Role of Embolization in Pain Management in Musculoskeletal Disease

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• **Speakers Bureau:** Terumo, Asahi Intech
• **Research Grants:** Terumo, Tokyo, Japan
• **Reference Unlabeled/Unapproved uses of drugs or products:** Imipenem cilastatin sodium (Primaxin, Merck & Co., Inc., Whitehouse Station, NJ, USA), which is approved as an antibiotics, as embolic material.
TRANSCATHETER ARTERIAL EMBOLIZATION USING IMIPENEM/CILASTATIN SODIUM FOR TENDINOPATHY AND ENTHESOPATHY REFRACTORY TO NONSURGICAL MANAGEMENT

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ABSTRACT

Purpose: To evaluate the feasibility and effects of transcatheter arterial embolization with imipenem/cilastatin sodium (CS) to treat tendinopathy and enthesisopathy that are refractory to traditional nonsurgical management.

Materials and Methods: Transcatheter arterial embolization with imipenem/CS as an embolic agent was performed in seven patients (five men; mean age, 51.7 y) with tendinopathy and enthesisopathy (patellar tendinopathy, n = 1; rotator cuff tendinopathy, n = 2; plantar fasciitis, n = 1; lateral epicondylitis, n = 1; iliotibial band syndrome, n = 1; and Achilles insertion tendinopathy, n = 1). All patients had unrelenting pain at the site of tendinopathy and enthesisopathy before the procedure. Technical success, adverse events, and changes in visual analog scale (VAS) scores were assessed.

Results: All procedures were technically successful, and no major adverse events developed. Compared with before the procedure, mean VAS scores were significantly decreased at 1 day, 1 week, and 1 and 4 months after the procedure (72.7 mm ± 9.9 vs 17.4 mm ± 18.5, 16.0 mm ± 18.1, 13.7 mm ± 7.3, and 9.7 mm ± 6.8, respectively; all P < .001).

Conclusions: Transcatheter arterial embolization with imipenem/CS was feasible and effectively relieved unrelenting pain associated with tendinopathy and enthesisopathy.
75y.o. female  Plantar fasciitis

Heel pain for more than 1 yr

Diagnosed as Plantar fasciitis

Refractory to standard treatments
  (rest, physical treatment, oral pain killer)

Severe pain (visual analog scale (VAS) : 72mm )
  was persistent.
<table>
<thead>
<tr>
<th>Fluoroscopic Image</th>
<th>Digital Subtraction Image</th>
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<tbody>
<tr>
<td><img src="image1.png" alt="Fluoroscopic Image" /></td>
<td><img src="image2.png" alt="Digital Subtraction Image" /></td>
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75y.o. female  Plantar fasciitis
Temporary Embolic particle

- Imipenem/cilastatin sodium (IPM/CS)
- Approved as an antibiotic
- Compound slightly soluble to water
- Forming small particle (diameter is 10-70 um) when we suspend with 5-10ml of contrast

- Already in use as an embolic agent in Japan from 1990 - to stop intestinal tumor bleeding (oozing) due to its safety profile

Woodhams et al. *Springerplus*. 2013
Temporary Embolic particle

Fig. 6. Microscopic findings of VX 2 tumor immediately after the infusion of IPM/CS suspension. IPM/CS emboli occluded tumor vessels (arrows). (H-E stain, Rt. × 100, Lt. × 200)

Aihara et al. Interv Radiol. 1999
Before Embolization

75y.o. female  Plantar fasciitis

After Embolization
Before

Early venous filling

After

Before Emobli
1 year follow up of first 12 patients with tendinopathy and enthesopathy

Pain scores (VAS) (mm)

- Rotator cuff tendinopathy
- Patellar tendinopathy
- Lateral epicondylitis
- Plantar fasciitis
- Iliotibial band syndrome
- Achilles insertion tendinopathy

weeks
Study Design of our Clinical Trial (Two stage design)

1st stage Entry

7 patients

Embolization Procedure

1 Month
3 Months
6 Months

Severe complications
No good response

Study would be terminated

Report the short term results

2nd stage Entry

Added 13-20 patients

1 year

Total 20 – 30 patients

Long term Follow-up (2 to 3 years)

Further Entry

Report the long term results

IRB approved

Severe complications
No good response

Total 20 – 30 patients

Study would be terminated

Report the short term results

Report the long term results
From 2012 to 2016

- Tendinopathy and Enthesopathy 90 cases
- MSK shoulder pain (Frozen shoulder etc) 115 cases
- Knee osteoarthritis 75 cases
- Sports injuries 40 cases
- Persistent pain after joint replacement 25 cases
- Others (hip, ankle, wrist, elbow, etc) 147 cases

Total n = 492
Frozen Shoulder

• Estimated prevalence is 2% to 3% in the general population

• Characterized by painful restriction of shoulder motion.

