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Mid-Term Results of Transcatheter Arterial Embolization for Adhesive Capsulitis Resistant to Conservative Treatment

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Abstract

Purpose To evaluate the mid-term clinical outcomes of transcatheter arterial embolization (TAE) for adhesive capsulitis (AC) resistant to medical treatments.

Materials and Methods This is a prospective analysis performed between February 2016 and February 2020. Inclusion criteria for TAE were shoulder pain, restriction of movement and no response to conservative treatment for at least 3 months. Demographic variables, risk factors, technical aspects, adverse events, changes by visual analogue scale (VAS) for pain and physical examination before and after TAE were assessed.

Results This study included 40 patients with AC (35 women and 5 men; mean age 50 ± 9 years old). Abnormal vessels were observed in 31/40 (77.5%) procedures. As embolic agent, imipenem/cilastatin was used. The mean follow-up was 21.2 ± 10.5 months. Significant differences were obtained in terms of pain reduction before and 6 months after TAE with the median visual analogue scale (VAS) of 8 vs. 0.5, $P = 0.0001$. Substantial differences were found regarding mobility in flexion and abduction before and 6 months after embolization, respectively (79.5° ± 18.5° vs. 133° ± 24.5°, $P = 0.0001$; 72.4° ± 18.8° vs. 129.7° ± 27.9°, $P = 0.0001$). No complications occurred. Complete recovery was obtained in 37/40 (92.5%) patients and partial recovery in 2/40 (5%). No clinical recurrence appeared.

Conclusions Clinical results of transcatheter arterial embolization with imipenem/cilastatin are effective and stable in the mid-term follow-up for patients presenting with AC resistant to conservative treatments.

Keywords Adhesive capsulitis · Shoulder · Stiffness · Imipenem/cilastatin sodium

Abbreviations

AC	Adhesive capsulitis
DSA	Digital subtraction angiography
IMP/CS	Imipenem/cilastatin sodium
MRI	Magnetic resonance imaging
ROM	Range of motion
TAE	Transcatheter arterial embolization
VAS	Visual analogue scale

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Introduction

Adhesive capsulitis (AC), also known as "frozen shoulder", causes shoulder pain (principally involving the anterior aspect), stiffness and gradual restriction of motion [1, 2]. The Upper Extremity Committee of International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (ISAKOS) defined "frozen shoulder" as an idiopathic stiff shoulder, without a known cause [3]. AC is an exclusion diagnosis when there are suspicious clinical symptoms and exploratory findings and no other causes of shoulder pain found on images. Its prevalence is 2–5% in the general population [1, 4], mostly women between 40 and 70 years old [5]; meanwhile male gender is considered as a risk factor for longer recovery and greater disability [3].

The pathophysiology of the AC is still unclear, it includes a chronic inflammatory response with fibroblastic proliferation, angiogenesis and a combination of synovitis and fibrotic contracture of the rotator interval, capsule and ligaments [1, 6, 7], and this thickening of the joint capsule causes inflammation and a stimulation on the adjacent nerve fibres [8, 9]. The most characteristic arthroscopic findings in AC include abnormality in the subscapular bursa and the origin of the long head of the biceps tendon, fibrosis of the capsule and increased vascularity [2, 7].

Many aetiologies such as trauma, breast cancer treatment or surgical interventions can be the cause of secondary shoulder stiffness [3, 10] but its pathophysiology is still uncertain. There are some predisposing factors associated with AC: diabetes, thyroid diseases, smoking, immobilization or Dupuytren's disease [3, 11–15].

The natural history of AC can last between 12 and 36 months [6]. It is classically considered a self-limiting entity [16] and three evolution phases have been described: painful or freezing, stiff or frozen and recovery or thawing [1]. However, there is a high rate of refractory cases to medical and rehabilitation treatment with residual deficits years after the beginning of the clinical [4, 6, 17, 18].

