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RESEARCH

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Role of geniculate artery embolization in the treatment of knee pain secondary to osteoarthritis

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Abstract

Background Osteoarthritis (OA) is a leading cause of chronic knee pain and disability with a reported prevalence of 25–30% of the population. Knee OA has traditionally been thought as a degenerative disease only related to chronic repetitive injury "wear and tear" mechanism, yet it is now considered as a much more complex disease of inflammatory nature induced by cytokines and inflammatory mediators through abnormal neo-vascularization (angiogenesis). The rational of geniculate artery embolization (GAE) is based on the hypothesis that suggesting a direct relationship between the abnormal angiogenesis and the chronic knee pain. As a novel treatment option based on occlusion of these abnormal neo-vessels via geniculate artery embolization, we postulated that such a mechanism will relieve pain and improve the quality of life. GAE has been previously approved as a safe and effective treatment in cases of post-knee arthroplasty hemarthrosis.

Purpose To evaluate the feasibility, safety, and efficacy of geniculate artery embolization for OA-related knee pain.

Materials and methods Sixteen patients with knee pain secondary to chronic OA refractory to conservative therapies for at least 6 months and not yet fit for total knee replacement were enrolled in a prospective single arm interventional study. GAE was performed using 150–300 µm microspheres. Patients were assessed and followed up using the visual analogue scale (VAS) for pain and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for the overall knee function at baseline and at 1 week, 1, 3, and 6 months post-embolization.

Results A total 16 patients presented by knee pain secondary to chronic OA were enrolled. All of them showed a remarkable improvement in the VAS and WOMAC scores, with better clinical outcome after GAE. Pre- versus post-embolization ± MDs in VAS score from 8.38 ± 0.81 (baseline) to 2.88 ± 1.54 after 6 months (post-embolization) equivalent to 66.66% improvement. There was also a satisfactory improvement in the WOMAC scores, with ± MDs drop from 77.94 ± 10.62 (baseline) to 49.69 ± 15.43 (post-embolization) equivalent to 37.41% improvement. No severe or life-threatening complications were reported.

Conclusions GAE holds promise as an effective minimally invasive procedure for the treatment of knee pain secondary to OA and could be introduced as a safe technique with no serious complications.

Keywords Osteoarthritis, Knee joint, Knee pain, Geniculate artery embolization, Interventional radiology

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Background

Knee osteoarthritis is a major cause of morbidity and disability, with a reported prevalence of 25–30% of the population [1]. Chronic knee pain secondary to OA requires diverse lines of medical approaches with subsequent decrease in the overall quality of life [2]. Various therapeutic approaches have been approved staring from the non-pharmacological management reaching up to total knee replacement [3].

Depending on the severity of the OA, the proper approach is tailored. In mild cases of knee OA, the initial suggested management is lifestyle modification in the form of weight reduction and regular physical exercise coupled with low doses of topical and oral medications [4]. Medications and intra-articular injections are considered as the pillars of management for patients not yet candidate for total knee replacement. However, persistent medication use has serious complications, including liver and renal impairment in addition to GIT ulcers. Besides, steroid and hyaluronic acid intra-articular injections revealed conflicting outcomes and sometimes necessitate repetitive treatment [5].

In spite of the fact that OA has been considered as a degenerative disease only due to continuous repetitive injury, now it has been categorized as an inflammatory disease induced by different types of cytokines and inflammatory mediators through abnormal neo-vascularization (angiogenesis) [6]. Angiogenesis has been linked to the formation of osteophytes, cartilage breakdown and neuro-sensitization [7]. So our target is to occlude these abnormal vessels preventing the transport of these inflammatory catabolic mediators and eventually breaking this vicious cycle.

As a novel minimally invasive treatment based on occlusion of these abnormal neo-vessels via geniculate artery embolization, we postulated that such a mechanism will relieve pain and improve the quality of life. Especially that GAE has been already endorsed as a safe and effective treatment in cases of post-knee replacement hemarthrosis [8].

To date, there has been a lack of cohesive data regarding the effectiveness of GAE techniques in the treatment of knee pain secondary to OA, particularly in comparison with the other treatment modalities (Tables 1, 2 and 3).

