Ultrasound-guided percutaneous thrombin injection following iatrogenic femoral artery pseudoaneurysm: patient selection and perspectives

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Abstract: Ultrasound-guided percutaneous thrombin injection (UGTI) following iatrogenic femoral artery pseudoaneurysms has been the standard of care as first-line treatment at many institutions since its initial description by Liau et al in 1997. UGTI underwent rapid adoption given its significant advantages to patients including shorter procedure times, decreased discomfort, lower rates of recurrence, and the avoidance of surgical intervention in appropriate cases. Despite the availability of less-invasive approaches, through numerous head-to-head studies, UGTI has demonstrated clear benefit over ultrasound-guided compression in the treatment of iatrogenic femoral artery pseudoaneurysms. Although newer interventions such as percutaneous coil embolization have attracted attention for their superior ability to manage those patients with high-level anticoagulation or allergies to thrombin, at this time they do not provide an equal alternative to thrombin injection. In this review, we focus on issues related to the selection of patients who benefit from UGTI for the treatment of iatrogenic pseudoaneurysms.

Keywords: false aneurysm, endovascular complication, cardiac catheterization, interventional radiology, autologous thrombin

Introduction
Pseudoaneurysms can arise from percutaneous access to the arterial system if the artery is not adequately sealed once a sheath is removed. These aneurysms are deemed “false” as they contain no elements of the arterial wall, but rather have a wall composed of thrombus and the surrounding soft tissues. They differ from a hematoma, a simple collection of blood in an extravascular space, as pseudoaneurysms have a defined neck communicating with an arteriotomy.1

This complication is well described in the literature, ranging from 1% in diagnostic procedures to as high as 8% in therapeutic interventions.2,3 This significantly exceeds the standards for acceptable incidence as established by numerous societies (as low as 0.2% for diagnostic studies) over 20 years ago,4 but highlights a persistent issue with current arterial access techniques. There are several factors associated with the formation of pseudoaneurysms. According to the Contemporary Management of Post Catheterization Pseudoaneurysms by Webber et al5 the factors include the use of antiplatelet agents, anticoagulation, sheath size >8 F, age >65 years, obesity, poor postprocedural compression, simultaneous artery and vein catheterization, hypertension, peripheral vascular disease, hemodialysis, complex interventions, and low or high puncture sites.

In early studies, the reported rates were much lower (0.05%–2.00%); however, these findings were retrospective and annotated only those complications which required
surgical correction. Further prospective sonographic studies show an increased incidence (1.1%–6.24%), but these studies evaluated only patients undergoing retrograde puncture of the artery with clinically suspected pseudoaneurysm or arteriovenous fistula. Further prospective studies which use routine duplex imaging show incidence as high as 7.7%, as many small, asymptomatic aneurysms were identified. A more recent study has demonstrated an incidence of 2.9% in ~500 consecutive patients undergoing cardiac catheterization.

### Diagnosis

The presence of pain, swelling, or pulsatile mass is the standard presentation of a large pseudoaneurysm after catheterization. Other, rarer symptoms can include neuropathy, venous thrombosis, claudication, or critical limb ischemia secondary to mass effect from a large pseudoaneurysm.

On examination, there may be a palpable, pulsatile mass with or without an underlying systolic bruit. Therefore, the presence of disproportionate pain or swelling at the site of arterial access, even in the absence of bruit, should initiate further workup.

The gold standard for diagnosis of pseudoaneurysm is duplex ultrasound with a sensitivity of 94% and a specificity of 97%. Contrast-enhanced computed tomography of the abdomen and pelvis may be of benefit if significant extension into the retroperitoneum is suspected during duplex ultrasound. Often, small iatrogenic pseudoaneurysms are asymptomatic, and those smaller than 1.8 cm have a high likelihood to spontaneously thrombose (although this should not preclude treatment for prevention of possible complications).

### History

Up until the early 1990s, the standard of care for nearly all femoral pseudoaneurysms was surgical intervention. While very effective, surgical therapy is not without risks. Lumsden et al describes a 20% complication risk for surgically treated groin complications following percutaneous cardiac procedures. The search for a safer but equally efficacious method was begun.

Throughout the 1990s, there were multiple studies done evaluating the natural history of pseudoaneurysms that did not meet criteria for acute surgical intervention, culminating with the work of Toursarkissian et al. They demonstrated that the vast majority of stable pseudoaneurysms, as many as 89%, can be managed with observation alone. The paper, however, failed to address those on anticoagulation, making these findings difficult to generalize to patients at greatest risk for pseudoaneurysm formation. Additionally, the study required a follow-up protocol with frequent visits and duplex ultrasound evaluation. Patients in the nonoperative arm underwent an average of 2.6 duplex scans after diagnosis compared to 1.4 for the operative group.

