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Cardiovascular Imaging PICTORIAL ESSAY

Ultrasound guided thrombin injection for treating iatrogenic femoral artery pseudoaneurysms: a review focusing upon sonographic diagnosis and treatment

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ABSTRACT

An exponential increase in the number of diagnostic and therapeutic endovascular interventions, as well as in the use of antiplatelet and anticoagulation therapy, has raised the incidence of iatrogenic femoral artery pseudoaneurysms. Historically accepted methods (spontaneous closure in non-anticoagulated patients, ultrasound-guided compression repair, surgical repair) have been introduced in the past as first line treatments, while more novel alternatives have also been suggested to replace them. The purpose of this review is to demonstrate the significance of femoral artery pseudoaneurysm formation, to evaluate the appropriate diagnosis with ultrasound (US) and to present US-guided thrombin injection (UGTI) as the most advocated method of treatment over surgical repair and US-guided compression repair. Complications of UGTI are also discussed, an algorithm for using this procedure is suggested and alternative treatments are reviewed.

KEY WORDS: femoral artery pseudoaneurysm; thrombin; ultrasound guided treatment

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1. Introduction

The increasing rate of percutaneous femoral artery catheterisation for diagnostic and interventional procedures and the wider use of anti-platelet and anticoagulation therapy have raised the incidence rate of femoral artery pseudoaneurysms up to 16% [1]. The more common use of complex procedures demanding larger sheaths (hence larger site of puncture) has also played its role in this pseudoaneurysm rate increase. Femoral artery pseudoaneurysms are a focal disruption of the arterial wall, which results in the presence of blood flow outside of the vessel's lumen into an abnormal chamber which is contained by adjacent tissue [2]. Pseudoaneurysms are a complication after angiography, observed in up to 0.2% of patients after diagnostic angiograms and up to 8% after interventional procedures. These rates may further increase with cardiac procedures due to several different factors (longer procedure duration, larger sheath sizes -at least 7 French (Fr)- and anti-platelet treatment). The need for treating femoral artery pseudoaneurysms is important in order to prevent the, potentially life threatening, complication of a massive bleeding of the pseudoaneurysm, which may be occult if retroperitoneal [3].

Historically, the golden standard for treating iatrogenic femoral artery pseudoaneurysms in the past has been open surgical repair [4]. However, this is a complex procedure with long recovery time. Fellmeth et al in 1991 were the first to describe an alternative therapy besides surgical repair, the ultrasound (US) guided compression repair (UGCR), by accurately applying blunt pressure with the US transducer on the pseudoaneurysm, until blood flow in the extraluminal track is eliminated [5]. This method was met with great acceptance, but often proved to be ineffective in up to 24% of cases [4] and, due to considerable limitations and specific patient exclusion criteria [1, 4], an alternative procedure was described by Kang et al: this used US as a guiding modality for the percutaneous injection of thrombin directly into the pseudoaneurysm sac [6], a technique which has proved to be fast and effective.

In this pictorial essay we demonstrate the significance of a femoral artery pseudoaneurysm formation and the appropriate diagnosis with US, as well as US-guided thrombin injection (UGTI) as the most advocated method of treatment, which is preferred over surgical repair and UGCR.

2. Pseudoaneurysm formation pathophysiology and clinical manifestations

A femoral artery pseudoaneurysm is formed when leakage of blood occurs into the soft tissue anterior to the femoral artery after arterial catheterisation, with subsequent fibrous encapsulation and failure of the defect wall tissue to heal. A patent channel is thus maintained between the vessel and the fluid space, with blood flowing into and out of the pseudoaneurysm during the cardiac cycle [7]. The resulting pseudoaneurysm consists of a perfused sac (the false lumen) connected to the femoral artery by a "neck". Clinical signs which suggest the presence of a pseudoaneurysm and should prompt further investigation include a focal mass near the site of arterial puncture, palpable pulsatility of the mass (a non-specific clinical sign), anaemia, leg weakness and audible bruit over the mass [2]. If the pseudoaneurysm ruptures, life-threatening haemorrhage may happen. If the pseudoaneurysm is large, complications due to pressure on adjacent structures, such as neuropathy, leg oedema, deep vein thrombosis, claudication and ischaemia may also be observed [8]. More serious secondary manifestations include infection, predisposing to rupture and distal septic emboli, while compartment syndrome, necrosis of overlying skin and subcutaneous tissues and significant blood loss have also been reported [2, 3].

3. Pseudoaneurysm diagnosis with US

Pseudoaneurysms are easily identified by US. A variety of transducers can be used, with frequencies ranging from 3.5 to 9.0 MHz. Doppler US has proved to be very useful for imaging pseudoaneurysms, with reported sensitivity rates ranging between 94% and 97% [1, 3, 9]. As in every sonographic examination, B-mode US is the first step: an aneurysm appears as a complex collection with anechoic portions near the puncture site of the femoral artery. The limitation of this B-mode US appearance is that it does not distinguish the sac from a simple haematoma, which does not include a communicative neck with neither the femoral artery nor the common femoral artery. In colour Doppler US, the sac can be seen to contain swirling blood flow, which appears as a two-colour signal: red and blue, due to the bidirectional movement of blood entering and leaving the sac. This sign is commonly been referred to as the "Korean flag yin-yang" sign. The same bidirectional blood flow is also noted in the pseudoaneurysm neck, which connects the artery with

