Journal of the American College of Cardiology
© 2002 by the American College of Cardiology Foundation
Published by Elsevier Science Inc.
Vol. 39, No. 8, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(02)01752-7

Efficacy and Safety of Percutaneous Treatment of Iatrogenic Femoral Artery Pseudoaneurysm by Biodegradable Collagen Injection

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OBJECTIVES The goal of this study was to assess the safety and efficacy of femoral artery pseudoaneurysm (FAP) closure by collagen injection.

BACKGROUND The FAP is an infrequent but troublesome complication after percutaneous transfemoral catheter procedures. If ultrasound-guided compression repair (UGCR) fails, vascular surgery is indicated. We have developed a less invasive method to close FAPs percutaneously by injecting collagen and, thus, inducing clotting within the aneurysm.

METHODS Via a 9F needle or 11F sheath, a biodegradable adhesive bovine collagen is injected percutaneously into the FAP, guided by angiography from the contralateral site.

RESULTS From 1993 to 2000, compression and UGCR had failed to obliterate 110 FAPs. These patients have been treated by collagen injection. Mean age of the patients was 65.6 ± 10.2 years (range: 32 to 85 years), and 50% were women. Immediate closure of the FAP was achieved in 107/110 patients (97.3%) without any complication or adverse effect. In one patient the collagen could not be applied due to unfavorable anatomy. One patient needed a second session of collagen injection. In one patient too much collagen was inserted, which resulted in external compression of the artery, and surgical intervention was required. The overall success rate was 108/110 (98%, 95% confidence interval: 93.5% to 99.8%). Among the patients with successful procedures, there were no recurrences during six months follow-up.

CONCLUSIONS The percutaneous treatment of iatrogenic FAP, by injection with collagen, is an effective and safe strategy. This method provides an excellent therapeutic alternative to the traditional surgical management. (J Am Coll Cardiol 2002;39:1297–304) © 2002 by the American College of Cardiology Foundation

Groin complications related to the femoral arterial access site used for various invasive cardiovascular procedures represent a significant problem. Among these, femoral artery pseudoaneurysm (FAP) is one of the most troublesome. In the last years, the magnitude of the problem has been growing with the exponential growth of interventional cardiology. The FAP occurs in 0.1% to 0.2% of diagnostic angiograms and 3.5% to 5.5% after interventional procedures (1–6). The incidence of the FAP has increased recently with the more frequent use of high doses of antiplatelet and anticoagulant therapy and the use of larger-sized cannulas for various interventional procedures. For large persistent pseudoaneurysms, ultrasound-guided compression repair (UGCR) is currently the first line of treatment in order to facilitate the clotting process within the aneurysm (7,8). However, this method has disadvantages and limitations. Moreover, its success is limited, and the recurrence rate is still 20% for patients who are receiving anticoagulants and antiplatelet therapy (9–11). Finally, surgical repair is indispensable, but this is often associated with the need for general anesthesia, with an increased length of hospital stay and with higher costs.

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Manuscript received September 25, 2001; revised manuscript received January 16, 2002, accepted January 28, 2002.

Several recent attempts have shown that minimal invasive management may be a reasonable alternative to achieve pseudoaneurysm thrombosis.

In the 1980s, we introduced the treatment with collagen insertion. We have developed a nonsurgical, minimally invasive method to close the FAP percutaneously with collagen. It has been our approach to use biodegradable adhesive bovine collagen to facilitate clotting within the false aneurysm and, thus, achieve the closure. The aim of this study was to evaluate the efficacy and safety of this method in a large consecutive group of patients with a FAP.

METHODS

Subjects. The study was conducted between 1993 to 2000. A total of 110 patients were candidates for treatment with percutaneous collagen injection at the St. Antonius Hospital at Nieuwegein. All had recently undergone catheterization procedures in our institution or in referring centers. All patients had initially been treated by UGCR, prolonged compression and bed rest, without success. The procedure was explained to the patients, and all patients signed an informed consent form.

These patients underwent ultrasound examination with duplex scanning along with pulsed and color Doppler flow mapping (Sonos 2000, Hewlett Packard, Amsterdam, the Netherlands) employing 7.5 MHz linear array transducer.

Abbreviations and Acronyms

CI = confidence interval
FAP = femoral artery pseudoaneurysm
UGCR = ultrasound-guided compression repair

The persistence of the FAP was defined as the presence of a hypoechogenic cavity with blood flow from the artery into the FAP in systole and inversely in diastole, visible by Doppler color flow imaging and pulsed ultrasound. Also, the size of the FAP was measured (Fig. 1).

