 8 ± 3 → 15 ± 6 mL/s
    - At 12 months, 91% increase
  - PVR decreased from 106 ± 77 → 40 ± 15 mL
  - TPV decreased from 100 ± 35 → 63 ± 28 cm³
    - At 12 months, down to 47 ± 21 cm³
  - No change in IIEF-5 score
    - At 12 months, no change
Clinical Outcomes

Pisco et al 2016:
- Largest cohort of pts, 630, with at least 6 month f/u
  - Prostate volume and PVR improved significantly (P<0.0001)
  - Clinical success
    - IPSS ≤ 15 or 25% decrease
    - QOL Score ≤ 3 or decrease of at least 1 point
      - At 3, 6, 12, 24, 48 and 78 months, clinical success rates of 90%, 88%, 85%, 82%, 81% and 76%

<table>
<thead>
<tr>
<th>F/U Duration</th>
<th>Mean IPSS Improvement</th>
<th>QOL Improvement</th>
<th>Qmax Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term (12 months)</td>
<td>-13.7 ± 7.2</td>
<td>-1.9 ± 1.2</td>
<td>3.1ml/s ± 5.8</td>
</tr>
<tr>
<td>Medium-term (1-3 years)</td>
<td>-14.5 ± 7.4</td>
<td>-2.0 ± 1.2</td>
<td>4.1ml/s ± 11.3</td>
</tr>
<tr>
<td>Long-term (3-6.5 years)</td>
<td>-16.9 ± 8.7</td>
<td>-1.7 ± 1.5</td>
<td>8.0ml/s ± 4.8</td>
</tr>
</tbody>
</table>
Clinical Outcomes

Kuang et al Meta-Analysis 2017:

- 788 patients from literature
- Significant improvement in multiple parameters
  - Prostate volume
  - PVR
  - Qmax
    - Mean 8.3mL/s to 14.3, 15.9 and 16.9 at 6, 12 and 24 months
  - IPSS
    - Mean 23.8 to 10.9, 9.3, and 8.9 at 6, 12 and 24 months (P<0.001)
  - QoL
    - Mean 4.6 to 2.5, 2.1, and 2.4 at 6, 12 and 24 months (P<0.001)
Gao et al RCT of PAE vs TURP:

- 114 pts, PAE (n=57) and TURP (n=57)
- TURP
  - Significantly better improvement in IPSS, QoL, Qmax and PVR at 1 and 3 months
  - Prostatic tissue must undergo necrosis and remodeling s/p PAE
- At 6 months, treatments equivalent
- Remain equivalent at 12 and 24 months
Clinical Outcomes

- TURP and Photoselective vaporization
  - Adverse sexual effects
    - Retrograde ejaculation or erectile dysfunction
- PAE successfully performed in 50/53 pts
  - SHIM Score at baseline, 1 and 3 months – 13.3, 13.5 and 16.2
  - At 3 months, 64% had improvement, 16% no change and 20% negative change
    - Change at 3 months, average +2.9, statistically significant
    - No new onset retrograde ejaculation
### Sexual Health Inventory For Men (SHIM)

**Instructions**
Each question has 5 possible responses. Circle the number that best describes your own situation. Select only 1 answer for each question.

**Over the past 6 months:**

1. How do you rate your confidence that you could keep an erection?
   - 1 Very low
   - 2 Low
   - 3 Moderate
   - 4 High
   - 5 Very high

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?
   - 1 Almost never or never
   - 2 A few times (much less than half the time)
   - 3 Sometimes (about half the time)
   - 4 Most times (much more than half the time)
   - 5 Almost always or always

3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
   - 1 Almost never or never
   - 2 A few times (much less than half the time)
   - 3 Sometimes (about half the time)
   - 4 Most times (much more than half the time)
   - 5 Almost always or always

4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
   - 1 Extremely difficult
   - 2 Very difficult
   - 3 Difficult
   - 4 Slightly difficult
   - 5 Not difficult

5. When you attempted sexual intercourse, how often was it satisfactory for you?
   - 1 Almost never or never
   - 2 A few times (much less than half the time)
   - 3 Sometimes (about half the time)
   - 4 Most times (much more than half the time)
   - 5 Almost always or always

---

Here are the results based on the SHIM scores:
- **22-25** No ED
- **17-21** Mild ED
- **12-16** Mild-to-moderate ED
- **8-11** Moderate ED
- **5-7** Severe ED
Clinical Outcomes

- **Mean IPSS**
  - Baseline, 1 and 3 months – 25.8, 8.8 and 7.4
- **QoL**
  - Baseline, 1 and 3 months – 4.9, 1.8 and 1.3
- **PV**
  - Baseline and 3 months – 110g and 71g
- **Complications**
  - Urosepsis tx with IV antibiotics

Prostate artery embolization may improve erectile function with no deleterious effect on ejaculation: a retrospective review of 53 patients

S Bhatia, S Tewari, C Gomez, B Kava, V Sinha and G Narayanan

PAE associated with statistically significant improvement in erectile function
Take-Home Points

- BPH is a common condition amongst aging men.
- Hematuria and LUTS due to BPH may be successfully treated with PAE.
- PAE is a safe, minimally invasive treatment option.
  - Acceptable side effect profile.
  - No resultant erectile dysfunction.
  - Enables patients to tolerate anticoagulation.
- Future applications are promising.
  - Possible chemotherapy/radiotherapy-augmented embolization in treatment of prostate cancer.
Additional Sources


Thank You

Special thanks to my Interventional Technologists & Nursing Staff