

Original Research Article

Effect of the combination of percutaneous transluminal angioplasty and pharmacological thrombolysis on hemodialysis patients

Liwen Yang*, Fengying Tang, Weiqiang Zhong

Department of Nephrology, Huizhou Municipal Central Hospital, China

*For correspondence: **Email:** vu908f@163.com; **Tel:** +86-015119086958

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Abstract

Purpose: To examine the efficacy of percutaneous transluminal angioplasty (PTA), combined with pharmacologic thrombolysis (PT) on thrombosis of autologous arteriovenous fistulas (AVFs), inflammatory factors, and β_2 microglobulin (β_2 -MG) levels in hemodialysis patients.

Methods: Seventy-eight patients with AVF thrombosis allocated randomly into a control group (CG) received PTA, and a study group (SG) received PTA combined with PT ($n = 39$ in each). The patency, vascular condition, inflammatory factors, viz, interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), β_2 -MG levels, vascular-related factors (VEGF-A and MCP-1), complications, and quality of life were determined.

Results: At three and six months after surgery, the SG exhibited a higher vascular patency than CG ($p < 0.05$). Serum levels of IL-6, hs-CRP, β_2 -MG, VEGF-A, and MCP-1 of the SG were lower than those of CG ($p < 0.05$). The SG showed higher cross-sectional area, inner diameter at the site of fistula, and better quality of life scores than CG ($p < 0.05$).

Conclusion: The combination of PTA and PT enhances efficacy, increases vascular patency, reduces inflammatory response, lowers the level of β_2 -MG, and improves quality of life in patients with AVFs without increasing complications. Thus, the combination treatment has potentials for the management of hemodialysis patients.

Keywords: Hemodialysis, Percutaneous transluminal angioplasty, Arteriovenous endovascular fistula, Thrombosis, Pharmacological thrombolysis, Inflammatory factors, β_2 Microglobulin

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INTRODUCTION

Similar to the number of patients with end-stage chronic kidney disease, the number of patients with end-stage renal disease has exceeded 2 million cases, and this is related to a remarkable decrease in the patient's quality of life [1,2]. Hemodialysis, peritoneal dialysis, and renal

transplantation are the main treatments for end-stage renal disease, and most patients prefer hemodialysis treatment, which effectively prolongs their survival [3]. Autologous arteriovenous endovascular fistula (AEF) is the primary means of vascular access for patients undergoing maintenance hemodialysis, and vascular access patency affects treatment

efficacy [4]. The long-term application of AEFs, combined with the weakened physical status of the patients, leads to a high incidence of thrombosis in arteriovenous fistula, which is a major cause of primary AV fistula failure [5,6]. Therefore, it is important to reduce the incidence of arteriovenous fistula (AVF) thrombosis, so as to improve the clinical outcomes of hemodialysis. Arteriovenous endovascular thrombosis is often treated with interventional procedures and pharmacological thrombolysis, both of which have a determined efficacy level [7]. One study found [8] that PTV significantly improves endovascular patency in patients with AVF thrombosis. It has also been reported [9] that thrombolytic therapy using urokinase, significantly improves endovascular patency in patients with AVF thrombosis. However, there are limited clinical studies on percutaneous transluminal angioplasty (PTA) combined with pharmacologic thrombolysis (PT) for the treatment of AVF thrombosis in hemodialysis patients. In this randomized control study, 78 patients with AVF thrombosis who underwent hemodialysis were selected to examine the effects of the combination of PTA and PT on inflammatory factors and β_2 -MG levels.

METHODS

Patient profile

This study was implemented with the approval of the Medical Ethics Committee of Huizhou Central People's Hospital (approval no. kyll2021073), and in compliance with the guidelines of Declaration of Helsinki. Seventy-eight patients with thrombosis in autologous AEFs between September 2019 and August 2020 were enrolled and allocated to a control group (CG) and a study group (SG) using the random number table ($n = 39$ in each group). The inclusion criteria: thrombosis of autologous AEF confirmed with ultrasound and other imaging examinations, duration of thrombosis ≤ 72 h, voluntary signing of the informed consent form, being on hemodialysis for \geq three months, compliance and active cooperation. Exclusion criteria were complete occlusion of the intravenous fistula, allergy to drugs such as urokinase, severe coagulation disorders, active bleeding, and presence of other serious diseases.

