Short-term results of transcatheter arterial embolization for abnormal neovessels in patients with adhesive capsulitis: a pilot study

Yuji Okuno, MD, PhD, Sota Oguro, MD, PhD, Wataru Iwamoto, MD, Takeshi Miyamoto, MD, PhD, Hiroyasu Ikegami, MD, PhD, Noboru Matsumura, MD, PhD

*Department of Orthopedic Surgery, Edogawa Hospital, Tokyo, Japan
\(^b\)Department of Orthopedic Surgery, School of Medicine, Keio University, Tokyo, Japan
\(^c\)Department of Radiology, School of Medicine, Keio University, Tokyo, Japan
\(^d\)Institute for Integrated Sports Medicine, School of Medicine, Keio University, Tokyo, Japan
\(^e\)Department of Orthopaedic Surgery, Toho University (Ohashi), Tokyo, Japan

**Background:** Neovessels and accompanying nerves are possible sources of pain. We postulated that transcatheter arterial embolization of abnormal neovessels would relieve pain and symptoms in patients with adhesive capsulitis.

**Methods:** Adhesive capsulitis was treated by transcatheter arterial embolization in 7 patients. Adverse events, changes in visual analog scale scores for night pain and overall shoulder pain, and changes in range of motion and American Shoulder and Elbow Surgeons scores were assessed at 1 week and at 1, 3, and 6 months after the procedure.

**Results:** Abnormal neovessels were identified at the rotator interval in all patients. No major or minor adverse events were associated with the procedures. Transcatheter arterial embolization rapidly decreased nighttime pain scores from 67 ± 14 mm to 27 ± 14 mm at 1 week after the procedure, with further improvement at 1 and 6 months (6 ± 8 mm and 2 ± 5 mm, respectively). The American Shoulder and Elbow Surgeons score significantly improved from 17.8 ± 4.5 to 39.8 ± 12.0, 64.3 ± 13.9, and 76.2 ± 4.4 at 1, 3, and 6 months, respectively.

**Conclusion:** All patients with adhesive capsulitis had abnormal neovessels at the rotator interval. Transcatheter arterial embolization was feasible, relieved unrelenting pain, and restored shoulder function.

**Level of evidence:** Level IV, Case Series, Treatment Study.

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**Keywords:** Shoulder pain; adhesive capsulitis; abnormal vessels; embolization

Adhesive capsulitis is a condition of uncertain etiology that is characterized by painful restriction of active and passive shoulder motion. The estimated prevalence of adhesive capsulitis is 2% to 3% in the general population.

The Institutional Review Board of Edogawa Hospital approved this study (assigned study number 2012-07).

*Reprint requests: Yuji Okuno, MD, PhD, Department of Orthopedic Surgery, Edogawa Hospital, 2-24-18 Higashikoiwa, Edogawa-ku, Tokyo 133-0052, Japan.

E-mail address: how_lowlow@yahoo.co.jp (Y. Okuno).
and 5% to 6% in patients who have been evaluated by a shoulder surgeon.17

The overall objective of treating adhesive capsulitis is to relieve pain and restore motion. Treatment regimens for adhesive capsulitis begin with a trial of conservative therapy, including anti-inflammatory medications, injections, and physical therapy.18 However, residual pain is one of the most important issues in the treatment of adhesive capsulitis. After nonsurgical treatment, 27% of patients had mild or moderate pain at 1.8 years’ follow-up,14 and another study reported that 35% of patients had mild pain at 7 years.27 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 on the optimal treatment for adhesive capsulitis that is resistant to traditional conservative treatments.

Despite the large number of patients affected by adhesive capsulitis, the source of pain has not been defined. Many investigators have described hypervascularity at the rotator interval with adhesive capsulitis. Open surgery and arthroscopic observation have confirmed that angiogenesis most commonly affects the rotator interval.7,10,30,35 Some groups have histologically confirmed obviously increased vascularity in fibrotic tissues from the rotator interval of patients with adhesive capsulitis.10,28 Bunker and Anthony7 described 12 patients who did not have improvement after manipulation. The patients were treated by surgical release of the coracohumeral ligament, and this tissue was hypervascular in all of them. Ryu et al25 described more intense immunostaining for vascular endothelial growth factor and CD34 (general marker for blood vessels) in the synovium of the rotator interval in patients with diabetic adhesive capsulitis compared with a control group. They postulated that secreted vascular endothelial growth factor might induce adhesive capsulitis. However, the relationship between this abnormal vasculature and symptoms of adhesive capsulitis has not been investigated.