The main goal for treatment in AC is to relieve the pain and to recover the mobility. Conservative measures are first-line treatment, such as physical therapy, anti-inflammatory medication or corticosteroid injections. When these fail [4, 17–19], more invasive approaches have been proposed for AC such as surgery or manipulation under anaesthesia [12, 20], but there is no consensus for refractory cases.

In recent years, based on hypervascularization observed in AC, Okuno et al. [21] proposed that the embolization of the arteries vascularizing the shoulder capsule would relieve the pain. A mixture of imipenem/cilastatin sodium (IMP/CS) and iodinated contrast media was used as embolic agent, with good results [22–24]. Imipenem is an antibiotic from the carbapenem group and cilastatin is an enzyme that prolongs its antibacterial effect. Paradoxically, the use of IMP/CS does not lie in its antibiotic mechanism of action: when IMP/CS is mixed with iodinated contrast media, it generates micron-sized particles that act as temporary embolic agent and show short-term embolic effects and near-complete recanalization within 48 h, with good previously reported results with a low risk of ischemia [21, 25–27].

Our purpose is to evaluate the mid-term clinical outcomes of transcatheter arterial embolization (TAE) in patients with AC resistant to conservative treatment.

Materials and Methods

Patients and Protocol

All patients received explanation about TAE and a written informed consent was obtained. Our hospital clinical research ethics committee approved this study.

This is a prospective analysis acquired by data of TAE in adhesive capsulitis performed between February 2016 and February 2020. Demographic and clinical data are summarized in Table 1.

Patient's selection was accomplished by a multidisciplinary approach in collaboration with orthopaedic surgeons, rehabilitation physicians and rheumatologists. The inclusion criteria were severe shoulder pain, restriction of

Table 1 Patient demographics and clinical characteristics

Variable	Value
Age, years	50 (33–69)
Sex, female/male	35/5
Clinical evolution, months	16.4 (3–42)
Affected side, right/left	20/20
Diabetes mellitus	7/40 (17.5%)
Smoke	15/40 (37.5%)
Thyroid disease	10/40 (25%)
Hypothyroidism	8 (80%)
Dupuytren's disease	1/40 (2.5%)
Clinical baseline evaluation	
Pain (VAS)	8.2 (6–10)
Nocturnal pain	34/40 (85%)
Analgesic oral medication	40/40 (100%)
Physical therapy	37/40 (92.5%)
Corticosteroids infiltration	24/40 (60%)

y years, *VAS* visual analogue scale

movement and no response to conservative treatment including anti-inflammatory drugs, corticosteroid infiltration and physiotherapy for at least 3 months. Magnetic resonance imaging (MRI) was performed before TAE to exclude other causes of painful shoulder as complete rotator cuff tear, shoulder instability, fracture or calcific tendinitis. MRI allows identify characteristic findings of AC as thickening of the coracohumeral ligament, the axillary pouch and the capsule at the rotator interval and fat obliteration at the rotator interval; however, a normal MRI does not exclude AC [28, 29]. In cases of MRI contraindication, ultrasound was performed. The exclusion criteria were spontaneous improvement before TAE, complete rotator cuff tear and stiffness shoulder secondary to a fracture or after surgical shoulder.

Forty patients were diagnosed of unknown AC and were eligible for the study; 15 patients were excluded because of postsurgical shoulder and other 5 people were excluded because of improvement.

Pain and physical examination before and after the procedure were assessed by the rehabilitation physicians but immediately before the procedure it was performed by the interventional radiologist to determine the painful areas. Pain was classified according to visual analogue scale (VAS); from 0 (absence of pain) to 10 (maximum intensity). In addition, pain was subdivided as mild 1–3, moderate 4–6 and severe 7–10. Range of motion (ROM) was documented with flexion, abduction and internal/external rotation [30, 31]. Shoulder functional targets were defined as 120° in flexion and abduction, reach the interscapular region in internal rotation and reach the top of head with the hand in external rotation, following the mobility of the constant scale [32].

Embolization Procedure Details

All cases were performed by the same interventional radiologist with more than 5 years of experience.

