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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-

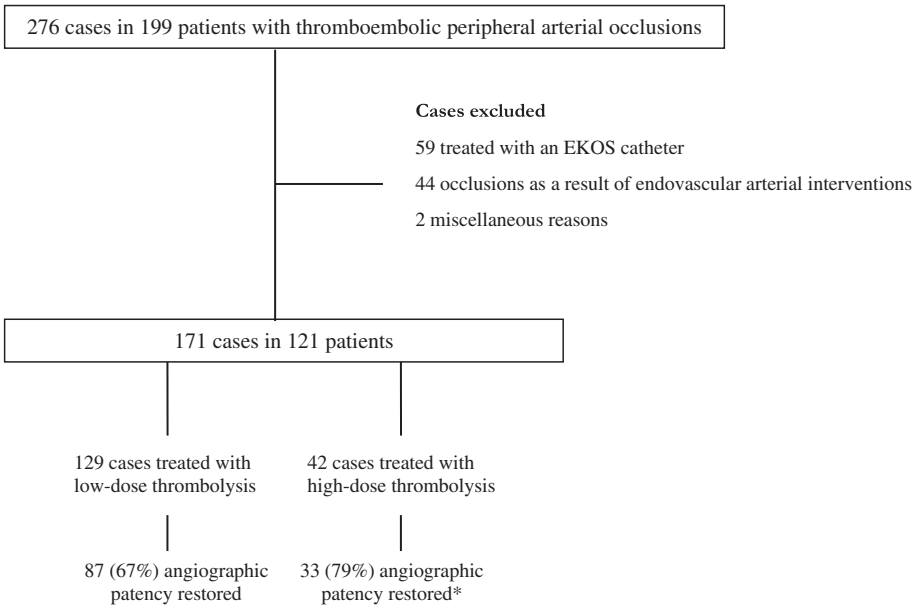

Figure 1. Ex- and included cases and outcome; values presented are cases. * Angiographic patency was restored in 87 cases (67%) in the low-dose versus 33 cases (79%) in the high-dose group ($p = .17$).

existing arterial occlusive disease presenting with hyperacute ischemia suggesting an embolic cause. Contraindications for thrombolysis were active internal bleeding, recent (<10 days) surgery or trauma, recent (<1 month) peptic ulcer or gastrointestinal bleeding, esophageal varices, recent (<3 months) intracranial bleeding, intracranial tumor, aneurysm or malformation, recent (<1 month) cardiopulmonary resuscitation, thrombocytopenia ($<150 \times 10^9$/L), and coagulation disorders.

The standard thrombolysis protocol consisted of a 500,000 IU UK (Medac GmbH, Hamburg, Germany) lacing dose, followed by a continuous infusion of 50,000 IU/h UK. After ipsilateral antegrade puncture or contralateral retrograde puncture under ultrasound guidance, an intra-arterial thrombolysis catheter (Royal Flush High-Flow, Cook Medical, Amsterdam, the Netherlands) was advanced via a guide wire and placed into the proximal end of the thrombus or as close as possible. A continuous dose of 4,800 IU/24 hr of heparin was infused through the side-port of the sheath to prevent peri-catheter clotting. After successful thrombolysis of the target artery, patients with residual hemodynamically significant stenoses in the in- or outflow tract underwent PTA or surgical revision in the absence of endovascular treatment options.

In the second half of 2011, the low-dose protocol was changed to a high-dose protocol for the reasons mentioned earlier. This protocol consisted of a 500,000 IU UK lacing dose, followed by continuous infusion of 100,000 IU/hr UK together with a continuous heparin dose of 9,600 IU/24 hr, a doubling of the continuous doses of urokinase and heparin. Decisions regarding follow-up angiograms, continuation of therapy, and additional procedures were made by a dedicated team of vascular surgeons and interventional radiologists. The number of follow-up angiograms per 24 hours depended on the severity of ischemia and the progression of thrombolysis. Patients were routinely treated on a standard surgical ward. All nurses and clinical residents involved in treatment underwent extensive training and had both paper and electronic access to the thrombolysis protocol at all times.

