

Safety evaluation of percutaneous ultrasound-guided thrombin injection into pseudoaneurysm

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B – Data Collection
C – Statistical Analysis
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G – Funds Collection

Marta Pająk, Robert Hasiura, Tomasz Stępień

¹Medical University of Lodz, Department of Endocrine, General and Vascular Surgery, Lodz, Poland; prof. dr hab. n. med. Krzysztof Kuzdak

²Department of General and Vascular Surgery, Regional Specialist Hospital M. Pirogowa in Lodz, Poland; dr n. med. Jerzy Okraszewski

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ABSTRACT:

Introduction: common application of endovascular procedures is frequently connected with increasing risk of pseudoaneurysm at the site of the artery puncture. The most frequent method of treatment of aneurysms is percutaneous ultrasound-guided thrombin injection.

The aim: The aim of this research was safety evaluation of treatment of pseudoaneurysm by thrombin injection based on own experience.

Methods and materials: 70 people (57% women, 43% men, average age $67,9 \pm 10,5$) with pseudoaneurysm and under ultrasound-guided thrombin injection treatment carried out between 2007 and 2018 in the Department of General and Vascular Surgery of Pirogow Hospital in Lodz were analysed. Patients were qualified to treatment based on aneurysm and channel morphology in ultrasound examination. Before application of medicine blood supply to the limb was clinically assessed and examined using sonography. The tip of the needle was imaged into the lumen of the aneurysm.

Results: In the research group, average aneurysm diameter was 29,9 mm ($\pm 17,2$ mm) within a range from 10 mm to 96 mm. Multi-chamber aneurysm was detected in 21% of patients. Mean channel length was 12 mm ($\pm 7,7$ mm), mean width 3,5 mm ($\pm 1,4$ mm), mean thrombin injected 1,7 ml ($\pm 0,7$ mm) within range from 0,5 ml to 4 ml. The treatment was successful in 94% of cases. Complications after thrombin injection occurred in 7% of cases (1 patient suffered from shock, 1 from thrombus in the saphenous vein, 3 from thrombus moving from aneurysm neck to femoral artery). No deterioration of blood supply in a limb was detected after obliteration of aneurysm. No relevant differences in aneurysm and channel dimensions were detected between groups with and without complications ($p > 0,05$).

Conclusions: Obliteration of the pseudoaneurysm by percutaneous ultrasound-guided thrombin injection is a highly effective method. This method is considered as safe, however, it requires experience. Its application may cause complications of which some are clinically significant and may lead to health and life threatening situations. In some specific cases surgical treatment of choice should be considered.

KEYWORDS:

pseudoaneurysm, thrombin therapy, ultrasonography

INTRODUCTION

In recent years endovascular treatment has been commonly used in interventional cardiology, vascular surgery, neurology, and oncology. It contributes to a higher number of complications associated with the site of vessel puncture and introduction of vascular sheath. Subcutaneous hematoma is one of the most frequent local complications of endovascular procedures. The frequency of its occurrence is between 1–8% according to literature [1].

Pseudoaneurysm can be treated using various methods. Until application of thrombin had been the first line choice, treatment was based on a surgical arterial suture hole with evacuation of the hematoma. Moreover, it was common to use controlled USG probe pressure. Other methods include: endovascular implantation of coated stent in the damaged artery and embolization of aneurysm using coils. In case of small aneurysm – prolonged pressure dressing, targeted manual compression and observations are used. All of the aforementioned methods, including thrombin injection, may cause complications.

The aim of this research is to assess the safety of treatment of pseudoaneurysm by thrombin injection, identify the threats of this method and factors causing their occurrence.

METHODS AND MATERIALS

Seventy people with femoral artery pseudoaneurysm participated in the study; they were initially treated with thrombin injection. Treatment was carried out in the Department of General and Vascular Surgery of the Pirogow Hospital in Lodz between 2007 and 2018.

Patients with skin necrosis or skin infected above pseudoaneurysm, large hematoma with compression symptoms on vessels or nerves were not qualified for thrombin therapy. Moreover, the following cases were excluded: arterial hemorrhage, hemodynamical instability, and arteriovenous fistula. In connection with the endovascular procedure, patients received double antiplatelet therapy (acetylsalicylic acid, clopidogrel) and low molecular weight heparin.

Pseudoaneurysm was assessed and treated with linear or convex probes for ultrasound scanners like Toshiba Xario, GE Logiq C5, and Toshiba Eccocee. For each patient qualified for thrombin therapy before and after administration of the medication, limb blood supply was assessed: clinically (limb temperature, pulse) and sonographically and to diagnose the presence of venous thrombosis.

The treatment was carried out after obtaining informed consent of the patient. Skin above the aneurysm was prepared in a sterile way.