Abnormal neovessels and accompanying nerves are possible sources of pain. Alfredson and colleagues1,5 showed vascular/neural ingrowth in areas of pain associated with chronic painful tendinopathy and immunohistochemically identified substance P–positive nerves located near the newly formed blood vessels in tendinopathy tissue. Gotoh et al13 measured levels of substance P in the subacromial bursa of patients with rotator cuff disease and found that the amount of nerve fibers immunoreactive to substance P was increased around the vessels.

Transcatheter arterial embolization is used to occlude blood flow by intra-arterially infusing an embolic agent through a catheter located at target vessels. On the basis of the notion that increased numbers of blood vessels and accompanying nerves are a possible source of pain and that occlusion of abnormal vessels might reduce such pain, we previously applied transcatheter arterial embolization in patients with painful tendinopathy and enthesisopathy refractory to traditional nonsurgical management.21 We located abnormal neovessels at pathologic sites in all patients and showed that embolization of these abnormal vessels resulted in excellent pain relief.

We postulated that abnormal neovessels at the rotator interval play an important role in adhesive capsulitis and that transcatheter arterial embolization of such neovessels could relieve pain associated with this condition. Therefore, this study prospectively evaluated the feasibility and effectiveness of transcatheter arterial embolization in patients with adhesive capsulitis refractory to traditional nonsurgical management.

Materials and methods

This is a prospective study of transcatheter arterial embolization for patients with adhesive capsulitis resistant to conservative therapies. All patients received an explanation about various management modalities and the potential risks, benefits, and outcomes of transcatheter arterial embolization and then provided written informed consent to undergo the procedure. The criteria for inclusion included night shoulder pain; painful restriction of both active and passive elevation to less than 100° and of external rotation to less than 50° of the contralateral side; normal radiologic findings; previous conservative therapies comprising rest, anti-inflammatory drugs, corticosteroid injections, and physical therapy for at least 3 months; persistent moderate to severe pain (visual analog scale [VAS] >50 mm); and completion of a 6-month follow-up period. All patients were assessed by ultrasound or magnetic resonance examinations, and those with full-thickness rotator cuff tears were excluded. Other exclusion criteria included local infection, malignancy, advanced atherosclerosis, rheumatoid arthritis, and prior shoulder surgery. All patients in the final resolving stages were excluded. We enrolled 7 patients (5 women and 2 men; mean age, 50.3 ± 10.4 years; age range, 39-68 years) in this study. Table I shows the baseline patient demographic and clinical data. The mean duration of symptoms was 6.6 ± 3.4 months (range, 3-12 months). All patients had been receiving nonsurgical treatments for symptoms that had persisted for more than 3 months (Table I). All patients had preprocedural physical findings of tenderness at the coracoid process.

All subsequent techniques proceeded with the patients under local anesthesia. We gained arterial access percutaneously using a 3-French introducer sheath (Super Sheath; Medikit, Tokyo, Japan). We selected the radial and femoral arteries as puncture sites in 5 patients and 2 patients, respectively. After the intravenous administration of 2000 IU of heparin sodium (Mitsubishi Tanabe Pharma, Osaka, Japan), we inserted a 3-French angiographic catheter (Multipurpose; Medikit) toward the axillary artery and acquired images using an Allura Xper FD10 angiography system (Philips Healthcare, Best, The Netherlands). Digital subtraction angiography then proceeded by manual injection of 3 to 5 mL of iodinated contrast medium (Hexabrix; Terumo, Tokyo, Japan). We examined the suprascapular artery, thoracodorsal artery, and anterior circumflex humeral artery, as well as the direct branch from the axillary artery, in all patients. Normal blood vessels were defined as tubular anatomic structures in the expected distribution of the known vascular anatomy, as well as normal variants (Fig. 1, A). Small arterial branches are undetectable in the normal shoulder. Abnormal neovessels were defined as new periaricular smaller vessels if an additional arterial supply was derived from the normal arteries of the shoulder.29 After the abnormal
neovessels were located, a 2.4-French microcatheter (Meister Cass; Medikit) was inserted coaxially through the 3-French catheter and selectively placed in the targeted arteries. Imipenem (IPM) and cilastatin sodium (CS) were the embolic agents selected based on a previous report. These compounds are slightly soluble in water, and when suspended in contrast agent, they form particles that exert embolic effects. A suspension of 0.5 g of IPM-CS (Primaxin; Merck & Co, Whitehouse Station, NJ, USA) in 5 mL of iodinated contrast agent was prepared by pumping syringes for 10 seconds, and it was then injected in 0.2-mL increments until blood flow stagnated. Figures 1 to 3 show examples of digital subtraction angiography images. Hemostasis was achieved by manual compression for 10 minutes and rest for 2 hours after the procedure. We measured the amount of time required to complete the procedure starting from puncture access and ending after catheter removal. We also recorded the amount of time required to complete the fluoroscopic assessment and estimated the dose-area product (an indicator of the total x-ray energy absorbed by a patient measured by use of a transmission chamber that was integrated into our system). The patients were discharged on the same day with instructions regarding range-of-motion exercises.

