PANEL DISCUSSION

# Genicular Artery Embolization: Building Evidence and Practice

Experts discuss current evidence and lessons learned, patient candidacy, go-to embolics and devices, barriers to widespread use, predictions for future practice, and more.

**With Mark W. Little, FRCR; Joaquim Maurício da Motta-Leal-Filho, MD, PhD; and Yuji Okuno, MD**


**Mark W. Little, FRCR**
Consultant Interventional Radiologist and Academic Lead
University Department of Radiology
Royal Berkshire NHS Foundation Trust
Reading, Berkshire, United Kingdom
mark.little@royalberkshire.nhs.uk

**Joaquim Maurício da Motta-Leal-Filho, MD, PhD**
Interventional Radiologist
Universidade de São Paulo (USP)
São Paulo, Brazil
jotamauf@yahoo.com.br

**Yuji Okuno, MD**
Chief Director
Okuno Clinic
Tokyo, Japan
okuno@okuno-y-clinic.com


## To start, what are your impressions and takeaways from the currently available evidence for genicular artery embolization (GAE)?

**Prof. Little:** GAE has burst onto the scene over the last 8 years as a potential new treatment for the millions of patients with osteoarthritis (OA) of the knee. New data are constantly emerging, which is extremely important as we learn and adapt. Currently, most studies are noncontrolled cohort studies. Despite differences in methodology, embolic choice, and patient demographics, there is data conformity—with appropriate training, GAE is reported as a safe procedure. Furthermore, responders experience a dramatic reduction in pain and improvement in function within the first 3 months after the procedure. The benefit is then maintained to midterm follow-up. The issue with the current state of the evidence is the lack of controlled data. As with all procedures designed to improve pain, we must consider the placebo effect. Sham-controlled trials are needed to confirm the efficacy of GAE. At present, there are two randomized, sham-controlled trials published on GAE elucidating a benefit of the procedure beyond a sham procedure when complete embolization is performed. It is an extremely exciting time to be involved in musculoskeletal (MSK) embolotherapy. We now need large, randomized, sham-controlled trials with longer-term follow-up to confirm efficacy.

**Prof. Motta-Leal-Filho:** My impressions and takeaways about the currently available evidence for GAE are:

- The GAE technique is effective and safe, whether with imipenem/cilastatin sodium (IPM/CS) or microspheres.
- The technical success rate is very high (I would say 100%) if you consider the embolization of at least one artery responsible for irrigating the inflamed area; the genicular arteries communicate with each other, and it is often possible to perform embolization of the target through one, two, or three arteries.
- GAE appears to work better for patients with less severe OA/Kellgren-Lawrence (KL) grade 1 and 2 (ie, patients with less joint deformity).

- The 1-year cumulative clinical success rate appears to be ≥ 60%, as measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Knee Injury and Osteoarthritis Outcome Score (KOOS).
- KOOS appears to better capture patients' clinical improvement.
- GAE promotes a significant reduction in the use of analgesics, opioids, anti-inflammatory drugs, and joint infiltrations by patients. This is perhaps a secondary endpoint and often undervalued, but I consider it as important as improving pain—remembering that these patients are chronic users of these medications.
- Serious complications are very rare (attributed to the caliber of the embolic agent and the technique) and self-limited, and some are part of the learning curve, but skin discoloration is a frequent adverse event (approximately 50%).

**Dr. Okuno:** From what has been shown so far, GAE can be safely performed. It is technically feasible, and interventional radiologists with experience in embolization procedures can perform it. Regarding its effectiveness, there is room for debate, but it could serve as a treatment option for patients who have not improved with injections, physical therapy, or conservative treatments and have not reached the point of undergoing joint replacement surgery.

