Am J Transl Res 2026;18(1):537-551
www.ajtr.org /ISSN:1943-8141/AJTR0168946

Original Article

Clinical value of targeted arterial infusion of ginkgo biloba extract combined with urokinase in thromboangiitis obliterans

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Received September 21, 2025; Accepted December 31, 2025; Epub January 15, 2026; Published January 30, 2026

Abstract: Objective: To investigate the clinical efficacy and safety of targeted artery infusion of Ginkgo biloba extract (GBE) combined with urokinase (URK) for treatment of thromboangiitis obliterans (TAO), and to provide a reference for the optimized treatment of TAO. Methods: A total of 108 male TAO patients (December 2021-December 2023) were retrospectively enrolled and divided into a GBE group (54 cases, single GBE infusion) and a GBE-URK group (54 cases, GBE+URK infusion) after propensity score matching. Both groups received 72-hour continuous infusion, followed by standardized adjuvant therapy and 12-month follow-up. Key indices (pain, hemodynamics, inflammation) and safety/recurrence were compared. Results: At 90 days, the GBE-URK group had lower FPS-R scores (1.89±0.84 vs 2.74±0.48, P<0.001), intermittent claudication scores (1.00±0.55 vs 1.69±0.61, P<0.001), and higher pain relief rate (94.44% vs 70.37%, P = 0.001). At 30 days, it had a higher ABI (1.14±0.22 vs 0.82±0.16, P<0.001), TBI (1.09±0.30 vs 0.76±0.26, P<0.001) and lower TNF-α (29.99±4.27 vs 39.99±5.14 pg/mL, P<0.001), ET-1 (189.85±19.20 vs 268.17±37.44 pg/mL, P<0.001). Adverse reaction rates were 7.41% vs 14.81% (P = 0.221); 12-month recurrence-free survival was higher in GBE-URK group (Log-rank P = 0.009). This was confirmed to be an independent factor by multivariable regression (P<0.05). Conclusions: GBE-URK infusion improves pain, hemodynamics, and long-term prognosis in TAO, providing a safe, minimally invasive strategy.

Keywords: Thromboangiitis obliterans, ginkgo biloba extract, urokinase, target artery infusion, clinical efficacy

Introduction

Thromboangiitis obliterans (TAO), also known as Buerger's disease, is a non-atherosclerotic vascular disorder characterized by segmental inflammatory thrombosis of small and medium-sized arteriovenous vessels [1]. It affects predominantly young and middle-aged men aged 20-40 years, with a global incidence of 0.6-1.2 per 100,000 population [2]. Notably, in recent years, the incidence among young women has climbed steadily due to factors such as smoking and hormonal changes, making it a growing public health concern [3]. The disease involves mainly the small and medium-sized arteriovenous vessels of the lower extremities. In the early stage, the clinical manifestations are mainly acral numbness, coolness, and intermittent claudication. As the disease progresses, rest pain, toe ulcers, and even gangrene may occur [4]. It is reported that 15%-30% of patients with advanced TAO require amputation, which significantly reduces the patient's quality of life and imposes a heavy economic burden on families and society [5].

At present, the clinical treatment of TAO still faces many challenges. Although smoking cessation is recognized as a basic treatment measure, it can only delay the progression of the disease and cannot effectively relieve the already existing ischemic symptoms [6]. Traditional open surgery (such as vascular bypass) has a 1-year patency rate of only 40%-50% due to the characteristics of segmental occlusion of diseased vessels and extensive collateral for-

https://doi.org/10.62347/VSMN2461

mation, and is associated with high surgical trauma and complication rates [7]. Endovascular interventional therapy (such as balloon dilation and stent implantation) is limited by the small caliber of diseased vessels and high restenosis rates (up to 60% within 2 years) [8]. Single-drug therapy (such as vasodilators and anticoagulants) often fails to meet the multiple needs of anti-inflammation, thrombolysis, and improvement of microcirculation, resulting in poor prognosis [9]. Therefore, exploring safe and effective combined treatment regimens is attracting attention in the field of vascular surgery.

