Int J Clin Exp Med 2018;11(2):812-817
www.ijcem.com /ISSN:1940-5901/IJCEM0062110

Original Article

Salvage of an occluded radiocephalic fistula using urokinase and a tourniquet for patients undergoing hemodialysis

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Received July 23, 2017; Accepted January 10, 2018; Epub February 15, 2018; Published February 28, 2018

Abstract: Objective: We prospectively assessed the safety and efficacy of high-dose bolus urokinase and a tourniquet for anticoagulation for a radiocephalic arteriovenous fistula (AVF) occlusion. Methods: We prospectively studied 52 radiocephalic AVF occlusion events in 38 patients who were treated with bolus 100,000-200,000 IU urokinase injected into the outflow vein near the occlusion after tourniquet compression of the outflow vein. Bleeding complications within one week were recorded. Salvage and patency were calculated and patients were followed up during regular hemodialysis sessions. Results: The therapy was successful for 47 cases and urokinase doses ranged from 150,000-450,000 IU (mean 27.8±9.2×10^4 IU). Successful thrombolysis was achieved 10-1200 min after urokinase treatment. No bleeding was observed. All patients were followed and 5 had an occlusion recurrence. The shortest time to recurrence was 1 month and the longest was 56 months (mean 17.5±15.2 months). Primary patency was 84.9% at 3 months (95% CI, 68.1-94.9%), 69.7% at 6 months (95% CI, 51.3-84.4%), and 33.3% at 24 months (95% CI, 18.0-51.3%). Assisted primary patency was 90.9% (95% CI, 75.7-98.1%) at 3 months, 75.8% at 6 months (95% CI, 57.7-88.9%) and 42.4% at 24 months (95% CI, 25.5-60.8%). Conclusion: Thrombolytic treatment with local urokinase and a tourniquet may be used to salvage occluded AVF and systemic complications of urokinase can be avoided using the tourniquet.

Keywords: Arteriovenous fistula, endovascular thrombolysis, hemodialysis, thrombus, urokinase

Introduction

Fistula thrombi are chief causes of arteriovenous fistula (AVF) dysfunction [1]. Re-establishment of AVF patency can involve percutaneous catheter-based thrombolysis, surgical embolectomy with a Fogarty catheter, or percutaneous transluminal angioplasty (PTA). Endovascular thrombolysis is also a minimally invasive approach that preserves AVF function [2].

Urokinase can be used for endovascular salvage of occluded AVFs [2-7], but studies are limited and the approach is limited by potential dissemination of urokinase into the systemic circulation, which may increase the rare risk of bleeding events [8, 9]. The 2006 revised K/DOQI clinical practice guidelines for vascular access emphasized a need to identify new urokinase protocols to maintain the patency of AVFs [10]. Therefore, we offer a novel approach for using a tourniquet to prevent urokinase dissemination during salvage of occluded AVF in patients under hemodialysis.

Material and methods

Study design and patients

This was a prospective study of patients who underwent endovascular regional salvage of occluded hemodialysis autologous AVF at the Department of Hemodialysis of Taizhou Second People's Hospital between January 2008 and August 2015. Diagnostic criteria were: 1) disappearance of fistula murmur and pulsations at the anastomotic site; 2) an originally filled but collapsed cephalic vein; and 3) sudden localized pain and the fistula was hard to the touch and tender.

Thirty-eight (52 events) patients were included. Inclusion criteria were: 1) patients under maintenance hemodialysis, 2-3 times/week using

Table 1. Patient characteristics

Variables	N (%) or mean ± SD
Number	
Patients	38
AVH thrombotic events	52
Male	20 (52.63%)
Age	50.5±14.4
Disease	
Chronic nephritis	31 (81.57%)
Diabetic nephropathy	5 (13.16%)
Polycystic kidney disease	1 (2.63%)
Obstructive nephropathy	1 (2.63%)
Suspected causes of thrombosis	
Lengthy tourniquet compression after hemodialysis	2 (3.85%)
Low blood pressure	9 (17.31%)
Tight cuff compressed anastomotic aneurysm	1 (1.92%)
Unknown	40 (76.92%)
Radio-cephalic AVF	
End-to-end anastomosis	20 (52.63%)
End-to-lateral anastomosis	18 (47.37%)
Time to thrombus formation	
<24 h	51
48 h	1
Events per patient	
1	29 (76.32%)
2	7 (18.42%)
3	2 (5.26%)
4	1 (2.63%)