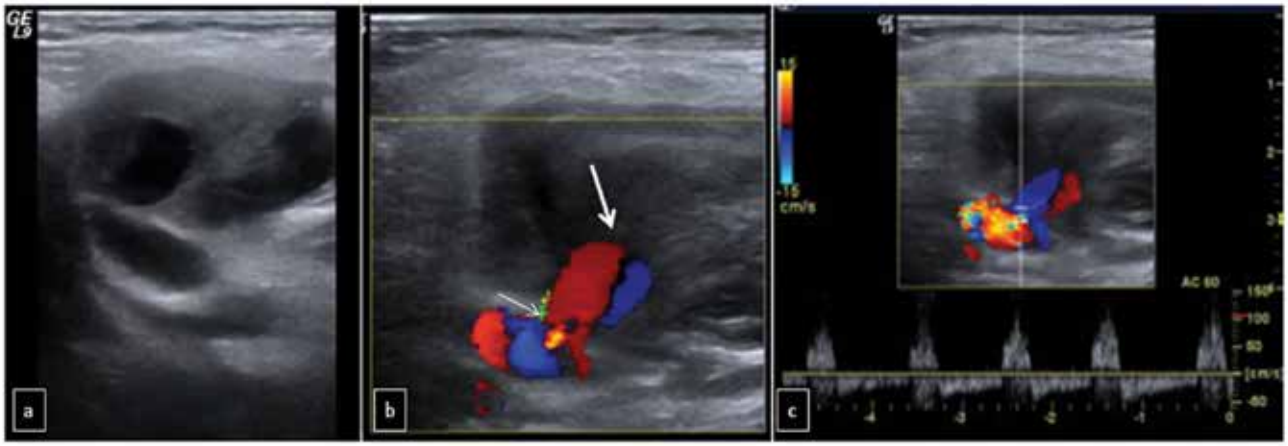

Fig. 1. *A femoral artery pseudoaneurysm is detected on B-mode US* ***(a)****. The neck (thin arrow) is noted on colour Doppler US* ***(b)****, while the yin-yang sign is seen in the sac (thick arrow). On Spectral Doppler* ***(c)****, the typical to-and-fro blood flow is evident.*

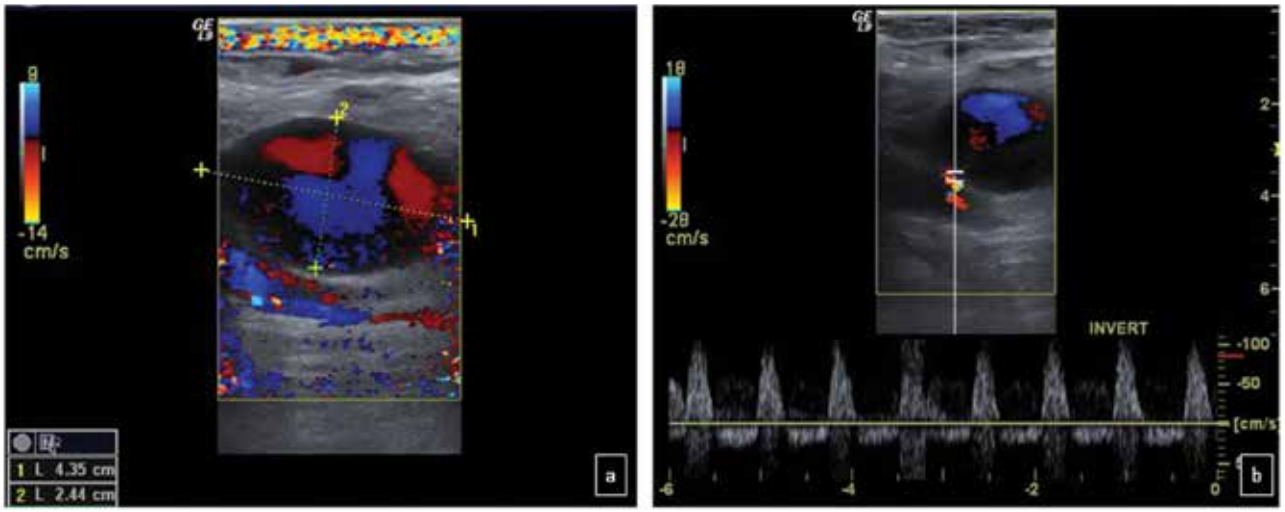

Fig. 2. *Colour Doppler US shows the yin-yang sign* ***(a)****. Spectral Doppler* ***(b)*** *shows bidirectional to-and-fro blood flow in the neck.*

the sac. This distinctive "to-and-fro" waveform at the neck of the pseudoaneurysm appears on spectral Doppler as a waveform over and under the baseline, consisting of high- frequency flow toward the transducer throughout systole and intermediate frequency throughout diastole [7]. During systole, the pressure is higher in the artery than in the pseudoaneurysm sac, leading to influx of blood into it, while in diastole the pressure of flow in the artery drops down to zero, and there may be even reversal of flow due to high resistance in the peripheral circulation. Blood then flows back through the neck as a result of the pressure gradient between the overdistended, high pressure pseudoaneurysm and the low pressure artery [10, 11]. These signs can confirm the real time sonographic diagnosis of a pseudoaneurysm and obviate angiography. The presence of "to-and-fro" waveform is the cornerstone of differential diagnosis [12] (**Fig. 1**). Simple pseudoaneurysms have only one sac (unilobar). Complex lesions may appear with two or more separate sacs (multilobar). Conclusively, the classic triad for the detection of a pseudoaneurysm includes the detection of a hypoechoic sac in the vicinity of the parent vessel, the swirling yin-yang Doppler sign and the to-and-fro type waveform (**Fig. 2**). Once all these signs are detected, the artery of origin must be identified and the geometrical characteristics of the pseudoaneurysm must be documented [13].

