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Long-term Outcome after Thrombolysis for Acute Lower Limb Ischaemia

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WHAT THIS STUDY ADDS

Reporting on the long-term outcome in a large cohort of patients treated with intra-arterial thrombolysis for acute lower limb ischaemia makes it possible to analyse the four main aetiological subgroups. Patients treated for occluded grafts, stents, or stent grafts had a higher risk of amputation and a lower amputation free survival, indicating the need for better treatment and follow-up. Re-interventions were most common after occluded grafts/stents/stent grafts, followed by occluded popliteal aneurysms, and native artery thrombosis, and least common after embolus. Overall, thrombolytic therapy achieved good medium and long-term clinical outcome and transformed an emergent into an elective situation.

Objectives: The purpose was to study long-term outcome after thrombolysis for acute arterial lower limb ischaemia, and to evaluate the results depending on the underlying aetiology of arterial occlusion.

Methods: This was a retrospective study of patients entered into a prospective database. Patients were identified in prospective databases from two vascular centres, including a large number of variables. Case records were analysed retrospectively. Through cross linkage with the Population Registry 100% accurate survival data were obtained. Between January 2001 and December 2013, 689 procedures were included. The aetiology of ischaemia was graft/stent/stent graft occlusion in 39.8%, arterial thrombosis in 27.7%, embolus in 25.1% and popliteal aneurysm in 7.4%.

Results: The mean follow-up was 59.4 months (95% CI, 56.1–62.7), during which 32.9% needed further re-interventions, 16.4% underwent amputation without re-intervention, and 50.7% had no re-intervention. The need for re-intervention during follow-up was 48.0% in the graft/stent occlusions group, 34.0% of the popliteal aneurysm group, 25.4% in the thrombosis group, and 16.3% in the embolus group ($p < .001$). The overall primary patency rates were 69.1% and 55.9% at 1 and 5 years, respectively. Primary patency at 5 years was higher for the embolus group (83.3%, $p = .002$) and lower for the occluded graft/stent group (43.3%, $p < .001$). Secondary patency rates were 80.1% and 75.2% at 1 and 5 years, respectively, without difference between the subgroups. The amputation rate was lower in the embolic group at 1 and 5 years (8.1% and 11.1%, respectively, $p = .001$). Survival was higher in the group with occluded popliteal aneurysms at 5 years (83.3%, $p = 0.004$). Amputation free survival was 72.1% and 45.2% at 1 and 5 years; lower in the occluded graft/stent group at five years (37.9%, $p = .007$).

Conclusion: Intra-arterial thrombolytic therapy achieves good medium and long-term clinical outcome, reducing the need of open surgical treatment in most patients.

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INTRODUCTION

The use of catheter directed thrombolysis as treatment of acute lower limb ischaemia (ALI) has become routine clinical care in the past three decades, following the publication of three randomised controlled trials that demonstrated similar efficacy compared with open surgery.[1–3] Since the publication of these trials, however, the treatment has evolved so that current thrombolytic therapy and technique differ significantly from those studied in the trials, different lytic agents are currently used, and the technique of administration has changed.[4] The main advantage with intra-arterial thrombolysis is the possibility of avoiding general anaesthesia, making the treatment of older patients and those with comorbidities safer.[5,6]

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Thrombolysis has also been shown to locally dissolve the clot even in the branches of the main occluded artery, with less endothelial injury and reduced risk of rethrombosis.[7] Furthermore, underlying stenoses may be discovered, simplifying subsequent treatment decisions, and potentially improving long-term results.[8]

Recent systematic reviews have focused on developing a technique that produces the best immediate or short-term patency, instead of comparing thrombolysis with open surgery.[9] Some studies have investigated the optimal infusion technique[10,11] and others have focused on which fibrinolytic agent to use.[12]

Although there has been much focus on the immediate efficacy of intra-arterial thrombolysis compared with surgery and different thrombolytic techniques, the long-term outcomes after thrombolysis are less well documented. Most studies include a follow-up time of 12–18 months.[7,13,14] A few small single centre reports have included a longer follow-up for patients with critical limb ischaemia treated with intra-arterial thrombolysis.[15–17]

The aim of this investigation was to study long-term outcomes in patients with ALI treated with thrombolysis, in particular re-interventions, amputations, and survival, as well as factors associated with outcomes.