Table 1 Comparison between the baseline VAS score and its follow-up at 1 week, 1, 3 and 6 months after embolization

VAS score	Baseline	1wk	1 month	3 months	6 months	Test value	*P*-value	Sig
Median (IQR)	8 (8–9)	3 (3–4)	3 (2–4)	2.5 (2–3.5)	3 (1.5–4)	40.878$^{\neq}$	< 0.001	HS
Mean ± SD	8.38 ± 0.81	3.31 ± 0.79	2.88 ± 1.02	2.75 ± 1.24	2.88 ± 1.54			
Range	7–10	2–5	1–4	1–5	1–6			
% of reduction	–	60.48 ± 8.38	66.26 ± 10.21	67.98 ± 12.04	66.66 ± 15.70			

Post hoc analysis

Baseline				1 Week			1 month		3 months
1wk	1 month	3 months	6 months	1 month	3 months	6 months	3 months	6 months	6 months
< 0.001	< 0.001	< 0.001	< 0.001	0.052	0.089	0.332	0.414	1.000	0.480

P-value > 0.05: Non-significant; *P*-value < 0.05: Significant; *P*-value < 0.01: Highly significant

$^{\neq}$: Friedman test

Table 2 Comparison between the baseline WOMAC score and its follow-up at 1 week, 1, 3 and 6 months after embolization

WOMAC score	Baseline	1wk	1 month	3 months	6 months	Test value	*P*-value	Sig
Mean ± SD	77.94 ± 10.62	52.38 ± 11.25	51.13 ± 13.31	50.13 ± 14.28	49.69 ± 15.43	174.731$^{\bullet}$	< 0.001	HS
Range	60–92	37–72	34–77	32–76	30–73			
% of reduction	–	33.26 ± 7.70	35.16 ± 10.22	36.62 ± 11.18	37.41 ± 12.43			

Post hoc analysis

Baseline				1 Week			1 month		3 months
1wk	1 month	3 months	6 months	1 month	3 months	6 months	3 months	6 months	6 months
< 0.001	< 0.001	< 0.001	< 0.001	1.000	0.644	0.816	0.839	1.000	1.000

P-value > 0.05: Non-significant; *P*-value < 0.05: Significant; *P*-value < 0.01: Highly significant

$^{\bullet}$: Repeated Measures ANOVA test

Table 3 The statistical data analysis for the number, BMI and the Kellgren–Lawrence score of the studied cases enrolled in our study regarding the isolated pure OA versus the associated comorbidities

		Isolated OA No. = 8	Co-morbid OA No. = 8	Test value	*P*-value	Sig
BMI	Mean ± SD	29.75 ± 2.31	33.25 ± 2.92	− 2.659•	0.019	S
	Range	27–34	29–38			
Kellgren–Lawrence score	Median (IQR)	2.5 (2–3)	3 (2–3)	− 0.488 ≠	0.626	NS
	Range	2–3	2–3			

P-value > 0.05: Non-significant; *P*-value < 0.05: Significant; *P*-value < 0.01: Highly significant

*: Chi-square test; •: Independent t-test; ≠: Mann–Whitney test

Aim of the work

The aim of the study is to evaluate the feasibility, safety, and efficacy of geniculate artery embolization as a recently developed endovascular minimally invasive procedure for the treatment of knee pain secondary to osteoarthritis.

Methods

This is a prospective single-arm interventional study conducted on 16 patients; their age ranged from 43 to 59 years with mean ± SD of 50.19 ± 5.09 years. They were 12 females (75%) and 4 males (25%) with body mass index ranged from 27 to 38 compatible with mean ± SD of 31.50 ± 3.12. The intervention radiologists recruited the patients from the orthopedic outpatient clinic under the supervision of the orthopedic consultant, the patients presented by knee OA fulfilling the following inclusion criteria included age > 40 years, mild-to-moderate knee OA as determined by plain radiographs demonstrating Kellgren–Lawrence grade 1 to 3, self-reported pain ≥ 3/10 according to the visual analogue scale (VAS) with 0 representing 'no pain' and 10 'the worst pain imaginable; this pain is refractory to the conservative therapies for at least 6 months. Patients were excluded if they had severe knee osteoarthritis (Kellgren–Lawrence grade higher than 3 candidate for total knee replacement), current local infection or malignancy, rheumatoid arthritis, prior intra-articular injection in the ipsilateral knee in the last 6 months, body weight greater than 150 kg, renal Impairment or irreversible coagulopathy.

Patients were evaluated before the procedure by full history taking and clinical examination performed by the orthopedic consultant with emphasis on the specific site of knee tenderness. The Western Ontario and McMaster University Osteoarthritis Index (WOMAC) questionnaire was administered to assess pain, stiffness, and overall decreased function. The pain severity was assessed using the visual analogue scale (VAS).

Baseline plain knee radiograph was obtained and evaluated by the intervention radiologists using the Kellgren–Lawrence grading scale. Also, baseline magnetic resonance imaging (MRI knee) was requested for meniscal, cartilaginous, and ligamentous assessment because the associated knee comorbidities in the form of meniscal tear, cartilaginous defect, or ligamentous injury were thought to be risk factors for pain recurrence after GAE in comparison with the pure isolated knee OA.

