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ORIGINAL ARTICLE

Outcomes and Complications after Intraarterial Thrombolysis for Limb Ischemia: a 4 Year Study at a Single Centre

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Summary
Introduction. The reason for using thrombolytic therapy is to eliminate vascular thrombosis and promote vascular permeability. Acute limb ischemia is associated with significant morbidity and mortality. ROCHESTER, STILE and TOPAS studies showed that thrombolytic therapy for acute limb ischemia decreases the rate of surgical interventions and significantly increases the rate of limb salvage.
Aim of the Study. The purpose of this study is to assess the efficacy and outcomes of intra-arterial thrombolysis in the treatment of acute occlusions of the lower limb over a four-year period.
Material and Methods. We analysed 103 patients who had been treated in our department. There were acute ischemias of stage IIa and IIb according to the Rutherford classification. The data prior to, and after thrombolysis was analysed. We used *Alteplase* as a thrombolytic agent (mean dose 62 mg ±23.5). Procedural success was based on angiographic and clinical outcomes. Statistics were calculated by SPSS 16.
Results. The mean duration of symptoms prior to hospitalisation was 2.5 days (IQR 5-96 hours). The mean age at the time of thrombolysis was 63±11 for males 69±10 years for females. The success of intraarterial thrombolysis was defined by angiographic and clinical outcomes (successful in 86.4% and failed in 13.6%). Adjunctive angioplasty was performed on 39 (37.9%) patients, and immediate reconstructive surgery was required on 19 (18.4%) patients. The incidence of complications was 17,4 %, with the most common being- bleeding from the puncture side, the urinary tract or the gastrointestinal tract. Overall mortality was 8.7%. The women who required thrombolysis were older (p=0,034) and with a higher death rate (p=0.047). A CDT (catheter-directed thrombolysis) for an abdominal aorta thrombosis carries a significantly high mortality rate (p=0.00013). There were no statistically significant differences between the duration of symptoms and limb amputation and between other analysed data.
Conclusions. Intraarterial thrombolysis is an effective treatment method in acute limb ischemia for selected patients, as long as accurate procedural monitoring is ensured. Thrombolysis often leads to the discovery of underlying vascular lesions. A CDT for an abdominal aorta thrombosis carries a significantly high mortality rate.
Key words: atherosclerosis, thrombolysis, limb ischemia

INTRODUCTION

Acute limb ischaemia (ALI) caused by arterial thrombosis of native vessels and grafts is a common and potentially serious condition. Obstruction of blood flow as a result of thrombotic events leads to malperfusion and dysfunction. Historically, open surgery was performed for vessel patency, however, with the arrival of thrombolytic agents, catheter-directed thrombolysis (CDT) became the obvious management method for ALI. Dotter et al (10) were the first to report CDT. Three clinical trials provided definitive evidence that patients with acute limb ischemia had clinical benefit from CDT (22, 29, 21). The consensus from these studies was that CDT should be considered as first-line treatment for ALI under the following conditions: where symptoms of limb ischemia present for less than 14 days, there are no absolute contraindications for thrombolysis and the predicted CDT time is short enough to preserve limb viability. Current recommendations suggest that CDT be used in patients with Rutherford class I and class IIa limb ischemia (22, 7).

Limb ischaemia by arterial thrombosis accounts for 85% of arterial occlusions and it occurs more often in the lower extremities. Despite the advancement of the diagnostic and therapeutic tools available today, ALI was associated with elevated major amputation and mortality rates (10-20%), usually because of co-morbidities (19, 12) CDT thrombolysis can be performed under local anaesthesia, which makes it possible to treat patients with co-morbidities in a safer way. CDT also helps in the discovery of underlying vascular lesions which can be further corrected by angioplasty or open surgery. The reported 24-month vessel patency rate after thrombolysis when the underlying lesion was identified and treated was significantly higher in comparison when it wasn`t (26). An inverse relationship between amputation after thrombolysis and the number of patient vessels, providing blood to the limb has also been reported (6).

There are analytical dosage regimens for the various thrombolytic agents (14). Heparin should be prescribed immediately after the procedure followed by anti-

platelet therapy. Low molecular weight heparin should be considered as an additional aid to double anti-platelet treatment.

