Comparison of the Clinical Efficacy of Bovine Thrombin and Compression Method in Femoral Pseudo Aneurysm of Patients Undergoing per Coetaneous Coronary Intervention at Shaheed Rajaie Cardiovascular Medical and Research Center

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Abstract

Background: Pseudo aneurysm has been an increasingly common complication of catheterization procedures during the past two decades, with the greatest incidence being in the femoral artery. Treatment of the iatrogenic femoral artery pseudo aneurysm with the injection of thrombin is reported to be an efficacious and safe procedure. In this study, we evaluated the efficacy and success rate of per coetaneous ultrasonographically-guided thrombin injection and compression method for the treatment of pseudo aneurysm and to determine the effect of thrombin injection on systemic coagulation parameters.

Methods: This Cohort clinical trial was conducted on patients with femoral pseudo aneurysm after percutaneous intervention (PCI) in Shaheed Rajaie Cardiovascular Medical and Research Center. The patients were divided into two randomized groups and treated with either the compression method or the percutaneous ultrasonographic-guided thrombin injection method. Pseudo aneurysm size, pseudo aneurysms neck size, thrombin dose, thrombosis time, outcome of therapy, and complications were documented prospectively. Duplex sonographic follow-up examinations were performed at 0 and 24 hours afterwards. Partial thrombin time as well as the Quick test (pro thrombin time) was monitored before and after the intervention.

Results: Thirty patients with femoral pseudoaneurysm following catheterization between 15 and 85 years of age were enrolled in this study. The mean size of the pseudo aneurysms length was 2.45 ± 1.15cm (SD) and pseudo aneurysms width was 2.06 ± 1.07cm. In total, 13 thrombin injections were administered. The mean thrombin dose was 500-2000 IU. The success rate of thrombin injection was %92.30 (12 of 13 patients), which was significantly higher than 82.35% (13 of 17 patients) in the compression method (p value<0.05). No thrombo embolic, infectious, or allergic complications occurred.

Conclusion: In this study, the percutaneous ultrasonographically-guided thrombin injection method was successful and safe in the management of femoral pseudoaneurysms. Changes in coagulating factors indicated the possibility of thrombin passage into the arterial circulation.


Keywords: Bovine — Thrombin Aneurysm — Coetaneous Coronary

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Introduction

Femoral artery pseudo aneurysm after PCI is an important complication to diagnose and treat. While the complication rate is barely 0.5%-1% for diagnostic examinations, the incidence increases to 3.2%-7.7% in interventions in which large-bore sheaths are used, or longer indwelling time, and anticoagulant and anti platelet therapy are needed. \(^1\) Traditional treatment of pseudo aneurysm has been surgical repair, but several nonsurgical techniques have been developed for the treatment. Sonographically guided compression has become the first-line treatment of pseudo aneurysms at many institutions. \(^2\) Because of the technical difficulties of the procedure, patient discomfort and variable results, alternative forms of treatment have been advocated. \(^3\) Compression method is a painful and time-consuming procedure that may require several attempts before succeeding. It is least likely to succeed in anti coagulated patients or when the pseudo aneurysm size is wide or not directly accessible for compression. \(^4\) Additionally, compression may require IV sedation to be tolerated by patient. \(^5\) Thirteen patients with iatrogenic femoral artery pseudoaneurysm were treated with thrombin injection. Ultrasound-guided Compression was successful in achieving thrombosis of the pseudo aneurysm without the need for operative intervention in 82.35% (14 of 17 patients) of cases. However, it also has a number of disadvantages including high failure rate, recurrence rates and patients’ discomfort. \(^6\) The use of thrombin for treatment of pseudo-aneurysms was introduced by Cope and Zeit in 1986. There was a 92.30% (12 of 13 patients) success rate in our patients, with an average dose of approximately 500 IU _2000IU of thrombin. None of the patients developed complications except for one patient who was referred to surgery because of incomplete thrombosis of the pseudoaneurysm. Thrombin originates from pro-thrombin, a circulating zymogene precursor protein, and plays a central role in blood clotting. First, thrombin is the only enzyme that can convert fibrinogen to fibrin. Second, thrombin activates pro-thrombin by means of positive feedback mechanisms and several coagulation factors (eg, factors V and VIII). \(^7\) In clinical medicine, thrombin has been used for more than 20 years to achieve local homeostasis, as well as in a variety of coagulation tests in the laboratory. Thrombin may be used to manage pseudo aneurysms by means of percutaneous injection into the pseudoaneurysm lobe. \(^2,\) \(^8\) An 18 to 20-gauge Lumber Puncture needle was introduced into the pseudo aneurysm. The needle tip was visualized and positioned at a site distant from the neck of the pseudo aneurysm. Increments of 0.1 cc (100 IU) of thrombin were slowly injected at a rate of approximately 1 cc during 5-10 second to achieve complete thrombosis. \(^9\) While small volumes of thrombin were injected, the flow within the pseudo aneurysm lobe was visualized directly with color duplex Ultra Sonography (US). A pseudoaneurysm is characterized by blood inflow from and outflow into the feeding artery. However, the neck of the aneurysm is not compressed regularly during the injection of thrombin. Thus, as a result of injecting thrombin into the pseudo aneurysm lobe, it is likely that thrombin will enter the arterial circulation, which leads to the risk of thrombus formation and allergic reactions. We should not rule out the fact that thrombin might have extra-vasation during or after injection. \(^4\) Distal pulses and changes associated with limb ischemia (temperature, color, and pain) were monitored after the treatment to detect potential thrombotic or embolic complications. If flow was identified in the pseudo aneurysm at follow-up, the procedure was repeated. Patients were kept at bed rest for 24 hr after treatment. \(^3,\) \(^10\) The purpose of this study was to determine the efficacy and safety of percutaneous US-guided thrombin injection versus compression in the treatment of femoral pseudo aneurysms and to evaluate the effects of thrombin injection on systemic coagulation parameters. \(^11\)

