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# Comparison of the Clinical Efficacy of Bovine Thrombin and Compression Method in Femoral Pseudoaneurysm of Patients Undergoing Percutaneous Coronary Intervention

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### ABSTRACT

Pseudoaneurysm 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 iatrogenic femoral artery pseudoaneurysm 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 percutaneous ultrasonographically-guided thrombin injection and compression method for the treatment of pseudoaneurysm and for studying of the effect of thrombin injection on systemic coagulation parameters. This cohort clinical trial was conducted on patients with femoral pseudoaneurysm 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 ultrasonographically-guided thrombin injection method. Pseudoaneurysm size, pseudoaneurysm 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 (prothrombin time) was monitored before and after the intervention. Thirty patients between 15 and 85 years of age with femoral pseudoaneurysm following catheterization were enrolled in this study. The average length and width of the pseudoaneurysms were respectively 2.45±1.15 cm and 2.06±1.07 cm. 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 that of compression 82.35% (13 of 17 patients) (p value<0.05). No thromboembolic, infectious, or allergic complications occurred. 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.

## 1. Introduction

Femoral artery pseudoaneurysm after PCI is an important complication to diagnose and treat. While the complication rate is 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, anticoagulant and antiplatelet therapy are needed. Traditional treatment of pseudoaneurysm has been surgical repair, but several nonsurgical techniques have been developed. Sonographically guided compression

has become the first-line treatment of pseudoaneurysms at many institutions.<sup>2</sup> Due to the technical difficulties of the procedure, variable results and patient discomfort, alternative forms of treatment have been advocated.<sup>3</sup> Compression method is a painful and time-consuming procedure and may require many attempts before it succeed. When the pseudoaneurysm size is wide or not directly accessible for compression or in anticoagulated patients the method may fail to succeed.<sup>4</sup> Additionally, compression may require IV sedation to be tolerated by

patient.<sup>5</sup> Thirteen patients with iatrogenic femoral artery pseudoaneurysm were treated with thrombin injection. Ultrasound-guided compression was successful in achieving thrombosis of the pseudoaneurysm 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 with recurrence and patients' discomfort. The use of thrombin for treatment of pseudoaneurysms was introduced by Cope and Zeit in 1986. There was a success rate of 92.30 % (12 of 13) in our patients, with the average dose of approximately 500-2000 IU 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, the circulating zymogen precursor protein, is proteolytically cleaved form of prothrombin and plays a central role in blood clotting. It is the only enzyme that acts to convert fibrinogen to fibrin and activates prothrombin through positive feedback mechanisms and several coagulation factors: factors V, VIII, and XI. Thrombin has clinically been used to achieve local homeostasis, and in a different coagulation tests in the laboratory for more than 20 years. Effective treatment of femoral pseudoaneurysms was previously reported by percutaneous injection of thrombin into the pseudoaneurysm lobe. associated with limb ischemia including: temperature, color, and pain and distal pulses and were reported after the treatment to detect potential complications<sup>2</sup> Percutaneous injection of thrombin was also repored to be successful and safe in the treatment of femoral pseudoaneurysms. In this study it is concluded that the increase of thrombin-antithrombin III complex shows the possibility of thrombin entrance into the arterial circulation. <sup>3, 11</sup>

## 2. Materials and 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. 30 patients were diagnosed with a pseudoaneurysm during 24 hours of removal of the arterial sheath. The pseudoaneurysms resulted from, cerebro-vascular, coronary arterial and renal arterial diseases plus diagnostic and therapeutic catheterizations for peripheral arterial <sup>2</sup> Lyophilized, sterilized, and virusinactivated 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.<sup>3</sup> Thrombin was injected in sterile condition by one of our four interventional radiologists under sonography guide. In most cases, seconds after receiving the initial thrombin injection aneurysmal thrombosis occurred. Complication rate with this technique was strikingly Low.2 The pseudoaneurysm's position and

geometry in relation to the artery, with the following parameters, were recorded before the injection for the US-guided compression procedures; the duration of compression was also documented. For the thrombin injections, the total injected dose, the number of injections, the time to pseudoaneurysm 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 done one after the other til the color signal had completely disappeared. During the thrombin injection the thrombin dose was documented and the pseudoaneurysm neck was not compressed. 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, pseudoaneurysm characteristics, and clinical variables were compared by using the Pearson  $\gamma^2$ (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.