All patients were reviewed at 1 week and at 1, 3, and 6 months after the embolization. We assessed the postprocedural occurrence of tissue necrosis, dermal ulcer, tendon or ligament rupture, peripheral paresthesia, and other complications and collected data regarding pain, range of motion, and function. We assessed overall pain and nighttime pain using the VAS score. Range of motion was documented with anterior elevation and external rotation. Changes in VAS score, range of motion, and American Shoulder and Elbow Surgeons (ASES) score were determined at study entry and at 1 week and 1, 3, and 6 months after the embolization.

All data were statistically analyzed by use of IBM SPSS Advanced Statistics software (version 20.0; IBM, Armonk, NY, USA). Baseline and outcome variables were compared by use of the Dunnett post hoc test to determine changes in VAS scores, ASES scores, and range-of-motion examination findings at each time point. P < .05 was considered to indicate a statistically significant difference.

Results

All procedures were performed successfully. The mean amounts of time required to complete the embolization and fluoroscopy were 35 ± 6 minutes (range, 29-45 minutes) and 9.8 ± 2.1 minutes (range, 8.2-13.3 minutes), respectively. The mean estimated dose-area product was 11.7 ± 1.2 Table 1

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Pain duration (mo)</th>
<th>Prior therapies</th>
<th>Targeted arteries</th>
<th>Embolic volume (mL)</th>
<th>Early venous drainage</th>
<th>Location of abnormal vessels</th>
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<td>39</td>
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<td>NSAIDs, CSI</td>
<td>Left TAA</td>
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<td>Evident</td>
<td>RI</td>
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<tr>
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<tr>
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<td>RI</td>
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<tr>
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<td>RI</td>
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<td>CSI, NSAIDs</td>
<td>Left TAA, SSA, ACHA, DB</td>
<td>1.6</td>
<td>Evident</td>
<td>Entire capsule</td>
</tr>
</tbody>
</table>

ACHA, Anterior circumflex humeral artery; CSI, corticosteroid injection; DB, direct branch from axillary artery; NSAIDs, nonsteroidal anti-inflammatory drugs; PT, physical therapy; RI, rotator interval; SSA, suprascapular artery; TAA, thoracoacromial artery.

Figure 1 Normal and abnormal vasculature of thoracoacromial artery. Angiographic findings of the left thoracoacromial artery are shown in a normal shoulder (A) and in a 39-year-old female patient with adhesive capsulitis in the left shoulder (B). (C) Abnormal neovessels are located at the rotator interval. Abnormal blood vessels (arrowhead) are located at the rotator interval. A, Acromion; C, coracoid; H, humeral head.
Gy/cm² (range, 10.1-13.1 Gy/cm²). No major or minor adverse events developed that were related to the procedures. Tissue necrosis, dermal ulcer, tendon or ligament rupture, or peripheral paresthesia did not arise in any embolized territory during the follow-up period.

Abnormal small vessels were evident at the sites of the rotator interval in all patients (Figs. 1-3). The main feeding artery was the thoracoacromial artery in 5 patients, and it arose directly from the axillary artery in 2 (Table I). Abnormal vessels were detected in the entire shoulder.
capsule, as well as in the rotator interval, in 1 patient (case 7). Early venous drainage was evident in 5 of 7 patients (Fig. 3, Table I).

The mean nighttime VAS score significantly improved from before embolization to 1 week, 1 month, 3 months, and 6 months after embolization (67±14 mm vs 27±14 mm, 6±8 mm, 2±6 mm, and 2±5 mm, respectively; all \( P < .001 \)) (Fig. 4). The mean overall VAS score also significantly decreased at 1 week (80±7 mm vs 53±23 mm, \( P = .014 \)) and at 1, 3, and 6 months (80±7 mm vs 28±19 mm, 14±12 mm, and 10±16 mm, respectively; all \( P < .001 \)) after embolization.

