Plasminogen Activator Inhibitor-1 Levels and Activity Decrease After Intervention in Patients with Critical Limb Ischaemia

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WHAT THIS PAPER ADDS

We hypothesised that patients with critical and acute limb ischaemia would have increased levels of plasminogen activator inhibitor-1 (PAI-1), leading to a prothrombotic state. The investigation showed a great individual variability in PAI-1 levels, with a large proportion of the patients having increased levels prior to treatment. An effective treatment of the ischaemic state normalised those levels, and it seemed that open surgery was more effective than endovascular treatment in this respect. Further studies on the prothrombotic state during and after treatment may result in better adjuvant treatment.

Objective/background: Patients with peripheral arterial occlusive disease (PAOD), in particular critical limb ischaemia (CLI), carry a high risk of thrombotic events. We hypothesised that patients undergoing conservative, endovascular, or open surgical treatment for CLI have increased levels of plasminogen activator inhibitor-1 (PAI-1), leading to a prothrombotic state. The objective was to determine levels of PAI-1 in patients with acute or chronic PAOD/CLI.

Methods: Thirty-two patients with a median age of 74 (49—90) years were included. Three underwent thrombolysis for acute limb-threatening ischaemia. Twenty-six patients with chronic ischaemia received endovascular ($n = 20$) or open ($n = 6$) surgical treatment. Three were treated conservatively. Biomarkers and ankle brachial index (ABI) were measured before and up to 1 month after intervention. Patency was studied with repeated duplex ultrasound.

Results: Ankle pressure and ABI improved after intervention ($p < .001$). C-reactive protein (CRP) increased from a median of 7.90 mg/L at baseline to 31.5 on day 1 ($p < .001$), 28.0 on day 6 ($p < .001$), and returned to baseline levels on day 30. PAI-1 antigen and activity decreased from day 6 and onwards post-intervention compared with baseline ($p < .05$). A great individual variability in PAI-1 antigen and activity was observed. Although most actively treated patients had normal PAI-1 activity, 11/29 (38%) were above that level of normality at baseline, 10/24 (42%) on day 1, 3/23 (13%) on day 6, and 5/27 (19%) on day 30 after intervention.

Conclusion: Endovascular and open surgical treatment resulted in improved ankle pressure and ABI. The intervention was followed by a transient increase in CRP and a sustained reduction in PAI-1 levels and activity.

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INTRODUCTION

Patients with peripheral arterial occlusive disease (PAOD) and, in particular, those with the most severe form of disease, critical limb ischaemia (CLI), carry a high risk of thrombotic events.[1] The prothrombotic state results in an increased risk of general cardiovascular events and local arterial thrombosis after intervention.[1] Antiplatelet therapy with 75—325 mg acetylsalicylic acid (ASA)/day reduced the number of vascular events by 25% and the number of re-occlusions after coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty, percutaneous transluminal angioplasty (PTA), or femoro-popliteal bypass by 40%.[2] The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study showed a further risk reduction by using clopidogrel instead of ASA.[3] Although the relative risk reduction was similar in different subgroups, the absolute risk reduction was greater among patients with multiple risk factors, which is typical

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for PAOD patients.[4] The importance of coagulation was shown in the Dutch Bypass Oral Anticoagulants or Aspirin study,[5] which randomised 2,621 patients after femoro-popliteo-distal bypass to receive ASA or anticoagulation. Patients with anticoagulation had better patency when a vein graft was used, but ASA was more effective with a prosthetic graft. That postoperative antiplatelet therapy is better with a prosthetic graft was recently verified in the Clopidogrel and Acetylsalicylic Acid in bypass Surgery for Peripheral Arterial Disease trial.[6] In other therapeutic situations, such as after endovascular treatment or venous bypass, coagulation and fibrinolysis can be equally important targets for secondary prophylaxis.

Critical for fibrinolysis is the activation of plasminogen to plasmin, the active enzyme responsible for the degradation of fibrin. Fibrin provides the basic framework for the formation of a blood clot. The role of plasminogen activator inhibitor-1 (PAI-1) is to stabilise a formed clot by inhibiting the plasminogen activator (t-PA). In a diseased state this activity can become prothrombotic.

