SAFETY AND EFFICACY OF THE PERCUTANEOUS ENDOVASCULAR INTERVENTION IN SUBJECTS WITH ACUTE LIMB ISCHEMIA

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ABSTRACT

Background: Acute lower limb ischemia associated with thrombotic events is a life-threatening condition. The treatment choice for this condition is catheter-directed thrombolysis considered the best treatment choice. An efficient and safe thrombolytic agent used is tissue plasminogen activator-like alteplase.

Aim: To assess the efficacy and safety of percutaneous endovascular intervention in acute limb ischemia.

Methods: In 72 subjects with acute thrombotic lower limb ischemia following thrombolysis limb salvage, clinical success, and technical success was assessed along with procedural complications.

Results: Clinical success as limb salvage was seen in 87.5% (n=28) subjects with Rutherford classification II a and in 65% (n=26) subjects with Rutherford II b classification. Rutherford II b subjects were significantly lower in the success group (p=0.001). Risk factors include hyperlipidemia, ischemic heart disease, and hypertension. Diabetes mellitus and smoking were significantly higher in the failure group compared to the success group with p= 0.001. Morbidly obese and normal weight subjects were significantly higher in the failure group compared to the success group, whereas, overweight and obese subjects were higher in the success group than the failure group with p=0.007. Males and female subjects were statistically comparable in success and failure groups with p=0.16. The subjects in different age ranges were comparable between the success and failure groups with p=0.44

Conclusion: Catheter-directed thrombolysis utilizing alteplase is an effective and safe management modality for acute thrombotic lower limb ischemia. Also, better results were seen in subjects with no associated comorbidity, less severe clinical presentation, and low BMI.

Keywords: acute limb ischemia, acute thrombotic ischemia, catheter-directed thrombolysis, ischemia, thrombolysis.

INTRODUCTION

ALI (acute limb ischemia) is a clinical condition identified as the sudden onset of ischemia signs or symptoms owing to a decrease in the peripheral limb perfusion.[1] ALI can be seen due to rapid progression of the disease in subjects with pre-existing symptoms of peripheral arterial disease or can be seen in subjects who were previously asymptomatic.[2] The etiology of acute limb ischemia is mainly considered to be either embolism or native thrombosis. Other less common etiologies are peripheral aneurysm causing emboli or thrombosis, graft/reconstruction thrombosis, acute arterial dissection, and/or trauma. Acute ischemia was clinically classified to assess the need for urgent intervention and to determine the direct

treatment. Grade I, II, and III ischemia suggest viable limb, threatened limb, and non-viable limb respectively.[3,4]

Appropriate management of acute limb ischemia is a controversial issue for the past few decades. Also, it is difficult to differentiate between thrombotic and embolic ischemia. Treatment choice and treatment decision making is also affected by limb status, ischemia severity, and demographics of the subjects.[5] Treatment of the viable threatened acute limb ischemia can be done by either open surgical revascularization (bypass, endarterectomy, and/or thrombo-embolectomy) or endovascular revascularization including the angioplasty, rheolytic, or aspiration thrombectomy, and/or intra-arterial thrombolysis.[6]

Catheter-directed thrombolysis is done in acute limb ischemia to dissolve the newly made thrombus with the use of fibrinolytic agents. Additional pharmaco-mechanical techniques have been advised in a few subjects to reduce the thrombolytic drug dose including the subjects with thrombosed prosthetic bypass grafts with visible distal runoff vessel, ischemia secondary to stent failure, and embolic ischemia.[7]

The treatment of acute thrombotic limb ischemia is to achieve two outcomes comprising of removing the newly formed thrombus followed by correcting the underlying stenosis or arterial occlusion via open surgery or endovascular technique in cases not suitable for endovascular intervention or cases with the previous failure.[8] The present study aimed to assess the efficacy and safety of percutaneous catheter-directed thrombolysis in managing acute limb ischemia.

MATERIALS AND METHODS

The present prospective observational study aimed to assess the efficacy and safety of percutaneous catheter-directed thrombolysis in managing acute limb ischemia. The study was done at Department of Orthopaedics, Basaveshwara Medical College and Hospital, Chitradurga, Karnataka. The study population was comprised of subjects from the Department of General Surgery of the Institute. After explaining the detailed study design, informed consent was taken from all the subjects in both verbal and written format.