## 3. Results

femoral pseudoaneurysm Thirty 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 infacrtion and 8 (26.7%) cases had bleeding at catheterization site. All the patients with femoral pseudoaneurysm 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 (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%) were taking warfarin, 9 (30%) plavix and 20 (70%) were taking aspirin (ASA). We measured PT and PTT in our patients whether or not they had clotting problems. 8 (26.7%) patients had high PTT and 17 (56.7%) patients had high PT and INR. Pseudoaneurysm in 30 patients with average length of 1.15±2.45 cm, the width of 1.07±2.06 cm and neck size in the range of 11-13 cm were measured. At least one episode of compression and a maximum of three episodes with a range of 10-70

minutes (31.18±17.45 min) 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 pseudoaneurysm 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 pseudoaneurysm cavity, the time required for thrombosis was 1.04±1.97 minutes that was quite significant compared to compression group (p<0.001). 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 in to the systemic circulation system. Comparison between thrombin dose and pseudoaneurysm 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 ultra sonography. Thrombin group included patients with pseudoaneurysm diameter more than 3 cm 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.

## 4. Discussion

In one retrospective study among 38,822 patients it was reported that the incidence of post catheterization pseudoaneurysm was 0.1% after radiologic procedures and 0.2% after cardiology procedures, <sup>3</sup> although rates as high as 7.7% have been reported. <sup>12</sup> Thrombus appears suddenly within the lobe of pseudoaneurysms, because at the time of diagnosis some pseudoaneurysms are partially thrombosed or some small pseudoaneurysms have a tendency to natural occlusion. <sup>13</sup> Three options are available for treatment of femoral pseudoaneurysms including surgical revision, percutaneous injection of compression.<sup>20</sup> guided and compression with sandbags or compression devices is uncomfortable for the management. The compression method is time consuming, has a high failure rate, and is

associated with thrombo embolic complications. Additionally, prolonged compression may result in necrosis, infection or skin ischemia. 15 Ultrasound-guided compression is a recently introduced successful treatment modality, which has become the choice procedure while initial non-guided external compression fails. However, it has several disadvantages. In the case that patient is receiving anticoagulants it is doubtful to succeed. 14 Managing femoral artery pseudoaneurysms while maintaining anticoagulation is extremely disadvantageous. In cardiac patients or if accurate compression cannot be achieved due to large hematoma in place or with a short, wide or posterior neck pseudoaneurysm and obesity, another choice must be considered. The Agarwal et al. 16 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 pseudoaneurysms initially managed with manual compression. Complete thrombosis using thrombin injection achieved in 1.97 min in the sonographic guided thrombin injection group, while in 31.18 min for achieving thrombosis in the sonographic guided compression group (p < 0.001). Non operative method of managing pseudoaneurysms through compressing the neck of the pseudoaneurysm following a sonographic probe to let the cavity to become thrombosed was highly effective in approximately 82.35% of patients, this technique rapidly preferred over surgery.<sup>2, 5, 10</sup> However, 1-2 hrs often are required to perform the compression procedure. In a recently published article, 20 10 percent increase in the failure was reported for patients who stopped therapy for technical reasons or for who have strong pain. In the study by Paulson et al <sup>22</sup>, obliteration of the pseudoaneurysm through US-guided compression reported to be successful in 74% of patients and it reached to 96% when thrombin was implemented. In comparative studies conducted by Pezzullo et al <sup>23</sup> and al,<sup>24</sup> successful obliteration Taylor et pseudoaneurysms was achieved by thrombin therapy, this resulted in more frequent obliteration in comparison to compression. In most studies, successful management was gained in more than 90% of patients. In just one study<sup>23</sup> the success rates were below 90%. For studies with 50 patients or more, the success rate are between 92% and 100%. 9-15, 17, 24 In our study success rate of compression was 82.35% and thrombin injection was 92.30%. Compared with the success rate of compression therapy, the success rate with percutaneous thrombin injection into pseudoaneurysm lobes is higher. Percutaneous injection of thrombin has the potential to become the initial method of choice in the treatment of postcatheterization pseudoaneurysms. However, a larger prospective trial is necessary to compare the relative benefits of each treatment. 11 In our study, we were able to show that the US-guided injection of bovine thrombin into the pseudoaneurysm lobe is a practical and safe method for management of femoral pseudoaneurysm.