• Persistent pain (mild - severe)
  44% at 3 years from symptoms onset
  35% at 7 years from symptom onset


• Optimal treatment for refractory cases has not reached consensus
Frozen shoulder (Adhesive Capsulitis)

- Characterized by painful restriction of shoulder motion.
- Uncertain etiology (the source of pain has not been defined)
- Many refractory cases (35% had residual pain at seven years [1])
- Optimal treatment for refractory cases has not reached consensus
Frozen shoulder

Normal shoulder

Frozen Shoulder

Results: **Angiographic findings**

Figure 3. Angiographic findings in a 60-year-old patient before and after transcatheter arterial embolization.
A, acromion; C, coracoid; H, humeral head.

Results 4: Effective

Change of Pain VAS Scores

- Overall Pain VAS
- Nighttime Pain VAS

Change of ASES Scores (Shoulder function)

Richly vascular area; small arteries are stained for their smooth muscle media by antibody to alpha smooth-muscle actin (immunoperoxidase ×100).
Why embolization of abnormal neovessels relieve pain?

- Improving inflammatory conditions
  (abnormal vessels maintain inflammation)


- Reducing stimulation from accompanying nerve fiber
  (Nerve fiber grow around neovessels)
Figure 1 Microscopic findings of shoulder capsule tissue from frozen shoulder (right) compared with control tissue (left). Nerve fibers were often located close to increased small vessels in frozen shoulder tissue.

Ljung et al 1999 J Orthop Res

in Tennis elbow tissue
• Pain-related nerve fibers
  increased small vessels
Histological study detecting Neovessels and Accompanying Nerve fibers

- Tennis Elbow

- Achilles tendinitis

- Patellar tendinitis

- Frozen shoulder

- Knee Osteoarthritis

- Shoulder Rotator cuff tear

- Chronic low back pain

- Anterior knee pain

- Temporomandibular disorder
Why embolization for **benign** painful conditions?

- Chronic pain in MSK disease
  - Many resistant cases
  - Reduce individual QOL
  - Great economic impact
Before and After Embolization (Angiographic findings)
Can Temporary material show prolonged effect?
Our embolization procedure

Target: increased abnormal vessels (small diameter)

Particle size: 40-70 μm

Treatment goal is not total vessels occlusion but decrease abnormal blood flow and remain physiological blood flow

TAME
(Transcatheter Arterial Micro-Embolization)
The Long term outcomes of TAME
The Long-term outcomes of TAME for resistant Frozen Shoulder

1\textsuperscript{st} and 2\textsuperscript{nd} stage entry
25 patients

TAME Procedure

1 Month
3 Months
6 Months
1 year

1 patient withdrew due to unrelated medical reason

Final Follow-up (Mean 3 years)
24 patients
Overall Pain score (VAS) (mm)

Mean 3.0

X = mean pain VAS score
Overall Pain sores (VAS) (mm)

<table>
<thead>
<tr>
<th>Years</th>
<th>Months</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>3</td>
<td>6</td>
<td>1</td>
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<tr>
<td>1</td>
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</tbody>
</table>

Mean 3.0
3 years follow-up TAME for Frozen Shoulder in 24 patients
(Change of overall VAS scores)

Severe pain (VAS: 70-100)
Moderate pain (VAS: 40-69)
Mild pain (VAS: 1-39)
No pain (VAS: 0)

87.5%
91.6%

J Shoulder Elbow Surg (Under review)
The Change of Range of Motion

Anterior Elevation

Graph showing the change in range of motion for anterior elevation over time, with measurements at different time points: pre, 1mo, 3mo, 6mo, 1y, and 3.0 y.
Knee Osteoarthritis

• Osteoarthritis is a common and major cause of pain and disability.