The study included 72 subjects having Grade IIa and IIb acute thrombotic limb ischemia following Rutherford's clinical classification. All 72 subjects were managed with catheter-directed thrombolysis using alteplase and were assessed for their safety and efficacy. At the time of presentation, risk factors and characteristics were assessed for all the subjects.

The inclusion criteria for the study were subjects with grade IIa and IIb acute thrombotic limb ischemia following Rutherford's clinical criteria, having conformed radiographic and clinical diagnosis on CTA and/or duplex, and willing to participate in the study. The exclusion criteria were subjects with ischemia secondary to the associated aneurysm and arterial dissection, extensive infection or gangrene, uncontrolled hypertension, bleeding risk, clinically active bleeding, and traumatic acute limb ischemia. After the final inclusion of the study subjects, detailed history was recorded followed by a clinical examination. The demographics recorded were comorbidities, smoking, BMI (body mass index), gender, and age. Preoperatively, cardiac assessment, ECG, and laboratory investigations were done on all the subjects.

After the admission of the subjects to the institute, the subjects were given proper analgesia and rehydration or intravenous fluids followed by IV heparin in bolus loading dose and then maintenance dose to prevent the propagation of the thrombus.

All subjects were angio suite monitored for electrocardiographic activities, heart rate, oxygen saturation, and blood pressure. At the access site, local anesthesia was given followed by sheath insertion. Diagnostic angiography was done to assess the level and anatomy of occlusion using an ipsilateral or contralateral approach. Alteplase was injected using a catheter, directly into the thrombotic lesion site. Each injection had 50 mg alteplase dissolved in a solution making it 1mg/ml. The infusion method adopted was 10mg alteplase administration followed by a 1.5 mg/hour infusion for the next 24-48 hours. All subjects were thoroughly monitored in ICU (intensive care unit) to assess vital signs, general status, complications, and ischemic limb manifestations. At follow-up, angiography was repeated at 24 and 48 hours of alteplase infusion to confirm the technical procedure outcomes. The remaining lesion was managed by angioplasty with or without the stent. After sheath removal at 4 hours of infusion stoppage, manual compression was done till good hemostasis was achieved. The arterial puncture site was covered with a compression bandage for the next 24 hours.

Postoperatively, all subjects were advised for anticoagulants including rivaroxaban 5-10 mg once daily or marivan 5 mg once daily, and low dose aspirin 75-150 mg/d for antiplatelet action. The outcomes assessed were technical success assessed non-interruption of the revascularized vessel and blood flow restoration at distal limb end and clinical success by acute ischemia symptom relief. Other outcomes assessed were infection, hemorrhage, complications, limb salvage avoiding inevitable major amputation, death, and other complications such as renal complications and edema.

The data collected were assessed statistically using logistic regression and multivariate statistical techniques. The data were presented in tabulated and descriptive formats. SPSS version 22.0, 2013, Armonk, NY: IBM Corp and chi-square and Fisher exact test were utilized. The data were expressed as mean and standard deviations and as percentages and numbers with a 0.05% significance level.

RESULTS

The study included 72 subjects having Grade IIa and IIb acute thrombotic limb ischemia following Rutherford's clinical classification. 44.4% (n=32) of subjects were in the classification of IIa and 55.5% of subjects were in Rutherford's classification IIb. Majority of the participants were in the age range of 51-60 years with 47.2% (n=34) subjects followed by 30.5% n=22) subjects from 61-70 years, 16.6% (n=12) subjects in 41-50 years, and least 5.55% (n=4) subjects in >70 years of age. There were 58.3% (n=42) males and 41.6% (n=30) females in the present study. The most common associated comorbidity was diabetes mellitus seen in 44.4% (n=32) study subjects followed by hypertension and smoking each in 41.6% (n=30) study subjects, and ischemic heart disease in 25% (n=18) study subjects respectively. Most of the study subjects were obese with 41.6% (n=30) subjects followed by 30.5% (n=22) overweight subjects, 19.4% (n=14) morbidly obese subjects, and 8.33% (n=6) subjects were obese as shown in Table 1.

On assessing the subject outcomes following catheter-directed thrombolysis using alteplase, it was seen that clinical success as limb salvage was seen in 87.5% (n=28) subjects with Rutherford classification II a and in 65% (n=26) subjects with Rutherford II b classification. The primary endpoint in the study was technical success which was seen in 81.25% (n=26) subjects with Rutherford II a and 60% (n=24) Rutherford II b classification. For secondary

endpoints, no death or infection was seen in any subject with Rutherford II a or Rutherford II b classification. Hemorrhage was not seen in any subject from Rutherford II a and in 10% (n=4) subjects with Rutherford II b (Table 2).