Purified bovine collagen has been used in surgical procedures as an adjunct to hemostasis when control of bleeding by ligature or other conventional methods remains ineffective. When collagen comes in contact with blood, platelets aggregate on the collagen and release coagulation factors that, together with plasma factors, result in the formation of a fibrin matrix. Once implanted into tissues of an organism, collagen is ultimately degraded and progressively resorbed by granulocytes and macrophages. VasoSeal (Datascope Corp., Montvale, New Jersey) was introduced initially as a vascular hemostasis device to seal femoral arterial puncture sites after cardiac catheterization and coronary angioplasty. It consists of a collagen plug which, when inserted adjacent to the arterial wall at the puncture site, induces the formation of a hemostatic cap directly over the arterial puncture (11). For patients with a FAP, these collagen plugs were inserted into the pseudoaneurysm to promote clotting in the FAP.

After our initial experience with collagen plugs, a biodegradable adhesive bovine collagen paste (Collagen, Datascope Corp., Montvale, New Jersey) was used to promote hemostasis and accelerate the clotting process within the pseudoaneurysm.

Contraindications to this procedure included suspected underlying infection and known allergy to collagen or beef products.

Procedure. Initially, the collagen was applied guided by selective angiography using the contralateral access site with a 4F sheath. After puncture of the contralateral femoral artery, the 4F catheter is introduced through the sheath and positioned across the iliac bifurcation in the affected proximal common femoral artery over a guidewire. The injection of iodine-containing contrast medium allows one to locate the FAP exactly and correctly, together with its tract and connections.

After applying routine local anesthesia with 1% lignocaine, the pseudoaneurysm cavity is then directly punctured, leading to high-pressure backflow of blood ensuring correct access to the pseudoaneurysm. The initial application of the Vasoseal (collagen plugs) required a larger 11F sheath. After puncture of the pseudoaneurysm, a guidewire was introduced through the needle to the pseudoaneurysm. The needle is then removed, leaving the guidewire in place. A sheath-dilatator is passed over the guidewire into the pseudoaneurysm cavity, and the guidewire and the dilatator are removed, leaving only the sheath through which VasoSeal plug could be inserted (Fig. 2). The application of the collagen paste allows use of a thinner needle. The pseudoaneurysm cavity is directly punctured percutaneously using a 9F needle. Then the collagen paste is applied directly through this 9F needle into the center of the FAP. This produces a very rapid filling and thrombosis of the pseudoaneurysm. After 1 to 2 min, a repeat angiogram is performed through

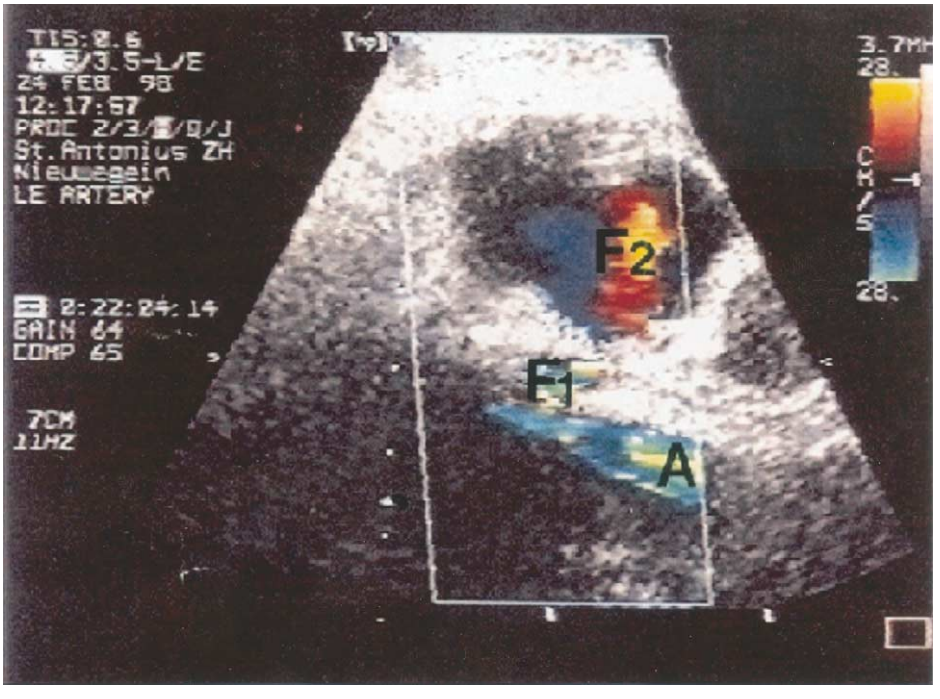

Figure 1. Color Doppler ultrasound shows a femoral pseudoaneurysm **(F2)**, its neck **(F1)** with flow from the femoral artery **(A)**.

