Ultrasound-Guided Thrombin Injection for the Treatment of Iatrogenic Pseudoaneurysm of the Femoral Artery

Allan I. Bloom MD[1], Talia Sasson MD[1], Anthony Verstandig MD[1], Yehuda G. Wolf MD[2], Haim Anner MD[2], Yakov Berlatzky MD[2], Inna Akopnick MD[2], Chaim Lotan MD[3], Richard Lederman MD[1] and Pinchas D. Lebensart MD[1]

Departments of [1]Radiology, [2]Vascular Surgery and [3]Cardiology, Hadassah University Hospital, Jerusalem, Israel

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Abstract

Background: Pseudoaneurysm occurring after catheterization of the femoral artery is associated with significant morbidity. Percutaneous ultrasound-guided thrombin injection has recently emerged as a potential first-line therapy.

Objectives: To evaluate the efficacy of this treatment in eight patients with iatrogenic femoral artery pseudoaneurysm.

Methods: After attempted treatment with external compression had failed, eight patients with iatrogenic femoral artery pseudoaneurysm were treated with thrombin injection. Treatment performed between 2 and 9 days following arterial puncture. The study group comprised seven males and one female ranging in age from 23 to 89 years (median 70). Seven had undergone cardiac catheterization with or without intervention, and five were receiving antiplatelet and/or anticoagulant drugs. Arterial pseudoaneurysm resulted from femoral vein catheterization in one patient. Using a sterile technique and real-time Doppler ultrasound guidance, a dilute solution of bovine thrombin (average dose 250 units, range 100–600), was slowly injected directly into the pseudoaneurysm until cessation of flow was seen. Patients were allowed to walk within 2 hours of the procedure and were followed up clinically and by color Doppler ultrasound during the admission.

Results: Cardiac catheterization had been inadvertently performed via the superficial or profunda femoris arteries in four of the eight patients. Thrombin injection was initially successful in all eight patients without complication. Thrombosis occurred immediately in every case. Early recanalization of pseudoaneurysm occurred in one patient despite repeat thrombin injection and attempted ultrasound-guided compression. He eventually required surgical repair. The final success rate was 87.5% (7/8).

Conclusion: Faulty puncture technique is an important risk factor for the development of post-catheterization femoral artery pseudoaneurysm. Ultrasound-guided thrombin injection is a safe, rapid, well-tolerated, inexpensive and successful therapy. If initial external compression with a sandbag fails to result in thrombosis of the pseudoaneurysm then thrombin injection should be considered as first-line therapy. If unsuccessful, it does not preclude the use of alternative treatment modalities. Further study is necessary to assess the long-term effects of thrombin injection.

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The incidence of iatrogenic pseudoaneurysm following catheterization of the femoral artery is reported to be 7–8% in patients undergoing diagnostic and therapeutic angiography [1]. Antegrade puncture, anticoagulation, large introducer sheaths, faulty puncture technique and inadequate compression are some of the known risk factors for the development of pseudoaneurysm. Accepted treatment includes non-directed compression with sandbags or external compression devices, ultrasound-guided compression, catheter embolization and surgical repair. Surgery is indicated when there is evidence of rapid expansion of the pseudoaneurysm (threatened rupture), limb ischemia or distal emboli, extensive soft tissue damage, infection, or if other techniques have failed. Ultrasound-guided compression is successful in achieving thrombosis of the pseudoaneurysm, without the need for operative intervention, in 62–95% of cases [1–3]. In recent years it has become the procedure of choice for most patients. By directly compressing the neck of the pseudoaneurysm, ultrasound-guided compression results in occlusion of blood flow in the pseudoaneurysm cavity. Thrombosis of the contents occurs due to the natural coagulation cascade. It is a painful and time-consuming procedure that may require several attempts before succeeding [2]. It is least likely to succeed in anticoagulated patients, or when the pseudoaneurysm neck is wide or not directly accessible for compression.