Methods

In a prospective study from March 2009 to September 2010 with 30 patients (16 men and 14 women) mean age were 58.13±15.51 years (from 20–77 years) were enrolled. The diagnosis of a pseudo aneurysm was rendered in 30 patients within 24 hours of removal of the arterial sheath. The pseudo aneurysms resulted from diagnostic and therapeutic catheterizations for peripheral arterial,
coronary arterial, cerebro-vascular and renal arterial
diseases. Lyophilized, sterilized, and virus-
inactivated bovine thrombin (1000 IU, Sigma
Aldrich; T4648, Germany) was dissolved in 1 cc of
isotonic saline (1000 IU in 1 cc of isotonic saline) in
clean room and drawn into a 1-mL syringe actually
before the injection. Thus, 0.1 cc of solution was
equivalent to 100 IU of thrombin.\textsuperscript{3} Thrombin was
injected in sterile condition by one of our four
interventional radiologists under sonography guide.
In most cases, aneurysmal thrombosis occurred
within seconds after receiving the initial thrombin
injection. Complication rate with this technique was
strikingly Low.\textsuperscript{2} The pseudo aneurysm’s geometry
and position in relation to the artery, along with the
following parameters, were documented
prospectively before the injection for the US-guided
compression procedures; the duration of
compression was recorded. For the thrombin
injections, the total injected dose, the number of
injections, the time to pseudo aneurysm thrombosis
for both the compression and thrombin procedures
were recorded. A success was considered to be
complete thrombosis of the flow lumen. The
injections were performed one after the other until
the color signal had disappeared completely. The
thrombin dose was recorded and the pseudo-
aneurysm neck was not compressed during the
thrombin injection. Perfusion in the artery that fed
the pseudoaneurysm was controlled and color-doted
duplex sonography (GE, minnoest; logic 7) was
performed to determine the same parameters at 0
and 24 hours after thrombin injections. Blood was
drawn immediately after the thrombin injection to
cheek PT and PTT. Patient demographics, clinical
variables, and pseudo-aneurysm characteristics were
compared by using the Pearson \( \chi^2 \) (categorical
variables) or paired t (continuous variables) tests
and one-sample kolmogorov-Smirnov. We used
SPSS 15 software (SPSS Inc,Chicago,Illinois) for
our analysis. All P- values are explorative value of
less than 0.05 were regarded as statistically
significant.