Hemoglobin (Hb), thrombocytes, Activated Partial Thromboplastin Time (APTT, normal range 25—40 seconds), Prothrombin Time measured as International Normalized Ratio (INR, normal range 0.80—1.20), and fibrinogen levels (normal range 200—400 mg/dL) were monitored at admission and daily. In cases with a fibrinogen level below 100 mg/dL, the UK dose was halved and the fibrinogen level was checked after 3 hours. If the fibrinogen level dropped below 50 mg/dL, UK infusion was stopped and the catheter perfused with NaCl 0.9%. After a period of 3 hours, the fibrinogen level was checked again and therapy was continued if the fibrinogen level had recovered to greater than 100 mg/dL. During therapy, aspirin was continued but no coumarines, low molecular weight heparins, or intravenous heparins were administered. Patients on coumarines or warfarin with INR greater than 3.5 at admission received vitamin K, and thrombolysis was initiated only when INR was less than 2.5. After successful thrombolysis, patients were routinely heparinized and oral anticoagulant treatment was started with a target INR range of 2.5—3.5.

Thrombolysis was considered successful when angiographic patency was restored, that is restoration of luminal continuity without significant residual thrombus. Intra- and retroperitoneal bleeding, intracranial bleeding, and all bleeding complications requiring blood transfusion or invasive procedures were considered potentially life-threatening, and therefore categorized as major bleeding complications. Minor bleeding

Table 2. Baseline characteristics of patients.

	Low-dose group ($n = 129$)	High-dose group ($n = 42$)	p
Age (in years, mean ± SD)	64 (±12)	64 (±10)	.94
Sex (% male)	57	67	.29
Vascular history (%)	77	86	.38
Cardiac history (%)	35	31	.75
Current tobacco use (%)	57	61	.70
Hypertension (%)	77	83	.37
Hyperlipidemia (%)	81	86	.47
Diabetes (%)	23	36	.11
Tissue necrosis at hospital admission (%)	14	10	.12
Duration of symptoms (d, mean ± SD)	8 (±11.8)	8 (±11.9)	.29

d = days.

Table 3. Occlusion characteristics.

		Low-dose group ($n = 129$) n (%)	High-dose group ($n = 42$) n (%)	p
Acute		102 (79)	31 (74)	.48
Non-acute		27 (21)	11 (26)	
Native artery		69 (53)	17 (40)	.14
Bypass graft		60 (47)	25 (60)	
Venous graft		14 (23)	5 (20)	.29
Prosthetic graft		45 (75)	19 (76)	
Combined graft		1 (2)	1 (4)	
Location occluded segment	Aorto-iliac	24 (19)	13 (31)	.18
	Femoral	73 (56)	23 (55)	
	Popliteal	24 (19)	3 (7)	
	Crural	8 (6)	3 (7)	

Acute is defined as occlusion with symptoms for less than 14 days. Non-acute is defined as occlusion with symptoms for 14 days or more. N = Number of cases.

complications were defined as bleeding at any other site not requiring blood transfusion or invasive treatment.

The data were analyzed using SPSS (IBM Statistics v20, Chicago, IL, USA). A Mann–Whitney-U test or an unpaired Student t test was used to compare continuous variables with (non)parametric distributions. A chi-square test was used to compare proportions between groups. A p value less than .05 was considered statistically significant.

RESULTS

During the inclusion period, thrombolysis was performed for 276 cases of lower extremity arterial occlusion in 199 patients. A total of 171 cases were included, 129 cases in 103 patients treated with low-dose thrombolysis and 42 cases in 29 patients treated with high-dose thrombolysis. Reasons for exclusion and patient outcomes are described in Fig. 1. Characteristics of included patients and occlusions are summarized in Tables 2 and 3, respectively. Baseline and occlusion characteristics were not significantly different between groups.

Treatment characteristics and results

Treatment characteristics of both groups are summarized in Table 4. The median duration of thrombolysis was 67 hours (range 4–304 hours) in the low-dose versus 49 hours (2–171 hours) in the high-dose group ($p = .027$), and the median frequency of follow-up angiograms was 1.0 (0.3–2.3) versus 1.5 (1.1–4.0) per 24 hours ($p < .001$). Angiographic patency was restored in 87 cases (67%) in the low-dose versus 33 cases (79%) in the high-dose group ($p = .17$). For the low-dose group, success rates increased in the second half of the inclusion period: in the period 2004–2008, patency was restored in 57% of the cases versus 77% in the period 2009–2013 ($p = .02$).

The median length of admission for all patients was 9 days (2–147 days). Patients successfully treated with thrombolysis had a significantly shorter in-hospital stay, independent of dose regimen, than patients in whom thrombolysis failed; 8 (2–82 days) versus 13 days (2–147 days), respectively ($p = .001$).

Success rates of thrombolysis for all cases were higher (although still non-significant) for acute compared with non-acute occlusions; 73% versus 61% respectively

Table 4. Treatment characteristics.