Bovine thrombin BioTrombina 400 Biomed Lublin was used to obliterate the pseudoaneurysm. It was used as a powder diluted in 2ml of a 0.9% solution of NaCl (200 units/ml), using 22G needles. During the procedure, the tip of the needle was identified in the aneurysm by ultrasonography before the actual injection. The medicine was steadily provided to the false aneurysm until reaching full thromboses. After obliteration of pseudoaneurysm, patients were immobilized for 6–12 hours after the treatment without local compression. No modification was introduced to antiplatelet therapy and heparin treatment. Another examination using Doppler sonography was carried out 12–24 hours after thrombin injection. In case of successful treatment, patients were discharged from hospital the following day after intervention.

STATISTICAL ANALYSIS

Nominal data was described as n (%) while quantitative data with the use of basic statistical description (mean, median, standard deviation, quarter spacing and range). The comparison of groups with and without complications after thrombin injection was performed using nonparametric Mann-Whitney U test due to different sizes of both groups. The test was two-sided at a level of significance of 0.05. The statistical analysis was carried out using R version 3.4.4 (<http://cran.r-project.org>).

RESULTS

The research was conveyed among 70 patients (57% women, 43% men) in whom pseudoaneurysm was diagnosed and thrombin was applied transdermally.

The mean age was 67.9 (± 10.5) and BMI was 26.4 (± 14.7). BMI had been estimated since 2016. To statistically evaluate the dependency of pseudoaneurysm dimensions and its channel from the risk of complications after thrombin treatment, patients were divided into two groups: with and without complications after treatment with thrombin.

Pseudoaneurysms in the research group had a mean channel length of 12 mm (± 7.7) with a range from 1 to 30 mm. Mean channel width was 3.5mm (± 1.4) with a range from 1.5 to 7.8 mm. The mean diameter of aneurysm in its widest place was 29.9 mm (± 17.2) with a range from 10 to 96 mm. The second measurement gave a mean size of 21.9 mm (± 7.8) with a range from 8 to 60 mm (Tab. I.). The presence of multi-chamber aneurysm was identified in 21% of patients. All pseudoaneurysms were localized below the inguinal ligament.

The mean amount of injected thrombin was 1.7 ml (± 0.7), the minimal dose was 0.5 ml, the maximal dose was 4 ml.

Complications after thrombin injection appeared among 7% of patients. It was 5 patients altogether – 1 patient suffered from allergic shock, 1 from saphenous vein thrombosis, and 3 from thrombus moving from pseudoaneurysm through its neck to the femoral artery. Assessment of blood supply including physical examination and blood flow with Doppler ultrasonography after thrombin injection indicates no changes among all patients. Inspection of the effectiveness of thrombin injection and its potential repetitive application was done in consecutive USG examinations. It

was indicated that the treatment was effective in 94% of all cases (86% after the 1st administration, 6% after the 2nd one and 2% after the 3rd) (Tab. II.).

Statistical analysis indicated no differences in particular dimensions of aneurysm between patient groups with and without complications after thrombin injection, $p > 0.05$ (Tab. III.).

DISCUSSION

The treatment of pseudoaneurysm by ultrasound-guided thrombin injection is a highly effective method whose success rate is defined at 90–100% [2–7]. It has substituted other treatment methods: prolonged compression dressing, ultrasonographic probe compression, surgery. In our research, the success rate of pseudoaneurysms obliteration using thrombin injection was 94%. The advantages of this kind of treatment are: minimal invasiveness, comfort for patient, little risk of complications, no anesthesia, fast mobilization afterwards, shorter hospitalization time, and lower medical costs. Based on the experience of Polish authors Słonina et al., we think that in the majority of cases, inspection of the treatment effectiveness done the following day is sufficient. Only in the case of large or multi-chamber aneurysm, ultrasound-guided control should be performed also the next day [8].

Thrombin injection to pseudoaneurysm is considered as a safe method with the frequency of complications estimated at 1–4% [9–11].

Edgerton and Moore describe a patient with tibial-fibular trunk who required immediate surgical embolectomy [2]. Gabrielli et al. published a case of a patient suffering from popliteal artery thrombosis and was treated with targeted fibrinolysis [12]. Horn et al. describe two patients with complications of embolism who required immediate surgical treatment. One of them had embolism of femoropopliteal bypass [13]. Ferguson et al. describe the occurrence of mobile thrombus in femoral artery moving from the neck of pseudoaneurysm which dissolved during several minutes of observation [14]. Polish authors Kurzawski et al. stated 15% of cases of peripheral microembolization among all complications after thrombin injection to pseudoaneurysm. However, none of them was clinically significant and pulmonary embolism was present in 0.3% of cases. They indicate that there is a correlation between channel length and repeated thrombin injections and risk of embolism [15]. In a paper published by Lewandowski et al., the frequency of peripheral embolism was higher in patients treated with faster rather than slower injection of thrombin to aneurysm lumen. Other criteria which they mentioned were: medicine dose, short neck of aneurysm and age above 80 [16].

In our research it was observed that three patients after thrombin injection had thrombus passing through the neck of aneurysm into the artery. In two of those cases there was a full obliteration of aneurysm, in the remaining one it was partial. The neck of one of the aneurysms was 12 mm long with irregular width (varying from 3.5 mm to 7.5 mm). In the remaining two cases, the channel was short (3–4 mm). None of the three cases included clinical deterioration of blood supply, nor was there deterioration of blood flow verified using ultrasonography. Routine checkup after 24 hours showed no thrombus - most probably they were dissolved. Moreover, in two cases pseudoaneurysm recanalization was observed.

