Benefits of Long Versus Short Thrombolysis Times for Acutely Thrombosed Hemodialysis Native Fistulas

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Abstract

Introduction: Local thrombolysis with a time of exposure to recombinant tissue plasminogen activator of 15 to 150 minutes is commonly used to declot acutely thrombosed hemodialysis fistulas. The duration of thrombolysis for the restoration of arteriovenous blood flow remains controversial. The aim of this study was to investigate the outcomes of long thrombolysis treatment (LTT, 3 hours or more) and short thrombolysis treatment (STT, less than 3 hours) in our institution. Methods: We retrospectively analyzed 86 interventional declotting procedures (28 STT and 58 LTT) applied to 86 acutely thrombosed hemodialysis fistulas. The intervention time (IT) following thrombolysis (from the initial fistulography to the end of the angioplasty maneuvers), the time of day of the intervention (ie, during working hours vs off-hours), and the need for temporary catheter placement (TCP) were assessed. Success was defined as complete access recanalization, and major adverse events were defined as ischemia, bleeding, and access rupture. Results: The ITs were reduced after LTT (63.3 [9.3] minutes) compared to STT (106.7 [24.7], P = .01), but there was no difference in success rate (85.7% STT, 89.7% LTT, P = .722). While all (100%, 58/58) of the angioplasty maneuvers after LTT were performed during regular working hours, 75% (21/28) of those following STT were managed during off-hours (P < .001). Despite the longer treatment, the need for TCP was not increased after LTT (10.7%) compared to STT (12.1%, P = .515), and the major complication rate was reduced (3.4% after LTT and 28.6% after STT, P = .004). Conclusion: Long thrombolysis treatment results in shorter and less complicated percutaneous stenosis treatments during regular working hours. Despite the LTT of up to 25 hours until access for dialysis was achieved, no increase in the risks of TCP or major adverse events were observed following LTT.

Keywords
hemodialysis access thrombosis, thrombolysis, recombinant tissue plasminogen activator, lyse and wait technique, temporary catheter placement

Introduction

Recombinant tissue plasminogen activator (rt-PA; Actilyse; Boehringer Ingelheim, Ingelheim am Rhein, Germany) is successfully used for local thrombolysis and the recanalization of clotted vascular access using various regimes and techniques.¹ The so-called “lyse-and-wait technique” is a commonly used percutaneous thrombolysis procedure with local thrombolysis reaction times from 20 to 60 minutes.² After short thrombolysis treatments (STTs), which ranged from 30 minutes to 3 hours, we documented extensive and challenging percutaneous angioplasty maneuvers that were primarily performed outside regular working hours.

Therefore, we applied longer thrombolysis time (LTT) of 3 up to 25 hours to perform the stenosis treatment and angioplasty maneuvers within regular working hours. We retrospectively analyzed and compared the outcomes of and follow-up data for STT and LTT at our institution. The goal of this study was to evaluate the differences in intervention times (ITs), timings (ie, within or out of regular working hours), major complication rates, and the need for temporary catheter placement (TCP) between STT and LTT.

Materials and Methods

Patient Population

From February 2007 to August 2011, 86 hemodialysis (HD) patients (28 females and 58 males) were identified at our institution. All patients presented with an acutely thrombosed HD fistula.

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native fistula as the first access event after surgical creation. All patients underwent a local thrombolysis procedure using rt-PA with varying exposure times. We retrospectively divided the patients into 2 procedure groups, that is, short thrombolysis treatment (STT, <3 hours) and long thrombolysis treatment (LTT, ≥3 hours) groups. Changes in the treatment details over time from shorter local reaction times in the beginning toward prolonged procedures enabled us to build these 2 groups. The decision to modify this technique toward a longer local reaction was undertaken by the colleagues of the institute of radiology. The main reason for modifying this technique was a preference for performing angioplasty maneuvers during regular working hours rather than during off-hours. Furthermore, the rt-PA dosage was reduced due to the fear that prolonged local thrombolysis reaction times could increase the risk of bleeding complications, particularly during the night or weekends.

All patients had end-stage renal disease with TCP for a mean of 30.7 months. The thrombosis diagnoses were based on the clinical criteria for the absence of thrill and bruit and were confirmed by ultrasound scan in each case. To reduce the attrition bias, we exclusively included the first access thromboses after creation. Furthermore, we excluded thrombolysis treatments of HD grafts.

