Ultrasound-Guided Thrombin Injection for the Treatment of Postcatheterization Pseudoaneurysms

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Background—This prospective study was designed to assess the safety and efficacy of using bovine thrombin injection to treat pseudoaneurysms.

Methods and Results—From April 1998 through December 1999, 70 pseudoaneurysm were injected with bovine thrombin under the guidance of color duplex ultrasound. The most superficial pseudoaneurysm chamber was entered with a 1.5-inch, 19- to 22-gauge or spinal needle. Bovine thrombin, in a 1000 U/cc solution, was injected into the chamber. A total of 36 women and 34 men underwent ultrasound-guided thrombin injection (UGTI). Their mean age was 69.5 years. Most pseudoaneurysms were associated with diagnostic cardiac catheterization or percutaneous coronary intervention (80%). Two pseudoaneurysms arose from the brachial artery; the remainder were in the groin. Twenty-one patients were being treated with either heparin or warfarin, and the majority of the others were on antiplatelet therapy (80%). Two pseudoaneurysms were repaired with stent graft placement and had short, wide tracts. Both of these patients required surgical repair of their pseudoaneurysms. The fourth patient had a nearly complete pseudoaneurysm thrombosis and was lost to follow-up on discharge. No arterial thrombotic events occurred. One patient had a soleal vein thrombosis in the ipsilateral leg.

Conclusions—UGTI was safe and effective in 94% of patients with postcatheterization pseudoaneurysms. Anticoagulant use did not hinder successful thrombosis. UGTI should be the initial treatment of choice for patients with postcatheterization pseudoaneurysms. (Circulation. 2000;102:2391-2395.)

Key Words: aneurysm, false ■ thrombin ■ ultrasonography, Doppler, duplex

Surgical repair and ultrasound-guided compression are effective in repairing postcatheterization pseudoaneurysms. Despite the efficacy of these approaches, each has its drawbacks. Surgery requires an incision and has a prolonged recovery time, and wound infection is common. In addition, surgical repair is problematic in the patient requiring ongoing anticoagulation and exposes the patient to the potential risks of anesthesia. Ultrasound-guided compression repair is uncomfortable for both the patient and the person who is compressing the pseudoaneurysm. The results are not as good as with surgery, and the time needed to thrombose the pseudoaneurysm increases in a patient on anticoagulation. Therefore, an alternative approach to the repair of postcatheterization pseudoaneurysms using ultrasound-guided thrombin injection (UGTI) has been proposed by several investigators.

The aim of this study was to determine prospectively the safety and efficacy of UGTI in a consecutive group of patients who presented with postcatheterization pseudoaneurysms.

Methods

From April 1998 through December 1999, 70 patients were prospectively and consecutively entered into the study. During this time period, 16 276 cardiac catheterizations were performed. Two-thirds of these were diagnostic cardiac catheterizations, and one-third were percutaneous coronary interventions. In addition, 5608 peripheral or neurological diagnostic procedures were performed, and ∼33% of these were interventions. Thus, the pseudoaneurysm rate was 0.3% of all diagnostic and interventional angiograms performed at the Cleveland Clinic Foundation. Only one patient who presented with a pseudoaneurysm during the enrollment period did not enter the consecutive series. This patient was taken directly to the operating room for urgent repair of a pseudoaneurysm because the groin was rapidly expanding and the patient was hemodynamically compromised.

This protocol was approved by the Institutional Review Board of The Cleveland Clinic Foundation. Informed consent was obtained from all patients. A total of 36 women and 34 men had their postcatheterization pseudoaneurysms injected with reconstituted bovine thrombin under ultrasound guidance. The demographic characteristics of the patients and the procedures that produced the pseudoaneurysms are shown in Table 1.

Arterial closure devices were used in 11 patients (15.7%). Five patients had a suture device (Perclose) implemented at the time of sheath removal. Five patients received a polyglycolic disc, braided suture, and collagen plug device (AngioSeal, Diag Inc). One patient underwent arterial closure with an investigational device.

An ultrasound was performed at the request of the attending physician to determine if a pseudoaneurysm was present. Pain, the
presence of a new bruit after the procedure, a pulsatile mass, and/or an expanding hematoma were the most frequent reasons for requesting an ultrasound.

All patients were studied in the accredited noninvasive vascular laboratory at the Cleveland Clinic Foundation using color flow duplex imaging with an HDI 5000 ultrasound (Advanced Technology Laboratories). The color flow duplex imaging used either a 7.5 or 5 MHz frequency ultrasound transducer. The native vessels were identified in transverse and longitudinal axes. The identification of a typical ultrasound image of a pseudoaneurysm and a tract arising from the native artery was confirmed by the identification of the characteristic “to and fro” Doppler flow (Figure 1).

