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Early Thrombosuction and Tirofiban Use in Knee and Below-Knee Arterial Thrombosis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 **Ulas Bildirici**
C 1 **Umut Celikyurt**
B 2 **Sadan Yavuz**
B 2 **Emir Dervis**
E 1 **Qurban Adina**
E 1 **Dilek Ural**

1 Department of Cardiology, Kocaeli University Medical Faculty, Kocaeli, Turkey
2 Department of Cardiovascular Surgery, Kocaeli University Medical Faculty, Kocaeli, Turkey

Corresponding Author: Ulas Bildirici, e-mail: ihubildir@gmail.com
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Background: Acute limb ischemia (ALI) is a clinical entity with a high rate of morbidity and mortality. Despite advances and variety of its management, there is still no criterion standard treatment. The goal of this study was to evaluate the effect of tirofiban use on the early and 6-month prognosis of patients with knee and below-knee arterial thrombosis who were treated with percutaneous thrombosuction (PT) within 24 h.

Material/Methods: Data of consecutive ALI patients who were diagnosed with popliteal and infra-popliteal arterial thrombosis and underwent PT procedure within 24 h between January 2010 and September 2015 were evaluated retrospectively. Patients were separated into 2 groups according to tirofiban usage.

Results: A total of 105 patients (mean age 67±16; 53% men) were included in the study. Atrial fibrillation (n 64, 61%) and hypertension (n 60, 57%) were the most frequent comorbidities in patients with thromboembolic events. A significantly higher rate of distal embolization (6% *vs.* 16%; p=0.01) and slow-flow (17% *vs.* 30%; p<0.01) developed in patients who were not treated with tirofiban after the PT procedure. Although major and minor bleeding were more frequent in the tirofiban group, only the rate minor bleeding was statistically significant (29% *vs.* 9%, p=0.001). Reverse embolic event ratio was similar in both groups. Although there was a higher rate of amputation in patients not treated with tirofiban, the difference was not significant.

Conclusions: Adding tirofiban to PT reduces angiographic thromboembolic complications. Usage of tirofiban in patients prone to thromboembolic events may be useful for improving success of the PT procedure, with a reasonable bleeding ratio.

MeSH Keywords: **Catheterization, Peripheral • Embolism and Thrombosis • Peripheral Arterial Disease**

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Background

Acute limb ischemia (ALI) is most commonly caused by thromboembolism [1]. The majority of emboli arise from the heart in association with atrial fibrillation, myocardial infarction, or valvular heart disease [2–4]. Approximately two-thirds of noncerebral emboli obstruct the lower extremities, involving aorto-ilio-femoral arteries in approximately two-thirds of the patients, with the most common site being the femoral artery [5]. Presentation of ALI varies from silent ischemia to acute extremity loss, depending on the presence and extent of atherosclerosis and collateral blood flow [3]. In ALI patients with certain comorbidities, loss of extremities and death are not rare outcomes. Without intervention, mortality, gangrene, and chronic ischemia rate in long-term follow-up are 13%, 27%, and 18%, respectively [6]. The 5-year survival rate after ALI caused by thrombosis is approximately 45% [7].

There is no criterion standard treatment for ALI. Surgery [7] and embolectomy with Fogarty catheter [8] have been the main therapeutic interventions. Contemporary effective methods are mechanical thromboembolectomy, percutaneous thrombosuction (PT), and catheter directed thrombolysis. Despite use of these therapies, ALI still carries a high risk for limb amputation (5–18%) and death (8–14%) [9–11].

Percutaneous removal of thrombi is a well-established treatment modality and is often used as the first-line therapy in ALI patients [12]. PT and mechanical thrombectomy are effective methods for thrombus removal, but they cannot be applied to all patients due to technical reasons [12–14]. Thrombolytic therapy is also challenging because of a higher incidence of complications [15]. Regardless of the treatment method, the success rate is lower in below-knee arteries compared to upper segments. PT method is easier than mechanical thromboembolectomy, with similar outcomes; nevertheless, residual thrombus, distal microembolization, and dissection are disadvantages of both methods [13,14].

Tirofiban is a strong antiaggregant that inhibits GpIIb/IIIa receptors and blocks 95% of platelet aggregation [16]. The reduction of thrombus load is a well-known effect of tirofiban in coronary interventions [17]. PT together with tirofiban decreases slow-flow/no-flow phenomenon in coronary interventions and improves coronary arterial circulation [17,18]. Despite being an established antiaggregant agent in patients with coronary thrombi, the efficacy and adverse effects of tirofiban in peripheral arterial diseases, especially in below-knee ALI, are not well defined [19,20].

