



ANGIO-SEAL VERSUS MANUAL
COMPRESSION CONCERNING
PUNCTURE SITE RELATED
COMPLICATIONS IN PERIPHERAL
ARTERIAL DISEASE.

End-of-degree project

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Mila esker nire familiari, sei urte hauetan emandako laguntzarengatik, zuei gabe gaurko eguna ezinezkoa izango litzake.

"El médico que sólo sabe Medicina, ni siquiera Medicina sabe"
Jose de Letamendi y Manjarrés (1828-1897)

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1. ABBREVIATIONS

- **AAS:** acetylsalicylic acid.
- **CEIC:** comité ético investigación clínica.
- **CFA:** Common femoral artery.
- **DFA:** Deep femoral artery.
- **CT:** Computed tomography.
- **DUS:** Doppler ultra-sonography.
- **F:** French
- **FDA:** Food and drug administration.
- **MC:** Manual compression
- **MR:** Magnetic resonance
- **PAD:** Peripheral arterial disease
- **PTA:** Percutaneous transluminal angioplasty
- **SFA:** Superficial femoral artery
- **TASC:** Trans-Atlantic Inter-Society Consensus Document on Management of
Peripheral Arterial Disease
- **VCD:** Vascular closure device

2.ABSTRACT

Background: *Endovascular surgery, allows us to treat and diagnose peripheral vascular disease of low extremity just with a minimal incision in the common femoral artery. Manual compression has been the gold standard for haemostasis of the puncture site, but in the early 1990s, Vascular Closure devices were introduced with the aim of reducing time to haemostasis, time of ambulation, time of discharge and intervention-related complications. However, its advantage over MC has not been extensively studied following interventional procedures.*

Objectives: *The aim of this study is to compare the vascular puncture-site related complications, using a VCD (Angio-Seal) instead of manual compression. This results will be evaluated in the 30 days' post-operative. Secondary objectives also include a diminution on the hospital discharge time, time to haemostasis and need for reintervention.*

Methods: *Randomized, controlled clinical trial. The study will be carried out for 3 years (2019-2022).*

Participants: *Patients diagnosed with peripheral arterial disease of the femoro-popliteal sector and indication for percutaneous transluminal angioplasty.*

Keywords: *Angio-seal, manual compression, percutaneous transluminal angioplasty, puncture site.*

3.INTRODUCTION

DEFINITION, EPIDIMIOLOGY AND RISK FACTORS

Peripheral arterial disease (PAD) is one manifestation of systemic atherosclerosis (9). It is a process that causes narrowing of the peripheral arterial vasculature, predominantly of the lower limbs. Is significantly related to disease of other territories such as coronary or cerebral, causing a clinically relevant disease (1,2,9).

Total disease prevalence based on objective testing has been evaluated in several epidemiologic studies and it is in the range between 3% to 10%, increasing to 15% -20% in persons over 70 years, and is estimated that affects more than 200 million people worldwide (6,12).

Atherosclerosis is characterized by intimal lesions called atheroma, or atheromatous plaques, which protrude into and obstruct vascular lumen and weaken the underlying media. This leads to a stenosis of the vessel, compromising the blood supply to the limb, in the case of PAD, or organ (2).

For the evaluation of PAD, is important to make an accurate clinical history and a physical examination. In the familiar history we have to take into account both cardiac and cerebrovascular disease, presence of aortic abdominal aneurisms or PAD. In personal previous events, is basic to evaluate all the CV risk factors and comorbidities of the patient. Also we have to interrogate about lifestyle (diet habits, walking, physical activity) (1).

The atherosclerotic risk factors responsible for PAD and other cardiovascular diseases are common to all these conditions. These predisposing risk factors have been well identified by means of several well-defined prospective studies (2).

- Age, sex, and ethnicity: Prevalence increase with age. The male/female ratio is commonly reported as 2:1. And black ethnicity is also an independent risk factor for PAD.
- Cigarette smoking: This is the most important modifiable risk factor for developing PAD.
- Diabetes is a major risk factor for PAD, mainly affecting the infra-popliteal arteries in these patients, and causing the so called diabetic foot.
- Hypertension: Each 10 mm Hg increase in SBP was associated with a 25% increased risk for developing PAD.
- Hyperlipidaemia: Studies found out that for every 10 mg increase in total cholesterol there is a 5% to 10% increment in risk for developing PAD.
- Other factors: chronic renal insufficiency, hyperhomocysteinemia and hiperviscosity state also seem to have a link with PAD, although there are not so well known.

When PAD of low extremity is suspected, the first step in our practice has to be the clinical examination. Both lower limbs should be completely exposed, and colour of skin, hair loss, nail damage or ulceration evaluated. Temperature of limb and capillary refill time should also be assessed (1,2).

It is mandatory in the evaluation of PAD to do a peripheral pulse palpation. In the lower limb, from proximal to distal, the femoral, popliteal, posterior tibial, and anterior tibial/dorsalis pedis pulses must be measured. (1,2).

DIAGNOSIS TESTS

Ankle-brachial index (ABI) it's the first diagnostic step following clinical evaluation. It's a non-invasive technique for detection and follow-up in patients with PAD (1). It's measured as the ratio of the ankle systolic pressure to the brachial systolic pressure (2).

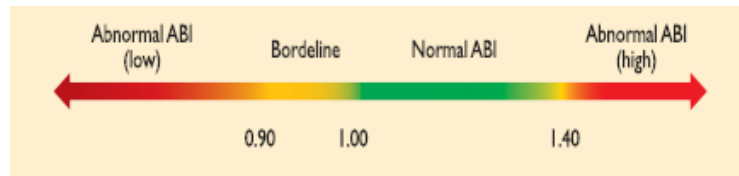


Figure 1. Interpretation of ABI (1)

IMAGING METHODS

The confirmation of the diagnosis is done by image tests, providing information of arterial anatomy, stenosis or occlusions and haemodynamic. Also, one of the main purpose of imaging is to identify an arterial lesion that is suitable for revascularization (1,2)

Duplex ultrasound. Provides extensive information on arterial anatomy and direction and velocity of blood flow through the artery (1,2). By the identification of areas of turbulence and determination of the velocity shift across a diseased segment provides an objective evaluation of the hemodynamic severity and extension of PAD (2). DUS cannot be used as single method to plan endovascular intervention, so, another imaging technique is usually required when revascularization is considered (1).

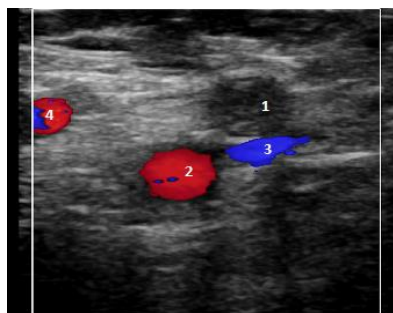


Figure 2. Complete occlusion of the SFA (Nº 1)
DFA (Nº2) Femoral vein (Nº3) lateral circumflex artery(Nº4)(4)

ADVANTAGES:

- Cheap and readily to use. (2)
- Non- Invasive (1-4)
- Good to asset the quality of vein vessels for bypass substitutes (1).
- Method of choice for routine follow-up after revascularization. (1-3)
- Avoids use of contrast and irradiation (3).