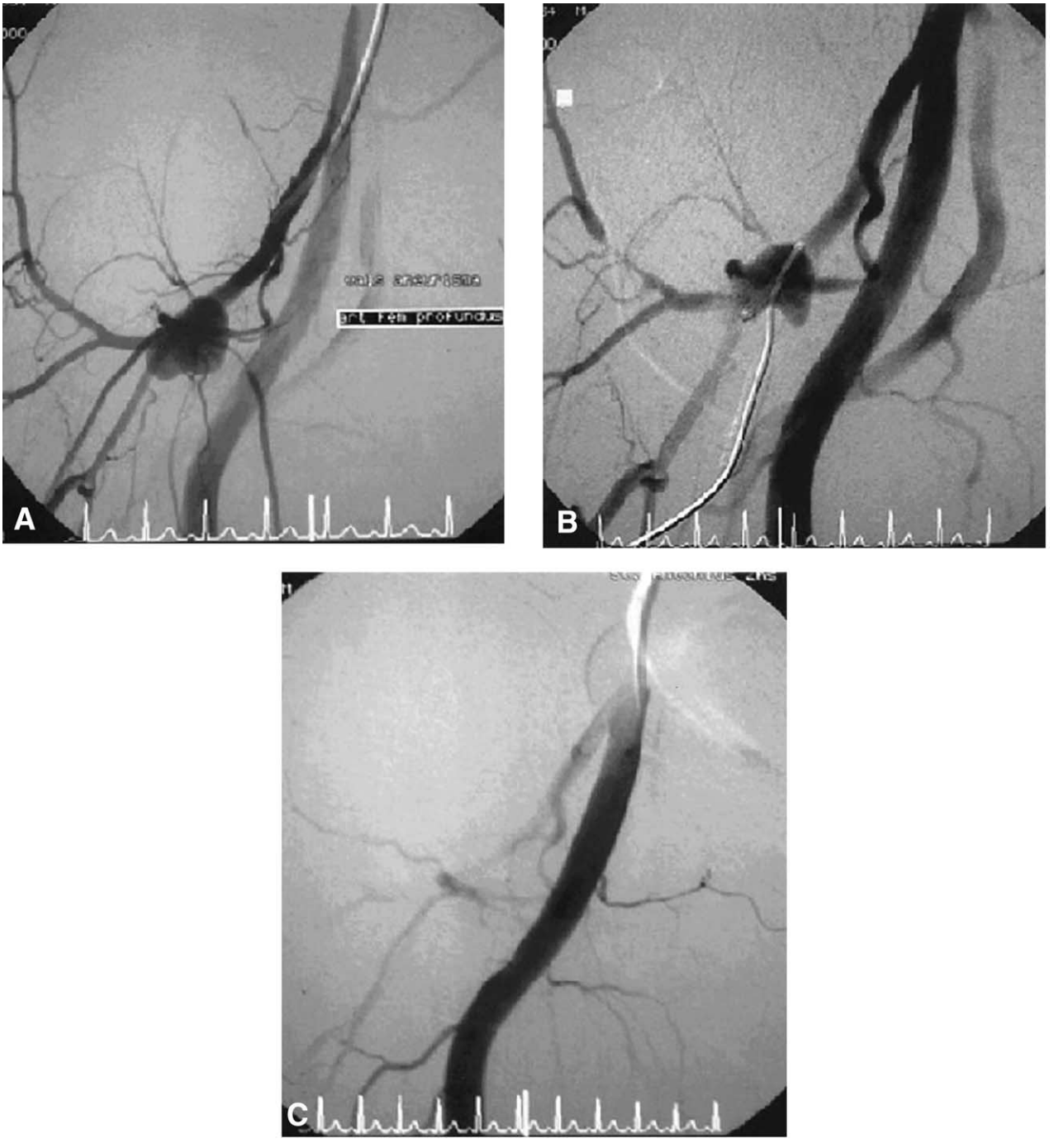

Figure 2. **(A)** Angiogram via contralateral site of a pseudoaneurysm of the right femoral artery profunda. **(B)** After insertion of a thin guidewire, an 11F catheter is introduced in the pseudoaneurysm. The collagen is applied through this catheter. **(C)** Final result after collagen injection, the aneurysm is completely obliterated.

the 4F sheath of the opposite access, to confirm aneurysm occlusion (Fig. 3).