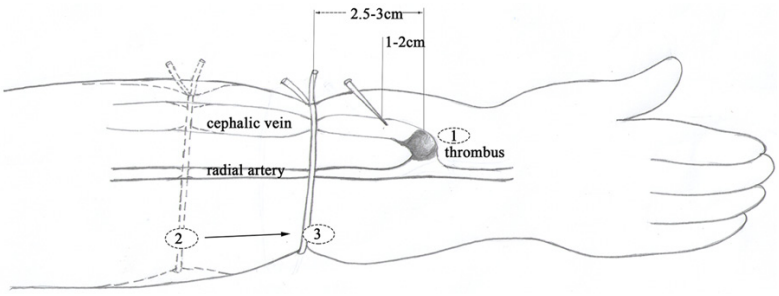

Figure 1. Steps in salvage of occluded radiocephalic fistula: ① Identification of the thrombus; ② ligature of the AVF outflow and puncture; and ③ adjustment of the tourniquet.

an AVF of the radial artery and cephalic vein in the forearm; 2) no active bleeding or bleeding tendency; 3) no active liver disease; and 4) no severe hypertension (defined as systolic blood pressure (SBP) >160 mmHg and/or diastolic blood pressure (DBP) >90 mmHg). Exclusion criteria were: 1) patients with disease causing abnormal coagulation; or 2) patients with comorbidities causing bleeding such as abnormal hepatic function.

The study was approved by the ethics committee of the hospital. Written informed consent was provided by each patient. Patient characteristics are presented in **Table 1**. The interval from the first hemodialysis treatment after AVF creation to fistula occlusion was 1-121 months. All 38 patients had autogenous radial-cephalic direct wrist access: 20 by end-to-end anastomosis and 18 by end-to-lateral anastomosis.

Urokinase treatment

All occlusion events were confirmed by clinical examination. Thrombi were reached along the radial artery, anastomosis, and AVF venous outflow tract. Patients were given aspirin (300 mg, po) as soon as possible after AVF occlusion diagnosis and blood pressure was maintained below 160/90 mmHg. The thrombus was visualized by palpation. A tourniquet was tied at the peripheral part of the AVF, near the fistula occlusion point, to prevent the AVF venous outflow. A 21-G needle was inserted into the outflow vein, 1-2 cm away from the thrombus occlusion point and some blood was aspirated to ensure the needle was in the vessel. The tourniquet was then adjusted 2.5-3.0 cm away the occlusion point. **Figure 1** provides a diagram of the technique. Then, 100,000-200,000 IU of urokinase (Tianjin Biochemist Pharmaceutical Co., Ltd., Tianjin, China) diluted in 1 ml of normal saline was injected towards the thrombus in a single injection. The infusion tube was clipped with a vascular clamp and a warm towel was placed

Table 2. Treatment effects

Variables	N (%) or mean ± SD
Urokinase dose (IU)	$27.76\pm9.20\times10^4$ $(0.15\text{-}4.5)\times10^5$
Success rate of thrombolytic therapy	47/52 (90.4%)
Time to signs of successful thrombolysis (minutes)	10-1200
Failed thrombolysis at first attempt	4/38 (10.53%)
Thrombus recurrence	5/47 (10.64%)
Thrombus recurrence time (months)	17.5±15.2 (2-56)

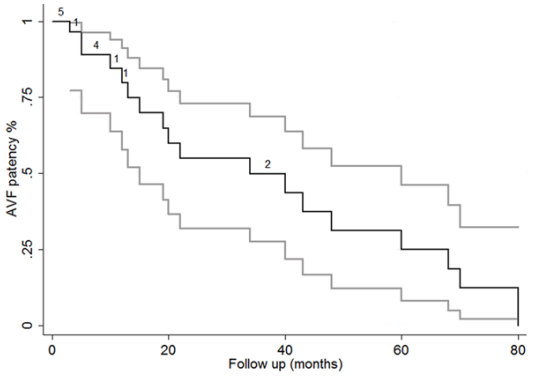

Figure 2. Primary patency after salvaging the occluded arteriovenous fistulas. 95% confidence intervals are shown (numbers indicate numbers of patients at risk at each time interval).