Laboratory tests including coagulation profile and serum creatinine level were obtained and revised by the intervention radiologists within 72 hours prior to the procedure. All patients were informed to fast 4–6 hours prior to the procedure for fear of contrast induced allergic reaction (vomiting and aspiration).

The procedure was performed by interventional radiologists experienced in the embolization procedures. Under local anesthesia, arterial access was gained to the contralateral femoral artery via a 6-Fr vascular sheath.

The geniculate arteries arise anatomically from the distal segment of the superficial femoral artery. A 5F Cobra head catheter (Boston Scientific, Marlborough, MA, USA) is introduced over a hydrophilic guide wire to catheterize the superficial femoral artery and then digital subtraction angiography (DSA) was obtained to assess the anatomical pattern of the geniculate arteries followed by selective catheterization to each one of them using a 2.7-F Progreat micro-catheter (Progreat, Terumo, Tokyo, Japan). After that selective geniculate artery angiogram in different views was done to identify the typical hyper vascular inflammatory synovial blush.

Embolization was performed using microspheres (150–300 μm) (Merit Medical Systems Inc., South Jordan, UT, USA) mixed with water-soluble iodinated contrast and saline in ratio 1:1 under continuous fluoroscopic guidance till complete stasis and absence of the distal inflammatory blush.

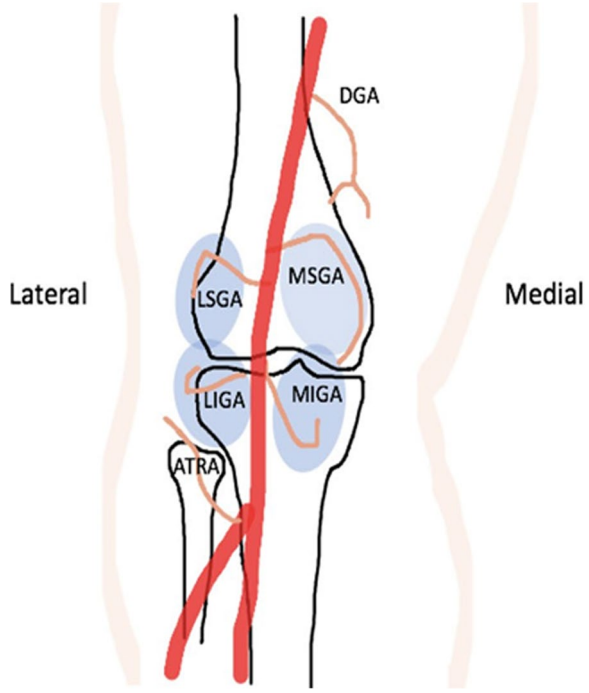

Fig. 1 Illustrative diagram shows the classic anatomy of the genicular arteries. DGA: Descending genicular artery; (MSGA) medial superior genicular artery, (MIGA) medial inferior genicular artery, (LSGA) lateral superior genicular artery, (LIGA) lateral inferior genicular artery and (ATRA) anterior tibial recurrent artery

At last, the femoral sheath was removed and manual compression was done over the puncture site until adequate homeostasis achieved. Patients were kept under observation for 4–6 hours to monitor the puncture site and manage any immediate postoperative symptoms.

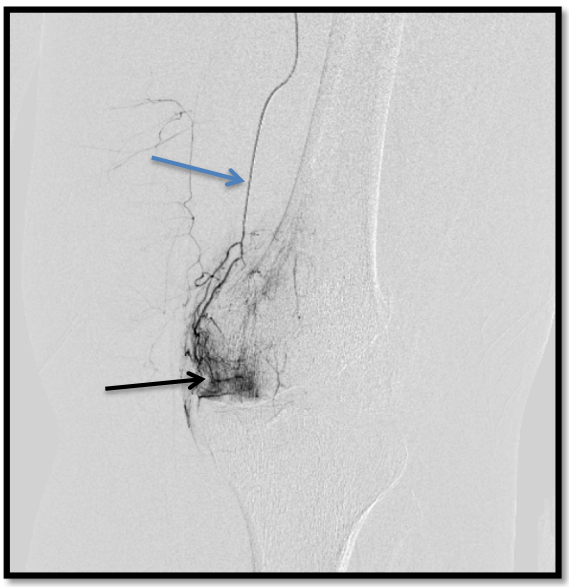

Fig. 2 Angiography of the descending genicular artery (blue arrow) shows hyper-vascular inflammatory "blush" (black arrow) over the medial aspect of the knee