Data Collection and Follow-Up

The electronic medical records were evaluated in terms of the patient’s baseline demographic information, comorbid conditions, HD histories, and treatment and outcome data. The long-term outcome data were recorded in all cases for a mean follow-up time of 25.4 (19.0) months (2-98 months). The follow-ups included clinical examinations of bruit and thrill and ultrasound duplex scans.

Procedure

The declotting procedure (procedure time [PT]) was performed in inpatient conditions and consisted of 2 parts:

1. The local lysis time (LT) was taken as the time from single-shot thrombus infiltration until the first fistulography. Direct thrombus infiltrations with rt-PA at mean dosages of 3.9 (1.1) mg (range 2-6 mg) for STT and 2.2 (0.7) mg (1-4 mg) for LTT were performed via ultrasound imaging using two 19- to 22-gauge Venflon at the proximal and distal ends of the thrombus formation. The correct positioning of the Venflon was documented either by ultrasound scan or fluoroscopically after the injection of a small amount of contrast media into the thrombus.

2. The IT was defined as the period from the first fistulography to the end of the stenosis treatment. One or two 5F to 7F introducer sheaths (Terumo, Tokyo, Japan) were inserted into the fistula, and the angioplasties of all identified stenoses were performed using 4- to 12-mm balloon catheters (Abbott Vascular, Illinois or Boston Scientific, Massachusetts). No stents were used in the interventions.

Definitions

The angioplasty maneuvers were divided according to when the interventions were performed (5 PM to 7 AM during the week or any time during the weekend or a public holiday). Success was defined as complete access recanalization with palpable thrill following treatment plus successful HD for at least 1 session.

The major adverse events were defined as ischemia distal to the extremity, bleeding leading to surgery, and access rupture. Specifically, access rupture was visualized on angiography or was diagnosed based on a hematoma after the intervention. The need for TCP was defined by the acute implantation of a central vein catheter as the only method to continue HD treatment.

The patency rates were as follows: The primary patency (PP) rate was defined as the interval following successful thrombolysis of the access thrombosis until the next access intervention caused by dysfunction or occlusion, and the secondary patency (SP) was defined as the interval after the intervention until the access was surgically declotted, revised, or abandoned due to the inability to treat the original lesion, the preference of the surgeon, or renal transplantation.3,4

Statistical Analysis

All statistical evaluations were performed with the IBM SPSS Statistics 21 software (version 21.0; SPSS Inc, Chicago, Illinois) for Windows. A P value <.05 was considered statistically significant.

To test for significant differences between the end point outcomes, Fisher exact tests were applied for categorical covariates (presented as the numbers and frequencies of subjects)
and t tests were applied for continuous covariates (presented as the means and standard deviations). The PP and SP at 1, 3, 6, 12, and 24 months were calculated using the Kaplan-Meier method, and log-rank testing was applied to compare patency between the groups.

**Results**

**Demographics and Treatment Data**

The demographic data, comorbidities, and HD histories are summarized in Table 1. The immediate and follow-up outcome data are provided in Table 2 and are presented in Figures 1A, B, 2, and 3.

**Off-Hour Interventions**

Seventy-five (21/28) angioplasty maneuvers after STT were performed outside regular working hours, whereas all 58 of the interventions after LTT were initiated during regular working hours ($P < .001$). In 7 cases (12%) after LTT, the interventions were initiated at the end of the working day and completed outside working hours.

**Failed Procedures and Catheter Placement**

The success rates were 85.7% after STT and 89.7% after LTT. Four and 6 procedures failed after STT and LTT, respectively, as defined by the unavoidability of surgical revision or the
creation of a new access. In 7 of these 10 cases, TCP was necessary to continue HD.

Within the first 30 days following the successful interventional declotting procedures, only 1 reocclusion in each group occurred. Subsequently, both failed fistulas were successfully declotted by STT and LTT. These data were excluded from the statistical analysis due to the above-mentioned inclusion criteria (ie, only the first access event after creation was included). There was no significant difference in the need for TCP between the STT and LTT groups (Figure 2).

Major Adverse Events
As illustrated in Figure 3, we observed a reduced major complication rate after LTT ($p = .004$). Moreover, we also documented no major bleeding complications after LTT.