The patients were observed for any adverse effects, and the status of the distal pulses were examined before and after the procedure. Patients underwent a 24-h follow-up clinical and duplex scanning examination (Fig. 4). This included duplex assessment of the pseudoaneurysm and physical examination of the patient.

The primary end points of this study were initial and six-month success rates and complications.

Data analysis. The hospital records of these patients were reviewed for the following information: age, gender, type of procedure, the time interval (in days) between arterial puncture and collagen injection. The lesion type and the localization (common, superficial or profunda femoral artery) were noted.

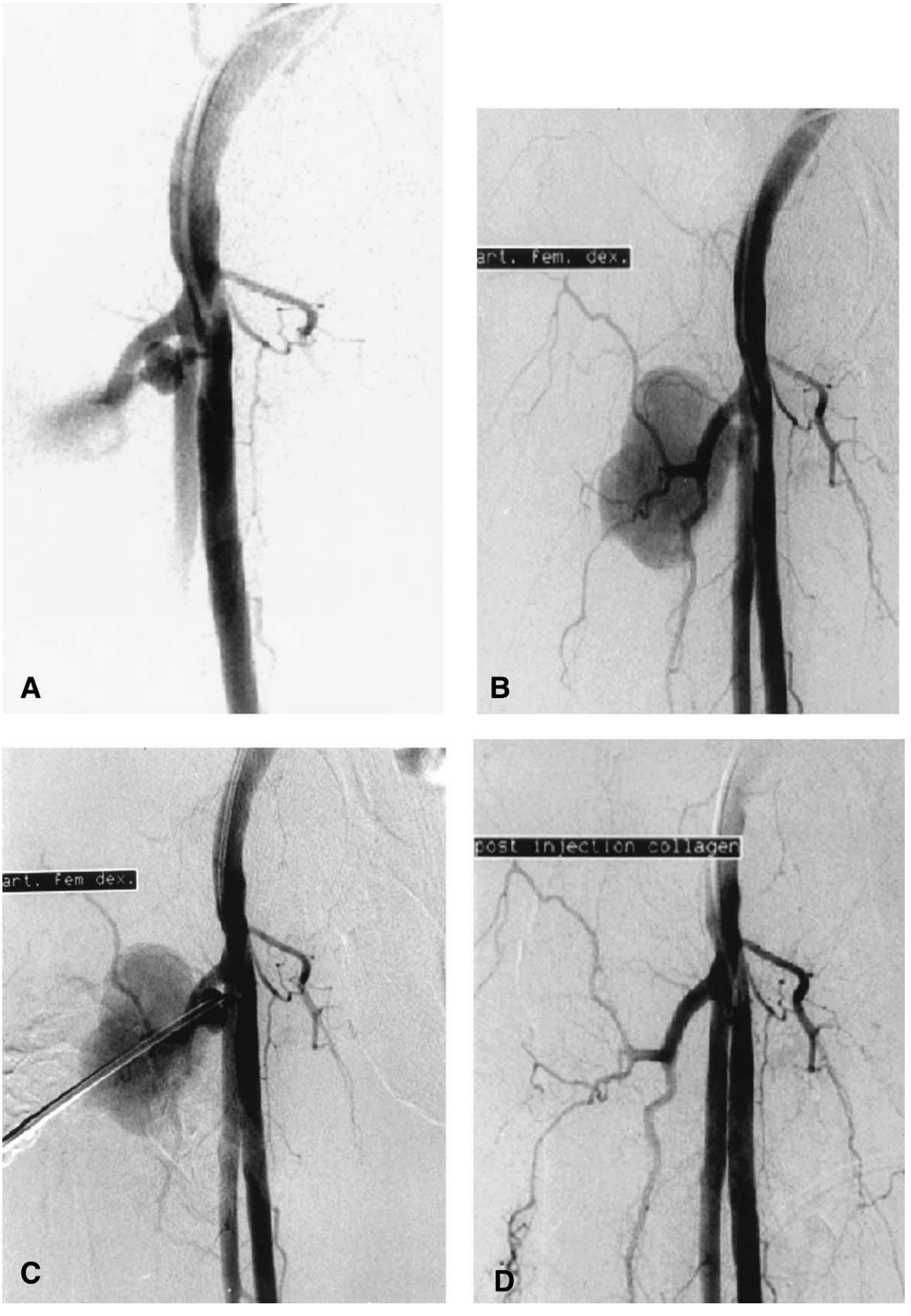

Figure 3. Angiogram of the right femoral artery via the contralateral site. **(A)** Bilobulated pseudoaneurysm with its neck arising from the superficial femoral artery. **(B)** The pseudoaneurysm is completely visualized. **(C)** Direct injection of collagen through a needle. **(D)** Final angiographic control, via the contralateral site, after obliteration of the pseudoaneurysm.