First, physical examination was performed to determine painful areas. Under local anaesthesia, percutaneous femoral arterial access was gained by using a 5-French (F) introducer sheath (Terumo, Tokyo, Japan). Selective catheterization of subclavian artery was obtained with a 5-F catheter vertebral curve (Cordis Corporation, Florida, US). Then, a digital subtraction angiography (DSA) was carried out using a 9.0 ml injection of iodinated contrast media (Iopromide 300 mg/ml, Ultravist, Bayer, Germany) at an injection rate of 3.0 ml/s (Fig. 1). According to previous reports [23], an ill-defined area of contrast enhancement in the joint capsule during the arterial phase with variable early venous drainage ("blush area") was considered an abnormal finding. Superselective catheterization of these "blush areas" feeding arteries were performed using coaxially 2.4-F (Progreat, Terumo, Tokyo, Japan), 2.0-F (Parkway Soft, Asahi Intecc, Nagoya, Japan) or 1.7-F (SL 10, Stryker, USA) microcatheters according to the size of targeting arteries. To confirm final embolization position, superselective angiograms were carried out by manual slow injection of contrast (Fig. 2).

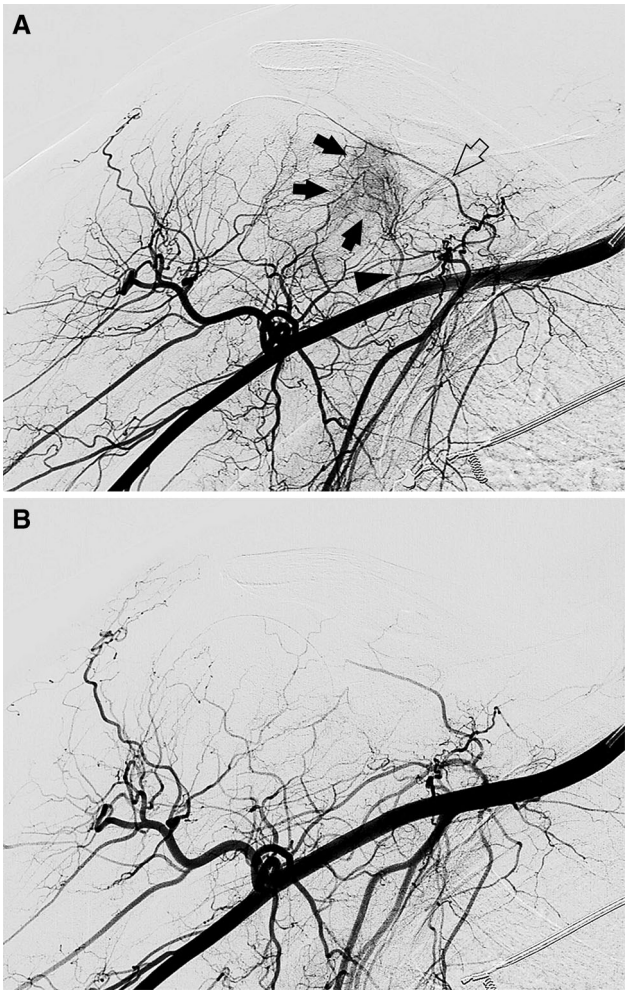

Fig. 1 38-year-old woman with 3 years of clinical history of severe shoulder pain, stiffness and functional limitation. (**A**) Digital subtraction angiography (DSA) performed from subclavian artery where capsular enhancement in rotator interval area (arrows) feeding from coracoid and acromial branches (arrowhead and open arrow in **A**, respectively). (**B**) Result after embolization where a normal angiographic pattern can be seen

A mixture of 500 mg IMP/CS (Aurovitas, Spain) with 5 ml of iodinated contrast media was used as embolic agent. This mixture was prepared using the Tessari method with two Luer lock disposable syringes and a three-way step lock pumping during 10 s. Embolic mixture injections were performed in 0.2–0.5 ml increments. We considered as embolization end-point a complete stasis over either three to five cardiac beats, complete stasis with reflux back along the microcatheter tip and/or absence of joint

