

Embolization for Osteoarthritis and Other Pain Relief Applications

Early reports on the progress of research in applying embolization to provide relief for resistant chronic pain from musculoskeletal conditions.

BY YUJI OKUNO, MD

Musculoskeletal disorders are common and can cause severe chronic pain and disability, leading to a significant socioeconomic burden. Despite the large number of patients affected by these conditions, the source of pain remains unclear, and a significant number of patients are resistant to conventional therapies. Studies have shown that angiogenesis may contribute to chronic pain by enabling growth of new unmyelinated sensory nerves along their path¹; these two phenomena are closely related. In fact, histopathological studies have demonstrated the existence of abnormal neovessels with accompanying nerve fibers in tissues from various painful conditions including osteoarthritis,² frozen shoulder,³ and overuse injuries such as tendinopathy and enthesopathy.⁴ In addition, angiogenesis is believed to contribute to the genesis of inflammation (and to its maintenance), and some researchers have demonstrated that pharmacological inhibition of angiogenesis could lead to improvement of inflammation and pain behavior in experimental animal models.⁵

With the advent of new interventional technologies and skills, embolization of small abnormal neovessels has become possible and appears to be a potential method for treating chronic pain in musculoskeletal conditions. We have previously reported the results of transarterial embolotherapy in patients with refractory tendinopathy and enthesopathy,⁶ frozen shoulder,⁷ and moderate knee osteoarthritis,⁸ as well as various other conditions that have not yet been reported. In

this article, we summarize our experiences to date (Table 1).

PATIENT COHORTS

In our experience, all patients have presented with chronic pain refractory to conventional therapies for at least 3 months. Nighttime pain was a specific symptom that was studied for shoulder adhesive capsulitis. All patients received complete information about available treatments and the potential risks, benefits, and out-

TABLE 1. RESISTANT PAINFUL MUSCULOSKELETAL CONDITIONS TREATED WITH EMBOLOTHERAPY

Disorders	Number of Cases Performed
Musculoskeletal shoulder pain (frozen shoulder, etc.)	75
Tendinopathy and enthesopathy	55
Mild, moderate, and severe knee osteoarthritis	25
Sports injuries (including national professional players)	20
Persistent pain after arthroscopic surgery	10
Persistent pain after joint replacement surgery	10