Ginkgo biloba extract (GBE) is a natural drug. Its main components, ginkgo flavonoids and ginkgolides, have significant antioxidant and anti-inflammatory effects, which can inhibit platelet aggregation, protect vascular endothelial function, and improve limb hemodynamics [10, 11]. Urokinase (URK) is a classic thrombolytic drug that can effectively dissolve microthrombi in diseased vessels and restore blood perfusion, especially suitable for fresh thrombi formed during the course of TAO [12]. Recent studies have confirmed that drug administration by targeted artery perfusion can increase the drug concentration at the lesion site, enhance local efficacy, and reduce systemic adverse reactions [13]. However, there is still a lack of systematic research on the synergistic effect and safety of GBE combined with URK through targeted artery perfusion in the treatment of TAO. Existing studies either focus on single-drug therapy or lack long-term follow-up data, failing to provide sufficient evidence for clinical application.

To address this gap, we designed the present study with two key focuses: on one hand, we combined URK's thrombolytic effect with GBE's anti-inflammatory and endothelial protective properties to form a "thrombolysis + vascular protection" strategy - targeting TAO's complex pathology (coexisting inflammation and thrombosis) that single treatments cannot fully address. On the other hand, to improve the reliability of this retrospective study, we used propensity score matching (PSM) to balance baseline data between groups, reducing selection bias. This design not only fills the evidence gap of combined GBE-URK perfusion in TAO treatment but also holds practical clinical value: it offers a minimally invasive, easily promoted alternative to traditional surgery or single drugs, which may reduce TAO patients' amputation risk and improve their quality of life. We used long-term follow-up to clarify the combined regimen's safety and recurrence-preventive effects, providing useful references for clinical decisions ini TAO.

In view of this, this study retrospectively analyzed the diagnosis and treatment data of patients who received different perfusion regimens (single GBE perfusion vs GBE combined with URK perfusion) in clinical practice.

Materials and methods

Patients selection

Study setting and patient search: This study was a single-center retrospective cohort study conducted in accordance with the Declaration of Helsinki and relevant ethical guidelines for medical research involving human subjects. Patients were identified through systematic searches of the hospital's electronic medical record system (EMRS), Picture Archiving and Communication System (PACS), and Laboratory Information System (LIS) for the period December 2021 to December 2023. Search terms included "thromboangiitis obliterans", "Buerger's disease", "target artery infusion", "Ginkgo biloba extract", and "urokinase". All searches were performed independently by two researchers (Ziyuan Liu and Fang Zheng) to ensure completeness.

Inclusion criteria: (1) Patients diagnosed with thromboangiitis obliterans (TAO) according to the internationally recognized Shionoya clinical diagnostic criteria [14], confirmed by lower extremity arteriography (DSA) or computed tomography angiography (CTA) for lower extremity arterial ischemic lesions. (2) Classified as grade II-IV according to the Rutherford criteria in TAO classification [15]. (3) Complete medical records, including treatment plans and follow-up data.

Exclusion criteria: (1) TAO lesions involving both lower extremities (to avoid bias in evaluating unilateral treatment efficacy). (2) Comorbidity with other lower extremity vascular diseases (e.g., lower extremity arterial embolism, arteriosclerosis obliterans, diabetic foot) or connective tissue diseases (e.g., rheumatoid arthritis), which may interfere with the judgment of TAO