\textbf{Results}

Thirty femoral pseudo-aneurysm age range
51.7±13.58 (years) with various reasons were
referred to catheterization laboratory: 1 case of
endocarditis, 1 case of recurrent pseudo-aneurysm,
6 (20\%) cases with coronary artery bypass surgery
history, 4 (13.3\%) coronary artery disease cases, 6
(20\%) cases of non ST elevation myocardial
infarction (NSTEMI), 4 (13.3\%) cases of ST
elevation myocardial infarction and 8 (26.7\%) cases
had bleeding at catheterization site. All the patients
with femoral pseudo aneurysm were identified in
the radiology department. We have compared two
treatment groups, one group of patients were
17(56.7\%) patients who were treated by the old and
conventional compression method. Thirteen
(43.3\%) underwent thrombin injection. Sixteen
(46.7\%) patients were male and 14 (53.3\%) were
female. Demographic characteristics of patients in
term of underlying diseases were as follows: 6
(20\%) patients were smokers, 11 (36.7\%) patients
had diabetes mellitus, 13(43.3\%) patients had
hyperlipidemia and 17(56.7\%) patients had
hypertension. From 30 patients, 2(6.7\%) patients had
high PTT and 17 (56.7\%) patients had high PT and INR.
Pseudo aneurysm in 30 patients with average length of
1.15±2.45cm and the width of 1.07±2.06cm and
neck size in the range of 11-13cm were measured.
At least one episode of compression and a
maximum of three episodes with a range of 10-70
minutes (31.18±17.45min) were applied in addition
to being time consuming process for most of
patients and being painful and not tolerable.
Compression under ultrasound was started until
thrombosis was performed. From 17 patients who
underwent compression method one patient died
because of septic shock and in three cases
compression failed and recurrent pseudo-aneurysm
with larger size recurred after a while. In another
group 13 patients under went ultrasound guided
thrombin injection in the range of 500-2000 IU
(11.84±626 IU). Every single drug injections were
equivalent to 100 units that every 5-10 seconds
were injected until no other flow was determined.
LP needles with size of 18-22 gauge was selected to
enter the pseudo-aneurysm cavity, the time required
for thrombosis was 1.04±1.97 minutes that was
quite significant compared to compression
Thrombin treatment in any of the patients had no history of receiving thrombin and all were completely treated by thrombin without any complications except one case that had incomplete thrombosis and after 24 hours there still remained 25% of the flow, so the patient was referred for surgical repair. After thrombin injection by interventional radiologist blood was taken from the patient to measure PT and PTT, with the result of statistical analysis there wasn’t any significant result, but due to differences in the PT and PTT there is a probability that thrombin has escaped into the systemic circulation system. Comparison between thrombin dose and pseudo aneurysm size with P-value=0.001 was significant. After treatment, 30 patients remained hospitalized and needed to have bed rest up to 24 hours afterwards to be monitored by duplex ultrasoundography. Thrombin group included patients with pseudo-aneurysm diameter more than 3cm that needed less time to make thrombosis, and thrombin injections proved to be comfortable, easy and more acceptable by the patients. Outcome of therapy was measured by thrombosis time between the two groups, and it was quite significant based on success rate of 92.30% in the thrombin injection group and 82.35% in the compression group.

