Results from a United States Investigational Device Study of Adhesive Capsulitis Embolization in the Treatment of Shoulder Pain: The Adhesive Capsulitis Embolization Study

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ABSTRACT

Purpose: To evaluate the safety and efficacy of arterial embolization to relieve shoulder pain secondary to adhesive capsulitis (AC).

Materials and Methods: In total, 20 patients (18 females, 2 males; mean age, 51 years) with AC resistant to >30 days of conservative treatment were enrolled in a multicenter prospective study. Adhesive capsulitis embolization was performed with 75-μm or 200-μm spherical particles. Subjects were assessed before and after the procedure with magnetic resonance imaging, visual analog scale (VAS; 0–100 mm) scores, Single Assessment Numeric Evaluation (SANE; 0–100) scores, and American Shoulder and Elbow Surgeons (ASES; 0–100) scores. Adverse events were recorded at all follow-up time points.

Results: Hypervascularity was identified and embolization was technically successful in all patients, with 83 arteries embolized in 20 patients. Baseline VAS, SANE, and ASES scores before the procedure were 89.2 mm, 27.2, and 30.9, respectively. The 1-month (n = 19), 3-month (n = 18), and 6-month (n = 12) follow-ups demonstrated significant improvements. At the 1-month follow-up, VAS score decreased by 31.8 (P = 1.2E–11), SANE score increased by 22.1 (P = 1.8E–8), and ASES score increased by 14.2 (P = 4.3E–5). At the 6-month follow-up, VAS score decreased by 62.1 (P = 7.0E–11), SANE score increased by 55.4 (P = 4.1E–10), and ASES score increased by 44.5 (P = 1.8E–6). Due to the coronavirus pandemic, the study ended early; 6 patients did not complete the 6-month follow-up. No major adverse events were noted.

Conclusions: Interim findings suggest that arterial embolization is safe and effective for patients with AC refractory to conservative treatment.

ABBREVIATIONS

AC = adhesive capsulitis, ACE = adhesive capsulitis embolization, AE = adverse event, ASES = American Shoulder and Elbow Surgeons, SANE = Single Assessment Numeric Evaluation, VAS = visual analog scale

Adhesive capsulitis (AC), or frozen shoulder, is initially an inflammatory condition characterized by pain and stiffness of the glenohumeral joint, progressing to fibrosis in later stages. The prevalence of AC ranges between 3% and 5% in the general population with higher incidence in women and patients with diabetes (1). The mainstay of treatment is conservative management that includes nonsteroidal pain medication, physical therapy, and corticosteroid injections. Surgical therapy, including the rotator interval capsular release, may be resorted to after 4–6 months of conservative therapy. Although AC is often a self-limiting condition that resolves in 1–3 years, 20%–50% of subjects can develop persistent symptoms for up to 10 years (2).

The pathophysiology of AC involves inflammation within the joint capsule, leading to reactive fibrosis and adhesion formation in the synovial lining of the joint (3,4), which is visualized on arthroscopy as a hypervascular joint capsule. Pain in AC has been linked to upregulated inflammatory growth factors that promote angiogenesis and accompanying nerve fiber growth (5). This model has been successfully used to perform particle embolization of abnormal microvessels in patients with osteoarthritis (6–12).

Okuno et al (13) (2014) were the first to utilize embolization in the setting of AC. Hypervascularity observed during angiography at the rotator interval was present in all

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RESEARCH HIGHLIGHTS

- Shoulder pain secondary to adhesive capsulitis was treated with arterial embolization of abnormal vessels in the shoulder joint.
- In total, 20 patients underwent adhesive capsulitis embolization with a significant reduction in pain and improvements in function at the 1-, 3-, and 6-month follow-ups.
- No major adverse events were noted, and minor skin discolorations in 9 patients self-resolved without intervention.
- Interim findings suggest that arterial embolization is safe and effective for patients with adhesive capsulitis refractory to conservative treatment.