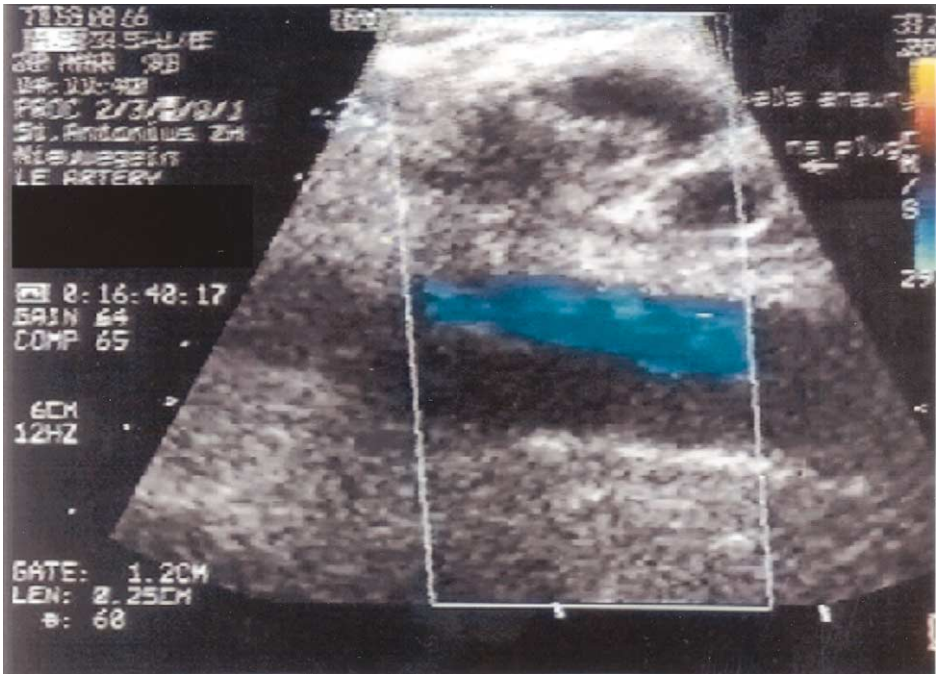

Figure 4. Color Doppler ultrasound image obtained after collagen injection shows complete thrombosis of the pseudoaneurysm.

Statistical analysis. Only descriptive statistics were used. The 95% confidence intervals (CIs) for rates were calculated with the exact binomial method.

RESULTS

There were 55 male and 55 female patients, with a mean age of 65.6 years (range: 32 to 85 years). Data about the delay between removal of the femoral catheter to the collagen injection were available in 106 cases (96%). Delay ranged from 0 to 96 days (mean 11 ± 12.8 days). There were 110 femoral pseudoaneurysms of which four were associated with an arteriovenous fistula (5%). Of the 110 pseudoaneurysms, 100 (90.6%) were uniloculated and 10 (9.4%) were multiloculated. The lesions were caused by diagnostic cardiac catheterization in 51%, by interventional procedures in 42.8% (29.6% after percutaneous transluminal balloon coronary angioplasty, 13.2% after placement of a stent) and by other cardiac procedures in 6%. The clinical baseline data of the patients are shown in Table 1.

In the vast majority of cases, arterial access had been through the right femoral artery. The location of the injury was the superficial femoral artery in 41.5% of pseudoaneurysms, the bifurcation of the common femoral artery in 56.9% of cases and the profunda femoral artery in 3.1% of cases. Data relating to the pseudoaneurysm site are shown in Table 2.

In the 110 patients, percutaneous collagen injection was attempted. No patient required either analgesia or sedation. There were no allergic reactions. In one patient the procedure was aborted because of unfavorable anatomy of the pseudoaneurysm, and he underwent operative repair. Therefore, this procedure was technically possible in 109 of the 110 patients (99.1%). Of the 109 patients who underwent collagen injection, 107 of 109 (98.1%) had initial successful obliteration of the pseudoaneurysm regardless of the anticoagulation status of the patient. Immediate thrombosis occurred usually within a few seconds after collagen application. The mean volume of collagen required for obliteration of the pseudoaneurysms depends on the volume of the FAP. Initially, 4 to 12 collagen plugs had to be inserted. Each plug contained 90 mg collagen. Thereafter, mean volume of 3 to 9 ml of collagen paste (10 mg collagen/ml) was injected into the cavity of the pseudoaneurysm.