The aims of this study were to evaluate the effects of early PT (within the first 24 h) and additional tirofiban usage on procedural success, long-term safety, and the need for amputation in knee and below-knee arterial ALI.

Material and Methods

Data from consecutive ALI patients with popliteal and infra-popliteal arterial thrombosis who underwent PT within the initial 24 h between January 2010 and September 2015 were analyzed retrospectively. Limbs were classified using the Society for Vascular Surgery/International Society for Cardiovascular Surgery (SVS/TSCVS) clinical categories of ALI (Rutherford category) [21]. The degree of baseline occlusion was determined by using the schema adapted from Ansel et al. [22]. The patients with Rutherford IIa or IIb, and patients with 91–100% arterial occlusion on angiography were included in the study. Patients are divided into 2 groups according to preprocedural use of tirofiban. Patients with a Rutherford class I or III, an INR higher than 1.5, serum creatinine >2.5 mg/dL, and with comorbidities requiring tirofiban use were excluded from the study.

Thrombosuction was performed with the Pronto extraction catheter (Vascular Solutions, Inc., Minneapolis, MN) using 7F (popliteal) and 6-5F (infra-popliteal) guiding catheters and a 0.014-inch wire in all 3 below-knee arteries until the thrombus completely disappears. The procedure was accepted as successful when 70% revascularization of the arterial lumen (thrombus removal) and maintenance of distal arterial blood flow were achieved.

Tirofiban use was not planned, but was used as a bailout strategy. Tirofiban was given as a 10 µg/kg bolus followed by a 0.15 µg/kg/min infusion for 12 h [23]. Unfractionated heparin (UFH) was administered at a bolus dose of 50–100 U/kg, with a target activated clotting time (ACT) of 250–300 s. UFH infusion continued for 24 h.

Slow-flow was defined as a TIMI-2 flow grade (i.e., requiring ≥3 beats to opacify the vessel) or a corrected TIMI frame count >27 frames [24]. Distal embolization was identified as disappearance or abrupt and unexpected occlusion of a distal vessel that had been visible in preprocedural cineangiograms.

Sheath removal for the tirofiban-treated group was time-based (60 min after infusion discontinuation). The sheath was removed if ACT was below 180 s.

Major bleedings were accepted as intra- and retroperitoneal bleeding, intracranial bleeding, any overt procedure-related bleeding with a hemoglobin drop of ≥5 g/dl, and transfusion needing or invasive procedure needing bleedings. Minor bleedings were accepted as bleedings which did not need any transfusion or invasive procedure.

Development of arterial occlusion or thrombus were checked in all patients by physical examination and Doppler ultrasonography at the end of 6-month follow-up. Lesions with more than 70% occlusion were accepted as significant.

Table 1. Demographic features of the ALI patients.

	PT only (57 patients)		PT and tirofiban (48 patients)		P
Age (years)	66±17		66.7±12		NS
Sex (M/F)	31/26		25/23		NS
Smoking	32	(56%)	22	(46%)	NS
Diabetes mellitus	23	(40%)	25	(52%)	0.05
Peripheral arterial disease	21	(37%)	12	(25%)	NS
Hypertension	28	(49%)	32	(67%)	NS
Hyperlipidemia	28	(49%)	21	(45%)	NS
Atrial fibrillation	36	(63%)	28	(58%)	NS
Heart disease	3	(5%)	10	(21%)	0.01
Renal insufficiency	0	(0%)	3	(6%)	NS
Rutherford IIa	25	(44%)	23	(48%)	NS
Rutherford IIb	32	(56%)	25	(52%)	NS
Infra-popliteal region	40	(70%)	32	(66%)	NS

F – female; M – male; NS – not significant; PAD – peripheral arterial disease; PT – percutaneous thrombosuction.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (SPSS version 19; SPSS, Inc., Chicago, IL). Data are presented as mean ± standard deviation or percentages. To assess the significances of differences, the *t* test was used for means and chi-square for percentages. The p-values below 0.05 were considered statistically significant.