4. Pseudoaneurysm treatment

Several treatment schemes can be followed when a pseu-

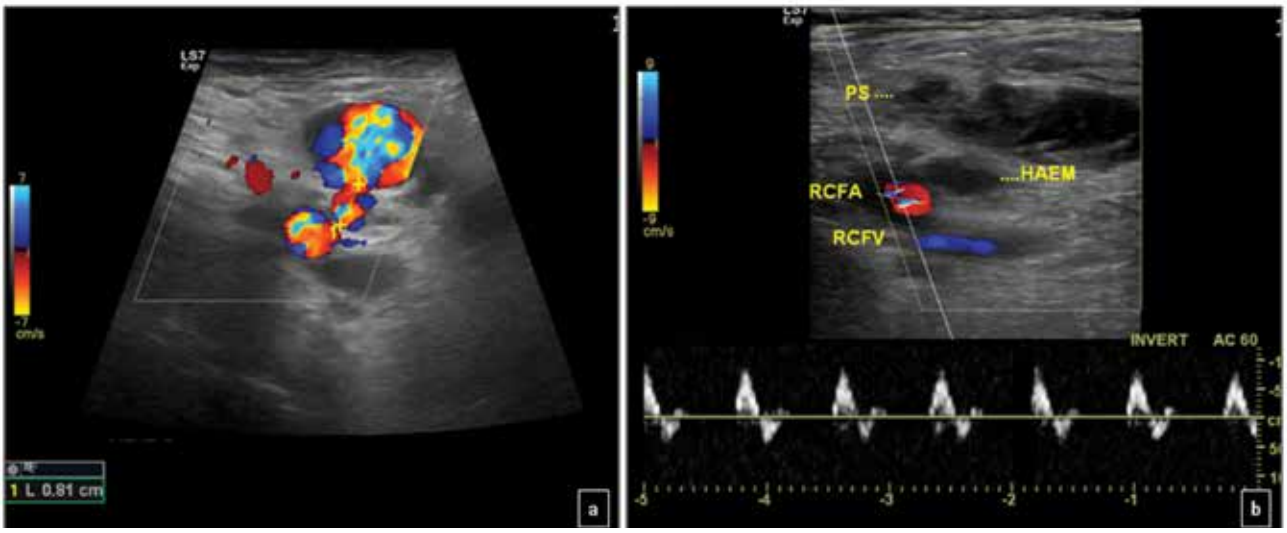

Fig 3. a. *A pseudoaneurysm is noted on colour Doppler US. The neck (between calipers) and sac are evident. The patient undergoes UGCR. On the next day* ***(b)****, the pseudoaneurysm sac (PS) is thrombosed. It originates from the right common femoral artery (RCFA), which is patent, as is the accompanying vein (RCFV). A small haematoma (HAEM) is also present.*

doaneurysm is diagnosed. If the pseudoaneurysm is small in a non-anticoagulated patient, it can be followed up for spontaneous closure [14]. This technique can have a success rate of up to 87% when the aneurysm's diameter is smaller than 3-3.5 cm [15, 16] and patient mobility is decreased [8]. Since original reports by Kotval et al [17] and Toursarkissian et al [15], a great number of studies have suggested that a portion of postcatheterisation pseudoaneurysms resolve spontaneously without any intervention. The disadvantages of this method include the inability to predict how often spontaneous thrombosis is successful, as well as the cost of following up the patient with US [2].

The second treatment option is UGCR, which was the treatment of choice until recently. The transducer is oriented to demonstrate the pseudoaneurysm neck and lumen. Straight downward compression is applied for 10–20 minute periods, in order to completely arrest flow into the sac. Then the pseudoaneurysm thrombosis is assessed periodically in order to verify the achievement of complete thrombosis, to reposition the transducer or to switch operators. If colour sonography shows signs of persistent extraluminar flow, the compression is reapplied for another 10 minutes. The procedure is repeated any number of times if the false lumen and neck are still patent. After the compression, patients are instructed to lie supine in bed with the affected leg in a stretched position for 4-6 hours, with frequent groin checks [3, 4] **(Fig. 3)**. Limitations of this method are that is a time consuming procedure, two physicians are often required for compressing, the patient feels discomfort and pain, while often the operator cannot maintain adequate pressure. In addition, not all pseudoaneurysms are amenable to UGCR (the technique is more appropriate for lesions smaller than 1 cm), while a high recurrence rate (25-35%) has been reported in patients receiving anticoagulant therapy [3, 5, 18, 19]. Higher failure rates have been noted when the sac diameter is larger than 4 cm, but no correlation with neck diameter and length has been reported [18]. Contraindications to UGCR include suspected infection, coexisting very large haematomas with impending compartment syndrome or overlying skin ischaemia, injuries above or near the inguinal ligament, where delayed rupture could be catastrophic, and severe groin tenderness precluding adequate compression [5]. The reported success rate has been shown to be as high as 98%.

The third available treatment is to surgically repair the pseudoaneurysm [5]. This therapeutic scheme has a high complication rate, up to 21% [20]. Complications include bleeding, infection, lymphocoele, radiculopathy and, less commonly, perioperative myocardial infarction or even death.

UGTI is the fourth available treatment and a useful alternative to the above mentioned therapies [21-24]. Thrombin, when injected into anticoagulated blood, re-

