Clinical Imaging 42 (2017) 96–105

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: http://www.clinicalimaging.org

Catheter-directed endovascular application of thrombin: Report of 3 cases and review of the literature

Majid Maybody [a,*], David C Madoff [b], Raymond H Thornton [a], Steven A Morales [c], Chaya S Moskowitz [d], Meier Hsu [d], Lynn A Brody [a], Karen T Brown [a], Anne M Covey [a]

[a] Memorial Sloan Kettering Cancer Center, Interventional Radiology Service, H1118, 1275 York Avenue, New York, NY 10065, USA
[b] Weill Cornell Medicine, Division of Interventional Radiology, 525 East 68th Street, P-518, New York, NY 10065, USA
[c] University of Iowa Hospitals and Clinics, Department of Radiology, 200 Hawkins Drive, Iowa City, IO 52242, USA
[d] Memorial Sloan Kettering Cancer Center, Department of Epidemiology and Biostatistics, 485 Lexington Avenue, New York, NY 10017, USA

ARTICLE INFO

Article history:
Received 29 August 2016
Received in revised form 15 November 2016
Accepted 28 November 2016
Available online xxxx

Keywords:
Catheter-directed
Endovascular
Thrombin
Pseudoaneurysm
Thrombosis

ABSTRACT

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.

1. 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 min of application is shown among all three

* Corresponding author.
E-mail addresses: maybodym@mskcc.org (M. Maybody), dcm9006@med.cornell.edu (D.C. Madoff), thorntor@mskcc.org (R.H. Thornton), steven-morales@uiowa.edu (S.A. Morales), moskowc1@mskcc.org (C.S. Moskowitz), hsum1@mskcc.org (M. Hsu), brodyl@mskcc.org (L.A. Brody), brown6@mskcc.org (K.T. Brown), coveya@mskcc.org (A.M. Covey).

http://dx.doi.org/10.1016/j.clinimag.2016.11.018
0899-7071/

Table 1
General information for topical thrombin formulations [5–7].

Trade name Derivative	Thrombin-JMI Bovine	Evithrom Human	Recothrom Human recombinant
Formulations	Powder for reconstitution: 5000 or 20,000 IU	Frozen solution:2 mL, 5 mL, or 20 mL vials containing 800–1200 IU/mL	Powder for reconstitution: 5000 or 20,000 IU
	Pump or syringe spray kit: 20,000 IU Epistaxis kit: 5000 IU		Spray applicator: 20,000 IU
Handling	Reconstituted with sterile saline.	Thaw 20 mL vials at 2–8 °C for 1 day or at 20–25 °C for 1 h.	Reconstituted with sterile saline.
	Store at 2–25 °C. Store at room temperature for up to 4 h after reconstitution	Thaw 2 mL and 5 mL vials at 37 °C for <10 min.	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)	[a]200–400 IU (0.2–0.4 mL)	200–400 IU (0.2–0.4 mL)	[a]200–400 IU (0.2–0.4 mL)
Pricing	5000 IU: $87 20,000 IU: $345	2 mL (2000 IU): $82 5 mL (5000 IU): $117 20 mL (20,000 IU): $458	5000 IU: $104 20,000 IU: $420

[a] 1000 units/mL diluted in 1 mL syringe with normal saline.

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.

1.1. 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 (Fig. 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.

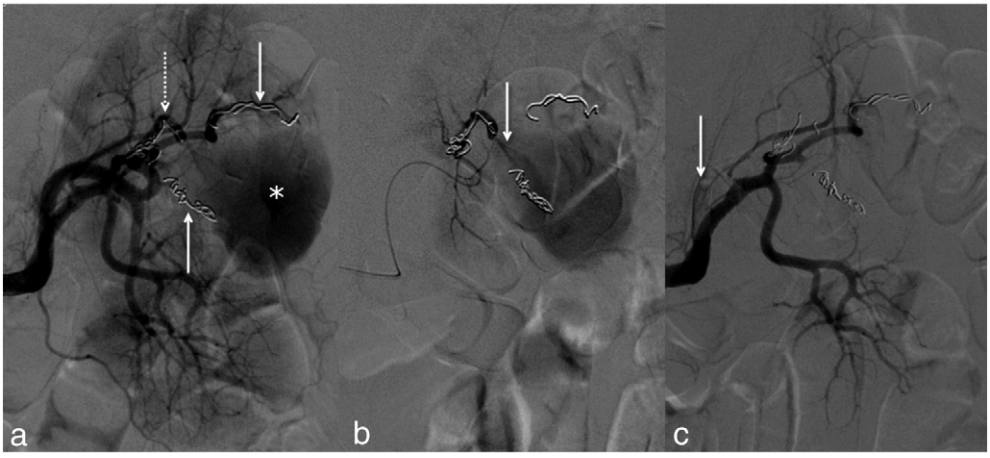

Fig. 1. a) Angiography 2 weeks after prior embolization shows filling of a 3.4 cm left renal artery pseudoaneurysm (asterisk) with jet phenomenon through a previously embolized branch (dotted arrow). Two other previously coil embolized branches are depicted with solid arrows. b) Selective injection of 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.