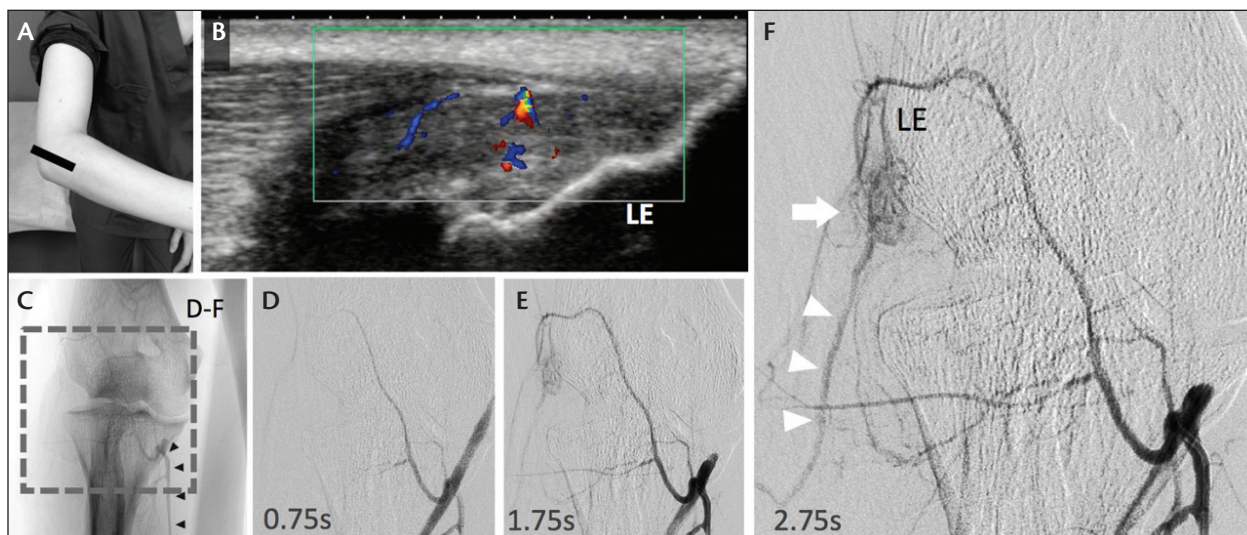


Figure 1. A 45-year-old man presented at the clinic with a diagnosis of lateral epicondylitis and a 6-month history of right elbow pain. Ultrasonography of the painful site (black line, A) demonstrated abnormal color Doppler signals within his entheses (B). An angiographic catheter (black arrowheads, C) was inserted to the radial recurrent artery in this patient. Angiographic series at each time point (D–F) demonstrated the abnormal neovessels (white arrow, F) and early venous drainage (white arrowheads, F). LE = lateral epicondyle.

comes of transarterial embolotherapy as an alternative treatment option. Exclusion criteria were local infection, malignancy, advanced atherosclerosis, rheumatoid arthritis, and previous surgery.

In our experience, patients with spontaneous pain, such as rest pain or nighttime pain, frequently had abnormal vessels (as seen on angiography) located in the painful area and appeared to be good candidates for embolotherapy. We have also noticed that local tenderness during physical examination is a good indicator of the existence of abnormal neovessels and thus is a sign suggesting that embolotherapy could be a suitable option.

Diagnostic imaging also contributes to proper patient selection. Abnormal hypervascularization can be seen on Doppler ultrasound and magnetic resonance imaging; this abnormal vascularization appears as high signal intensity in fluid-sensitive sequences, such as STIR (short tau inversion recovery), and as an enhancement after paramagnetic contrast agent administration (gadolinium). As an example, synovial inflammation in knee osteoarthritis will appear as a thickened and enhanced synovial layer on magnetic resonance imaging.

EMBOLIZATION PROCEDURAL CONSIDERATIONS

Arterial Access

Radial artery access is selected for elbow or shoulder procedures, and femoral artery access is used in an ipsi-

lateral anterograde fashion when we target knee and foot joints. We use a 3- or 4-F catheter system.

Diagnostic Imaging

In our previous studies, neovascularization at the site of pain was clearly visible on digital subtraction angiography. Abnormal neovessels were excessive, disorganized, and contained arteriovenous shunts, according to the findings of early venous drainage (Figure 1).

Embolic Material

We use two types of embolic materials: imipenem/cilastatin sodium (IPM/CS) and calibrated microspheres. IPM/CS has been approved by the US Food and Drug Administration as an antibiotic, is slightly soluble in water, and when suspended in contrast agent, forms 10- to 70- μ m particles that exert an embolic effect.⁹ A suspension of 0.5 g of IPM/CS in 5 mL of iodinated contrast agent is prepared by pumping syringes for 10 seconds and injected in 0.2-mL increments until blood flow stagnates. We have also introduced small-sized (75 μ m) and well-calibrated microspheres as embolic agents.⁸

ONGOING RESEARCH

Currently, we have published on a series of transcatheter arterial embolization cases in three refractory painful conditions: knee osteoarthritis, frozen shoulder (adhesive capsulitis), and tendinopathy/enthesopathy.

