6-6-2024

Clinical Research Protocol



1 General Information

1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

Title: prospective randomized trial evaluating the role of genicular artery embolization versus genicular nerve ablation in treatment of persistent pain in patients with severe knee osteoarthritis.

ICT23J/003/11

1.2 Name and address of the sponsor and monitor (if other than the sponsor).

KAIMRC

1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

Dr. Omar Batouk, Orthopedic surgery consultant, National Guard Hospital, Jeddah

1.4 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

Dr. Omar Ali Batouk Orthopedic consultant

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1.5 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

Same as investigator above

1.6 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

The study will be conducted in King Abdulaziz Medical City, National guard hospital, Jeddah, Saudi Arabia

Cooperation will be between orthopedic surgery departement and interventional radiology suite in achieving the objectives of this research, also wih cooperation with other members to inhance the efficacy in the working process of this research

In the orthopedic department, Dr. Batouk's clinic will oversee this trial, involving the orthopedic consultant Dr. Batouk, and the orthopedic residents: Dr. Majd Saemaldahar as well as Dr. Ammar Aljefri, also Medical Intern Dr. Arwa Almutairi

This will be conducted at King Abdul-Aziz Medical City, Jeddah, National Guard Hospital, King Abdullah center for neurosurgery and trauma.

In the interventional radiology department, the procedures will be conducted by two interventional radiologists, Dr. Majed Abdulhaq, and Dr. Ghassan Attasi at King Abdul-Aziz Medical City, Prince Norah Oncology centre, Jeddah, National Guard Hospital.

All authors have critically reviewed and approved and participated in the process done until now. All authors confirm the authenticity of the data and the study thereof. Dr. Omar Batouk and Dr. Majd saemaldahar conceptualized and reviewed the Proposal and the study protocol. Dr. Ammar and Dr. Arwa designed the study, performed literature search, and wrote the initial draft. Dr. Anwar Khan will do the statistical analysis. Our Interventional Radiologists Dr. Ghassan Attasi and Dr. Majed Abdulhaq will perform the procedures (RFA and GAE). Further roles will be divided after approving the study

2 Background Information

2.1 Name and description of the investigational product(s).

Osteoarthritis (OA) is a common chronic and progressive condition that affects the joint complex, and is marked by the degeneration of the articular cartilage. Its incidence rises with age and frequently seen among the elderly population with an overall prevalence of 18.9%.[1] OA results in joint pain that varies in severity and, in some cases, a disability. The condition mainly affects weight-bearing joints and joints that are heavily used, such as the hip, knee, and hand with the knee being the most commonly affected.[2] The primary objective in treating knee OA is pain management as well as enhancement in function. For patients with mild to moderate OA, nonoperative approaches like NSAIDs, steroid injection, and physical therapy are feasible options. However, in severe cases, surgical intervention is often necessary. Total knee arthroplasty (TKA) is considered the preferred treatment for severe knee OA offering postoperative pain relief and improved function.[2] Nonetheless, not all patients, especially those with comorbidities or other factors, may be suitable candidates for TKA.

In cases where surgical intervention is not suitable, genicular nerve radiofrequency ablation (RFA), and Genicular artery embolization (GAE) may be alternative options.

Genicular nerve radiofrequency ablation (RFA) is a minimally invasive procedure used in the management of symptomatic knee OA including conventional, cooled, and pulsed techniques. This procedure involves the precise application of thermal energy directed at the nerves which leads to the suppression of nociceptive signal transmission, subsequently reducing its capacity to convey pain signals.

Given that the genicular nerves that innervates the knee originate from branches of the femoral, common peroneal, saphenous, tibial, and obturator nerves, there are several potential sites for ablation that can be targeted for the treatment of intra-articular nerve endings [3]. Overall, genicular nerve RFA offers a targeted approach to managing knee OA-related pain, which provides patients with a minimally invasive alternative to traditional pain management

Genicular artery embolization (GAE) is a minimally invasive procedure, performed under moderate sedation, designed to address the underlying pathology of knee osteoarthritis (OA). GAE involves the selective catheterization of the genicular artery during an angiogram to target abnormal neo-vasculature associated with knee osteoarthritis OA. The injection of small calibrated microspheres results in a reduction in arterial flow, which may in turn reduce synovial inflammation. This procedure aims to target the underlying cause of synovial inflammation and offers potential relief for knee OA pain.

