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Catheter-directed Endovascular Application of Thrombin: Report of 3 Cases and Review of the Literature

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Abstract

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Purpose—To report 3 new cases of catheter-directed endovascular application of thrombin and explore trends by analysis of published case series.

Materials and Methods—Institutional Review Board approved this retrospective study. All cases of non-tumoral arterial embolization performed from January 2003 to January 2015 at our institution were retrospectively reviewed. Thrombin was used in 7 of 589 cases. In 3 cases intra arterial thrombin was injected via catheter to treat active hemorrhage. Four cases were excluded due to percutaneous injection into visceral pseudoaneurysms (n=3) and making ex vivo autologous clot to be injected via catheter (n=1). Fisher's exact and the Wilcoxon rank sum tests were used to assess for association with acute nontarget thrombosis.

Results—Catheter-directed thrombin was used in 3/589 (0.5%) cases at our institution. All three cases were technically successful with no further bleeding (100%). Nontarget thrombosis of proximal branches occurred in 2 patients (67%) with no significant clinical consequences. Including our 3 cases, a total of 28 cases were reviewed. Of the variables examined - location (p=0.99), size (p=0.66) and etiology of vascular lesion (p=0.92), pseudoaneurysm neck anatomy (p=0.14), thrombin units (p=0.47), volume (p=0.76) or technique of use of small doses (p=0.99), use of other embolic material (p=0.67) and use of adjunct techniques (p=0.99) - none were found to be significantly associated with acute nontarget thrombosis. Technical success was 96% with no reports of reperfusion after treatment.

Conclusions—Catheter-directed endovascular thrombin can be an additional tool to treat pseudoaneurysms not amenable to conventional embolization. Further studies are required to optimize technique and outcomes.

Introduction

Thrombin acts at the last step of coagulation cascade by converting fibrinogen into fibrin, which eventually forms clot. Thrombin also activates platelets and causes vasoconstriction. In the early 1900s a fibrin emulsion was used on incision sites to promote healing. A purified version of human thrombin was extracted in the 1930s and in World War II thrombin together with fibrin was used as a treatment of burn injuries [1]. The application of human derived thrombin products posed a risk of viral hepatitis transmission and in fact, this affected many treated during the war [2]. Bovine derived thrombin ultimately replaced human derivatives to eliminate this risk. However the bovine formulation presented a challenge of its own: the induction of autoantibody coagulopathies. This earned bovine derived thrombin an FDA black box warning in 1996 [3]. A recombinant variant has since reduced this problem and today thrombin is most often used as a topical hemostatic agent.

Topical application is the only FDA approved application of thrombin. Topical thrombin is available as a reconstituted powder or solution that is directly applied to an open wound. It can be used alone or in combination with a fibrin-based product or a hemostatic sponge [4]. Currently there are three types of topical thrombin available (Table 1) [5–7]; human plasma derived (h-thrombin), bovine plasma derived (b-thrombin) and recombinant (r-thrombin). An overall 88% hemostasis rate within 10 minutes of application is shown amongst all three topical thrombin formulations [8]. B-thrombin has the highest rate of immunogenic reactions; however both h-thrombin and r-thrombin have been showed to induce allergic

reactions with repeated use. Although all three forms of topical thrombin carry a specific warning of “do not inject” due to concern for intravascular thrombus propagation, they are used off-label for percutaneous injections to cause thrombosis mainly of superficial angiography access site pseudoaneurysms (PSA). Cope and Zeit first described this approach in 1986, in a case series of 3 successfully treated pseudoaneurysms [9].

Percutaneous ultrasound guided injection of thrombin into superficial PSA has almost replaced surgical repair. It has a success rate approaching 95% [10]. Thrombin injection has also been used to treat deep pseudoaneurysms usually when endovascular approach is not possible [11] or as a fist-line treatment [12].

Thrombin has also been used to make ex vivo autologous clot to use as an embolic agent during transcatheter embolization [13]. Catheter delivered endovascular use of thrombin, however, is rarely reported. The purpose of this study is to report 3 additional cases to add to the small number of cases existing in the literature, to review the literature that is currently available and to provide the reader with a potentially useful clinical tool for the management of a difficult clinical entity.

Case series

Case 1

A 72-year-old male with history of left partial nephrectomy for renal cell carcinoma presented with recurrent hematuria 2 weeks after coil embolization of a large left renal PSA. Selective left renal arteriogram via a 5 French Cobra catheter showed prompt opacification of the PSA. One small branch supplied the PSA. This vessel had been packed with multiple coils from a prior embolization and could not be cannulated beyond the first set of coils. Through the microcatheter 1500 units in 1.5 mL volume of bovine thrombin was injected through a microcatheter positioned proximal to the coils in the target vessel. Following thrombin injection, thrombosis in the target vessel resulted in no further filling of the PSA. The proximal renal artery branch was also thrombosed. Blood flow was preserved to the other division of the left renal artery (Figure 1). The patient had no further bleeding episodes. Renal ultrasound at 2 days showed no flow in PSA and at 7 months the PSA had resolved with no atrophy. The creatinine level remained within normal range. This patient was lost to follow-up 9 years after embolization.