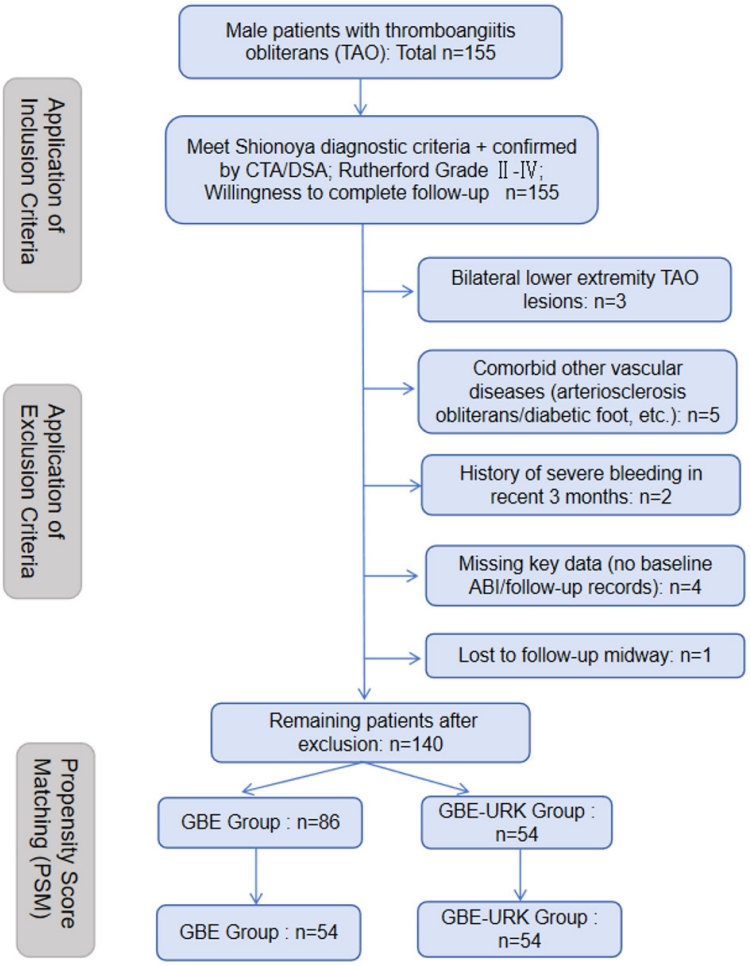

Figure 1. Study flow diagram of patient enrollment. TAO: thromboangiitis obliterans; GBE: Ginkgo Biloba Extract; GBE-URK: Ginkgo Biloba Extract combined with Urokinase; PSM: propensity score matching; CTA/DSA: computed tomographic angiography/digital subtraction angiography; ABI: ankle-brachial index.

treatment efficacy. (3) Missing key data in medical records. All data were extracted from the hospital's electronic medical record system, picture archiving and communication system (PACS), and laboratory information system (LIS). This study was approved by the Ethics Committee of Zhengzhou People's Hospital. The specific study flow is shown in **Figure 1**.

Grouping strategy

All treatment regimens (target artery infusion of GBE alone vs GBE combined with URK) were determined by a multidisciplinary team of vascular surgeons (with ≥5 years of TAO management experience) based on individualized patient assessments, rather than random assignment or patient self-selection. The decision-making process integrated key clinical factors extracted from electronic medical records (EMRs): thrombus characteristics, bleeding risk, disease severity, and patient suitability. Before treatment, the team provided detailed written informed consent to patients, explicitly outlining each regimen's advantages, limitations, and alternative options. All patients signed consent forms, which were archived in the EMR system for retrospective verification.

Patients were retrospectively grouped according to the actual treatment regimens documented in their surgical records and medication logs: 86 patients who received single GBE infusion were initially assigned to the GBE group, and 54 patients who received combined GBE-URK infusion to the GBE-URK group. To ensure the comparability of baseline data between the two groups, propensity score matching (PSM) was used for grouping. With "whether to receive combined treatment" as the dependent variable, baseline indicators such as age, disease duration, Rutherford classification, smoking history, complicated hypertension, and migratory superficial phlebitis were taken as covariates. A matched cohort was constructed through 1:1 nearest neighbor matching (with a caliper value set at 0.02). Finally, the baseline data of the two groups were balanced and comparable (all $P>0.05$), so as to reduce selection bias in retrospective studies.

Data extraction

Extraction methods: Data were extracted by two trained researchers (Ziyuan Liu and Guanghui Lu) using a pre-designed standardized form. Discrepancies between extractors were resolved through discussion with a third

senior researcher (Fang Zheng) to ensure consistency.

Extracted data content: (1) Demographics (age, BMI), clinical characteristics (disease duration, smoking history, Rutherford grade, affected side, comorbidities), and baseline laboratory/imaging indexes (ABI, TBI, TNF-α, ET-1). (2) Details of target artery infusion (catheterization method, drug dosage, perfusion duration), adjuvant therapy (low-molecular-weight heparin, alprostadil), and surgical records. (3) Postoperative indexes (pain scores, ABI/TBI, inflammatory/endothelial factors) at 7/30/90 days, adverse events, and 12-month recurrence of vascular occlusion (confirmed by CTA).

Data validation: Extracted data were cross-validated against original sources: (1) Baseline and outcome indexes were verified with LIS reports and PACS images; (2) Treatment details were confirmed with surgical and nursing records; (3) Follow-up data were checked against outpatient revisit logs. Missing data (≤5% of total) were imputed using the last observation carried forward method.

Outcome measures

Assessments were conducted using follow-up data (from outpatient revisit records and inpatient progress notes) at pre-operation and 7 days, 30 days, and 90 days post-operation. Meanwhile, follow-up records within 12 months after operation were extracted for the recurrence of lower extremity vascular occlusion.

