Role of percutaneous catheter-directed thrombolysis in acute limb ischemia: predictors of outcome

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Objectives
Acute thrombotic ischemia is a very dangerous limb-threatening and life-threatening disease. It is better treated by catheter-directed thrombolysis. Now, tissue plasminogen activator like alteplase is safer than streptokinase or urokinase. The current study is designed to show its efficacy and safety and to investigate variables that correlate with outcome.

Patients and methods
This is a prospective cohort study. It included patients with acute thrombotic limb ischemia. Excluded ones were acute ischemia due to embolism, trauma, arterial dissection, complicated aneurysm, bleeding risk, history of recent intracranial bleeding, massive gangrene, or uncontrolled hypertension. The study is approved by ethical committee of Beni-Suef University. Primary end points were technical success, clinical success, and limb salvage. Secondary end points were procedural complications.

Results
A total of 36 patients were enrolled in the study from March 2019 to February 2020 in Beni-Suef University Hospital. It included 21 (58.33%) male patients. The patients' mean age was 58.42 years and mean BMI was 31.56 kg/m^2. Risk factors were smoking in 15 (41.67%) patients, diabetes mellitus in 16 (44.44%) patients, hypertension in 15 (41.67%) patients, ischemic heart disease in nine (25%) patients, and hyperlipidemia in 14 (38.89%) patients. Clinical presentation showed that 16 (44.44%) patients were in Rutherford IIa category and 20 (55.56%) patients were in Rutherford IIb category. Limb salvage was achieved in 14/16 (87.5%) of patients in Rutherford IIa category and 12/20 (60%) of patients in Rutherford IIb category. Statistical analysis showed a correlation of BMI and severity of ischemia with outcome. Moreover, the frequency of risk factors was correlated with outcome.

Conclusion
Catheter-directed thrombolysis using alteplase is effective and safe to treat acute thrombotic limb ischemia. Its outcome is better with lower BMI, less severe ischemia, and less or no comorbid disease.

Keywords:
acute ischemia, acute thrombosis, catheter-directed thrombolysis

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Introduction

Acute limb ischemia is defined as a sudden or acute onset of ischemic limb manifestation (coldness, pain, paresis, or paralysis), which can happen de novo or in already a limb with chronic ischemic manifestation [1]. The most common causes are embolism or acute thrombosis. Other less common causes are dissection, arterial injury, aneurysm with microemboli, and massive DVT [2]. Clinical classification of acute ischemia was designed to help to direct treatment and urgency of intervention. Grade I indicates viable limb, grade II indicates threatened limb, and grade III indicates nonviable limb [3]. Optimum treatment of acute ischemia has become a major source of debate over the past 2 decades. This is in addition to difficulty in differentiation between embolic and thrombotic ischemia. Moreover, demography of the patient, severity of ischemia, and status of the limb affect the process of decision making to treat acute limb ischemia [4]. Treatment options for viable threatened acute limb ischemia include endovascular (intra-arterial thrombolysis, aspiration or rheolytic thrombectomy, and/or angioplasty) or open surgical (thromboembolectomy, endarterectomy, and/or bypass) revascularization [5]. Catheter-directed thrombolysis aims to dissolute the newly formed thrombus using fibrinolytic drugs [6]. Adjunctive

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pharmacomechanical techniques have been advocated for some patients to minimize the dose of thrombolytic drug, embolic ischemia, and ischemia secondary to a stent failure or thrombosed prosthetic bypass grafts with an identifiable distal runoff vessel [7]. Treatment of acute thrombotic limb ischemia constitutes two goals. First is the removal of the newly formed thrombus, and second is the correction of underlying arterial occlusion or stenosis through endovascular technique or open surgery in case failed or not suitable endovascular options [4]. The current study was designed to show the efficacy and safety of catheter-directed thrombolysis in treating acute thrombotic limb ischemia and show their predictors of outcome.

Patients and methods

Study design

This is a prospective interventional cohort study including patients who presented with acute thrombotic ischemia. Inclusion criteria were patients who presented with acute thrombotic limb ischemia proved by a decrease in peripheral limb perfusion.

Exclusion criteria

The following were the exclusion criteria:

(1) Traumatic acute limb ischemia.
(2) Acute embolic limb ischemia.
(3) Significant clinically active bleeding.
(4) Potential bleeding risk.
(5) Uncontrolled hypertension.
(6) History of recent intracranial hemorrhage.
(7) Extensive gangrene or infection beyond salvage.
(8) Acute ischemia due to arterial dissection or associated aneurysm.