Recently, several reports have suggested that ultrasound-guided thrombin injection is a safe, effective and rapid therapy for the treatment of pseudoaneurysm, without the limitations of ultrasound-guided compression [4–8]. We report here our initial results using this technique.

Materials and Methods

Between February and July 2000, eight patients with iatrogenic femoral artery pseudoaneurysm were referred for thrombin injection. Four had undergone cardiac catheterization at this institution. One was referred from the intensive care unit following insertion of a femoral vein dialysis catheter. Three were referred from other hospitals after cardiac catheterization. The patients included seven males and one female with an age range of 23–89 years (median 70 years). Attempted external compression using either sandbags or compression devices had failed in seven. Table 1 summarizes the patients' data.

Approval from the local institutional review board (Helsinki) was obtained (due to the "off-label" usage of the drug) and

Table 1. Patient characteristics and treatment data

Patient	Age/ Gender	Time from angiography (days)	Artery	Pseudo-aneurysm cavity (cm)	Pseudo-aneurysm neck (mm)	Relevant medications	Thrombin dose (units)
1	89 M	9	PFA	3.9x3.7x2.7	5x2	Aspirin/ticlopidine	500
2	68 M	9	PFA	2.2x1.4x1.3	12.1x1.6	Warfarin	100
3	76 F	7	PFA	2.4x1.8x1.5	3x2	None	150
4	69 M	2	CFA	2.5x1.5x1.5	3.4x2.4	Heparin/aspirin	100
5	23 M	3	PFA	3.0x2.0x1.8	6x2.7	None	100
6	70 M	9	SFA	2.6x1.5x1.0	4x1.8	None	250
7	70 M	8	CFA	4.2x3.4x2.3	19x5.8	Enoxaperin/aspirin/ ticlopidine	600
8	72M	3	CFA	2.7x1.4x1.3	10.4x2.2	Enoxaperin/aspirin	100

PFA = profunda femoris artery, CFA = common femoral artery, SFA = superficial femoral artery

patients gave informed consent for the procedure. Exclusion criteria for thrombin injection included all indications for surgical repair or known hypersensitivity to thrombin. Initially, the diagnosis was confirmed by clinical and color Doppler ultrasound examination [Figure 1]. The precise location, origin and dimensions of the pseudoaneurysm were documented prior to thrombin Injection [Table 1]. Ankle brachial indices were measured bilaterally.

The procedure was performed with a sterile technique. A 20 gauge co-axial needle was inserted into the cavity of the pseudoaneurysm using real-time sonographic guidance with a 'freehand' technique. The needle tip was directed away from the neck of the pseudoaneurysm. Thrombin solution (Bovine, Topical Thrombin, USP, Jones Pharma Inc, USA), diluted to 200 units/ml, was then slowly injected until color Doppler flow within the pseudoaneurysm cavity ceased [Figure 2]. Repeat color Doppler ultrasound evaluation of the nearby femoral vessels was performed to confirm patency. Ipsilateral peripheral limb pulses were evaluated before and immediately after thrombin injection. Patients were allowed to get out of bed 2 hours following the procedure. Repeat clinical and sonographic evaluation was performed prior to discharge from hospital, together with measurement of ankle brachial indices.

Results

Seven pseudoaneurysms occurred after diagnostic or therapeutic cardiac angiography (87.5%). The eighth resulted from accidental arterial injury during insertion of a temporary hemodialysis catheter into the common femoral vein. The neck of the pseudoaneurysm arose from the profunda femoris artery in four patients, the common femoral artery in three and the superficial femoris artery in one [Table 1]. Thrombin injection was performed between 2 and 9 days (median 7 days) after arterial puncture. Six of the eight patients were receiving antiplatelet and/or anticoagulant medications.