One patient had partial obliteration of the pseudoaneurysm and needed a second successful session of collagen injection. Closure of the pseudoaneurysm was confirmed by

Table 1. Clinical Baseline Data

Gender	
Male	55 (50%)
Female	55 (50%)
Catheterization	
Diagnostic	51%
Angioplasty	30%
Stent placement	12%
Other	7%

Table 2. Lesion Characteristics

Lesions	
Pseudoaneurysms	95%
Pseudoaneurysms and arteriovenous fistulas	5%
Lesions locations	
Common femoral artery (mostly bifurcation)	56%
Superficial femoral artery	41%
Profunda femoral artery	3%

Table 3. Success Rates of Collagen Injection

		95% CI
Initial		
Success	107/110 (97.3%)	92.2–99.4
Failure	2/110 (1.8%)	0.2–6.4
Final		
Success	108/110 (98.2%)	93.5–99.8
Failure	2/110 (1.8%)	0.2–6.4

CI = confidence interval.

the cardiac catheterization laboratory with a second angiogram via the contralateral artery.

There was one failure; too much collagen paste was injected, with protrusion to the vessel without peripheral migration, which required surgical intervention. Otherwise, we observed no major complications. In particular, no peripheral embolic events were documented. No patients have developed another iatrogenic injury at the contralateral puncture site. No other adverse effects or local groin complications were observed.

Immediate procedural success with complete closure of the pseudoaneurysm was achieved by collagen injection in 107 of 109 cases (97.3%, 95% CI: 92.2% to 99.4%). With one case of delayed success, the overall success rate was 98.2% (108 of 109 patients, 95% CI: 93.5% to 99.8%) (Table 3).

Unless other clinical signs prevented discharge, all patients were discharged from hospital the following day once repeat duplex scanning had confirmed the absence of any arterial flow within the earlier cavity. At outpatient clinical follow-up after six months, no groin problems related to the collagen injection or recurrences of FAP were noted.

DISCUSSION

Treatment modalities. Iatrogenic FAP in patients who underwent a diagnostic or therapeutic percutaneous catheter intervention is not an uncommon complication. Usually, FAPs are caused by punctures of the femoral artery, which are too distal, that is, the bifurcation of the femoral artery or below. Several therapeutic strategies, such as UGCR, surgical repair and minimally invasive percutaneous treatments (thrombin injection, coil embolization and insertion of covered stents) have been developed to treat this complication.

In the last decade, UCGR has become the treatment of choice (Fellmeth et al. 1991) (7,8). The introduction of this method has significantly reduced the need for surgical repair of FAP. Nevertheless, several restrictions for application of this method, such as long procedure times, discomfort of patients, relatively high recurrence rate in patients receiving anticoagulant therapy should be taken into consideration (7–10,12–16). Furthermore, UGCR requires the availability of an ultrasound device and the presence of skilled personnel during the procedure.

Since the first description of an attempt to close a FAP by percutaneous thrombin injection in the FAP by Cope and Zeit (17) and subsequently Walker et al. (18) in 1986 and 1987, several publications inspired by this simplified technique have followed (19–23).

The first attempts to close a FAP with ultrasound-guided thrombin injections were not without complications. Two cases of distal migration of the thrombin have been described (24,25). These adverse events raise the question: were these complications due to the nature of the injected thrombin or was it caused by the way it is used? We believe that, because thrombin is used in liquid form, it can easily diffuse from the cavity through the neck of the FAP toward the lumen of the artery or leave the cavity through an arteriovenous fistula. It is also possible that if the thrombin is injected in a too diluted concentration, it does not remain in the cavity of the FAP long enough to form a clot.

Furthermore, it has been described that patients receiving thrombin are at risk for developing anti-factor V antibodies, which may expose them to an immunologic cross-reaction to human factor V (26,27).

One of the other treatments that have been described for closure of FAP is the placement of a covered stent in the femoral artery. This appears not to be an ideal solution for FAPs that are located near the femoral bifurcation or the femoral artery itself. This precludes subsequent access of the femoral artery by the Judkins technique, which is not a desired situation in patients with coronary artery disease who may need percutaneous interventions in the future. Besides that, in 12% to 17% of patients, stent occlusion occurs within one year (28,29).

Collagen injection. We started to use collagen for the treatment of FAP in 1993. The initial results proved to be encouraging because the treatment was safe, efficacious and without complications. Eventually, this method was developed in our department as an alternative choice for either primary treatment of this iatrogenic pathology or treatment in the majority of cases where UGCR was unsuccessful.