The study was approved by the ethical committee of the Faculty of Medicine, Beni-Suef University, and its assignment number was FWA00015574. A written consent was obtained from participating patients. Patients' characteristics and demography were obtained, such as age, sex, BMI, smoking, and comorbidities. Preoperative laboratory evaluation, ECG, and cardiac assessment were done for every patient.

Enrolment of patients

Patients with acute limb ischemia who attended Beni-Suef University Hospital (emergency department or outpatient clinic) were included. These patients had acute onset of ischemic symptoms (rest pain, paresthesia, sensory loss, or motor weakness) and signs (coldness, cyanosis, or pulselessness) from clinical history and physical examination. Routine laboratory, electrocardiogram, and imaging studies (duplex and/or computed tomographic angiography) were done. A provisional diagnosis of acute thrombotic limb ischemia was confirmed and then patients were asked to be enrolled in the study. After explaining the study concept, a written consent was taken from the patients. All patients were interfered within 3 days of onset of acute insult. All patients were monitored in the angio suite. They were given local anesthesia at access site. The sheath was inserted. Initial diagnostic arteriography was done to demonstrate the anatomy and level of occlusion using either a contralateral or ipsilateral approach. Fountain infusion catheter was used (Merit Medical Systems Inc., South Jordan, UT 84095, United States) to inject alteplase (Boehringer Ingelheim, Ingelheim, Germany) directly into the site of thrombotic lesion. Each alteplase vial contains 50-mg alteplase in powder form accompanied by another 50-ml solvent vial; so, after dissolution of the vial, the resulting vial contains alteplase in concentration of 1 mg/ml. The method of infusion used was bolus administration of 15-mg alteplase followed by continuous infusion of 1.5 ml/h for 24–48 h. The sheath and catheter were looped in the groin, draped, and fixed in position. Patients were monitored thoroughly in ICU especially regarding the vital signs, ischemic manifestations of the limb, and possible bleeding complications.

Follow-up angiography in theater was done at 24 and 48 h after alteplase infusion for confirmation of technical outcome of the procedure. Significant residual lesions were dealt with angioplasty±stenting. Sheath was removed 4 h after cessation of infusion of thrombolytic agent followed by manual compression till ensuring good hemostasis and then, a compressing bandage was applied to the site of arterial puncture for 24 h.

Postoperative care

Patients were discharged on medical treatment, which includes low-dose aspirin (75–150 mg) and clopidogrel 75 mg twice daily.

Outcome parameters

Several parameters were used to assess early and late outcomes, which include the following:

(1) Primary end points:
    (a) Technical success: uninterrupted patency of the revascularized vessel with restoration of blood flow to the distal end of the limb.
    (b) Clinical success: relief of acute ischemic symptoms and return to at least a preocclusive clinical baseline level.

(c) Limb salvage: avoidance of inevitable major amputation.

(2) Complications (secondary end points): hemorrhage, infection, death, and/or other complications like pulmonary edema or renal complications.

Statistical processing

The patients were distributed into different categories according to their age, sex, BMI, risk factors, and Rutherford's classification. Data were summarized using means and SD and frequencies and percentages for categorical factors. The data were analyzed using SAS (2013) software (SPSS Inc.). Patients were divided into two groups according to their outcome either success group or failure group. The FREQ procedure was used in this analysis with χ^2 test option to determine statistical differences. The significance of the results was assessed in the form of *P* value, which was differentiated into nonsignificant when *P* value more than 0.05 and significant when *P* value less than or equal to 0.05.

Results

The current study was conducted in Beni-Suef University Hospital from March 2019 to February 2020. It included 36 patients. They all presented with acute thrombotic lower limb ischemia. They were informed about the intervention, and consent was taken before being recruited in the study.

Patients' characteristics

Table 1 shows patients' characteristics and presentation in the current study. It included 21 (58.33%) male patients and 15 (41.67%) female patients. The patients' mean age was 58.42, and they were divided into four age groups: the first group included six patients (41–50 years old), the second group included 17 patients (51–60 years old), the third group included 11 patients (61–70 years old), and the fourth group included two patients older than 70 years.

The patients' mean BMI was 31.56 kg/m^2 in four groups; three patients in the first group had normal weight (BMI 18.5–24.9 kg/m^2), 11 patients in the second group were overweight (BMI 25–29.9 kg/m^2), 15 patients in the third group were obese (BMI 30–34.9 kg/m^2), and seven patients in the fourth group were morbidly obese (BMI ≥35 kg/m^2).