	Low-dose group ($n = 129$)	High-dose group ($n = 42$)	p
Treatment duration (in hr, median + range)	67 (4–304)	49 (2–171)	.03
Total UK dose (in million IU, mean ± SD)	4.7 (±3.1)	6.1 (±3.8)	.02
Angiography frequency (per 24 hr, median + range)	1.0 (0.3–2.3)	1.5 (1.1–4.0)	<.001
APTT (in s, mean ± SD)	59 (±30)	65 s (±52)	.29
INR (ratio, mean ± SD)	1.5 (±0.4)	1.7 (±0.6)	.04
Fibrinogen (in mg/dL, mean ± SD)	264 (±114)	204 (±65)	.002
Technical success rate (%)	99	100	.75
Patency rate (%)	67	79	.17
Major bleeding complications (%)	0	5	.01
Minor bleeding complications (%)	5	7	.39
30-d mortality rate (%)	1	5	.15
6 mo amputation-free rate (%)	81	88	.32

APTT = Activated Partial Thromboplastin Time; d = days; hr = hours; INR = International Normalized Ratio; mo = months.

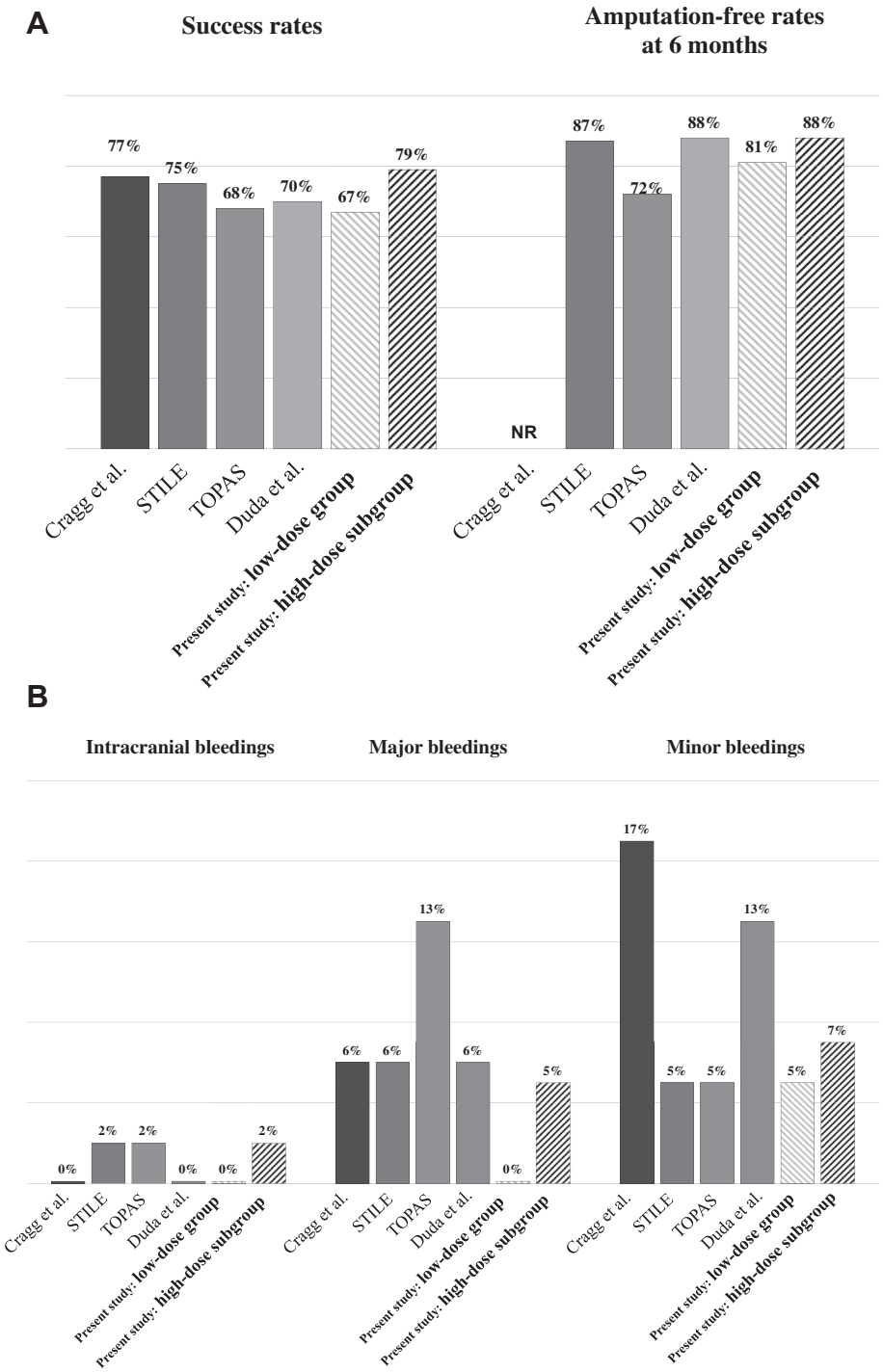

Figure 2. Comparison of results with literature. (A) Success rates, amputation-free rates at 6 months. (B) Bleeding complications. NR = not reported.

($p = .14$). However, the median duration of symptoms in patients successfully treated with thrombolysis compared with non-successfully treated patients was significantly shorter at 3 days (0—67 days) versus 7 days (0—60 days), respectively ($p = .006$). The success rates of thrombolysis for occluded native arteries and bypass occlusions did not differ (70% vs. 71%), and thrombolysis of prosthetic bypasses was significantly more successful than thrombolysis of venous bypasses at 77% versus 53%, respectively ($p = .04$). All of the above outcome parameters were independent of dose regimen. Univariate analysis showed that a variety of factors including history of vascular interventions, cardiac history, diabetes, smoking, hyperlipidemia, and hypertension did not significantly influence thrombolytic success.

Complications

Although no major bleeds occurred in the low-dose group, minor bleeding was noted in six cases (5%), including bleeding at the puncture site in five cases and hematuria in

a single case. Two of these six cases developed a groin hematoma, which led to the premature cessation of thrombolytic therapy. Other complications included delirium (2 cases), compartment syndrome of the leg (2), pseudoaneurysm formation (1), ischemic stroke (1), and temporary kidney failure (1).