Previous studies have reported that patients with ALI respond differently to the thrombolytic therapy depending on the underlying disease that caused the ischaemia.[9,13,18] Thus, a secondary aim was to compare the outcomes depending on the underlying aetiology of the ALI.

METHODS

This study was a collaboration between Uppsala University Hospital and the Vascular Centre, Malmö, two of Sweden's largest vascular centres. Both are tertiary referral centres for vascular disease with a combined primary catchment area of approximately 1.1 million, and a tertiary catchment area of approximately 3.5 million inhabitants.

Study population

In a previous publication the short-term results after thrombolysis of arterial occlusions with and without continuous heparin infusions were analysed.[18] Part of the same cohort was analysed in the present study. Stricter inclusion criteria were applied since only patients with ALI with occlusions below the abdominal aorta were included. The study period was prolonged, now including all thrombolytic procedures between January 1, 2001, and December 31, 2013. Patients were identified through the local Swedvasc registry (a national register for vascular procedures with high validity)[19–21] and local endovascular databases. The data in the Swedvasc registry are entered prospectively but the case records were analysed retrospectively. Patients were followed from the day of admission until death or June 30, 2015. Information on patient mortality is reported automatically within 2 weeks from the Swedish Population registry. Cross linking was based on the patient's personal identity number (PIN), a 10 digit unique number that is given to each child at birth. Twenty-six patients (3.8%) had moved to other parts of Sweden and were therefore lost to follow-up regarding re-interventions. Information about amputations for these patients, however, was retrieved through contact with the local vascular surgeons, and survival was checked through the National Population registry.

The regional ethics review board in Lund approved the study.

Local intra-arterial thrombolysis

Arterial access was normally achieved through puncture of the common femoral artery in the non-diseased leg. A long thrombolysis catheter equipped with multiple side holes was advanced over the aortic bifurcation and through the occlusion. The lytic agent used was recombinant tissue plasminogen activator (rtPA) (Actilyse; Boehringer Ingelheim, Ingelheim, Germany). The total dose of rtPA was decided individually based on the duration and extent of the arterial occlusion, the degree of ischaemia, and the patient's age. The procedures were all performed under local anaesthesia. The detailed technique used to deliver thrombolysis has been described in a previous publication.[18]

Definitions and study endpoints

Limb condition at presentation, including sensory and motor deficit, rest pain, ischaemic ulceration, and ankle brachial index (ABI), was recorded and scored according to the Rutherford classification.[22] Distal runoff was evaluated both at procedure initiation and at completion, using angiographic images. Definitions of comorbidities are shown in Table S1.[22,23]

The primary endpoint was amputation free survival. Secondary endpoints were primary patency, secondary patency, major amputation, and survival. Each limb was analysed independently. If not otherwise stated, amputation refers to major amputation, defined as above foot level. Patency was determined according to Rutherford's guidelines,[22] and was evaluated by clinical examination as documented in the case records, and by scrutinising angiographic images (conventional, computed tomography, or magnetic resonance). Primary patency applied to a vessel or graft that remained patent after the initial procedure without requiring additional intervention. Secondary patency referred to revascularisation after a complete occlusion of the vessel or graft. Patency was considered lost in patients who needed a subsequent surgical bypass or endovascular recanalisation. Re-intervention was defined as restenosis or occlusion in the same arterial segment as previously thrombolysed, leading to endovascular or surgical intervention.

For the purpose of this analysis the patients were further divided into subgroups depending on the aetiology of the occlusion: native artery thrombosis, embolus, occluded popliteal artery aneurysm (PAA), and occluded grafts/stents. The occluded graft/stent group included grafts (venous and synthetic) stents (bare metal, self, and balloon

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