CDT is not without risk: approximately 10 % of patients suffering from haemorrhage, require a blood transfusion or reoperation and this can even be fatal (3). The reported rates of distal embolization ranges from 3.8 to nearly 24%. There are absolute and relative contraindications for CDT including ongoing bleeding, intracranial haemorrhage, compartment syndrome, trauma and surgery within past 10 days, intracranial tumour, recent eye surgery and gastrointestinal bleeding within 10 days (28).

AIM OF THE STUDY

The aim of this study was to evaluate efficacy and outcomes with regard to limb salvage, bleeding complications and survival rate in acute limbs with thrombosis over a four-year period.

MATERIAL AND METHODS

All vascular patients admitted to Riga Eastern Clinical University Hospital were analysed between 1 January 2011 and 31 December 2014. Patient's records were retrieved and analysed according to a predetermined protocol. The study was approved by the hospital`s Ethics committee. Case records were analysed retrospectively. All complications were noted during the thrombolysis and up to the discharge from the hospital. Limb ischemia was defined according to the guidelines of the European Society for Vascular Surgery (2).

A full blood count, activated partial prothrombin time (APPT), prothrombin complex, creatinine phosphokinase, urea, a creatinine and glomerular filtration rate, were performed before and after thrombolysis. Vascular imaging such as computed tomography angiography and digital subtraction angiography were used before CDT. Intra-arterial, catheter-directed thrombolysis access was achieved through puncture of the common femoral artery for infrainguinal thrombolysis or the brachial artery for suprainguinal thrombolysis. Ultrasound imaging was not employed routinely for arterial puncturing.

The lytic agent used was rtPA (Actilyse®; Boehringer Ingelheim, Ingelheim, Germany) by intraarterial catheter directly in to the thrombus (28). The total dose of rtPA was decided individually depending on the duration of symptoms, the extent of the arterial occlusion, the degree of ischaemia, co-morbidities and the patient`s age. The thrombolytic procedure started with a bolus dose of 4 mg rtPA, followed by 4 to 7 mg/h for a complete dose of 50mg. Control angiography was performed every 10 – 12 h, and depending on the finding suspension of thrombolysis, PTA, repeated CDT or operative therapy was performed. The complete reestablishment of the occluded arteries without major amputation and death was considered to be a successful clinical outcome. During CDT patients were observed in the intensive care unit.

Data management and statistical analysis were done with the SPSS® software package version 16. Statistical analysis for paired samples was performed using the Student *t* test and one-way analysis of variance. A probability error of p less than 0.005 was considered to be statistically significant.

RESULTS

We analysed 103 patients treated in our department during the years 2011 (22 patients), 2012 (32 patients), 2013 (18 patients) and 2014 (31 patients) (Fig.2)

The median age of the patients was 64 (range 36-86) years (Table 1). During the four-year period, 11(11.3%) patients were re-hospitalized for CDT, (8 patients twice, 1 patient three times, 1 patient four times and 1 patient six times). The mean duration of symptoms prior to hospitalisation was 61.9 hours (IQR 5-96) and the mean hospitalisation time was 9.7 days (IQR 4-12).

The aetiology of analysed arterial occlusions differed (Fig.1). Prosthesis graft occlusions were treated more commonly. The majority of patients (59%) corresponded to the Rutherford IIa classification.

The mean dose of rtPA was 62 (range 5-120) mg and the mean rate of administration was 6.9 (range 3-10) mg/h. Twenty-one (20%) patients underwent CDT therapy more than once during a single hospital stay. Successful CDT was observed in 89 (86 %) of patients. Nineteen (18%) procedures were followed by a subsequent open operation and thirty-nine (38%) were followed by a subsequent PTA. An unsuccessful CDT required an immediate major amputation (Table 2). Evidence of bleeding complications was observed on the access site for 11 patients. Bleeding complications requiring a blood transfusion occurred with 3 (3%) patients. One of them required an open way to fix a. brachialis pseudoaneurysm after CDT. Four patients had an intracranial haemorrhage, and of these, three patients died. These patients were 50, 58 and 78 years old and had multiple co-morbidities. They received 75mg, 50mg and 50 mg rtPA respectively. Three of the intracranial haemorrhages occurred on the second day after thrombolysis, and one four days after the thrombolysis. There was one haemorrhage from the urinary tract observed at the beginning of CDT and the thrombolysis was stopped and converted to open surgery. One bleeding occurred from the gastrointestinal tract followed by myocardial infarction. One progressive renal insufficiency was observed.