Two cases with major bleeding complications occurred in the high-dose group, including one case of intracranial bleeding and one of intra-abdominal bleeding. These cases resulted in a major bleeding complication rate of 5% in the high-dose group versus 0% in the low-dose group ($p = .01$). The high-dose group also included three minor bleeds (7%), with bleeding at the puncture site, versus six cases (5%) in the low-dose group ($p = .39$). Total UK dose was not significantly different between patients who developed a major hemorrhage and patients who did not, 5.5 million IU (3.7—7.3) versus 4.5 million IU (0.7—17.6) ($p = .61$).

Pseudoaneurysm formation of the femoral artery occurred in one patient in the high-dose group.

Follow-up of low-dose cases

Of the 87 cases successfully treated with low-dose thrombolysis, 42 (48%) underwent an additional percutaneous intervention and eight (9%) underwent an additional surgical intervention (revision of bypass anastomosis, lumbar sympathectomy, toe amputation, or below knee amputation) within the period of admission. The causes of unrestored patency in the remaining 42 cases were no or marginal lysis in 33, initial lysis followed by direct re-occlusion in four, cessation of therapy because of complications in three (catheter luxation because of a fall out of bed in one case, groin hematoma in two cases), technical failure (not possible to advance catheter) in one, and non-compliance in one case. In 21 cases without restored patency, surgical revascularization was attempted (thromboembolectomy in 11 and bypass surgery in 10 cases; five of these cases underwent additional major amputation within 30 days) and direct major amputation was performed in 12 cases. One patient refused further treatment and in the remaining eight cases, despite lack of restoration of patency in the target artery, thrombolysis resulted in clinical improvement and the patients could return home without any additional intervention.

Follow-up of high-dose cases

Of the 33 cases successfully treated with high-dose thrombolysis, 11 (33%) underwent an additional percutaneous intervention and three (9%) underwent an additional surgical intervention (revision of bypass anastomosis, toe amputation) within the period of admission. In the high-dose group, nine cases showed unrestored patency with causes including no or only marginal lysis in six, cessation of the procedure because of complications in two, and initial lysis followed by direct re-occlusion in one case. Major amputation followed for four of these nine cases, and two cases underwent thromboembolectomy. Although patency of the target artery was not restored in two cases, thrombolysis resulted in clinical improvement and the patients could return home without any additional intervention. Finally, one patient underwent a second course of thrombolysis treatment.

