ORIGINAL ARTICLE

REVASCULARIZATION OF LATE-PRESENTING ACUTE LIMB ISCHAEMIA AND LIMB SALVAGE

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Background: Late-presenting acute limb ischaemia represents a challenging vascular emergency. The purpose of this study was to evaluate the outcome in patients following revascularization and management of existing or impending reperfusion injury of ischaemic limbs over a 12-year period (2002–2014). **Methods:** Routine procedural codes were used to label consecutive patients admitted 72 hours following onset of symptoms for surgical revascularization of an acutely ischaemic limb. Data collected included demography, clinical presentation, synchronous morbidities, procedural specifics and outcomes of surgical management of all patients. **Results:** The study sample included 206 patients, (117 male and 89 female, average age =49.4±14.6 years) presenting with a diagnosis of acute limb ischemia. The most frequent cause of acute thromboembolic limbs was cardiac disease (n=148). Femoral artery exploration with embolectomy was the most common procedure and was used for aortic, iliac, infrainguinal and distal occlusion. Thirty-four patients required additional vascular surgery due to failure of revascularization by embolectomy. Fasciotomy was performed in 45.6% of cases for existing or impending compartment syndrome when the patient presented very late. Surgical site infection occurred in 8.25% of cases, repeat embolectomy was required in 10.68% of cases; amputation in 13.1% and mortality was 5.8%. Predictors of morbidity and mortality included age of the patient, time of presentation and specific comorbidities. The 5-year amputation-free and survival estimate was 80%. **Conclusion:** Our study suggests that late revascularization of acute leg ischaemia improves blood supply to the limb, thereby reducing the number of amputations. The results suggest that revascularization is clinically warranted, even one week following the onset of acute ischaemia. Additional surgical procedures including fasciotomy further reduce the morbidity and mortality.

Keywords: Acute ischaemia, revascularization, embolectomy, fasciotomy, amputation, reperfusion injury, compartment syndrome

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INTRODUCTION

In an ischaemic organ or tissue, following revascularization, a cascade of pathophysiological events often occurs known as reperfusion injury. First identified in patients in whom blood flow was re-established to ischaemic extremities, reperfusion injury has also been associated with heart surgery, organ transplantation, and revascularization of ischaemic bowel. This syndrome consists of two essential components: local events that can result in increasing damage from ischaemia and more widespread, systemic events that can result in secondary failure of organs and tissues remote from the ischaemic site. It remains difficult to predict how to prevent this syndrome from resulting in damage to both local and distal organs. The progressive changes that occur following reperfusion of the organ are directly related to the timing of reperfusion and longevity of the ischaemic period where blood supply is abruptly ceased. The tolerance of tissue for ischaemia varies with the specific tissue type and/or the presence or absence of collateral flow. Under normo-thermic conditions, ischaemic injury has been shown to be reversible after 4 hours of ischaemia in muscle, 8 hours in nervous system tissue, 13 hours in fat, 24 hours in skin, and up to 4 days of ischemia in bone.[1] Skeletal muscle is known to be most vulnerable to ischemia.[2] Because muscle comprises the primary tissue mass in the extremities, damage to muscle remains the most critical aspect of limb reperfusion syndrome. Although the degree of skeletal muscle injury is known to correlate directly with the severity and duration of the ischemia[3,4], it remains difficult to predict when muscle tissue is going to die following acute ischemia. Since reperfusion injury to the local tissue, associated with revascularization, is exacerbated by raised compartmental pressure in the tight facial compartments of the limb, the rise of compartmental pressure can be prevented by performing a surgical fasciotomy. However, while fasciotomy is known to be an effective treatment for existing or impending compartment syndrome, it is also associated with increased morbidity that must be weighed against impending limb loss. The purpose of this study was to evaluate the outcome in patients following revascularization and management of existing or impending reperfusion injury of ischaemic limbs over a 12-year period (2002–2014).