Case 2

A 74 year old male with prostate and rectal cancer and history of abdominal perineal resection and pelvic radiation treatment had several episodes of intermittent severe arterial hemorrhage from an open perineal wound over three years. During that time he underwent coil embolization of branches of both internal iliac arteries twice. Subsequently, he presented with massive hemorrhage from the perineal wound resulting in cardiopulmonary arrest that responded to resuscitation. Emergent angiography showed active extravasation from a 5.5 cm right internal iliac artery PSA into the open perineal wound. Several coils were deployed at the right internal iliac artery but they were forcefully expelled into the PSA with no effect on blood flow. A 10 mm balloon occlusion catheter (Edwards Lifesciences,

Irvine, CA, USA) was advanced over a wire into the right internal iliac artery origin and contrast was injected to assure lack of reflux into the common iliac artery. With the balloon inflated to occlude flow, 3000 units (3 mL) of bovine thrombin was administered through the end hole of balloon catheter in three 1 mL doses with contrast injection performed after each dose of 1000 units. After the third injection there was no flow in the PSA. The balloon was deflated and the balloon occlusion catheter was exchanged over a wire for 5 French directional catheter. A microcatheter was advanced into the right internal iliac artery and the artery proximal to the PSA was embolized with coils. Completion angiography showed no flow into the PSA (Figure 2) and the patient had no further episodes of hemorrhage. Contrast enhanced CT scan of pelvis five days after embolization showed a large right pelvic side wall PSA containing coils and high density material representing “trapped contrast” within the clot. Gas bubbles within the clot were presumed to be due to communication with the perineal wound. Trapped contrast made definitive assessment of flow within the PSA difficult. CT angiography performed two weeks after embolization showed resolution of trapped contrast with persistent lack of flow in the PSA (Figure 3). Two months after embolization the patient underwent small bowel bypass, ligation of the right common iliac artery and a left to right femoral-femoral artery bypass. He expired six years later from progression of disease.

Case 3

An 82 year old female with history of uterine and ovarian cancer was incidentally found to have a 1.1 cm segment 8 hepatic artery PSA which had been treated with coil embolization one year earlier. On surveillance CT imaging, persistent flow was identified in the PSA despite the presence of coils. Deployment of additional coils failed to achieve stasis in the PSA. Through a microcatheter, 1500 units (1.5 mL) of recombinant thrombin (RecoThrom, ZymoGenetics, Seattle, WA, USA) was administered into the PSA until there was complete cessation of flow in the feeding artery. The inflow artery was then embolized again with a coil. Completion angiography showed no residual filling of the PSA and also thrombosis of a proximal side branch of segment 8 hepatic artery. Contrast enhanced CT imaging 6 weeks and 6 months after embolization showed no flow in the PSA. Patient expired two and half years later due to progression of disease.

Discussion

Historically, surgery has been and continues to be one of the main treatment options for aneurysms. Higher morbidity and mortality of surgical treatment has pushed investigators to seek less invasive options. Initial attempts at endovascular treatment of aneurysms began in late 18th century with insertion of needles into aneurysms to induce thrombosis. Injection of medications including potassium iodide, vinegar, alcohol, sodium chloride among others were attempted next. Electrothrombosis was tried next when induction of thrombosis in the aneurysm was caused by application of electricity through needles. The first report of application of metallic wire into a thoracic aneurysm to induce thrombosis was published in 1864. In the following years wire insertion found widespread use and some of the complications such as hemorrhage from subtotal packing, sepsis and distal embolization of wire became more evident. A combination of surgical exploration with endovascular

treatment was the routine approach until late 1970s when investigators were able to access aneurysms solely by endovascular approach. Detachable balloons and pushable coils were attempted next. Subsequently application of pushable coils found widespread use due to its superior performance. Liquid embolics such as isobutyl 2-cyanoacrylate followed in treatment of hemorrhage and aneurysms. In early 1980s detachable coils and stents found their first clinical application [14,15]. Today, coils, liquid embolics and stent grafts are the mainline endovascular treatment options for hemorrhage and aneurysms. Sporadic case reports on endovascular application of thrombin for this indication exist with no strong conclusions.

For the literature review, a Google Scholar search for specific terms “thrombin”, “embolization”, “endovascular”, “arterial” and “transcatheter” was done and all cases of this specific application of thrombin were analyzed. The small sample sizes combined with significant heterogeneity among the studies the published cases precluded any meaningful meta-analysis of data. All cases of catheter-directed endovascular application of thrombin are summarized in Table 2 [16–33].

We found 18 manuscripts describing endovascular injection of thrombin in 22 patients with a total of 25 vascular lesions. Badran et al. reported a patient with two separate thoracic aortic pseudoaneurysms treated 3 months apart [24]. Lagana et al. treated three hepatic artery aneurysms in a single patient in one session [26]. With the inclusion of our 3 cases, we analyzed a total of 28 vascular lesions treated in 25 patients over the course of 29 years since Walker et al.’s first report in 1987 [16].