STUDY DETAILS

Study type: Prospective, non-randomized trial

Study phase: Pilot

subjects, and embolization led to a significant long-term reduction in pain and improvements in mobility. Two subsequent overseas studies reported similar results using temporary embolics (14,15). The authors present the results from a prospective U.S. Investigational Device Exemption study to evaluate the safety and efficacy of adhesive capsulitis embolization (ACE) with microspheres.

MATERIALS AND METHODS

The current prospective multicenter study was approved by the institutional review board (The Western Institutional Review Board protocol number: 20181853) and received an Investigational Device Exemption (IDE NCT03676829) from the U.S. Food and Drug Administration. All study-related activities followed Health Insurance Portability and Accountability Act regulations. Subjects who presented with pain secondary to AC at an orthopedic clinic at 2 separate institutions between September 2018 and October 2019 were screened for enrollment. In total, 20 subjects were enrolled after screening 25 patients; written consent was obtained from all subjects.

The inclusion criteria included a diagnosis of AC by an orthopedic surgeon (nighttime shoulder pain, painful restriction of both active and passive forward elevation of <100° and external rotation to <50% of the contralateral side, normal plain radiographic appearance, and no secondary causes), moderate-to-severe shoulder pain with visual analog scale (VAS) of >40 mm, age of >21 years, and pain refractory to at least 30 days of conservative therapy (pain medications, physical therapy, injections, etc). The exclusion criteria were current local infection, life expectancy of <6 months, known advanced upper extremity symptomatic atherosclerosis, rheumatoid or infectious arthritis, prior shoulder replacement surgery, irreversible coagulopathy, and a previous history of complete full-thickness tear of the rotator cuff.

All enrolled subjects were evaluated with magnetic resonance (MR) imaging at baseline and at the 1-month follow-up visit. Baseline scores were obtained by an interviewer (S.B. and R.P.) during the initial presentation at the clinic. A standard multiplanar multisequence MR imaging of the shoulder (3-mm slice thickness) was performed without gadolinium and reviewed for soft tissue and ischemic changes by 2 radiologists with 15 and 18 years of experience in analyzing MR images. A 1.5-T MR scanner was used with the following sequences: proton density weighted, T2-weighted fat-suppressed, T1-weighted, T2-weighted, and proton density weighted fat-suppressed. Shoulder pain was assessed using VAS (0–100 mm), and function was reported with the Single Assessment Numeric Evaluation (SANE; 0–100) and American Shoulder and Elbow Surgeons (ASES; 0–100) scores. VAS, SANE, and ASES scores were recorded at baseline and 1-month, 3-month, and 6-month intervals.

Baseline demographics are summarized in Table 1. In total, 18 females and 2 males were enrolled (mean age, 51 years). The mean body mass index was 29.8 kg/m^2, and 9 subjects were considered obese (body mass index range, 30–34 kg/m^2). Failed conservative therapies included intra-articular injections (11 subjects), physical therapy (14 subjects), and analgesic medications (16 subjects).

Embolization Procedure

Two interventional radiologists (S.B. and R.P.) with 10–15 years of experience in performing embolization procedures performed all procedures. Percutaneous arterial access was obtained using a 4-F sheath from the ipsilateral radial or ulnar artery. The ulnar artery was preferred when the radial artery was considered inadequate for access. Upper extremity digital subtraction angiography was performed from both the subclavian and axillary arteries to identify all target shoulder vasculatures as described in the previous reports (13). A 2-F microcatheter (Progreat Alpha; Terumo, Somerset, New Jersey) was used to catheterize all visible arteries supplying the shoulder capsule (Fig 1). Selective angiography was performed to evaluate for abnormal microvessels. Prior to embolization, an embolic solution was created by mixing 2 mL of either 75-μm or 200-μm spherical particles (HydroPearl; Terumo) with 9 mL of iodinated contrast material. Embolization was subsequently performed by administering 0.2-mL aliquots of the embolic solution followed by repeat angiography (Fig 2). The embolization end point was the absence of hypervascularity with patency of the target vessel with the antegrade flow. Following the procedure, all subjects were discharged the same day. Subjects underwent adverse event (AE) evaluations in person and/or via