MATERIAL AND METHODS

This study was conducted on 206 patients, admitted to our hospitals with a diagnosis of late-presenting, acute lower extremity arterial occlusion, who were operated on between January 2002 and February 2014. Late presentation of arterial occlusion was defined as occlusion occurring 72 or more hours after initial manifestation of patient complaint related to the affected lower extremity. We excluded all patients from our study who presented within the early hours after the onset of disease or who presented with additional venous occlusion. All patients were diagnosed on the basis of clinical history, physical examination, and Doppler studies of limb vessels. Duplex examination of the effected limbs was conducted post operatively as well. During the examination, the viability of the limb, presence or absence of irreversible changes in the limb and source of thromboembolism were determined. Embolectomies of the lower limbs were performed under local anaesthesia while spinal/epidural anaesthesia was used for patients requiring popliteal embolectomy and bypass procedures using 3F, 4F and 5F Fogarty embolectomy catheters. A total of 85 patients underwent pre-emptive fasciotomy, opening up all the compartments of lower limb due to the suspicion of reperfusion injury, while 9 patients who were not subjected to pre-emptive fasciotomy required fasciotomy after they developed limb- threatening compartment syndrome. A total of 33 patients required additional surgical procedures to re-vascularize the limb while 22 patients required repeat embolectomy (Table-1).

The arteriotomy was closed after by washing the distal arterial bed with 5000 U of heparin diluted in 100 mL of 0.9% normal saline solution. After embolectomy, all patients who continued to show clinical signs of limb ischemia were subjected to additional surgical procedures performed after CT angiography or conventional angiography.

SPSS Windows 10.0 statistical software package was used for statistical analysis of patient records. Continuous variables are presented as means±standard deviation. A p-value <0.05 was considered as statistically significant. Ethical approval to conduct the study was obtained from the Institutional Review Board before the commencement of the study. Written informed consent was obtained from the patients for the publication of this report.

RESULTS

Out of a total of 206 patients presenting with acute limb ischemia enrolled in our study, 117 were male and 89 female with an average age of 49.4±14.6 years (Table-1). The predominant clinical symptoms at the time of admission, as well as the frequency and average duration of the disease are presented in table-2. The most frequent cause of acute thromboembolic events in the limbs were determined to be cardiac pathologies in 148 cases: Atrial fibrillation (69 cases), a history of myocardial infarction (9 cases), mitral stenosis (18 cases), endocarditis (15 cases), combined mitral stenosis and atrial fibrillation (11 cases) and the presence of prosthetic cardiac valves (7 cases,). In the remaining 58 cases, thromboembolic disease of the limb was associated with vascular trauma (27 cases), atherosclerosis (18 cases), iatrogenic injuries associated with surgical procedures of the pelvis and groin regions (6 cases), abdominal aortic aneurisms (3 cases) and angiographic procedures involving the femoral route (3 cases). Twenty-two patients required re-embolectomy while 17 patients were found to have life-threatening ongoing ischemia despite fasciotomy that required amputation (9 above the knee and 8 below the knee amputations). Thirty-four patients required additional vascular surgical procedures due to failure of revascularization by embolectomy and fasciotomy. We performed pre-emptive fasciotomy in 85 patients who presented with a history of 7 days or more of limb ischemia while 9 patients who did not have pre-emptive fasciotomy required secondary fasciotomy after developing limb threatening compartment syndrome.

Surgical-site infection was encountered in 17 patients (8.25%). Three patients had graft infections that resulted in limb amputation. Two patients died due to septicaemia and multiple organs failure while one patient with graft infection required removal of the graft and subsequent revascularization after resolution of the infection. All other infections were treated successfully with intravenous antibiotics. Of the nine patients who presented within six days of onset of the disease developed compartment syndrome, one patient developed severe renal reperfusion injury requiring dialysis and ultimately died of severe reperfusion syndrome. Of the six patients who developed deep vein thrombosis, three subsequently developed pulmonary embolisms resulting in two deaths from massive pulmonary embolism. Of the 22 patients requiring repeat embolectomy, three patients lost their limbs. Nine patients were diagnosed with nephrotic reperfusion syndrome. Twenty-seven patients had amputation (16 above the knee and 11 below the knee with one patient requiring bilateral below-knee amputation).