## What are the most important lessons to be learned from ongoing trials or the next generation of studies?

**Dr. Okuno:** Prof. Little is conducting the GENESIS 2 trial to investigate the differences with the placebo group.[1] Dr. Sandeep Bagla is examining outcomes compared to steroid injections in the MOTION trial (NCT05818150). The results of these studies will be crucial in determining how much benefit there is compared to only undergoing observation or receiving steroid injections. Furthermore, in the GAUCHO study in Brazil (see *GAUCHO Trial Summary* sidebar), investigators are researching the differences in clinical outcomes between IPM/CS and permanent embolization materials, so determining which embolization material is optimal will also be important.[2]

**Prof. Little:** The interventional radiology (IR) community must focus on producing level 1 data for GAE so that it may be incorporated into treatment guidelines. The procedure has the potential to change the way in which knee OA is treated. Such a paradigm shift will only be possible with robust data and continued monitoring of these patients over time. I am also interested to see the emerging data correlating imaging and biomarkers with treatment outcome. These data alongside efficacy and safety data will enable us to refine patient selection and technique, which will optimize clinical success.

**Prof. Motta-Leal-Filho:** For future studies, there are several important questions must be defined, including:

- Should definitive or temporary particulate embolic agents (bioabsorbable) be chosen?
- Is there room for use of a liquid embolic agent?
- Is the association of GAE and joint infiltration with hyaluronic acid better or equal to GAE or infiltration alone?
- Is GAE better than taking medicine and/or joint infiltrations?
- Does GAE immediately before knee replacement surgery for KL grade 4 patients improve postoperative pain control? (Postoperative pain after knee surgery limits or delays the patient's recovery.)
- Can physiotherapy, rehabilitation, and strength training increase the longevity of clinical success obtained with GAE?

## In your practice, how do you work up patients to ensure candidacy? What are some essentials in your office setup and imaging?

**Prof. Motta-Leal-Filho:** I work following the eligibility criteria previously defined for patient selection of our study, the same criteria that were defined for the research protocol and published in Correa et al.[2] At this moment and due to the good results of our studies, we have started to discuss with the orthopedic team new indications for the technique (and other groups of patients with potential benefits, even if limited).

During the medical consultation, in addition to collecting the clinical history, we apply the symptom questionnaires (WOMAC and KOOS) and the visual analogue scale (VAS). During the physical examination, we palpate the four quadrants of the knees and the patella to determine the VAS score in each of the five regions examined. The mobility and range of movement of the joint are also assessed. An MRI with contrast is also performed, seeking to identify not only signs of synovitis but also whether there are fractures, osteophytes, deformities, and ligament or meniscus injuries.

**Prof. Little:** Patients are referred from orthopedics, rheumatology, physiotherapy, or general practice, or they are self-referred. All patients have an x-ray to assess disease severity. As part of the GENESIS trials, we are currently only offering GAE to patients with mild to moderate knee OA. I see patients in a dedicated clinic. I take a detailed history of their knee problems and past medical

## GAUCHO TRIAL SUMMARY

By Joaquim Maurício da Motta-Leal-Filho, MD, PhD

Yuji Okuno, MD, began to perform inflammatory embolization with IPM/CS because there were already records in Japan on use of this material for treatment of gastrointestinal hemorrhage and chemoembolization. When mixed with contrast, IPM/CS precipitates, forming crystals of 10 to 70 µm and becoming a "temporary embolic agent." Dr. Okuno knew he needed to test his hypothesis—reducing or eliminating the pain of OA by treating synovitis through embolization—without causing osteonecrosis. However, IPM/CS is a drug rather than a device, so there are regulatory issues. Additionally, indiscriminate use of IPM/CS can contribute to antibiotic resistance, it has the potential to cause allergy/anaphylaxis, and calibration is heterogeneous depending on the amount of contrast that is mixed. The mechanism of action involved in pain relief is unknown, nor is it known how long vessel occlusion lasts. In parallel, researchers from the United States and Europe started to successfully use microspheres to perform GAE in cohort studies but not in RCTs.