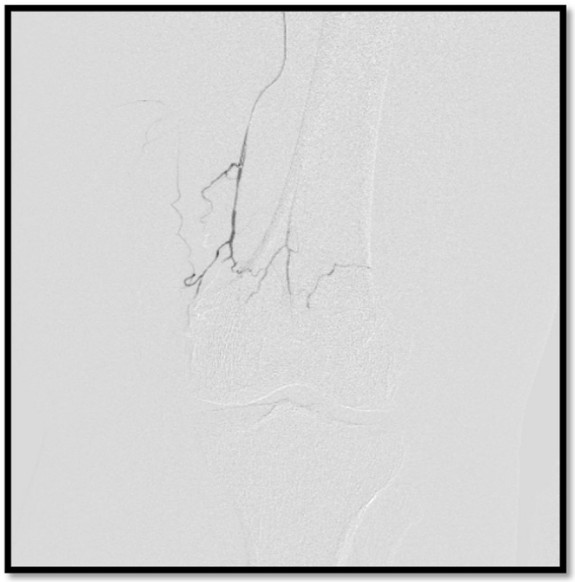

Fig. 3 Angiography post-embolization revealed the absence of the inflammatory blush. The parent genicular artery remains patent

Patients were discharged on the same day and informed by the follow up schedule as 1 week, 1, 3 and 6 months post-procedure at the intervention clinic (Figs. 1, 2, 3).

Treatment in cases of complications

In complications settings, the patients were managed according to the guidelines in each case according to its severity. Three of the patients developed allergic reaction to the contrast medium; IV antihistaminic and steroid medications were injected through the already inserted plastic cannula. Three of the patients developed transient cutaneous ischemia in the form of small region of just cutaneous discoloration that resolved within two to three weeks without intervention. Two of the patients developed transient plantar numbness, which resolved within one to two months without intervention as recommended by the neurology consultant; it is a self-limited minor condition and if it lasting more oral steroid, gabapentin will be prescribed then.

Results

Outcome measures

Visual analogue scale (VAS)

The previous table shows that there was highly statistically significant decrease in the VAS score. Pre- versus post-embolization ± MDs from 8.38 ± 0.81 (baseline) to 2.88 ± 1.54 after 6 months (post-embolization) equivalent to 66.66% improvement. Regarding the post hoc

analysis that compares each follow-up visit in relation to the previous one, there was highly statistically significant decrease in the VAS score from the baseline and 1 week after embolization, yet a very minimal statistical difference in each follow-up visit after the first week till the end of the study, suggesting that the best outcome occurred from the baseline and first week after-embolization, the difference after that is statistically non-significant (Fig. 4).

Western Ontario and McMaster Universities osteoarthritis index (WOMAC)

The previous table shows that there was a satisfactory improvement in the WOMAC scores, with ± MDs drop from 77.94 ± 10.62 (baseline) to 49.69 ± 15.43 (after 6 months post-embolization) equivalent to 37.41% improvement. Regarding the post hoc analysis, there was a statistically significant decrease in