Of those patients presenting with late-onset limb ischaemia who received pre-emptive fasciotomy, 17 required amputation (10 above-knee and 7 below-knee amputations). Although none of these patients developed venous thrombosis, 6 required repeat embolectomy, and the infection rate was found to be notably higher than in those where fasciotomy was not

performed. In those patients who presented earlier than seven days after the onset of disease, 9 developed compartment syndrome with severe reperfusion injury leading to amputation of the limb even after fasciotomy (Table-4).

Of the 206 patients enrolled in our study, 12 patients died; six from associated cardiac events in the post-operative period, two from sepsis leading to multiple organ and systems failure, two due to deep veins thrombosis leading to massive pulmonary embolism, one from renal failure and one from a cerebrovascular accident. When the patients were admitted to the hospital after 72 hours, mortality was not affected by acute limb ischaemia alone. However, morbidity was found to be significantly higher for patients admitted after 7 days (Table-5). A subgroup of patients was also found to have one or more factors (synchronous diseases) that may have contributed to the morbidity and mortality observed in these patients (Table-6). The 5-year amputation-free survival estimate was 80% in patients who survived their acute limb ischaemia.

Table-1: Surgical procedure conducted on 206 patients

Surgical procedure	Number	Percentage
Femoral embolectomy	141	68.4
Popliteal embolectomy	12	5.8
Repeat embolectomy	22	10.7
Aortofemoral Bypass	7	3.4
Illiofemoral Bypass	5	2.4
Femoro-femoral bypass	13	6.3
Femoro-popliteal bypass	09	4.4
Fasciotomy	94	45.6

Table-2: Demographic data of 206 patients

Age of the patients	Male	Female
49.4±14.6 (Average)	117 (56.8%)	89 (43.2%)

Duration of the disease at presentation, 2–6 days=121 patients (58.73%), 7 days and more= 85 patients (41.26%)

Table-3: Predominant clinical symptoms at presentation

Clinical Symptoms	No of Patients	Percentage
Severe pain	198	96.1
Coldness	179	87.0
Pallor	163	79.1
Paresthesia	112	54.4
Loss of sensation	34	16.5
Cyanosis	26	12.6
Loss of motor function	9	4.36

Table-4: Causes of increased morbidity

Causes	Number of patients	Percentage
Re-embolectomy	22	10.67%
Infection	17	8.25%
Fasciotomy	94	45.6%
Venous thrombosis	6	2.91%
Amputation	26	13.1%
Renal impairment	9	4.36%
Cerebrovascular accidents	5	2.42%
Cardiac events	17	8.25%

Table-5: Causes of mortality in 12 patients

Causes	No. of patients	Percentage
Myocardial infarction	4	1.94%
Congestive heart failure	2	0.97%
Septicemia (MOS)	2	0.97%
Venous thromboembolic disease	2	0.97%
Renal failure	1	0.48%
Cerebrovascular accident	1	0.48%

Table-6: Synchronous disease in study population

Diseases	No. of patients	Percentage
Rheumatic heart disease	41	19.9%
Valvular heart disease	23	11.2%
Atrial fibrillation	92	44.7%
Ischaemic heart disease	37	18.0%
Congestive heart disease	14	6.79%
Diabetes mellitus	69	33.5%
Hypertension	46	22.3%