Thus, Mateus Picada Correa, MD, and I decided to run the GAUCHO trial, a single-center, prospective, blind, RCT comparing the safety and efficacy of both embolic agents, with the goal of determining whether one is superior. Sixty patients (KL grade 1-3) with refractory to conservative management at least for 6 months were enrolled, with 30 patients in each arm (block randomization method, 3:3 allocation). Technical success was defined as superselective catheterization and embolization (using IPM/CS or Embospheres 100–300 µm) of at least one feeding artery supplying the hyperemic synovium. Primary endpoints included clinical and sustained clinical success, which were defined as improvement in symptoms, 50% reduction in WOMAC pain score, or increase of ≥ 10 points in KOOS at 3- and 12-month follow-up, respectively. Secondary endpoints included improvement in synovitis (using Whole-Organ MRI Score/MRI) and reduced need for medication to relieve pain and/or conservative therapies. To date, we have performed 100% of the GAE procedures (60 patients/82 knees), and 60 (100%), 54 (90%), and 48 (80%) patients have completed the 1-, 3-, and 12-month follow-up, respectively. The last six patients completed 12-month follow-up in December 2023. Six patients were lost to follow-up. The full protocol was published in Correa et al.[1]

1. Correa MP, Motta-Leal-Filho JM, Lugokeski R, et al. GAUCHO - trial genicular artery embolization using imipenem/cilastatin vs. microsphere for knee osteoarthritis: a randomized controlled trial. Cardiovasc Intervent Radiol. 2022;45:903-910. doi: 10.1007/s00270-022-03089-z

and surgical history. I also explore analgesia use and how the condition affects their life. I examine the knee joint, assessing range of motion and areas of pain. Patients then undergo contrast-enhanced MRI, which allows me to assess the severity and distribution of OA. Contrast enhancement enables me to assess the distribution and severity of synovitis, which is used to guide embolization. The MRI also allows me to look for other causes of knee pain that would not benefit from GAE, such as cruciate ligament injury. It is important to exclude patients with peripheral vascular disease and inflammatory or infective arthropathy.

**Dr. Okuno:** MRI examination with or without contrast medium is required, and we check two specific aspects. The first is confirmation of the presence of inflammation. This is confirmed by findings such as the presence of effusion, edema, or contrast enhancement. The second is assessment of any structural defects. Specifically, we investigate severe meniscus injuries, ligament ruptures, and poor prognosis bone marrow lesions. Such serious structural defects can lead to a poor prognosis for GAE, so it is important to identify them in advance. Additionally, psychologic and social factors cannot be ignored. Patients with abnormally high Hospital Anxiety and Depression Scale or Pain Catastrophizing Scale scores tend to have difficulty responding to any pain treatment, not just GAE.

### How have you built and grown your referral base? What advice do you have for interventionalists as they start their own practices?

**Dr. Okuno:** At the beginning of my career, I used to attend outpatient consultations with orthopedic surgeons and collaborate to evaluate and discuss patients undergoing conservative therapy for knee OA. If interventional radiologists could dedicate even half a day a week to such interactions, it could lead to a highly beneficial professional relationship.

Presentations within the orthopedic community are also important. It would be a good idea to present cases of GAE for both recurrent knee hemoarthritis and knee OA. Marketing through social media and the web is also crucial. Currently, we are developing a system to support IRs who want to enhance their web marketing efforts.

**Prof. Little:** We are currently offering GAE as part of the GENESIS 2 trial. We were the first European group to commence GAE for knee OA in 2018 with the GENESIS 1 trial. We are very fortunate to work collaboratively with the department of orthopedics. Referrals have grown as word has spread about the technique, and as with any new procedure, when people hear that patients have done well, more referrals come! One of our first GAE patients is now at 5-year follow-up; this gentleman in his early 70s went from walking with a stick to recently completing a long walking tour. His journey is what inspires me to keep working to produce data and improve our understanding of GAE.

**Prof. Motta-Leal-Filho:** My advice is to work with the orthopedic team to appropriately select patients to receive GAE so that you can demonstrate the benefits of the technique to the orthopedic team. Selected patients ideally have chronic pain and less joint wear, are refractory to analgesics and infiltrations, and do not have arthritis or inflammatory disease. The possible benefits of the procedure, as well as its limitations, should be explained to the orthopedic team and the patients. Select appropriate patients and start with the cases that have the greatest chance of success.