GAE can be performed via either a radial or femoral approach. Initially, the distal superficial femoral artery of the affected limb is catheterized, followed by digital subtraction angiography to identify the target genicular arteries. Subsequently, embolization is then performed with the endpoint typically characterized as pruning of the genicular arteries involved. Once this is achieved, the catheter is removed and hemostasis is achieved. [4] By targeting the underlying cause of synovial inflammation, GAE offers the potential to provide significant relief for patients suffering from knee OA symptoms. Furthermore, its minimally invasive nature makes it an attractive alternative to more invasive surgical interventions.

In patients who are unfit for surgery, these new modalities might become of benefit if proven as beneficial and safe, hence the need for more research to be done. Moreover, the lack of local studies necessitates the establishment of a local comprehensive study. Thus, our aim in this prospective randomized trial is to evaluate the role of genicular artery embolization versus genicular nerve ablation in treatment of persistent pain in patients with severe knee osteoarthritis.

2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

- A systematic review and meta-analysis conducted by Pooya Torkian, et al., states that mild to moderate osteoarthritis treated by GAE using (Embozene, polyvinyl alcohol, resorbable microspheres, or imipenem/cilastatin) are safe treatments with no reported serious complications. Pre-emoblization and post-embolization scores were collected at 1 week and at 1, 3, 6, 12, and 24 month follow-up. Results indicated that the mean difference at those respective time points was 32 (95% CI, 14.9- 49), 36.67 (95% CI, 28.2-45), 40.75 (95% CI, 30-51.4), 42.80 (95% CI, 26.5-59), 45.79 (95% CI, 19.7-71.8), and 58 (95% CI, 53.3-62.6). P values were all <0.00001) therefore, knee pain, based on the subjective measure of acute and chronic knee pain, had significantly improved even within the first week after GAE. [5]

- A systematic review and meta-analysis conducted by Taslakian B et al., which included 9 studies, involving 270 patients with knee osteoarthritis. The study demonstrated that genicular artery embolization was technically successful in 99.7% of cases. A few minor complications were reported with transient skin discoloration being the most common. [6]

- In an article published by Andrew Tran et al., “Cooled radiofrequency ablation has been demonstrated to be clinically effective by disrupting the integrity of deep sensory nerves and hence interfering with transmission of pain signal. For knee OA, CRFA clinical studies have reported clear benefit managing pain for up to 12 months, with

some studies observing a positive treatment response up to 24 months. For post-TKA pain, the data is scarcer, but the available literature suggests a similar reduction in pain after CRF". [7]

- in a systematic review conducted by Prabjit Ajrawat et al., which included thirty-three studies with 1,512 patients (mean age ¼ 64.3 years, 32.5% males). "All 33/33 (100%) studies reported alleviation of OA-related knee pain from baseline until three to 12 months with RF modalities, with six comparative studies reporting 194/296 (65.5%) and 29/150 (19.3%) RF and control patients achieving >50% pain relief, respectively. Three of the 33 studies reported QOL, with three of three studies (100%) achieving improvements in disease-specific QOL from baseline until three to 12 months. 28 of the 33 studies reported functional outcomes, with 27/28 (96%) studies obtaining enhanced functionality from baseline up until three to 12 months. Ten of the 33 studies reported patient satisfaction, with eight of 10 studies (80%) indicating that patients were significantly satisfied after RF procedures, and from these eight studies, four were comparative studies that indicated that 86/154 (56%) and 33/104 (32%) RF and control patients were extremely satisfied or satisfied, respectively." [8]

- In a study conducted by Okuno Y et al., states that patients with severe knee pain as well as mild or minimal degenerative changes (Kellgren–Lawrence grade 2 degenerative changes) were significantly relieved by transcatheter arterial embolization treatment. The study also adds "The findings indicate that pain in osteoarthritis does not necessarily come from the degenerative site or from cartilage loss." [9]