Treatments

Control group (CG)

Patients were treated with PTA, and the AEF was examined using color Doppler ultrasonography to verify the location and

severity of thrombosis as well as vascular stenosis. The > 30 mm proximal end of the thrombus was selected as the puncture point, and the AVFs were punctured in reverse. A matching guidewire was placed along the puncture needle, and the needle was withdrawn. A Y-shaped sheath was placed along the guidewire, and the dilator tube and guidewire were withdrawn. The hydrophilic-coated guidewire was pushed toward the thrombus via the sheath, and the position of the guidewire was confirmed with color Doppler ultrasonography. A dilating balloon catheter was inserted, then the guidewire was withdrawn, and dilatation therapy was performed, repeatedly 3 – 5 times, each time for 1 – 3 min. Routine anticoagulation was administered postoperatively, and hemodialysis treatment was performed to drain the contrast agent on the postoperative day.

Study group (SG)

Based on percutaneous endoluminal angioplasty treatment, urokinase (Qingdao Guanlong Bio-Pharmaceutical Co., Ltd. State Drug Quantifier H20184169) was used for thrombolytic treatment, and 250,000 U urokinase + 50 mL of sodium chloride solution were injected into the direction of the thrombus through the sheath tube.

Evaluation of outcomes/indices

Vascular patency

All patients were followed up and investigated through outpatient review for six months, and vascular patency (Vp) was examined at one, three, and six months after surgery.

$$Vp (\%) = (Vc/T)100 \dots\dots\dots (1)$$

where Vc is the number of vascular patency cases and T the total no. of cases)

Vascular conditions

The cross-sectional area and inner diameter of the vessels at the site of the endovascular stenosis were measured before and after treatment using color Doppler ultrasonography.

Inflammatory factors

Fasting venous blood (3 mL) was drawn before and after treatment, and the serum was collected after centrifugation. Serum levels of IL-6 and hs-CRP were measured with enzyme-linked immunosorbent assay (Beijing Kangjia Hong yuan Biotechnology Co., Beijing, China).

Levels of β_2 -MG

Fasting venous blood (3 mL) was drawn before and after treatment, and the serum was collected after centrifugation. Serum β_2 -MG levels were measured using an immunoturbidimetric assay before and after treatment (Guangzhou Aptar Biotechnology Co. Guangzhou, China).

Vascular-related factors

Fasting venous blood (3 mL) was drawn before and after treatment, and the serum was collected after centrifugation. Levels of vascular endothelial growth factor-A (VEGF-A) and monocyte chemotactic protein-1 (MCP-1) were measured by enzyme-linked immunosorbent assay (Chengdu Zhengneng Biotechnology Co., Chengdu, China) before and after treatment.

Complications

Complications such as swelling of the dorsum of the hand, hematoma at the puncture site, and bleeding were noted in both groups.

Quality of life

The Quality-of-Life Short Form (WHOQOL-BREF) was used to assess quality of life of patients before, and three months after treatment. It is a 26-item scale divided into four domains: social, environmental, physical and psychological relations, and higher scores represent better quality of life.

Statistical analysis

Statistical analyses were conducted using SPSS statistical analysis software (26.0). Measurement data (vascular cross-sectional area, inner diameter, serum levels IL-6, hs-CRP, β_2 -MG, VEGF-A, MCP-1, and quality of life scores) are expressed as mean \pm SD, while inter-group and intra-group comparisons were made using independent and paired sample t-tests, respectively. Count data (vascular patency, complications) are expressed as percentages and analyzed using the χ^2 test. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline data

Patient profile of both groups showed no significant difference ($p > 0.05$), which was comparable (Table 1).

Vascular patency

One month after surgery, both groups exhibited no statistically significant difference in vascular patency ($p > 0.05$). However, at three and six months after surgery, the SG showed higher vascular patency than the CG ($p < 0.05$), revealing that PTA combined with PT improves the vascular patency (Table 2).

Vascular condition

After treatment, the cross-sectional area and inner diameter of the blood vessel at the endovascular stenosis site were increased in both groups, but the area and diameter were much higher in the SG ($p < 0.05$), indicating that the combination of PTA and PT improves the vascular condition at the site of endovascular stenosis (Table 3).

Inflammatory factors and β_2 -MG levels

After treatment, IL-6, hs-CRP, and β_2 -MG were reduced in both groups, and were much lower in the SG ($p < 0.05$), suggesting that PTA combined with PT can effectively reduce the inflammatory response and lower β_2 -MG levels in patients (Figure 1).