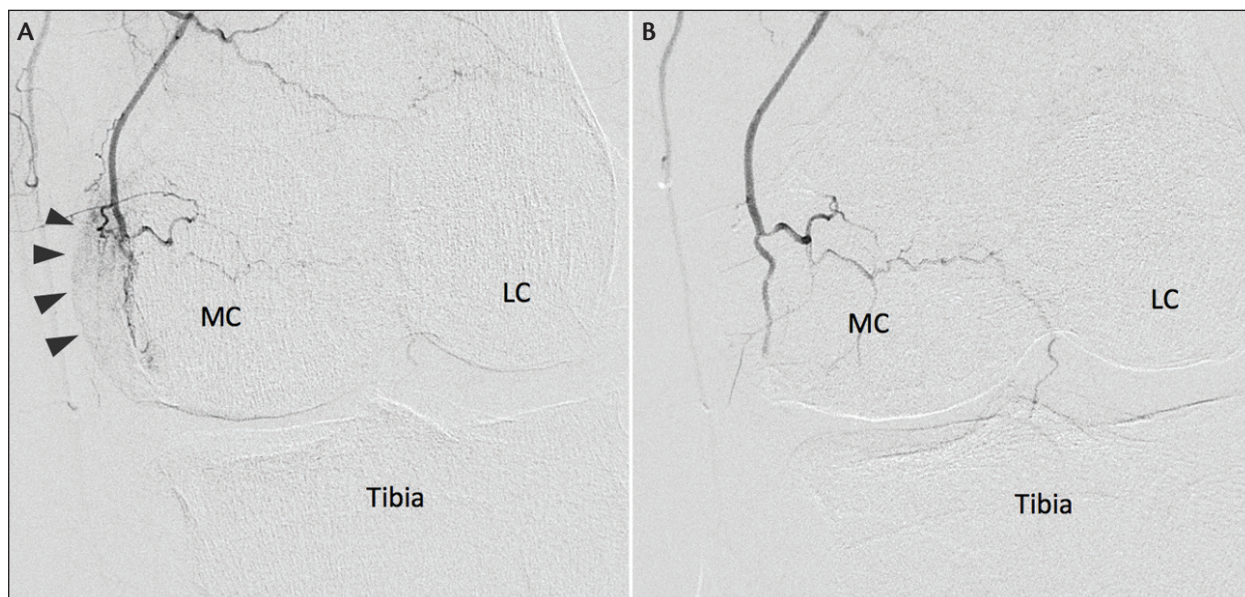


Figure 2. Angiographic findings before (A) and after (B) transcatheter arterial embolization in a 61-year-old woman with moderate medial knee osteoarthritis. Selective angiography from the descending genicular artery before embolization shows abnormal neovessels (black arrowheads) adjacent to the medial condyle (A). A postembolization angiogram shows elimination of this abnormal angiogenesis (B). LC = lateral condyle, MC = medial condyle.

Knee Osteoarthritis

Knee osteoarthritis is a major source of pain and disability in the aging population. Minor symptoms can be managed with pain relievers, and severe and end-stage osteoarthritis can be treated with total joint arthroplasty. However, moderate arthritis that is resistant to nonsurgical options and is not severe enough to warrant joint replacement surgery represents a challenge in its management.

In our study,⁸ patients with mild or minimal degenerative changes and severe symptoms experienced significant relief after undergoing embolization treatment. In addition, excellent pain relief was seen in patients with moderate degenerative changes (Figure 2). These findings indicate that pain in osteoarthritis does not necessarily come from the degenerative site nor cartilage loss. Angiographic findings in this study showed abnormal neovessels within several periarticular soft tissues including the synovium and periosteum around the medial condyle, the infrapatellar fat pad, the medial meniscus base, and the medial side of the joint capsule. From our experience, there were two distinct time points when pain and symptoms improved. One is soon after embolization (patients stated that their tenderness decreased a few minutes after infusing the IPM/CS suspension or 75- μ m calibrated microspheres), and the other occurs later (ie, several weeks or months after embolization).