- In a study conducted by Padia S et al., where 40 subjects were enrolled with a media age of 69 years old, and a knee osteoarthritis severity rate ranging between 2 to 4, with various ethnic backgrounds and a wide range of BMI values (range, 19 to 44 kg/m2). The same embolic material (100 mm of Embozene) was used in all subjects. The study resulted in marked reductions in pain and improvement in overall function (indicated by a decrease in WOMAC and VAS scores) in 68% of subjects. Furthermore, the maximum response was seen at 3 months and persisted at 12 months. [10]

- A randomized controlled trial conducted by Landers S et al., included 58 participants with knee osteoarthritis and a kellgren-lawrence grade 2. At 12 months, pain scores (using the Osteoarthritis Outcome Score KOOS) improved by 41.3% and 29.4% in the intervention and control groups, respectively, with no reported adverse events documented. A subgroup analysis was also conducted and revealed significantly better KOOS Sports and Recreation, Osteoarthritis Outcome Score KOOS Quality of Life, and Global Change scores by 76.5% in comparison to 37.9% of the control group. [11]

- In a systematic review conducted by Chalidis B et al., 9 studies were included involving 899 patients with symptomatic knee osteoarthritis. The radiofrequency ablation

procedure resulted in improved knee pain relief at 3-, 6- and 12-month follow-up. Moreover, functional improvement was also reported and was greater in RFA group than the comparison group that received hyaluronic acid (HA), steroid or platelet-rich plasma (PRP) injections. The study concluded that RFA appears to be more effective than intra-articular injections in alleviating pain and improving joint function. The overall procedural complication rate of RFA was 10.2. However, no severe adverse events were reported. [12]

2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

Benefits:

RFA is an effective and safe method in providing pain relief within 24 weeks, alongside significant improvement in knee function [13].

study reported a 67% reduction in pain at 3-month follow-up, with 95% of these patients still experiencing pain relief at the 6-month follow-up [14].

GAE effectively reduces knee OA pain for up to 24 months with an 86.3% clinical success rate at 6-month follow-up [6].

“Cooled radiofrequency ablation was shown to be clinically effective through disrupting the integrity of deep sensory nerves and therefore interfering with transmission of pain signal. The analgesic effect after c-RFA has been reported up to 24 months.” [7]

Patients with severe knee pain as well as mild or minimal degenerative changes (Kellgren–Lawrence grade 2 degenerative changes) were significantly relieved by transcatheter arterial embolization treatment. The study also adds “The findings indicate that pain in osteoarthritis does not necessarily come from the degenerative site or from cartilage loss.” [9]

At 12 months, pain scores (using the Osteoarthritis Outcome Score KOOS) improved by 41.3% , in addition to better KOOS Sports and Recreation, Osteoarthritis Outcome Score KOOS Quality of Life. [11]

Knee pain relief at 3-, 6- and 12-month follow-up, as well as, functional improvement following RFA, which was greater than what intra-articular injections provide. [12]

Side effects:

- Genicular nerve radiofrequency ablation (RFA)

The vast majority of studies reported no severe complications. However, a few cases were documented to have complications as mentioned in the following.

1- In a nonrandomized study by Ikeuchi, M et al., prolonged hypoesthesia at the site of infrapatellar branch of the saphenous nerve region was observed only in patients of the RF group (14 out of 18 patients), lasting for 2–6 weeks after the initial treatment. The study adds, “The size of hypoesthesia area gradually shrank and disappeared. All of the patients who responded to the RF treatment showed prolonged hypoesthesia.” [15]
2- In a nonrandomized study by M Mogahed et al., comparing intraarticular pulsed radiofrequency against radiofrequency neurotomy stated that subcutaneous hematoma appeared in six patients (related to needle puncture) in six of 50 (12%) following Intraarticular Pulsed Radiofrequency. [16]
3- A case series conducted by Khan D et al., reported a clinically significant hematoma as a complication of cooled radiofrequency ablation of the genicular nerves within the distal vastus medialis muscle, which is suggestive of superior medial genicular artery injury. [17]
4- A case report conducted by Zachary L et al., recorded a case of a third-degree skin burn at the site of the inferomedial genicular nerve following a conventional thermal RFA procedure. Furthermore, the study explains “RFA lesion extension to the dermis with subsequent superficial necrosis is possible at the inferiomedial genicular nerve site in patients with minimal subcutaneous tissue overlying the medial tibial flare.” [18]
5- A case report published by Ankur K et al., reported the first case of septic arthritis post radiofrequency ablation presumably caused by the procedure. Within the subsequent 24 hours, the patient reported a feeling of fullness and increasing pain in the knee. Knee joint aspiration was then made revealing septic arthritis, with a culture revealing methicillin-sensitive Staphylococcus aureus. The patient was then treated with intravenous ceftriaxone and vancomycin empirically, followed by knee arthroscopy with washout, then intravenous cefazolin. Three months following the procedure, the infection was cleared, and a total knee arthroplasty was made five months later. [19]