Only in 1 of 110 (0.9%) patients, in whom a collagen closure attempt was not undertaken, this method appeared to be not feasible due to an unfavorable anatomy of the FAP. This results in an overall feasibility of 99.1%. In contrast to the aforementioned materials that have been used for percutaneous treatment of FAP, none of the 109 patients treated with collagen showed a local or systemic adverse reaction. Obliteration of the FAP cavity was achieved in 107 of 109 patients with a single collagen injection; in 1 patient an additional injection was required; this results in an initial success rate of 97.3% and a final success rate of 98.2%. These results rank collagen injection among the most successful minimally invasive percutaneous FAP closure techniques.

Injection of collagen is easily accepted by the patients, and during the procedure there was no need for systemic analgesic medication. Complete obliteration was usually achieved within some 10 s, which is comparable to thrombin closure. Whether or not the patient is receiving anticoagulant therapy does not appear to impair the results.

One therapy failure was noted. In this case, the failure was caused by the excessive amount of collagen that was to be injected. Surgical exploration of the groin showed that the FAP cavity was well obliterated, but collagen that was present around the FAP caused a compression of the vessel, without migration of the collagen into the arterial lumen. No other complications were noted.

The advantages of collagen lie in its physical-chemical properties. The fact that it consists of long paste fibers allows the collagen to remain within the FAP cavity, which putatively reduces the risk of migration through the neck of the FAP or through a fistula.

Due to its procedural simplicity, ultrasound-guided injection of thrombin remains an appealing treatment. We have performed the injection of collagen under fluoroscopic guiding because this made better angiographic visualization possible, but as with thrombin injection, ultrasound-guided injection of collagen is certainly feasible. The first FAP closures in our hospital were realized with the aid of a collagen plug, which was initially developed for closure of arterial puncture sites. However, insertion of collagen plugs in FAPs requires the use of large introducer sheaths (11F). Subsequently, the development of a paste-like application form of collagen permitted us to use smaller introducer sheaths (9F). At present, our research efforts are directed at developing a sponge-like application form of collagen. Then, small quantities of sponge-like collagen would suffice to obliterate the FAP cavity, the percutaneous injection of which could be monitored by ultrasound.

During 24-h follow-up, clinical inspection of the groin and lower extremities and ultrasound imaging did not reveal any recurrences or complications.

Our encouraging preliminary results need further verification and confirmation by a prospective trial comparing collagen closure with other forms of minimally invasive percutaneous closure of FAP. This will help to establish success rates, clinical efficacy and cost-effectiveness of the respective procedures.

Limitations of collagen injection. Utilizing puncture of the contralateral femoral artery to establish vascular access as was done in this study appears to make the procedure more complex. The reason for this approach was to achieve optimal sterility. In fact, we thought it initially to be difficult to guarantee procedural sterility if collagen injection is performed under ultrasound guidance. In the latter case, the sterile work space is narrow because of the presence of an ultrasound transducer and gel. Another limitation may be because this study was performed in a single center.

Conclusions. In view of our experience with direct injection of collagen, we are convinced that this technique is safe and efficacious, and these results suggest that this method may be used not only after failure of traditional closure techniques, but also as primary treatment of FAP. Collagen injection is a fast, expeditious method permitting early mobilization and discharge.