DISADVANTAGES

- Requires trained technicians and experience in reading scans (1)(3)
- DUS does not present as a roadmap the entire vasculature (1)
- Not useful to plan endovascular interventions (1)

Computed tomography angiography. It provides detailed assessment of vascular anatomy, disease burden and location, and lesion character (3), with a nearly 100% sensibility and specify (1)

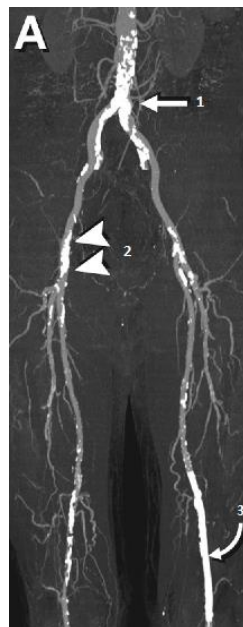


Figure 3. Arterial calcifications near the aortic bifurcation (Nº1), in the right and left CMA (Nº2) A stent in the left femoropopliteal segment (Nº3) (5)

ADVANTAGES

- Decreased examination time (4) (3)
- It can be used to evaluate the iliac artery (4)
- Less affected by the operator's experience (4)
- Allows the of calcifications, clips, stents, bypasses and concomitant aneurysms (1) (3)

DISADVANTAGES

- High radiation exposure (1-3)
- Use of iodinated contrast, which is nephrotoxic and can cause allergies too (1-3)
- Severe calcifications may act as masks of stenosis, especially at distal levels (1)

Magnetic resonance angiography (MRA) It's the preferred second-line test for PAD diagnosis, when patients cannot undergo CTA (2).



Figure 4. Diffuse disease of the calf blood vessels (2)

ADVANTAGES

- No irradiation (1-3)
- Good image of the tibial arteries (1)

DISADVANTAGES

- Gives an overestimation of stenosis grade (1)
- Difficulty in interpretation of calcified arteries (1)
- Use of gadolinium contrast can lead to a nephrogenic systemic fibrosis (1-3)
- No visualization of steel stents (1)
- Long execution time (3)

CLINICAL PRESENTATION

The majority of patients with a diagnosis of PAD are initially asymptomatic (up to 75%), and diagnosis is reached by a low ABI (<0.90) or by the absence of pulses. Moreover, some patients represent a big challenge, as they can have severe disease which remains asymptomatic because of other comorbidities, such as heart failure and, specially, diabetic neuropathy. This condition is known as 'masked PAD' (1,2)

Even asymptomatic PAD is well related to a high risk of CV events. In symptomatic patients, clinic can be divided into intermittent claudication and critical limb ischemia (1-3). Among these, the most typical presentation is IC.

INTERMITTENT CLAUDICATION

Typical intermittent claudication of patients suffering PAD is defined as the appearance of pain in muscle groups associated with the start of walking and relieved by stopping.

Pain always appears in the same muscle groups, after traveling a similar distance with same slope and speed. This is basic to be able to differentiate it from non-vascular claudication, since it doesn't show such a close relationship with walking or with the constant affected muscle groups (13).

Our study will be directed to patients with femoro-popliteal disease, since they are the ones that can benefit from the interventional technique of our study. Therefore, our patients will usually refer pain in the gastrocnemius area.

IC represents a progression of arterial obstruction, located in the femoro-popliteal arteries mostly (70%), causing an obstructive PAD which leads to limb ischemia and restriction of daily activity. This limitation of lifestyle is what dictates largely the indication for revascularization, and is measured by the Fontaine classification (Figure 5). Usually the risk of limb loss is low, this can be increased by other CV risk factors like diabetes (3).

Fontaine classification		
Stage		Symptoms
I		Asymptomatic
II	IIa	Non-disabling intermittent claudication
	IIb	Disabling intermittent claudication
III		Ischaemic rest pain
IV		Ulceration or gangrene

Figure 5. Fontaine classification (1)

CRITICAL LIMB ISCHEMIA

Representing the most severe clinical manifestation of chronic PAD, CLI is defined by the presence of ischemic rest pain, with or without ulceration, gangrene or infection. This is caused by a critical diminution of blood perfusion, attributable to occlusive arterial

disease and generally associated with an ABI<0.4 and toe pressure <30 mm Hg, although CLI is a clinical diagnosis (1,3). Also, usually relates to Fontaine stages III and IV (3).

This represents a really severe situation, in which revascularization is vital to avoid amputation (2).

MANAGEMENT OF PAD.

The basics of the PAD treatment is to improve limb symptoms or salvage. The therapeutic approach to patients with PADs includes two aspects. The first is to address CV risk factors, by reducing related events and mortality. This includes the smoking cessation, lipid-lowering drugs, antithrombotic drugs and anti-hypertensive drugs. The second one addresses the resolution of a specific lesion by open surgery or endovascular intervention (1) This second is in which we will deepen, because it is what we will indicate in the patients of our study.

When talking about PAD, we can group lesions according to their location in: aorta-iliac disease, femoro-popliteal disease or infra-popliteal disease.

This clinical trial is aimed at patients with femoro-popliteal disease, which are tributaries of endovascular revascularization, therefore, we will now focus on explaining the indications and characteristics of this intervention.

CLASSIFICATION OF LESIONS

The new TASC II guidelines published a classification of lesions in the femoro-popliteal disease that allows the division of the lesions according to the territory they affect and the size of them. This is essential when deciding whether the patient is a tributary to endovascular surgery, which is the preferred technique, or not (6,7).

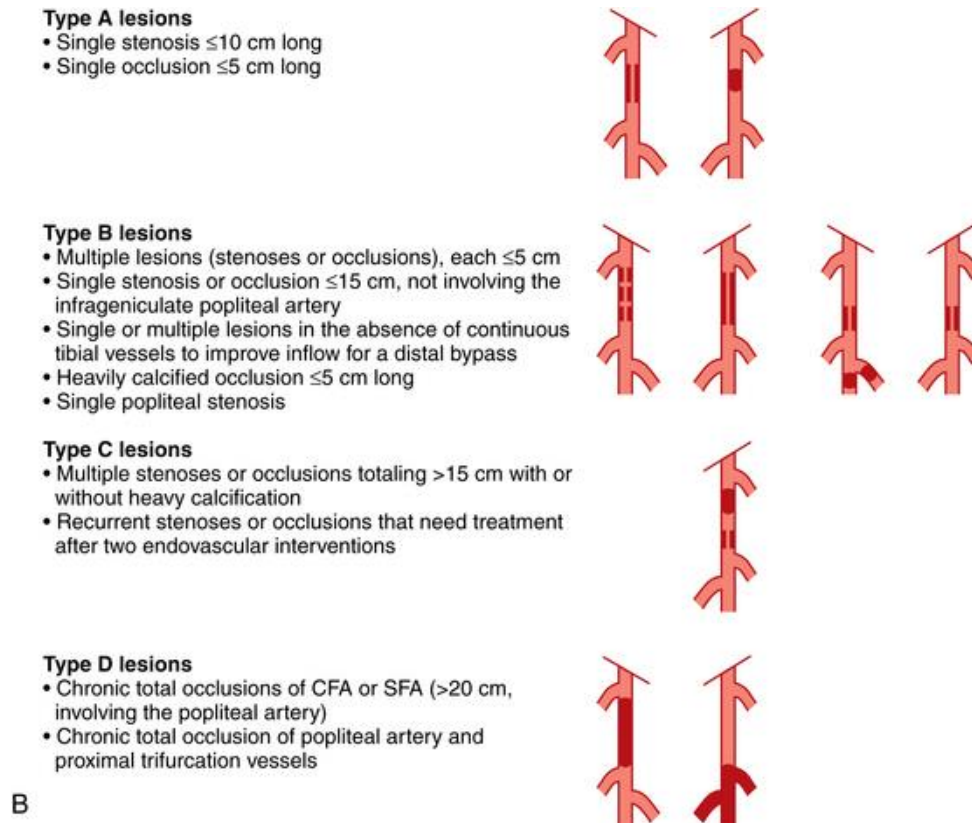


Figure 6. TASC II classification in femoropopliteal disease. (7)

Based on this classification, we can obtain the recommendations for the treatment of PAD (7-22):

- TASC A: Endovascular therapy is The treatment of choice.
- TASC B: Endovascular treatment is the preferred treatment for type B although it can also be surgical depending on the clinical scenario.
- TASC C: Surgery is the preferred treatment for good-risk patients with type C lesions
- TASC D: surgery is the treatment of choice for type D lesions.
- Indications for type A and D are pretty clear, but for type B and C patient's comorbidities, patient's preference and operator's experience must be considered when making a treatment decision.