Table 1. Summary of Patient Demographics and Baseline Patient Data

Patient	Age, y	Gender	BMI, kg/m^2	Laterality	VAS, mm	SANE	ASES
1	67	Female	25.1	Left	78.0	25.0	30.0
2	57	Female	25.6	Right	99.0	40.0	36.7
3	48	Female	27.6	Left	100.0	40.0	13.4
4	58	Female	30.4	Right	98.0	30.0	15.0
5	39	Female	20.4	Left	71.0	20.0	31.7
6	53	Male	27.2	Left	77.0	30.0	45.1
7	45	Female	22.5	Right	83.0	40.0	40.1
8	54	Female	31.8	Right	91.0	17.0	33.4
9	65	Female	28.7	Left	100.0	20.0	8.4
10	52	Female	30.0	Right	95.0	65.0	46.7
11	45	Female	37.2	Left	86.0	20.0	21.7
12	38	Female	40.8	Right	100.0	10.0	16.7
13	53	Female	29.5	Right	66.0	30.0	38.4
14	39	Female	41.1	Left	100.0	2.0	28.4
15	65	Female	23.4	Right	95.0	0.0	55.0
16	57	Female	26.2	Right	88.0	20.0	53.4
17	32	Female	37.9	Left	100.0	30.0	20.0
18	46	Female	21.6	Left	62.0	40.0	46.7
19	45	Female	33.6	Right	100.0	35.0	15.0
20	57	Male	35.0	Right	94.0	30.0	21.7
Summary	Mean, 50.8 SD, 9.4	Female, 18 Male, 2	Mean, 29.8 SD, 6.0	Right, 11 Left, 9	Mean, 89.2 SD, 12.0	Mean, 27.2 SD, 14.4	Mean, 30.9 SD, 13.7

ASES = American Shoulder and Elbow Surgeons; BMI = body mass index; SANE = Single Assessment Numeric Evaluation; VAS = visual analog scale.

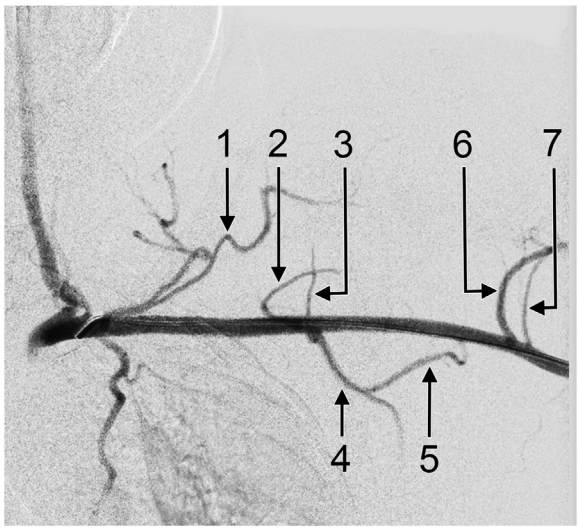

Figure 1. Digital subtraction angiography of the left axillary artery demonstrating the vessels of interest: suprascapular artery (1), thoracoacromial artery (2), coracoid branch (3), subscapular artery (4), circumflex scapular branch of subscapular artery (5), posterior circumflex humeral artery (6), and anterior circumflex humeral artery (7).

telephone at 1 day, 1 month, 3 months, and 6 months. All posttreatment assessments were performed by nonoperator research personnel to avoid bias; however, all reported AEs were evaluated by the investigators (S.B. and R.P.) for potential clinical treatment required. AEs were reported according to the Clavien-Dindo classification system (16).

Statistical Analysis

The study was powered to detect a 16% difference in mean ASES at 6 months. At the time of the current study design, one previous study had reported ACE for AC with a baseline ASES of 16.1 ± 3.6. The primary outcome for that study was a reduction of 6.4 from baseline in the ASES score. Using the baseline total score from that study, a sample size of 15 was determined to have an 80% power to detect a 16% difference (7.8 points), assuming a standard deviation of 10 points. In total, 20 subjects were ultimately enrolled to protect against potential loss to follow-up.