The risk factors associated with acute thrombotic lower limb ischemia found in our study were smoking in 15 (41.67%) patients, diabetes mellitus in 16 (44.44%) patients, hypertension in 15 (41.67%) patients, ischemic heart disease in nine (25%) patients, and hyperlipidemia in 14 (38.89%) patients.

Patients' presentation

Patients were classified according to Rutherford's clinical classification of acute limb ischemia; 16 (44.44%) patients were in Rutherford IIa category and 20 (55.56%) patients were in Rutherford IIb category. Table 1 demonstrates patients' characteristics and presentation.

Primary end points

Technical success was achieved in 13/16 (81.25%) of patients in Rutherford IIa category and 12/20 (60%) of patients in Rutherford IIb category.

Clinical success was achieved in 14/16 (87.5%) of patients in Rutherford IIa category and 12/20 (60%) of patients in Rutherford IIb category.

Limb salvage was achieved in 14/16 (87.5%) of patients in Rutherford IIa category and 12/20 (60%) of patients in Rutherford IIb category.

Secondary end points

No complications happened in all patients except minor groin hematoma in only two patients distributed to Rutherford IIb category. It

Table 1 Patients' characteristics and presentations

	n (%)
Sex	
Male	21 (58.33)
Female	15 (41.67)
Age	
41–50	6 (16.67)
51–60	17 (47.22)
61–70	11 (30.56)
>70	2 (5.56)
BMI	
Normal weight 18.5–24.9	3 (8.33)
Overweight 25–29.9	11 (30.56)
Obese 30–34.9	15 (41.67)
Morbidly obese ≥35	7 (19.44)
Risk factors	
Smoking	15 (41.67)
Diabetes mellitus	16 (44.44)
Hypertension	15 (41.67)
Ischemic heart disease	9 (25)
Hyperlipidemia	14 (38.89)
Rutherford's classification	
Rutherford IIa	16 (44.44)
Rutherford IIb	20 (55.56)

Table 2 Patients' outcome

Primary end point	Rutherford IIa [*n* (%)]	Rutherford IIb [*n* (%)]
Technical success	13/16 (81.25)	12/20 (60)
Clinical success	14/16 (87.5)	12/20 (60)
Limb salvage	14/16 (87.5)	12/20 (60)
Secondary end point		
Hemorrhage	0/16	2/20 (10)
Infection	0/16	0/20
Death	0/16	0/20

spontaneously disappeared during follow-up. Table 2 shows the study end points.

Correlation of patients' characteristics and presentation to patients' outcome

Table 3 shows the correlation of patients' characteristics and presentation with their outcome. Catheter-directed thrombolysis was successful in 26 (72.22%) of 36 patients. They were distributed into different groups according to age, sex, BMI, risk factors, and Rutherford's clinical classification of acute limb ischemia. Catheter-directed thrombolysis was failed in 10 (27.78%) of 36 patients and distributed into the same former groups. Statistical comparison was done between both groups for different variables.

(1) Regarding age, catheter-directed thrombolysis was successful in five patients in the first age group (41–50 years), 12 in the second age group (51–60 years), nine in the third age group (61–70 years), and none in the fourth age group (71 years or more). It was failed in one patient in the first age group, five in the second age group, two in the third age group, and two in the fourth age group (P=0.4619).
(2) Regarding sex, catheter-directed thrombolysis was successful in 16 male and 10 female patients. It was failed in five male and five female patients (P=0.1413).
(3) BMI: catheter-directed thrombolysis was successful in one normal weight, eight overweight, 13 obese, and four morbidly obese patients. It was failed in two patients with normal weight, three overweight, two obese, and three morbidly obese patients (P=0.0074).
(4) Regarding classification of risk factors, catheter-directed thrombolysis was successful in 10/26 smokers versus 5/10 patients in failed group (P=0.1841). It was successful in 11/26 diabetics versus 5/10 in failed patients (P=0.42). It was successful in 10/26 hypertensive patients versus 5/10 patients in failed group (P=0.5286). Moreover, it was successful in 10/26 patients with ischemic heart disease versus 5/10 failed patients (P=0.1008). It was successful in 9/26 hyperlipidemic patients versus 5/10 failed patients (P=0.8579).
(5) Regarding Rutherford's clinical classification of acute limb ischemia, catheter-directed thrombolysis was successful in 14/16 (87.5%) patients in Rutherford IIa category and 12/20 (60%) patients in Rutherford IIb category (P=0.0143, being a statistically significant value).

