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New Frontiers in Embolization

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KEYWORDS
• Prostate artery embolization • Geniculate artery embolization • Knee • Osteoarthritis • Pain • BPH

KEY POINTS
- Prostatic artery embolization is a procedure with a growing level of scientific evidence to support its use in patients with benign prostatic hyperplasia.
- Osteoarthritis-related knee pain is thought to result in synovial hypervascularity that originates from early inflammatory changes in the knee joint.
- Geniculate artery embolization offers promise as a novel procedure to help patients with knee pain.

GENICULATE ARTERY EMBOLIZATION

Knee osteoarthritis (OA) affects more than 30 million Americans, with pain being the hallmark symptom. Pain management is the mainstay of treatment for most patients, as most are not yet candidates for knee replacement surgery. There are mixed success rates with pharmacologic therapies, and relatively high morbidity and mortality associated with these therapies. Nonsteroidal anti-inflammatory medications (NSAIDs) are associated with side effects, including gastrointestinal (GI) bleeding, renal toxicity, and bronchospasm. Specifically, there are more than 100,000 annual hospitalizations annually related to GI toxicity from NSAIDs alone. The number of deaths from NSAID-related GI bleeding has been estimated at 16,500 [1].

Opioid medications, which are also commonly used for knee-OA–related pain, are chemically addictive and cause harmful side effects, including constipation, decreased mental awareness, and nausea. Nonsurgical treatments for knee OA pain, such as corticosteroid and hyaluronic acid injections, have not demonstrated consistent efficacy in clinical trials. Given these limitations, there remains a need for a minimally invasive, durable therapy that can relieve pain and delay total knee arthroplasty (TKA) in younger patients.

Although OA has traditionally been thought of as a degenerative disease related to chronic repetitive injury, it now well accepted that there is an underlying low-grade inflammatory process. This inflammation leads to an increase in angiogenesis through the release of growth factors such as vascular endothelial growth factor (VEGF) [2,3]. Angiogenesis has further been implicated as a contributor to the formation of osteophytes, cartilage breakdown, and an increase in knee pain. This increase in synovial vascularity has been the focus of multiple recent studies evaluating the use of geniculate artery embolization (GAE) of this hypervascular tissue [4,5].

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Particulate embolization of geniculate artery branches supplying hypervascular joint tissue has been previously described as a safe treatment for hemorrhage after TKA in multiple reports [6–9]. In a series of 13 cases, with a mean follow-up of 24 months, there was a >90% success in treating hemarthrosis with spherical embolics [8]. Finally, in 2016 a fourth report of 14 embolization procedures was published in which there were no major complications and 2 minor complications (transient cutaneous ischemia) [7].

Embolization of hypervascular joint tissue for the treatment of pain has been pioneered by Dr Okuno and his colleagues [10] in Japan. They initially reported a case series in which they were able to reduce pain related to refractory tendinopathy and enthesopathy in multiple joints in 7 patients using an antibiotic particulate for embolization without major complication [10]. Subsequently, the same team published its experience with transcatheter embolization of hypervascular tissue within the shoulder joint in 7 patients diagnosed with adhesive capsulitis. The procedure successfully resulted in pain reduction without significant complications [11].

In 2015, Okuno and colleagues [4] also published their pilot study using synovial embolization in patients with painful knee OA. The procedure was performed on 14 patients with no major complications. There was significant pain reduction and decreased difficulty of movement at 4 months after embolization. Medication frequency also decreased after embolization. Most recently, the same group [5] published a larger cohort of 72 patients with midterm follow-up. GAE was technically successful in all patients and was clinically successful in 86.3% of patients at 6 months and 79.8% at 3 years. Clinical success was defined as $\geq$50% decrease in pain from baseline. Magnetic resonance imaging follow-up demonstrated no osteonecrosis or other evidence of progression of degenerative changes at 2 years post-GAE. Within the United States, preliminary data from a multicenter pilot study demonstrated improvement in pain and function of 13 patients who underwent GAE with permanent embolic agents, and the same team is conducting a randomized placebo-controlled study currently (Fig. 1).

GAE is a unique treatment option, with promising results, for improving pain and disability related to OA. Although the rationale is intriguing, there are unanswered questions at this time. The role of placebo in any palliative procedure must be evaluated. Other outstanding questions center around the optimal embolic agent, embolic endpoints, and the role of potential reintervention. With the increasing obesity prevalence in the United States, and the rise in patients with knee OA, as well as the increased risk of surgery in this population, early studies are promising that GAE may play a role in reducing the pain and disability associated with OA, while potentially

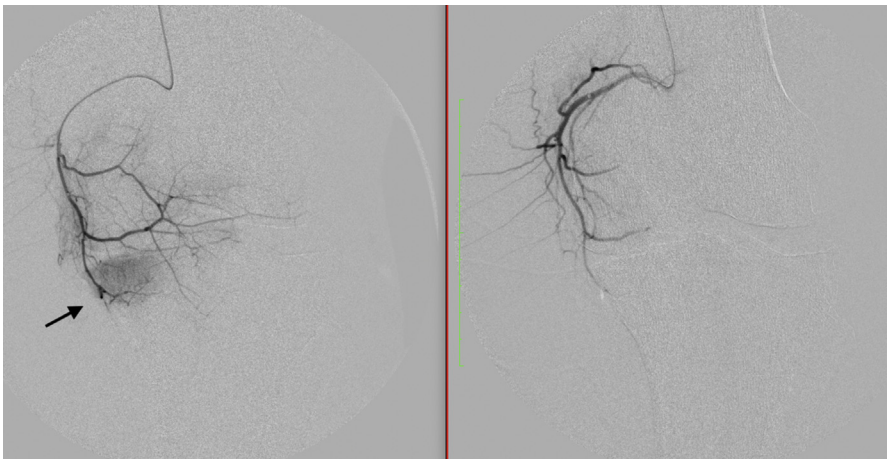

FIG. 1 Digital subtraction angiography of the left knee in a patient with OA and medial knee pain. Selective catheterization of the superior medial genicular artery demonstrating extensive "tumor blush" vascularity of the medial knee synovium and overlying the medial tibial plateau. Image after embolization with microspheres demonstrating the pruning of the distal abnormal vasculature, with maintained patency of the parent genicular artery.

targeting the cause of inflammation in the degenerating knee joint.