There were fourteen major amputations - thirteen above the knee and one below the knee. There were three cases of death after the amputation. One fasciotomy was done immediately after thrombolysis. The frequency of amputation after CDT depending on the side of the thrombosis, is shown in Fig. 3.

Patients with an amputation were at a higher risk of death (P=0.036). The men were younger than the women (63 years old *versus* 69 respectively; P = 0.034), and the women had a worse outcome after CDT compared to the men (4 deaths among the 16 women,

but 5 deaths among the 78 men ; P=0.047). CDT for abdominal aorta thrombosis carry a significantly high mortality rate (9 aorta thrombosis/ 6 exitus letalis ; p=0.00013).Patients with a Rutherford class IIb had the trend of a higher risk for a worse outcome. There were no statistically significant differences between duration of symptoms and between the other analysed data.

DISCUSSION

Our study evaluated the factors which were associated with success and complications with CDT. The amputation-free rate of 86 % in this study is similar to previous reported studies (29, 21, 24). In our study, angiographic patency was used to define the success of thrombolysis (23, 29, 8). Despite the restoration of luminal flow in the target artery, poor distal run-off might result in early re-occlusion with subsequent re-hospitalisation and repeated treatment (11.3%). In addition, clinical success without lysis of the target artery might also occur by lysis of the thrombus in important collateral or outflow arteries and is followed by subsequent re- interventions (Table 2).

CDT was used more frequently for a prosthesis graft because of the previously observed advantage of thrombolysis over vein grafts (20, 16, 23). We found the trend of a better outcome for prosthesis grafts and a lower subsequent invasion rate after CDT in our study (Fig.3). This and the previous findings may raise the question of whether CDT is the best therapy for occluded vein grafts in the future.

In our study, the overall mortality rate of 8.7% and the complication rate of 17.4% were higher in comparison with the STILE trial (29) (4%), Cragg et al. trial (8) (2%) and other recently published trials (12, 13). The CDT for aortic thrombosis was not included in the previous mentioned studies. Aortic thrombosis patients (9 aorta thrombosis/ 6 exitus letalis) were severely ill, most with both leg ischemia, renal, mesenterial ischemia and alcohol intoxication. This parameter may have severely increased the morbidity and mortality rates in our study. In addition, the relatively higher mortality rate in our study can be explained by several factors including the high dose used of Actilyse, the older analysed population with severe

co-morbidities, the patients included in the study with relative contraindications (especially with severe hypertension and alcohol intoxication), and the absence of regular monitoring of APTT and fibrinogen after CDT in the intensive care unit.

A high dose of rtPA accelerates the thrombolysis and achieves the faster restoration of blood flow. It is a potential advantage to patients with acute ischemia where the time interval is essential, but there is a higher rate of bleeding complications (17, 4). The risk of bleeding must be assessed against the risk of surgery or amputation before the CDT for every patient.

Weight-based and non-weight-based dosing regimens for the continuous infusion of Actilyse have been used and there was no evidence that either of the regimens is more advantageous (27). An advisory panel from the Society of Interventional Radiologists recommended a maximum dose of 2 mg/h of Actilyse for a maximum total infusion of 40 mg (27). It has been shown that a dose > 1mg/h does not improve efficacy but does increase bleeding complications (24, 5). In future, the use of a lower dose and a slow thrombolytic protocol may be considered in selected patients to avoid major complications.

Another explanation could be the usage of heparin after CDT (13). Continuous heparin infusion requires adjustment of the infusion rate and regular monitoring of APTT values. Another drawback of heparin use is the induction of thrombocytopenia thrombosis, which is associated with a high morbidity and mortality (1).

The clinical monitoring of fibrinogen is controversial. Fibrinogen depletion was identified as a risk factor for bleeding complications during CDT (29). However, the suspected finding was not confirmed in other randomized trials.

We found that the men included in the study were significantly younger compared to with the women (63 *versus* 69 years) and this was also observed in another trail (13). This finding could be explained by the androgens and they receptors found more in men, which are one of the major risk factors for cardiovascular diseases and atherosclerosis, while oestrogens have a protective effect (14).

We observed that the outcome of CDT was significantly worse for women compared to men. This can be explained by the older population of women analysed and consequently more co-morbidities which could increase the risk of a worse clinical outcome. This means, that a multidisciplinary approach should be used, involving anesthesiologists, haematologists, interventional radiologists and vascular surgeons to significantly improve the clinical outcome of CDT therapy.(30).