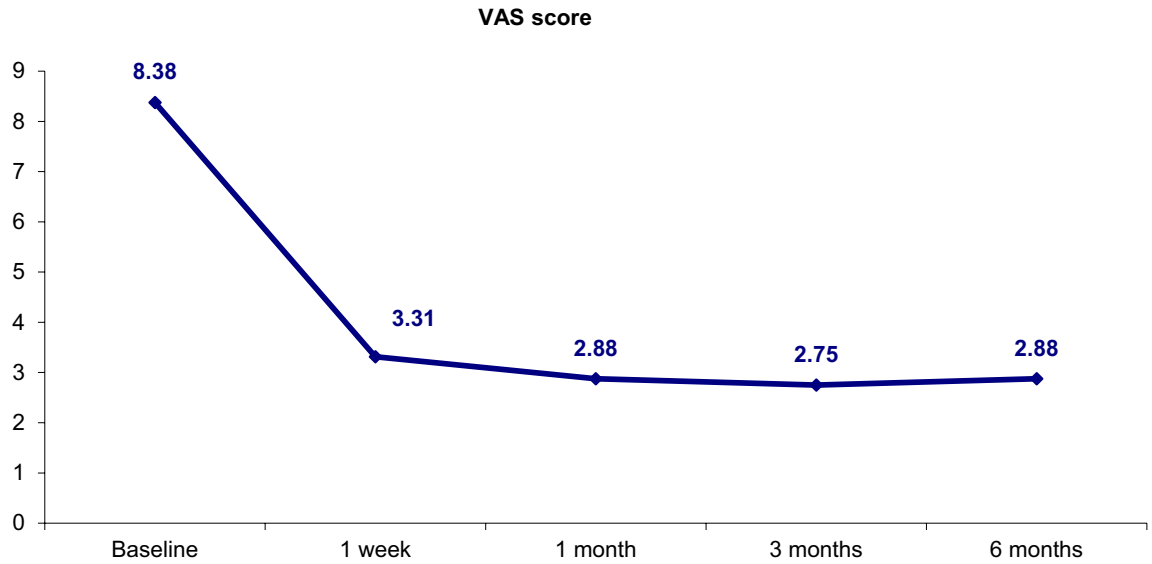

Fig. 4 The previous graph illustrates the relationship of VAS score in relation to time (at baseline and at 1 week, 1, 3 and 6 months post-embolization follow up) with the maximum improvement in the VAS score from the baseline and 1 week after embolization

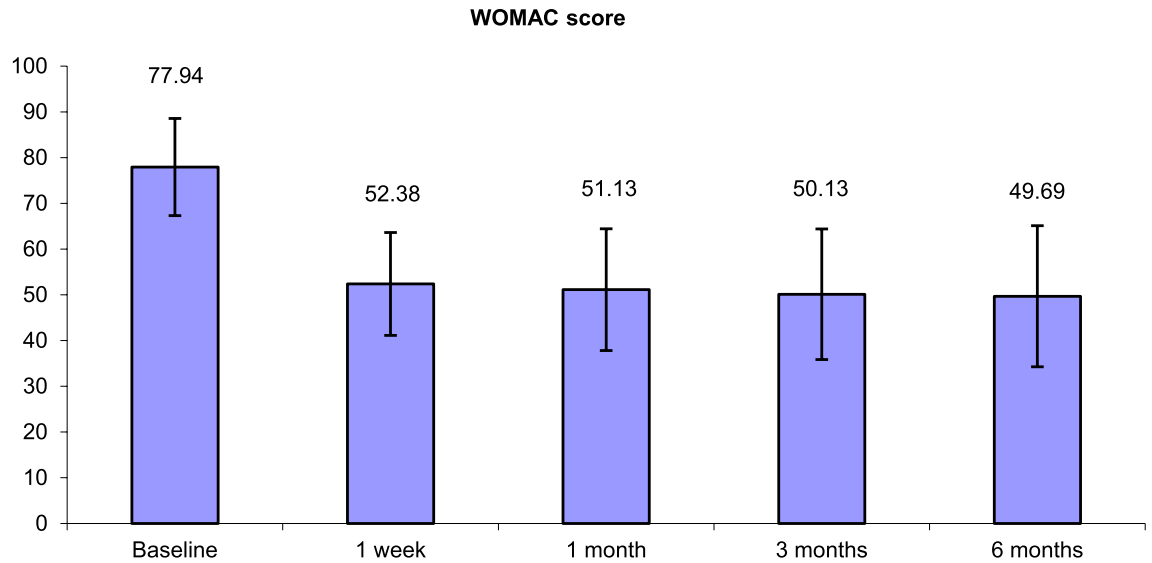

Fig. 5 The graph illustrates the relationship of WOMAC score in relation to time (baseline and at 1 week, 1, 3 and 6 months post-embolization follow-up)

the WOMAC score from the baseline and 1 week after embolization, yet a very minimal statistical difference in each follow-up visit after the first week till the end of the study, suggesting that the best outcome occurred from the baseline and 1 week post-embolization.

The previous table shows that there was 8 patients (50%) presented by isolated knee OA with BMI ranged from 27 to 34 compatible with mean ± SD of 29.75 ± 2.3 and Kellgren–Lawrence score ranged from 2 to 3 compatible with median(IQR) 2.5; on the other hand, the rest of the patients was 8 patients (50%) presented by associated knee comorbidities in the form of meniscal tear, focal cartilaginous defects and ligamentous tear with BMI ranged from 29 to 38 compatible with mean ± SD of 33.25 ± 2.92 and Kellgren–Lawrence score ranged from 2 to 3 compatible with median (IQR) 3.

