Outcomes of Intra-operative Thrombolysis in Late Acute Arterial Embolism of the Lower Limb in a Cohort of Patients in Thailand

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Background: *Patients with acute arterial embolism of the lower limb who present early and are treated promptly. Surgical embolectomy is successful more than 90%. Patients with late presentation of acute arterial embolism of the lower limb with immediate threatened severity (Rutherford grade IIB), need emergency revascularization. Surgical embolectomy without adjunctive treatment is successful in only 60 to 70%. The patients need to get intraoperative thrombolysis to improve the outcome of treatment.*

Objective: *We sought to establish the outcomes of Thai patients undergoing intra-operative thrombolysis combined with surgical embolectomy for late acute arterial embolism of the lower limb who presented with immediately threatened severity (Rutherford grade IIB). We aimed to use our findings to inform the development of new treatment guidelines and protocols in Thailand.*

Material and Method: *We reviewed the records of 37 late-presenting patients with immediately threatened severity lower limb ischemia who underwent embolectomy with intra-operative thrombolysis between January 1995 and December 2014 under the care of the Department of Vascular Surgery, Siriraj Hospital, Bangkok, Thailand. We recorded patients' demographic data, intra-operative data, postoperative complications, limb salvageability rate and mortality rate 1 month and 1 year after treatment.*

Results: *The median time that elapsed between symptom onset and revascularization was 7 day (range 1 to 120 day). Twenty-two patients (59.5%) were treated with streptokinase, with the remainder treated with recombinant tissue plasminogen activator. The limb salvageability rate within 1 month and 1 year showed the same results (89.2%). The mortality rate within 1 month was 5.4% but 10.8% at 1 year. The recovery of four patients was complicated by hemorrhage, seven by re-thrombosis, three by wound hematoma, one by postoperative myocardial infarction, one by surgical site infection and one by gangrene.*

Conclusion: *Intra-operative thrombolysis is a safe and effective adjunct to embolectomy that increases limb salvageability in Thai patients with late acute arterial embolism of the lower limb.*

Keywords: *acute arterial occlusion, embolism, lower limb ischemia, thrombolysis*

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Acute limb ischemia may threaten life or limb if revascularization is delayed or fails. Patients with acute arterial embolism of the lower limb with immediately threatened severity (Rutherford grade IIB) need emergency revascularization, and surgical embolectomy is the treatment modality of choice[1]. Embolectomy without adjunctive treatment is successful in only 60 to 70% of late-presenting patients, who make up the majority of patients with acute embolism[2], compared with more than 90% of those who present earlier and are treated promptly[2,3]. This is likely a consequence of increased adhesion between the emboli and the endothelium of the occluded arterial segment when the duration of occlusion exceeds 24 hour.

Incomplete thromboembolectomy is observed in more than 30% of late-presenting cases, either due to persistent occlusion at the original site or in

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inaccessible distal vessels[4]. As this increases the likelihood of amputation, additional techniques are needed to facilitate the complete removal of thrombus and increase limb salvageability rate. The therapeutic benefits of intra-operative intra-arterial thrombolysis following embolectomy are well established[5-7], particularly as the risk of hemorrhage does not appear to be increased[8]. Nonetheless, in Thailand intra-operative thrombolysis was not widely undertaken due to a lack of approved protocols and guidelines[9].

We sought to demonstrate the outcomes of intra-operative thrombolysis combined with surgical embolectomy in late-presenting patients with acute arterial embolism of the lower limb of Rutherford grade IIB severity, to inform the development of clinical management guidelines for Thai patients.

Material and Method

Conduct of the study was approved by Siriraj Hospital Institutional Review Board. The medical records of 37 patients presenting late with acute arterial embolism of the lower limb with Rutherford grade IIB severity and who underwent embolectomy with intra-operative thrombolysis between January 1995 and December 2014 under the care of the Department of Vascular Surgery, Siriraj Hospital, Bangkok, Thailand, were reviewed retrospectively. We recorded patients' demographic and clinical characteristics, including intra-operative data, postoperative complications, limb salvage ability and mortality at 1 month and 1 year. Cases in which data were incomplete or missing, and those lost to follow-up within the first year were excluded.