The treatment may cause a complication of vein thrombosis due to accidental injection of the thrombin solution to the neighboring vein or as a result of compression of the vein by a large hematoma. Kang et al. inform about massive pulmonary embolism after thrombin injection to pseudoaneurysm coexisting with arteriovenous fistula [11]. In one of our patients after obliteration of a 9 mm active part diameter of false aneurysm with a 4.5 mm channel, a new thrombus was detected. It was found in the saphenous vein in the neighborhood of the femoral vein.

The thrombus did not move to deep veins. During the checkup done the following day, recanalization of the active part of aneurysm together with its neck was observed. Repetitive exposure to bovine thrombin may lead to production of antibodies against the foreign protein. They may react with human thrombin and V clotting factor and cause coagulopathy [17–19] and allergic reactions together with severe anaphylactic shock. In 2000, Pope and Johnston were the first to describe the occurrence of an anaphylactic reaction after thrombin injection to pseudoaneurysm [20] in *J Vasc Surg*. The occurrence of anaphylaxis was also reported in 2015 by Jalaiean and Misselt [21] and in 2018 by Wu and Ma [22].

A patient treated in our Department reported general malaise, dyspnea and numbness of limbs a couple of minutes after thrombin injection to pseudoaneurysm while still remaining in the USG room. The patient had undetectable blood pressure, tachycardia, pulse detectable only at carotid arteries. The physician identified symptoms of shock. Corticoid, antihistamine, adrenaline, fluid and oxygen therapy were applied. The reaction to treatment was good. The symptoms gradually vanished. There were no thromboembolic complications detected. The patient did not report exposure to thrombin beforehand during an interview.

Pope and Johnston [20] emphasize that it is important to verify the patient's previous exposure before bovine thrombin injection. Moreover, skin tests should be performed in case of a positive response in an interview to the patient's guarantee safety and protect them against severe allergic reactions. Other rarer complications include abscess and the postembolization syndrome first described by Orawczyk et al. [23], whose symptoms are: pain, reddening, and increased temperature of the injection site which disappear without further consequences.

CONCLUSIONS

1. Obliteration of pseudoaneurysms with ultrasound-guided thrombin injection is a safe and effective treatment method.
2. Adverse events occurring during the procedure are seldom significant from the clinical point of view. Life or health threatening complications (e.g., shock) are very rare.
3. What needs to be verified is prior exposure to bovine thrombin. In case of confirmation during the interview, skin tests should be considered.

Tab. I. Characteristic of pseudoaneurysm in the research group.

VARIABLE	N	MEAN	MEDIAN	SD	QUARTER SPACING	RANGE
Channel length, mm	61	12.0	12.0	7.7	4.5–18.0	1.0–30.0
Channel width, mm	43	3.5	3.5	1.4	2.6–4.0	1.5–7.8
Aneurysm size 1, mm	69	29.9	25.0	17.2	20.0–32.0	10.0–96.0
Aneurysm size 2, mm	69	21.9	19.5	7.8	15.0–25.0	8.0–60.0

Tab. II. Assessment of thrombin therapy.

VARIABLE	N		N	%
Occurrence of complications after injection of thrombin	70	No	65	92.9%
		Yes	5	7.1%
Assessment of blood supply after thrombin injection (physically)	70	No change	70	100%
		Deterioration	0	0%
Assessment of blood supply after thrombin injection (blood flow in USG)	70	No change	70	100%
		Deterioration	0	0%
Effectiveness assessment of obliteration after thrombin injection	63	Effective (after 1st administration)	56	86.2%
		Effective (after 2nd administration)	4	6.2%
		Effective (after 3rd administration)	1	1.5%
		Ineffective	4	6.2%

Tab. III. Size comparison of pseudoaneurysm among patients with and without complications after thrombin application.

VARIABLE	N	COMPLICATIONS (MEDIAN)	N	NO COMPLICATIONS (MEDIAN)	P VALUE
Channel length, mm	5	9.0	56	13.0	0.356
Channel width, mm	5	3.5	38	3.0	0.275
Aneurysm size 1, mm	5	26.0	64	23.5	0.982
Aneurysm size 2, mm	5	26.0	64	18.5	0.206

4. In qualification to treatment, the following criteria should be taken into account: morphology of pseudoaneurysm, its channel, presence of arteriovenous fistula, size of hematoma, and presence of compression symptoms.
5. In the case of limited safety of thrombin injection, especially when having little experience with the method, surgical treatment should be considered as the method of choice.

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Corresponding author: Marta Pająk; Wojewódzki Specjalistyczny Szpital im. M. Pirogowa w Łodzi; ul. Wólczańska 191/195, 90-531 Łódź; Tel./fax: +48 42 636 86 51; E-mail: mrt.pjk@gmail.com

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