**Discussion**

One retrospective study of 38,822 patients showed that the incidence of post catheterization pseudo aneurysm after cardiology procedures was 0.2% and 0.1% after radiologic procedures, although rates as high as 7.7% have been reported. Thrombus forms spontaneously within the lobe of pseudo aneurysms, as is demonstrated by the fact that some pseudo aneurysms are partially thrombosed at the time of diagnosis or small pseudo aneurysms have a tendency toward spontaneous occlusion. Three options are available for management of femoral pseudo aneurysms: surgical revision, US guided compression, and percutaneous injection of thrombin. External compression with sandbags or compression devices is uncomfortable for The compression method is time consuming, has a high failure rate, and is associated with thromboembolic complications. Additionally, prolonged compression may result in skin ischemia, necrosis, or infection. Ultrasound-guided compression is a recently introduced successful treatment modality. It has become the procedure of choice when initial non-guided external compression fails. However, it has several disadvantages. It is unlikely to succeed if the patient is receiving anticoagulants. Treating femoral artery pseudo aneurysms while maintaining anticoagulation is highly disadvantageous. In cardiac patients or if accurate compression cannot be achieved due to obesity, large hematoma in place or with a short, wide or posterior neck pseudo-aneurysm, another decision must be made. The Agarwal et al. described a mean compression time of 104.1 ± 63.0 min to achieve a 100% occlusion rate. We report a success rate of 82.35% for 17 pseudo aneurysms initially treated with manual compression. Complete thrombosis by thrombin injection achieved in a mean procedure time of 1.97 min in the sonographic guided thrombin injection group compared with a mean time of 31.18 min to achieve thrombosis in the sonographic guided compression group (p < 0.001). Non operative method of treating pseudo aneurysms by compressing the neck of the pseudo aneurysm with a sonographic probe to allow the cavity to be thrombosed was effective in approximately 82.35% of patients, this technique rapidly gained favor over surgery. However, the procedure often requires compression times of 1–2 hr. In a recently published article, the failure rate increased from 38% to 48% when patients who stopped therapy for technical reasons or strong pain were included. In the study by Paulson et al., obliteration of the pseudo aneurysm by means of US-guided compression was successful in 74% of patients and in 96% when thrombin was used. In comparative studies conducted by Pezzullo et al. and Taylor et al. thrombin therapy led to successful obliteration of pseudo aneurysms more frequently than did compression. In most studies, successful treatment was accomplished in more than 90% of patients. In only one study the success rates were lower than 90%. When studies involving more than 50 patients are considered, the success rate ranges between 92% and 100%.
pseudo aneurysms are rare. Compared with the success rate of compression therapy, the success rate with per coetaneous thrombin injection into pseudo aneurysm lobes is higher. Percutananeous injection of thrombin has the potential to become the initial method of choice in the treatment of post-catheterization pseudo aneurysms. However, a larger prospective trial comparing the relative benefits of each treatment option is warranted. In our study, we were able to show that the US-guided injection of bovine thrombin into the pseudo aneurysm lobe is a practical and safe method for management of femoral pseudo aneurysm. Thrombin (factor IIa) is a 34 kilo-Dalton polypeptide derived in vivo from pro thrombin (factor II) by the action of factor Xa, factor Va, phospholipids, and calcium. It is the activated form of pro thrombin, a circulating zymogene that cleaves fibrinogen to fibrin, which in turn participates directly in the formation of a blood clot. Cope and Zeit introduced the use of thrombin to treat pseudo aneurysms in 1986, although it took another 11 years for the technique to gain popularity. We ensured sterile conditions during the injection and did not encounter local infections after thrombin treatment of pseudo aneurysms and we induced local anesthesia in all 13 patients before puncturing the pseudo aneurysm for thrombin injection. Nevertheless, local infections are conceivable. A groin abscess after percutaneous thrombin injection was described recently in the literature in patients requiring anticoagulation therapy it can be discontinued prior to thrombin injection and shortly after. We have not directly proved the passage of thrombin into the feeding artery. However, the risk remains that thrombin enters the feeding artery for three reasons, as described in the literature. In addition, changes in systemic coagulation parameters after thrombin injection presumably indicate that thrombin passes into the arterial blood stream, with the risk of thromboembolic and allergic complications. A case of allergic urticaria after thrombin treatment of a pseudo aneurysm was published recently. In another patient, long-term fever after thrombin injection was interpreted as allergic response to bovine thrombin. Allergic reactions to thrombin injected for the treatment of pseudo aneurysms are rare. Quarmby et al have thus proposed injecting autologous thrombin for the treatment of pseudo aneurysms. Thromboembolic complication, the second type of complication that we observed, is a serious side effect. Thromboembolic complications occur for several reasons. One type of thromboembolic complication occurs when thrombin is injected into the artery so injection into the artery should be strictly avoided. No case of hemorrhage occurred after injection of thrombin in our patients in this study. The recommendations given in the literature for documenting previous thrombin exposure should be complied by documenting the type and nature of thrombin exposure and keeping mandatory records of the batch numbers. The average dose of thrombin reported in the literature was approximately 1100 U, with a range of 100-5000 U. In our study we used average dose of 1184.62 U with the range of 500-2000 U. A correlation was found between pseudo aneurysm diameter and thrombin dose. Pezzullo et al recently found a correlation between pseudo aneurysm volume and the required thrombin dose with only 22 patients. The relationship between thrombin dose and pseudo aneurysm-neck diameter may also prove of interest. The size of the pseudo aneurysm lobe and INR effects success rates in our study. In another report, Kang ET al postulate that the thrombin dose is dependent on the size of the pseudo aneurysm lobe. This hypothesis could be confirmed by the results in our study. Early recurrence of pseudo aneurysm was seen in seven patients in Kang's series. Five of them responded to repeat thrombin injection and two required surgical repair. However, it should be noted that reperfusion may occur a few days after successful thrombin injection treatment. In our study, one patient had residual perfusion after thrombin injection. In a series by Paulson ET al, perfusion of the pseudo aneurysm neck occurred in six of 26 treated pseudo aneurysms, four of which had thrombosed spontaneously by the time of follow-up. No recurrent perfusions were observed in patients of Sheiman and Brophy. Data in our study and those in the literature indicate support for bed rest of 24 hours. In our study, no serious complications were observed at the follow-up examinations in the patients with pseudo aneurysms. In conclusion, US-guided per
coetaneous injection of thrombin for the management of pseudo aneurysms is an effective, time-saving and safe method. Injection of thrombin can be regarded as the therapy of choice for the management of post-catheterization pseudo aneurysms. In our study, pseudo aneurysm geometry, group and INR proved to be a key factor influencing the thrombosis time and success of the treatment. Changes in systemic coagulation parameters allow the interpretation that thrombin passes into the arterial blood stream and that there is a risk of thromboembolic and allergic complications.2

References
9. Pezzullo JA, Dupuy DE, Cronan JJ. Percutaneous injection of thrombin for the treatment of