Results

Patients

We included 110 patients fulfilling the inclusion criteria in the study. From these, 105 patients (mean age 67±16 years; 53% men) had 6-month follow-up. The patients treated with tirofiban constituted 46% (N=48) of the patients. This was not a randomized study. Characteristics of the study population by treatment approach are presented in Table 1. The majority of patients (69%) had infra-popliteal occlusion and below-knee atrial thrombus (67%) presenting with a slightly higher frequency (54%) of Rutherford IIb clinical status. Overall, atrial fibrillation (n 64, 61%) and hypertension (n 60, 57%) were the most important comorbidities. Clinical features of the tirofiban-treated and -untreated patients were similar to each other, except for a higher frequency of diabetes (52% *vs.* 40%; p=0.05) and structural heart disease (5% *vs.* 21% p=0.001) in the tirofiban-treated group.

Slow flow entity was significantly higher in patients with diabetes mellitus (67%) and in smokers (57%). Post-procedural slow flow rate (17% *vs.* 30%; p<0.01) and distal embolization (6% *vs.* 16%; p=0.01) were significantly lower in patients receiving tirofiban. Rate of major (8% *vs.* 5%) and minor (29% *vs.* 9%) bleeds were higher in the tirofiban group, but the only statistically significant difference was minor bleeding rate.

Follow-up

During 6-month follow-up, post-procedural hemodialysis requirement, need for amputation, recurrent emboli, significant vessel lesions, and mortality were recorded in all patients. Only 1 death occurred in the total study population. The amputation rate was 9% and the rate of new occlusion was 19%. In both groups, hemodialysis requirement and recurrent emboli rates were the same (Table 2). Also, development of significant occlusion in the thrombus region was similar between those receiving and not receiving tirofiban (Table 2).

Discussion

Early PT intervention in ALI even without tirofiban use is an easy and effective approach. Additional use of tirofiban has reduced distal embolization and slow flow. Although need for amputation is lower, it is not significant. Major bleeding rate has not increased but the minor bleeding rate was high. In all groups of patients, additional procedures increased the success rate to 91.5%. This may be related to the early intervention

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Table 2. Periprocedural complications, 6-month follow-up data.

	PT only (N=57)		PT and tirofiban (N=48)		P
Periprocedural complications					
Procedural success	48	(84%)	44	(92%)	NS
Addition procedure success rate	52	(92%)	46	(96%)	NS
Slow flow	17	(30%)	6	(13%)	<0.01
Distal emboli	9	(16%)	3	(6%)	0.01
Amputation	6	(11%)	3	(6%)	NA
Dissection disturbing blood flow	5	(9%)	3	(6%)	NS
Renal insufficiency needing hemodialysis	1	(2%)	0	(0%)	NS
Major bleeding	3	(5%)	4	(8%)	NS
Minor bleeding	5	(9%)	14	(29%)	0.001
6-month follow-up					
Mortality	0	(0%)	1	(2%)	NS
Recurrent emboli	5	(9%)	2	(4%)	NS
Follow-up significant occlusion	11	(19%)	9	(19%)	NS

of patients. Slow flow rate was high in patients with DM and smoking. However, with exclusion, none of the patients were in Rutherford III stage in the first 24 h.

There is not any criterion standard invasive or medical treatment approach in ALI. Though knee and below-knee region thromboses rate are 50% of all cases, their response rate to treatment is lower than in upper segments [6]. Below-knee arterial thromboses occurred in 67% of our cases; they were complicated lesions for successful bypass or thrombectomy [1,20]. Even if the operation is successful, the surgical mortality rate can reach to 20%, especially in old and comorbid patients [25]. Thrombectomy is only applied above popliteal arteries [6]. Its use in knee and below-knee arterial thromboses is rare and not easy. Catheter-mediated thrombolytic therapy can be performed in these situations [1,26–30]. The rates of major and minor bleeding using the thrombolytic approach are 6–17% and up to 17%, respectively [27–30]. The average success rate is around 70% [29–32]. The 6-month amputation rate is around 12–28% [27–31]. In addition, thrombolytic use is contraindicated in 15–20% of ALI cases [19]. The low success rate in thrombolytic treatment is due to slow revascularization effect, inability to prevent myocardial infarction, organization of thrombus with different ages, and resistance to thrombolytic therapy [32]. Mechanical thrombectomy is another effective approach to below-knee arterial thromboses, with a success rate of 90% [14]. However, the procedure is complicated and the rate of recurrent emboli high [33,34]. Acute renal insufficiency and hemoglobinuria are other complications [33,34]. Other possible complications are residual occlusion, distal embolization, dissection, or lesions which need balloon or stent. Acute renal insufficiency due to hemoglobinuria caused by extreme muscle damage during or after mechanical thromboembolectomy may occur [13,14,33,34].