Immediate cessation of flow within the pseudoaneurysm was achieved with a single thrombin injection in seven patients. A second injection was necessary in one patient who had a multiloculated pseudoaneurysm. The average thrombin dose was 250 units (range 100–600 units). Repeat Doppler sonography prior to discharge from hospital confirmed thrombosis of the pseudoaneurysm in all cases. One patient (# 2), who was receiving continuous warfarin therapy, returned to hospital 48 hours after the procedure and was diagnosed with recanalization of the pseudoaneurysm. A repeat thrombin injection resulted in thrombosis of the pseudoaneurysm, however a 48 hour follow-up sonogram demonstrated repeat recanalization.

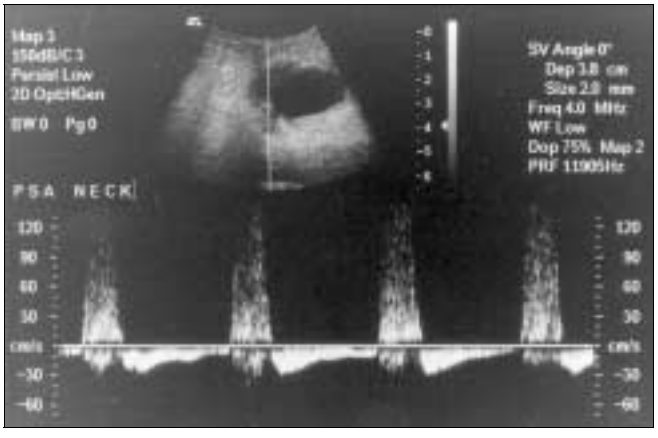

Figure 1. Doppler ultrasound of a right common femoral artery pseudoaneurysm with maximal diameter of 4.2 cm. A typical "to-and-fro" waveform in the neck of the pseudoaneurysm is demonstrated.

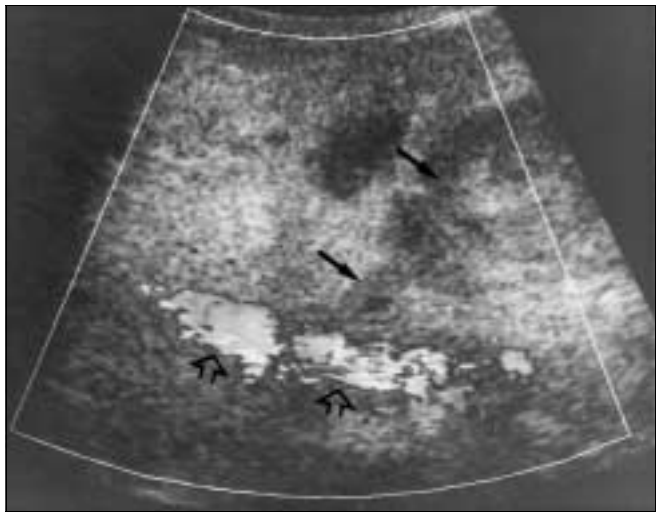

Figure 2. Doppler ultrasound performed immediately after thrombin injection in the same patient. There is no flow within the pseudoaneurysm. Echogenic fresh thrombus is seen within the neck and cavity of the pseudoaneurysm (arrows). Flow remains unchanged in the native artery (open arrows).

Ultrasound-guided compression was performed but was unsuccessful, and the artery was repaired surgically.

There were no adverse effects associated with thrombin injection. Clinical examination, repeat ankle brachial indices, and Doppler studies demonstrated immediate resolution of the pseudoaneurysm without evidence of peripheral emboli or ischemia. The overall success rate of thrombin injection was 87.5% (seven of eight patients).

Discussion

The incidence of post-catheterization pseudoaneurysm of the femoral artery ranges between 7% and 8%. Identified risk factors include anticoagulation, large introducer sheaths and faulty puncture technique. Similarly, inadequate compression, antegrade puncture, obesity and hypertension are associated with the development of pseudoaneurysm [1]. In our series, faulty puncture technique appears to be an important etiological factor in the development of pseudoaneurysm. In five of our patients the profunda femoral or superficial femoral arteries were the site of injury. In order to achieve hemostasis of the punctured vessel it must be compressed against the underlying femoral head. Adequate compression is reliably performed only when the common femoral artery is punctured.