Recent data from patients with thrombosis, such as those with acute myocardial infarction,[7] as well as patients with risk factors for thrombosis, such as obesity,[8] show elevated PAI-1 levels. Progression of PAI-1 levels over time, as well as high baseline levels, is also associated with incident type 2 diabetes[9]—possibly the most important risk factor for PAOD/CLI. A direct pathogenetic connection between these elevated PAI-1 levels and the risk of thrombosis has, however, not yet been established in humans. Theoretically, inhibition of PAI-1 could be beneficial for a patient at elevated risk of thrombosis/vascular occlusion. Additionally, animal experiments with models of thrombosis have shown that thrombus formation can be prevented by inhibiting PAI-1 with antibodies[10] or with PAI-1 antagonists.[11]

The primary aim of this study was to characterise the absolute levels and changes in circulating concentration of PAI-1 and PAI-1 activity among patients with acute or chronic PAOD/CLI before and after conservative, endovascular, or open surgical treatment. As there were no previous data on this group of patients no power calculation was possible and the study was hypothesis-generating. A secondary aim was to study the logistics of including patients with CLI into clinical trials on PAOD.

PATIENTS AND METHODS

Study design

This was a prospective study in patients with limb-threatening lower limb ischaemia referred to the Department of Vascular Surgery in Uppsala for possible revascularisation. The study protocol was approved by the Regional Ethics Committee of the Uppsala/Örebro region. All patients gave oral and written informed consent. The study design is described in Fig. 1.

Inclusion/exclusion criteria

The aim was to include all eligible patients with limb-threatening acute or chronic lower limb ischaemia, who had infrainguinal disease. Predefined exclusion criteria were age below 18 years; need for immediate amputation; intolerance to blood sampling owing to anaemia (haemoglobin < 100 g/L) or lack of peripheral veins suitable for blood-sampling; previous intervention for lower limb ischaemia within the last 3 months; mental condition not allowing informed consent; or practical problems preventing follow-up and/or blood-sampling.

Enrolled patients in whom blood samples could not be obtained at baseline or after intervention were excluded from analysis.

Subgroups based on planned interventions

Based on the planned interventions, four predetermined subgroups were defined (Table 1). Although open surgical embolectomy, thrombectomy, and bypass surgery are still performed, the standard contemporary treatment for acute lower limb ischaemia is catheter-guided thrombolysis, followed by subsequent PTA and/or stenting. This subgroup of patients has a high risk of cardiovascular thrombotic events,[1] and was thought to be of particular interest to study.

Chronic CLI was defined as Fontaine's stages III—IV or Rutherford's categories 4—6.[1] Rest pain (Rutherford 4) had a minimum duration of 4 weeks and required morphine-like analgesia. In patients with chronic CLI, where revascularisation was not possible, the intervention used was pain relief and, if necessary, amputation at a later date. The

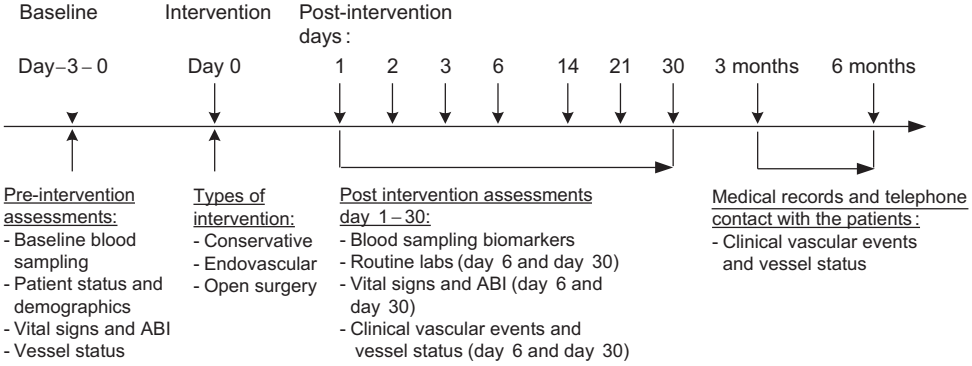

Figure 1. Study design: clinical assessments and blood sampling. *Note*. ABI = ankle brachial index.