US-guided percutaneous thrombin injection of postcatheterization pseudoaneurysms

Kamil Gürel, Serkan Gür, Uğur Özkan, Güven Tekbaş, Hakan Önder, Levent Oğuzkurt

PURPOSE
This study retrospectively evaluated ultrasonography-guided (US-guided) percutaneous thrombin injection for the treatment of postcatheterization femoral and brachial artery pseudoaneurysms.

MATERIALS AND METHODS
Fifty-five patients with postcatheterization femoral artery (n=53) or brachial artery (n=2) pseudoaneurysms were treated using US-guided human thrombin (500 IU/mL) injection. Pseudoaneurysm size, thrombin dose, therapy outcome, and complications were documented. Follow-up color Doppler US was performed 7 and 30 days after treatment. Short-duration supplemental compression was applied to six patients at the first week follow-up examination after a reinjection of thrombin had failed.

RESULTS
Mean pseudoaneurysm volume was 20.3±18.7 cm³. The mean injected thrombin dose was 478±238 IU. Thirty-eight (69.1%) of the 55 pseudoaneurysms were thrombosed with a single injection, and 11 of 17 pseudoaneurysms were thrombosed after a second injection. All (100%) of the 41 pseudoaneurysms that were diagnosed within the first two weeks of postcatheterization were successfully treated. The overall primary success rate was 89.1% (49 of 55 pseudoaneurysms). Supplemental compression promoted thrombosis in four of the six patients who had treatment failure with thrombin injection. The secondary success rate was 96.4% (53 of 55 pseudoaneurysms). There were no complications.

CONCLUSION
US-guided thrombin injection was most successful within the first two weeks, and the supplemental compression might aid in the closure of partially thrombosed pseudoaneurysms. Key words: • pseudoaneurysm • therapeutic embolization • thrombin

emoral artery pseudoaneurysms are among the most frequent complications of angiography. Factors that predispose a patient to pseudoaneurysm formation are inadequate compression, simultaneous artery and vein catheterization, hypotension, obesity, hemodialysis, heavily calcified arteries, and low femoral puncture. The risk of pseudoaneurysm formation also increases when large-bore sheaths, postprocedural anticoagulation therapy, and/or antiplatelet therapy are used as interventions (1, 2). The incidence of femoral pseudoaneurysms ranges from 0.05% to 4% (2). Color Doppler scanning reveals a prevalence of 7.7% in all postcatheterization patients regardless of symptoms, but the prevalence may increase up to 16% with more complex procedures that necessitate larger sheaths (2, 3).

Open surgical repair was the gold standard for iatrogenic pseudoaneurysms till the development of percutaneous therapeutic options. One prominent disadvantage of the surgical repair of pseudoaneurysms is the remarkably high complication rate. Ultrasonography-guided (US-guided) compression repair is relatively safe and effective, but it has considerable limitations. Specifically, the duration of compression is lengthy, the procedure is painful and may require conscious sedation, and the success rate is approximately 75%. The US-guided injection of thrombin has emerged as an alternative to US-guided compression repair with success rates of 91% to 100%. The complication rate is approximately 2% (2, 4). The US-guided injection of thrombin has become the first-line treatment for pseudoaneurysms, and it is increasingly popular for the treatment of iatrogenic pseudoaneurysms in many institutions. This study reports our experience with the use of US-guided percutaneous thrombin injection for the treatment of iatrogenic femoral artery and brachial artery pseudoaneurysms.