Another possibility for improving the clinical outcome is to use intra-arterial thrombolysis guided with a balloon catheter (9). It's possible to enhance local thrombolysis through this method, to use smaller quantities of a thrombolysis agent and to improve the outcome for even relatively old arterial thrombosis.

We included only acute patients with an onset of symptoms of less than 14 days (mean 61.9 hours, IQR 5.0-96.0) in the study (15). There was no correlation between the duration of symptoms and the clinical outcome or duration of the symptoms and the hospital stay which was found in previous studies (29, 21, 18). This may possibly be revealed in future studies which include one-year amputation rates.

CONCLUSIONS

Intraarterial thrombolysis is an effective treatment method in acute limb ischemia for selected patients, as long as accurate procedural monitoring is ensured. Thrombolysis often leads to discovery of the underlying vascular lesions. A CDT for an abdominal aorta thrombosis carries a significantly high mortality rate.

Conflict of interest: None

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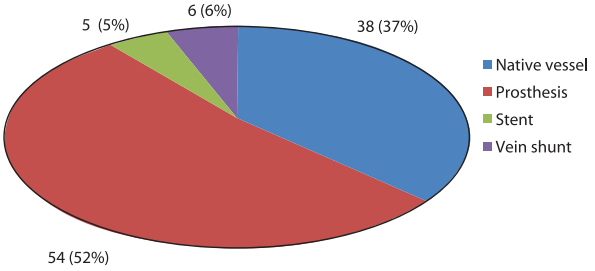

Fig. 1. The site of thrombosis

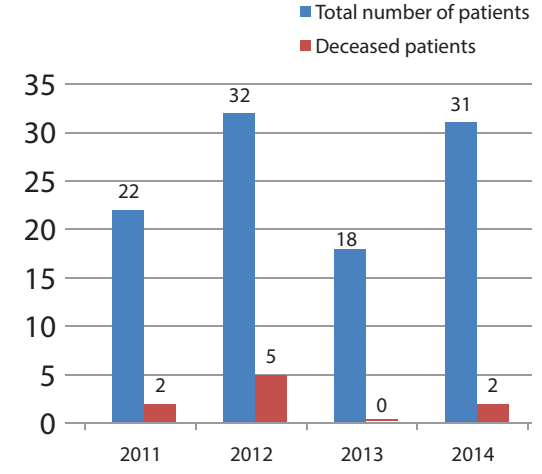

Fig. 2. Patients within the four-year period

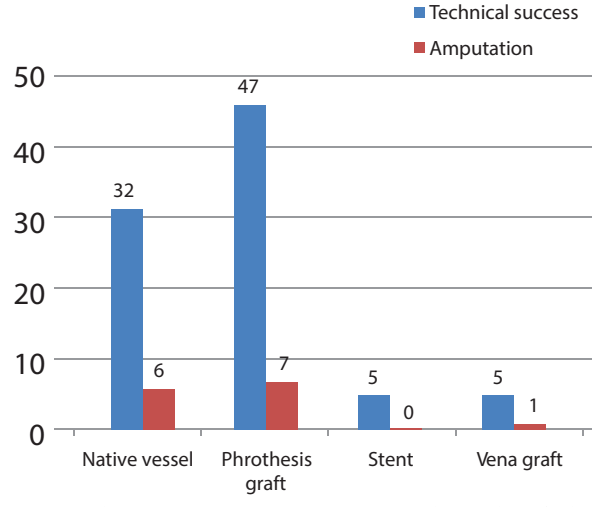

Fig. 3. The outcome in relation to the side of the thrombosis

Table 1. Demographical characteristics of patients

Total number of patients	103
Male	83 (80%)
Female	20 (20%)
Mean age male (years)	63 ± 11
Mean age female (years)	69 ± 10
Major risk factors	Uncontrolled arterial hypertension, Alcohol intoxication

Table 2. Clinical outcomes and complications after thrombolysis

Outcomes	Numbers (%)
Complications	18(17.4)[1]
Limb amputation	14 (13.6)
Subsequent operation	19 (18.4)
Subsequent PTA	39 (37.9)
Repeated thrombolysis	21 (20.4)[2]
Exitus letalis	9 (8.7)[3]

[1] puncture side haematoma, haematuria, intracranial haematoma, renal insufficiency, gastrointestinal bleeding

[2] five amputations

[3] from them 6 (5.8) aortic thrombosis

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