DISCUSSION

Critical limb ischemia is defined as an abrupt decrease in tissue perfusion, with impending threat of viability of the extremity. Profound local limb ischaemia leads to a sequence of pathological events in the tissue, ultimately resulting in systemic complications[1]. The first successful embolectomy was performed by Georges Labey in 1911.[1,2] Since that time, the embolectomy catheters devised by Fogarty have facilitated this operation and increased the likelihood of its success.[2] Catheter embolectomy remains a routine surgical revascularization procedure for patients suffering from thromboembolic disease of the limb.[3] Following clinical attempts at revascularization, the amputation rate has been reported to be 9–15% in non-salvageable limbs vs. 25% for both non-salvageable limbs and limbs thought to be salvageable.[4] Abbott and colleagues published the largest experience with embolectomy, documenting a limb salvage rate of 93% in patients presenting within 12 hours of thromboembolic insults to the limb.[5] However, the limb salvage rate fell to 78% and mortality increased to 31% when the patients presented 12 hours or later from the onset of clinical symptoms.

Several studies have established a linear relationship between the delay in intervention and outcome of patients presenting with acute limb ischaemia.[6–8] When patients present late after the onset of an ischaemic episode and the decision to intervene is questionable, clinical acumen based on experience and established guidelines with rapid imaging analysis is mandatory for successful management.[4,7] However, whether to attempt revascularization of an acutely ischaemic limb when presented late remains controversial. When critical ischaemia of the limb occurs, several clinical measures may be employed to save the useful limb and prevent further morbidity. An attempt at revascularization is currently considered clinically acceptable if (1) there is relatively little damage to the arterial intima; (2) thrombi not adhering to the intima are present with no secondary thrombus on

the intima visible; (3) patent distal arterial tree has been documented, despite embolization; and (4) anticoagulation has been initiated prior to surgery[7]. When these conditions are maintained, adequate circulation can be achieved in the extremities of patients with the use of delayed embolectomy.[8] However, mortality and morbidity risk persists even when the factors underlying acute ischaemia are removed and perfusion to the limb is attained. Moreover, even when extremity reperfusion has been completely restored by removal of the underlying cause of acute ischemia, a pathogenic cascade may result in loss of the extremity, acute kidney and respiratory failure, or functional deterioration in tissues such as heart, intestine, brain, or spleen.[9]

Traditional medical convention states that the earlier the embolectomy, the better the result in reversing the acutely ischaemic limb. Nevertheless, cases of effective embolectomies performed several days after acute limb occlusion have also been described.[9] Reperfusion injury after revascularization must be carefully assessed and those patients presenting late are known have a greater likelihood of local and systemic reperfusion injury leading to limb loss and even death. Our results suggest that early fasciotomy is required to prevent ischemia and complications that may occur. To predict the success of therapy designed for late-presenting acute limb ischaemia, certain factors play an important role, e.g., the time between the onset of ischaemia and revascularization, the factors underlying embolization, the location and extent of the embolus and the presence of synchronous pathologies.[10]

When the limb is re-vascularized after a prolonged ischaemic insult, free oxygen radicals generated by the ischaemic tissue interact with vascular endothelium and neutrophils, causing a rapid increase in lipid peroxidation leading to several local and systemic events. Cellular oedema, the presence of various toxins, cellular oedema and myoglobulin release associated with free oxygen radical release may cause systemic damage such as acute renal failure, pulmonary oedema and adult respiratory distress syndrome (ARDS) damage to liver and other organs[11]. It has been established that prolonged free oxygen radical release and its pathologic sequelae represents a major cause of mortality and morbidity associated with late presenting acute limb ischemia. Moreover, persistent systemic and local damage may occur if the compartmental pressure in the leg remains high following revascularization.[12] The reported amputation rate following revascularization is 2.1–5.9% when patient presents within the first 12 hours following the onset of ischaemia (mortality=12.5%) and increases to 39.2% when patient presents after 12 hours (mortality=37.7%).[13] To prevent complications, it is therefore crucial to intervene as early as possible to reverse both local and systemic tissue damage and loss associated with acute limb ischaemia.[14] It is also imperative to understand and manage impending or existing compartment syndrome (an important consequence of reperfusion injury), in those patients undergoing embolectomy, especially when the patient presents late.[15] The timing of intervention for the management of reperfusion injury is even more important. Early fasciotomy has been shown to be necessary to prevent ischemia and related complications, including those associated with local and systemic reperfusion.[16]