Materials and methods
All of the procedures on humans were performed in accordance with the ethical standards of the World Medical Association. Written consent was obtained from all patients following instructions on the nature and risks of the intervention. In this retrospective study, 55 consecutive patients with a mean age of 60.1±12.7 years (26 men, aged 35 to 79 years [mean, 58.2 years]; 29 women, aged 32 to 85 years [mean, 61.9 years]) who were treated from December 2006 to June 2010 and who received a diagnosis of pseudoaneurysm of the femoral or brachial artery with the guidance of color Doppler US (CDUS) were included in this analysis. Patients with any of the following criteria were excluded from this study: a rapid expansion of the pseudoaneurysm, especially in unstable patients, distal ischemia due to femoral artery compression, infection of the pseudoaneurysm, neuropathy, overlying soft tissue or skin ischemia, or impending compartment syndrome. No patients were excluded for these reasons during the study period. The morphology
Diagnostic US and US-guided thrombin injections were performed with a 9.4- or 13.5-MHz transducer (Antares, Siemens, Erlangen, Germany). The diagnosis of a pseudoaneurysm included a swirling color flow in a mass that was separate from the underlying artery, a color flow signal in a track leading from the artery to the mass consistent with a pseudoaneurysm neck, and a to-and-fro Doppler waveform in the pseudoaneurysm neck (2). The relationship between the lumen and the underlying neck and artery was delineated. The soft tissues surrounding the pseudoaneurysm were examined for evidence of an arteriovenous fistula or additional interconnecting pseudoaneurysm lobes. The patency of the artery and the vein were confirmed. The following parameters were documented prospectively prior to the injection:

1) Number of pseudoaneurysm lobes: Simple pseudoaneurysms have one lobe, and complex pseudoaneurysms have two or more lobes that are separated from each other. The lobe closest to the artery was defined as the proximal lobe, and the lobe most distant from the artery was defined as the distal lobe.

2) Lobe volume was calculated as length×height×width×0.52.

The methodology of the study is summarized in Fig. 1.
Human thrombin (500 U/mL) (Tisseel VH, Baxter, Glendale, California, USA) was used as the thrombosing agent. Human thrombin is a component of a fibrin sealant kit that consists of human thrombin and calcium chloride solution. Freeze-dried human thrombin was reconstituted with the calcium chloride solution and drawn into a 2-mL syringe. The solution was withdrawn from the 2-mL syringe into a 1-mL syringe for meticulous injection. The residual solution within the 2-mL syringe served as a reservoir if additional doses were required. A 1-mL solution contained 500 IU of thrombin. The puncture point was sterilized, and local anesthesia (1 mL of 2% prilocaine hydrochloride; Citanest, AstraZeneca International, London, England) was administered. A 7 cm, 21 G needle (Cook, Bloomington, Indiana, USA) was advanced into the pseudoaneurysm under US guidance parallel to the transducer. The tip of the needle was placed into the lobe of the pseudoaneurysm (Fig. 2). Puncture of the proximal pseudoaneurysm lobe was achieved for complex pseudoaneurysms. Puncture of the pseudoaneurysm neck was avoided. The needle tip was placed in the midpoint of the pseudoaneurysm lobe (Fig. 3a), and thrombin was injected slowly at doses of 100 IU with color-coded US guidance at a low-pulse repetition frequency (Fig. 3b). Injections were continued until the color signal in the aneurysm lobe and the neck disappeared completely (Fig. 3c and 3d). If the color signal remained in the neck but disappeared from the lobe, the injection was continued at a slower rate from the same point until the neck completely clotted. The thrombin dose was recorded. The pseudoaneurysm neck was not compressed during the thrombin injection.

Patients were instructed to maintain bed rest for two hours following the procedure. No dressing wrapping was used around the thigh. CDUS examination was repeated after two hours, and residual blood flow in the pseudoaneurysm neck or lobe(s) was noted. If evidence of blood flow in the pseudoaneurysm remained, another dose of thrombin was injected as described above. The patients were instructed to maintain bed rest for two additional hours and were sent home. A follow-up examination was scheduled a week later (the “wait-and-see” method) if complete thrombosis of the pseudoaneurysm sac could not be obtained.

Patients were examined using CDUS after 7 and 30 days. A US-guided thrombin injection was repeated if persistent blood flow was observed in the aneurysm on follow-up examination. The procedure was not repeated when persistent flow at the aneurysm neck remained after two sessions of thrombin injection in the same day. In these cases, manual compression was performed at the pseudoaneurysm neck under CDUS guidance to promote thrombosis and avoid surgical treatment. The procedure was regarded as failure if perfusion in the sac remained after all of these treatments, and surgical treatment was performed.