ENDOVASCULAR THERAPY FOR FEMORO-POPLITEAL AREA

Percutaneous transluminal angioplasty is a minimally invasive therapy for the treatment of patients suffering IC or critical limb ischemia due to a peripheral arterial disease. Among its advantages, it stands out its low rate of complications (between 0'5% and 4%), high technical success rate and an acceptable clinical outcome (10).

Furthermore, there is no need for general anaesthesia, and the patient can be discharged on the same day of treatment, returning to normal activity within 24 to 48h (9). Among its limitations, the high rate of restenosis stands out. That is why, during the last years, several novel technologies have been developed for endovascular treatment of lower-limb arteries (10,23,24).

Intervention is performed from the contralateral limb, accessing by the CFA. Then we made the crossing and tried to overcome the possible stenosis or occlusions using a paclitaxel-coated balloon, trying in addition to inhibit the restenosis and maintain the vessel patency. Sometimes, and depending the vessel we are approaching, the colocation of a stent to prevent the restenosis can be needed, but there is not a consensus regarding which stent is indicated in different cases, especially the ones regarding the SFA. (9,10,12,23)

HAEMOSTASIS OF PUNCTURE SITE

Since the development of endovascular surgery and until the appearance and wide development of VCDs, manual compression has been the chosen method, despite is time consuming, as the operator has to remain up to 20-30 minutes of MC. Also, the patients needs a longer bed rest after the intervention and the discharge time from

hospital is delayed. Furthermore, achieving haemostasis with MC in obese patients or patients on anticoagulant or antiplatelet therapy presents a higher difficulty (8,11).

For these reason, in the 1990, VCDs were developed. They were announced as a quicker, more effective and convenient way to achieve haemostasis.

In order to categorize VCDs, we use their mechanism of action, dividing them into active approximators and passive aproximators (11):

- Active aproximators: These devices physically close the punction site by using either a nitinol clip or a suture. We can find 3 of them approved by the FDA, and usually are used for bigger sheaths, as Proglide, which can be used in sheaths up to 21 F.
- Passive aproximators: They don't employ a physical close, instead, they use a plug, a sealant, or gel. We can distinguish 6 approved devices in this category, but we highlight Angio-Seal, the device we will be using in our study. Angio-Seal consists of an intraluminal anchor wich secures an absorbable collagen plug that closes the arteriotomy. Used in 5, 6, 7, and 8 F sheaths (see inerventions and ANNEX 1)

It has been shown that in percutaneous procedures, complications related to the puncture site are a significant cause of morbidity, ranging from 1% to 11%. These complications result in a longer time of hospitalization, greater use of resources and even the need for transfusion or reintervention. In addition, it has also been shown that in moderate-severe complications, mortality was higher (30-day mortality (6.1% vs 1.4%, P <.001) (8).

With these results, the benefits that VCDs can provide to both patients and surgeons are clear, however, given the relevance that the access-related complications present, more evidence is needed to confirm their greater safety compared to MC.

4. JUSTIFICATION

Lower limb PAD constitutes one of the biggest challenges for vascular surgeons in their day to day, since it affects more than 200 million inhabitants worldwide (8) Since the appearance of the PTA in 1979, the endovascular techniques have advanced enormously (14) this has given rise to the appearance of different complications that differ from the traditional ones referred to the open surgery.

One of the main advances, was developed in the 90's, with the apparition of VCD. These have shown an overall improvement in the satisfaction of surgeons and patients, as it has shown a decreased time to haemostasis (from 30' to even 1''). Also, there is no need to long rest on completion (up to 4-8 hours) and patients can be discharged on the same day (8).

Despite the apparent benefit of VCD over MC, it's superiority regarding security is still on debate. This is due to the fact that it has not been proven that it is safer. During the last years there have been numerous studies, which have yielded all kinds of results, without reaching any consensus (8,11,15-18). It is important to note that most of the studies that have obtained favourable results on VCD have been studying patients undergoing cardiac catheterization (8,16-18). And, furthermore, most patients with significant PAD are excluded in these studies. This can be explained by the fact that VCDs affect the inner arterial lumen, which can represent an extra source of complications in patients with PAD of the lower limbs (16).

The VCDs have also been studied between them, and several studies have determined that Angio-Seal is the safest among them, so we will select it to carry out our study (8,15-

17). Although certain cases of mayor complications have been reported, especially distal limb ischemia, and groin infections (8,15,19,20,21) we believe that Angio-Seal is the most suitable device for our study, since our surgeons have been trained with it and have extensive experience.

Further randomized trials with larger sample sizes comparing safety and efficacy between VCD and MC in patients with significant PAD of the lower extremities are required, and with these study we aim to verify the safety of Angio-Seal, as we believe it has several advantages over MC, regarding patient recovery, patient turnaround time, and efficiency in the operation room.

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6. HYPOTHESIS

6.1 PRIMARY HYPOTHESIS

In endovascular treatment of peripheral arterial disease, Angio-Seal closure device can be used safely, and rate of complications won't be higher comparing to the use of manual compression.

6.2 SECONDARY HYPOTHESIS

Patients using Angio-Seal will have a lower time to haemostasis, the need for interventions and time in-hospital will be lower too, and the overall level of satisfaction will be higher comparing to MC group.

7. OBJETIVES

6.1 PRIMARY OBJECTIVES

The main objective of this study is to carry out a comparison of the puncture site related complications in endovascular femoral surgery of the femoro-popliteal sector, considering the use of Angio-Seal rather than manual compression to obtain haemostasis of the puncture site. Main complications to be evaluated:

- Haematoma: palpable mass of at least 5 cm.
- Pseudoaneurysm on the puncture site.
- Ipsilateral leg ischemia.
- Retroperitoneal haematoma.
- Local infection.

6.2 SECONDARY OBJECTIVES

- Discharging time
- Need for reintervention
- Time to haemostasis

8. METHODS

8.1. DESIGN

A randomized clinical trial: The use of Angio-Seal or manual compression in the endovascular intervention of the femoral artery. Blinding can only be applied to the patients.

8.1.1. RANDOMIZATION METHODS

Simple random sampling is a form of sampling in which a number of distinct subjects are selected randomly from the population in a way that each unit has equal chance to be selected in order to control possible confusion. In order to get this, we will be using the SPSS software.

24 hours before each surgery, the surgeon will be able to access to information about the type of haemostasis he needs to perform. This must be done in order to minimize any selection bias.

8.1.2. DEGREE OF BLINDING

A simple-blinding will be used in this trial. Just the patients can be blinded, as the surgeons must know if they are using Angio-seal or either manual compression.

8.2. STUDY POPULATION

In this study, patients with peripheral arterial disease of low extremity and indication of endovascular repair will be included. Patients will be both diagnosed and treated in Hospital Universitari Dr. Josep Trueta.

8.2.1. INCLUSION CRITERIA

- Men or women above 18 years.
- Patients with indication for PTA of the femoro-popliteal sector, typically considered in patients with PAD who have developed limiting claudication.
- Elective surgery must be indicated for our study. Because of that, we will not be considering patients with acute limb ischemia.
- -The procedure and the informed consent must be properly explained to all the patients, and they have to sign it, otherwise we can't include them.