The diagnosis of pseudoaneurysm is suspected clinically due to the presence of a painful, pulsating, enlarging groin mass at the site of catheterization. A thrill may be palpated, or a bruit heard on auscultation. Pseudoaneurysm is confirmed by color Doppler ultrasound examination, which can reliably identify the pseudoaneurysm, the vessel of origin and the 'neck' connecting them. Traditional treatment strategies for femoral pseudoaneurysm include observation, external compression, ultrasound-guided compression, catheter embolization, and surgical repair. Although spontaneous thrombosis may occur in small pseudoaneurysms, it may not be possible to accurately predict this in advance [1]. Spontaneous thrombosis is less likely if the volume of the pseudoaneurysm is greater than 6 ml (1.8 cm diameter) or in the presence of continued anticoagulation. Therefore, if initial conservative measures have failed, intervention should be considered to prevent rupture. External compression with sandbags or compression devices is uncomfortable for the patient, time consuming, has a high failure rate, and is associated with thromboembolic complications. Additionally, prolonged compression may result in skin ischemia, necrosis, or infection. Ultrasound-guided compression is a recent, successful treatment modality. It has rapidly become the procedure of choice when initial non-guided external compression has failed. However, it has several disadvantages. In some cases procedure-related pain necessitates the administration of intravenous sedation or anesthesia. Repeated compression is required in some patients and the procedure is time consuming. It is unlikely to succeed if the patient is receiving anticoagulants, or if accurate compression cannot be achieved due to obesity, a large hematoma, or a short, wide or posterior neck. Furthermore, the recurrence rate after ultrasound-guided compression may be as high as 20% [5].

Surgical repair is generally reserved for patients in whom ultrasound-guided compression has failed, aneurysm rupture is threatened, distal ischemia is present, the pseudoaneurysm is infected (mycotic pseudoaneurysm), or if there is significant tissue damage. Surgery is associated with significant morbidity and increased hospital stay [2]. Percutaneous transcatheter embolization may provide an alternative to surgical repair, but this procedure is invasive and requires contrast administration that may be undesirable in patients with known contrast hypersensitivity or decreased renal function. In fact, transcatheter embolization itself could potentially result in the development of a pseudoaneurysm.

For the above reasons, a safe, rapid, minimally invasive and comfortable treatment modality that does not require discontinuation of anticoagulant or antiplatelet drugs would be appealing. Ultrasound-guided thrombin injection has recently emerged as a potential alternative therapy after failure of initial external non-guided compression, and in place of ultrasound-guided compression. Thrombin directly stimulates the conversion of fibrinogen to fibrin in the final pathway of the coagulation cascade, and has been in use for many years in surgical and radiological applications [9]. Because it is a potent coagulating agent, intravascular injection of thrombin raises concern for a systemic effect such as disseminated intravascular coagulation. In experimental animal models, large doses of intravascular thrombin are tolerated without significant adverse effects [5,6,9]. However, since the activity of thrombin is dose-related, it seems reasonable to use the smallest possible amount necessary to achieve pseudoaneurysm thrombosis. Should inadvertent intravascular injection occur, this approach will minimize the likelihood of a systemic effect.