Regarding the previous results, a statistically significant improvement of the total scores was noticed in the isolated pure osteo-arthritic patients in comparison with the other patients with associated knee comorbidities. Regarding the VAS score, the isolated OA patients showed significant decrease from a mean value ± SD of 7.75 ± 0.46 (baseline values) to 1.63 ± 0.74 after 6 months (post-embolization) with 79.02% percentage pain reduction, in comparison with the comorbid patients that showed drop from a mean value ± SD of 9.00 ± 0.53 (baseline values) to 4.13 ± 0.99 after 6 months (post-embolization) with 54.31% percentage pain reduction. Regarding the WOMAC score, the isolated OA patients showed significant decrease from a mean value ± SD of 68.75 ± 5.18 (baseline values) to 36.13 ± 3.98 after 6 months (post-embolization) with 47.35% percentage functional improvement, in comparison with the comorbid patients that showed improvement from a mean value ± SD of 87.13 ± 4.70 (baseline values) to 63.25 ± 8.58 after 6 months (post-embolization) with 27.47% percentage functional improvement (Fig. 5).

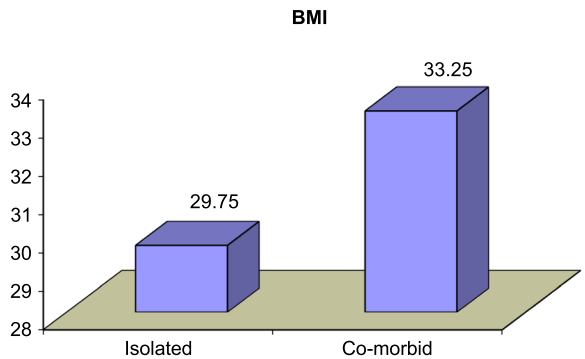

Fig. 6 The graph illustrates the relationship between the BMI and the isolated versus the comorbid status of the patients. The higher the BMI, the more the risk of knee comorbidities

• Interpretation of results

Technical success with the geniculate artery embolization is defined by the absence of the synovial inflammatory blush.

All patients are interviewed with the visual analogue scale (VAS) for pain assessment and with WOMAC score for overall functional status assessment just prior to the procedure and 1 week, 1, 3 and 6 months following the procedure (Fig. 6).

Degree of pain relief is assessed in the following three grades:

- Significantly effective (VAS score of 0–2, or improvement of ≥ 5 points).
- Effective (improvement of 2–4 points).
- Ineffective (improvement of < 2 points).

Statistical analysis

The collected data will be revised, coded, tabulated and introduced to a PC using Statistical Package for Social Science (SPSS 15.0.1 for windows; SPSS Inc., Chicago, IL, 2001). Data will be presented as mean and standard deviation (± SD) for quantitative parametric data, and median and Interquartile range for quantitative nonparametric data. Frequency and percentage will be used for presenting qualitative data. Suitable analysis will be done according to the type of data obtained. Student's T test or Mann–Whitney test will be used to analyze quantitative data, while Chi-square test and Fisher's exact test will be used to analyze qualitative data. P-value level of significance:

- $P > 0.05$: Non-significant (NS)
- $P < 0.05$: Significant (S)
- $P < 0.01$: Highly significant (HS)

Statistical Package Statistical Package for Social Science (SPSS 15.0.1 for windows; SPSS Inc., Chicago, IL, 2001) (Figs. 7, 8).

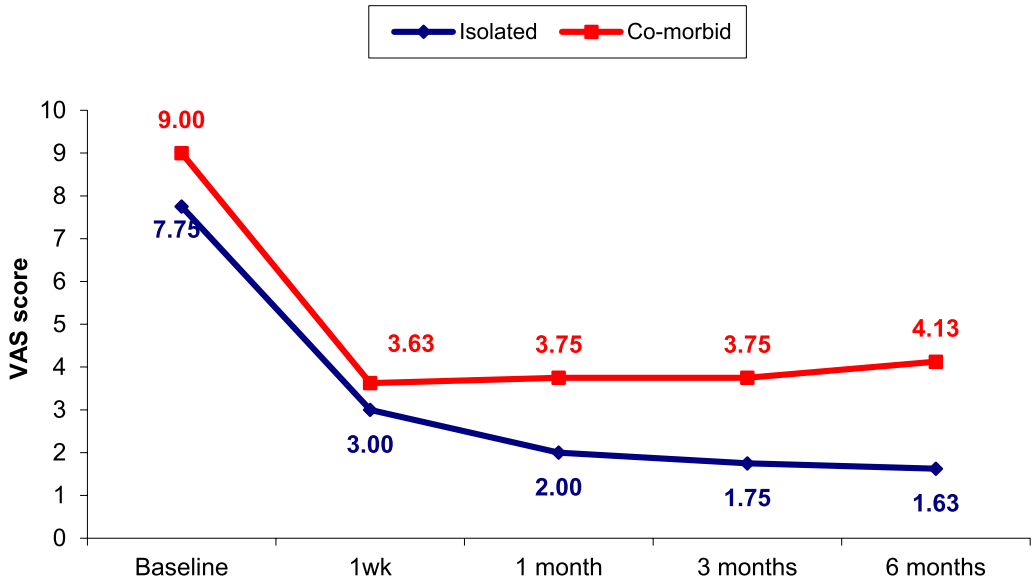

Fig. 7 The graph illustrates the relationship between the VAS score and the isolated versus the comorbid status of the patients