Once recognized as a pseudoaneurysm, the artery of origin was identified and recorded. The other parameters recorded as part of the data included depth of the neck of the pseudoaneurysm, the length of the tract, and the size (in centimeters) and number of chambers. The measurements of the pseudoaneurysm chamber dimensions were taken in the transverse view. The first 25 patients who underwent UGTI also had a complete venous duplex ultrasound of the affected limb, as well as an ankle-brachial index and pulse-volume recording ankle tracing, before and after injection.

Bovine thrombin (5000 U; GenTrac, Inc) was reconstituted in 5 cc of normal saline as a 1000 U/cc solution. A 3-way stopcock was used to perform injections (Figure 2). Thrombin and saline were drawn up in separate 3-cc syringes and were loaded to the stopcock that was turned “off” to the thrombin and “on” to the saline syringe. The needle length was chosen on the basis of the depth to the center of the most superficial pseudoaneurysm chamber from the skin surface. Under most circumstances, a 1.5-inch, 19- to 22-gauge needle was used; for pseudoaneurysms that were deep, a spinal needle was used.

While withdrawing the saline syringe, the needle was inserted into the pseudoaneurysm chamber. Once blood returned into the saline syringe, saline was then injected into the chamber to confirm placement into the pseudoaneurysm. Color duplex imaging allows confirmation of needle placement on visualization of a “color flash” in the pseudoaneurysm chamber with injection of saline. The tip of the needle can often be clearly visualized after saline injection. The stopcock was then turned “off” to saline and “on” to the thrombin, and small aliquots of thrombin (0.2 cc) were injected while observing the ultrasound image (Figure 2). Injections were continued until the pseudoaneurysm cavity thrombosed. If patients had >1 pseudoaneurysm cavity, the most superficial cavity was injected first. Frequently, all cavities thrombosed with this method (Figure 3). Occasionally, a second injection was required for the deeper cavities.
After thrombus formation was visualized, success of the thrombin injection was confirmed by demonstrating an absence of color flow and an absence of Doppler flow through the tract. Patients were placed on bed rest for 2 hours after the injection and then allowed normal activity as tolerated. At 24 to 48 hours after successful thrombin injection, patients were rechecked for continued success using the same color duplex ultrasound technique.

Results

The majority of the pseudoaneurysms arose from the common femoral artery (Table 1). The average number of chambers was 1.4 (range, 1 to 3), the average length of the pseudoaneurysm tract was 14 mm, and the average depth of the pseudoaneurysm neck arising from the native artery was 30.2 mm. The mean transverse dimensions of the pseudoaneurysm chamber(s) were 2.46 by 2.14 cm (range, 0.8 to 8 cm by 0.75 to 8 cm).

Although most pseudoaneurysms were detected within 48 hours of the procedure, one was not detected for 4.5 months. This patient had undergone a diagnostic mesenteric angiogram and was on warfarin therapy with an international normalized ratio of 3.2.

The average dose of reconstituted bovine thrombin was 1.15 cc (1150 U). The number or size of the chambers did not correlate with the amount of thrombin required.

A total of 66 of the 70 patients (94%) had successful injections with reconstituted bovine thrombin (Table 2). The pseudoaneurysms thrombosed within seconds in most patients. However, 26 patients (37%) required >1 injection to achieve complete obliteration of the pseudoaneurysm cavity. Three patients had the pseudoaneurysm cavity obliterated on the first injection but, on an ultrasound recheck the next day,
the pseudoaneurysm was again present. These patients required a second injection and, in all cases, the pseudoaneurysms were successfully thrombosed. Twenty-one patients (30%) were receiving antithrombotic therapy with heparin (n = 14), warfarin (n = 6), or both (n = 1) at the time of the procedure. The majority of the others were on antiplatelet therapy with aspirin or clopidogrel. Eleven patients on heparin had an activated partial thromboplastin time >50 seconds, and 5 patients on warfarin had an international normalized ratio >1.5. All patients receiving antithrombotic therapy (except for the first patient injected) had a successful result.

Continued success was found on follow-up duplex in all 66 patients. The first unsuccessful injection occurred in the first patient in the series. We were not using the 3-way stopcock method, and we could not get the needle into the pseudoaneurysm cavity. The patient underwent 2 injection attempts and refused subsequent attempts. Two other unsuccessful injections involved patients who had undergone endovascular stent graft placement for the treatment of aortic aneurysms. These procedures require large bore sheaths. The ultrasound demonstrated a wide, short pseudoaneurysm tract. Despite multiple injections into the pseudoaneurysm cavity, thrombosis could not be achieved. One patient had near-complete resolution of her pseudoaneurysm and was scheduled for follow-up duplex and possible reinjection. Several attempts had been made to contact the patient without success. Three patients had both an arteriovenous fistula and a pseudoaneurysm. In one patient the pseudoaneurysm thrombosed and the fistula closed after injection of the pseudoaneurysm.

No arterial thrombotic events occurred after injection. In the first 25 patients, pulse volume recordings and venous duplex ultrasounds were obtained before and after injection. No change occurred in the arterial wave forms or pressures, and no episodes of venous thrombosis occurred immediately after the procedure. One patient noted calf pain at the time of his follow-up duplex examination, and a venous duplex ultrasound identified a small soleal vein thrombus. The patient was treated with low-molecular-weight heparin followed by warfarin for 3 months.