Late-presenting patients with acute arterial embolism were defined as those with acute limb ischemia caused emboli presenting more than 24 hour after symptom onset. Immediately threatened severity (Rutherford grade IIB) was characterized by sensory loss above the toes with rest pain, mild to moderate muscle weakness and audible venous Doppler signals in the absence of arterial flow[10].

The primary outcome measures were limb salvageability rate within 1 month and 1 year of treatment; the secondary outcomes were mortality rate within 1 month and 1 year of treatment, and the incidence of postoperative complications.

Surgical technique

All cases were treated as emergencies. Femoral exploration was undertaken under local infiltration anesthesia, and general or regional anesthesia was used for popliteal exploration. Embolectomy was performed by a direct approach to the artery followed by the removal of the embolus with a Fogarty balloon catheter. If persistent emboli were evident on intra-operative arteriography, thrombolytic agents were infused directly into distal arterial lumen through the arteriotomy. Streptokinase (SK) or recombinant tissue plasminogen activator (rt-PA) was used. After 30 min, repeat arteriography was performed, and if the residual obstruction of the distal artery had completely resolved, the arteriotomy was closed with 6/0 Prolene (Ethicon). Thrombolysis and arteriography were repeated if persistent emboli were still visible, and a second attempt at embolectomy was made until the embolus was completely removed and the arteriotomy was closed. Should this strategy have proved unsuccessful, an assessment of the patency of the distal artery was made and arterial bypass surgery or angioplasty were attempted (Fig. 1). The dose of the thrombolytic drug used was informed by the serum fibrinogen concentration, which was maintained >100 mg/dL. The total dose of SK ranged from 150,000 to 300,000 units, and 5 to 50 mg for rt-PA.

Statistical analysis

All data were analyzed using SPSS® version 16.0 (SPSS Inc., Chicago, IL). Parameters were reported as number and proportion (percentage), and mean or median with the standard deviation. Groups were compared using the Chi-squared test. Kaplan-Meier plots were constructed to examine postoperative limb survival and mortality. A p-value <0.05 was considered statistically significant.

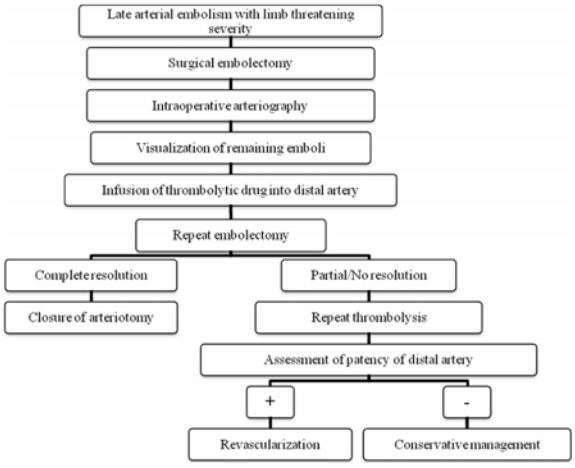

Fig. 1 Flow diagram outlining the surgical strategy used to treat lower limb ischemia.

Results

Patients' demographic and clinical characteristics are shown in Table 1. Two-thirds were men. The median age was 61 year (range 21 to 93 year). Hypertension and smoking were the most common comorbidities (each was observed in more than 50% of patients). Atrial fibrillation, a well-recognized cause of thromboembolism, was found in 16.2%. The median duration of symptoms before revascularization was 7 day (range 1 to 120 day), with just under half patients (40.5%) experiencing symptoms for 7 to 14 day before treatment. The femoral artery was the most common site of occlusion (62.2%), followed by the popliteal artery (24.3%).