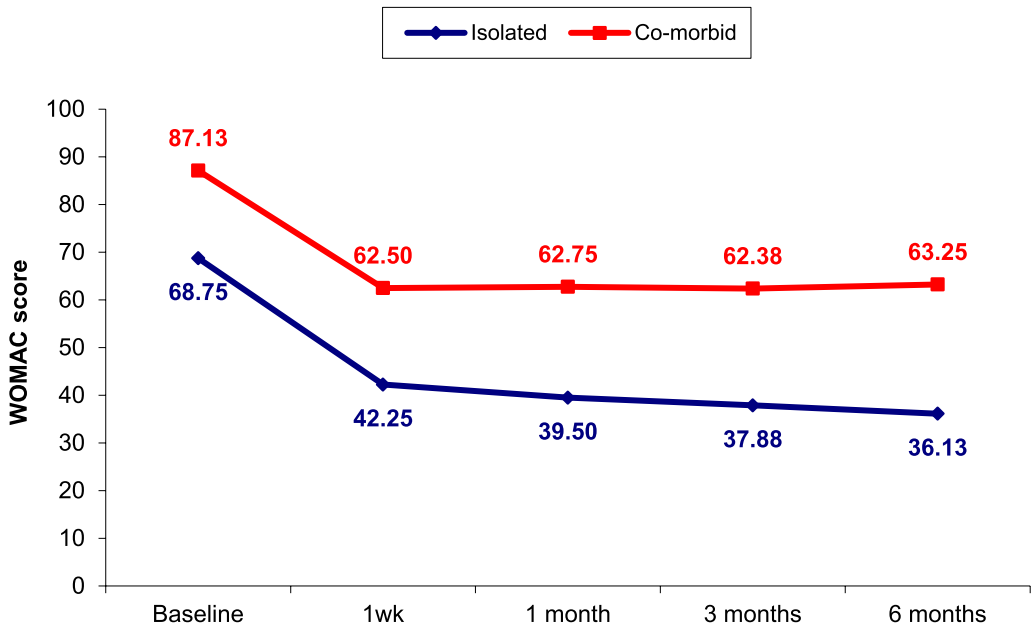

Fig. 8 The graph illustrates the relationship between the WOMAC score and the isolated versus the comorbid status of the patients

Discussion

Knee OA had been categorized as a pure degenerative disease for a long time; however, now the main event in the knee OA is the inflammatory process with the recognition of a vicious circle of chemical cascade through formation of abnormal blood vessels (angiogenesis). So our target in this study is to occlude these abnormal hyperemic vessels preventing the continuous release of the inflammatory and catabolic factors breaking this vicious circle [9, 10].

The results of our study revealed that GAE used in the treatment of knee pain secondary to OA could be considered as an effective, feasible, and safe line of treatment with no serious complications. It shows a significant pain reduction and better functional status. Up to date, we have no randomized controlled trials to assess the efficacy of GAE [11, 12].

Within the past 3 years, different groups from Japan, China, and USA have published results of 186 GAE

treatments for knee OA. All these studies concluded that GAE is an effective technique in the management of knee pain secondary to chronic OA, with 80–100% clinical success, defined by 25–50% reduction in pain scores lasting for at least 6 months to 2 years after embolization. These studies showed average clinical outcome as early as 1 day and 1 month after embolization, with clinically non-significant further improvement through 1 and 2 years after the embolization, as in our study we suggest that early outcomes correlate with the maximum treatment response [13].

Whereas these are promising preliminary results, we still have no available adequate clinical trials or effective comparison between the studies due to variable inclusion criteria, embolic agents, and outcome measurements. Lee et al. enrolled patients with marked knee OA; they did not show durable treatment response at 3–6 months, driving the authors to conclude that GAE has a very limited role in the management of severe OA. They suggested that this could be due to mechanical bone-on-bone friction that continue after the embolization, responsible for the continuous sub-chondral bone degeneration, persistent inflammation and furthermore pain [14].

The embolic agent utilized in two of these studies was an antibiotic crystal mixture (IPM/CS) that forms particles when blinded with iodinated contrast giving transient embolic effect. In contrast and as in our study, Bagla et al. used permanent embolic agent microspheres exclusively. Okuno et al. used both embolic agents and concluded that there was no significant difference in the clinical outcome between the two types of agents [10].