At the same time that Toursarkissian et al were performing their work, several other groups were looking at conservative management strategies for femoral artery pseudoaneurysms.

### Development of the thrombin method

The first description of the use of thrombin for the treatment of pseudoaneurysms was by Cope and Zeit in a 1986 case report, but it was not until 1997 when Lian et al produced a detailed description of the treatment of iatrogenic femoral artery pseudoaneurysm with percutaneous thrombin injection that the technique was widely adopted and eventually became the standard first-line modality for the management of this complication. In the initial paper, which included only 5 patients, they were able to demonstrate a simple, nonmorbid, and highly successful treatment without recurrence at a mean follow-up time of 11.6 months. Numerous studies show that the technique is widely adopted and eventually became the standard first-line modality for the management of this complication. In the initial paper, which included only 5 patients, they were able to demonstrate a simple, nonmorbid, and highly successful treatment without recurrence at a mean follow-up time of 11.6 months. Numerous studies
performed throughout the ensuing decade demonstrated excellent success rates for ultrasound-guided percutaneous thrombin injection (UGTI) ranging from 93% to 100% with minimal recurrence (6%–14%) and low incidence of complication (1%–2%).

There are two prospective randomized control trials that evaluate ultrasound-guided compression compared to UGTI for the treatment of iatrogenic femoral artery pseudoaneurysm. In 2004, Lonn et al evaluated 30 consecutive patients with iatrogenic pseudoaneurysms over a 22 month period. Exclusion criteria included: any indication for surgical intervention, local infection, previous exposure to bovine thrombin with a known allergy, or a pseudoaneurysm neck >10 mm. The patients were then randomized to either compression (using FemoStop II Plus compression device RadiMedical Systems, Uppsala, Sweden) or thrombin injection via standard technique. The two groups were matched for age, sex, etiology of pseudoaneurysm, and the use of antiplatelet drugs. The primary outcome measured was successful thrombosis of the pseudoaneurysm at 24 hours. Secondary outcomes measured the presence or absence of thrombosis at 48 hours, complications, and length of hospital stay. The study found successful thrombosis in all 15 patients in the thrombin injection arm at 24 hours compared with only two (13%) in the compression arm during the same time period. Six patients (40%) had successful thrombosis 48 hours after repeat treatment (p<0.001). All remaining pseudoaneurysms were successfully treated with thrombin injection. There were no complications or significant differences in length of stay noted.

A second study completed in 2006 by Liu et al evaluated 38 patients with iatrogenic pseudoaneurysms. Neither exclusion criteria nor age and sex distribution were stated. The patients were randomized into an UGTI or ultrasound-guided compression group. Patients were evaluated at 3 and 7 days, with primary outcomes measuring successful thrombosis at 72 hours. Secondary outcomes evaluated thrombosis at 7 days and change in volume of hematoma. The study found successful thrombosis in all 19 patients within the thrombin group and 13 (68%) in those managed with ultrasound-guided compression at 3 days. They also reported complete thrombosis of all pseudoaneurysms at 7 days (risk ratio [RR]: 1.44; 95% CI: 1.06–1.97).

Further analysis in a 2013 Cochrane review merging data from the above studies, with notations made accepting the limitations of different study designs and measures, found that percutaneous thrombin injection was not significantly more effective than ultrasound-guided compression (RR: 2.81; 95% CI: 0.44–18.13) based on the parameters measured. All told, however, UGTI has supplanted ultrasound-guided compression and operative intervention unless otherwise indicated as it is thought to provide more rapid thrombosis, decreased procedure time, reduced pain, and improved success.

**Patient selection**

There are no consensus guidelines regarding patient selection for ideal management of femoral artery pseudoaneurysms. Certainly, variables such as size, flow, lumen, and patient anticoagulation status should be considered. Current data suggest that pseudoaneurysms smaller than 3 cm in diameter will thrombose spontaneously; however, this occurs at a mean of 23 days. Samuels et al found that the greatest predictor of spontaneous thrombosis was aneurysmal neck length. An aneurysm neck >0.9 cm would spontaneously thrombose at 9 days vs 52 days for those with a shorter neck length. Watchful waiting was also noted to have, as expected, a higher average number of follow-up visits and duplex examinations (2.6 vs 1.4 for immediate intervention group).

Consensus data have shown that reliable patients with asymptomatic pseudoaneurysms smaller than 2 cm in diameter may follow-up with frequent duplex assessment. Intervention is recommended in the remaining patients.