22 patients (59.5%) were treated with SK and the remainder with rt-PA. Embolectomy was undertaken through a femoral arteriotomy in the majority of patients (29, 78.4%). Embolectomy and intra-operative intra-arterial thrombolysis were sufficient to resolve arterial obstruction in 23 patients (62.2%), but seven (18.9%) needed additional bypass surgery, Six (16.2%) underwent angioplasty and one patient (2.7%) was treated with angioplasty and bypass surgery (Table 2). Mean intra-operative blood loss was 471±583 mL (20 to 2,500 mL); there was no significant difference between those who received SK and those who were treated with rt-PA (Table 3). Five patients (13.5%) required perioperative blood transfusion; the mean volume transfused was 0.21 units. No patient had a severe allergic reaction.

The limb salvage ability rate within 1 month of treatment of the entire cohort was 89.2% (33 of 37 patients, (Table 4); 20 of the 22 patients (90.9%) who received SK and thirteen of the 15 (86.7%) who received rt-PA. At 1 year, limb salvage ability rate of the surviving cohort was 89.2% (33 out of 37 patients); 90.9% (20 out of 22 patients) who received SK and 86.7% (13 out of 15) who received rt-PA. There was no statistical significance between the SK and rt-PA groups in terms of limb salvage ability or mortality (Fig. 2 and 3, Table 4). All-cause mortality within 1 month was 5.4% (two out of 37 patients), which represented 4.5% of the SK group and 6.7% of the rt-PA group. All cause mortality at 1 year was 10.8% (four deaths out of 37 patients); one of the 15 surviving patients who had received SK, died (6.7%), and three of the 15 who had received rt-PA (20.0%, Table 4). Limb salvage ability at 1 month was 82.6% in the 23 patients treated with thrombolytic therapy alone, compared with 78.6% in the 14 patients who required additional procedures (Table 5).

The recovery of four patients was complicated by postoperative hemorrhage, seven by re-thrombosis, three by wound hematoma, one by postoperative myocardial infarction, one by surgical site infection and one by gangrene (Table 6). There were no incidences of intracranial hemorrhage. Hemorrhage was not life threatening in any of the four patients

Table 1. Demographic data

	n = 37
Gender	
Male	24 (64.9%)
Female	13 (35.1%)
Age (year)	
Range	21 to 93
Median	61
Comorbidities	
DM	6 (16.2%)
HTN	20 (54.1%)
DLP	7 (18.9%)
CAD	4 (10.8%)
AF	6 (16.2%)
Smoking	20 (54.1%)
Duration of symptoms (day)	
Range	1 to 120
Median	7
<7 days	14 (37.8%)
7 to 14 days	15 (40.5%)
>14 days	8 (21.6%)
Side (right/left)	22/15 (59.5%/40.5%)
Sites of arterial occlusion (n)	
Iliac	3 (8.1%)
Femoral	23 (62.2%)
Popliteal	9 (24.3%)
Others	2 (5.4%)

Table 2. Operative details

	n
Thrombolytic agent	
Streptokinase	22 (59.5%)
rt-PA	15 (40.5%)
Embolectomy site	
Femoral	29 (78.4%)
Popliteal	8 (21.6%)
Embolectomy + Thrombolysis	23 (62.2%)
Embolectomy + Thrombolysis + Additional procedure	
Bypass	7 (18.9%)
Angioplasty	6 (16.2%)
Combined	1 (2.7%)

Table 3. Perioperative data

	Total (n = 37)	SK (n = 22)	rt-PA (n = 15)	*p*-value
Intraoperative blood loss (ml)				
Range	20 to 2,500	20 to 2,500	20 to 1,100	
Mean ± SD	471±583	407±571	561±493	NS
Median	300	250	450	
No. of pts required blood transfusion	5 (13.5%)	3 (13.6%)	2 (13.3%)	NS
Average blood replacement (unit)	0.21	0.18	0.27	NS
Severe allergic reaction	0	0	0	NS

Table 4. Outcome data

	Total	SK	rt-PA	*p*-value
Limb salvage in 1 month	33/37 (89.2%)	20/22 (90.9%)	13/15 (86.7%)	NS
Limb salvage in 1 year	33/37 (89.2%)	20/22 (90.9%)	13/15 (86.7%)	NS
Mortality in 1 month	2/37 (5.4%)	1/22 (4.5%)	1/15 (6.7%)	NS
Mortality in 1 year	4/37 (10.8%)	1/15 (6.7%)	3/15 (20.0%)	NS