Frozen Shoulder (Adhesive Capsulitis)

Frozen shoulder is a condition of uncertain etiology that is characterized by painful restriction of shoulder motion. It is a self-limiting disorder that usually resolves in the range of 1 to 3 years, but residual pain is one of the most important issues in its management. After nonsurgical treatment, 27% of patients had mild or moderate pain at 1.8 years of follow-up,¹⁰ and another study reported that 35% had residual pain at 7 years.¹¹ When conservative therapy is not effective, more-invasive approaches are sometimes required, such as capsular distention, manipulation under anesthesia, or arthroscopic capsular release. Nevertheless, a consensus has not been reached regarding the optimal treatment for adhesive capsulitis that is resistant to traditional conservative options.

Transcatheter arterial embolization using IPM/CS has been safely performed and has resulted in significant improvement in pain symptoms, range of motion, and shoulder function at short-term follow-up (Figures 3 and 4).⁷ At our center, we have performed transcatheter arterial embolization in 75 patients with musculoskeletal shoulder pain (including frozen shoulder but also other disorders). We have surveyed these patients regarding the time to pain relief after the procedure, as well as the time to recurrence of pain. The results of the surveys are presented in Figure 5.

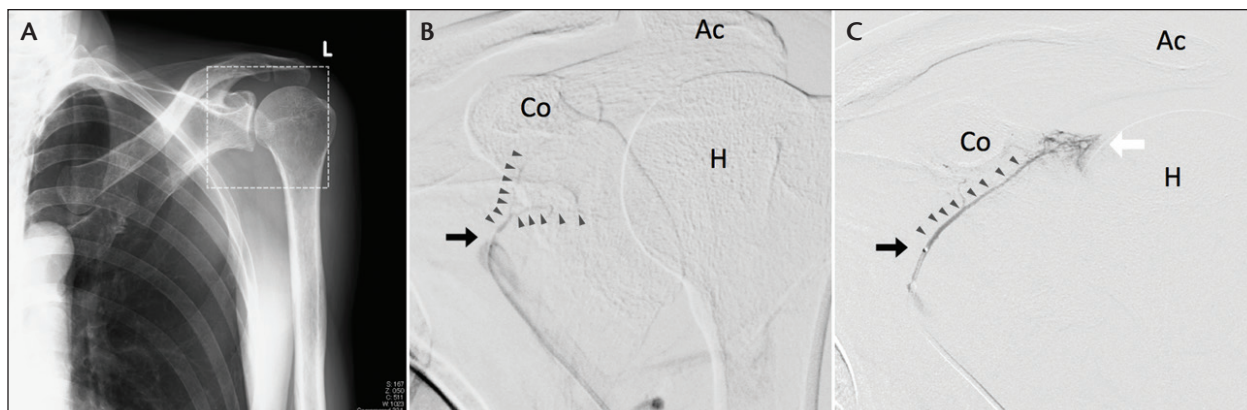


Figure 3. Panel A shows the angiographic region of interest. Angiographic findings of a direct branch from the axillary artery (black arrowheads) in a normal shoulder (B) and from a 50-year-old man with frozen shoulder (C) in which focal abnormal hypervascularization (white arrow) is clearly depictable. The black arrow shows the catheter tip. Ac = acromion, Co = coracoid, H = humeral head.