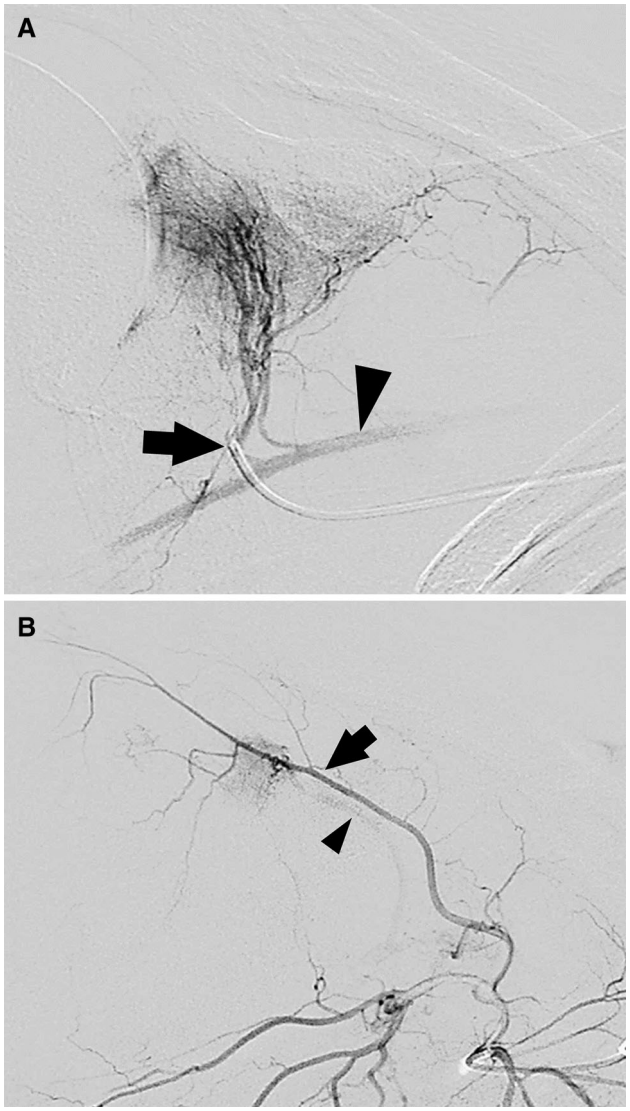

Fig. 2 Superselective arteriograms in patient described in Fig. 1. Manual injections from coracoid branch and acromial branch (arrows in **A** and **B**, respectively). Capsular enhancement of rotator interval area in the arterial phase with early venous drainage (arrowheads in **A** and **B**, respectively) can be observed

enhancement in control angiography after embolization. The procedure time was also measured. Technical success was defined as feasibility in embolization of at least one of the "blush area"/painful area feeding arteries. Haemostasis was achieved by manual compression. The patients were discharged after 8 h and were told to rest that day and move the shoulder one day after. Complications were collected according to the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) [33].

Follow-Up, Safety and Evaluation Outcomes Measured

All patients were interviewed at 1 week and 1, 3, 6 and 12 months after procedure. They were asked about pain and adverse as peripheral paraesthesia, shoulder instability, change in skin colour or muscle weakness. In addition, a functional shoulder examination was performed. Patients were classified as complete recovery (absence or mild pain and reach the target grades in ROM); partial recovery (decrease in pain and/or increase mobility without reaching the target grades); and no recovery (no changes in pain or mobility). Also, all classified patients as complete recovery, have been recently contacted by telephone. Clinical stability was considered the absence of clinical recurrence in 12 months of follow-up.

Statistical Analysis

Statistical analysis was performed by using SPSS software (version 26; SPSS, Chicago, Illinois). A P value <0.05 was considered statistically significant. Categorical variables are expressed as absolute number and percentages; continuous variables are expressed as means, medians and standard deviations. The Student t test was applied to analyse differences in ROM before and after the procedure. The Wilcoxon signed-rank sum test was applied to compare baseline and follow-up VAS scores. The Mann–Whitney test was applied for comparing the initial pain scale with whether or not there was blush enhancement.