The primary success of pseudoaneurysm repair was defined as the complete obliteration of the pseudoaneurysm after the initial treatment with one or two thrombin injections. Secondary success was defined as the complete obliteration of the pseudoaneurysm with repeated thrombin injections or added manual compression after the initial treatment. We questioned every patient at each follow-up examination for the new occurrence or an exacerbation of claudication symptoms. Every patient had a CDUS examination of the ankle arteries (dorsalis pedis and posterior tibial artery) before and after each procedure.

A statistical analysis was performed using a computer software (Statistical Package for Social Sciences version 11.0, SPSS Inc., Chicago, Illinois, USA). Patient demographics, clinical variables, and pseudoaneurysm characteristics were compared using the Pearson chi-square (categorical variables) or paired t (continuous variables) tests. Single and complex pseudoaneurysms were compared. Patients who were treated with a single thrombin injection were compared with the patients who were treated with repeated thrombin injections. The primary and secondary success rates were compared. The statistical test results were considered significant at P values of 0.05 or less.

Results

The right common femoral artery was the pseudoaneurysm vessel of origin in 27 patients. The superficial femoral artery was the pseudoaneurysm vessel of origin in 23 patients (right, n=19; left, n=4). The right deep femoral artery was the pseudoaneurysm vessel of origin in two patients. The right persistent sciatic artery was the pseudoaneurysm vessel of origin in one patient. The right brachial artery was the pseudoaneurysm vessel...
of origin in one patient, and the left brachial artery was the pseudoaneurysm vessel of origin in one patient. A simple one-lobe pseudoaneurysm was treated in 42 patients (23 women, 19 men). A complex pseudoaneurysm was treated in 13 patients (six women, seven men). The complex pseudoaneurysm was bilobulated in 12 patients and six-lobed in one patient. Six right common femoral artery, four right superficial femoral artery, one superficial femoral artery, and one brachial artery aneurysm were bilobulated. One of the right superficial femoral artery pseudoaneurysms had six lobes. The mean volumes of the simple and complex pseudoaneurysms were $19.3\pm16.29 \text{ cm}^3$ and $23.7\pm25.36 \text{ cm}^3$, respectively ($P = 0.46$).

The total thrombin dose that was required for the primary repair of the pseudoaneurysms ranged from 100 to 1100 IU (mean dose, $478\pm238$ IU). The mean thrombin dose that was required to repair the simple pseudoaneurysms ($454\pm246$ IU) was lower than the dose that was required to repair the complex pseudoaneurysms ($555\pm1985$ IU) ($P = 0.18$).

Pseudoaneurysms in seven patients (12.8%) failed to thrombose after the first injection. The reperfusion of a previously thrombosed pseudoaneurysm was observed in ten patients (18.1%) after a two-hour bed rest. Only 38 of 55 (69.1%) pseudoaneurysms were successfully treated with a single injection of thrombin. The treatment was repeated in 17 (15 simple and 2 complex) pseudoaneurysms at the two-hour follow-up examination. Eleven of the 17 pseudoaneurysms were thrombosed with a second injection of thrombin. The primary therapeutic success rate (success rate of twice injection) was 89.1% (49 of 55 patients) for all pseudoaneurysms. Primary therapeutic success was achieved in 36 of the 42 (85.7%) simple pseudoaneurysms and 13 of the 13 (100%) complex pseudoaneurysms ($P = 0.15$).

The injection was repeated in six of 26 men (23.1%) and 11 of 29 women (37.9%). There was no significant difference in gender between the repeated injection application and non-application groups ($P = 0.23$). There was no difference between the mean ages of the repeated treatment application