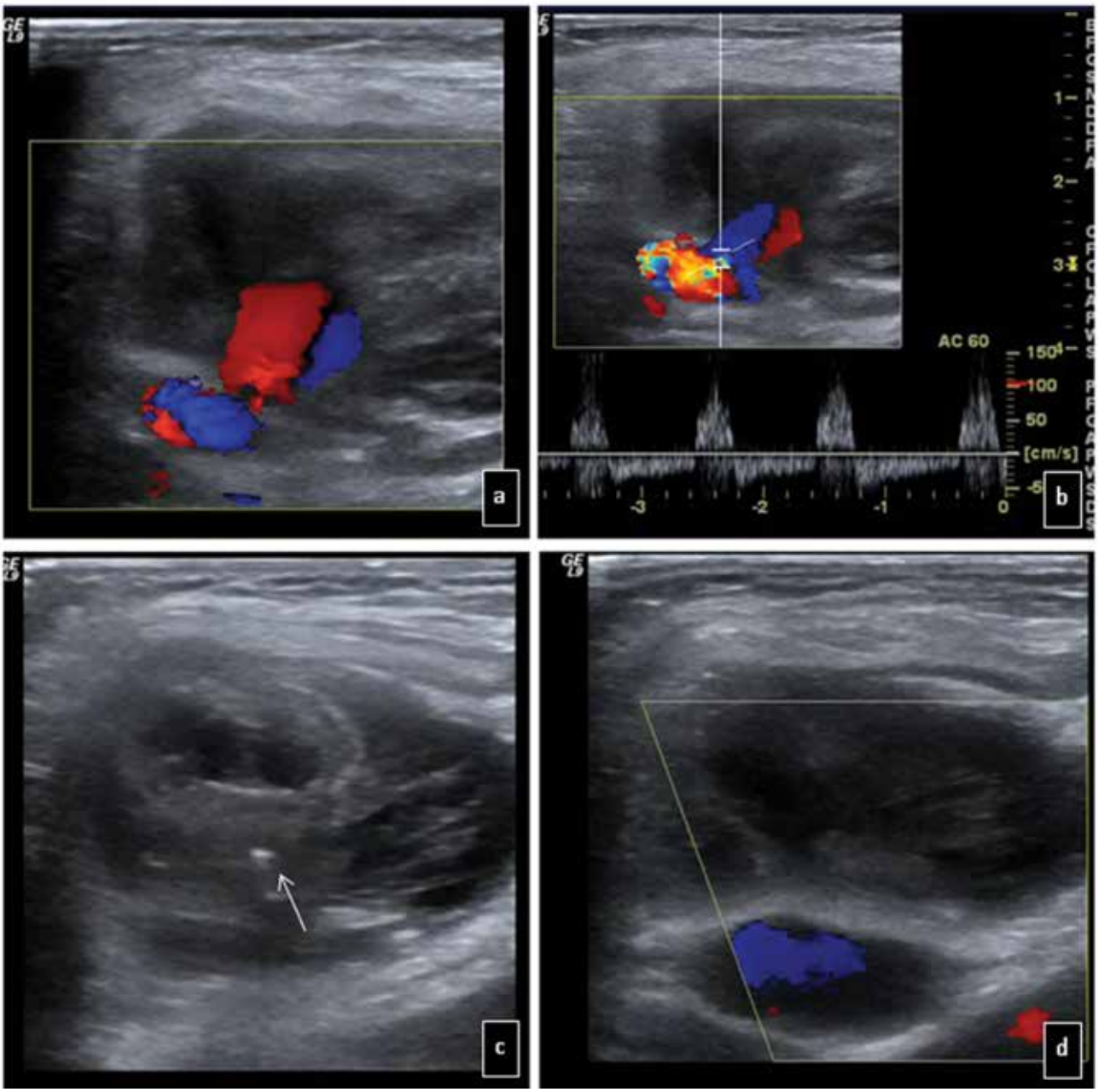

Fig. 4. *A femoral artery pseudoaneurysm is seen on colour Doppler US, with a bidirectional flow yin-yang sign* ***(a)****. On Spectral Doppler, to-and-fro blood flow is evident in its neck* ***(b)****. Thrombin is injected via needle (the needle's tip is shown by arrow in* ***c)****. Post injection of thrombin the pseudoaneurysm is thrombosed, with no remaining blood flow on colour Doppler US* ***(d)****.*

sults in thrombosis, as the final trail of blood coagulation [6]. This is a procedure which is not affected by anticoagulation drugs, contrary to manual compression [13, 25]. It is faster than compression [4], with reported success rates in medical literature as high as 94-100% [8]. It has been suggested as the first therapy to be performed in patients with post-catheterisation femoral artery pseudoaneurysms, as well as for patients on double or triple antiplatelet therapy due to the presence of coronary stent [1, 26].

Endovascular approaches can also be considered in the therapy of pseudoaneurysms. Catheter guided embolisation with coils or detachable balloons or even stent-grafts are considered as alternatives, providing lower morbility and mortality rates, compared to surgical approach [10].

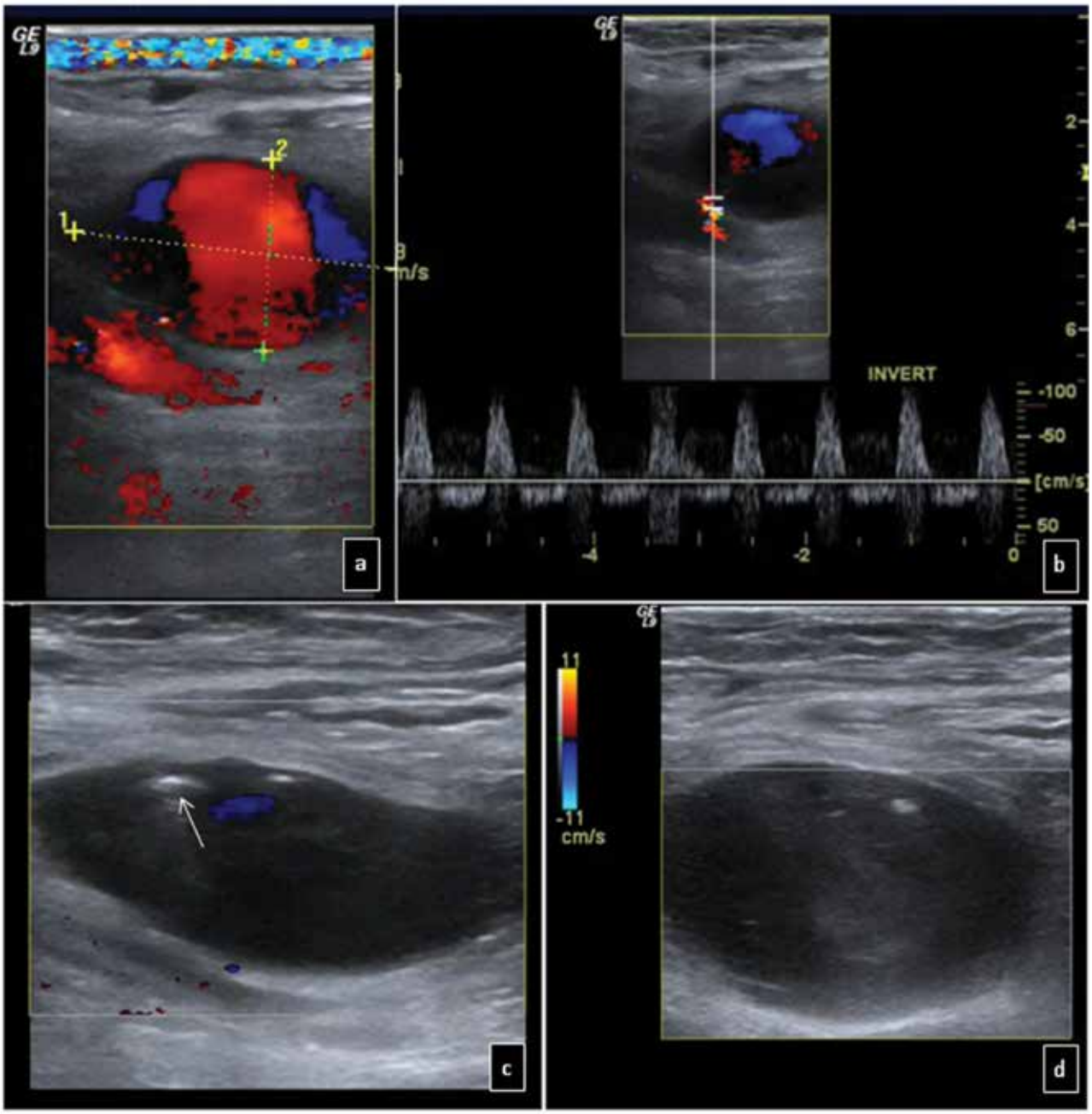

Fig 5. *On Colour Doppler US* ***(a)*** *a large femoral artery pseudoaneurysm measuring 3.9 x 2.3 cm is seen. On Spectral Doppler* ***(b)*** *bi-directional blood flow in the neck is noted. Thrombin is injected under US guidance (needle tip is shown with an arrow in* ***c)****. Subsequently the pseudoaneurysm thrombosis sac is completely thrombosed with no remaining blood flow on colour Doppler US* ***(d)****.*