8.2.2. EXCLUSION CRITERIA

- Procedures requiring a sheath or larger bore arterial access than 8F will be excluded.
- Previous intervention of the common femoral artery in the previous month.
- Patients with morbid obesity (IMC >40).
- Life expectancy < 2 year.
- Anatomic contraindications: Calcification in the common femoral artery too large to be able to perform an endovascular procedure. Patients with an arteriovenous fistula or an aneurysm in the femoral artery will also be excluded.
- Allergy to any of the used materials or to the contrast.

- Medical contraindications: Grade 3-4 cardiac failure (NYHA scale); renal insufficiency grade 3-5 (National Kidney foundation)
- Functional status: If the patient is unable to perform normal daily activities such as meeting of basic needs, fulfill usual roles, and maintain health and well-being and also his walking ability is seriously compromised by other cause rather than PAD.
- Severe arterial hypertension (>220/110 mm Hg)
- Local or systemic infection.

8.3. SAMPLING

8.3.1. PATIENT SELECTION

Patients for the sample will be recruited at H.U. Josep Trueta of Girona. The sample recruitment will take place at Hospital Universitari Dr. Josep Trueta of Girona. A consecutive, non-probabilistic and proportional to the number of admission sampling will be taken, in a period of 18 months. All patients must meet the inclusion criteria and be exempt from any exclusion criteria

If they meet this requirement, they will be given an information sheet, regarding all of the important points they must take into account before agreeing the study. Once they agree to participate in our study, we have to provide them the informed consent form, which has to be signed.

8.3.2. SAMPLE SIZE

In a bilateral contrast, with a level of signification (alpha risk) of 0.05 and a beta risk (β) of 0.2, with a value or statistical power of 0.8 ($1-\beta$), and, since we will measure it in the first month and being an intervention without a significant mortality rate, we expect a

1% of follow-up losses. Additionally, a moderate complication rate will be assumed (due to the wide heterogeneity found in literature) This results in a sample size of 196 patients each arm.

Sample size has been calculated with the Professor Marc Saenz's software based on the library 'pwr' of the free statistical environment R (version3.5.1)

8.4 VARIABLES

INDEPENDENT VARIABLE

The independent variable on this study is to be allocated in the Angio-Seal group or in the manual compression group while performing an endovascular procedure on the femoral artery for the treatment of PAD. This is a dichotomous qualitative variable.

DEPENDENT VARIABLE

The dependent variable in this study is the apparition of complications associated with the haemostasis method within the first 30 days' post-operation. These are defined as.

- **Local haematoma:** Palpable mass of >5 cm measured with Doppler ultrasonography.
- **Pseudoaneurysm:** Demonstration of a pseudoaneurysm neck with periodic flow signal in the puncture site by Doppler ultrasonography.
- **Acute ischemia in the ipsilateral leg:** demonstrated by loss of pulses, rest pain, pale and cold extremity and vessel occlusion shown by Doppler ultrasonography or Angio-TC.
- **Angio-Seal device failure:** The device failures in getting the haemostasis of the arteriotomy, and a reintervention is needed.

- **Retroperitoneal haematoma:** Demonstrated by TC both the haematoma and its origin (the punctured femoral artery)
- **Local infection:** defined as infected skin or soft tissue lesion at the vascular puncture site that requires antibiotic treatment

Every of them will be measured as dichotomous qualitative variables. (YES/NO)

SECONDARY VARIABLE

- **Hospital discharge delay:** Defined as the prolongation of hospital stay due to any vascular complication, measured in the number of hours from the expected time of discharge. This is a continuous quantitative variable.
- **Time to haemostasis:** Required time measured in minutes between sheath removal and observed haemostasis. This is a continuous quantitative variable.
- **Need for reintervention:** Referred as a need of reintervention due to a vascular complication in the first month following the intervention. It is a nominal dichotomous qualitative variable (YES/NO).

COVARIATIES

- Gender (male/female)
- Age (years)
- Anticoagulant treatment prior to intervention (yes/ no)
- Antiplatelet treatment prior to intervention (yes/no)
- Index body mass (kg/m²)
- Tobacco (current smoker and ex-smoker/non-smoker)
- Socio-economical level approached by education and occupation. Measured as a qualitative polytomic.

8.5 DATA COLLECTION

FIRST VISIT

Patients will come to our vascular surgery consults to be evaluated under the suspicions of PAD. In this visit, an accurate anamnesis and physical examination will be made. Patient's will be interrogated about familiar and personal history, tobacco consumption and regular drugs. In the physical examination, we will include:

- Palpation of all peripheral pulses of both extremities,
- Blood pressure will be measured with an electronic tensiometer and the ABI index will be determined
- Ischemia assessment according to the scale of Fountaine.
- An Eco-Doppler of the lower extremity will be performed as well.

If indication of surgery is decided, all patients will be programmed with an Angio-CT scan. Also, a preoperative visit with the anaesthesiology team will be scheduled, including a cardiac and a pulmonary assessment and a general blood analysis with haematocrit, haemoglobin and creatinine values.

SECOND VISIT

The results of the CT scan will be reviewed, and we will evaluate if the patient is suitable for PTA intervention of the femoro-popliteal sector. If the patient meets all the inclusion criteria's, and none of the exclusion ones, we will determine that the patient is suitable for our study. Therefore, we will explain all the details of the study, and give them and information sheet, also any questions will be answered. Once the patient agrees to take part in our study, we'll provide the informed consent that must be signed by the patient.

HOSPITALIZATION

All patients will be admitted the same morning of the intervention. They will be asked to fast 6 hours prior to surgery. Nurses will measure their blood pressure, heart rates and temperature. If patients need contrast protection, they will be given a desensitization line. This will consist of hydrocortisone 200 mg IV before administering the contrast, plus deschlorpheniramine 5 mg. IM 1 hour before the intervention.

SURGICAL INTERVENTION

The intervention will be performed by vascular surgeons, instrumentalist nurses and an anaesthesiologist. Intra spinal anaesthesia will be used. A nurse will be recording total procedure time, and size of the used sheath will be registered as well.

Interventions will be performed in the operating room and radiology imaging will be obtained with high quality portable C-arm fluoroscopic unit. Irradiation time and contrast volume administered will be recorded too.

POST-OPERATIVE

Once the intervention is concluded, patients will be admitted in the reanimation unit, where they will recover for the intervention and the anaesthesia. In a period of 2 or 8 they will be moved to the vascular surgery service. If the patient has been placed in the Angio-Seal group, complete bed rest will be required for 2 hours, whereas in the MC group, total rest will be up to 8 hours.

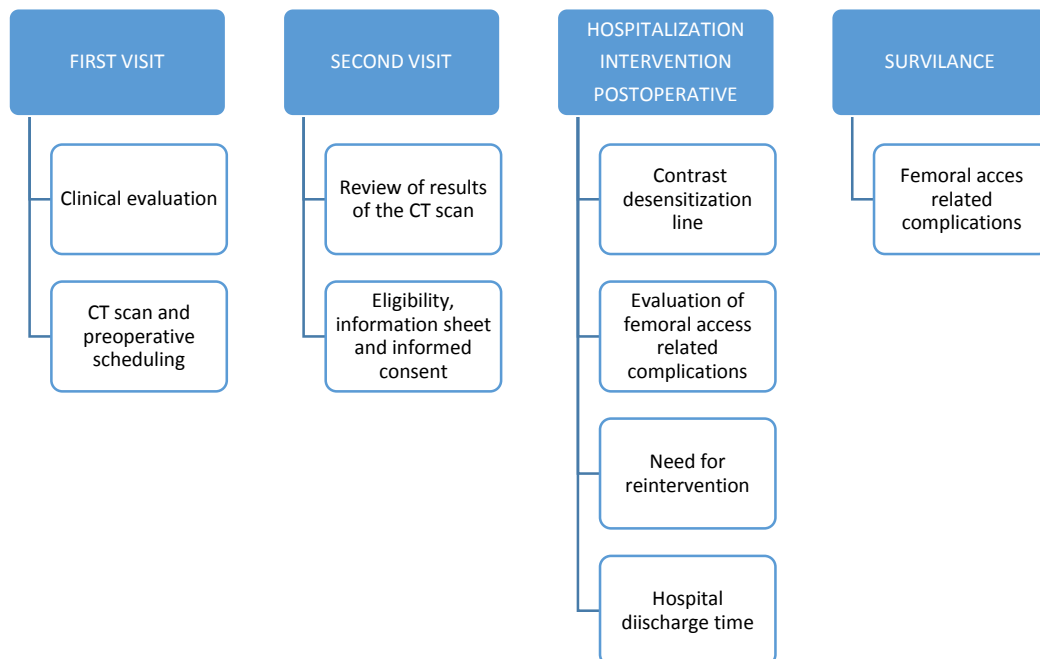
Close monitoring will be carried out, being very attentive to the possible complications that we may encounter, and before discharge, vascular surgeons will perform a thorough physical examination of the area of the wound and evaluate the pulses of the extremity (discarding a possible acute ischemia). In addition, a blood analysis will be