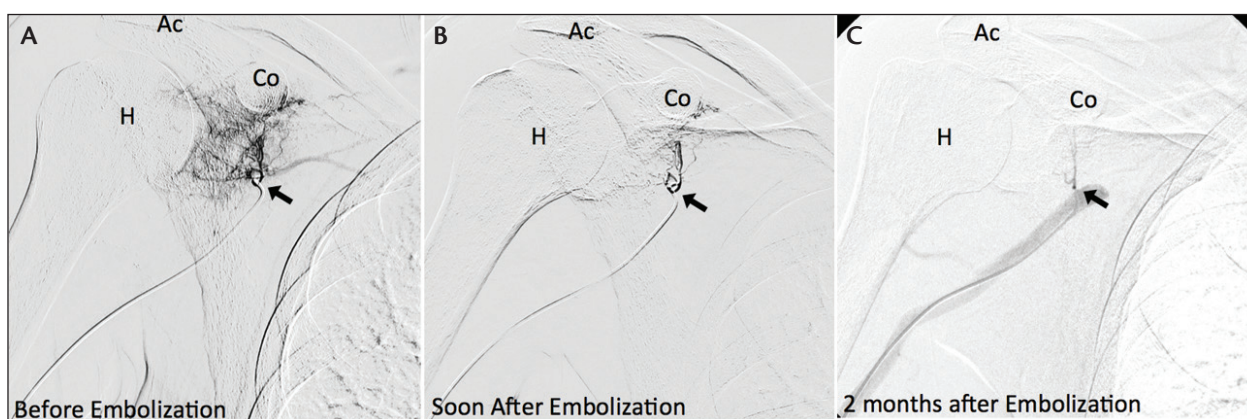


Figure 4. A 62-year-old man presented at the clinic with a 6-year history of severe pain in his right shoulder, which was worse at night. We performed embolotherapy, and his nighttime pain was relieved the same day. Angiographic findings of a direct branch from the right axillary artery before (A), soon after (B), and 2 months after (C) embolization. Abnormal neovessels were depicted at the anterior shoulder capsule by selective angiography (A). An angiogram 2 months after embolotherapy (C) shows elimination of abnormal hypervascularization. The black arrow shows the catheter tip. Ac = acromion, Co = coracoid, H = humeral head.

Tendinopathy and Enthesopathy

Normal adult human tendons and enthesis have relatively low vascularization due to the limited metabolic requirements, but they do have a well-organized network of blood vessels. In cases of tendinopathy and enthesopathy, our angiographic findings revealed disorganized hypervascularity with early venous drainage; this indicates the presence of arteriovenous shunts. We hypothesize that this increased abnormal blood flow with arteriovenous shunting might not contribute to tissue healing, as blood is shunted and probably does not reach the capillaries of tissues. This hypothesis is in agreement with the findings of Pufe et al indicating that increased vascularity might be involved in the

pathogenesis of tendinopathy.¹² From our previous experiences, more than 90% of patients with these various musculoskeletal conditions have demonstrated abnormal and disorganized vessels.

CONCLUSION

To date, we continue to perform embolotherapy for resistant painful musculoskeletal conditions. In our experience, this innovative endovascular approach to treating resistant musculoskeletal pain seems promising and could offer a new and effective option for pain control. It is obvious that the efficacy and safety profile of this new application of embolization should be studied on a larger scale and should be tested in

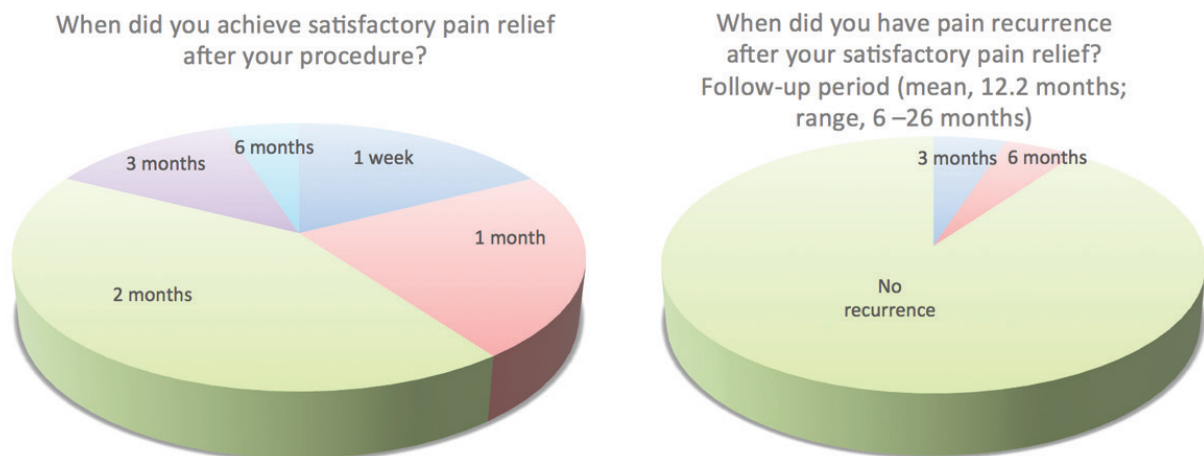


Figure 5. Graphs representing survey responses from patients regarding time to pain relief and pain recurrence postprocedure.

high-quality controlled trials to evaluate the true effectiveness of this procedure.