- Genicular artery embolization (GAE)

The vast majority of studies reported no severe complications. However, a few cases were documented to have complications as mentioned in the following.

1- A study conducted by Padia, S et al., with the inclusion of 40 patients documented the following: One of the patients had a small groin hematoma (from the femoral arterial access site), for which an overnight hospital observation was arranged. Transfusion was not required, and follow-up ultrasound showed a normal femoral artery without sequelae. [10]
2- In the same study previously mentioned above, 7 to 10 days post-procedure, seven patients (18%) faced focal epidermal layer skin ulceration (1 cm in diameter) at the knee, (likely due to embolization of nontarget cutaneous branches). The ulceration resolved with no treatment within 3 days. And the study adds. “After the 7th case of ulceration, the treatment protocol was modified to place an ice pack on the skin during the embolization. Following this modification, no further cases of ulceration occurred.” [10]
3- Continuing with the same study, the MRI conducted at 3 moths post procedure revealed Two cases of clinically asymptomatic focal bone infarct, 1 in the tibia and 1 in the patella. Both infarcts measured <2 cm in size and occurred in the non-weight-bearing portions of the joint. [10]
4- In the same study, one case of focal fat necrosis in the lower thigh was also documented, presenting as firmness of the deep tissues. [10]
5- In the same study, adding “imaging with knee radiographs at 12 months showed 1 patient (3%) with mild progression of the OA, and the remaining patients had no progression.” [10]
6- In a study conducted by Little, M et al., including thirty-eight patients, four of which (12.5%) experienced mild self-limiting skin discoloration over the embolized territory (as a result of non-target cutaneous embolization) that resolved within 3 weeks. [20]
7- In the same study by Little, M et al., one patient experienced a small self-limiting groin hematoma. Moreover, From the 16 patients completing 1-year follow-up, there were no cases of osteonecrosis of the knee joint detected on MRI. [20]

2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

Radiofrequency Ablation:

Radiofrequency Generator Machine The Cosman G4 Radiofrequency Generator to perform conventional thermal GNRFA. Other radiofrequency generator machines that can be used for this procedure include those manufactured by NeuroTherm, Halyard Health, and Stryker.

Position and prepare the patient for the ablation procedure, Place the patient in the supine position. Place a bump behind the knee to allow for 30° of flexion. Prepare the knee with chloride-based or an iodine-based product and drape the knee in a sterile manner.
Place the ground pad on the contralateral or ipsilateral extremity, which depends on the radiofrequency machine that is used for the procedure. The position is not dependent on the presence of an existing joint implant. Wrinkles in the ground pad can lead to skin burns.

Skin Preparation; Provide appropriate skin analgesia prior to ablation.

Use fluoroscopy to identify the 3 entry sites for the planned percutaneous insertion of the cannulas at the base of the medial and lateral femoral condyles and at the base of the medial tibial condyle. Inject the lidocaine (1% or 2%) to form a skin wheal over the 3 sites where the cannulas are to be inserted.