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REFERENCES

1. Bourassa MG, Noble J. Complication rate of coronary arteriography. Circulation 1973;53:106–14.
2. Kresowik TF, Khoury MD, Miller BV, et al. A prospective study of the incidence and natural history of femoral vascular complications after percutaneous transluminal coronary angioplasty. J Vasc Surg 1991;3:328–36.
3. Wyman RM, Safian RD, Portway V, et al. Current complications of diagnostic and therapeutic cardiac catheterization. J Am Coll Cardiol 1988;12:1400–6.
4. Altin RS, Flicker S, Naidech HJ. Pseudoaneurysm and arteriovenous fistula after femoral artery catheterization: association with low femoral punctures. Am J Radiol 1989;152:629–31.
5. Babu SC, Piccoreli GO, Shah PM, Claus RH. Incidence and results of arterial complications among 16,530 patients undergoing cardiac catheterization. J Vasc Surg 1989;10:113–6.
6. Messina LM, Brothers TE, Wakefield TW, et al. Clinical characteristics and surgical management of vascular complications in patients undergoing cardiac catheterization: interventional versus diagnostic procedures. J Vasc Surg 1991;13:593–600.
7. Fellmeth BD, Roberts AC. Postangiographic artery injuries: nonsurgical repair with US-guided compression. Radiology 1991;178:671–5.
8. Fellmeth BD, Baron SB. Repair of postcatheterization femoral pseudoaneurysm by color flow ultrasound guided compression. Am Heart J 1992;2:547–51.
9. Agrawal SK, Pinheiro L, Roubin GS, et al. Nonsurgical closure of femoral pseudoaneurysms complicating cardiac catheterization and percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1992;20:610–5.
10. Coley BD, Roberts AC, Fellmeth BD, et al. Postangiographic femoral artery pseudoaneurysms: further experience with US-guided compression repair. Radiology 1995;194:307–11.
11. Ernst JMPG, Tjonjoegin RM, Schrader R, et al. Immediate sealing of arterial puncture sites after cardiac catheterization and coronary angioplasty using a biodegradable collagen plug: result of an international registry. J Am Coll Cardiol 1993;21:851–5.
12. Hood DB, Mattos MA, Douglas MG, et al. Determinants of success of color-flow duplex-guided compression repair of femoral pseudoaneurysms. Surgery 1996;120:585–90.
13. Cox GS, Young JR, Gray BR, Grubb MW, Hertzer NR. Ultrasound-guided compression repair of postcatheterization pseudoaneurysms: results of treatment in one hundred cases. J Vasc Surg 1994;19:683–6.
14. Hertz SM, Brener BJ. Ultrasound-guided pseudoaneurysm compression: efficacy after coronary stenting and angioplasty. J Vasc Surg 1997;26:913–8.
15. Agarwal R, Agarwal SK, Roubin GS, et al. Clinically guided closure of femoral arterial pseudoaneurysms complicating cardiac catheterization and coronary angioplasty. Cathet Cardiovasc Diagn 1993;30:96–100.
16. Hajarizadech H, LaRosa CR, Cardulla P, Rohrer MJ, Culter BS. Ultrasound-guided compression of iatrogenic femoral pseudoaneurysm failure, recurrence, and long-term results. J Vasc Surg 1995;22:425–33.
17. Cope C, Zeit R. Coagulation of aneurysms by direct percutaneous thrombin injection. Am J Roentgenol 1986;147:383–7.
18. Walker TG, Geller SC, Brewster DC. Transcatheter occlusion of a profunda femoral artery pseudoaneurysm using thrombin. Am J Roentgenol 1987;149:185–6.
19. Liau SS, Ho MF, Lee YT. Treatment of iatrogenic femoral artery pseudoaneurysm with percutaneous thrombin injection. J Vasc Surg 1997;26:18–23.
20. Kang SS, Labbropoulos N, Mansour MA, Baker WH. Percutaneous ultrasound guided thrombin injection: a new method for treating postcatheterization femoral pseudoaneurysms. J Vasc Surg 1998;27:1032–8.
21. Kang SS, Labropoulos N, Mansour A, et al. Expanded indications for ultrasound-guided thrombin injection of pseudoaneurysms. J Vasc Surg 2000;31:289–98.

22. Paulison EK, Sheafor DH, Liewer MA, et al. Treatment of iatrogenic femoral arterial pseudoaneuysms: comparison of US-guided thrombin injection with compression repair. Radiology 2000;215:403–8.
23. Taylor BS, Rhee RY, Muluk S, et al. Thrombin injection versus compression of femoral artery pseudoaneurysms. J Vasc Surg 1999;30: 1052–9.
24. Lennox A, Griffin M, Nicoliades A, Mansfield A. Regarding "percutaneous ultrasound guided thrombin injection: a new method for treating postcatheterization femoral pseudoaneurysms" [letter]. J Vasc Surg 1998;28:1120–1.
25. Kang SS. Regarding "percutaneous ultrasound guided thrombin injection: a new method for treating postcatheterization femoral pseudoaneurysms" [letter reply]. J Vasc Surg 1998;28:1121.
26. Spotnitz WD. Fibrin sealant in the United States: clinical use at the University of Virginia. Thromb Haemost 1995;74:482–5.
27. Jackson MR, MacPhee MJ, Drohan WN, Alving BM. Fibrin sealant: current and potential clinical applications. Blood Coagul Fibrinol 1996;7:737–46.
28. Waigand J, Uhlich F, Gross CM, Talhammer C, Dietz R. Percutaneous treatment of pseudoaneurysm and arteriovenous fistulas after invasive vascular procedures. Cathet Cardiovasc Intervent 1999;47: 154–64.
29. Thalammer C, Kirchherr AS, Uhlich F, Waigand J, Gross CM. Postcatheterization pseudoaneurysms and arteriovenous fistulas: repair with percutaneous implantation of endovascular covered stents. Radiology 2000;214:127–31.