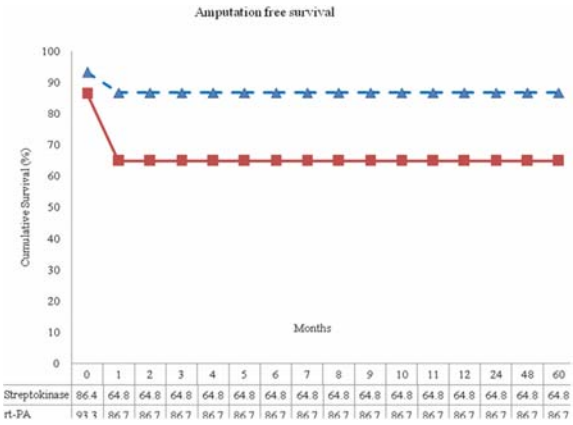

Fig. 2 Kaplan-Meier plot showing amputation-free survival of those who received streptokinase compared with those treated with rt-PA.

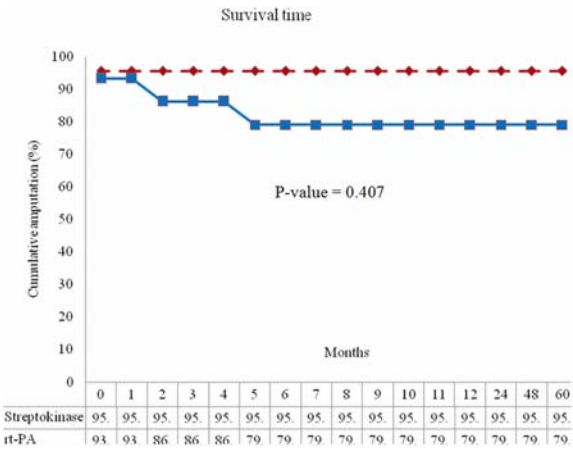

Fig. 3 Kaplan-Meier plot showing overall survival of those who received streptokinase compared with those treated with rt-PA.

who bled. The causes of death included two cases of wound infection, one of septicemia caused by urinary tract infection and one of myocardial infarction.

Discussion

Incomplete embolectomy in late-presenting patients with acute arterial embolism may be a consequence of adhesive emboli, residual emboli or inaccessibility of the infrapopliteal vessels to the balloon catheter, and can result in inadequate revascularization and an increased risk of amputation[9]. Intra-operative intra-arterial thrombolysis reportedly dissolves residual thrombus and improves revascularization: Parent et al reported a success rate of 88% in 17 limbs using streptokinase or urokinase[5]. Quinones-Baldrich et al reported the return of pulses and audible Doppler flow signals after intra-arterial SK infusion in five limbs of questionable viability after balloon-catheter thromboembolectomy[7]. A retrospective review of 21 patients with acute limb ischemia who underwent intra-arterial urokinase infusion after failed embolectomy found that complete lysis was achieved in 14 cases and partial lysis in

Table 5. Amputation rates in 1 month between thrombolytic therapy alone and with additional procedures

	Thrombolysis alone			With Additional procedures		
	SK	rt-PA	Total	SK	rt-PA	Total
Amputation	3 (20.0%)	1 (12.5%)	4 (17.4%)	2 (28.6%)	1 (14.3%)	3 (21.4%)
No amputation	12 (80.0%)	7 (87.5%)	19 (82.6%)	5 (71.4%)	6 (85.7%)	11 (78.6%)
Total	15 (100%)	8 (100%)	23 (100%)	7 (100%)	7 (100%)	14 (100%)