Correlation of frequency of risk factors in one patient to his outcome

The frequency of risk factors was assigned in each patient. Catheter-directed thrombolysis was successful in 26 patients; 2/26 had no risk factors versus 0/10 (P=0.0082). Moreover, it is successful in 6/26 patients with one risk factor versus 0/10 (P=0.0022). It is successful in 14/26 patients with two risk factors versus 7/10 patients (P=0.1025). It was successful in 4/26 with three risk factors versus 3/10 in failed group (P=0.1025). Table 4 shows the correlation of frequency of risk factors observed in the patients and their outcome.

The statistical analysis of the results shows no significant difference between success group and failure group regarding age (χ^2 value=7.7143, P=0.4618) and sex (χ^2 value=13.5, P=0.1413). These values indicate that both age and sex are not a predictive parameter for either success or failure of catheter-directed thrombolysis as a line of treatment in acute limb ischemia.

BMI statistical analysis shows significant difference between success group and failure group (χ^2 value=12, $P<0.05$). This indicates that BMI is a valuable predictive parameter for successful catheter-directed thrombolysis in acute limb ischemia. The lower is the BMI, the higher is the probability of successful results.

The frequency of risk factors is also a valuable predictive parameter for a successful catheter-directed thrombolysis in acute limb ischemia. The statistical analysis of risk factors shows significant difference between success and failure groups (χ^2 value=15, $P<0.05$). The probability of a successful catheter-directed thrombolysis in acute limb ischemia is higher in patients with lesser or no risk factors.

Patients who presented early and allocated in Rutherford IIb category showed better results than those who were allocated to Rutherford III category.

Table 3 Correlation of patients' demography and presentation to their outcome

Parameters	Category	Success [*n* (%)]	Failure [*n* (%)]	*P* value
Age	41–50	5 out of 26 (19.23)	1 out of 10 (10)	0.4619
	51–60	12 out of 26 (46.15)	5 out of 10 (50)	
	61–70	9 out of 26 (34.62)	2 out of 10 (20)	
	>70	0 out of 26	2 out of 10 (20)	
Sex	Male	16 out of 26 (61.54)	5 out of 10 (50)	0.1413
	Female	10 out of 26 (38.46)	5 out of 10 (50)	
BMI	Normal weight	1 out of 26 (3.85)	2 out of 10 (20)	0.0074*
	Overweight	8 out of 26 (30.77)	3 out of 10 (30)	
	Obese	13 out of 26 (50)	2 out of 10 (20)	
	Morbidly obese	4 out of 26 (15.38)	3 out of 10 (30)	
Risk factors	Smoking	10 out of 26 (38.46)	5 out of 10 (50)	0.1841
	DM	11 out of 26 (42.31)	5 out of 10 (50)	0.42
	HTN	10 out of 26 (38.46)	5 out of 10 (50)	0.5286
	IHD	6 out of 26 (23.08)	3 out of 10 (30)	0.1008
	Hyperlipidemia	9 out of 26 (34.62)	5 out of 10 (50)	0.8579
Rutherford classification	IIa	14 out of 16 (87.5)	2 out of 16 (12.5)	0.0143*
	IIb	12 out of 20 (60)	8 out of 20 (40)	

DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease. *Indicates statistically significant value.

Table 4 The frequency of risk factors observed in the patients in relation to their outcome

	Successful group [*n* (%)]	Failure group [*n* (%)]	*P* value
No risk factor	2 out of 26 (7.69)	0 out of 10 (0)	0.0082*
1 risk factor	6 out of 26 (23.08)	0 out of 10 (0)	0.0022*
2 risk factors	14 out of 26 (53.85)	7 out of 10 (70)	0.1025
3 risk factors	4 out of 26 (15.38)	3 out of 10 (30)	0.1025

*Indicates statistically significant value.

Regarding the statistical analysis of these results, there is a significant difference between success and failure groups (χ^2=6, P<0.05). So, the severity of ischemia at the time of presentation is of a valuable predictive value.