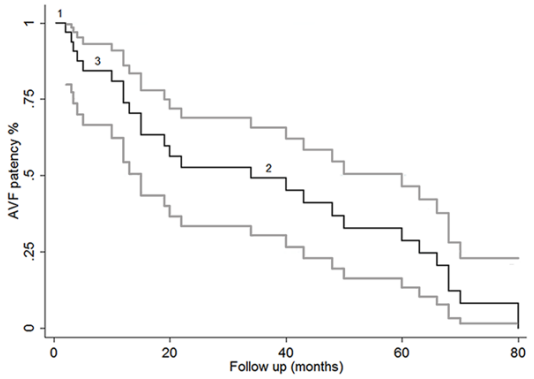

Figure 3. Assisted primary patency after salvaging occluded arteriovenous fistulas. 95% confidence intervals are shown (numbers indicate numbers of patients at risk at each time interval).

on the arm to provide the best working conditions to the urokinase. The AVF was examined every 10-20 min. If the outflow vein of AVF returned the pulse and blood fluctuated in the infusion tube, the tourniquet was released for the return of thrill by palpation and for bruit by auscultation. If urokinase did not work within 30 min, the same dose of urokinase was injected again. The needle was removed when the thrombus was dissolved. The total injected dose of urokinase was recorded. Then, 5,000 IU of low molecular weight heparin (LMWH) was subcutaneously injected immediately [11]. LMWH (5,000 IU, sc) was used once a day for the following 6 days along with aspirin (100 mg/day, po). If urokinase did not dissolve the thrombus within 1.5 h, treatment was stopped with a single injection of LMWH (5,000 IU).

Observational indices

Thrombus dissolution was considered successful when the following criteria were observed after urokinase treatment: 1) thrill on palpation and bruit on auscultation by a stethoscope; and 2) at least one hemodialysis session was performed and blood flow was >200 ml/min according to the dialysis machine. Otherwise, the treatment was considered a failure.

The time from urokinase administration to thrombus dissolution was calculated. Complications within 24 h after urokinase administration (fever, rash, bleeding, splanchnic embolism, and tourniquet-related) were observed. Bleeding complications within one week were recorded. Thrombus recurrence was analyzed until the last follow-up visit. The time to the next AVF event was calculated. The patients were followed up at the same time as their regular hemodialysis treatments.

Statistical analysis

Continuous variables are presented as means ± standard deviation and compared using a Student t test. Categorical variables are presented as frequencies and percents, and a Pearson chi-square test was used for comparison. Kaplan-Meier curves were used to analyze the long-term patency of the AVFs. Stata 12.0 (StataCorp LP, College Station, TX) was used to analyze results. Two-sided $p<0.05$ were considered statistically significant.

Results

Table 1 presents patient characteristics and **Table 2** presents salvage outcomes. Comparing successful and first-time failures, thrombophlebitis and low blood flow were higher in the fail-

ure group ($p<0.05$). There was no significant difference between the two groups for other traits. All patients were followed up. **Figures 2** and **3** show Kaplan-Meier analysis of AVF primary patency [12] and assisted primary patency [12] after urokinase treatment, respectively. The only complication was hand swelling after tourniquet use for more than 1 h, but the swelling gradually returned to normal after releasing the tourniquet.

Discussion

Thrombus is a major cause of AVF failure [1]. Numerous prophylactic measures can be taken to prevent a first occlusion event, but the risk of thrombus remains high [13-15]. Compared with percutaneous catheter-based thrombolysis and angioplasty, surgical embolectomy with a Fogarty catheter, and percutaneous transluminal angioplasty (PTA), endovascular thrombolysis is less invasive and offers better preservation of vessel function [2]. If the thrombus burden is small, endovascular methods can be used [16, 17]. Urokinase can be used for AVF salvage, but its systemic dissemination is associated with bleeding complications [2-8].