Thrombin (factor IIa) is a 34 kilodalton 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.<sup>23, 25</sup> Cope and Zeit <sup>16</sup> introduced the use of thrombin to treat pseudoaneurysms in 1986, although it took another 11 years for the technique to gain popularity. <sup>24</sup> We ensured sterile conditions during the injection and did not encounter local infections after thrombin treatment of pseudoaneurysms and we induced local anesthesia in all 13 patients before puncturing the pseudoaneurysm for thrombin injection. Local infections are also possible. Recently the reports of a groin abscess in patients requiring anticoagulation therapy after percutaneous thrombin injection were published, which can be discontinued prior to thrombin injection or shortly after. The passage of thrombin into the feeding artery was not proven. Nevertheless, the risk remains that thrombin can enter the feeding artery for three reasons, which are described in the literature. 5,10,21,23,24 In addition, changes in systemic coagulation parameters after thrombin injection most probably indicate that thrombin enter sinto the arterial blood stream, and can cause thromboembolic and allergic complications. Recently, there was a report of a case of allergic urticaria after thrombin treatment of a pseudoaneurysm. In a different patient, after thrombin injection, bovine thrombin lead to allergic response and durable fever <sup>24</sup>. However, allergic reactions to thrombin as the treatment of pseudoaneurysms are infrequent.<sup>26</sup> In order to prevent such complications, Quarmby et al 25 have sugested injecting autologous thrombin for the treatment of pseudoaneurysms. Thromboembolic complication, the second type of complication that we observed, is a serious side effect. Thromboembolic complications occur for several reasons. When thrombin is injected into the artery one type of thromboembolic complication occurs 15, 25 thus injection of thrombin into the artery must be 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, <sup>27</sup> 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 pseudoaneurysm diameter and thrombin dose. The correlation between pseudoaneurysm volume and the required thrombin dose was recently reported by Pezzullo et al.<sup>23</sup> with only 22 patients. The corelationship of pseudoaneurysm-neck diameter and thrombin dose may also prove of interest.<sup>23</sup> The size of the pseudoaneurysm lobe and INR effects success rates in

our study. In another report, Kang et al<sup>27</sup> hypothesized that the thrombin dose is correlated with the size of the pseudoaneurysm lobe. This hypothesis could be confirmed by the results in our study. Early recurrence of pseudoaneurysm was documented in seven patients in Kang's series.<sup>8</sup> Repeated thrombin injection was administered for five of them but surgical repair was required for another two patients. Nevertheless, 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,<sup>22</sup> perfusion of the pseudoaneurysm neck observed in 6 of 26 treated pseudoaneurysms, four of them had thrombosed spontaneously after thrombin injection by the time of follow-up. No recurrent perfusions were observed in patients of Sheiman and Brophy.9 In our study data indicate support for bed rest of 24 hours which is consistent with literature. In our study, no serious complications in the patients with pseudoaneurysms were occoured at the follow-up examinations. We conclud that, US-guided percutaneous injection of thrombin for the management of pseudoaneurysms is an effective, safe and time saving method. Thrombin injection can be regarded as the therapy of choice for the management of post catheterization pseudoaneurysms. In our study, pseudoaneurysm geometry, group and INR proved to be a key factor influencing the thrombosis time and success of the treatment. However, if changes in systemic coagulation parameters occurs this could allow the interpretation that thrombin enters into the arterial blood stream and this may lead to a risk of thromboembolic and allergic complications.<sup>2</sup>

#### Ethical issues

The study was approved by the Ethical Committee of the University.

#### **Conflict of interests**

No conflict of interest to be declared.

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