The immediate and long-term immunological impact of bovine thrombin injection is unclear. Despite its antigenic potential, allergic-type responses appear to be extremely uncommon, although a recent report of a prolonged generalized urticarial reaction following thrombin injection of a pseudoaneurysm is cause for concern [10]. Moreover, there is evidence to suggest the presence of immunoglobulin G and M antibodies to bovine thrombin following topical application [4]. Since repeated exposure appears to increase the risk of developing antibodies to coagulation factors, most authors consider prior exposure to thrombin to contraindicate its use for treating pseudoaneurysm. Unfortunately, this may be difficult to confirm as the patient is unlikely to know of prior exposure, and previous detailed surgical records are not always available. As more patients undergo this procedure, future thrombin use may be limited due to concerns about allergic-type reactions. We have opted to use a dilute solution of thrombin, 200 units/ ml, based on reports by other authors of good results without complications using low dose injection [7]. The injection is performed with continuous color Doppler ultrasound guidance and is discontinued as soon as coagulation of blood within the pseudoaneurysm is observed. A second injection may be

necessary for a multiloculated or a large pseudoaneurysm. To date, we have been treating relatively small pseudoaneurysms, none of which have required more than 600 units of thrombin (3 ml).

The reported success rate of thrombin injection in the literature varies between 93% and 100% [4–8]. Kang et al. [8] recently reported an initial success rate of over 98% in 82 patients. There was a single complication: acute ischemia of the hand following inadvertent direct injection of thrombin into the brachial artery; however thrombosis of the artery resolved with conservative treatment. The possibility of inadvertent injection of thrombin into native vessels can be limited by accurate anatomical evaluation prior to thrombin injection, by directing the needle tip away from the pseudoaneurysm neck, by avoiding 'over-injection' and by excluding patients with a very large pseudoaneurysm with a short, wide neck and a small native vessel.

The size of the pseudoaneurysm and the concurrent use of aspirin, ticlopidine, or heparin appear to be unimportant in predicting the success of thrombin injection [4,8]. Four of the patients in our series were receiving these drugs. Our results support the consensus in the literature that it is not necessary to discontinue antiplatelet drugs prior to thrombin injection. When possible we prefer to discontinue heparin, and recommence it 1–2 hours after thrombin injection.

Early recurrence of pseudoaneurysm was seen in seven patients in Kang's series [8]. Five of them responded to repeat thrombin injection and two required surgical repair. The eventual failure of the technique in these two patients was related to the presence of arteriovenous fistula or multiple defects connecting the artery and pseudoaneurysm. In our series, early recanalization of the pseudoaneurysm and ultimate failure of thrombin injection occurred in one patient who was receiving continuous warfarin therapy, although at a non-therapeutic dose. At the time of surgical repair no evidence of arteriovenous fistula or multiple arterial defects was identified. Based on this experience we feel it is prudent to discontinue warfarin therapy prior to thrombin injection. Patients requiring anticoagulation can be placed temporarily on intravenous heparin that is discontinued prior to thrombin injection and recommenced after.

Our overall success rate of 87.5% compares favorably with that of Kang et al. (96%). The published results of thrombin injection are equivalent to the best-published success rates for ultrasound-guided compression. Thrombin injection has the added advantage of a high success rate, up to 100%, in patients in whom ultrasound-guided compression has failed [4].

Interestingly, other authors have also recently reported the use of percutaneous thrombin injection for the treatment of temporal, subclavian, brachial, radial and tibial artery pseudoaneurysm [8,11,12].

In conclusion, ultrasound-guided thrombin injection appears to be an effective, safe, rapid and inexpensive therapy for iatrogenic pseudoaneurysm. It is more comfortable and more successful than ultrasound-guided compression and does not require discontinuation of antiplatelet drugs. Despite the realistic concern regarding significant hematological and immunological complications, these appear to be rare. Nonetheless, the long-term impact of exposure to bovine thrombin requires further study. Our experience together with that in the recently published literature suggests that thrombin injection should be considered as the first-line therapy for suitable patients with iatrogenic pseudoaneurysm after failure of initial short-term, non-guided compression.

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Correspondence: Dr. A. I. Bloom, Dept. of Radiology, Hadassah University Hospital, P.O. Box 12141, Jerusalem 91120, Israel. Phone: (972-2) 677-6502, Fax: (972-2) 643-7531, email: blumy2k@yahoo.co.uk