done to evaluate the renal function. Discharge is expected on the next day for both groups. Patients will receive a dual antiplatelet therapy after discharge: Clopidogrel 75 mg and AAS 100 mg between 3 and 6 months.

SURVILANCE

One week after the intervention, patients will be visited in in the vascular surgery consult at H. U. Dr. Josep Trueta by any vascular surgeon of the team. Physical examination will be repeated, paying special attention to the look of the groin wound. An Eco-Doppler ultrasound well be performed as well. One month later, same evaluation will be done. From this time, patients will continue their follow-up as expected for their disease, but no longer being part of this study.

SUMMARY



8.6 INTERVENTIONS

PERCUTANEUS INTRALUMINAL ANGIOPLASTY

All the interventions will be done in a conventional operating room by the same vascular surgeons' team. A high quality fluoroscopy and a suitable mobile operating table for radiological work and long measure devices are needed. Time of procedure and irradiation dose will be measured as well. All patients will be monitored with continuous electrocardiographic control, blood pressure, oxygen saturation and pulse. Afterwards a protamine sulphate neutralization will be done.

This endovascular procedure can be performed with intra spinal anaesthesia. Heparin is usually used for periprocedural anticoagulation. Also, if stent placement is planned, prophylactic antibiotic should be given. Usually, with 2 mg of cefazolin.

For access site, the CFA can be detected by touching or by ultrasound guidance. When found, a site free of plaque in the anterior artery wall is chosen for puncture, with an Abocath® puncture system. When puncture is achieved, the J-end of a short entry guidewire (between 0.018 and 0.035 ′′) is advanced through the needle. At this point, we can use fluorescence to evaluate the position of the wire and while passing through the iliac artery. Frequently, the wire can curl in the CFA or in the iliac artery while is being advanced. In this situation, can be resolved by slight rotation or repositioning the needle and re-advancing the wire under fluoroscopic visualization.

Once the wire is positioned in the iliac artery, and there is fluoroscopic confirmation that there are no kinks, loops or significant deviations in the course of the wire, a sheath can be inserted into the wire. The sheath size must be as small as possible for the chosen balloon catheter, and in our study, a maximum of 8 F will be allowed. The sheath is

advanced over the wire, and can be controlled by fluoroscopy. Once the sheath is advanced to the hub, it is important to re-evaluate the situation fluoroscopically before withdrawing the wire, because the sheath may be curled in the subcutaneous tissue instead of the artery.

The balloon catheter is wiped and the guide wire lumen is flushed with heparinised saline solution. The balloon should be aspirated with 25% or 50% strength contrast solution to exchange the pre-existing air inside the balloon shaft with liquid. This is important to avoid air embolization in case of balloon rupture, and allows a better visualization of the balloon under fluoroscopy. It is preferred to start with a smaller diameter balloon and upsize as needed to avoid over dilatation. Once the lesion is treated, or stent placement is required, the balloon is removed. Afterwards, completion arteriography is performed to evaluate the results of PTA.

CLOSURE WITH ANGIO-SEAL

Angio-Seal, is a passive approximator that deploys a collagen plug over the arteriotomy site with the aid of an intraluminal anchor. After intraluminal placement is confirmed, an anchor abuts the wall and a collagen plug is deployed over the arteriotomy. The plug expands when it enters the subcutaneous tissue and accelerates the clotting cascade. The anchor and plug are resorbed over time.

Step by step:

1. Locate the artery: First of all, we need to place the closure device, by assembling the sheath of the Angio-Seal and the arteriotomy locator. Once is fixed, we

placed into the arteriotomy and look for a return of blood, which is going to indicate us that the device is correctly placed.

2. Set the anchor: The artery locator is take out, and replaced by the by-pass tubing. When it's on his right position, the anchor is settled and locked intravascularly.
3. Seal the puncture: Gently, the device is pulled back until the suture has stopped spooling. Upward tension is maintained on the device while compaction tube is advanced. Finally, we cut the suture and remove the device.

MANUAL COMPRESSION

MC to achieve haemostasis after the removal of arteriotomy access device is a simple procedure that must be learned and practiced to achieve optimal results. In retrograde femoral access the arterial puncture site is usually proximal to the skin. Apply pressure with only as much force as needed for prevent the bleeding. Usually with one or two fingers pressuring the arteriotomy is enough for prevent bleeding. Limb perfusion must be controlled all along the procedure, which usually takes from 15 to 20 minutes, but it can be extended up to 30 minutes. Plus, after the intervention, the patient must complete a 6 hours bed rest.

9. STATISTICAL ANALYSIS.

DESCRIPTIVE ANALYSIS

All the dependent variables, the secondary variable “need for reintervention”, as well as the qualitative variables will be summarized using proportions, stratifying by groups of the independent variable (Angio-Seal or MC).

The rest of secondary dependent variables, and quantitative variables will be measured using means (standard deviation) and medians (interquartile range IQR), also stratified by groups of the independent variable (Angio-Seal or MC).

BIVARIATE INFERENCE

The differences of proportions of the principal dependent variables, the secondary “need for reintervention”, and qualitative co-variables will be measured between the groups of the independent variable using the contrast Chi-square or the Fischer’s exact test, if expected frequencies are less than 5.

Differences of medians between groups of the independent variable and differences of means will be contrasted using t of Student and U of Mann-Whitney, respectively.

MULTIVARIANTE ANALYSIS

Logistic regressions will be made for principal dependent variable and the secondary “need for reintervention”. Lineal regressions will be used for remaining secondary dependent variables. The explanatory variable of interest in the independent (Angio-Seal or MC) is adjusted by all the co-variables.

10. WORK PLAN

- Investigators: Lydia Garcia-Mendoza, Dr. Omar Andrés Navarro
- Collaborators: Vascular surgeons, anaesthetists and nurse staff of H. U. Dr. Josep Trueta of Girona, statisticians.

Stage 1. Design and approbation of research protocol (March 2019-April 2019)

- The team will carry out a revision of this protocol, with the intention of correcting any error, or making any necessary changes in the hypothesis, the variables or the methodology.
- Once is ready, it will be submitted to the CEIC for its approval.

Stage 2. Organization (May 2019- June 2019)

- The members of the surgical team and the nursing staff will be informed about the clinical trial. A protocol regarding information about patient recruitment and data processing will be explained to the surgeons. If any surgeon isn't familiarised with Angio-Seal, he or she will receive training during this period.
- The schedule will be defined as well, and shared with the nurses and anaesthesiologist. Roles of each person taking part into the trial must be defined by the end of this period.
- The statistic will be introduced to the staff at this phase and a meeting every six months will be settled. During this meetings, possibly doubts or problems will be clarified.