Placement of the Radiofrequency Cannulas, Use C-arm fluoroscopy guidance when inserting the cannulas. Use a fluoroscopic anteroposterior image to target the superior lateral genicular nerve by advancing the 20- gauge, 8.9-cm cannula with a 10-mm active tip percutaneously down to the junction of the femoral shaft and lateral epicondyle, contacting bone. Using the fluoroscopic anteroposterior image, target the superior medial genicular nerve. Percutaneously advance a second cannula to the medial aspect of the distal femoral diaphysis approximately 1 cm anterior to the adductor tubercle until the bone is contacted

Using the fluoroscopic anteroposterior view, target the inferior medial genicular nerve and advance a third cannula percutaneously to the proximal tibial diaphysis, along the margin of the medial tibial condyle, until the needle contacts the bone.

Obtain a fluoroscopic true lateral image to confirm cannula placement at the midpoint of the diaphysis in both the tibia and the femur.

Conduct Sensory and Motor Testing Using Lesion Generator, Conduct electrical testing to confirm that the cannulas are positioned near the 3 genicular nerves.

Sensory confirmation is desirable, but not absolutely required, prior to ablation. Conduct sensory testing at approximately 50 Hz to confirm correct placement of the cannula at

the targeted genicular nerves. Sensory testing is completed once the patient experiences pain or pressure that may be consistent with his or her usual knee pain.

Once localization by sensory stimulation is achieved, conduct motor stimulation using the parameters of 2 V and 2 Hz. Perform motor stimulation to ensure the absence of undesired motor fiber activity such as fasciculations and to avoid ablating motor nerves. If there is motor activation during motor stimulation, the radiofrequency ablation needles should be repositioned and retested. The procedure is aborted if the patient cannot tolerate it.

Provide lidocaine to reduce pain associated with the ablation.

Prior to the deep injection of lidocaine, withdraw each cannula 2 to 3 mm.

Inject 1 mL of 1% lidocaine prior to ablation through each cannula.

Wait 90 seconds for lidocaine to have a full effect before proceeding with ablation.

Ablation and Post-Ablation Procedures Insert the radiofrequency electrode through the cannulas, increase the temperature, and then advance the cannulas and repeat ablation.

Insert the radiofrequency electrode through the cannulas and increase the temperature to 80°C for 1 minute. Then advance the cannulas at each site 3 to 5 mm (which is done to achieve a slight increase in the lesion volume in the anteroposterior dimension) and repeat the ablation using the same settings.

After the ablation procedure, inject a 1-mL solution containing 27 mg of methylprednisolone through each cannula to decrease postoperative pain and possible neuritis. Then remove the cannulas and apply bandages.

GAE: Genicular artery embolization GAE

To be performed under local anesthesia by two interventional radiologists

- Immediately prior to the procedure, the focal areas of pain identified by the patient should be marked with a radiopaque marker.

- Local anesthetic (10 cc of 1% lidocaine) should be administered for a trans- femoral approach.

Access to the ipsilateral common femoral artery is performed with a 21-gauge needle, with exchange to a 3-French vascular sheath which is replaced by 5 French one 11 cm length by using a metallic guide wire.

- 4Fr. 65-cm–angled Glidecath to be advanced into the mid-to-distal portion of the superficial femoral artery, proximal to the descending genicular artery origin.

- Nonselective angiography to be performed utilizing antero-posterior, oblique and craniocaudal views as needed.

- The selection of which artery to embolize is based on the angiographic evidence of hyperemia at the cartilage level which correspond to the pain area and in comparison to the MR angiogram (if available), which typically demonstrate a dominant feeding vessel supplying the hypertrophic synovium.

- The Genicular arteries which demonstrating hyperemia is selected using a microcatheter with the help of glidecath (Cobra C 2 or vertebral), and 1.7 to 2.4-F microcatheter with 0.018 in micro guidewire (the specific genicular arteries supplying the areas of the pain is catheterized). - Microspheres (Embosphere; Merit Medical) ranging in size from 40 to 700 μm to be used for embolization.

- Embolization is performed with 100-300mm Embozene particles. Embolization is performed until distal hypervascularity resolved, yet normal arterial flows is preserved within the selected artery.

- After embolization, a completion femoral artery angiogram should be performed.

- Compression for 5 minutes is applied on the puncture site after inroducer sheath removal, Closure devices, AngioSeal or perclose may be used

- Following the procedure, patients to be instructed to keep the leg straight for 6 hours in accordance with standard practice following arterial puncture.