Results

Patients Characteristics

In this study, 40 TAE in 40 patients were performed. There were 35/40 (87.5%) women and 5/40 (12.5%) men with a mean age of 50 years old (range 33–69 years). In all patients, the aetiology of AC was unknown. The median time of clinical evolution was 12 months. All patients underwent conservative treatment previously for at least 3 months that included physical therapy in 37/40 (92.5%) and corticosteroids infiltration in 24/40 (60%) patients. Three patients did not undergo physical therapy due to intense pain. Assessment of shoulder motion before and after TAE is summarized in Table 2.

Diagnostic Imaging

In 39/40 (97.5%) patients, an MRI was performed before TAE. In 22/39 (56.4%), there were signs of capsulitis on imaging. Findings on MRI studies included thickening of

Table 2 Mobility evaluation before and at 6 months after transarterial embolization

Range of motion (ROM)	Before TAE	After TAE
Flexion		
Mean (SD)	79.5° (18.5°)	133° (24.6°)
Reached ≤90°	32/40 (80%)	4/40 (10%)
Reached 91–110°	8/40 (20%)	7/40 (17.5%)
Reached 111–149°	0/40	5/40 (12.5%)
Reached ≥150°	0/40	24/40 (60%)
Abduction		
Mean (SD)	72.4° (18.8°)	129.7° (27.9°)
Reached ≤90°	36/40 (90%)	5/40 (12.5%)
Reached 91–110°	4/40 (10%)	9/40 (22.5%)
Reached 111–149°	0/40	2/40 (5%)
Reached ≥150°	0/40	24/40 (60%)
Internal rotation		
Not reached lumbosacral junction	29/40 (72.5%)	1/40 (2.5%)
Reached twelfth dorsal vertebra	10/40 (25%)	11/40 (27.5%)
Reached interscapular region	1/40 (2.5%)	28/40 (70%)
External rotation		
Not reached hand behind head	22/40 (55%)	1/40 (2.5%)
Hand behind head, elbow back	15/40 (37.5%)	7/40 (17.5%)
Hand on top of head	3/40 (7.5%)	32/40 (80%)

TAE transarterial embolization, *SD* standard deviation

the coracohumeral ligament, the axillary pouch and the capsule at the rotator interval in 6/22 (27.2%) patients; thickening of the axillary pouch in 6/22 (27.2%) and fat obliteration at the rotator interval in 10/22 (45.4%) patients. Shoulder ultrasound was performed in one patient due to claustrophobia and no findings of capsulitis were found.

Embolization Procedure

Technical success was achieved in all patients. In 31/40 (77.5%) patients, "blush areas" were observed. In 19/31 (61.3%) procedures, there was only one area of blush enhancement, but in 12/31 (38.7%) patients there were more than one. The capsular area most frequently affected was rotator interval (14/31, 45%).

In these described "pathological areas", the most frequent feeding artery was anterior circumflex humeral artery (23/40, 57.5% procedures) followed by posterior circumflex humeral artery (19/40, 47.5% procedures). In those 9/40 (22.5%) patients where no obvious enhancement was visualized, it was decided to embolize those branches corresponding to the painful areas previously reported on physically exploration. These patients also obtained clinical improvement in spite of the absence of hypervascularization, with no substantial differences by comparing presence or not of arterial enhancement and pain reduction after TAE ($P = 0.27$), even if they evolved towards total or partial recovery ($P = 1.00$).

Femoral access was performed in all procedures, 39/40 (97.5%) by right femoral approach. The mean amount of embolic agent applied in each procedure was 1.6 ml (0.2–3.1 ml). The mean time of the procedure was 48 ± 17.2 min. The procedure was well tolerated and none patient required hospitalization. There were no immediate or delayed major complications. As minor complications, two patients (2/40, 5%) reported groin discomfort associated with a haematoma in the arterial puncture site one day after TAE. The mean follow-up was 21.2 months (range 12–48 months). All patients referred that they underwent the TAE again if necessary and would recommend it to other patients.