Concerning the association of patient outcomes to the number of risk factors in study subjects, in the success group no risk factor was seen in 7.69% (n=4) study subjects, 1 risk factor in 23.07% (n=12) study subjects, and 2 risk factors in 53.8% (n=28) study subjects which were statistically significant with p-values of 0.007, 0.007, and 0.0001 respectively. For 4 risk factors, success was seen in 15.38% (n=8) study subjects which were statistically non-significant with p=0.07. In the failure group, no subjects had 0 or 1 risk factor which was statistically significant with p=0.007 for both. For failure, 2 and 3 risk factors were present in 70% (n=14) and 30% (n=6) of study subjects respectively which was statistically non-significant with p=0.12 for both as shown in Table 3.

In the success and failure group, there were 60% (n=28) and 87.5% (n=24) subjects from Rutherford II a and 12.5% (n=4) and 40% (n=16) subjects from Rutherford II b respectively which was significantly higher for Rutherford IIa subjects in success group (p=0.01) and Rutherford II b subjects were significantly lower in success group (p=0.001). Risk factors include hyperlipidemia, ischemic heart disease, and hypertension. Diabetes mellitus and smoking were significantly higher in the failure group compared to the success group with p= 0.001. Morbidly obese and normal weight subjects were significantly higher in the failure group compared to the success group, whereas, overweight and obese subjects were higher in the success group than the failure group with p=0.007. Males and female subjects were statistically comparable in success and failure groups with p=0.16. The subjects in different age ranges were comparable between the success and failure groups with p=0.44 as shown in Table 4.

DISCUSSION

The study included 72 subjects having Grade IIa and IIb acute thrombotic limb ischemia following Rutherford's clinical classification. 44.4% (n=32) of subjects were in the classification of IIa and 55.5% of subjects were in Rutherford's classification IIb. Majority of the participants were in the age range of 51-60 years with 47.2% (n=34) subjects followed by 30.5% n=22) subjects from 61-70 years, 16.6% (n=12) subjects in 41-50 years, and least 5.55% (n=4) subjects in >70 years of age. There were 58.3% (n=42) males and 41.6% (n=30) females in the present study. The most common associated comorbidity was diabetes mellitus seen in 44.4% (n=32) study subjects followed by hypertension and smoking each in 41.6% (n=30) study subjects, and ischemic heart disease in 25% (n=18) study subjects respectively. Most of the study subjects were obese with 41.6% (n=30) subjects followed by 30.5% (n=22) overweight subjects, 19.4% (n=14) morbidly obese subjects, and 8.33% (n=6) subjects were obese. These data were compared to the studies of Branco BC et al[9] in 2015 and Kuoppala M et al[10] in 2008 where authors assessed subjects with demographics comparable to the present study.

The study results showed that following catheter-directed thrombolysis using alteplase, it was seen that clinical success as limb salvage was seen in 87.5% (n=28) subjects with Rutherford classification II a and in 65% (n=26) subjects with Rutherford II b classification. The primary endpoint in the study was technical success which was seen in 81.25% (n=26) subjects with Rutherford II a and 60% (n=24) Rutherford II b classification. For secondary endpoints, no

death or infection was seen in any subject with Rutherford II a or Rutherford II b classification. Hemorrhage was not seen in any subject from Rutherford II a and in 10% (n=4) subjects with Rutherford II b. These results were consistent with the studies of Enezate TH et al[11] in 2017 and Lian WS et al[12] in 2020 where authors reported comparable success rates of catheter-directed thrombolysis as in the present study.

For the association of patient outcomes to the number of risk factors in study subjects, in the success group no risk factor was seen in 7.69% (n=4) study subjects, 1 risk factor in 23.07% (n=12) study subjects, and 2 risk factors in 53.8% (n=28) study subjects which were statistically significant with p-values of 0.007, 0.007, and 0.0001 respectively. For 4 risk factors, success was seen in 15.38% (n=8) study subjects which were statistically non-significant with p=0.07. In the failure group, no subjects had 0 or 1 risk factor which was statistically significant with p=0.007 for both. For failure, 2 and 3 risk factors were present in 70% (n=14) and 30% (n=6) study subjects respectively which was statistically non-significant with p=0.12 for both. These findings were in agreement with the findings of Urbak L et al[13] in 2017 and Robertson I et al[14] in 2013 where authors reported comparable association of risk factors and patient outcomes in their studies as in the present study.