Pain (Through VAS score) and function (Through WOMAC score) variables will be collected in the following manner:

- Pre procedure
- Six weeks after the procedure
- 3 months after the procedure

- 6 months after the procedure

2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

This randomized controlled trial, prospective randomized trial evaluating the role of genicular artery embolization versus genicular nerve ablation in treatment of persistent pain in patients with severe knee osteoarthritis,' will be conducted in adherence to the approved protocol. The trial will be carried out in compliance with Good Clinical Practice (GCP) guidelines and all applicable regulatory requirements. Ensuring the highest standards of ethical conduct, data integrity, and participant safety throughout the entirety of the study.

2.6 Description of the population to be studied.

Inclusion Criteria:

Adults more than 18 years both gender with knee osteoarthritis Kellgren-Lawrence score of 3 minimum (explained below) Resistant to conservative therapy at least 3 months. (Conservative therapy includes: NSAIDS, physiotherapy, weight reduction program, Intraarticular injections)

patients with multiple comorbidity who need to undergo operative procedure like total knee arthroplasty for their pain but they cannot because of their medical status

Exclusion criteria:

Adults with knee osteoarthritis who underwent procedure such as knee arthroplasty in the same affected knee.

Known case of malignancy or local infection or rheumatoid arthritis or prior Intraarticular injection in the ipsilateral knee in the last 6 months, body weight greater than 150 kg, renal Impairment or irreversible coagulopathy and peripheral vascular disease.

The included patient population will be selected from King Abdulaziz Medical City, National guard hospital, Jeddah, Saudi Arabia.

2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

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3 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

This randomized controlled trial aims to evaluate the role of genicular artery embolization versus genicular nerve ablation in treatment of persistent pain in patient with severe knee osteoarthritis.

Primary objective:

To evaluate the role of genicular artery embolization versus genicular nerve ablation in treatment of persistent pain in patients with severe knee osteoarthritis.

Secondary objective:

To evaluate the role of genicular artery embolization versus genicular nerve ablation in improving functional status in patients with severe knee osteoarthritis.

4 Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design.
A description of the trial design, should include:

4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

- Assessment of pain status following radiofrequency ablation (RFA) in comparison with conservative therapy as well as genicular artery embolization (GAE) utilizing WOMAC and VAS scores

- Assessment of pain status following genicular artery embolization (GAE) in comparison with conservative therapy as well as radiofrequency ablation (RFA) utilizing WOMAC and VAS scores

- Assessment of functional status following genicular artery embolization (GAE) in comparison with conservative therapy as well as radiofrequency ablation (RFA) utilizing WOMAC score

- Assessment of functional status following radiofrequency ablation (RFA) in comparison with conservative therapy as well as genicular artery embolization (GAE) utilizing WOMAC score

  Pain and function variables will be collected in the following manner:

- **-** **Pre procedure**
- **-** **Six weeks after the procedure**
- **-** **3 months after the procedure**
- **-** **6 months after the procedure**

4.2 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

This is a Randomized control trial. In the sealed opaque envelope method is assuming that each participant has an equal chance of being assigned to any group. Each treatment limb will be allocated certain number on a paper and will be kept in an opaque sealed envelope treatment. Once a patient has consented to enter a trial, an envelope will be selected and opened by the patient, then the allocated treatment regimen will be offered to the patient. Blinding cannot be done in this method of randomization as the patient and the surgeon will know the procedure to perform.

First limb: The control limb which will be on regular conservative treatment

Second limb: Patients who will undergo RFA

Third limb: Patients who will undergo GAE

The intervention of interest is radiofrequency ablation versus embolization and our main outcome is assessing pain post procedure.

The control group will be patients on conservative therapy such as (NSAIDS, physiotherapy, weight reduction program, Intraarticular injections)

This control group will be compared to the other two limbs of the study which are patient who undergo RFA and patients who undergo embolization.