Clinical Results

Before TAE, no patient referred pain VAS <6 and 28/40 (70%) patients reported pain ≥8; even 8/28 (28.6%) of them referred 10 in pain VAS.

Mean pain VAS after TAE decreased to less than 4 (3.7 ± 1.2) in 26/40 (65%) patients at 1-week follow-up, less or equal to 3 (2.1 ± 1.8) in 28/40 (70%) at 1-month follow-up and 2.1 ± 1.8 at 3-month follow-up; these data can be seen in Fig. 3. At 12-month follow-up interview, 33/40 (82.5%) reported a progressive decreasing in pain VAS up to ≤3, considering that 20/40 (50%) patients referred no pain (VAS = 0) at that time. None patient referred pain worsening after TAE procedure.

On the other hand, 22.5% (9/40) of patients reported pain VAS ≥6 at the end of follow-up and in 2/40 (5%) patients the pain decreased on the first week after TAE but return to worsening at 1 month, the re-embolization was considered but the patient did not want to.

In terms of median pain VAS reduction, comparative before and 6 months after TAE, significant differences were obtained (8 vs 0.5, $P = 0.0001$). Six months after the procedure, 26/40 (65%) of the patients did not take oral analgesic medication and 8/40 (20%) patients did so occasionally, whereas all of the patients reported taking it continuously previous TAE.

Regarding the ROM, the median flexion and abduction grades after embolization were 150°, respectively. Significant differences were found in terms of increased mobility in flexion before and 6 months after TAE, respectively (79.5° ± 18.5° vs. 133° ± 24.5°, $P = 0.0001$). Similar result was obtained for abduction (72.4° ± 18.8° vs. 129.7° ± 27.9°, $P = 0.0001$). There was also a substantial

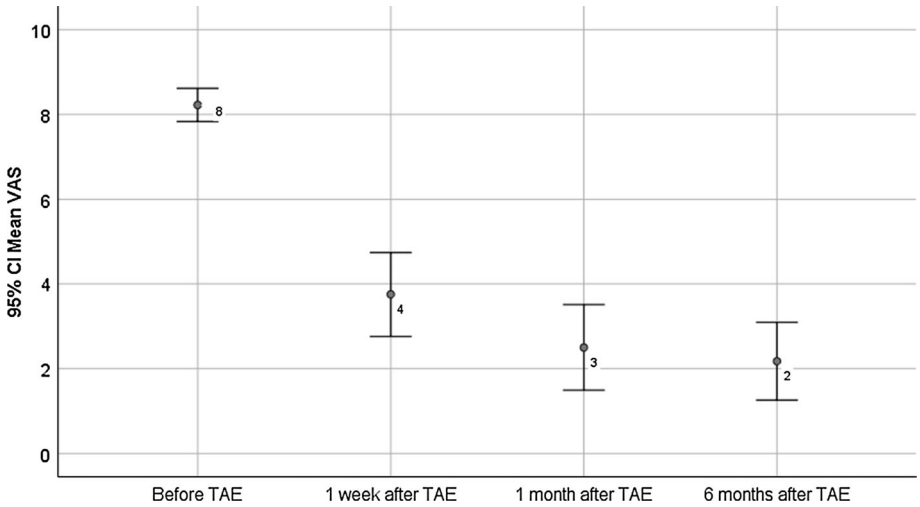

Fig. 3 Box-and-whisker diagram where the evolution changes in mean pain after transcatheter arterial embolization (TAE) is summarized. A significant reduction in pain by visual analogue scale (VAS) can be observed

improvement in internal and external rotation before and 6 months after embolization; these data can be observed in Fig. 4. 13/40 (32.5%) patients, who did not reach the lumbosacral junction before TAE, reached interscapular region at 6 months; in addition, 39/40 (97.5%) patients reached twelfth dorsal vertebra or higher at the end of follow-up. About external rotation, 32/40 (80%) patients reached the target mobility at 6 months after TAE. Results attending to ROM are described in Table 2.