Discussion

Percutaneous thrombolysis using alteplase is a well-known, safe, and accepted option to treat patients presented with acute thrombotic ischemia. Its outcome may be affected by some variables. The current study is designed to show these variables. The obtained study results showed 58.33% of patients were males, and ~78% of patients between 51 and 70 years. Overall, 9% were average weight, 31% were overweight, 42% were obese, and nearly 20% were morbidly obese. Moreover, 42% were smoker, 45% were diabetics, 42% were hypertensive, 25% were ischemic heart disease and 39% were hyperlipidemic. In addition, 44% of patients were distributed to Rutherford's classification IIa and 56% to IIb. Limb salvage is achieved in 87.5% of patients with Rutherford IIa category and 60% of patients in Rutherford IIb category. With correlation of patients' demography and clinical presentation with outcome, some variables were found to be correlated. BMI and clinical limb status were correlated. Moreover, the frequency of risk factors in an individual patient was found to be correlated. These results were supported by those of Plate *et al.* [8] who showed nonsevere ischemia predicts initially successful thrombolysis. However, BMI and frequency of risk factors to outcome were not analyzed by Plate in his study. Earnshaw *et al.* [9] investigated clinical variable affecting outcome performed on a large national audit of thrombolysis for acute leg ischemia (NATALI). Earnshaw and colleagues detected that diabetes, increasing age, and severe ischemia were associated with worse outcome. However, shorter duration of ischemia was associated with better outcome. The current study did not show an association of sex and age with outcome, which is supported by Rajan and colleagues who reported that sex and age do not have a significant effect on the outcome of thrombolysis. Moreover, Kuoppala *et al.* [10] did not find any association between increasing age and outcome.

Ouriel and Veith [11] proved a correlation between body weight and patient's outcome. However, they showed improved outcome in heavier patients. A criticism that could be directed that Ouriel and Veith used bare body weight instead of BMI in their study in contrast to what the current study did. That may explain this controversy. Of interest, Ouriel and Veith themselves assume that it was an

accidental association rather than causality correlation. Certainly, they declared that if somebody looks at 28 variables at the 0.05 level, some may be significant by chance alone.

Many authors [9–12] have reported a strong correlation between the severity of ischemia and clinical outcome with thrombolytic treatment.

Limitations of the current study include relatively low number of patients; some variables were not assessed like patients' imaging and level of arterial occlusion, as well as outflow vessels. In addition, it is a single-center study. Future studies may investigate more options of revascularization like mechanical thrombectomy, combined methods and adjuvant techniques for revascularization like hybrid endovascular and surgical intervention.

Conclusion

Percutaneous catheter-directed thrombolysis using alteplase is well known to be effective and safe in treating acute thrombotic ischemia. Its outcome is better with lower BMI and less severe clinical manifestations. Patients with less or no comorbid disease are more likely to have better results.

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Conflicts of interest

There are no conflicts of interest.

References

1 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. TASC II Working Group.Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg 2007; 45(Suppl S): S5–S67.

2 Berridge DC, Kessel DO, Robertson I. Surgery versus thrombolysis for initial management of acute limb ischemia. Cochrane Database Syst Rev 2013; 6:CD002784.

3 Lyden SP. Endovascular treatment of acute limb ischemia: review of current plasminogen activators and mechanical thrombectomy devices. Perspect Vasc Surg Endovasc Ther 2010; 22:219–222.

4 Branco BC, Montero-Baker MF, Mills JL Sr. The pros and cons of endovascular and open surgical treatments for patients with acute limb ischemia. J Cardiovasc Surg 2015; 56:1–2.

5 Enezate TH, Omran J, Mahmud E, Patel M, Abu-Fadel MS, White CJ, Al-Dadah AS. Endovascular versus surgical treatment for acute limb ischemia: a systematic review and meta-analysis of clinical trials. Cardiovasc Diagn Ther 2017; 7:264–271.

6 Robertson I, Kessel DO, Berridge DC. Fibrinolytic agents for peripheral arterial occlusion. Cochrane Database Syst Rev 2013; 12:CD001099.

7 Byrne RM, Taha AG, Avgerinos E, Marone LK, Makaroun MS, Chaer RA. Contemporary out-comes of endovascular interventions for acute limb ischemia. J Vasc Surg 2014; 59:988–995.

8 Plate G, Oredsson S, Lanke J. When is thrombolysis for acute lower limb ischemia worthwhile? Eur J Vasc Endovasc Surg 2009; 37:206–212.

9 Earnshaw JJ, Whitman B, Foy C. National audit of thrombolysisfor acute leg ischemia (NATALI): clinical factors associated with early outcome. J Vasc Surg 2004; 39:1018–1025.

10 Kuoppala M, Franzen S, Lindblad B, Acosta S. Long-term prog-nostic factors after thrombolysis for lower limb ischemia. J Vasc Surg 2008; 47:1243–1250.

11 Ouriel K, Veith F. Acute lower limb ischemia: determinant of outcome. Surgery 1998; 124:336–342.

12 Rajan DK, Patel NH, Valji K, Cardella JF, Bakal C, Brown D, *et al.* Quality improvement guidelines for percutaneous management of acute limb ischemia. J Vasc Interv Radiol 2005; 16:585–595.