The study results showed that in the success and failure group, there were 60% (n=28) and 87.5% (n=24) subjects from Rutherford II a and 12.5% (n=4) and 40% (n=16) subjects from Rutherford II b respectively which was significantly higher for Rutherford II in success group (p=0.01) and Rutherford II b subjects were significantly lower in success group (p=0.001). Risk factors include hyperlipidemia, ischemic heart disease, and hypertension. Diabetes mellitus and smoking were significantly higher in the failure group compared to the success group with p= 0.001. Morbidly obese and normal weight subjects were significantly higher in the failure group compared to the success group, whereas, overweight and obese subjects were higher in the success group than the failure group with p=0.007. Males and female subjects were statistically comparable in success and failure groups with p=0.16. The subjects in different age ranges were comparable between the success and failure groups with p=0.44. These results were in line with the studies of Byrne RM et al[15] in 2014 and Berridge DC et al[16] in 2013 where authors suggested similar success and failure rates following catheter-directed thrombolysis in subjects with acute limb ischemia.

CONCLUSION

Considering its limitations, the present study concludes that Catheter-directed thrombolysis utilizing alteplase is an effective and safe management modality for acute thrombotic lower limb ischemia. Also, better results were seen in subjects with no associated comorbidity, less severe clinical presentation, and low BMI. The limitations of this study were smaller considered population, shirt monitoring, and biased related to the geographic location warranting further long-term studies planned longitudinally.

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TABLES

Characteristics	**Percentage (%)**	**Number (n=72)**
Rutherford's classification		
II a	44.4	32
II b	55.5	40
Age range (years)		
41-50	16.6	12
51-60	47.2	34
61-70	30.5	22
>70	5.55	4
Gender		
Males	58.3	42
Females	41.6	30
Risk factors		
Hyperlipidemia	38.8	28
Ischemic heart disease	25	18
Hypertension	41.6	30
Diabetes mellitus	44.4	32
Smoking	41.6	30
BMI (kg/m2)		
Normal (18.5-24.9)	8.33	6
Overweight (25-29.9)	30.5	22
Obese (30-34.9)	41.6	30
Morbidly obese (≥35)	19.4	14

Table 1: Demographic and disease characteristics of the study subjects

S. No	**Success**	**Rutherford II a**		**Rutherford II b**	
		Percentage (%)	**Number (n=32)**	**Percentage (%)**	**Number (n=40)**
1.	**Clinical success**				
a)	Limb salvage	87.5	28	65	26
2.	**Primary endpoint**				
a)	Technical success	81.25	26	60	24
3.	**Secondary endpoint**				
a)	Death	0	0	0	0
b)	Infection	0	0	0	0
c)	Hemorrhage	0	0	10	4

Table 2: Outcomes in study subjects following catheter-directed thrombolysis using alteplase

Risk factors	Success Group			Failure Group		
	%	n= 52	p-value	%	n= 20	p-value
No	7.69	4	0.007	0	0	0.007
1	23.07	12	0.007	0	0	0.007
2	53.8	28	**0.0001**	70	14	0.12
3	15.38	8	0.07	30	6	0.12

Table 3: Association of patient outcomes to the number of risk factors in study subjects

Parameter	Success		Failure		p-value
	%	n	%	n	
Rutherford classification					
II a	60	28	12.5	4	**0.01**
II b	87.5	24	40	16	
Risk factors					
Hyperlipidemia	34.6	18	50	10	**0.001**
Ischemic heart disease	23	12	30	6	
Hypertension	38.4	20	50	10	
Diabetes mellitus	42.3	22	50	10	
Smoking	38.4	20	50	10	
BMI					
Normal (18.5-24.9)	3.85	2	20	4	**0.007**
Overweight (25-29.9)	30.7	16	30	6	
Obese (30-34.9)	50	26	20	4	
Morbidly obese (≥35)	15.3	8	30	6	
Gender					
Males	61.5	32	50	10	0.16
Females	38.4	20	50	10	
Age range (years)					
41-50	19.2	10	10	2	0.44
51-60	46.1	22	50	10	
61-70	34.6	18	20	4	
>70	0	0	20	4	

Table 4: Correlation of demographics and outcomes in the study participants