Stage 3. Patient recruitment and intervention (July 2019- March 2021)

- Patients will come to the vascular consult of H. U. Josep Trueta on suspicious of PAD of the femoro-popliteal sector. Once the diagnosis and suitability for the study is confirmed, we will inform to the patients about the trial.
- A detailed explanation will be given, with the information sheet, if the patient agrees to take part in the study, the informed consent form must be signed. Afterwards, the patient data sheet must be filled by the surgeon, and the intervention is planned.
- All the interventions are going to be performed by the same surgeon and nursing staff. Clinical evaluation concerning femoral access site complications will be held prior to the patients discharge, and the first week after the intervention as well.

Stage 4. Data collection and processing database (July 2019-April 2021)

- Surgeon in charge of the intervention will inform about any incident occurred. Also, the nursing staff will perform the necessary tests to collect all the data needed to cover all the objectives of the study. It will be divided in to times:
- First data: Information about the intervention itself will be reported (time to haemostasis, total procedure time, need for reintervention due to device failure...)
- Second data: Any complications due to the femoral access site must be informed, also any delays in the expected discharge time and need for re-

intervention for a related cause to the arteriotomy closure This information will be recruited from the end of the intervention until the follow-up ends, one month after the intervention

Stage 5. Statistical analysis (May 2021- September 2021)

- All data collected will be analysed by a professional statistician.

Stage 6. Results and publications (October2021- March 2022)

- Once the statistical analysis is performed, a final report with the evaluation and interpretation of al outcomes will be drafted.
- Articles will be written for their publications in different journals and if possible, we will attend to conferences to present the results.

CROHONOGRAM

	Mar.2019 Apr. 2019	May2019 Jun.2019	July 2019 Mar.2021	July 2019 Apr.2021	May 2021 Sep. 2021	Oct.2021 Mar.2022	Responsible
1.Design & approbation protocol							Investigators
2.Organization							Investigators vascular surgeons nursing staff anaesthetist
3.Patient recruitment & intervention							Investigator vascular surgeons
4.Data collection and processing database							Investigator vascular surgeons nursing staff
5.Statistical analysis							Investigators Statistician
6. Results and publications							Investigators

11. FEASIBILITY

RESEARCH TEAM

For our study, we need trained surgical and nursery staff, familiarised with endovascular procedures and with Angio-Seal as well. All the interventions will be performed by chief of vascular surgery, Dr. Omar Andres. He is a surgeon with great experience in the endovascular field. All the vascular surgeons of the department are responsible of the patient's follow up with ultrasound monitoring.

IdIBGi will provide a statistician to carry out the data analysis.

AVAILABLE MEANS

Carrying on this study will require means for diagnostic and follow-up, such as blood pressure cuffs, a Doppler ultrasound scan and a CT or RM scan. For the intervention we will need an operating room adapted for endovascular interventions, with fluoroscopic and adapted table. Also surgical and endovascular material (wires, sheaths, balloons).

All means needed are available in our hospital, and our staff is familiar to them.

PATIENTS

In our hospital, last year about 260 patients with PAD of the femoro-popliteal sector were treated with percutaneous treatment. It is estimated that this number will increase about a 10% per year, due to the continuous advances in endovascular interventions. As we need to treat 392 patients, and assuming that not all patients will enrol in our study, we expect to collect our sample size in 18 months. If it is not possible, this period should be enlarged.

12. LEGAL AND ETHICAL ASPECTS

This study will be conducted in accordance to the Human Rights and to the Ethical Principles established by World Medical Association in the Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects (last actualization, October 2013).

Once this protocol will be finished, it will be sent to the Clinical Research Ethics Committee (CEIC) of Hospital Universitari Dr. Josep Trueta in Girona in order to be evaluated and approved, and their recommendations will be taken into account to carry out the study. Once approved, it will be registered in ClinicalTrials.gov and in EudraCT.

According to the “Ley 41/2002 Básica reguladora de la autonomía del paciente y derechos y obligaciones en materia de información y documentación clínica” all participants interested in being part of the study, will be asked to sign voluntarily the informed consent (see ANNEX 2).

The use of the device Angio-Seal is approved by the “Real Decreto Legislativo 1/2015 de 24 de julio, artículo 2” which involves the use of any medical product. The procedure (PTA) will follow the “Ley 14/2007, de 3 de julio” which regulates the invasive procedure.

This clinical trial guarantees that all the information obtained will be confidential and anonymous according to the “Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales”. All the obtained information will be only used for the purpose of the study.

13. LIMITATIONS

- The use of a triple blind is inviable, because the surgeon must know how is going to perform the closure of the arteriotomy. It is only possible to maintain the patients' blind. To overcome this limitation, the statistician will be blind and will not be aware of which participant belongs to which group.
- As the same surgeon will perform all the interventions, we can accept a good internal validity, however, we cannot ensure the generalization of our results (external validity).
- Most of patients enrolled in the study will be previously treated with an antiplatelet treatment whit AAS which won't be suspended for the intervention, furthermore, heparin is used during the procedure. It is known that this can compromise the outcomes for MC group, although, its suspension during the intervention would be meaningless.
- Most of the studies regarding the complication rates between Angio-Seal and Manual compression didn't include patients with severe peripheral arterial disease. For these reason, exact model information couldn't be treated. However, this was an encouraging situation to carry on this study.
- To carry out this study, the sample size was calculated only for the primary objective, so it is possible not to achieve feasible conclusions for the secondary objectives.

14. BUDGET

Performing this clinical trial is not related with an increase of the costs of the surgical procedure. The interventional procedure performed in the study has been implemented in the vascular service for several years. So, it will not be needed extra training, extra surgery material, extra medical or nursery staff or extra intervention costs.

In addition, the estimated hospitalization time is the usual after this intervention, so it will not involve any increase of the hospitalizing days required. The only increase from the usual intervention will be in the number of visits, as we are planning one extra visit one week after the procedure, which will include and Eco-Doppler. We estimate that this will increase our budget in 19.600€. Despite this, all this costs are in charge of the National Health System and does not suppose an increase of the final budget. A statistical expert for data analysis is needed. We estimated that the hours of work required for the statistical analysis will be 100 with the cost of 30€/h, increasing the budget in 3000€. The cost of printing materials for information sheets, informed consent and participant data sheet is estimated in 120€.

Publishing the study in international scientific journals will cost 2500€. The dissemination of the study which include attendance to the International Symposium of Endovascular Surgery registration (SEACV) will cost 1000€, adding 900€ more for transportation, accommodation and food.

Expenses for the staff

Statistical expert for data analysis 100h x 30 € = 3000€

Services

Extra Eco-Doppler 50€ x 392 patients = 19.600€

Material

Printing and papers 120€

Publication and presentation costs

Publish in Journal of Vascular Surgery 2500 €

International Symposium of
Endovascular Surgery registration (SEACV)

- Inscription 1000 €
- Transport to Madrid 200€
- Accommodation and diets 700 €

TOTAL 27.120€

15. PROJECT IMPACT AND APPLICABILITY

With this study we want to get deeper information about the safety of Angio-Seal in PTA procedures of the CFA, in patients suffering PDA.

In the past few years, there have been several studies comparing the safety of VCDs to MC, but they haven't reached to a consensus regarding to their safety. Furthermore, this studies exclude patients with PDA most of the times.