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**Figure 3.** a–d. Gray-scale and color Doppler US images obtained in a sagittal (longitudinal) direction in a patient with a simple pseudoaneurysm originating from the right common femoral artery. The pseudoaneurysm lobe is shown as a $3.9\times3.2$ cm anechoic fluid collection located anterior to the femoral artery on a gray-scale image. The echogenic tip and the needle shaft are observed within the pseudoaneurysm prior to injection (a). Color-coded duplex sonograms illustrate the typical swirling pattern of flow into the pseudoaneurysm with flow into the pseudoaneurysm in one portion of the lumen (blue) and flow out of the pseudoaneurysm in other portion (red) of pseudoaneurysm prior to the thrombin injection (b). The continued flow in the neck and the diminished flow in the pseudoaneurysm lobe are shown during the thrombin injection (c). Image obtained immediately after the injection of 400 IU thrombin shows the complete occlusion of the pseudoaneurysm lobe and the neck (d).
group (59.3±11.25 years) and the non-application group (60.5±13.5 years) \( (P = 0.76) \). Although the pseudoaneurysm size and the total thrombin volume for the first injection were higher in the repeated treatment application group (24.2±24.89 cm\(^3\) and 547±217 IU, respectively) compared with the non-application group (18.6±15.16 cm\(^3\) and 447±243 IU, respectively), no significant differences between groups \( (P = 0.30 \) and \( P = 0.15, \) respectively) were observed. Although the duration of pseudoaneurysm formation was an important factor for repeated intervention, this difference did not reach statistical significance \( (57.1±174.2 \) days for the repeated treatment application group and 8.8±49.43 days for the non-application group, \( P = 0.09) \). No difference in pseudoaneurysm lobe number between groups was observed \( (P = 0.17) \).

Six of 42 simple pseudoaneurysms had minimal residual flow after all of the repeated injections. These patients were followed-up for spontaneous occlusion of their pseudoaneurysms for one week. All pseudoaneurysms were perfusing at the one-week follow-up examination, and a new session of percutaneous thrombin injections was initiated. Total permanent occlusion was not achieved in any of these pseudoaneurysms after repeated injections. We preferred manual compression under CDUS to achieve thrombosis of the pseudoaneurysms because most parts of the pseudoaneurysms were thrombosed in these patients. Complete thrombosis was achieved in four of the pseudoaneurysms following 3–5 min of compression. Secondary therapeutic success was observed in 53 (96.4%) of the 55 pseudoaneurysms: 40 (95.2%) of the 42 simple pseudoaneurysms and 13 (100%) of 13 complex pseudoaneurysms. We referred two patients to vascular surgery for operative repair. The first patient was a 65-year-old man with a 49.2 cm\(^3\) simple pseudoaneurysm that was detected 30 days after the removal of the arterial sheath. The other patient was a 63-year-old woman with a 90 cm\(^3\) simple pseudoaneurysm that was detected two years after the removal of the arterial sheath.

All 41 patients (100%) in group 1 (pseudoaneurysms diagnosed within the first two weeks after angiography) had successful treatment of their pseudoaneurysms. Twelve of the 14 patients (86%) in Group 2 (pseudoaneurysms diagnosed after more than two weeks) had successful treatment. Two patients (14%) remained not thrombosed despite all therapeutic attempts. The difference in success in these two groups was prominent, but it did not reach statistical significance \( (P = 0.06) \).

One patient had a slight transient leg pain after the procedure that spontaneously improved within 12 hours after the thrombin treatment. No patient underwent surgical or interventional procedures because of complications to thrombin injections. Follow-up CDUS and clinical examinations were performed in all 55 (100%) patients on day 7 (early follow-up) and in 38 patients (69%) on day 30 (late follow-up) after thrombin injection treatment. No pseudoaneurysm recurrence was observed at the long-term follow-up examinations.

**Discussion**

The overall success rate of thrombin injection for pseudoaneurysm treatment in the current study was 96.4% (53 of 55 patients). The primary therapeutic success rate was 89% (49 of 55 patients) for all pseudoaneurysms, but it was only 69% using a single injection. US-guided thrombin injection was most successful for pseudoaneurysms that were detected within the first two weeks of formation. All of the patients in this period had successful treatment. Two patients with pseudoaneurysms that were detected more than two weeks after formation required surgical treatment without adverse sequel. The difference in treatment success before and after two weeks was clinically important, but it did not reach statistical significance. Applications of short-duration (a few minutes) manual compression for pseudoaneurysms that were partially thrombosed after one or repeated thrombin injections promoted thrombosis in most patients.