Statistical analysis

Fisher’s exact and the Wilcoxon rank sum tests were used to assess for association with acute nontarget thrombosis. None of the variables examined - location ($p=0.99$), size ($p=0.66$) and etiology of vascular lesion ($p=0.92$), PSA neck anatomy ($p=0.14$), thrombin units ($p=0.47$) or volume ($p=0.76$) or technique of use of small doses followed by contrast injection ($p=0.99$), use of other embolic material ($p=0.67$) and use of adjunct techniques ($p=0.99$) — were found to be significantly associated with acute nontarget thrombosis (Table 3).

Percentage of use

The overall percentage of use of endovascular thrombin is not known. At our institution from January 2003 to January 2015 intraarterial thrombin was used in this fashion in 3 out of a total of 589 non-tumor embolizations (0.5%).

Planning

In most interventions (19/28, 68%) endovascular thrombin was selected for use at the discretion of angiographer at the time of angiography. In 9 interventions (32%) endovascular thrombin use was planned ahead of angiography.

Indications

The pre-planned utilization of thrombin (32%) was usually to treat PSA in the setting of active infection [32], active infection and large size of PSA [20], or large PSA precluding coils or glue, due to lack of safe landing zones for stent grafting [22, 25, 28, 33] or endoleak [19, 23].

All three of our cases were performed after prior embolizations failed, and in two when repeat conventional techniques were unsuccessful. Catheter directed endovascular thrombin was used in our 3 cases at the discretion of angiographer at the time of repeat angiography. Application of embolic agents such as glue or Onyx in our first and third cases were possible options. Our second case could be treated with a stent graft however the possibility of ongoing infection from chronic communication between the pseudoaneurysm and the skin precluded its use. Landy et al. [18] used thrombin to treat a right hepatic artery PSA because of ongoing need for anticoagulation for mitral valve replacement. Busch et al. [19] and Wijeyaratne et al. [21] used thrombin to treat an abdominal aortic endoleak and a left third lumbar artery PSA respectively because of communication of index vascular lesions with multiple feeder arteries that could not each be selectively embolized.

Based on our experience and literature review, thrombin appears to be a reasonable intraarterial agent in the following scenarios: 1- Large pseudoaneurysms with narrow neck that cannot be isolated with stent graft and are too large for treatment by coils or glue, 2- infected pseudoaneurysms or when ongoing sepsis precludes embolization with foreign material such as stents and coils and 3- in patients who are fully anticoagulated or have coagulation issues as intact coagulation system is required to cause thrombosis around coils[34].

Target vascular lesions

The vascular lesions treated in order of frequency are visceral arteries (n=14; 5 hepatic, 3 renal, 3 superior mesenteric, 1 splenic, 1 left gastric, 1gastroduodenal), aorta (n=7; 4 abdominal, 3 thoracic), pelvic and musculoskeletal arteries (n=5; internal iliac, lumbar, inferior gluteal, profunda femoris and superficial femoral) followed by one case of pulmonary artery and one case of superior vena cava (SVC). The most common body parts location is abdomen and pelvis (n=21) followed by thorax (n=5) and lower extremity (n=2). The vascular lesions are pseudoaneurysm/endoleak (n=22) and aneurysm (n=6). The majority of vascular lesions are arterial (n=26) with one reported case of pulmonary artery [29] and one case of SVC [33]. There is no specified definition for the anatomy of the neck of PSA in body angiography compared to the ones in neuro angiography literature. Unless “narrow” or “wide” anatomy of PSA neck was specified by the authors, we used the general rule of dome/neck ratio of 1.5 or more to define “narrow” neck. The most common anatomy of the “neck” of the treated PSAs is “narrow” (n = 17) followed by “wide” (n= 4). In 5 cases the anatomy of the neck of treated lesion was not reported. In 2 cases thrombin was injected in an arterial branch[19, case 1 in this report]. The etiology of pseudoaneurysms and endoleaks are post surgical (n=13), mycotic (n=3), trauma (n=2), gunshot wound (n=2) and unknown (n=2).

The size of vascular lesions ranged from 1 cm to 10 cm (mean 4.0 cm, median 3.4 cm). In two reports the size of vascular lesions (abdominal aortic aneurysm endoleak and abdominal aortic PSA) were not reported and could not be measured based on provided figures [19, 24]. Both of these lesions appear to be larger than 3 cm. Tucker et al. reported a case of abdominal aortic PSA where the size of PSA, dose and volume of thrombin were not reported [24].

Type of thrombin

All but two authors used one of three derivatives of bovine, human or recombinant thrombin. Bovine thrombin was used for our first 2 cases before our institution switched to recombinant thrombin in November 2010 which was used for our third case. Lagana et al. [26] used a premixed solution of thrombin and collagen containing 500 units thrombin/mL (DStat, Vascular Solutions, Minneapolis, MN, USA) in treating 4 lesions and Schellhammer et al. [29] used a premixed solution of thrombin and fibrin containing 500 units thrombin/mL (Tissucol Duo, Baxter International Inc., Deerfield, IL, USA) in treating 4 lesions.