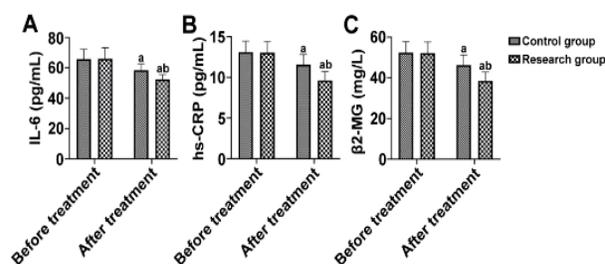


Figure 1: Comparison of inflammatory factors and β_2 -MG levels between the CG and SG. Note: (A) IL-6; (B) CRP; (C) β_2 -MG. Compared with pre-treatment, ^a $p < 0.001$; compared with CG; ^b $p < 0.001$

Vascular-related factors

After treatment, serum levels of VEGF-A and MCP-1 were reduced in both groups, but were much lower in the SG ($p < 0.05$), suggesting that the combination of PTA and PT reduces the levels of vascular-related factors (Table 4).

Complications

Both groups exhibited no statistically significant difference in complications ($p > 0.05$), suggesting that PTA combined with PT does not increase the complication rate (Table 5).

Table 1: Comparison of profile (n, \bar{x} mean \pm SD) between the CG and SG

Group	Gender		Mean age (years)	Mean duration of dialysis (years)	Type of primary disease			Time to patency of autogenous arteriovenous endovascular fistula (months)
	Male	Female			Diabetic nephropathy	Chronic nephritis	Other	
CG (n=39)	22	17	56.64 \pm 4.53	3.85 \pm 1.25	12	23	4	20.23 \pm 5.32
SG (n=39)	21	18	56.21 \pm 5.03	3.77 \pm 1.32	11	22	6	20.67 \pm 5.22

Table 2: Comparison of vascular patency [n (%)] between the CG and SG

Group	1 month postoperative	3 months postoperative	6 months postoperative
CG (n=39)	36 (92.31)	28 (71.79)	23 (58.97)
SG (n=39)	39 (100.00)	35 (89.74) [#]	31 (79.49) [#]

[#]P < 0.05 compared with CG

Table 3: Comparison of vascular conditions (mean ± SD) between the CG and SG

Group	Vascular cross-sectional area (mm ²)		Vascular inner diameter (mm)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
CG (n=39)	3.47±0.82	12.85±2.14 ^{***}	2.34±0.62	3.51±0.58 ^{***}
SG (n=39)	3.54±0.84	17.24±1.98 ^{####}	2.41±0.65	4.22±0.67 ^{####}

Note: ^{####}P < 0.001: compared with CG; ^{***}p < 0.001: compared with pre-treatment

Table 4: Comparison of vascular-related factor levels (mean ± SD, pg/ml) between CG and SG

Group	VEGF-A		MCP-1	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
CG (n=39)	252.31±25.30	218.63±22.52 ^{***}	64.85±6.02	57.08±5.24 ^{***}
SG (n=39)	251.67±24.85	197.52±21.08 ^{####}	64.73±5.72	51.07±5.14 ^{####}

Note: ^{####}P < 0.001, compared with the CG; ^{***}p < 0.001, compared to pre-treatment

Table 5: Comparison of incidence of complications [n (%)] between the CG and SG

Group	Dorsal hand edema	Hematoma at puncture site	Bleeding	Total
CG (n=39)	1 (2.56)	1 (2.56)	0 (0.00)	2 (5.13)
SG (n=39)	2 (5.13)	1 (2.56)	1 (2.56)	4 (10.26)

Quality of life

The scores of social relationship, physiology, and psychology were increased in both groups after treatment, but were much higher in the SG (p < 0.05), suggesting that combination of PTA and PT improves the patient’s quality of life (Figure 2).

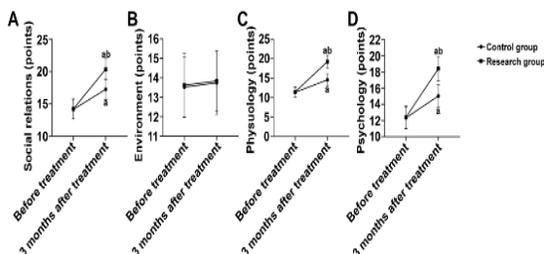


Figure 2: Quality of life in CG and SG. (A) Social relationship scores; (B) Environmental scores; (C) Physical scores; (D) Psychological scores; ^ap < 0.001, compared with pre-treatment; ^bp < 0.001, compared with CG

DISCUSSION

Autologous AEF is an important means of vascular access for hemodialysis. However, thrombosis is a common complication of autologous AEF, which leads to the loss of vascular access and thus affects the therapeutic outcome [10]. Percutaneous transluminal angioplasty and pharmacological thrombolysis are treatment modalities for thrombosis in autologous AEFs, both of which have a certain efficacy. However, the effects of these methods need to be improved [11].

