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Outcome after thrombolysis for occluded endoprosthesis, bypasses and native arteries in patients with lower limb ischemia

Monica Kuoppala [a], Jonas Åkeson [b], Stefan Acosta [a,*]

[a] Vascular Center, Malmö University Hospital, Malmö, Sweden
[b] Department of Anesthesiology and Intensive Care Medicine, Malmö University Hospital, Malmö, Sweden

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ABSTRACT

Introduction: To report contemporary outcomes, and evaluate differences after thrombolysis for occluded endoprosthesis, bypasses and native artery occlusion in patients with lower limb ischemia.
Methods: Patients undergoing local intra-arterial thrombolysis for lower limb ischemia between 2001 and 2010 were identified in the prospective database for endovascular intervention, and analysis was performed retrospectively.
Results: There was an increase in thrombolysis for occluded endoprosthesis and a decrease in thrombolysis for occluded bypasses during the study period ($p = 0.001$). The technical success rate for thrombolysis in occluded endoprosthesis, bypasses and native artery occlusion was 91%, 89% and 73%, respectively. The overall major amputation rate, mortality rate and amputation-free survival rate at 1 year was 19%, 14% and 73%, respectively, without differences between groups. The major amputation rate at long-term was highest, 45%, for patients with occluded synthetic bypass grafts. Female gender (HR 1.7; 95% CI 1.1–2.7), ischemic heart disease (HR 1.8; 95% CI 1.1–2.8), anemia at admission (HR 1.9; 95% CI 1.2–3.0), foot ulcer (HR 4.4; 95% CI 2.4–8.0), motor deficit at admission (HR 2.5; 95% CI 1.4–4.3), occluded synthetic bypass graft (HR 3.3; 95% CI 1.9–5.7) and failure of thrombolysis (HR 4.8; 95% CI 2.9–7.7) were independently associated with an increased long-term risk of major amputation.
Conclusions: Thrombolysis for occluded endoprosthesis, bypasses and native artery occlusion was effective. Female gender, ischemic heart disease, anemia, foot ulcer, motor deficit, occluded synthetic bypass graft and failure of thrombolysis were independently associated with an increased risk of major amputation.

Introduction

In the mid 1990s, several randomized trials of catheter directed thrombolysis versus operative revascularization in patients with acute lower extremity ischemia were performed [1]. There was no overall difference in limb salvage or death at one year between initial surgery and initial thrombolysis. However, the results from these randomized trials do not apply to current management [2]. For instance, in one of these randomized studies, it was not possible to correctly place a catheter for thrombolytic infusion in a high proportion (39%) of the patients, who then subsequently required surgical revascularization [3]. The worldwide rapid parallel development of both vascular imaging, with computed tomography and magnetic resonance angiography, and refined endovascular techniques, has made imaging-based catheter-directed thrombolytic therapy the treatment modality of choice in most patients with acute lower limb ischemia in many vascular units. The main advantage of local thrombolytic therapy is the minimally invasive nature of the procedure, avoiding general anaesthesia and operation room resources in these often fragile patients. Recent systematic reviews have, instead of comparing thrombolysis with open vascular surgery, focused on various infusion techniques [4] or fibrinolytic agents [5] during thrombolysis.

The Vascular Centre, Malmö-Lund, Sweden, is a highly specialized endovascular unit with long experience of treating acute lower limb ischemia with local thrombolysis. It is anticipated that this first-line endovascular approach, also is associated with an increasing number of thrombolysis for occluded endoprosthesis. In a previous report based on 220 thrombolysis between 2001 and 2005, few thrombolysis for occluded endoprosthesis was performed [6]. The aim of the present study was to extend this study period to 2010, report contemporary outcomes, and evaluate differences after thrombolysis for occluded endoprosthesis, bypasses and native artery occlusion in patients with lower limb ischemia.

* Corresponding author at: Vascular Center, Malmö University Hospital, 205 02 Malmö, Sweden. Fax: +46 40338097.
E-mail address: Stefan.acosta@telia.com (S. Acosta).

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Methods

Setting

The Vascular Center, Malmö-Lund is a tertiary referral center with a primary catchment population of approximately 800 000 inhabitants.

Study population

This study comprised all patients with lower limb ischemia who underwent intra-arterial thrombolysis between January 1, 2001, and December 31, 2010. The patients were identified in the prospective database for endovascular intervention.

Patients included from 2001 – 2005 have been evaluated in a previous report [6].

Local intra-arterial thrombolysis

Arterial puncture is typically performed in the common femoral artery in the nondiseased leg, and a long thrombolysis catheter, equipped with multiple side holes, is advanced to the contralateral diseased leg over the aortic bifurcation and positioned in the occlusion to be able to deposit high concentrations of lytic agent. Infusion of alteplase (Actilyse; Boehringer Ingelheim, Stockholm, Sweden) commences at the ICU, with repeated measurements of coagulation status throughout the treatment.