Follow-Up
During the mean follow-up period of 25.4 months (2-98 months), 10 patients were lost to follow-up (1 after STT and 9 after LTT) and 8 patients died due to causes unrelated to the access (3 after STT and 5 after LTT). Surgical revision was the secondary end point in 38 patients (16 STT and 22 LTT) and occurred after a median of 23.8 months (4-98 months). Until this point, the performance of 1 to 5 reinterventions to maintain blood flow of the arteriovenous fistula (AVF) was necessary for all of these 38 patients. The reasons for surgical revision and therefore the ends of the follow-up periods were aneurysms in 11 cases and recurrent stenosis of the vessel walls in 17 cases. In our opinion, both the aneurysms and stenoses were due to multiple access punctures during dialysis treatment. At the end of the follow-up period, abandonment was necessary for 6 HD accesses (4 in the STT group and 2 in the LTT group). All 6 of these patients received prior renal transplantation and were not on HD at the time of access abandonment. There were no significant differences in cumulative PP or SP rates following STT and LTT (Figure 4A and B).

Discussion
Hemodialysis access thrombosis is one of the most frequently reported complications and occurs on average approximately 2 to 3 times per year. The decision regarding treatment modality, that is, endovascular, surgical, or combined, should be made within 48 hours and have an outcome goal of at least a PP of 50% at 6 months.

Surgical thrombectomy can be performed quickly with simultaneous stenosis repair, but this approach can be very challenging and therefore unsuccessful in cases of more central lesions. In 2002, surgery was considered the gold standard treatment in terms of success and patency rates. However, using modern endovascular techniques with which central and peripheral stenoses can be treated, many studies have demonstrated better outcomes for interventional repairs. Often, surgical treatment cannot salvage the original fistula and therefore involves grafts to maintain blood flow, whereas the AVF is usually salvaged following interventions. Nevertheless, after multiple access events, surgical revision and occasionally the creation of a new
fistula seem to elicit the best PP and SPs (71% and 98%, respectively) at 1 year of follow-up. However, there is a high risk of TCP during the maturation of a newly created fistula. Therefore, interventional declotting procedures, such as thrombolysis, are becoming increasingly important. Table 3 summarizes previously published and available data regarding treatment and outcome details after the local thrombolysis of HD fistulas. The times from the initiation of the thrombolysis procedure via thrombus infiltration until the performance of percutaneous angioplasty have been reported to be in the range of 15 to 150 minutes. There is little available data about the numbers of TCPs that are necessary while awaiting the end of the thrombolysis and stenosis treatments. These data are comparable to our results.

Recently, it has been proposed that endovascular techniques should be the first-line treatments for acute HD access.

![Figure 4](image_url)

**Figure 4.** (A) Comparison of cumulative primary patency rates. (B) Comparison of cumulative secondary patency rates.

**Table 3.** Published Literature on Thrombolysis of Clotted Hemodialysis Access.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>n</th>
<th>Initial Success Rate (%)</th>
<th>Temporary Catheter Placement</th>
<th>Lysis Time, min</th>
<th>Primary Patency Rate</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poulain</td>
<td>1991</td>
<td>64</td>
<td>59</td>
<td>NA</td>
<td>NA</td>
<td>59% (3 months)</td>
<td>NA</td>
</tr>
<tr>
<td>Sands</td>
<td>1994</td>
<td>71</td>
<td>81</td>
<td>NA</td>
<td>15</td>
<td>44% (1 month)</td>
<td>250 000 IE Urokinase</td>
</tr>
<tr>
<td>Vogel</td>
<td>2001</td>
<td>40</td>
<td>95</td>
<td>NA</td>
<td>19</td>
<td>65% (3 months)</td>
<td>4.0 mg rt-PA</td>
</tr>
<tr>
<td>Sofoceous</td>
<td>2002</td>
<td>27</td>
<td>94</td>
<td>NA</td>
<td>20</td>
<td>87% (1 month)</td>
<td>4.13 mg rt-PA</td>
</tr>
<tr>
<td>Schon</td>
<td>2003</td>
<td>25</td>
<td>92</td>
<td>NA</td>
<td>NA</td>
<td>65% (3 months)</td>
<td>2.3 (0.3) mg rt-PA</td>
</tr>
<tr>
<td>Vashchenko</td>
<td>2010</td>
<td>427</td>
<td>99</td>
<td>NA</td>
<td>20-40</td>
<td>62% (3 months)</td>
<td>250 000 IE Urokinase</td>
</tr>
<tr>
<td>Tseke</td>
<td>2011</td>
<td>40</td>
<td>55</td>
<td>NA</td>
<td>60-90</td>
<td>91% (1 month)</td>
<td>3.0 (1.5) mg rt-PA</td>
</tr>
<tr>
<td>Choi</td>
<td>2012</td>
<td>279</td>
<td>95</td>
<td>NA</td>
<td>25</td>
<td>80% (3 months)</td>
<td>200 000 IE Urokinase</td>
</tr>
<tr>
<td>Umanath</td>
<td>2012</td>
<td>321</td>
<td>74</td>
<td>11.2%</td>
<td>30-150</td>
<td>2-16 mg rt-PA</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: rt-PA, recombinant tissue plasminogen activator; NA, not available.
thrombosis.\textsuperscript{21} The time required for these interventions has been reported to reach 123 minutes.\textsuperscript{22} Furthermore, these procedures can be performed without general anesthesia and occasionally even in outpatient settings, and these factors could provide great benefits for the often multimorbid patients. The 6-month PP and SPs have been reported to be 34\% to 81\% and 53\% to 86\%, respectively.\textsuperscript{9,10,23,24} For these reasons, we began to conduct the local thrombolyces of acute thrombose HD accesses in year 2006.