To evaluate differences in metrics between baseline and subsequent time points, a random coefficients growth model for each outcome was utilized (17). The data were transformed into long format such that there was 1 observation per patient per time point. Time points were considered nested within a patient, and the modeling was adjusted for this nesting accordingly (18). A random coefficient model was preferred to allow a separate outcome trajectory over time for each patient. In this context, the fixed effect estimates represent trajectories averaged over the subjects in this study. The full model included a random intercept, linear slope, and quadratic slope along with a fixed effect intercept, linear slope, and quadratic slope. The largest positive random effects structure was subsequently chosen to yield the "final model" to reduce parsimony. The "final models" as derived in

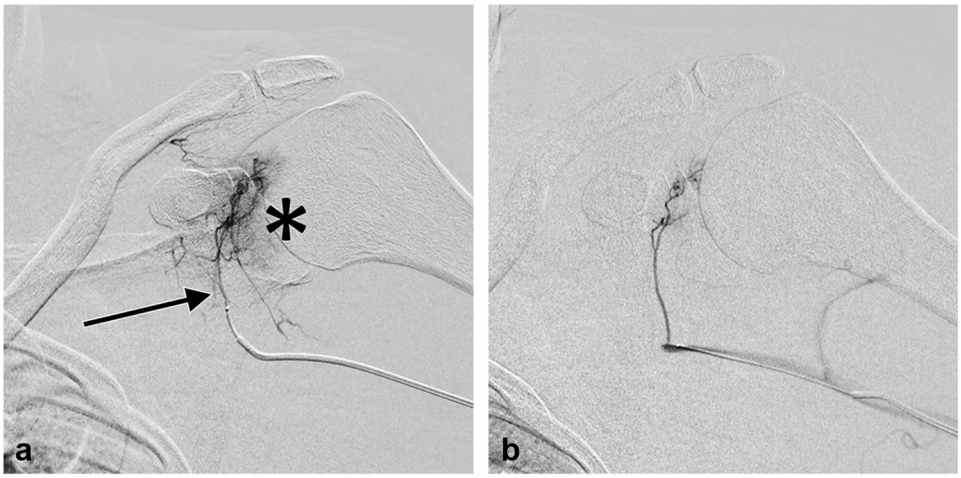

Figure 2. (a) Digital subtraction angiography of the coracoid branch artery (arrow) demonstrated marked hypervascularity (asterisk), similar to "tumor blush." **(b)** After embolization, hypervascularity was resolved.

the description above were used for each outcome to address whether there were differences between baseline and subsequent time points by computing predicted mean differences and using *t* tests to test whether these differences were equal to zero. A nominal type I error rate of 0.05 was preserved by adjusting *P* values using the false discovery rate method. Adjusted *P* values of <.05 were considered evidence of a significant difference. A sensitivity analysis was also conducted for the missing 6 patients (related to the coronavirus pandemic) using baseline data for the 6 patients. All analyses were performed using SAS software (version 9.4, package PROC GLIMMIX; SAS Institute, Cary, North Carolina).

Follow-up

One patient was excluded from the study after receiving escalating therapy, a steroid injection, before the 3-month period. Another patient was lost to follow-up before the 1-month follow-up as the patient physically relocated after the procedure. Lastly, 6 patients were lost to follow-up after 3 months due to restrictions stemming from the severe acute respiratory syndrome coronavirus 2 pandemic. Of the 20 total patients, 19 patients were available at the 1-month follow-up, followed by 18 patients at the 3-month follow-up and 12 patients at the 6-month follow-up (Table 2).