**Discussion**

An arterial pseudoaneurysm is defined as a disruption of the arterial wall with resultant extra luminal flow into a chamber contained by adjacent tissue. The clinical presentation varies depending on the size and location of the pseudoaneurysm. Pain, a pulsatile mass, groin expansion, the presence of a new bruit, anemia, and leg weakness are common clinical presentations.

The incidence of postcatheterization pseudoaneurysm is low. It is estimated to occur in 0.05% to 0.5% of all diagnostic and therapeutic percutaneous arterial and coronary catheterizations. Despite this relatively low incidence, postcatheterization pseudoaneurysms may cause significant morbidity to the patient. Vessel rupture, thromboembolism, extrinsic compression of nearby neurovascular structures, necrosis of overlying skin and subcutaneous tissue, and significant blood loss have all been associated with postcatheterization pseudoaneurysms.

Surgical repair was the standard of care for pseudoaneurysms in the past. Observation has been advocated by some investigators for asymptomatic patients not on anticoagulation therapy who have a pseudoaneurysm <3.5 cm in diameter. However, the inability to predict spontaneous thrombosis of these small pseudoaneurysms and the cost of surveillance with serial duplex ultrasound studies make this approach less practical.

Surgical repair was performed as the treatment of choice until 1991, when ultrasound-guided compression was introduced. Lumsden et al. demonstrated complication rates as high as 21% in patients undergoing surgical repair. Bleeding, wound infection, lymphocele, and radiculopathy were the most prevalent complications. Perioperative myocardial infarction and death were also reported in this series.

Since 1991, ultrasound-guided compression repair has been the first-line approach for the treatment of postcatheterization pseudoaneurysms. It has a low rate of complications and is very effective. However, this procedure is both time and labor intensive. It may require 2 technologists or physicians to compress the tract of the pseudoaneurysm to obliterate flow. Patients generally require intravenous analgesia or sedation to tolerate the procedure. The failure rate is in the range of 5% to 15%, and the recurrence rate is reported to be as high as 30% in the face of ongoing anticoagulation.

Technical ease, excellent clinical results, negligible complication rates, and patient comfort are elements that make UGTI the treatment of choice for repairing postcatheterization pseudoaneurysms. It is important to clearly visualize the full extent of the pseudoaneurysm and tract. Confirmation of needle placement into the center of the pseudoaneurysm cavity is imperative to avoid injection into a native vessel. Compression of the tract while injecting it with thrombin, although hypothetically appealing as a method to avoid tract injection, is technically fraught with difficulty. This method would obliterate the pseudoaneurysm cavity and make visualization of the pseudoaneurysm chamber impossible. Therefore, it is preferable to optimize visualization of the pseudoaneurysm chamber under ultrasound guidance to avoid tract injection. Arterial thrombosis, although not reported in this series, is a potential complication if inadvertent injection into the artery occurs. For this reason, injection into the tract should be avoided. In a few cases, the pseudoaneurysm cavity thrombosed but all or part of the tract remained. We continued to observe these patients, and the tract invariably thrombosed on later follow-up.

Venous thrombosis occurred in 1 patient in this series after thrombin injection. The thrombus was identified in the soleal leg.
vein after the patient developed calf pain. It is unlikely that this isolated soleal deep venous thrombosis was related to UGTI. It is important to avoid the iliac, common femoral, or superficial femoral veins during injection to avoid postinjection deep venous thrombosis.

Predictors of UGTI failure must be further evaluated. Large bore catheters and sheaths such as those used to place aortic stent grafts may cause a short, wide tract that makes thrombosis with thrombin very difficult.

Hypotension and bradycardia are documented potential reactions to exposure to bovine thrombin.\textsuperscript{13} Case reports of acquired coagulation factor inhibitors secondary to immune cross-reactivity to bovine thrombin have been reported.\textsuperscript{14–16} Unfortunately, the dose required to trigger hypotension and bradycardia or coagulation factor inhibitors is not well established. No instances of these complications occurred in the current series, and they have not been reported in the literature.\textsuperscript{2–5} We propose that more purified preparations of bovine thrombin are associated with less likelihood of these types of reaction. A recent article described a case of anaphylaxis after thrombin injection of a femoral pseudoaneurysm in a patient who had repeated exposures to bovine thrombin. The authors suggested that patients who have had prior exposure to bovine thrombin undergo skin prick testing to detect possible allergy.\textsuperscript{17}

In summary, the percutaneous injection of reconstituted bovine thrombin is well tolerated by patients and results in rapid thrombosis of the pseudoaneurysm. This procedure has a low morbidity rate and a success rate of 94%, with no significant complications. Therefore, UGTI should be considered a first-line approach for the treatment of postcatheterization pseudoaneurysms in the hemodynamically stable patient.

References
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