Follow-up comparisons

30-day mortality rates were not significantly different between low- and high-dose groups, 1% versus 5% ($p = .09$). Amputation-free- and re-intervention-free rates at 6 months for the low- versus high-dose groups were 81% versus 88% ($p = .22$) and 82% versus 71% ($p = .14$), respectively, on an intention to treat basis In the low-dose group, the death of one patient was caused by (pre-existing) heart failure, and one patient in the high-dose group died from (pre-existing) heart failure and a concomitant refusal of further therapy. An additional patient died 2 weeks after hospital discharge in good condition because of a traumatic subdural hematoma complicated by renal failure.

Laboratory values

Although the mean APTT values over the whole treatment period did not differ between groups (low vs. high) at 59 seconds (±30 s) versus 65 seconds (±52 s) ($p = .29$), the mean INR in the high-dose group was significantly higher at 1.5 (±0.4) versus 1.7 (±0.6) ($p = .04$). Mean fibrinogen levels were also significantly higher in the low-dose group compared with the high-dose group, 260 (±110) versus 200 (±60) mg/dL, respectively ($p = .002$). All cases with major and minor bleeding complications showed fibrinogen levels greater than 100 mg/dL, and APTT and INR were within normal ranges on the day of the bleeding complication.

The APTT exceeded 60 seconds at least once within the treatment period in 67% of the cases in the low-dose group versus 55% in the high-dose group, indicating therapeutic treatment ranges despite the low-dose intra-arterial heparin administration. Furthermore, 51% of the cases in the low-dose group versus 48% in the high-dose group showed an INR greater than 2.0 at least once within the treatment period, indicating that INR levels were also within therapeutic ranges. Fibrinogen levels dropped below 100 mg/dL in 12% of the cases in the low-dose group (13 of 16 within the first 24 hours of therapy) and in 21% of the cases (4 of 9 within the first 24 hours of therapy) in the high-dose group. Two per cent of the cases in the low-dose group showed fibrinogen levels of less than or equal to 50 mg/dL versus 7% in the high-dose group.

DISCUSSION

An evidence-based guideline on optimal urokinase and heparin doses for the thrombolysis of thromboembolic peripheral arterial occlusions has not been produced to date. High-dose urokinase protocols are frequently used but are accompanied by high rates of major (6—13%) and minor (up to 17%) bleeding complications.[1,2,7,8] Although the success rate of

low-dose thrombolysis in the present study was comparable with the success rates of high-dose studies published in the literature (Fig. 2A), the most significant finding of this study was that comparable angiographic patency rates were achieved without major bleeding complications (Fig. 2B). Interestingly, results using low-dose thrombolysis also improved over time, from 57% patency in the period 2004–2008 to 77% in the period 2009–2013 ($p = .02$), while baseline and occlusion characteristics remained stable. This improvement may be attributable to improved radiological skills. Overall, thrombolysis in prosthetic grafts was more successful than in venous grafts (77% vs. 53% respectively, $p = .04$), a finding also reported by several other studies.[10,11] This again raises the question of whether initial thrombolysis is the best therapy for occluded vein grafts.

Similar rates of major bleeding complications were observed in the high-dose thrombolysis group when compared with the literature, once again emphasizing the increased bleeding risk associated with treatment with higher doses of fibrinolytics and heparin. The overall 30-day mortality rate in this study was 2%, comparable with the 2% mortality rate reported by Cragg et al., but lower than the 4% reported for the STILE trial.[2,8] The TOPAS trial did not report 30-day mortality rates.

The low rate of bleeding complications in the low-dose group can be explained by the low-dose infusion of urokinase, as well as by the low dose of the concomitantly administered heparin. Which of these factors contributes most to the favorable outcome cannot be determined from the present study. Despite the intended subtherapeutic intra-arterial administration of heparin to prevent peri-catheter clotting, APTT levels were within therapeutic ranges in the majority of patients at least once within the treatment period. This may be because of the potential synergistic effects of urokinase and heparin.[12,13] The concomitant use of unfractionated intravenous heparin during thrombolysis remains controversial.[14,15] In the TOPAS trial, the use of intravenous heparin (intended APTT 1.5–2 times the control value) was aborted after treatment of 62 patients, when the safety monitoring committee identified an unacceptably high rate (4.8%) of intracranial bleeding.[1] The initial requirement for therapeutic doses of systemic heparin was abandoned and replaced by subtherapeutic amounts of heparin, administered through the arterial sheath. This resulted in a drop in the rate of intracranial bleeding to 0.5%, suggesting a significant link between the co-administration of intravenous therapeutic doses of heparin and the risk of major bleeding. Another drawback of heparin use is the possible induction of heparin-induced thrombocytopenia thrombosis (HITT), which is rare but is associated with a high morbidity and mortality.[16] To the authors' knowledge, a randomized trial of thrombolysis with and without concomitant heparin administration has not been performed. The necessity for and safety of concomitant heparin infusion, whether intended as therapeutic or as subtherapeutic to prevent peri-catheter clotting and potential thrombus propagation, is questionable and should be further investigated.