Therefore, we examined the effects and safety of urokinase and a tourniquet in the treatment of occluded radiocephalic fistulas. Salvage was successful for 47 cases and data show that thrombolytic treatment with local urokinase with a tourniquet may be effective for salvaging occluded AVF. Systemic complications of urokinase were avoided with the tourniquet and this provides a novel method for preventing systemic dissemination of urokinase and to ensure maximum local contact with the thrombus.

Urokinase is a serine protease that digests the peptide bond between arginine 560 and valine 561 of plasminogen. Urokinase activates plasmin and degrades fibrins, achieving thrombolysis [18]. Its half-life is 15 minutes and its effects disappear within 24 h [19]. Urokinase is not routinely used in the United Stated for salvage of occluded AVF, but its use has been reported elsewhere [2, 20, 21]. In the present study, urokinase was successful in dissolving the thrombus in 90.4% of events, outcomes were similar to previous studies with interventional radiology with a technical success of 95% [3] and 100% [22], but much higher than in studies by Mangiarotti [4] and Rajan's group [5], who had 65% and 73% reported success, respectively. A study using a combination of urokinase and mechanical methods achieved success of 78-98% [23] and the urokinase dose may play a role in these discrepancies, but Duszak's group [3] used doses much lower than in this present study (6,667 IU vs. 27,7600 IU) and achieved success similar to ours. This may be due to interventional methods, thrombi affecting different body parts, and sample size. However, compared with complex interventions in studies by Duszak's group [3], our method here is simple and economically feasible.

We used a tourniquet tied proximal to the thrombus and the injection needle was inserted into the AVF outflow vein, 1-2 cm away from the thrombus. Then the tourniquet was placed 2.5-3 cm peripheral to the thrombus. If there were vascular branches, they were compressed with fingers to avoid systemic dissemination of urokinase before thrombi dissolution. In addition, the urokinase bolus was diluted in 1 ml of normal saline, increasing the local urokinase concentration and perhaps increasing its initial patency.

We report that the patency rate of the AVF at 1 month was 91.5% and was >50% at 9 months, which was greater than the 6-month patency of 30-50% observed in previous studies for arteriovenous graft and AVF [24, 25]. However, these previous studies used a combination of drugs and mechanical methods, and there were differences in vascular access and secondary prophylaxis. Indeed, LMWH helps release of plasminogen activator, activates the fibrinolytic system, and induces thrombolysis [26]. Therefore, the few recurrences and high long-term patency could be due, at least in part, to this secondary prophylactic approach. A previous study of urokinase by intravenous drip infusion and LMWH for secondary prophylaxis prevented recurrences [6]. Here, aspirin (100 mg po qn) and LMWH (5,000 IU ih qd, for 6 days) were used, but more work is required to confirm that these methods are optimal.

The use of urokinase as a thrombolysis agent has been associated with some complications. Wall's group [7] reported 575 cases of myocardial infarction for which urokinase was used for thrombolysis, and severe or life-threatening bleeding complications were observed in only <1% of patients. The most common complication of urokinase is local hemorrhage but other severe complications such as pulmonary, cerebral, or peripheral embolism, and severe bleeding have been reported [6, 8, 19, 26]. Another

previous study reported some minor complications, but no severe ones [22]. We found no complication other than edema during the use of the tourniquet, but the small sample size may suggest this to be insignificant.

The present study has some limitations. First, the sample size was small and from a single center and the lack of a control group prevented assessment in-depth assessment of this approach. Finally, clinical causes of AVF acute occlusion were unknown for 77% of the events. Additional well-designed randomized controlled trials should be performed to validate our preliminary data.

In conclusion, we suggest a novel approach for salvaging the function of occluded AVF that involves thrombolytic treatment with local urokinase with a tourniquet to prevent systemic dissemination of urokinase. Systemic complications of urokinase can be avoided by this approach, but additional studies are needed to confirm our preliminary results.

Acknowledgements

The authors thank Cunping Shi, Hongying Peng and Haihua Shen for clinical work.

Disclosure of conflict of interest

None.

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