Administration of PT in the coronary system or in acute myocardial infarction effectively reduces thrombus load and prevents no-reflow/slow flow [17]. In myocardial infarction, aspiration of the thrombus and cleaning of atherosclerosis material before stent implantation has improved blood flow in arterioles and capillaries [35]. There are studies that show PT administration in ALI is effective [36]. However, distal microembolization and dissection are disadvantages of PT use [14]. In our study, the most important disadvantage was dissection via catheter, which significantly interrupts the flow (8%). This could be related to our catheter selection according to the vessel diameter for PT. Even with the thrombolytic approach, catheter-related trauma is 1.4%. In our cases, all dissections were mended by stenting.

Irreversible tissue damage in case of ALI starts after 6–8 h [37,38]. Although ALI can be treated up to 14 days after injury, early intervention reduces tissue damage and improves success [39]. Interventions within 24 h has good outcomes [40,41]. In our study, we have seen the same outcomes. Additional intervention had a 91.5% success outcome in all patients. Good outcomes and high success rate are due to intervention within 24 h. In the early stages, the thrombus is

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softer and more mobile. Later, the thrombus gets more organized and does not respond to thrombus aspiration and other medical procedures. Outcomes are also good in long-term follow-up (amputation 9%, survival rate 99%). In our study, no patient with clinical stage of Rutherford III was included within 24 h. This shows that early intervention prevented irreversible damage. This has affects the long-term success rate. Acute renal insufficiency due to extreme tissue damage in ALI is a serious problem. We observed no acute renal insufficiency case in our study, due to early intervention that reduces tissue damage and reopens the vessels. It has the same early revascularization benefits in myocardial infarction and cerebrovascular events, and in our study we had the same results.

Distal embolization is another factor affecting amputation and success rates of the procedure. In our study, the distal embolization rate was 1–20% [21,42,43]. Amputation could be needed despite successful revascularization. In our study, the amputation rate was 11%, and in the tirofiban group it was lower (6%). In other trials, tirofiban has also been effective on distal embolization. AHA and ESC have recommended tirofiban use in patients with massive thrombus, no-flow, slow flow, and thrombolytic complications for ST segment elevation myocardial infarction [44,45]. Tirofiban is effective in peripheral arterial disease with massive thrombus load, and using ALI with tpA has been shown to be effective and safe [19,36]. Decreased distal microembolization, platelet aggregation, and vascular thrombus formation potentially decreased abrupt PPI closure have increased the efficacy of thrombolytic therapy and improved long-term revascularization rates, with a potential decreased need for secondary re-interventions, especially in the diabetic ALI population [19,20]. PT in ALI has not been evaluated yet. In our study, tirofiban was effective and useful on slow flow and distal embolization. The importance of slow flow in ALI is not known well, but slow flow is associated with distal embolization [46]. Diabetes mellitus and smoking, which are risk factors for slow flow, are also risk factor for slow flow entity in ALI [47–49].

Despite the different amputation rates, it is lower in the tirofiban group (11% *vs.* 6%). The amputation rate was not significant in our study, probably due to patient number; however, significant outcomes could be reached in studies with more patients. Amputation can be secondary to distal embolization [50], so a lower amputation rate can be due to lower slow flow and distal emboli rate. As mentioned before, tirofiban is useful when applied to peripheric vascular disease for slow flow and distal microemboli. So during or post-surgical intervention, when slow flow or distal embolization is seen, tirofiban infusion can improve long-term success of the intervention. Tirofiban can be a good choice for patients with massive thrombus load.

Tirofiban increased the minor bleeding rate significantly (29%). However, the adverse effect of bleeding on mortality and morbidity (8%) was lower than with other methods like thrombolytic approach. Significant major bleeding was not increased. In the thrombolytic approach, major bleeding and minor bleeding rates were 6–13% and 5–17%, respectively [45,51]. In ALI when patients' other diseases are taken in account, tirofiban has a negative effect on them but not on the procedure-related morbidity.

Our study has some limitations: it was a non-randomized retrospective study, and the number of patients in the study group was small because of inclusion of patients presenting within 24 h of symptom onset and the localization of the thrombus.

Conclusions

PT approach only within 24 h of symptoms of ALI in knee and below-knee arteries is impressively effective, with satisfactory results. Furthermore, implementation is easy. For these reasons, early PT therapy could be better than other methods. However, this study did not compare the different techniques. Bailout usage of tirofiban does have better impact on angiographic outcomes. Tirofiban could be used effectively in patients with slow flow entity and distal embolization, without increasing further risk.

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