Compared with before embolization, the mean range of motion of anterior elevation increased at 1 week and at 1, 3, and 6 months (65°±19° vs 74°±15°, 99°±23°, 130°±35°, and 150°±28°, \( P < .001 \)) (Fig. 5, A). The mean range of motion of external rotation also increased at these time points compared with the pre-embolization values (9°±11° vs 11°±11°, 20°±8°, 44°±17°, and 59°±14°, \( P < .001 \)), respectively.

The ASES scores before embolization significantly improved at 1 week and at 1, 3, and 6 months (17.8±4.5 vs 24.5±12.0, 39.9±12.0, and 64.2±13.9, \( P < .001 \)), respectively (Fig. 5, B).

These improvements were maintained in all patients at the final follow-up examination at a mean of 10±3 months (range, 6-16 months).

**Discussion**

All patients with adhesive capsulitis had abnormal neo-vessels that were excessive and disorganized and contained arteriovenous shunts, according to the findings of early venous drainage. Thus, increased blood flow under these conditions does not necessarily distribute to peripheral tissues. Therefore, we considered that infused embolic agents would normalize the abnormal blood flow distribution. Transcatheter arterial embolization using IPM-CS was safely performed and resulted in significant improvements in pain symptoms, range of motion, and shoulder function at short-term follow-up.

Adhesive capsulitis involves abnormalities of the coracohumeral ligament and rotator interval. Zhao et al.\(^{34}\) found that the most characteristic magnetic resonance imaging findings in patients with adhesive capsulitis were thickening of the coracohumeral ligament and the capsule at the rotator interval and complete obliteration of the fat triangle under the coracoid process. Open surgical exploration has shown that the coracohumeral ligament is the most palpably thickened and abnormal part of the capsule.\(^{16,20,22}\) Arthroscopic studies also suggest that the rotator interval is the area most affected by angiogenesis.\(^{30,33}\) Berghs et al.\(^{4}\) reported findings of abundant angiogenesis, especially in the rotator interval area; they also found that arthroscopic excision of this area resulted in rapid pain relief. Our angiographic findings showed...
abnormal neovessels at the rotator interval and surrounding tissue, thought to be the fat triangle under the coracoid process, and transcatheter arterial embolization of these lesions relieved pain symptoms. These findings indicate that hypervascularity at the rotator interval and surrounding tissues plays an important role in adhesive capsulitis. This study showed that a physical finding of tenderness at the coracoid process is a common feature of adhesive capsulitis. This finding might reflect inflammation of the rotator interval and the fat triangle below the coracoid process. We detected abnormal neovessels in the entire shoulder joint capsule, as well as in the rotator interval, in 1 patient. This indicates that adhesive capsulitis might manifest differently among patients.

The mechanism through which transcatheter arterial embolization relieves symptoms remains unclear. However, the results of this study suggest that occluding abnormal vessels induces therapeutic effects. Transcatheter arterial embolization temporarily or permanently occludes blood vessels using an embolic agent, which was an IPM-CS suspension in our study. This agent is approved as an antibiotic in the United States, is slightly soluble in water, and forms 10- to 70-μm particles that exert an embolic effect when suspended in contrast agent. Infusing this suspension occludes tiny blood vessels. Some patients in our study commented that their pain was relieved within several minutes of infusion with the embolic agent, suggesting a close relationship between blood flow and pain symptoms. Xu et al immunohistochemically analyzed shoulder capsule tissues collected from patients with adhesive capsulitis and from patients with rotator cuff tears without stiffness. They found significantly higher expression levels of nerve markers in capsule tissue associated with adhesive capsulitis than rotator cuff tears. Furthermore, nerve fibers were often located close to small blood vessels in adhesive capsulitis tissues. Although these findings and our data do not constitute direct proof, they indicate that abnormal blood vessels and accompanying nerves at the rotator interval are sources of pain and that occlusion of these vessels relieves pain. Further examination is required to prove this assertion.

Another possible mechanism of the described treatment is the suppression of inflammation induced by occlusion of blood vessels. Costa et al reported that angiogenesis and inflammation are often closely integrated and that angiogenesis could facilitate inflammation. Ashraf et al reduced synovial inflammation, joint damage, and pain behavior using a specific angiogenesis inhibitor in an experimental animal model of osteoarthritis. Therefore, embolization in our study might have suppressed inflammation that was otherwise enhanced by angiogenesis.