We studied patients admitted to our clinic for the last 12 years with a diagnosis of late-presenting acute lower extremity arterial occlusion who were treated for acute ischaemia and related complications. Our results are comparable those studies where patients presented relatively early. We performed fasciotomy on 94 patients who developed or at high risk for reperfusion injury, with a particular emphasis on those patients presenting after 7 days of onset of the disease. We found significantly higher morbidity in patients admitted after 7 days. A large percentage of our study population also had one or more other contributing factors (synchronous diseases) that may have contributed to the morbidity and mortality observed in these patients: We achieved a 5-year amputation-free survival estimate of 80% in patients who survived the acute limb ischaemia following effective surgical intervention[17]. Although our rate of fasciotomy was higher than previously reported studies, our results remain encouraging and we were able to significantly reduce the incidence of both amputation and mortality.[18] While the risk of wound infection and morbidity remains higher in patients undergoing open fasciotomy, limb loss and death has been associated with persistent ischemia and synchronous systemic diseases, but not with complications caused by open fasciotomy.[19]

A review of the literature indicates that several systemic and local factors are responsible for reperfusion injury syndrome, including persistently elevated compartmental pressure which results from 6 to 8 hours of skeletal muscle ischemia and is associated with the production of ischemic metabolites, myoglobulinemia and myoglobulinurea following revascularization.[20] The rates of metabolite production are directly related to the timing of onset of ischaemic revascularization.[21] In the present study, we observed that the pathogenic cascade initiated by the development of local reperfusion occurred even in those patients who presented very late where preventive measures were taken for reperfusion injury. While mortality was not affected by acute limb ischaemia in patients admitted within 72 hours of onset, morbidity was significantly higher in patients admitted after 7 days after onset of ischaemia.[22] Although the mortality rate of patients

receiving embolectomy 12 hours after the onset of acute ischaemia has been reported to be elevated[23], only 12 patients (5.82%) died in our study, most presenting with synchronous disease. In view of the morbidity and mortality rates observed in the present study, we conclude that performing additional surgical procedures such as fasciotomy (and, where required, vascular bypass) in acute leg ischaemia is warranted even if the patient presents later than a week following onset of ischaemia.

CONCLUSION

Revascularization of an acutely ischaemic limb should be performed even in those patients who present later than one week following onset. Delayed reperfusion of acutely ischaemic limb carries acceptable morbidity and mortality. Complications surrounding revascularization and the deleterious effects of reperfusion injury may be markedly reduced by performing additional surgical procedures including early fasciotomy. Rapid referral of all patients with acute limb ischaemia is essential, where prompt diagnosis and treatment can be initiated without hesitation even in delayed cases where the limb may appear non-viable. We believe that late revascularization in cases of acute leg ischaemia may markedly enhance blood flow to the limb and reduce the number of required amputations.

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AUTHOR'S CONTRIBUTIONS

MIK carried out conception and design, acquisition of data, analysis, interpretation, and writing manuscript; IAN carried out carried out data extraction, interpretation and drafting manuscript.

All authors read and approved the final manuscript.