## What is your go-to embolic and why?

**Prof. Little:** I used 100–300-µm Embosphere particles (Merit Medical Systems, Inc.) for GENESIS 1 and 100-µm Embozene particles (Varian Medical Systems) for GENESIS 2. A review of the literature shows a geographic disparity between embolic use. In eastern and southeastern Asia, IPM/CS (an antibiotic that acts as a temporary embolic agent in blood) is frequently used for GAE. In the United Kingdom, IPM/CS is not licensed as an embolic agent, and it would be extremely challenging to use it. There is a need for purposely designed temporary embolic agents for use in MSK embolotherapy. These would have a role in GAE but also in other MSK conditions where permanent embolic agents pose too great a risk of nontarget embolization.

**Prof. Motta-Leal-Filho:** For GAE, my preferred embolic agent is microspheres between 100–300-µm calibration. Because these microspheres are dedicated to embolization, safe, and reach the endpoint (disappearance of blush) earlier, there is a reduced exposure to radiation and less contrast use during the procedure.

**Dr. Okuno:** Our current first-line material for GAE is Nexsphere-F (Nextbiomedical; size 100–300 µm, dissolves in 8 hours). In our experience, it excels in both safety and effectiveness, has been shown to be as safe as IPM/CS, and delivers better treatment outcomes than IPM/CS.

## What other types of devices are essential to the procedure?

**Prof. Motta-Leal-Filho:** Our essential items include a diagnostic catheter with reverse tip for catheterization of the ostium of the genicular arteries, a 5-F internal mammary catheter to facilitate catheterization with the microcatheter and save procedure time, a 2-F or smaller straight tip microcatheter, and a 0.014-inch moldable-tip guidewire.

**Dr. Okuno:** A Judkins right angiographic catheter, because the shape is suitable for selecting the genicular artery, as well as a 1.7-F microcatheter.

**Prof. Little:** It is essential to have a sound knowledge and experience of microcatheters. The technical skills and anatomic variants encountered in GAE can be extremely challenging. I would suggest that having experience in prostate artery embolization is useful before commencing GAE. Gaining proctorship and attending training on anatomy, technique, and embolization endpoint are advised to perform safe and effective GAE. The genicular arteries are small and prone to spasm. A 2-F microcatheter is my standard catheter for GAE. The liberal use of nitrate is also recommended to optimize anterograde flow into the pathologic hyperemic process while minimizing spasm.

## What are your top tips for procedural success?

**Prof. Little:** Learn the anatomy, do cases with a colleague, and get a proctor.

**Dr. Okuno:** First, optimizing the embolic material volume is crucial. Overembolization can lead to decreased clinical outcomes, so it is essential to stop administration when abnormal blood vessels disappear, leaving normal blood flow. Second, check the painful point tenderness before the procedure—as well as after embolization—to ensure and verify a significant reduction or disappearance. If point tenderness remains, it indicates that some amounts of abnormal blood vessels are still untreated.

**Prof. Motta-Leal-Filho:** The main tips are (1) select the patient with KL grade 1 or 2 OA and with synovitis on MRI; (2) use antegrade femoral access (the shortest route to the genicular arteries); (3) use a diagnostic catheter with a reverse tip to catheterize the ostium of the genicular arteries (5-F internal mammary catheter); (4) perform GAE with 0.3-mL aliquots of the embolic agent

solution using a 1-mL syringe; and (5) after pain improves, encourage muscle strengthening to prolong clinical success.

## What are the barriers to wider use, and how can these be addressed?

**Dr. Okuno:** There are few technical barriers. The biggest obstacle lies in whether we get public insurance coverage. Additionally, strategies are needed to attract patients. Establishing good relationships with orthopedic surgeons and other medical professionals is required. Alternatively, marketing strategies using the internet, social media, and traditional media may be necessary to attract patients.