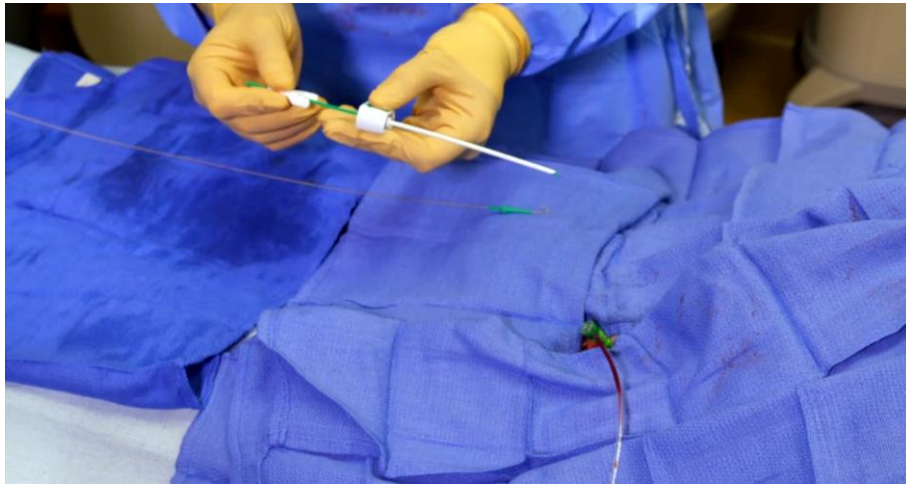
There is also a concerning about severe complications which can be caused by the use of Angio-seal, such as low limb emboli and groin infection. With this study, we want to show that these complications are residuals, and the overall benefit-risk of Angio-seal is favourable, comparing to MC.

Additionally, if the results of these study are favourable, we will demonstrate that the use of Angio-seal reduces the time of intervention, patients will be discharged within the same day, and there will be a decrease of hospital costs.

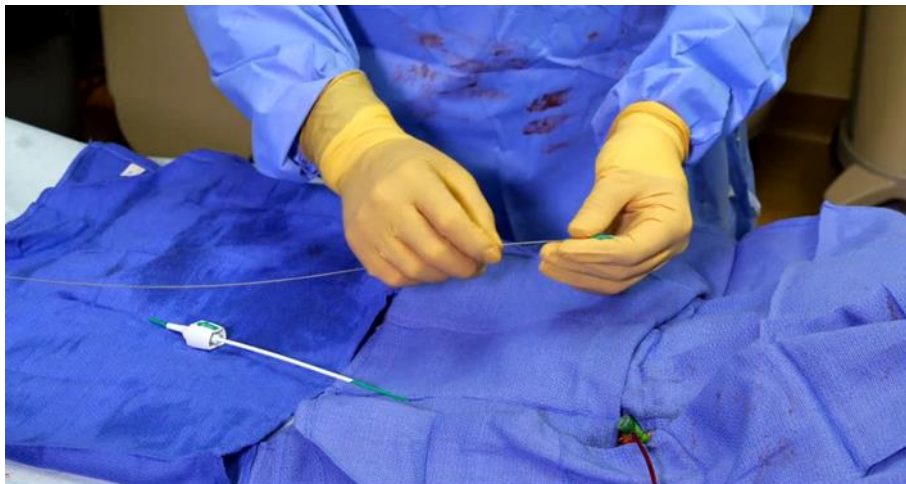
In summary, we expect that this study provides more information regarding the security of Angio-seal, as we believe the patient's safety has to be our first priority in order to allow its wide implantation in endovascular procedures. This protocol can be reported by others future studies and can increase the pool of data available for analysis.

16. ANNEXES

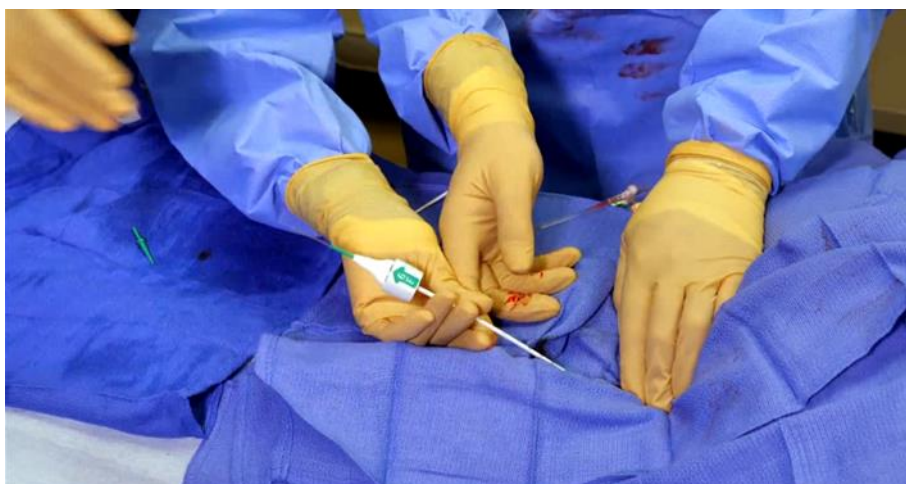
ANNEX 1: ANGIO-SEAL PROCEDURE PHOTOS



Insertion of the arteriotomy locator into the Angio-Seal insertion sheath.



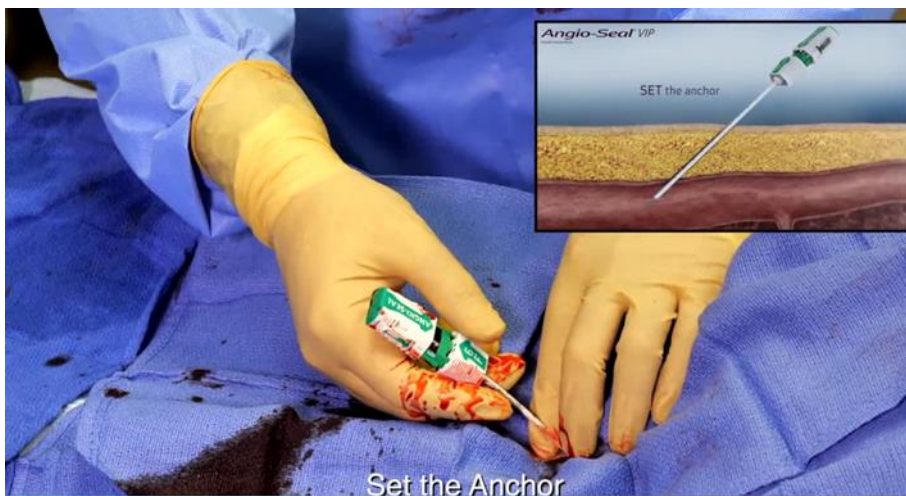
Angio-Seal guidewire is advanced through the procedure sheath



The device is placed following the wire, looking for the right position into the artery



The by-pass tubing is inserted, and when it's fully placed, the anchor will go out.



Set the Anchor

Then, the device is pulled back, so the anchor can be set up.



Seal the Puncture

The anchor is positioned against the vessel wall



When the tamper tube appears, grip the tamper and gently advance the knot and collagen



Continue to maintain tension on the suture while continuing to advance the knot and collagen, until complete seal is achieved.



Cut the suture below the clear stop.

All the images: <http://www.terumo.com/products/closure/angio-seal-vascular-closure-devices/angio-seal.html>

ANNEX 2: HOJA DE INFORMACIÓN AL PACIENTE

INTRODUCCIÓN

Las arterias que conducen la sangre a las piernas se pueden ir estrechando por múltiples causas, principalmente arteriosclerosis. Al no llegar suficiente sangre aparecen dolor al caminar (claudicación intermitente), dolor en reposo, o zonas de necrosis o heridas que no cicatrizan en los pies o los dedos. Si la enfermedad evoluciona y deja de llegar sangre por completo se termina produciendo una gangrena.