Quantity of thrombin

In 27 cases where the amount of thrombin used is reported, it ranged from 100 to 10,000 units (mean 1479 units, median 1000 units). The volume of thrombin used in 21 reported cases ranged from 0.5 mL to 10 mL (mean 2.3 mL, median 1.4 mL). In seven cases the volume of thrombin used was not reported [19, 22, 24, 25, 30–32]. Lack of an optimized dosing for thrombin is evident by the significant range difference among the size of vascular lesions (10 times, 1–10 cm), volume of thrombin (20 times, 0.5–10 mL) and units of thrombin used (100 times, 100–10,000 units). For example Carmo et al. [28] treated a 9.5 cm SMA PSA with 10,000 units of thrombin in 10 mL volume while Jargiello et al. [33] treated a comparable 10 cm SVC PSA with only 800 units of thrombin in 10 mL volume.

Embolic material used in each case

In 18 cases (64%) thrombin was the only embolic agent used while in 10 cases (36%) other embolic agents such as coils (n=8), gelfoam (n=1) and isobutyl 2-cyanoacrylate glue (n=1) were used as well. Criado et al. used two aortic stent grafts and a celiac origin stent at the conclusion of thrombin embolization of an abdominal aortic PSA [23].

Techniques

There is no reported technique for rendering thrombin radioopaque at the time of injection. Coaxial technique (a microcatheter through a guiding catheter) was utilized in all 28 interventions reported; and at least one adjunct technique to minimize non-target embolization was used in 20 interventions. Busch et al. [19] used a mixture of thrombin, lipiodol and Gelfoam in treating an abdominal aortic endoleak which caused “trapped contrast” on angiographic and follow-up CT images. Injecting thrombin in smaller individual doses each followed by contrast injection is a commonly reported technique. In treating our case 2, three separate doses of 1000 units of thrombin in 1 mL volume were injected each followed by small amount of contrast injection to allow for evaluation of flow.

Injecting thrombin in 2–3 small doses is reported in treatment of 9 lesions [21, 22, 26, 28, case 2 in this report]. Landy et al. used a 7 French guiding catheter to tamponade the narrow neck of a hepatic artery PSA [18] while injecting thrombin. Geckeis et al. used the same technique with an 8 French guiding catheter in treating an abdominal aortic PSA [25]. Occlusion balloons were used in 2 different methods. Lin et al. [20] injected thrombin through a 6 French Fogarty thrombectomy catheter that was inflated to seal the neck of an ascending aortic PSA. Criado et al. injected thrombin through an occlusion balloon that was inflated across the neck of an abdominal aortic PSA [23]. The same technique was used in treating our case 2. The second method is when an occlusion balloon is used to seal the origin of a vascular lesion while a separate catheter is used for thrombin injection. This method requires 2 vascular accesses and was used by Damodharan et al. [32] to treat an infected superficial femoral artery PSA and by Jargiello et al. [33] to treat a saccular aneurysm of SVC. Juszkat et al. deployed a distal embolic protective device to treat a superior mesenteric artery (SMA) PSA prior to injecting thrombin [31]. Badran et al. [22] measured the luminal volume of microcatheter and flushed with the same volume of saline (0.7 mL) after each thrombin dose. Schellhammer et al. [29] positioned the microcatheter deep into the dome of PSA for thrombin injection in all 4 cases and measured the volume of pseudoaneurysms by contrast injection before injecting thrombin using the same volume.

Trapped contrast

Trapped contrast in the fresh thrombus is common when thrombin is used. It is usually encountered during the end of the embolization procedure if contrast was injected between small doses of thrombin or in close follow-up CT angiography examinations [19, 22, 25, case 2 in this report]. Recognizing this phenomenon is crucial in proper interpretation of angiographic and cross sectional imaging studies.

Complications

Considering our 3 cases, acute nontarget thrombosis of proximal branches occurred in 2 cases (67%) with no clinically significant manifestation. In reviewing all 28 cases, no complications occurred in 20 cases (71%). Acute nontarget thrombosis occurred in 8 cases (29%). This may have been due to reflux of thrombin or propagation of thrombus from the site of injection. Two cases (7.1%) resulted in class D major complication according to Society of Interventional Radiology (SIR) classification [35]. Busch et al. [19] treated an abdominal aortic aneurysm endoleak via SMA and marginal artery. Sigmoidal artery branches were thrombosed on final angiograms resulting in necrosis of sigmoid colon and acute abdomen requiring urgent left hemicolectomy and transverse colostomy. Lin et al. [20] treated a mycotic ascending aortic PSA by injecting thrombin through a Fogarty thrombectomy balloon which was inflated across the wide neck of PSA. The patient developed transient ischemic attack from propagation of thrombus into the right and left carotid arteries immediately after removal of the Fogarty catheter. The patient was immediately started on intravenous antiplatelet agent abciximab in the angiography suite which resulted in resolution of intracranial thrombus and neurologic deficits within 30 minutes. The other 6 complications (21%) were minor A or B by SIR classification, including thrombosis of side branches [21, 29, cases 1 and 3 in this report], partial splenic infarction in a patient who had two splenic artery pseudoaneurysms treated [26] and non-

occlusive thrombus extending into SVC after treatment of a saccular aneurysm of SVC which was treated with 24 hours of intravenous heparin [33].