**Benefits and Criticisms of Long-Term Thrombolysis**

Initially, we tested the widely used “lyse-and-wait technique” with local reaction times of approximately 15 to 150 minutes.\textsuperscript{2} In most cases, the subsequently percutaneous angioplasty maneuvers were challenging and highly time-consuming. Longer thrombolysis time allows clinicians, especially interventional radiologists, to perform angioplasty during regular working hours. This appears to produce quicker angioplasty maneuvers and fewer complications. These beneficial effects can be explained by a reduction in remaining clots after the prolonged rt-PA exposure time, which could account for the less extensive interventions and the reduced risk of access rupture during intervention. In the present study, there were no access ruptures after LTT and 4 (14\%) following STT. Recently, access ruptures have been reported as a major complication in approximately 8\% of cases.\textsuperscript{25} These data are consistent with the presented results after STT. Finally, another reason for the reduced IT after LTT could be the performance of the stenosis treatment during regular working hours, which guarantees the presence of highly trained interventional radiologists and assistants, whereas the presence of these personnel cannot be guaranteed at night or during the weekend. This notion is supported by the results of this study, particularly the finding that the angioplasty maneuvers after LTT began during regular working hours, whereas only 25\% of the procedures after STT were performed during working hours. In this context, it has been reported that patients with myocardial infarction exhibit better outcomes following duty-hour angioplasties than off-hour procedures.\textsuperscript{26}

Initially, we feared that the prolonged thrombolysis period would increase the need for TCP and the risk of bleeding complications. However, these apprehensions remain unconfirmed because the risk of TCP after a prolonged thrombolysis time was not increased. Furthermore, the rate of major complications, particularly bleeding requiring surgery, was significantly reduced following the long compared to the short thrombolyses. One explanation for this observation could be the reduced dosage of rt-PA applied in the LTT.

**Limitations**

One criticism of the present study could be performance bias due to the training curve of the interventional radiologists during the reviewed time period. Most of the STTs were performed in the years of 2006 and 2007, whereas the majority of the LTTs were performed after 2007. We attempted to reduce this bias by excluding thrombolysis procedures that occurred before 2007, which ensured that the procedure experience durations of each of the performing interventionalists exceeded 1 year.

Another limitation of this study is its retrospective and non-randomized design. Therefore, we were not able to evaluate minor complications, such as asymptomatic pulmonary artery embolisms (PAEs). It is assumed that most patients with PAE after percutaneous venous procedures exhibit no clinical symptoms. In the present study, no routine chest computed tomography scans were performed to exclude pulmonary embolism. However, no patient exhibited the typical complaints of chest pain or dyspnea. Although PAEs have been described following angioplasty,\textsuperscript{27} in most cases, they are minor and asymptomatic, and thus, routine investigation is not performed. Within this study, this standard practice was followed; thus, the incidence of minor PAE could not be defined. Therefore, PAE could represent a serious complication, and further prospective studies might be necessary to estimate the incidence of this mostly asymptomatic but potentially life-threatening complication.

**Conclusion**

Thrombolysis with prolonged rt-PA exposure time resulted in shorter and less challenging stenosis treatments that could be performed during regular working hours. Moreover, the risk of major complications, particularly access rupture during angioplasty, was significantly reduced. Furthermore, there was no increased need for TCP, despite the extension of the PT up to 25 hours. We believe that LTT is an effective and safe modification of the commonly used “lyse-and-wait technique”.

**Declaration of Conflicting Interests**

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