• Symptoms of knee osteoarthritis are seen in an approximately 10% of people over 55 year-old.
Staging of Knee Osteoarthritis

KL grade = Kellgren-Lawrence grade
Staging of Knee Osteoarthritis

KL 1
KL 2
KL 3
KL 4

Conservative treatments (pain relievers etc)
Joint Replacement Surgery
Staging of Knee Osteoarthritis

- There are many cases who are resistant to conservative treatments

- For years, arthroscopic surgeries have been performed for these conditions. (650,000 procedures/year in USA) before 2002

- Comparing to sham procedure, effectiveness of arthroscopic surgery was not proven in a double-blinded, randomized, placebo-controlled trial.

Moseley et al. *NEJM* 2002
Figure 1. Normal and abnormal vasculature of descending genicular artery
MC, medial condyle; LC, lateral condyle.
The Long-term outcomes of TAME for Mild Knee Osteoarthritis

1st and 2nd stage entry

TAME Procedure

1 Month
3 Months
6 Months
1 year

Final Follow-up (2 to 3 years)

20 patients
Results 2: Angiographic findings

Before Embolization

After Embolization

MC
LC
Tibia

MC
LC
Tibia
Staging of Knee Osteoarthritis

KL 1

KL 2

KL 3

KL 4
The population of good response at 6 months year after TAME according to KL stage knee OA.

KL: Kellgren-Lawrence scores

<table>
<thead>
<tr>
<th>KL</th>
<th>Number of patients</th>
<th>Good response</th>
<th>Not Good response</th>
</tr>
</thead>
<tbody>
<tr>
<td>KL1,2</td>
<td>19</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>KL3</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KL4</td>
<td>8</td>
<td></td>
<td>0</td>
</tr>
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KL: Kellgren-Lawrence scores
Is TAME safe?
Patients

Tendinopathy and Enthesopathy  n=35
Frozen shoulder  n=20
Early Knee OA  n=17
MSK shoulder pain without surgical indication  n=15
Persistent pain after Knee Replacement Surgery  n=13

Total  n = 100

All patients are refractory to standard conservative treatments
<table>
<thead>
<tr>
<th>Complications</th>
<th>CTCAE Grade</th>
<th>Number</th>
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</thead>
<tbody>
<tr>
<td>Pain during procedure</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Subcutaneous hematoma</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Radial artery spasm</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Post procedure pain</td>
<td>1-2</td>
<td>4</td>
</tr>
<tr>
<td>vomiting (CE side effect)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fever ( &gt;38)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral paresthesia</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>Joint instability</td>
<td>none</td>
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Any affect to musculoskeletal component?

MRI study 2-3 year after TAME for mild knee OA
Pre Embolization

MRI T2 Coronal

2 years after Embolization

Effusion
<table>
<thead>
<tr>
<th>Pre Embolization</th>
<th>2 years after Embolization</th>
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<tr>
<td><img src="image1" alt="MRI" /></td>
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<td><img src="image3" alt="MRI" /></td>
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<td><img src="image5" alt="MRI" /></td>
<td><img src="image6" alt="MRI" /></td>
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mild-moderate Knee osteoarthritis

MRI findings at 2 years after TAME (n = 20)

<table>
<thead>
<tr>
<th>Findings</th>
<th>2 years after TAME</th>
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<tbody>
<tr>
<td>Bone marrow necrosis</td>
<td>0</td>
</tr>
<tr>
<td>Aggressive degenerative change</td>
<td>0</td>
</tr>
<tr>
<td>Obvious cartilage loss from baseline</td>
<td>0</td>
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How often patients had abnormal vessels?

Frozen shoulder
48/48 cases
100%(95%CI: 89-100%)

Total MSK shoulder pain
103/115 cases
89.6%(95%CI: 83-95%)
How often patients had abnormal vessels?

Knee Osteoarthritis
72/75 cases
100% (95% CE: 89-100%)

visible 72

invisible 3
Pain recurrence?

Patients’ self-report of follow-up survey

When did you have pain recurrence after your satisfied pain relief?

- Frozen shoulder: No recurrence 100%
- Tendinopathy and Enthesopathy:
  - No recurrence 79%
  - Before 6 months: 15%
  - After 6 months: 6%

No recurrence 100%
How about using Microsphere?

Small study TAME using Embozene 75um for mild knee OA
Changes of pain score after TAME using EZ 75um
Transit dermal rash after TAME using 75μm Embozene

1 week after TAME

3 week after TAME
Ongoing Plan and Future Plan

• Animal study
to investigate mechanism
to find appropriate embolic material

• RCT
  TAME vs other treatment
  TAME vs placebo procedure