5. Thrombin injection under US guidance: description of the technique

Initially the anatomic area of the pseudoaneurysm and surrounding region are specified [6]. Using a 3.5 to 9.0 MHz linear array or curved array transducer, the puncture site is scanned. It is important to differentiate between an arteriovenous fistula, a unilobar or a multilobar pseudoaneurysm as well as to delineate the route of the artery and the vein. After discussing with the patient regarding alternatives, possible complications and side effects of thrombin, a written informed consent is obtained. A sterile sleeve is applied to the transducer. After the puncture site has been selected, the overlying skin is

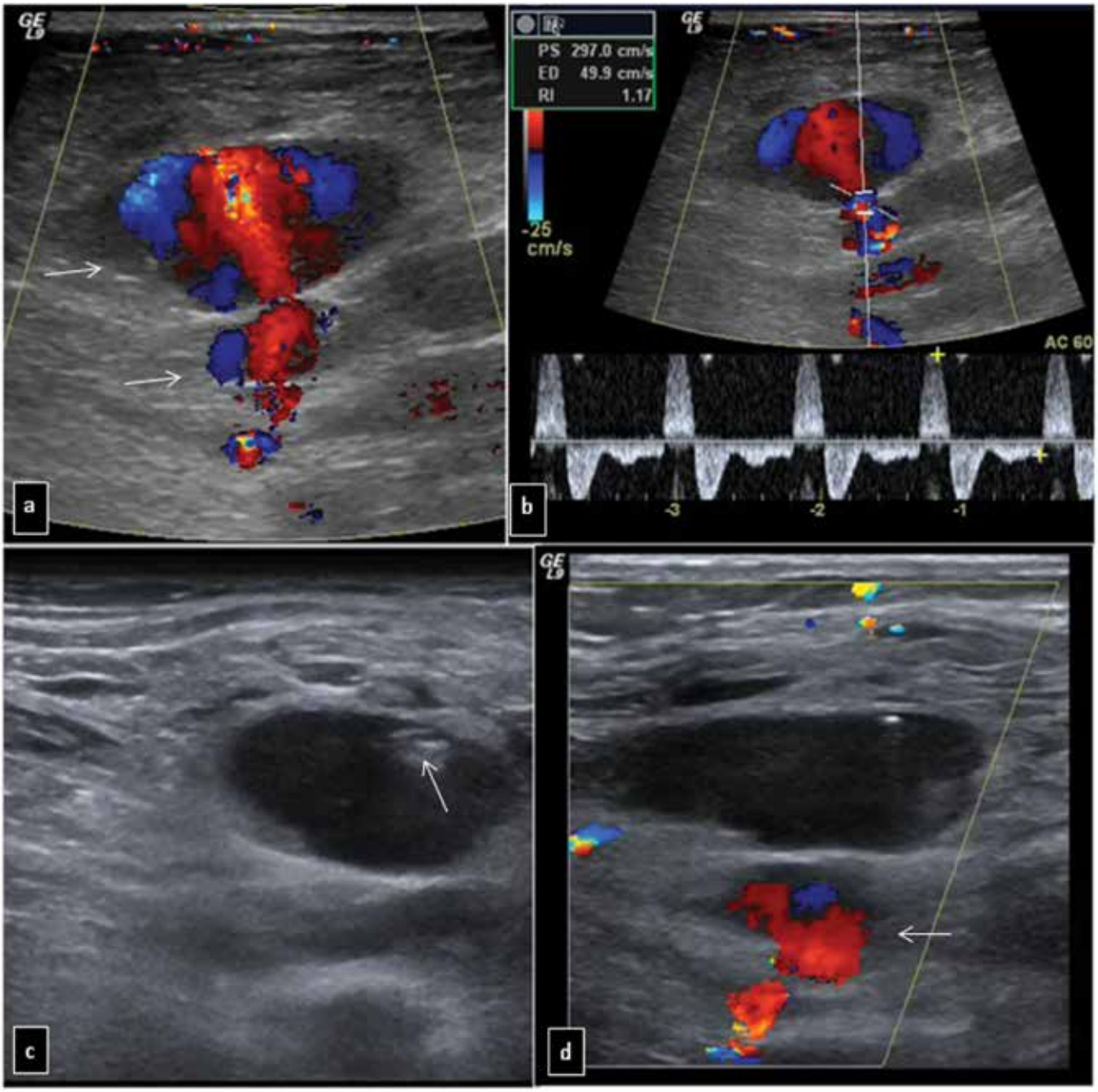

Fig. 6. *A complex pseudoaneurysm with two sacs (arrows in* ***a****) is seen on Colour Doppler US. Spectral Doppler* ***(b)*** *shows bidirectional flow in the neck between the two chambers. Thrombin is injected in the most superficial sac (needle tip is shown by arrow in* ***c)****. The largest pseudoaneurysm is thrombosed* ***(d)****, but the smaller sac is not thrombosed, with perfusion still present (arrow in* ***d****).*

prepared with iodine for sterilisation and covered with a sterile drape. Local anaesthesia with xylocaine administration subcutaneously follows.

Several thrombin preparations are commercially available. In our department we apply human thrombin (500 IU/mL), a component of a fibrin sealant kit. In practice, this consists of freeze-dried human thrombin reconstituted with calcium chloride solution and subsequently drawn into a 2-mL syringe. A 21 gauge needle is then inserted into the pseudoaneurysm sac under US surveillance. It is very important to minimise the possibility of thrombin escaping from the sac to the femoral artery. Therefore, it is preferable for the needle to be placed at a point where blood flow is far away from the pseudoaneurysm neck. Understandably, it is of utmost importance to check the needle tip at all times.