**Prof. Motta-Leal-Filho:** For now, I think that the biggest barrier to using GAE more widely is the level of scientific evidence for the procedure; more research (RCTs, high level) is needed. But, in my opinion, this will be resolved as the results of ongoing or upcoming clinical studies are published. Once this is resolved, I think another barrier will be referral from the orthopedic team for the interventional radiologist to perform GAE. The solution may be to perform combined procedures such as GAE plus infiltration, for example.

**Prof. Little:** As discussed previously, GAE has the potential to revolutionize the treatment for knee OA. We need to ensure that the IR community produces high-level, generalizable evidence so that the procedure can be offered to patients worldwide as part of evidence-based guidelines.

## What do you predict for the near future of GAE practice? What are the keys to growing awareness and acceptance of the procedure?

**Prof. Little:** GAE can help patients with knee OA that is resistant to conservative treatment but not yet severe enough to warrant joint replacement surgery. This group of patients has an unmet treatment need and is challenging to manage. Engagement with orthopedic surgery, rheumatology, and general practice will identify potential patients and should help these services by offering a potential new treatment strategy.

**Dr. Okuno:** In the near future, GAE is likely to be applied to sports injuries. Utilizing this as a treatment for sports injuries also shows excellent results compared to other therapies.[3] Conditions such as "jumper's knee," pes anserine bursitis, and "runner's knee" can benefit from GAE treatment. Applying these treatments to high-level athletes (in sports such as football, American football, baseball) will contribute to increased awareness and recognition of GAE.

**Prof. Motta-Leal-Filho:** I predict that GAE will be considered as an alternative to the treatment of chronic knee joint pain associated with synovitis. I think GAE can gain more acceptance for its respective disease than the prostatic artery embolization technique for treatment of benign prostatic hyperplasia (a technique developed by us in 2008 at the Hospital das Clínicas of the University of São Paulo) and also more quickly enter the treatment guidelines for OA. There is also a greater potential in the volume of procedures given that the disease affects both men and women and most human beings have two knees. I also believe that the technique can be applied to the entire spectrum of patients (KL grades 1-4) who have chronic pain and synovitis, obeying the following criteria: (1) KL grade 1 to 3, young or old, with chronic pain refractory to conservative treatment and still no indication for knee prosthesis surgery; (2) KL grade 4 who underwent knee replacement surgery and continued to experience pain (this happens in up to 20% of cases); (3) KL grade 4 without clinical conditions for knee prosthesis surgery; and (4) hemarthrosis.

To increase awareness and acceptance, quality scientific studies must be conducted to increase the scientific evidence of the procedure. Discussion and debate must be had with the orthopedic team and rheumatologists, demonstrating to them the benefits of GAE, precisely in those patients for whom they "have nothing else to offer." The GAE technique must be shown to be associated with existing treatments such as infiltrations. ■

1. Little MW, Harrison R, MacGill S, et al. Genicular artery embolisation in patients with osteoarthritis of the knee (GENESIS 2): protocol for a double-blind randomised sham-controlled trial. Cardiovasc Intervent Radiol. 2023;46:1276-1282. doi: 10.1007/s00270-023-03477-z
2. Correa MP, Motta-Leal-Filho JM, Lugokeski R, et al. GAUCHO - trial genicular artery embolization using imipenem/cilastatin vs. microsphere for knee osteoarthritis: a randomized controlled trial. Cardiovasc Intervent Radiol. 2022;45:903-910. doi: 10.1007/s00270-022-03089-z
3. Okuno Y. Transarterial embolization for refractory overuse sports injury: pictorial case reports. Cardiovasc Intervent Radiol. 2023;46:1525-1537. doi: 10.1007/s00270-023-03496-w

*Disclosures*
*Prof. Little: Consultant to Merit Medical, Crannmed, Boston Scientific Corporation, and Guerbet; has received research grant funding from Varian Medical and Merit Medical.*
*Prof. Motta-Leal-Filho: None.*
*Dr. Okuno: Consulting fees received from Asahi Intecc, Shimadzu Corporation, and Terumo Corporation; medical advisor to ClearDynamic Inc and Nextbiomedical; research grant received from Guerbet, Nextbiomedical, and ENGAIN.*