No allergic reactions were reported with the endovascular application of thrombin in contrast to patients who received repeated topical applications. Badran et al. treated two thoracic aortic pseudoaneurysms in a patient three months apart with no allergic reactions [22].

Complications and anatomy of target vascular lesions

Acute nontarget thrombosis occurred in 5 out of 17 lesions with narrow neck anatomy (29%), one out of 4 lesions with wide neck anatomy (25%) and 2 out of 2 treated branches (100%). The 2 major complications occurred in a wide neck PSA (n=1) and an arterial branch (n=1). All 5 complications reported with narrow neck pseudoaneurysms were minor.

Complications and technique

Injection of thrombin in 2–3 small doses each followed by a small amount of contrast injection for evaluation of flow is reported for treatment of 9 lesions [21, 22, 26, 28, case 2 of current report]. Only one minor complication of nonocclusive thrombus in a left third lumbar artery occurred with this technique [21].

Treatment of complications

Acute nontarget vessel thrombosis is caused by reflux of thrombin or propagation of fresh thrombus that is both fresh and platelet-rich. Busch et al. [19] chose clinical observation after documenting thrombosis of sigmoidal arteries at the end of treatment of an abdominal aortic endoleak. This resulted in an acute abdomen requiring urgent left hemicolectomy and transverse colostomy. However, Lin et al. [20] treated transient ischemic attack from propagation of thrombus into the right and left carotid arteries by immediately starting intravenous antiplatelet agent abciximab in the angiography suite. This resulted in resolution of intracranial thrombus and neurologic deficits within 30 minutes. Although tPA has not been reported to treat thrombotic complications of intravascular thrombin, but Sadiq and Ibrahim used intra arterial tPA infusion to successfully treat an extensive acute lower extremity arterial thromboembolism complicating percutaneous thrombin injection into a left common femoral PSA [36].

Follow up and outcomes

27 cases of catheter directed thrombin injection reported imaging and clinical follow up ranging from 7 days to 9 years (mean: 10.4 months, median: 5 months). Walker et al. [16] treated a traumatic profunda femoris PSA with thrombin. The patient underwent surgical exploration the next day and surgical ligation of PSA neck was deemed unnecessary. Wallace et al. reported no filling of a SMA branch PSA with repeat angiography 24 days after treatment with stent-graft and thrombin injection [27]. Reperfusion of treated vascular lesions is not reported. All of our 3 reported cases were technically successful (100%). In the total 28 cases, technical success was achieved in 27 (96%). Schellhammer et al. reported one case of partial technical success (4%) with persisted flow in the neck of a gastroduodenal artery PSA on final angiographic images which remained stable on CT angiography

examination 7 days after treatment [29]. In much larger case series of superficial pseudoaneurysms treated with percutaneous thrombin it has been shown that reperfusion of PSA after retraction of thrombus is clinically rare [37].

Conclusion

While not FDA approved for catheter-directed endovascular use, thrombin can be considered when conventional embolic agents fail, in large pseudoaneurysms with a narrow neck where stent grafting is not possible or in cases where infection makes deployment of foreign bodies (coils, stents) undesirable. It can also be considered in patients who need continuous anticoagulation which may render conventional embolic agents less successful. Thrombin is readily available, inexpensive and easy to use. Unlike glue it does not require dextrose for flushing and does not cause the catheter to adhere to the vessel. Thrombin is capable of inducing large volume of thrombus with a small dose and leaves no foreign body. Its endovascular application has a 96% reported technical success rate with no reported cases of target lesion reperfusion. The optimal dose and volume are not lesion-dependent, and in some cases lower doses may be equally efficacious as higher doses. There is no generally accepted protocol for making thrombin radioopaque. Using small doses in small volumes (for example 200 units of thrombin in 0.2 mL saline) each followed by small amounts of slow contrast injection appears to be a practical technique to avoid non-target propagation of clot. Clinically significant acute nontarget thromboembolic complications have been successfully treated with systemic intravenous abciximab or intra-arterial TPA infusion.

This study is limited by the small number of patients and is prone to publication bias due to diversity of styles of reported cases. Catheter directed endovascular application of thrombin may not be superior to the available embolic agents for all indications. However, it can be an additional useful tool in treating acute hemorrhage from lesions not amenable to conventional embolization. Further studies are required to investigate optimal volume, dose and technique of administration of endovascular thrombin.

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Highlights

- Thrombin is readily available, inexpensive and easy to use.
- It does not need dextrose for flushing and does not pose the catheter to adhere to the vessel.
- A small amount can create a large amount of thrombus.
- Infected pseudoaneurysms, lesions too large for treatment by glue or coils and when stent grafting is not anatomically possible are utilization scenarios.