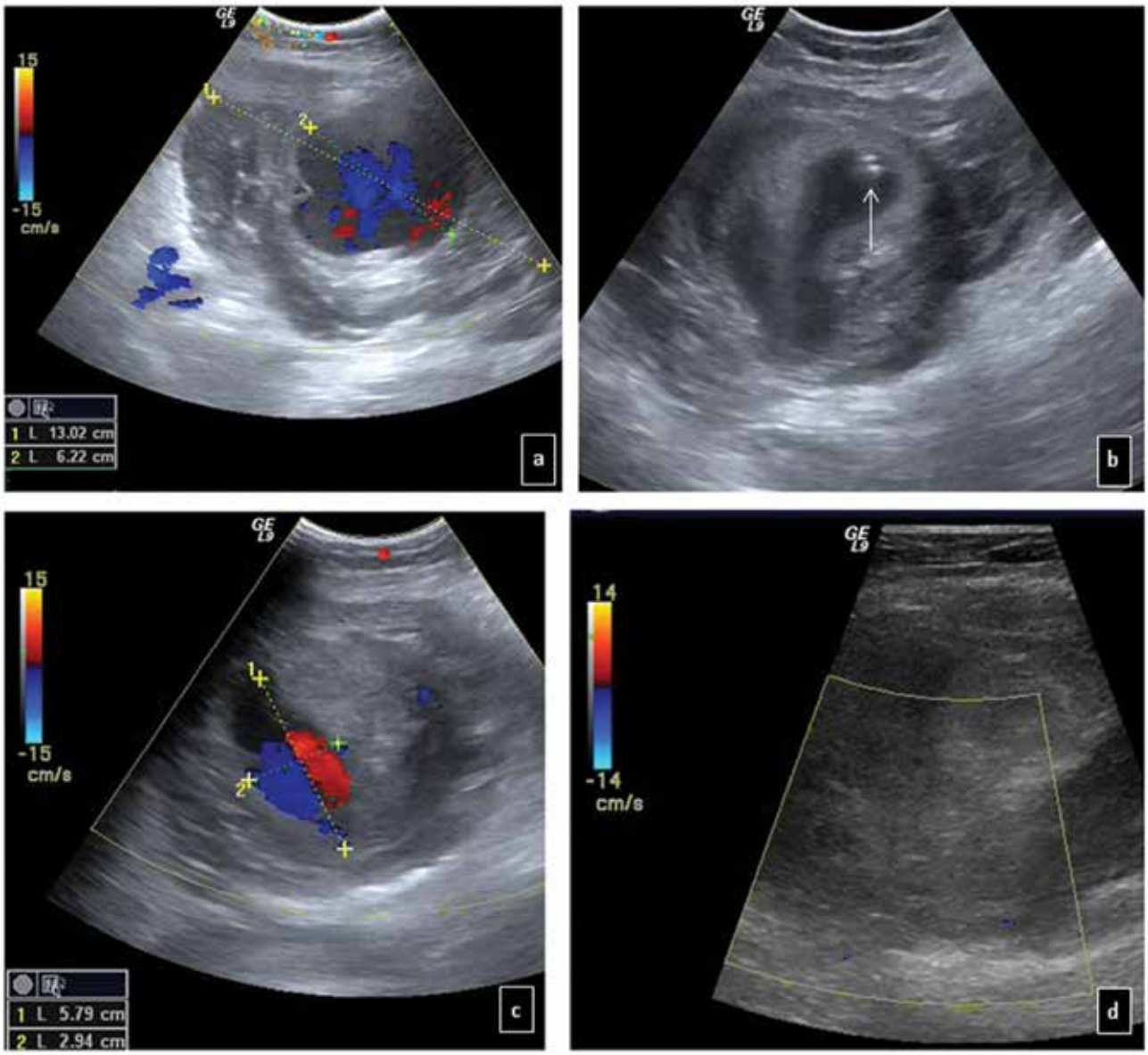

Fig. 7. *A huge 13 cm pseudoaneurysm is evident on colour Doppler US* ***(a)****. Thrombin is injected (arrow in* ***b*** *shows the needle tip), but part of the sac is still patent* ***(c)****. A second thrombin injection follows (not shown). Subsequently, the pseudoaneurysm is completely thrombosed and no perfusion is noted on colour Doppler US* ***(d)****.*

The best visualisation of the tip is achieved using grey-scale imaging (**Fig. 4**). Once the needle is placed into the optimum position, colour Doppler US can monitor the effect of the injected thrombin on flow. A colour "jet" emanating from the needle tip is seen while the first 0.1-0.3 mL of thrombin are injected over 3-5 seconds. If complete thrombosis is not achieved, a second injection of 0.1-0.3 mL is applied. The needle may need to be repositioned until complete thrombosis of the pseudoaneurysm sac is achieved (**Fig. 5**).

Typically patients receive 500-1000 IU/mL of thrombin for treating a simple femoral pseudoaneurysm. In practice, about half the produced dose is usually injected for treating pseudoaneurysms of 1-2 cm in diameter. If on a 5 min follow up with US the sac is still patent, the same amount can be administered for a second dose. The whole dose is injected for larger lesions of 2-3 cm, while a second full dose is usually needed for treating aneurysms larger than 3 cm. If blood flow is still seen in the pseudoaneurysm neck, the injection can be continued at a slower rate until the neck is totally obstructed, always keeping in mind not to administer thrombin inside