Assessing pain as primary objective and function as secondary objective will be through used tools such as WOMAC score and VAS, score

15 workplan: (*Instructions: Please use this form as a template for the timeline of your project*)

Task	**Number of Months**											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Proposal approval												
Data collection												
Data analysis												
Manuscript writing												
publication												
Progress report												

4.3 A description of the measures taken to minimize/avoid bias, including: (a) Randomization. (b) Blinding.

This is a Randomized control trial. In the sealed opaque envelope method is assuming that each participant has an equal chance of being assigned to any group. Each treatment limb will be allocated certain number on a paper and will be kept in an opaque sealed envelope treatment. Once a patient has consented to enter a trial, an envelope will be selected and opened by the patient, then the allocated treatment regimen will be offered to the patient. Blinding cannot be done in this method of randomization as the patient and the surgeon will know the procedure to perform

4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

- **Genicular nerve radiofrequency ablation (GNRFA) Mentioned above in section 2.4**
- **Genicular artery embolization (GAE) Mentioned above in section 2.4**

4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

The duration of patients included in the study is estimated to be around 12 months.

Phase 1: The trial period starts with a pre-procedure appointment, following patient's consent and approval to participate in the trial.

Phase 2: The Randomization of patients into three groups/limbs

Group 1: Patients that will undergo conservative treatment. As explained previously in details

Group 2: Patients that will undergo radiofrequency ablation (RFA). As explained previously in details

Group 3: Patients that will undergo Genicular artery embolization (GAE). As explained previously in details

Phase 3: The treatment and procedure phase, as patients will undergo the designated procedure or specified treatment assigned to them.

Phase 4: Initial post-procedure assessment for pain and function, Six-weeks post-procedure.

Phase 5: second post-procedure assessment for pain and function, Three-months post-procedure.

Phase 6: third post-procedure assessment for pain and function, Six-months post-procedure.

4.6 A description of the “stopping rules” or “discontinuation criteria” for individual subjects, parts of trial and entire trial.

Stopping rules for individual subjects

1- the participant suddenly refused to continue the trial
2- Any complications that occurs to the participant from the procedures as discussed in complications section
3- Loss of follow up the participant

Stopping rules of entire trial:

1- Procedures of the trial is not anymore available in the national guard hospital Jeddah

4.7 Maintenance of trial treatment randomization codes and procedures for breaking codes.

In the sealed opaque envelope method is assuming that each participant has an equal chance of being assigned to any group. Each treatment limb will be allocated certain number on a paper and will be kept in an opaque sealed envelope treatment for example (1,2,3…). Once a patient has consented to enter a trial, an envelope will be selected and opened by the patient, then the allocated treatment regimen will be offered to the patient. Blinding cannot be done in this method of randomization as the patient and the surgeon will know the procedure to perform or undergoing.

4.8 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

All data will be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

5 Selection and Withdrawal of Subjects

5.1 Subject inclusion criteria.

As described above in section 2.6

5.2 Subject exclusion criteria.

As described above in section 2.6

5.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
(a) When and how to withdraw subjects from the trial/ investigational product treatment.

As described above in section 4.6

(b) The type and timing of the data to be collected for withdrawn subjects.

1- If the patient completed the at least the first post procedure follow up data collection (6 weeks post procedure) and then the participant withdrew, all collected data at that time will be included in analysis and further data will be considered missing

(c) Whether and how subjects are to be replaced.

1- If the patient withdrew before having the procedure done will be replaced by another participant
(Replacing the participant will also not include blinding because the replaced participant will have discussion on his upcoming procedure which the other participant withdrew from)

(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

1- If the patient completed the at least the first post procedure follow up data collection (6 weeks post procedure) and then the participant withdrew, all collected data at that time will be included in analysis and further data will be considered missing

6 Treatment of Subjects

6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

- **Described in details including the treatment periods in section 2.4**

6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

There are no prohibited medication before or during the trial

And for the permitted medication and treatment will be for conservative management (NSAIDS, physiotherapy, weight reduction program, Intraarticular injections) and for other limbs RFA and GAE as discussed above in details

6.3 Procedures for monitoring subject compliance.

Follow up visits

7 Assessment of Efficacy

7.1 Specification of the efficacy parameters.

For the WOMAC score it includes 3 parameters which are pain, stiffness, and physical function and scored from 0 to 4 having 0 as None and 4 as the most extreme. [21]