Indications for immediate surgical repair regardless of size include the following: hemodynamic instability, active bleeding, an expanding mass, distal ischemia, overlying skin necrosis, infection, or neurological deficit. Also, contraindications exist to the treatment of femoral artery pseudoaneurysms with thrombin injection. Certainly, percutaneous thrombin injection should only be performed in patients who develop the pseudoaneurysm secondary to a catheterization procedure. Those that arise spontaneously should be highly suspicious for a mycotic pseudoaneurysm and thus should be managed via other measures. Additionally, pseudoaneurysms occurring at the anastomosis of a synthetic graft to native artery should be managed surgically. Relative contraindications to thrombin injection include a large aneurysm (>5 cm), wide neck (>1.0 cm), or failure of repeated ultrasound-guided treatments.

**Recurrence and repeat intervention**

Conservative management (ie, ultrasound-guided compression alone) is not without risk of failure or recurrence, as demonstrated by Cox et al in their study of 100 consecutive patients. They found that those on systemic anticoagulation were significantly more likely to fail intervention with compression than similarly matched patients without anticoagula-
tion (98% vs 86%, \( p = 0.019 \)), further supporting the pursuit of thrombin injection.

The question remains then as to which subset of femoral artery pseudoneurysms will be refractory to percutaneous thrombin injection. Sheiman and Mastromatteo\(^2\) evaluated 54 consecutive iatrogenic pseudoneurysms of the common femoral artery and had complete thrombosis in 49 after a single injection. Of the five that failed, four obtained obliteration on ultrasound 10 minutes after injection but recurred within 24 hours (clinically suspected, sonographically confirmed) while in the fifth only partial thrombosis was obtained despite repeated injection. All were referred for surgical management, and four out of five were found to have a laceration at the arteriotomy site of at least 0.8 mm (24 F). There was no obvious laceration on ultrasound, even in retrospective review. One patient was found to have an infection at the common femoral artery site requiring bypass.

There exists no contraindication to repeated injection; however, some authors warn that failure despite repeat injections or early failure within 24 hours should be viewed with suspicion and be potential selection criteria for operative management. No other studies reviewed discussed further criteria for potential failure of UGTI.

### Alternatives

Alternative techniques exist to those discussed in detail above and they include para-aneurysmal saline injection, use of autologous thrombin, coil embolization, and placement of covered vascular stents. In 2003, Gehling et al\(^2\) demonstrated success in a small case series (6 patients) of femoral artery pseudoneurysms managed with para-aneurysmal injection of saline (52±33 mL of physiologic saline) with good success. This was followed up by a series of 64 consecutive patients who showed 92.2% success via similar technique (all failures were managed successfully with direct compression or thrombin injection),\(^2\) thus demonstrating a cost-effective, safe, minimally invasive, fast, and effective treatment.

While the use of bovine thrombin has been demonstrated to be an effective and relatively safe treatment, there remains some concern regarding long-term outcomes, including the low but potential risk of prion transmission and the risk of peri-procedural anaphylaxis. Therefore, the use of autologous thrombin for treatment of pseudoneurysms has been explored. Initially described in a small group of patients by Quarmby et al,\(^2\) it has since been shown in larger trials to be highly effective and, in head-to-head comparisons with bovine thrombin, has shown equivalent results while being as much as 29% less expensive per treatment.\(^2\)

Injection of cyanoacrylate glue has been demonstrated as a viable technique for management of visceral artery aneurysms and has since been shown to be safe and efficacious in small trials for femoral artery pseudoneurysms after percutaneous access.\(^30,33\) However, opponents argue that such techniques are not as cost-effective and they may serve as a nidus for infection. Percutaneous coil embolization too has been demonstrated as a safe, effective alternative\(^32\) but is subject to similar criticism. Finally, a 2000 German study evaluated repair of postcatheterization pseudaneurysms and arteriovenous fistulas with endovascular covered stents in the setting of failed compression therapy. They demonstrated a safe and effective technique; however, follow-up was limited (~1 year) and stent thrombosis was present in 17% of patients. Additionally, procedures are much more costly, invasive, and may be limited by anatomy.\(^33\)

### Conclusion

As demonstrated, femoral artery pseudoneurysm after percutaneous access is a common complication and will continue to present itself as more endovascular procedures are performed. Duplex ultrasound will remain the diagnostic modality of choice as it is accurate, noninvasive, and cost-effective. While ultrasound-guided compression has been demonstrated as a safe and effective therapy, it has significant limitations (most notably length of procedure and patient discomfort/intolerance). Thus, in the absence of a surgical indication, ultrasound-guided thrombin injection has been demonstrated to be an effective first-line treatment for iatrogenic femoral artery pseudoneurysm with an excellent success rate of 97% and low rate of complications at <1.3%.\(^3\)

### Disclosure

The authors report no conflicts of interest in this work.

### References