Table 6. Postoperative complications

	SK (n = 22)	rt-PA (n = 15)	Total (n = 37)
Bleeding	1 (4.5%)	3 (20.0%)	4 (10.8%)
Re-thrombosis	3 (13.6%)	4 (26.7%)	7 (18.9%)
Wound hematoma	2 (9.1%)	1 (6.7%)	3 (8.1%)
Myocardial infarction	1 (4.5%)	0	1 (2.7%)
Sepsis	0	1 (6.7%)	1 (2.7%)
Infected limb gangrene	1 (4.5%)	0	1 (2.7%)
Stroke	0	0	0

three[11]. In our series, 89.2% of limbs had been salvaged 1 month after intraoperative thrombolysis following incomplete embolectomy, which is broadly comparable with other reports. A previous study conducted at our institution found that of the majority of patients with limb ischemia presented to hospital more than 24 hour after symptom onset (65.9%), and of these, only 58.3% had a favorable outcome compared with 83.9% in those who presented sooner[2]. Wolosker et al reported similar findings[3]: favorable outcomes were achieved in 94% of those who presented within 24 hour of symptom onset, but in only 65% of those in whom presentation was delayed. Our study demonstrates that intra-operative thrombolysis appears to be an effective adjunct that could improve the incidence of positive outcome in late-presentation limb ischemia from about half to 89.2%.

We found that an 82.6% limb salvage rate could be achieved in patients in whom embolectomy was unsuccessful by adding thrombolytic therapy. Furthermore, intraoperative thrombolysis reportedly increases the chances of successful revascularization of the distal extremity by bypass surgery or an endovascular procedure if thrombolytic treatment had not dissolved all emboli but intra-operative arteriography showed that the distal artery was patent[12]. In our study, the limb salvage rate of the 14 patients who needed additional procedures was 78.6%. Even though thrombolysis could not lyse all emboli in all cases, the resultant improvement in arterial flow allowed distal vascular patency to be adequately visualized to allow planning of other revascularization strategies and hence increase the probability of limb salvage.

In a prospective randomized controlled trial, intra-arterial thrombolysis was reported to achieve high local drug concentrations in the proximity of residual thrombi without significantly depleting systemic fibrinogen, or provoking intraoperative bleeding or wound hematoma formation[8]. In this study, major hemorrhage occurred in 5% of patients, and minor hemorrhage in 15%[13], with no significant difference between patients treated with streptokinase or rt-PA. In our cohort the incidence of bleeding was 10.8%, but none was life threatening. In one patient treated with SK, fibrinogen depletion after thrombolysis was corrected by transfusion of blood products. Thrombolysis appears to be safe when the dose is carefully titrated against systemic fibrinogen concentration. Streptokinase was found to be as effective as rt-PA without increasing either the incidence of bleeding or allergic reactions.

Although our survival analysis raised the possibility that amputation-free survival was higher in those treated with rt-PA, and mortality was lower in those treated with SK, the differences between the

groups were not statistically significant. This is likely a consequence of our small sample size, and further study will be needed to draw firm conclusions. Another limitation is the retrospective nature of our study, as data may not be complete and complications may have been underreported.

Conclusion

Intra-operative thrombolysis appears to be a safe adjunct to embolectomy to increase limb salvage ability in late-presenting Thai patients with acute arterial embolism in the lower limb.

What is already known on this topic?

Acute limb ischemia may threaten life or limb if revascularization is delayed or fail. Patients with acute arterial embolism of the lower limb who present earlier and are treated promptly, surgical embolectomy is successful more than 90%. The patients who present late for surgical embolectomy without adjunctive treatment, it is successful in only 60 to 70%. The patients need to get intra-operative thrombolysis to improve the outcome of treatment.

What is study adds?

Intra-operative thrombolysis is a safe and effective adjunct to embolectomy that increases limb salvage ability in Thai patients with late acute arterial embolism of the lower limb.

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Potential conflicts of interest

None.