For VAS score it is used to assess the pain only from 0 to 10 having 0 is None and 10 is the most Extreme. [22]

Kellgren-Lawrence score is a xray based score to grade knee osteoarthritis from 0-4 having 0 is the normal and 4 is the most severe. [23]

7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

The basic data for the patients will be collected through data sheet attached from the national guard data base (Best Care) like demographics (Age, gender, BMI…)

Other variables for pain and function pre procedure and post interventional procedure such as WOMAC score and VAS score will be taken through interviewing the patient after taking informed conscent from him

Kellgren-Lawrence score will be used as the score for grading knee osteoarthritis on xray

Failure of conservative management defined as:

- Failing of knee pain to improve despite using NSAIDS, physiotherapy, weight reduction programm, or Intrarticular injections for at least 3 months

Timing already described before in section 2.6

8 Assessment of Safety

8.1 Specification of safety parameters.

To ensure safety of the participant, good explanation of the procedure to the patient will be done. Also, monitoring the participant physically while undergoing the procedure and observing him after doing the procedure will be ensured

Following up the patient on regular basis will be done to ensure also safety of the patient

8.2 The methods and timing for assessing, recording, and analysing safety parameters.

As discussed above the patient will be monitored before, during, and after the procedure apart from following him up in clinic visits, Vitals and local or systemic reactions to the procedure will be monitored

8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

The patient will be discarded from the trial following the stopping rules as discussed above

The complication will be documented and reported in the trial results

The patient will be followed closely to manage the complication and referred to the appropriate specialty as needed

8.4 The type and duration of the follow-up of subjects after adverse events.

The patient will be followed closely within 1-3 days at first to ensure safety of the patient and then can be followed weekly or as needed to manage the complication and referred to the appropriate specialty as needed

6.9 Statistics

9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

- All analyses will be performed using the IBM SPSS version.22. - Descriptive statistics will be used to calculate quantitative data, which will be

checked for normality using histograms, means, and standard deviations to

describe subjects' characteristics, in case of normality. - Medians and IQR will be used for skewed data, while qualitative data will be

calculated as frequency and percentage. - For inferential statistics, Student t-Test, Paired T test/ANOVA will be utilized

for quantitative data and Chi-Square Test for qualitative data. - Multivariate regression analysis

There is no timing for planned interim analysis

The primary objective and secondary objective will be assessed through mean/median according to normality and the results will be interpreted.

9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

Sample size was calculated by using the Clincalc sample size calculator.

The prevalence of OA is found to be 18.5% for one group while for the second group it was taken as 35.4%. [24,25] The sample size was estimated at the power of the study as 80% with a margin of error of ±5%. The required minimum sample size was determined to be 107 in each group.

Therefore, a total of 321 patients will be enrolled for the three limbs assessed.

9.3 The level of significance to be used.

Statistical significance will be determined using the 95% confidence interval,

and a p-value of<0.05 will be considered significant.

9.4 Criteria for the termination of the trial.

1- **Described above in section 4.6**

9.5 Procedure for accounting for missing, unused, and spurious data.

Missing data will be specified and will be reflected in the analysis

9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

Not Applicable

9.7 The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

The selection of the subjects will be all the subjects meeting the inclusion and exclusion criteria after the process of randomization which is discussed previously

10 Direct Access to Source Data/Documents.

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

No Sponsor

11 Quality Control and Quality Assurance

12 Ethics

Description of ethical considerations relating to the trial.

Informed written consent will be taken from the patient which declares the title of the study and the principles investigator name.

Also, the intervention that will be done including risks and complications and the outcome expected

A witness will also be available.

13 Data Handling and Record Keeping

Data will be collected and entered on Microsoft excel and will be stored in PI computer and it will be password protected and only the researcher will have access to it and no names or addresses will be collected for confidentiality

Also data collection sheet is attached to review

14 Financing and Insurance

No Financial support needed

15 Publication Policy

Publication policy will be discussed after finishing analysis depending on the desired journal that will be published in