Regarding the outcome measures, Okuno et al. and Bagla et al. used the WOMAC score, a self-administered questionnaire with 24 items in three subsections (5 for pain, 2 for stiffness and 17 for physical function) commonly used for hip and knee osteoarthritis. In our study, we also depended on the WOMAC score as it broadly used and has been introduced as one of best outcome measures for knee OA regarding the validity, reliability and feasibility [15].

Clinical success was assessed at different time points across the studies. This success was defined by 20–50% reduction in pain scores. Lee et al. reported clinical success in all patients with mild-to-moderate knee OA at 3 months and lasted for a mean of 10 months (range 6–19 months), defined by 50% reduction in the VAS score. Bagla et al. demonstrated 85% clinical success at 6 months defined by 20% reduction in the VAS score. All three studies reported a decrease in the conservative therapy use post-GAE (between 65 and 100%).

In our study, we demonstrated clinical success at 6 months defined by 66.66% reduction in the VAS score and about 37.41 % improvement in the WOMAC score; we also concluded that patients with isolated pure knee OA carry better clinical response in comparison with the others with associated meniscal, cartilaginous and ligamentous co-morbidities.

The complications observed in our study were thought to be due to non-target embolization occluding small cutaneous and neuronal arterial branches. The transient cutaneous discoloration is considered as the most prevalent minor complication, which happened more often and lasted longer when using permanent embolic agents microspheres (63% and lasted 1–2 months) in comparison with the temporary embolic agent IPM/CS (2.5% and lasted 3 weeks). This occurred despite great care by the operators regarding the proper position of the microcatheters as selectively as possible trying to avoid reflux and non-target embolization.

Up to date, there are no available studies to deliver a biochemical laboratory success standard like the measurement of the inflammatory bio-marker changes pre- and post-intervention [16].

No serious complications were noticed following the GAE technique. Early pain reduction and functional improvement in addition to the low complication rates should raise the interest in GAE technique.

Now, the available studies recommend GAE as a feasible, safe, and effective line of treatment to reduce pain, decrease the need for analgesics and injections, and improve the overall quality of life. Patients experiencing GAE may hypothetically encounter knee joint replacement at older age than the others without GAE [3].

The limitations of our study

The primary limitation of our study was the absence of a control arm to assess how much of the reported effect was due to placebo effect.

Additionally, the study has been reported from a small number of subjects within rather short period of time that was not long enough to determine the durability of GAE in this study population. Also, there was no measurable joint fluid aspirate or blood-based inflammatory biomarkers related to the knee osteoarthritis, pre- and post-intervention for comparison.

Thus, furthermore studies and clinical trials about the GAE safety and efficacy are required with a larger sample size and longer follow-up duration.

Conclusions

Our current study revealed that GAE holds promise as an effective minimally invasive procedure for the treatment of knee pain secondary to OA, especially in isolated pure

OA patients and could be introduced as a safe technique with no serious complications.

However, because of the paucity of high-quality trials, furthermore researches are required to compare between the GAE and the other treatment avenues especially regarding the long-term efficacy.

Abbreviations

GAE	Geniculate artery embolization
OA	Osteoarthritis
VAS	Visual analogue scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
MDs	Mean differences
SD	Standard deviation
IQR	Interquartile range
CBC	Complete blood count
INR	International normalized ratio
PT	Pro-thrombin time
PTT	Partial thromboplastin time
GIT	Gastrointestinal tract
MRI	Magnetic resonance imaging
BMI	Body mass index
IPM/CS	Imipenem/cilastatin sodium
DSA	Digital subtraction angiography

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Author contributions
MS was the first author contributed by performing the embolization practical part and interpretation of the data. MM was the corresponding author, contributed by taking detailed history, doing physical examination, providing the pre-operative investigations for all the patients enrolled in the study and helped in editing the manuscript and reference collection. WN, the co-author, helped in the clinical orthopedic assessment and follow-up. AE, the co-author, helped in reading and approving the submitted version as well as paper editing and revision. HN, the co-author, helped in the dealing with the collected data and approving the final submitted version of the paper.

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Availability of data and materials
All data are available on a software system owned by each of the authors and the corresponding author has the authority to respond if there is any query.

Declarations

Ethics approval and consent to participate
The protocol was checked and approved by the Research Ethics Committee of the faculty of Medicine, Ain Shams University in Egypt on 3/02/2021; reference Number of approval: FWA000017585.FMASU MD 35/2021. All patients had been given written consents to participate in this work.

Consent for publication
All patients had given their written consents for publication of this work.

Competing interests
The authors declare that they have no competing interests.

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