Table 2. Changes in visual analog scale, American Shoulder and Elbow Surgeons, and Single Assessment Numeric Evaluation Scores from Baseline to Follow-up

Time	n	VAS, mean (SD)	SANE, mean (SD)	ASES, mean (SD)
Baseline	20	89.2 (12.4)	27.2 (14.8)	30.9 (14.1)
1 month	19	35.9 (28.8) $P \leq .0001$*	54.3 (29.0) $P = .00079$*	52.7 (25.6) $P = .00016$*
3 months	18	20.1 (24.3) $P \leq .0001$†	77.8 (21.4) $P \leq .0001$†	65.2 (23.6) $P = .00040$†
6 months	12	13.9 (20.2) $P = .00049$‡	86.8 (13.9) $P = .00098$‡	80.1 (19.4) $P = .00049$‡
Sensitivity	20	$P = .00049$§	$P = .00098$§	$P = .00049$§

ASES = American Shoulder and Elbow Surgeons; SANE = Single Assessment Numeric Evaluation; VAS = visual analog scale.
*P value from Wilcoxon signed-rank test for comparison of 1-month scores to baseline scores.
†P value from Wilcoxon signed-rank test for comparison of 3-month scores to baseline scores.
‡P value from Wilcoxon signed-rank test for comparison of 6-month scores to baseline scores.
§P value from Wilcoxon signed-rank test for comparison of 6-month scores to baseline scores, substituting baseline scores for missing 6-month scores.

RESULTS

All patients demonstrated abnormal hypervascularity in the shoulder vessels. A total of 83 arteries were embolized in 20 procedures. The most commonly treated arteries were the coracoid branch (20.5%), the thoracoacromial (19.3%), the posterior circumflex humeral (19.3%), the anterior circumflex humeral (16.9%), the circumflex scapular (14.5%), and the suprascapular (9.6%) arteries. Embolization was performed using 75-μm particles in 20 of the 20 patients with 1 patient receiving additional 200-μm particles. The mean procedural time, defined as the time from arterial access to placement of a compression device, was 69.3 minutes ± 26.9 with an average fluoroscopy time of 28.6 minutes ± 22.5 and administered reference air kerma of 73.1 mGy ± 39.2.

Outcomes

The final model included the linear and quadratic fixed effect slopes as well as a random intercept. The predicted mean difference was tested between baseline and the 1-, 3-, and 6-month scores. Among responders, VAS significantly decreased at 1, 3, and 6 months compared with baseline (Table 3). Among responders, SANE scores significantly increased at 1, 3, and 6 months compared with baseline (Table 4). Among responders, ASES scores significantly increased at 1, 3, and 6 months compared with baseline (Table 5). A sensitivity analysis was conducted and

Table 3. Visual Analog Scale Outcome

Observation	Label	Estimate	LCL	UCL	*P* value	Adjusted *P* value
1	Predicted mean difference, 1-month vs baseline	−31.8888	−39.0043	−24.7733	<.0000001	1.2189E−11
2	Predicted mean difference, 3-month vs baseline	−69.8190	−83.7185	−55.9195	<.0000001	6.8458E−13
3	Predicted mean difference, 6-month vs baseline	−62.0960	−77.0072	−47.1849	<.0000001	6.9964E−11

LCL = lower cutoff/control limit; UCL = upper cutoff/control limit.

Table 4. Single Assessment Numeric Evaluation Score Outcome

Observation	Label	Estimate	LCL	UCL	*P* value	Adjusted *P* value
1	Predicted mean difference, 1-month vs baseline	22.0977	15.5347	28.6608	<.0000001	1.80343E−8
2	Predicted mean difference, 3-month vs baseline	50.8491	38.0314	63.6668	<.0000001	4.0819E−10
3	Predicted mean difference, 6-month vs baseline	55.3657	41.6781	69.0533	<.0000001	4.0819E−10

LCL = lower cutoff/control limit; UCL = upper cutoff/control limit.