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ผลการรักษาผู้ป่วยหลอดเลือดแดงของขาอุดตันเฉียบพลันที่มาพบแพทย์ล่าช้าด้วยวิธีการผ่าตัดเอาลิ่มเลือดออกร่วมกับการให้ยาละลายลิ่มเลือดในระหว่างผ่าตัด

เฉนียน เรืองเศรษฐกิจ, วิภาวี นิยมในธรรม, คามิน ชินศักดิ์ชัย, ชุมพล วงวานิช, ณัฐวุฒิ เสริมสาธนสวัสดิ์, ประมุข มุทิรางกูร, สุธีคณิต หัถพรสวรรค์

ภูมิหลัง: ผู้ป่วยหลอดเลือดแดงของขาอุดตันเฉียบพลันที่มาพบแพทย์ภายใน 24 ชั่วโมง การผ่าตัดเอาลิ่มเลือดออกได้ผลการรักษาดีมากกว่าร้อยละ 90 ในผู้ป่วยที่มาล่าช้าและมีภาวะของการขาดเลือดของขารุนแรง (Rutherford grade IIB) การผ่าตัดเอาลิ่มเลือดออกได้ผลสำเร็จประมาณร้อยละ 60 ถึง 70 จำเป็นต้องมีการรักษาด้วยยาละลายลิ่มเลือดร่วมด้วย

วัตถุประสงค์: เพื่อศึกษาผลการรักษาผู้ป่วยหลอดเลือดแดงของขาอุดตันเฉียบพลันที่มาพบแพทย์ล่าช้าและมีภาวะการขาดเลือดรุนแรงที่ได้รับการรักษาด้วยการผ่าตัดเอาลิ่มเลือดออกร่วมกับการให้ยาละลายลิ่มเลือดระหว่างผ่าตัด เพื่อให้เป็นแนวทางในการดูแลรักษาผู้ป่วยกลุ่มนี้ในประเทศไทย

วัสดุและวิธีการ: การศึกษาย้อนหลังผู้ป่วยหลอดเลือดแดงของขาอุดตันเฉียบพลันที่มาพบแพทย์ล่าช้าและมีภาวะการขาดเลือดรุนแรงที่ได้รับการรักษาด้วยการผ่าตัดเอาลิ่มเลือดออกร่วมกับการให้ยาละลายลิ่มเลือดระหว่างผ่าตัดจำนวน 37 คน ระหว่าง เดือนมกราคม พ.ศ. 2538 ถึง เดือนธันวาคม พ.ศ. 2557 ที่รักษาโดยสาขาวิชาศัลยศาสตร์หลอดเลือด ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล โดยศึกษาข้อมูลทั่วไปของผู้ป่วย ข้อมูลระหว่างผ่าตัด ภาวะแทรกซ้อนภายหลังการผ่าตัด การอยู่รอดของขา และอัตราการเสียชีวิตภายหลังการผ่าตัดใน 1 เดือน, และ 1 ปี

ผลการศึกษา: เวลาที่ผู้ป่วยมาพบแพทย์ส่วนใหญ่อยู่ที่ 7 วัน (ช่วง 1 ถึง 120 วัน) 2 ใน 3 ของผู้ป่วย (ร้อยละ 59.5) ได้รับการรักษาด้วยยาละลายลิ่มเลือดชนิด streptokinase และ recombinant tissue plasminogen activator อัตราการไม่สูญเสียขาภายใน 1 เดือน และ 1 ปี เป็นร้อยละ 89.2 อัตราการเสียชีวิตภายใน 1 เดือนและ 1 ปี คือ ร้อยละ 5.4 และ 10.8 ตามลำดับ ภาวะแทรกซ้อนภายหลังการผ่าตัดพบว่ามีปัญหาเลือดออก 4 ราย การอุดตันหลอดเลือดแดงซ้ำ 7 ราย แผลผ่าตัดมีก้อนเลือด 3 ราย หัวใจขาดเลือด 1 ราย ติดเชื้อบริเวณแผลผ่าตัด 1 ราย และขาขาดเลือด 1 ราย

สรุป: การรักษาผู้ป่วยหลอดเลือดแดงของขาอุดตันเฉียบพลันที่มาพบแพทย์ล่าช้าและมีภาวะการขาดเลือดรุนแรงที่ได้รับการรักษาด้วยการผ่าตัดเอาลิ่มเลือดออกร่วมกับการให้ยาละลายลิ่มเลือดระหว่างผ่าตัด ลดอัตราการสูญเสียขามีความปลอดภัยมีประสิทธิภาพ และเพิ่มคุณภาพชีวิตให้กับผู้ป่วยได้