Initially, a dosage of 1 to 2 mg/h may be administered during the first 4 hours, followed by 0.5 to 1 mg/h, depending on the age and extent of the occlusion, the degree of ischemia, and the patient's age. Parallel with this, heparin (Heparin Leo, LEO Pharma, Malmö, Sweden) is first given as a bolus dosage of 5000 IU and then continuously through the side hole of the introducer, which is placed with its tip above the occlusion. The heparin infusion is adjusted according to APTT values, which should be two to three times above the reference value during therapy.

Medication at discharge

Patients undergoing successful thrombolysis were usually treated aggressively with antithrombotic and/or anticoagulation medication, more aggressive treatment during the latter stages of the study period. Patients with occluded endoprosthesis, with or without stent stenosis were usually treated with dual anti-platelet therapy for at least six month. Patients with occluded bypasses without a diagnosed cause of underlying occlusive lesion or embolic occlusions, were usually treated with low molecular weight heparin first and then life-long warfarin.

Retrieval of patient data

Apart from prospectively collected data from the endovascular database, data was retrieved retrospectively from patient records.

Follow-up

All patients were monitored from the day of thrombolysis until death or January 17, 2012. Median follow-up time was 45 (IQR 21 – 76) months. Follow-up mortality data was retrieved from the Swedish Population Registry. This study was approved by the Research Ethics Committee at the University of Lund.

Definitions

Hypertension was considered if a patient previously had been diagnosed with hypertension or was taking antihypertensive medication. *Cerebrovascular disease* was considered if there was a history of stroke (cerebral bleeding or infarction) or transient ischemic attack (TIA). *Ischemic heart disease* was considered if there was a history of myocardial infarction, angina pectoris, coronary artery bypass graft, or percutaneous coronary angioplasty. *Smoking* included both current and former tobacco smokers. Hemoglobin (Hb) and creatinine levels at admission were analyzed. *Anemia* was defined as Hb < 134 g/L in men and < 117 g/L in women, and *renal insufficiency* was present if serum creatinine reached levels >105 μmol/L in men and >90 μmol/L in women.

Acute ischemia in the lower limb was defined as a sudden decrease in or deterioration of limb perfusion causing a potential threat to viability of the extremity [7]. Degree of lysis was stated as *complete*, *partial*, *lysis but no run-off*, or *no lysis* [8]. *Successful thrombolysis* refers to complete or partial lysis, whereas *failure of thrombolysis* refers to lysis but no run-off or no run-off. *Major amputation* was defined as any amputation above the level of the tarso-metatarsal joint.

Statistical methods

Data management and statistical analysis were performed using SPSS 17.0 software (SPSS Inc, Chicago, Ill). Differences in proportions were evaluated using chi-square test or Kendall´s tau-b test. Continuous variables were expressed as median and interquartile range (IQR), and comparisons between three groups were made with the Kruskal-Wallis test. Amputation-free survival was analyzed according to the Kaplan-Meier method with Life tables. Factors associated ($p < 0.05$) with major amputation, mortality or major amputation/mortality at end of follow up in a uni-variable Cox regression analysis, were further tested in a multi-variable Cox regression model. Significant associations were expressed in terms of hazard ratios (HR) with 95% confidence intervals (CI) and $p < 0.05$ was considered significant.

Results

Patient characteristics

Four hundred and thirty-one thrombolysis were performed for lower limb ischemia in 359 patients during the ten-year study period. Re-thrombolysis was performed more than once in 46 patients (1 patient, 11 times; 1 patient 7 times; 1 patient 6 times; 4 patients 4 times; 10 patients, 3 times; and 29 patients, 2 times). The median age was 68 years (IQR 61 – 77) among men undergoing 231 thrombolysis, and 74 years (IQR 65 - 80) among women undergoing 200 thrombolysis ($p = 0.001$). Co-morbidity, medication, laboratory data at admission and vascular status at admission are shown in Table 1, left column.

Thrombolysis for occlusion of endoprosthesis

Thrombolysis for occluded endoprosthesis were performed on 77 occasions, 55 were index thrombolysis and 22 re-thrombolysis. Among these 77 thrombolysis, 62 (81%) were treated due to occlusion of a stent(s) and 34 (44%) due to occlusion of a stentgraft(s). Nineteen (25%) thrombolysis were performed due to both an occluded stent and occluded stentgraft in the same procedure. There was a clear trend that there were an increasing number of thrombolysis performed due to endoprosthesis occlusion in relation to native artery occlusion or bypass occlusion throughout the study period (Fig. 1) ($p = 0.001$). There were 0 and 18 thrombolytic procedures due to endoprosthesis occlusion infra- and suprainguinally, respectively, between 2001 and 2005, increasing ($p = 0.010$) to 17 respective 42 cases between 2006 and 2010. Failure of an iliac artery endoprosthesis was the most common reason for thrombolysis in the endoprosthesis group (Table 2).

Thrombolysis after late failure of an endovascular aortic aneurysm repair (EVAR) was performed in 14 patients (18%), and 13 were successful. Eight out of 14 (57%) EVAR cases had acute lower leg ischemia versus 349 (84%) out of 417 non-EVAR cases ($p = 0.020$). No patient