Improvements in ROM was variable in time, appearing 24 h after TAE in 18/40 (45%) procedures and only after further physical therapy in 20/40 (50%) patients. In these, physical therapy began in the first 2 weeks after TAE in 38/40 (95%) patients, being the average physiotherapy time of 30 sessions. Physical therapy was not necessary in two patients. Only 2/40 patients (5%) did not refer any improvement in mobility after TAE.

Complete recovery occurred in 37/40 (92.5%) patients, partial recovery in 2/40 (5%), and 1/40 (2.5%) patient was classified as "no recovery". These results were the same at 6 months and at 12 months after TAE. In those 2/40 (5%) patients that did not show any improvement in mobility, surgery was necessary 10 and 14 months after TAE, respectively. They were classified as partial recovery based on them downstaging in pain VAS (8 to 2 and 10 to 0, respectively).

The mean follow-up was 21.2 ± 10.5 months and the results were stable in all patients. No clinical recurrence appeared in any patient classified as complete recovery, even after 48 months.

In our series, there were no relevant clinical outcomes differences after TAE in AC adjusted by previously reported imaging findings suggestive of capsulitis on MRI ($P = 0.14$) or risk factors for AC such as smoking ($P = 0.45$) or diabetes ($P = 0.33$). There were also no statistical differences between the presence or not of joint enhancement in the angiography and pain VAS reduction after TAE ($P = 0.27$); moreover, if those patients evolved towards total or partial recovery ($P = 1.00$).

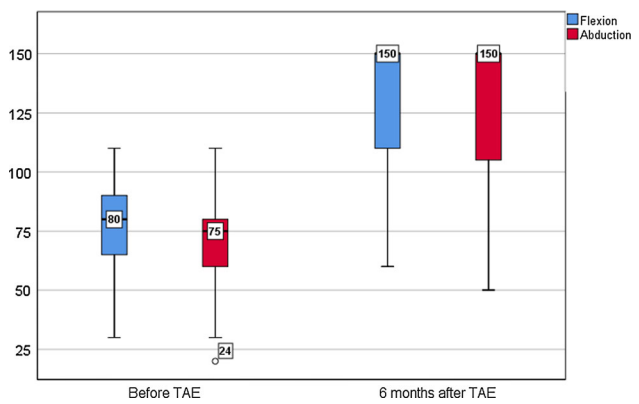

Fig. 4 Box-and-whisker diagram where the evolution changes in median flexion and abduction grades before and 6 months after transcatheter arterial embolization (TAE) can be visualized

Discussion

In this series, 40 patients presenting with idiopathic AC that did not respond to conservative management, experienced a significant reduction of pain within a week after TAE. It was also significant the improvement of mobility comparing before and 6 months after embolization, in flexion and abduction, respectively. These results were stable during follow-up.

There are some predisposing factors associated with AC such as diabetes, thyroid diseases, smoking, trauma, long immobilization, Dupuytren's disease [3, 11–15]. In our series, there were 7/40 (17.5%) diabetics, 10/40 (25%) had thyroid disease, 15/40 (37.5%) were smokers, one patient (2.5%) had Dupuytren's disease.

Coracohumeral ligament thickness and also thickening in the joint capsule at the level of rotator cuff interval, as well as the subcoracoid triangle sign, are characteristic MRI findings in AC [29, 34]. However, MRI should be reserved for the evaluation of other causes of shoulder pain, stiffness and restriction of motion, not to confirm a diagnosis of AC, being known that a normal MRI does not exclude AC [28]. According to this, 17/39 (43.5%) of the patients in our series showed no signs of capsulitis on MRI. AC is an exclusion diagnosis when there are clinical symptoms and suspicious exploratory findings.