Figure 1.

a) Angiography 2 weeks after prior embolization shows filling of a 3.4 cm left renal artery pseudoaneurysm (asterisk) with jet phenomenon through a previously embolized branch (dotted arrow). Two other previously coil embolized branches are depicted with solid arrows. b) Selective injection of the culprit vessel just proximal to the indwelling coils. The jet phenomenon is depicted with solid arrow. c) Injection of the left renal artery after embolization with 1500 units of thrombin shows cessation of flow in the pseudoaneurysm and the culprit branch as well as thrombosis of the proximal renal artery branch (solid arrow). The other main renal artery branch remained patent.

Figure 2.

a) Large right pelvic pseudoaneurysm (PSA, asterisk) arising a few centimeters distal to the origin of the internal iliac artery. Some of the coils (arrow) from prior embolizations are visible. b) Angiography via an occlusion balloon (solid arrow) into the bilobed PSA (asterisks) which communicated with the perineal wound (not shown). Coils deployed initially at this intervention (dotted arrow) were forcefully expelled into the PSA with no effect on flow. c) Final angiogram after thrombin injection and additional coils show no flow into the PSA.

Figure 3.

CT scan of pelvis performed five days post embolization (a) showed a large right pelvic side wall pseudoaneurysm containing coils, high density material representing trapped contrast within the clot (asterisk) and gas bubbles from communication with the perineal wound. Trapped contrast made definitive assessment of flow within the pseudoaneurysm difficult. CT angiography performed two weeks after embolization (b) showed resolution of trapped contrast with no flow in the pseudoaneurysm (asterisk). Coils and gas bubbles are again seen.

Table 1

General information for topical thrombin formulations [5–7].

Trade Name	Thrombin-JMI	Evithrom	Recothrom
Derivative	Bovine	Human	Human Recombinant
Formulations	Powder for reconstitution: 5,000 or 20,000 IU Pump or syringe spray kit: 20,000 IU Epistaxis kit: 5000 IU	Frozen solution: 2 ml, 5 ml, or 20 ml vials containing 800–1200 IU/ml	Powder for reconstitution: 5,000 or 20,000 IU Spray applicator: 20,000 IU
Handling	Reconstituted with sterile saline. Store at 2–25°C. Store at room temperature for up to 4 hours after reconstitution	Thaw 20 ml vials at 2–8°C for 1 day or at 20–25°C for 1 hour. Thaw 2 ml and 5 ml vials at 37°C for < 10 min.	Reconstituted with sterile saline. Store at 2–25°C.
Dosage (topical)	1000 units/ml. Total volume depends on surface area of bleeding.	1000 units/ml. Total volume depends on surface area of bleeding.	1000 units/ml. Total volume depends on surface area of bleeding.
Off-label Dosage (Percutaneous injection)	*200–400 IU (0.2–0.4 ml)	200–400 IU (0.2–0.4 ml)	*200–400 IU (0.2–0.4 ml)
Pricing	5,000 IU: \$87 20,000 IU: \$345	2 ml (2,000 IU): \$82 5 ml (5,000 IU): \$117 20 ml 20,000 IU): \$458	5,000 IU: \$104 20,000 IU: \$420

* 1000 units/ml diluted in 1 ml syringe with normal saline

Table 2

Cases of catheter-directed endovascular application of thrombin.