The clinical use of laboratory tests during thrombolysis is controversial.[17] Although fibrinogen depletion was identified in the STILE trial as a risk factor for bleeding complications during thrombolysis with urokinase,[2] a lack of other randomized controlled trials in the literature means that this is still an isolated finding. In this study, fibrinogen levels of patients with bleeding complications were all >100 mg/dL on the day of occurrence.

In the present study and in other studies, angiographic patency, that is restoration of luminal continuity, was used to define success of thrombolysis.[1,2,7,8,18] However, despite restoration of luminal continuity of the target artery, poor distal run-off might result in early reocclusion and thus hamper clinical improvement and indicate failed treatment. The opposite — clinical improvement without successful lysis of the target artery — might also occur and could be explained by lysis of a thrombus in important collateral or outflow arteries, leading to relief of ischemia. In 5% of the cases, angiographic blood flow was restored but no clinical improvement was found, necessitating additional surgical therapy (bypass-revision, thromboembolectomy, or major amputation). By contrast, in 4% of the cases clinical improvement was seen without restoration of luminal patency in the target artery.

In this study, thrombolysis was continued as long as progression of lysis was observed on follow-up angiograms, without clinical deterioration demanding a change of therapy. The median duration of therapy in the low-dose group was nearly 3 days. Other studies have described protocols that stop thrombolytic treatment at defined points such as 7, 24, 36, or 48 hours,[1,2,7,8] although reasons for this strict discontinuation of thrombolysis at predefined time points were not reported. The relatively long duration of therapy in this study might be partly explained by the lower dose of urokinase. Despite the longer therapy duration in the low-dose group, which might also influence limb salvage, the 6-month amputation-free rate of 81% is comparable with that reported in the literature[1,2,7,8] (Fig. 2A). The frequency of follow-up angiograms might also influence therapy duration, with a higher frequency potentially resulting in earlier cessation of therapy. In the high-dose group, more angiograms were performed because faster reperfusion was anticipated, preventing unnecessary overnight continuation of thrombolysis. Duration of ischemia is another factor that might influence success of thrombolysis and risk of major amputation. The STILE investigators found a non-significant trend towards an advantage for surgery compared with thrombolysis in the combined death and amputation outcome (9.9% vs. 17.8%; $p = .08$) in the group with symptoms lasting more than 14 days. However, in the group with symptoms of less than 14 days duration thrombolysis performed significantly better than surgery, 15.3% versus 37.5% respectively ($p = .01$).[2] This resulted in guidelines advising thrombolysis only for recent occlusive events, defined as symptoms lasting for a maximum of 14 days.[17] The patency rates of thrombolysis in the present study were (non-significantly) higher for acute compared with non-acute occlusions, 73% versus 61%, respectively

($p = .14$). In addition, patients successfully treated with thrombolysis compared with non-successfully treated patients had a shorter history of symptoms, 3 versus 7 days, respectively ($p = .006$). In the present data series, thrombolysis was successful in five out of eight cases with occlusions with a duration of 1 month or longer. Patients with long-lasting occlusions who are unfit to undergo surgical intervention might therefore be considered candidates for thrombolysis. Additionally, as more than half of patients receiving thrombolysis in the STILE trial underwent reduced surgical procedures,[2] thrombolysis might reduce the magnitude of additional interventions.

Limitations

Although this was a retrospective study, the authors consider this study relevant, as there is a lack of available evidence on optimal thrombolytic dosage for peripheral arterial occlusions and major hemorrhage still remains a significant problem of this minimal invasive technique.[4]

Potential bias could have been introduced by the comparison of non-contemporaneous groups. However, the authors do not think that this could have influenced the hemorrhage rate.

Finally, because of the absence of major bleeding complications, performing low-dose thrombolysis on a general surgical ward appears to be safe. With an increasing number of patients undergoing thrombolysis, this option could reduce the logistic burden on special care units and might also lower the costs of therapy.

Conclusion

Based on the present data series, low-dose thrombolysis for thromboembolic lower extremity arterial occlusions appears to be as effective as high-dose thrombolysis. In addition, low-dose thrombolysis results in a substantially lower risk of major bleeding complications.

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CONFLICT OF INTEREST

None.

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