Many authors have pointed out the relevance of hypervascularization of the capsule in the pathophysiology of AC. Okuno et al. reported an angiographic abnormal vascularization in all patients of their series [21–23]. However, only in 31/40 (77.5%) patients of our study presented this "blush" enhancement. The microscopic hypervascularization described in the studies carried out on samples of capsular tissues in patients with AC [6, 7] is not related in all occasions with increased vascularization in the angiographic study. In those 9/40 (22.5%) patients without capsule "blush", treatment was performed by deployment of embolic agent in those arteries corresponding to the painful areas previously observed on physical examination. When a capsular area is embolized in which an abnormal vascularization is not identified, the pain referred by the patient associated with AC is reproduced and the same occurs when a blush enhancement area is embolized. These patients also obtained clinical improvement in spite of the absence of hypervascularization, with no substantial differences by comparing presence or not of arterial enhancement and pain reduction after TAE ($P = 0.27$), even if they evolved towards total or partial recovery ($P = 1.00$).

Reported complications related to the arterial embolization range between 0.4% and 12%, including ischemia, non-target embolization and overall major complications [33]. In our series, there were no major complications. Ischemic events after embolization are lower when using IPM/CS as embolic agent compared to other embolic agents as microspheres, due to IMP/CS—iodinated contrast media mixture generates a micron-sized particle acting as a temporary embolic agent and in a period between 1 and 48 h are reabsorbed [22, 25, 27]. Using microspheres, paraesthesia and skin complications such as transient erythema during 1 month after embolization of epicondylitis, and up to 3 months after embolization of knee osteoarthritis have been described [24, 35].

Even when AC is considered a self-limiting entity, it could last up to 24 months where three phases are classically described, painful-stiff-recovery [16, 36, 37]. However, many investigators consider that there is not a completely recovery without treatment [4, 17–19]. In our series, there was an overall progressive decreasing of pain after TAE in 33/40 (82.5%) patients where most patients, 26/40 (65%) patients presented less than 3 pain VAS score at 1-week follow-up after TAE, and 28/40 (70%) at 1-month follow-up. Our results in terms of pain reduction correlate with the literature. Okuno et al. have published in two studies of 7 and 25 patients that the mean VAS score significantly decreased at 1 week, 1, 3 and 6 months, respectively, after embolization. Also, there was no recurrence during follow-up up to 16 months [22, 23]. The improvement in pain is reflected in the decrease in analgesic consumption, the same that the results presented by Okuno et al. [23].

Regarding ROM, significant improvements were found before and 6 months after TAE, from 79.5° to 133° in flexion. These results were consistent over time and no clinical or functional recurrence appeared. Similar results were obtained to the literature. Significant improvements of flexion at 6 months after TAE in a study of 25 patients with AC are described, where the mean range increased from 65° to 150° compared to pre-embolization values [22]. Thus, the clinical relevance of TAE is to not only accelerate pain relief and shoulder motion, but also to be considered as an effective therapy for those patients refractive to conservative treatments.

In 2013, TAE for shoulder pain was described for the first time [21]. After that, other studies have demonstrated good results of TAE for the treatment of the frozen shoulder [22–24], and this study, to our knowledge with the largest number of patients to date, supports them. Limitations could be considered based on the absence of a control group, lack of blindness to treatment and a single-centre design that reduces the validation for the reproducibility of the outcomes. Also, after the TAE procedures, the patients continued the physiotherapy so the contribution of each treatment cannot be clearly assessed in the study. Interviews and physical examinations during follow-up have been performed by rehabilitation physicians and interventional radiologists; it could be source of bias because the same people have been involved in the procedure of TAE.

Further studies case–control comparative studies are required to formally including this technique in the treatment of shoulder AC.

In conclusion, the arterial embolization in adhesive capsulitis relieves pain and allows shoulder motion recovery in a shorter period of time compared with the natural history of the disease and these clinical results are consistent in the mid-term follow-up.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval The study performed was in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Institutional Review Board (IRB). Our hospital clinical research ethics committee approved this study.

Consent for Publication Consent for publication was obtained for every individual person's data included in the study.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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