Table 5. American Shoulder and Elbow Surgeons Score Outcome

Observation	Label	Estimate	LCL	UCL	*P* value	Adjusted *P* value
1	Predicted mean difference, 1-month vs baseline	14.2559	7.8941	20.6177	.0000434	.000043416
2	Predicted mean difference, 3-month vs baseline	34.5559	21.7730	47.3388	.0000019	.000002827
3	Predicted mean difference, 6-month vs baseline	44.4764	28.9397	60.0131	.0000006	.000001867

LCL = lower cutoff/control limit; UCL = upper cutoff/control limit.

demonstrated that the 6-month reductions were significant using the baseline values for the missing 6 patients.

Adverse Events

Analgesic use was only reported in 4 subjects at the 1-month follow-up, and no subjects reported analgesic use at the 3- and 6-month follow-ups. MR imaging at 1-month after embolization did not demonstrate evidence for bone marrow edema, infarction, or worsening inflammatory change. There were no major AEs. There were 9 minor events (Grade 1 Clavien-Dindo Classification) that included skin discoloration without ulcers (n = 7, 41.1%) and itchiness (n = 2, 11.8%). The size of the superficial skin discoloration ranged from 1 to 3 cm and mainly involved the anterior and posterior aspects of the shoulder. All AEs resolved without intervention by the 3-month follow-up evaluation.

DISCUSSION

In the present study, ACE significantly reduced pain and improved shoulder function in subjects with AC who did not respond to prior conservative management. Statistically significant clinical improvements in VAS, SANE, and ASES scores were observed at 1-month and lasted until the 6-month follow-up. The procedure was also not associated with any major AEs, and minor AEs self-resolved without intervention.

The treatment targets the abnormal hypervascularity found in subjects with AC. Angiogenesis accompanies chronic inflammation and is known to intensify the inflammatory process (19). Specifically, inflammatory neovascularity leads to new unmyelinated sensory nerve growth, a phenomenon that has been observed in histopathologic studies of subjects with AC (5,20). Given this background, embolization of the neovascularity could decrease the inflammatory process, resulting in reduced pain and improved shoulder function. Further basic science and long-term embolization studies are warranted to confirm this hypothesis.

The AEs noted in the current study are associated with nontarget embolization. The skin discoloration was likely a result of inadvertent embolization of cutaneous arteries. This phenomenon can be difficult to avoid, given the size and location of these branch vessels. One possible solution is to use larger embolic particles that would be too large to travel distally within the cutaneous arterial branches. However, it is unknown whether increasing the size of the embolic particles would affect the clinical efficacy of the procedure.

The current results are comparable to those of the previously reported studies on transarterial embolization for AC. The main embolic material used in the studies by Okuno et al (13,14) and Hwang et al (15) was imipenem/cilastatin (40–50 μm). One patient in the study by Hwang et al (15) was treated successfully with Embospheres (Merit Medical, South Jordan, Utah). Given previous success seen with permanent embolics for genicular artery embolization, only permanent embolics were used in the current study.

Another major difference with previous studies included a higher baseline ASES score than the current cohort. Okuno et al (14) reported a baseline ASES score of 16.1, whereas, in the present study, the baseline ASES score was 30.9. Despite the differences, baseline VAS and SANE scores were comparable, and the overall reduction in pain and disability was similar.

The primary limitation of this study was the absence of a control group. Given the chronic nature of AC, it is difficult to evaluate the efficacy of the treatment without comparing it with the natural course of the disease or conservative therapy. Since residual pain in AC can last approximately 15 years, a longer follow-up period is needed to assess the durability and long-term benefits of the procedure. Additionally, a total of 8 patients were excluded from this study by the 6-month follow-up. Only 1 patient required additional pain medication, whereas the remaining subjects reported decreased analgesic use. The coronavirus pandemic prevented patients from returning to the office, and these patients (n = 6) were subsequently lost to follow-up. Although the overall results are encouraging, the excluded subjects may have had poor outcomes and the reported results may be mildly skewed.

In conclusion, interim results suggest that ACE is a safe treatment option for managing pain secondary to AC. Although the reduction in shoulder pain and improvements in function are encouraging, further testing with a control group is needed to understand the true efficacy of ACE.

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