Surgery currently plays a minor but important role in the management of pseudoaneurysms, especially in the treatment of complications. The major danger of pseudoaneurysms is rupture with potentially life-threatening hemorrhage. Other complications include compression of neurovascular structures with resultant neuropathy, lower extremity edema, deep vein thrombosis, claudication, and ischemia. Infection of pseudoaneurysms is another serious complication that predisposes to rupture and limb-threatening distal septic emboli. Indications for the surgical repair of pseudoaneurysms include the following factors: rapid expansion, especially in an unstable patient, distal ischemia due to femoral artery compression, infection of the pseudoaneurysm, neuropathy, overlying soft tissue or skin ischemia, impending compartment syndrome, and the failure of percutaneous treatment \( (2) \). Two of 55 patients (3.6%) underwent surgery because of the failure of all percutaneous therapeutic attempts in the current study. Surgical complications occur in approximately 20% of patients who have operative repair \( (2) \). The first option in small pseudoaneurysms in patients who are not anticoagulated is to wait and follow the pseudoaneurysms for spontaneous thrombosis while limiting the patient’s activity. Tournasissian et al. \( (5) \) reported that small pseudoaneurysms less than 3 cm in diameter (approximate volume of 14 cm\(^3\) ) spontaneously thrombosed at an average of 23 days in 87% of patients. The mean size of pseudoaneurysms in the current study was similar to previous reports of a pseudoaneurysm size of 3–3.5 cm \( (2) \). However, the volume was much larger than in one previous report \( (1) \). Compression can be attempted if small pseudoaneurysms do not thrombose spontaneously \( (2) \). Compression is relatively safe and effective, but its limitations include an often lengthy and a painful procedure, and a success rate of approximately 75%, which is lower in patients under anticoagulation. The success rate decreases in larger pseudoaneurysms, pseudoaneurysms lasting longer than two weeks, and patients who are receiving anticoagulation therapy \( (3) \). Finally, some pseudoaneurysms are not amenable to compression, including pseudoaneurysms in which arrest of the flow in the pseudoaneurysm neck is impossible, pseudoaneurysms associated with exquisite groin tenderness, and pseudoaneurysms that arise above the inguinal ligament \( (6) \).

US-guided injection of thrombin is an alternative to US-guided compression repair. The addition of sufficient amounts of thrombin to anticoagulated...
blood will reliably induce thrombosis because the final pathway of blood coagulation is the generation of thrombin (7). Unlike compression repair, anticoagulation does not affect the success of thrombin injection (2, 8). The thrombin injection procedures are extremely quick compared with compression repair (6). Previous studies have reported success rates of 94%–100%. On the basis of the results of the current and previous studies, we are convinced that repeated thrombin injections should be the treatment of choice for reperfused pseudoaneurysms (1, 2). Reported thrombosis rates following a single injection were 63% to 79%. A second, third, or fourth injection is required during the initial treatment session in 15%, 5%, and 1% of patients, respectively (4). In the current study, the thrombosis rate was 69% (38 of 55 pseudoaneurysms) following a single injection and the primary therapeutic success rate (success rate of two injections) was 89% (49 of 55 pseudoaneurysms). Although the primary success rate (89%) was lower than in previous reports (1–3), the secondary success rate (96%) was similar to previous reports (1, 2, 4, 6). No significant differences in success were observed with respect to pseudoaneurysm size (P = 0.30) and lobe number (P = 0.17). These results are parallel to the results of Kang et al. (7). However, higher failure rates with complex multicompartamental pseudoaneurysms have been reported (9). The current study demonstrated that the success rate was 100% for complex aneurysms, and the age of the pseudoaneurysm was an important factor for success. These results are comparable with US-guided compression therapy (3). No statistically significant differences in successful outcome were observed between patients with a pseudoaneurysm for less than and greater than two weeks (P = 0.06). All of the patients with a pseudoaneurysm that was diagnosed within the first two weeks of formation had successful treatment. This success might be due to the limited number of cases that were required to achieve statistical significance. All therapeutic failures included pseudoaneurysms that were diagnosed more than two weeks prior to treatment. This failure might be the result of a matured intimal coating within the pseudoaneurysm lobe.