One of the most important findings of this study is the relatively rapid relief of pain, especially nighttime pain, that was achieved after transcatheter arterial embolization. Nighttime pain in all of our patients was obviously decreased at 1 week after embolization and further improved at 1 and 6 months later. Alleviation of nighttime pain is an important challenge in orthopaedics. Farrell et al described mild to severe residual nighttime pain in 6 of 19 shoulders at a mean of 15 years after manipulation. The results of our study advance our understanding of nighttime pain, and our therapeutic strategy appears to be a viable option for the relief of such symptoms.

Although pain scores improved at an early phase in this study, range of motion remained restricted for several months after embolization in some patients. However, the ASES scores gradually improved as shoulder motion recovered. Other nonsurgical approaches such as steroid injection can offer comparable pain relief and the subsequent amelioration of functional scores. Our results indicate that transcatheter arterial embolization rapidly relieves pain, which can subsequently facilitate rehabilitative exercises to increase shoulder motion. Because a thickened shoulder capsule or contracted coracohumeral ligament could delay recovery, surgical release or manipulation under anesthesia might bring about the early restoration of shoulder motion. However, transcatheter arterial embolization of abnormal neovessels confers advantages even with late motion recovery because it is far less invasive than capsular release.

One concern about the clinical application of the described technique is exposing patients to radiation because fluoroscopically guided procedures are associated with a risk of radiation damage, especially to the skin. The mean estimated dose-area product during the procedures in this study was lower than that associated with coronary angiography and percutaneous transluminal coronary angioplasty (11.7 Gy/cm² vs 49.1 Gy/cm² and 66.8 Gy/cm², respectively), and the estimated risk of injury during cardiac interventions is less than 0.03%. The dose for our procedure was equivalent to that used in percutaneous dorsolumbar spinal osteosynthesis (10.3 Gy/cm²). Although the risk of radiation exposure during these procedures is quite low, the appropriate measurement of radiation doses is nevertheless important for the optimal application of these interventional procedures.

Another concern is complications related to the actual transarterial embolic procedure. General complication rates are highly variable, with ranges from 0.4% to 8%, 0.6% to 5.5%, and 0.8% to 12% for target ischemia, non-target embolization, and overall major complications, respectively. Complication rates depend on various factors including the type of embolic agent, vascular territory, and clinical status of the patient. In general, the incidence of complications increases in high-risk populations such as patients with hemodynamic instability, multiorgan failure, malignancies, renal failure, and infection. Thus, the indications for clinical practice must be carefully considered. The risk of ischemic events after applying IPM-CS, which is the embolic agent that we used, is lower than that for other embolic agents. Woodhams et al found that ischemic events did not arise in the small intestine after
transcatheter arterial embolization using IPM-CS to treat intestinal bleeding from the relatively proximal points of branches feeding target sites. Although embolized organs are different, these findings might support the safety of IPM-CS as an embolic agent. However, the true incidence of these complications after applying transcatheter arterial embolization could not be meaningfully determined in this study because of the very small patient cohort. Thus, more experience and profiles of complications are required.

This study is the first to determine the angiographic findings of adhesive capsulitis, but it has several limitations. We did not have a control group, and the patients were not blinded to their treatment. Our results indicated that transcatheter arterial embolization could be an option for treating adhesive capsulitis that is refractory to conservative treatment. Nevertheless, adhesive capsulitis can improve with spontaneous pain relief followed by restoration of shoulder range of motion. Drawing any definitive conclusion about whether this technique actually modifies the natural history of this condition is difficult. Furthermore, embolization appears to immediately offer pain relief, and the results of other nonsurgical therapies are comparable. Thus, a direct comparison between different modalities with a randomized controlled trial is required to clarify whether transcatheter arterial embolization is more effective than other modalities. Moreover, the patient cohort was small, and the follow-up period was short. Adhesive capsulitis does not appear to recur during long-term follow-up, but further studies are needed to validate the long-term outcomes of transcatheter arterial embolization.

Conclusion

All patients with adhesive capsulitis had abnormal neo-vessels at the rotator interval. Transcatheter arterial embolization of these lesions was feasible and effectively relieved unrelenting pain and restored shoulder function.

Disclaimer

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