Por ello creemos que en su situación es conveniente realizar un tratamiento endovascular del sector femoro-poplíteo. Esta intervención normalmente consiste en “dilatar” la arteria desde dentro y en ocasiones colocar un dispositivo para que no vuelva a cerrarse (stent). El procedimiento se realiza de manera endovascular, esto es, se realiza un pequeño agujero en la piel mediante el cual se accede a la arteria. Nuestra experiencia y numerosos estudios hacen ver que esta técnica resulta más segura y más cómoda para los pacientes, ya que pueden retomar su vida con total normalidad en un periodo de tiempo muy corto. Sin embargo, en lo referente al cierre de la pequeña incisión de la arteria, aún no hay consenso, y no se ha demostrado que el uso de dispositivos vasculares reduzca las complicaciones en comparación con la compresión manual empleada tradicionalmente. La tasa de complicaciones es pequeña en ambos casos, pero creemos que estos dispositivos pueden aportar mayores beneficios. Es por ello, que nos gustaría certificar la seguridad de uno de estos dispositivos mediante este estudio.

OBJETIVOS DEL ESTUDIO

Nuestro objetivo es comparar el dispositivo Angio-Seal y la compresión manual para cerrar la arteria mediante la cual accedemos para realizar la intervención. En esta comparación, valoraremos especialmente la tasa de complicaciones entre ambas, para poder certificar cuál de las dos es más segura. Este estudio tiene una previsión de duración de 3 años.

DESCRIPCIÓN DEL ESTUDIO

Si usted acepta participar en este estudio, se le asignará aleatoriamente a uno de los dos grupos, uno en el que se cerrará la arteria con el dispositivo Angio-Seal u otro en el que la arteria se cerrará mediante compresión manual.

Después de la intervención se valorarán las posibles complicaciones, y se le realizara un control clínico y ecográfico antes del alta, una semana después y al mes de la intervención.

POSIBLES BENEFICIOS

Con este estudio, pretendemos demostrar la menor tasa de complicaciones de Angio-Seal respecto a la compresión manual. Los resultados esperados son, además de una mayor seguridad, un menor tiempo de inmovilización post-operatoria, un menor tiempo de hospitalización y una vuelta a la rutina más rápida.

POSIBLES RIESGOS Y MOLESTIAS

Pueden producirse complicaciones específicas como:

- A) Por pinchar la arteria:
- Pueden aparecer hematomas.
 - Es posible que se haga una lesión en la arteria o incluso que se rompa. Se producirá un hematoma importante o una hemorragia.
 - Pueden quedar “comunicadas” la arteria y la vena que está a su lado (fístula artero-venosa).
 - Puede hacerse una dilatación en la zona de la arteria pinchada (pseudoaneurisma).
 - Pueden formarse trombos y hacer que deje de llegar sangre al brazo o la pierna (isquemia).

En ocasiones estas complicaciones pueden ser importantes e incluso necesitar una operación posterior, muchas veces de urgencia.

B) Por el contraste:

- Pueden producirse reacciones alérgicas, desde leves (picores o enrojecimiento de la piel) hasta muy graves (shock anafiláctico).
- Puede deteriorar el funcionamiento de los riñones.

C) Por la dilatación /stent:

- Que se produzca una isquemia distal. ¿Por qué?
 - Para realizar este procedimiento es necesario atravesar la zona estrecha con distintos catéteres que rozan la superficie y pueden desprender pequeños fragmentos de ateroma o trombos pequeños que se muevan hacia las arterias del pie (embolización).
 - La zona que se dilata puede quedar “rugosa” y formarse coágulos que produzcan una obstrucción. Esto puede ocurrir en las horas o días siguientes a la operación.

TRATAMIENTOS ALTERNATIVOS

Como alternativa para el tratamiento de estas lesiones se puede realizar una revascularización quirúrgica (endarterectomía (limpiar la arteria por dentro con una operación en la pierna) o “saltar” el segmento obstruido (bypass femoro-poplíteo)

También es posible NO actuar sobre la arteria enferma y sólo tratar de mejorar los síntomas con medicamentos, ejercicio, y un régimen de vida más sano.

PARTICIPACIÓN VOLUNTARIA

Su participación en el estudio es totalmente libre y voluntaria. Usted puede no aceptar participar en el mismo. Además, debe saber que usted puede abandonar el estudio en cualquier momento sin necesidad de dar ninguna explicación. Ninguna de estas circunstancias va a influir sobre los cuidados que usted reciba en el futuro.

CONFIDENCIALIDAD

El acceso a sus datos clínicos se realizará guardando la más estricta confidencialidad, de forma que no se viole su intimidad ni la de los demás participantes en el estudio. Sus datos clínicos estarán a disposición de los monitores del estudio y se incluirán (junto con los de los otros pacientes que participen en el mismo) en las publicaciones derivadas del estudio, pero de forma anónima, de manera que su nombre e identidad se mantendrán siempre en secreto. Durante la realización del estudio se le garantiza el estricto cumplimiento de la “Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales”.

CONTACTO

Para cualquier duda, usted podrá ponerse en contacto con una de las investigadoras de este proyecto, Lydia Garcia-Mendoza a través de este correo electrónico: lydia.gmendoza@gmail.com

ANNEX 3: CONSENTIMIENTO INFORMADO

Consiento mi participación en el estudio “Angio-Seal versus Manual compression concerning puncture site related complications in peripheral arterial disease”

Y por ello, declaro bajo mi responsabilidad que yo:

- He leído la hoja de información que se me ha entregado.
- He podido preguntar acerca del estudio todas las dudas que he tenido.
- Comprendo que mi participación es voluntaria y que puedo retirarme del estudio cuando quiera sin tener que dar explicaciones y sin que ello repercuta en mis cuidados médicos.
- Consiento en que el monitor del estudio tenga acceso a mis datos médicos que serán absolutamente confidenciales y que podrán ser incluidos, de forma anónima, en las publicaciones que deriven del estudio.
- Presto libremente mi conformidad para participar en el estudio.

En _____ (lugar y fecha).

Fdo.: El/la Médico Fdo.: El Paciente Fdo.: El representante legal, familiar o allegado

ANNEX 4: HOJA DE PARTICIPACIÓN

INFORMACIÓN GENERAL

NOMBRE	
APELLIDOS	
EDAD	
SEXO	
RAZA	
FECHA INTERVENCIÓN	

FACTORES DE RIESGO

TABACO	
HTA	
DISLIPEMIA	
ARTERIOPATIA PERIFERICA	
INSUFICIENCIA RENAL	
DIABETES MELLITUS	
OTROS	

- **ENFERMEDADES RELEVANTES:**
- **USO ANTICOAGULANTE/ PAUTA:** *NOMBRE Y DOSIS*
- **USO ANTIAGREGANTE/PAUTA:** *NOMBRE Y DOSIS*

DATOS PREOPERATORIOS

CLINICA:

Grado de isquemia según clasificación Fontaine

Grado I	
Grado IIa	
Grado IIb	
Grado III	
Grado IV	

EXPLORACIÓN FÍSICA:

ITB: _____

ECO-DOPPLER (femoro-poplíteo): _____

ANGIO-TC:

Longitud de la lesión (mm): _____

Presencia de calcificaciones: _____

Nº Arterias afectadas: _____

ANALITICA:

Hemoglobina (mg/dl): _____

Hematocrito (%): _____

Creatinina (mg/dl): _____

DATOS INTRAOPERATORIOS

USO ANGIO SEAL USO COMPRESION MANUAL:

Tiempo quirúrgico (min): _____

Cantidad de contraste (cc): _____

Tiempo de fluoroscopia (seg): _____

Tiempo de hemostasia(min): _____

Necesidad de recurrir a otro método de cierre: SI/NO

Complicaciones durante intervención:

DATOS POSTOPERATORIOS

Tiempo de estancia en unidad de reanimación (horas): _____

Tiempo de ingreso en planta de cirugía vascular (horas): _____

SEGUIMIENTO

ANGIO-SEAL:

COMPRESION MANUAL:

	ALTA	1ª SEMANA	1º MES
Aspecto herida			
Tª extremidad			
Pulsos			
Eco-Doppler			
Complicaciones			