Thromboembolic complications with thrombin injection for pseudoaneurysm are a rare (about 1%) but serious side effect (1, 2, 4, 6). Arterial thrombosis is probably rare because needles and catheters create the hole in the artery. This hole is rarely more than a few millimeters wide, which is likely too small for the passage of a large clot. If the thrombin itself leaked into the artery, it could be effectively neutralized by dilution and anticoagulant factors on the endothelium and in the circulating blood, such as thrombomodulin and antithrombin III (2, 4, 7). Thromboembolic complication occurs when an inadvertent injection of thrombin into the artery or injection is performed too close to the pseudoaneurysm neck. Therefore, the tip of the needle must be well visualized and appropriately located within the pseudoaneurysm lumen. The tip of the needle must be as far away from the neck as possible. Poor visualization of the needle should be considered a contraindication to the procedure. A wide pseudoaneurysm neck is listed as a contraindication to thrombin injection because it predisposes patients to thromboembolic complications (10). For this reason, the distal pulses must be checked prior to the procedure and periodically rechecked after the procedure. No complications were experienced in the current study, except for a slight transient limb pain in one patient. These results demonstrate the safety of this procedure. The other reported complications include allergic and anaphylactic reactions due to use of the bovine thrombin, deep venous thrombosis due to compression, and groin pain after thrombin injections in some patients (1). An association of the pseudoaneurysm with an arteriovenous fistula has the potential risk of pulmonary embolus (2). Special care was undertaken to prevent the arterial thromboembolic complications. First, tip of the needle was well visualized, and it was maintained as far from the neck as possible. Second, if small residual perfusion existed in the neck after the use of one kit of thrombin (1000 IU), the injection was stopped, and perfusion was examined after two hours of bed rest (i.e., the “wait-and-see” approach). Most patients with residual blood flow in the neck experienced spontaneous thrombosis (1, 8). However, perfusion persisted after two
thrombin injection potentiates complete thrombosis once the flow is arrested with compression (4). A trend toward minimal medication to decrease the amount of thrombin that is injected into the pseudoaneurysms might supplement compression in selected patients. However, the selection criteria of patients who would benefit from supplemental compression are not clear. Compression was applied after the first week if a new thrombin injection failed in the current study. This supplemental compression technique was more successful than the “wait-and-see” technique. Supplemental compression can be applied instead of the “wait-and-see” technique for small residual perfusion following the first thrombin injection.

Different methods for the closure of a postcatheterization pseudoaneurysm have been described. Mechanical closure devices can be used for the treatment of pseudoaneurysms (11). The injection of saline beneath the communication tract of the pseudoaneurysm for rapid occlusion prior to US-guided compression has been described as an alternative treatment method (12). US-guided compression assisted by the percutaneous application of removable coils has also been reported (13). These methods require further investigation. Occlusion of the pseudoaneurysm neck by balloon placement into the feeding artery during a fibrin adhesive injection is another method for the treatment of pseudoaneurysms (14). This method is substantially more invasive, costly, and time consuming, but it has only been performed in isolated cases.

Our study has several limitations. This study was a retrospective study with its inherent limitations. The blood pressure, body mass index, and the sheath size that was used for the catheterization were not measured. These factors could be important for the success and failure of the procedure (2). The size of the pseudoaneurysm neck was not recorded. The wideness or shortness of the pseudoaneurysm neck may influence the thrombin dose, systemic complications, and success rate (2).

In conclusion, our study demonstrated that US-guided thrombin injection was very successful within the first two weeks of pseudoaneurysm formation. This method was also successful after this period with a low rate of failure. Thrombin injection is a simple and safe method for this patient group. Successful treatment outcome was high in simple and complex multi-lobed pseudoaneurysms. Manual compression of a short duration may be more efficacious than the “wait-and-see” approach in patients with treatment failure after two sessions of thrombin injections.

Conflict of interest disclosure

The authors declared no conflicts of interest.

References