Low-dose Thrombolysis for Thromboembolic Lower Extremity Arterial Occlusions is Effective Without Major Hemorrhagic Complications

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WHAT THIS PAPER ADDS

An evidence-based guideline on optimal urokinase and heparin doses for thrombolysis of thromboembolic peripheral arterial occlusions has not been produced to date. High-dose urokinase protocols are commonly used, but are accompanied by high rates of major and minor bleeding complications. This study shows that low-dose thrombolysis appears to be as effective as high-dose thrombolysis. In addition, low-dose thrombolysis results in a substantially lower risk of major bleeding complications.

Objective: To evaluate the efficacy and bleeding complications associated with a low-dose thrombolysis protocol for thromboembolic lower extremity arterial occlusions.

Design: A retrospective cohort study.

Materials and methods: A retrospective analysis was performed using data from all consecutive patients who underwent catheter-directed, intra-arterial thrombolysis for thromboembolic lower extremity arterial occlusions between January 2004 and May 2013. All patients were treated on a standard surgical ward. Endpoints were incidence of bleeding complications, duration of thrombolysis, angiographic patency rate, 30-day mortality rate, and amputation-free rate at 6 months.

Results: Of the 171 cases analyzed, 129 cases underwent low-dose thrombolysis and 42 underwent high-dose thrombolysis. No major bleeding complications occurred in the low-dose group versus 5% in the high-dose group ($p = .01$). The median duration of thrombolysis was 67 hours (4–304 hours) in the low-dose and 49 hours (2–171 hours) in the high-dose group ($p = .027$). Angiographic patency was restored in 67% of the cases in the low-dose group versus 79% of the high-dose group ($p = .17$). The 30-day mortality rates were 1% in the low-dose versus 5% in the high-dose group ($p = .09$). However, this higher mortality rate was not related to bleeding complications. Major amputation-free rates at 6 months were 81% in the low-dose group and 88% in the high-dose group ($p = .22$).

Conclusions: Based on this data series, low-dose thrombolysis for thromboembolic lower extremity arterial occlusions is as effective as high-dose thrombolysis; however, the risk of major bleeding complications is substantially lower when using low-dose thrombolysis.

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INTRODUCTION

Prior to the 1990s, the standard treatment for acute leg ischemia was surgical thromboembolectomy. The publication of several prospective randomized trials in the 1990s showed that thrombolysis might represent an effective alternative to primary surgical intervention.[1,2] Since these landmark trials, a consensus has been reached that thrombolysis can be viewed as a first-line treatment for many cases of thromboembolic lower extremity arterial occlusion.[3–5] Although a range of fibrinolytic agents and a variety of dose protocols have been used for thrombolysis,[6] most studies have reported results of urokinase (UK) at doses of more than 100,000 IU/hr, together with varying doses of heparin. These studies reported major bleeding rates ranging from 6% to 13%, including 2% intracranial bleeding, and minor bleeding complications in 5% to 17% of patients.[1,2,7,8] Overall, success rates for high-dose thrombolysis are reported to be around 70% (Table 1).

Before 2011, a low-dose thrombolysis protocol consisting of a 500,000 IU UK intra-arterial bolus, followed by continuous infusion of 50,000 IU UK/hr and 4,800 IU of

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Table 1. High-dose urokinase thrombolysis protocols.

Author	*N*	Urokinase dose	Heparin dose	Success rate	Major bleeding	Intracranial bleeding	Minor bleeding	Amputation-free rate	Mortality
Cragg 1991[8]	35	250,000 IU bolus	Intravenous heparin: 2—3 × APTT	77%	6%	None	17%	92% at 30 d	2% at 30 d
		250,000 IU/hr for 4 hr							
		125,000 IU/hr up to 24 hr							
STILE 1994[2]	66	250,000 IU bolus	5,000 IU bolus + 1,000	75%	6%	2%	5%	87% at 6 mo	4% at 30 d 8% at 6 mo
		240,000 IU/hr for 4 hr	IU/hr intravenous heparin:						
		120,000 IU/hr up to 36 hr	1.5—2 × APTT + intra-arterial heparin following institutional protocol						
Ouriel 1998[1]	272	240,000 IU/hr for 2 hr	Intravenous heparin: 1.5—2 × APTT (>only first 67 patients, hereafter: subtherapeutic)	68%	13%	2%	5%	72% at 6 mo	16% at 6 mo
		120,000 IU/hr up to 48 hr							
Duda 2001[7]	70	25,000 IU bolus per 10 cm thrombus	50 IU/kg bolus + 7 IU/kg/hr intravenous heparin	70%	6%	None	13%	88% at 6 mo	8% at 6 mo
		240,000 IU/hr for 2 hr							
		120,000 IU/hr for 2 hr							
		240,000 IU/hr for 2 hr							

d = day(s); hr = hour(s); mo = month(s); *N* = number of cases.

heparin per 24 hours was routinely used in our university hospital. In mid-2011 this protocol was replaced by a high-dose protocol (100,000 IU UK/hr and 9,600 heparin/24 hr). Two factors triggered this decision: a nationwide survey on thrombolysis practice revealed that most Dutch hospitals use high-dose protocols, and the successful use of a high-dose protocol during a clinical trial to evaluate ultrasound-accelerated thrombolysis compared with standard thrombolysis. However, the safety and effectiveness of high-dose thrombolysis was called into question at the VU University Medical Center following two incidents of major bleeding complications in rapid succession. This was the rationale underlying the decision to retrospectively evaluate thrombolysis success rates and bleeding complications of both the low- and high-dose thrombolysis protocols.

MATERIALS AND METHODS

This retrospective analysis included data from all consecutive patients who underwent thrombolysis for thromboembolic occlusions of native arteries or bypass grafts distal to the aortic bifurcation in the period January 2004—May 2013. Approval was granted from the institutional ethics review board. The results for patients treated with low- and high-dose protocols were analyzed separately.

Clinical and outpatient records, radiological reports, surgeons' and nurses' reports were all reviewed. Patients were excluded on the basis of a thromboembolic occlusion directly caused by an endovascular intervention and when treated with an EKOS EndoWave infusion catheter system,[9] as patency rates, lysis duration, doses of urokinase and heparin, and therefore risk of hemorrhagic complications, are probably influenced by this new thrombolysis technique. Recommendations in the literature were followed, so occlusions in patients with symptoms of less than 14 days duration were defined as acute, and those with symptoms of 14 days or more as non-acute.[2]

At the VU University Medical Center, thrombolysis is only performed as a primary treatment for suspected thromboembolic peripheral arterial occlusions in patients with viable extremities, that is not in immediately threatened limbs (Rutherford IIb/III) or in patients without evident pre-