Author Year [reference]	Pts	Vascular lesion (size)	Etiology	Thrombin units (volume)	Other embolic material used in the same session	Adjunct technique	Reason for thrombin injection	Complications of thrombin injection	Notes	Follow up
Walker 1987 [16]	1	R * profunda femoris artery branch PSA (7 cm)	Surgical fixation of right femoral neck fracture	1000 (1 mL)	Coil		Failed coils and gelfoam initially due to high flow and large size of PSA	None	Narrow PSA neck. Surgical ligation of PSA neck was not required	Surgical exploration the next day. Clinical for 2 months.
Routh 1990 [17]	1	L renal artery aneurysm (3 cm)		1000 (1 mL)	0.3 mL isobutyl 2-cyanoacrylate glue		Failed initial coils	None	Narrow aneurysm neck	Radionuclide renogram at 7 and 9 months.
Landy 1995 [18]	1	R hepatic artery PSA (3 cm)	Cholecystectomy	200 (1 mL)	Coils	7 F catheter used to access PSA. Coils were soaked with thrombin.	Long term anticoagulation required for mitral valve prosthesis	None	Narrow PSA neck. Full anticoagulation was resumed immediately after embolization	CT at 1 week. Clinical for 6 months.
Busch 2001 [19]	1	AAA Type II endoleak by IMA (not reported)	Endovascular repair	2000 (not reported)	Gelfoam (1 g)	Lipiodol (2 mL) was injected with thrombin and Gelfoam.	Suspicion for other patent side branches in addition to IMA contributing to the endoleak.	Acute abdomen with necrosis of sigmoid colon requiring left hemicolectomy and transverse colectomy.	IMA was accessed via SMA and marginal artery.	“Trapped contrast” on immediate angiograms. CT at 3 months.
Lin 2001 [20]	1	Ascending aortic PSA (5 cm)	Mycotic from sternal osteomyelitis and mediastinitis after coronary artery bypass grafting	2000 (2 mL)	None	Injection of thrombin was done through a 6 French Fogarty thromboaspiration catheter. The balloon inflated to seal the PSA neck.	Large size of PSA and active infection precluded treatment with coil and stent graft. Wide PSA neck.	Transient ischemic attack from propagation of thrombus into right and left carotid arteries immediately after removal of the Fogarty catheter.	Wide PSA neck. Intracranial thrombus and neurologic deficits resolved with intravenous abxiximab within 30 minutes.	Aortogram after 30 minutes. CT at 8 months.
Wijayaratne 2001 [21]	1	L 3rd lumbar artery PSA (3 cm)	Gunshot wound	300 (0.3 mL) + 300 (0.3 mL)	None	Thrombin was injected in two doses	Numerous small branches arising distal to the PSA with the potential to back fill the PSA	Non occlusive thrombus in L3 artery. This did not progress.	Narrow PSA neck.	CT at 1 week
Badran 2003 [22]	1	PSA of thoracic aorta (posterior) (6.5 cm)	Marfan syndrome. Post surgical repair.	500 (1 mL) + 250 (0.5 mL)	None	Luminal volume of catheter was measured and same volume (0.7 mL) saline was used to flush thrombin	Unfavorable anatomy for stent graft. PSA too large for coils or glue.	None	Narrow PSA neck. The two treatments were 3 months apart.	“Trapped contrast” on CT at day 4. CT at 3 months.
		PSA of thoracic aorta (anterior) (5.5 cm)		450 (not reported)	None			None		CT at 3 months.
Criado 2004 [23]	1	Abdominal aortic PSA (5 cm)	Mycotic from bacterial endocarditis (infection resolved)	4000 (4 mL)	None	Occlusion balloon across PSA neck in aorta. Thrombin injected via occlusion balloon catheter. Two aortic stent grafts and a celiac origin stent placed.	Endoleak anticipated due to complex anatomy.	None	Wide PSA neck. Curative lung cancer resection 2 weeks after thrombin injection.	CT at 6 months.
Tucker 2005 [24]	1	Abdominal aortic PSA (not reported)	Gunshot wound	Dose and volume not reported	Coil		Multiple abdominal explorations. Thrombin injection was performed on day 67 after trauma.	None		
Ceekleis 2006 [25]	1	Abdominal aortic PSA (6.2 cm)	Surgical repair of type B aortic dissection	1500 units (not reported)	None	8 F catheter used to access PSA neck.	Stent graft placement was precluded due to recent patch aortoplasty and fenestration.	None	Narrow PSA neck. Successful stent grafting of thoracic aorta to treat the entry tear of aortic dissection 4 weeks after thrombin injection.	“Trapped contrast” on immediate angiography and CT scan done next day. CT at 12 months.
Lagana 2006 [26]	2	Splenic artery aneurysm (2 cm)		500 (0.5mL) + 500 (0.5mL)	None	Each 0.5 mL thrombin was injected with contrast	Discretion of angiographer	Partial spleen infarction	Another splenic artery aneurysm treated with coils	6 months
		Hepatic artery aneurysm (1.5 cm)		500 (0.5mL) + 500 (0.5mL)	None			None		Death from cerebral aneurysm rupture 7 days later
		Hepatic artery aneurysm (1 cm)		500 (0.5mL) + 500 (0.5mL)	Coils					
		Hepatic artery aneurysm (2.5 cm)		500 (0.5mL) + 500 (0.5mL) + 500 (0.5mL)	Coils					