The findings of this research exhibited that at three and six months postoperatively, the SG showed higher vascular patency than the CG, and the vascular cross-sectional area, inner diameter, and quality of life scores were increased in both groups after treatment, whereas the two groups showed no significant difference in complications. Bountouris et al [7] found that the combination of PTA and urokinase thrombolysis for the treatment of thrombosis in autologous AEFs improved endovascular

patency, which is in agreement with the findings of this study. The combination of PTA and PT safely improves vascular patency and quality of life. This may be due to the fact that this combination therapy improves clinical efficacy by significantly shortening the time to restore blood flow and improving vascular stenosis through balloon maceration of the thrombus and its pharmacological dissolution [12,13]. The presence of a thrombus for a long time can lead to the mechanization and formation of granular tissue that adheres to the inner wall of the vessel. It not only increases the difficulty of maceration of the thrombus, but also increases the risk of triggering pulmonary embolism if the thrombus is accidentally dislodged during removal [14]. Therefore, drug thrombolysis was applied first, and then thrombus aspiration was performed, which reduced the difficulty in fragmentation of the thrombus while avoiding the occurrence of thrombus reflux with blood into the pulmonary artery.

Clinically, maintenance hemodialysis patients have varying degrees of microinflammation [15,16]. This microinflammatory state is induced by the complementary system and endotoxins which activate the mononuclear macrophages, and triggers the release of many inflammatory factors. As the inflammatory response is aggravated, renal function continues to decline [17]. One study found [18] that patients who underwent maintenance hemodialysis had remarkably higher serum levels of TNF- α and IL-6 than normal controls. Changes in IL-6 and hs-CRP levels indicate changes in the microinflammatory status of patients [19]. This study showed that the serum IL-6 and hs-CRP levels were reduced in both groups after treatment, and were much lower in the SG. This indicates that PTA combined with PT can effectively reduce the degree of inflammatory response *in vivo* in patients undergoing hemodialysis, and promote the recovery of renal function. β_2 -MG is a small protein that can be detected in a variety of body fluids, such as urine, blood and cerebrospinal fluid. Many investigations have indicated that serum β_2 -MG level can be used as an indicator of renal function [20,21]. β_2 -MG has a small molecular weight and is mostly reabsorbed and catabolized by renal tubules. During acute kidney injury, β_2 -MG rises earlier than blood creatinine and is not affected by muscle metabolism. The findings of this study showed that serum β_2 -MG levels were reduced in both groups after treatment, and were much lower in the SG. This indicates that PTA combined with PT can effectively improve renal

function in patients with autologous AEF thrombosis.

The pathogenesis of autologous AEF thrombosis is closely related to venous endothelial cell proliferation. Vascular-related factors such as VEGF-A and MCP-1 play important roles in venous endothelial cell proliferation [22]. As a pro-angiogenic factor, VEGF-A is involved in promoting vascular endothelial cell proliferation and vascular remodeling [23]. Monocyte chemotactic protein-1 is a chemokine which promotes inflammatory response and also regulates angiogenesis [24]. In this study, serum levels of VEGF-A and MCP-1 were reduced in both groups after treatment, but were much lower in the SG. This indicates that PTA combined with PT effectively regulates the levels of VEGF-A, MCP-1, and other vascular-related factors in patients undergoing hemodialysis.

Limitations of the study

As this is a single-center study, the sample size was small and follow-up time was short, leading to some degree of biased results. The specific mechanism of action of PTA combined with pharmacological thrombolysis for the treatment of thrombosis in hemodialysis patients requires further investigation.

CONCLUSION

PTA combined with pharmacological thrombolysis for the treatment of thrombosis in hemodialysis patients with autologous AEFs enhances efficacy, increases vascular patency, reduces inflammatory response, lowers the level of β_2 -MG, and improves quality of life. Thus, the combination treatment provides a suitable approach for the management of hemodialysis patients.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities

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