It is important to keep in mind that this procedure remains more invasive than other routinely used minimally invasive treatments for pain control, and thus its added value in pain management must be rigorously proven. The limitations of our experience include the small number of patients treated for each of a wide variety of disorders, and that we do not have a control group. However, to date, our work represents a solid proof of concept and a sound basis for further studies. ■

Yuji Okuno, MD, is Director of Musculoskeletal Intervention Center at Edogawa Hospital in Tokyo, Japan. He has disclosed that he has no financial interests related to this article. Dr. Okuno may be reached at okuno@edogawa.or.jp.

1. Mapp PI, Walsh DA. Mechanisms and targets of angiogenesis and nerve growth in osteoarthritis. *Nat Rev Rheumatol*. 2012;8:390-398.
2. Walsh DA, Bonnet CS, Turner EL, et al. Angiogenesis in the synovium and at the osteochondral junction in osteoarthritis. *Osteoarthr Cartil*. 2007;15:743-751.
3. Xu Y, Bonar F, Murrell GA. Enhanced expression of neuronal proteins in idiopathic frozen shoulder. *J Shoulder Elbow Surg*. 2012;21:1391-1397.
4. Alfredson H, Ohberg L, Forsgren S. Is vasculo-neural ingrowth the cause of pain in chronic Achilles tendinosis? An investigation using ultrasonography and colour Doppler, immunohistochemistry, and diagnostic injections. *Knee Surg Sports Traumatol Arthrosc*. 2003;11:334-338.
5. Ashraf S, Mapp PI, Walsh DA. Contributions of angiogenesis to inflammation, joint damage, and pain in a rat model of osteoarthritis. *Arthritis Rheum*. 2011;63:2700-2710.
6. Okuno Y, Matsumura N, Oguro S. Transcatheter arterial embolization using imipenem/cilastatin sodium for tendinopathy and enthesopathy refractory to nonsurgical management. *J Vasc Interv Radiol*. 2013;24:787-792.
7. Okuno Y, Oguro S, Iwamoto W, et al. Short-term results of transcatheter arterial embolization for abnormal neovessels in patients with adhesive capsulitis: a pilot study. *J Shoulder Elbow Surg*. 2014;23:e199-206.
8. Okuno Y, Korchi AM, Shinjo T, et al. Transcatheter arterial embolization as a treatment for medial knee pain in patients with mild to moderate osteoarthritis. *Cardiovasc Intervent Radiol*. 2015;38:336-343.
9. Woodhams R, Nishimaki H, Ogasawara G, et al. Imipenem/cilastatin sodium (IPM/CS) as an embolic agent for transcatheter arterial embolisation: a preliminary clinical study of gastrointestinal bleeding from neoplasms. *Springerplus*. 2013;2:344.
10. Griggs SM, Ahn A, Green A. Idiopathic adhesive capsulitis. A prospective functional outcome study of nonoperative treatment. *J Bone Joint Surg Am*. 2000;82-A:1398-1407.
11. Shaffer B, Tibone JE, Kerlan RK. Frozen shoulder. A long-term follow-up. *J Bone Joint Surg Am*. 1992;74:738-746.
12. Pufe T, Petersen WJ, Mentlein R, et al. The role of vasculature and angiogenesis for the pathogenesis of degenerative tendons disease. *Scand J Med Sci Sports*. 2005;15:211-222.