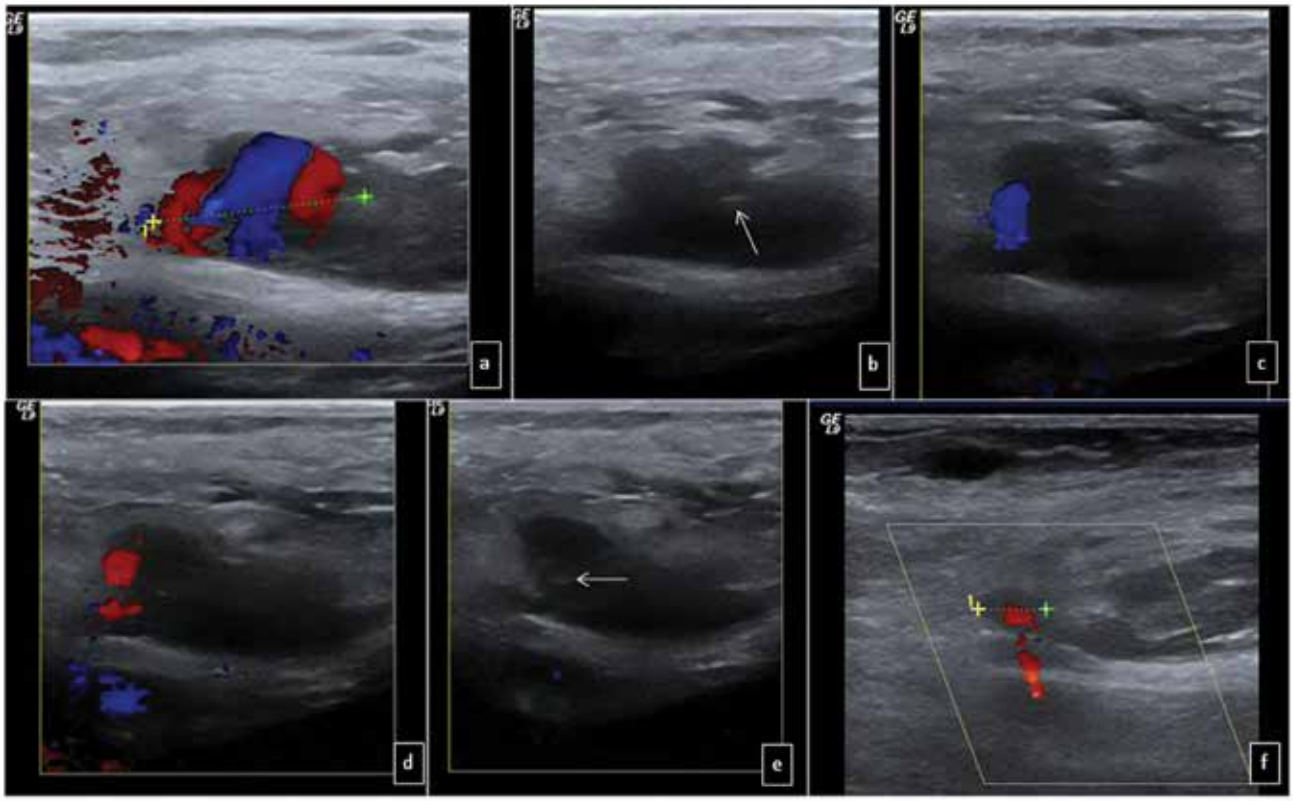

Fig. 8. *Colour Doppler US* ***(a)*** *shows a large pseudoaneurysm. The patient is treated with trombin injection (arrow in* ***b*** *shows the needle tip). The sac is still partially perfusing* ***(c)*** *and the injection is repeated. However, partial patency is again seen 24 hours later* ***(d)****. A second injection session follows (needle tip noted with arrow in* ***e****). Again, part of the aneurysm is still perfusing (between calipers in* ***f****). The patient is referred for surgical repair.*

the femoral artery lumen. A dose of 1000 IU of thrombin for pseudoaneurysm thrombosis may be an indirect sign of a large arteriotomy site defect, which requires closer clinical follow-up. This may be due to the fact that damaged endothelium at sites of large arteriotomy or laceration produces thrombomodulin, which complexes with thrombin to activate protein C. Activated protein C activates an anticoagulation pathway and reduces the relative size and number of fibrin fibers within maturing thrombus [27, 28].

There are controversial studies referring to the appropriate dose and technique for complex pseudoaneurysms. In our department, in pseudoaneurysms with more than one sacs, the puncture site is performed at the most proximal one (**Fig. 6**). Thrombin is then administered at a slow rate, at doses of 100 IU/mL, until there is no colour signal in the aneurysm sac and neck. According to Sheiman et al, complex femoral pseudoaneurysms require more than 1000 IU/mL of thrombin, due to the fact that blood flow in the sac is not occluded totally with only one injection [9]. On the opposite side, Mohler et al registered that complex pseudoaneurysms can be cured with 1000 IU/ml thrombin, highlighting that the preferred approach is initial injection of the sac closest to the skin followed by these in deeper layers [14]. When the pseudoaneurysm neck is absent or short and wide, thrombin injection can theoretically be safer with simultaneous balloon occlusion across the pseudoaneurysm entry site [29, 30].

After the injection, the patient is instructed to lie supine in bed keeping a straight leg position for six hours. A follow up scanning with US is performed 24 hours later with the patient still in bed. If needed, a second session of thrombin injection can follow (**Fig. 7**). If after this second session persistent flow is observed in the neck and the pseudoaneurysm is not completely thrombosed, surgical treatment is advised (**Fig. 8**). This management protocol is described in detail in **Fig. 9**. It is partially based on the flowchart suggested by Gürel et al [8]. In our experience, it has proved to be successful for the treatment of most of pseudoaneurysm cases. It has been suggested