REFERENCES

1. Ouriel K. Acute limb ischemia. In: Rutherfort RB, editor. Vascular surgery. 6th ed. Philadelphia: Elsevier; 2005;959–86.
2. Fogarty TJ. Management of arterial emboli. Surg Clin North Am1979;59(4):749–53.
3. Eliason JL, Wainess RM, Proctor MC, Dimick JB, Cowan Jr JA, Upchurch Jr GR, *et al*. A national and single institutional experience in the contemporary treatment of acute lower extremity ischemia. Ann Surg 2003;238(3):382–90.
4. Ouriel K, Veith FJ. Acute lower limb ischemia: determinants of outcome. Surgery 1998;124(2):336–41.
5. Abbott WM, Maloney RD, McCabe CC, Lee CE, Wirthlin LS. Arterial embolism: a 44 year perspective. Am J Surg 1982; 143(4):460–4.
6. Elliott JP Jr, Hageman JH, Szilagyi E, Ramakrishnan V, Bravo JJ, Smith RF. Arterial embolization: problems of source, multiplicity, recurrence and delayed treatment. Surgery 1980; 88(6):833–45.
7. Iyem H, Eren MN. Should embolectomy be performed in late acute lower extremity arterial occlusions? Vasc Health Risk Manag 2009; 5:621–6.
8. Blecha MJ. Critical Limb Ischemia. Surg Clin North Am 2013; 93(4):789–812.
9. Shifrin EG, Anner H, Eid A, Romanoff H. Practice and theory of 'delayed' embolectomy. A 22 year perspective. J Cardiovasc Surg (Torino) 1986;27(5):553–6.
10. Panetta T, Thompson JE, Talkington CM, Garrett WV, Smith BL. Arterial embolectomy: A 34-year experience with 400 cases. Surg Clin North Am 1986;66(2):339–53.
11. Yangni AH, Adoubi A, Adoh M, Yapobi Y, Coulibaly AO. Acute nontraumatic limb ischemia. West Afr J Med. 2006;25(2):101–4.
12. Morris-Stiff G, D'Souza J, Raman S, Paulvannan S, Lewis MH. Update experience of surgery for acute limb ischaemia in a district general hospital - are we getting any better? Ann R Coll Surg Engl 2009;91(8):637–40.
13. Karapolat S, Dag O, Abanoz M, Aslan M. Arterial embolectomy: a retrospective evaluation of 730 cases over 20 years. Surg Today 2006;36(5):416–9.
14. Tiwari A, Haq AI, Myint F, Hamilton G. Acute compartment syndromes. Br J Surg 2002;89(4):397–412.
15. Creager MA, Kaufman JA, Conte MS. Clinical practice. Acute Limb Ischemia. N Engl J Med 2012;366(23):2198–206.
16. Ernst CB, Kaufer H. Fibulectomy-fasciotomy: An important adjunct in the management of lower extremity arterial trauma. J Trauma 1971;11(5):365–80.
17. Elsharawy MA. Elsaid A, Elsharawi I. Reperfusion of Delayed Acute Occlusive Limb Ischemia: Is It Worthwhile? World J Cardiovasc Dis. 2014;4(12):580.
18. Rush DS, Frame SB, Bell RM, Berg EE, Kerstein, MD, Haynes JL. Does open fasciotomy contribute to morbidity and mortality after acute lower extremity ischemia and revascularization? J Vasc Surg 1989;10(3):343–50.
19. Arumugam TV, Shiels IA, Woodruff TM, Granger DN, Taylor SM. The role of the complement system in ischemia-reperfusion injury. Shock 2004;21(5):401–9.
20. Rutherford RB. Clinical staging of acute limb ischemia as the basis for choice of revascularization method: when and how to intervene; Semin Vasc Surg 2009;22(1):5–9.
21. J. P. Simons, P. P. Goodney, B. W. Nolan, J. L. Cronenwett, L. M. Messina, and A. Schanzer, "Failure to achieve clinical improvement despite graft patency in patients undergoing infrainguinal lower extremity bypass for critical limb ischemia," Journal of Vascular Surgery, vol. 51, no. 6, pp. 1419–1424, 2010
22. Dag O, Kaygın, M, Erkut B. Analysis of risk factors for amputation in 822 cases with acute arterial emboli. Sci World J 2012;2012:673483.
23. Kempe K, Starr B, Stafford JM, Islam A, Mooney A, Lagergren E, *et al*. Results of surgical management of acute thromboembolic lower extremity ischemia. J Vasc Surg 2014;60(3):702–7.

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