PROSTATE ARTERY EMBOLIZATION

Prostatic artery embolization (PAE) is a minimally invasive procedure to treat lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). Historically, selective catheterization of the prostatic artery was used only to treat hematuria of prostatic origin. In 2000, a case report described improvement of LUTS after PAE for hematuria [12]. This observation spurred on numerous investigations throughout the world that has led to PAE now being used routinely to treat BPH.

PAE involves selective catheterization of the artery supplying the central prostate gland, a branch of the inferior vesical artery (Fig. 2). Embolization is then performed with particles ranging in size from less than 100 μm to 500 μm. Subsequent ischemia or necrosis results in a reduction in prostatic volume of 20% to 50% [13,14]. There is also a softening of the prostate that is detectable on digital rectal examination. This is thought to be secondary to ischemic neurolysis of the alpha-adrenergic neurons innervating the smooth muscle within the prostate [15]. The procedure is most effective if bilateral central gland arteries are embolized [16]. Improvement of urinary symptoms is not immediate after the procedure, but is usually noted 1 to 3 weeks afterward. Average duration of clinical improvement is not well known at this time, but sustained improvement has been reported at 7.5 years [13].

Randomized trials comparing PAE with transurethral resection of the prostate (TURP), the gold standard surgical treatment for BPH, have shown PAE to be similar or inferior to TURP in reducing urinary symptoms. However, PAE has also proven safer with fewer major complications including sexual side effects, incontinence, and hemorrhage requiring transfusion [17–19]. PAE is performed without general anesthesia, providing a treatment option for patients with comorbidities preventing surgery. In addition, because of its minimally invasive nature, PAE can be safely performed on patients who cannot suspend anticoagulation medications or are coagulopathic. Finally, PAE has been shown to be effective on patients with very large volume prostates, for which surgical treatment options are limited [20].

A limitation of PAE is that it is a technically challenging procedure due to the complicated pelvic arterial anatomy and small caliber and tortuosity of the target vessels. Patients with advanced atherosclerotic disease are not good candidates due to the high probability of technical failure. Also, patients who have moderate to severe renal insufficiency have a higher chance of contrast-induced nephropathy secondary to the use of iodinated contrast material during PAE. Last, patients who have had prior internal iliac artery embolization,

FIG. 2 Digital subtraction angiography with selective catheterization of the right hypogastric artery in a patient with BPH. Note the prostatic artery (*dashed arrow*) originating from the pudendal artery and crossing to the midline. Second image after microcatheter selection of the prostatic artery (*white arrow*) demonstrates classic appearance of prostatic parenchyma with microvascularity tortuosity and delayed washout, outlining the shape of the right hemi-prostate. Nontarget collateral to the rectum is noted (*black solid arrow*). This vessel should be excluded with either distal catheterization of the PA, or coil embolization of the collateral to minimize nontarget sequelae.

commonly used during endovascular repair of the aorta, also would not be good candidates because of the inability to access the prostatic artery.

There are still questions regarding PAE that require further investigation. One of the most controversial is the optimal particle size for treatment. In general, during embolization, smaller particles tend to result in increased necrosis, an outcome that might be favorable in PAE. However, an early comparison demonstrated that when smaller particles were used for PAE, there were more minor complications without increased efficacy [21]. Since this report, conflicting data have been published demonstrating improved efficacy with the combination of smaller particles and large particles compared with larger particles alone [14]. Additional procedural elements that lack a consensus opinion among operators include the optimal microcatheter position for initial embolization, the necessity to embolize the capsular branch of the prostate artery, the management of extraprostatic arterial anastomoses, and the role of balloon-occlusion embolization.

The most recently studied application of PAE is the treatment of prostate cancer. Still in early clinical investigation, bland embolization has been ineffective in eradicating cancer from the prostate altogether, but has demonstrated the ability to completely treat individual lesions in several cases [22]. A single report using chemoembolization has demonstrated more promise. A sustained biochemical response was seen in 62% of patients at 1-year follow-up [23]. There are still many questions that need to be answered with regard to PAE for the treatment of cancer, including where in the treatment algorithm embolization may fit, what are the most effective chemotherapeutic agents to use during embolization, and if selective internal radiation therapy (radioembolization) may play a role.

In summary, PAE is an additional treatment option for men suffering from LUTS secondary to BPH. It specifically is beneficial for patients who are concerned about preserving sexual function or who have comorbidities that prevent surgery. It is a technically challenging procedure with a steep learning curve. Despite the Food and Drug Administration granting indications for the treatment of BPH to multiple embolic particles, PAE is still struggling to gain wide acceptance within the American urology community. In contrast, it has been added to the BPH standard of care treatment algorithm in the United Kingdom [24]. The next frontier for PAE is the treatment of cancer, with clinical investigation under way.

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