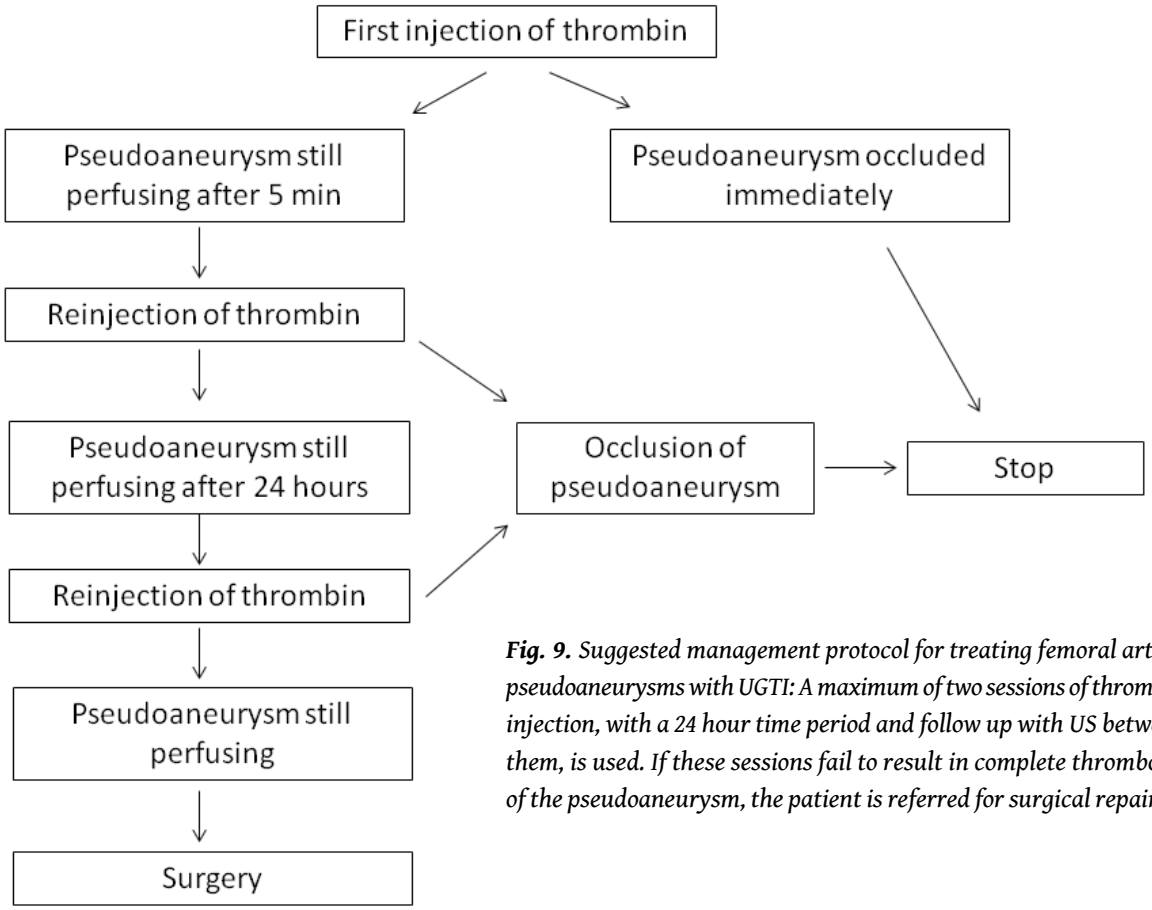

Fig. 9. *Suggested management protocol for treating femoral artery pseudoaneurysms with UGTI: A maximum of two sessions of thrombin injection, with a 24 hour time period and follow up with US between them, is used. If these sessions fail to result in complete thrombosis of the pseudoaneurysm, the patient is referred for surgical repair.*

that pseudoaneurysms larger than 2 cm and thrombocytopaenia are significant independent predictors of post-procedural pseudoaneurysm recurrence [31].

A relative contraindication for thrombin injection is when the width of the pseudoaneurysm's neck is over 10 mm, due to a slightly higher risk of distal embolisation [4]. A pseudoaneurysm with wide neck may be the result of placement of large bore catheters and sheaths, as in aortic stent graft placement. These pseudoaneurysms can make thrombosis with thrombin injection very difficult [1]. Absolute contraindications for thrombin injection are pseudoaneurysms with small diameter and length of neck, indefinable neck, direct adjacency to vessels as well as coexistence of arteriovenous fistula (the latter due to the potential risk of venous thrombosis [12]). UGTI is an effective therapy even in the morbidly obese patients [32].

6. Complications of thrombin injection

Complications are uncommon (seen in 1-3.6% of cases) but serious [3, 4, 12, 33-35]. These include native arterial thrombosis from thrombin leaking out of the pseudoaneurysm into the feeding artery, enlargement of pseudoaneurysm sac and potential rupture, skin necrosis, distal embolisation and venous thrombosis. Thrombosis of the artery lumen itself is rare. Thromboembolic complication is possible if thrombin is accidentally injected into the artery or too close to the pseudoaneurysm neck, instead of inside the sac. This is a situation that can be avoided if the needle tip is visualised at all times inside the pseudoaneurysm sac, at a safe distance from its neck. If the needle tip is not well visualised, the injection should be interrupted or aborted. The reason for thrombin diffusing out of the pseudoaneurysm neck is a very much diluted concentration of the solution [36].

It is possible to have an allergic reaction if bovine thrombin is administered, with some case reports published regarding a reaction of this kind. After bovine thrombin injection, it is possible for antibodies to be produced, that may cross react with human thrombin and

factor V, leading to abnormalities in haemostasis or anaphylactic reactions mediated by IgE antibodies. A predisposing factor is repeated exposures to topical thrombin, such as during dialysis or previous operations, while it is prudent to inquire the patient's history before administering bovine thrombin. If there is repeated exposure to bovine thrombin, a skin pick test is suggested. In the literature cases with anaphylactic reactions after UGTI with diffuse itching, shortness of breath, generalised oedema and hypotension have been reported [32, 37]. In patients found to be allergic, an alternative option could be autologous thrombin [38].

Another consideration gaining great acceptance scientifically is the danger of bovine spongiform encephalopathy transmission (BSE), commonly known as mad cow disease, due to injection of bovine thrombin. According to Tawes et al., autologous fibrin glue is an alternative, while it is proven that the nature of the product obviates the risk of disease transmission as well as the anaphylactic reactions [39].

Other complications include deep vein thrombosis, due to manual compression and groin pain, hypotension and bradycardia [40]. Finally, if an arteriovenous fistula is also present, pulmonary embolism is a possible risk [12].

7. Application of alternative materials

Besides the administration of thrombin, other materials have also been used for treating femoral artery pseudoaneurysms. These include saline injection on the surrounding tissues of the pseudoaneurysm, collagen injection, transcatheter injection of bucrylate glue, coils, stent grafts, detachable balloons and gelfoam [3, 41, 42].

Collagen consists of long paste fibers which remain within the pseudoaneurysm sac, thus reducing the complication rate of UGTI and making distal embolisation less likely [3, 36]. Normal saline injected into the tissue surrounding the neck of the pseudoaneurysm is followed by manual pressure of short duration. A 18-gauge needle mounted on a syringe filled with normal saline is positioned near the neck of the sac and, after confirming the extravascular and extra-aneurysmal needle position, saline is injected, obliterating the communicative pathway mediated by the surrounding tissue swelling. Repositioning of the needle and reinjecting could be necessary if insufficient compression of the pseudoaneurysm neck is performed. This technique also results in high success rates, as high as 92% [43-45].

If thrombin injection fails in patients with recanalised pseudoaneurysm and others with signs of haemorrhagic shock, tissue adhesive glues could be considered as a treatment option. A special delivery device for the simultaneous injection of the solutions is placed in the pseudoaneurysm chamber. These tissue glues quickly form a clot which is furthermore stabilised by the present of aprotinin in the solution, a protease inhibitor with antifibrinolytic activity. They have more rapid results than human or bovine thrombin and the clot is less susceptible to endogenous fibrinolysis, but they are more expensive. They have the same potential complications [46].

8. Conclusion

Percutaneous injection of thrombin under US guidance is an effective method for treating femoral artery pseudoaneurysms, well tolerated by patients with high success rate. The procedure is fast and complications are rare. It should be considered a first-line approach for treating postcatheterisation femoral artery pseudoaneurysms before surgical repair.

Conflict of interest

The authors declared no conflicts of interest.

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