Author Year [reference]	Pts	Vascular lesion (size)	Etiology	Thrombin units (volume)	Other embolic material used in the same session	Adjunct technique	Reason for thrombin injection	Complications of thrombin injection	Notes	Follow up
Wallace 2007 [27]	1	SMA branch PSA (3 cm)	Whipple surgery	500 (0.5 mL)	Coil		Failed stent graft	None	Narrow PSA neck.	CT (date not reported); angiography on day 24.
Curno 2008 [28]	1	SMA branch PSA (9.5 cm)	Unknown – probably due to occluded celiac origin	5000 (5 mL) + 5000 (5 mL)	None		Surgical resection was deemed difficult due to large size. Central location precluded percutaneous treatment.	None	Narrow PSA neck.	CT at 32 months.
Schellhammer 2008 [29]	4	L gastric artery PSA (3.7 cm)	Gastric surgery	500 (1 mL)	None	Microcatheter was positioned at the dome of PSA	Unfavorable anatomy for stent graft. PSA too large for coil and glue embolization. Narrow PSA neck.	PSA ruptured during angiography. Thrombosis of a side branch.	Narrow PSA neck.	Mean follow-up with CT: 7.6+ -3.7 months (range: 1–12 months)
		GDA/PSA (6.6 cm)	Whipple surgery	700 (1.4 mL)				None	Narrow PSA neck. Neck of PSA remained patent but PSA remained thrombosed.	
		Pulmonary artery PSA (3.4 cm)	Embolectomy	1700 (3.4 mL)				None	Narrow PSA neck.	
		Renal artery PSA (1.6 cm)	Postsurgical	250 (0.5 mL)				None	Narrow PSA neck.	
Juezkat 2010 [30]	1	Inferior gluteal artery PSA (4 cm)	Trauma	400 (not reported)	None		The vessel too small for stent placement. Proximity of PSA to sciatic nerve and ongoing bleeding precluded percutaneous treatment.	None	Narrow PSA neck.	US at 1 month.
Juezkat 2011 [31]	1	SMA PSA (1.2 cm)	Trauma	100 (not reported)	None	An embolic protective device deployed distal to PSA. Microcatheter positioned at the dome of PSA.	Prior abdominal surgeries.	None	Wide PSA neck.	Clinical at 1 month.
Dumodhuran 2013 [32]	1	R SFA PSA (6 cm)	Infection from IV drug abuse and chronic overlying open skin wound	1000 (not reported)	None	Occlusion balloon deployed across the neck of the PSA.	Overlying skin infection precluded percutaneous treatment. Surgery, coil and stenting not possible due to infection.	None	Wide PSA neck.	US at 3 months.
Jargiello 2014 [33]	1	Saccular aneurysm of SVC (10 cm)	Congenital	800 (10 mL)	None	Occlusion balloon at the SVC	Presence of superficial vascular malformation precluded surgery and location of aneurysm precluded stent grafting. Large size	Nonocclusive thrombus extending into SVC.	Narrow neck of PSA. Heparin drip (1,000 U/hour) for 24 hours for SVC thrombus.	Echocardiography at 4 days. CT at 3, 6 and 12 months.
Current report	3	L Renal artery PSA (3.4 cm)	Partial nephrectomy	1000–2000 (1–2 mL)	None		Failed coil embolization 2 weeks prior. Inability to negotiate microcatheter beyond indwelling coils.	Thrombosis of the main proximal renal artery branch.	Injection from a branch. No impact on renal function.	US at 2 days and 7 months. Clinical for 9 years.
		R internal iliac artery PSA (5.5 cm)	Surgery and radiation	1000 (1 mL) + 1000 (1 mL) + 1000 (1 mL)	Coils	Occlusion balloon at the right internal iliac artery. Thrombin injected via occlusion balloon catheter.	Life-threatening hemorrhage. Failed coils initially due to high flow and large size of PSA. Possible infection.	None	Narrow neck of PSA. “Trapped contrast” on CT at day 5 made assessment of flow in the PSA difficult.	CT at 5 days and 2 weeks. Bypass surgery 2 months later.
		Segment 8 hepatic artery PSA (1.1 cm)	Unknown	1500 (1.5 mL)	Coils		Failure of coils to achieve hemostasis one year prior and also initially at the time of new angiography.	Thrombosis of a proximal side branch of segment 8 hepatic artery.	Narrow neck of PSA.	CT at 6 weeks and 6 months. Clinical for 2 and half years.

* Pts: patients; R: right, L: left, PSA: Pseudoaneurysm, F: French, CT: Computed tomography, AAA: abdominal aortic aneurysm, IMA: inferior mesenteric artery, SMA: superior mesenteric artery, GDA: Gastroduodenal artery, US: Ultrasound, SFA: Superficial femoral artery, SVC: Superior vena cava

Table 3

Association of variables with any complications (acute nontarget thrombosis).

Variable	Strata	None (N=20)	Any Complication (N=8)	pvalue
Location of vascular lesion				0.99
	Visceral	10 (71%)	4 (29%)	
	Aorta	5 (71%)	2 (29%)	
	Other	5 (71%)	2 (29%)	
Anatomy of vascular lesion				0.14
	Narrow neck	16 (76%)	5 (24%)	
	Wide neck	3 (75%)	1 (25%)	
	Branch	0 (0%)	2 (100%)	
Etiology of vascular lesion				0.92
	Surgery	10 (77%)	3 (23%)	
	Trauma	3 (75%)	1 (25%)	
	Infection	2 (67%)	1 (33%)	
	Other	5 (63%)	3 (38%)	
Thrombin administered in small doses				0.99
	No	13 (68%)	6 (32%)	
	Yes	7 (78%)	2 (22%)	
Use of other embolics				0.67
	No	12 (67%)	6 (33%)	
	Yes	8 (80%)	2 (20%)	
Use of adjunct techniques				0.99
	No	6 (75%)	2 (25%)	
	Yes	14 (70%)	6 (30%)	
Fisher's exact test was used to assess for association with any complications. Raw percentages are shown.				
Variable		None	Any Complication	pvalue
Size of vascular lesion (cm)	Median (Range)	4 (1–9.5)	3.4 (1.1–10)	0.66
	Missing	1	1	
Thrombin (Units)	Median (Range)	1000 (100–10000)	1250 (500–2000)	0.47
	Missing	1	0	
Thrombin (Volume)	Median (Range)	1.2 (0.5–10)	1.5 (0.6–10)	0.76
	Missing	6	1	
The Wilcoxon rank sum test was used to assess for association with any complications				