The primary outcome was defined as the 90-day postoperative Wong-Baker Faces Pain Rating Scale (FPS-R) score - this is the core indicator to evaluate symptom relief in TAO patients. The FPS-R scale ranges from 0 to 10 (0 = no pain, 10 = worst pain imaginable), and a lower score indicates better pain relief (the key goal of this study's treatment).

Additionally, to further quantify pain relief efficacy, we defined a "clinical pain relief endpoint" based on the FPS-R score: pain relief was defined as a ≥2-point decrease in FPS-R score from baseline (consistent with the minimal clinically important difference for TAO pain assessment). We recorded the time to reach this endpoint and calculated the cumulative pain relief rate at 30/90 days postoperatively, to supplement the primary outcome evaluation.

Three categories of secondary outcome were set to supplement the primary efficacy and assess safety/long-term effects: (1) Hemodynamic improvement: This included two aspects - first, the intermittent claudication distance score, which was assigned according to walking distance (≥500 m = 0 point, 400-500 m = 1 point, 300-400 m = 2 points, 100-300 m = 3 points, <100 m or rest pain = 4 points); second, hemodynamic indicators (ankle-brachial index [ABI] and toe-brachial index [TBI]), which were measured using a Nihon Kohden ES-1000SP Doppler vascular detector. (2) Biomarker changes: It covered both inflammatory factors and vascular endothelial injury factors - for levels of inflammatory factors, fasting venous blood was collected before operation and at 30 days after operation, and enzyme-linked immunosorbent assay (ELISA) was used to detect serum levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) to evaluate the degree of vascular wall inflammation; for levels of vascular endothelial injury factors, venous blood was also collected before operation and at 30 days after operation to detect serum levels of endothelin-1 (ET-1) and intercellular adhesion molecule-1 (ICAM-1), which reflect the status of vascular endothelial injury. (3) Safety and long-term efficacy: This included three parts - safety indicators, where the occurrence of adverse reactions during treatment (such as dizziness, skin pruritus, bleeding at puncture site or subcutaneous, and drug allergy) was recorded; recurrence of lower extremity vascular occlusion, where follow-up was conducted until 12 months after operation, recurrence was defined as the progression of Rutherford classification after operation (e.g., stage II progressing to stage III) and confirmation of target vessel re-occlusion (stenosis degree ≥70%) by lower extremity CTA, and the occurrence time and number of recurrence events in both groups were recorded; additionally, for missing data at some time points, the last observation carried forward method was used for processing. (4) Analysis of factors associated with outcomes: To confirm the independent effect of the treatment regimen on core outcomes (excluding the impact of baseline confounders), we performed multivariable regression analysis. The dependent variables were the 90-day postoperative FPS-R

score (primary outcome) and 12-month vascular occlusion recurrence (key secondary outcome); the independent variable was the treatment regimen (GBE alone vs GBE-URK combined); potential confounders (age, BMI, disease duration, TAO affected side, Rutherford classification, smoking history, hypertension, coronary heart disease, migratory superficial phlebitis) were included as adjustment variables. This analysis aimed to verify whether the treatment regimen independently affected outcomes after balancing baseline differences.

Statistical analysis

All data in this study were analyzed and graphed using SPSS 27.0 statistical software and GraphPad Prism 8.0. Measured data conforming to a normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$), while those not conforming to a normal distribution were expressed as median (interquartile range) [M (P_{25}, P_{75})]; counted data were expressed as cases (percentage) [n (%)]. For the comparison of baseline data between groups, measured data were first compared using the independent samples t-test (for normal distribution) or Mann-Whitney U test (for non-normal distribution), and counted data were compared using the χ^2 test or Fisher's exact probability method. If there were baseline differences, comparisons between groups were performed after correction using propensity score matching (PSM, 1:1 nearest neighbor matching with a caliper value of 0.02). Repeated measures analysis of variance was used to compare indicators at different time points within and between groups. Additionally, for the analysis of factors associated with core outcomes, univariable and multivariable regression analysis was further conducted: models were selected based on dependent variable types (linear regression for continuous variables, binary logistic regression for binary variables), with the "forced entry method" for variable inclusion (core independent variable: treatment regimen; adjustment variables: key baseline confounders); multicollinearity was validated by variance inflation factor (VIF<5). β coefficients and 95% confidence intervals (95% CI) were reported for linear regression, while odds ratios (OR) and 95% CI were reported for logistic regression. For survival analysis of lower extremity vascular occlusion recurrence, the Kaplan-Meier method was used to draw recurrence-free survival curves, and the Log-rank test was used to compare differences in recurrence risk between groups. The strength of association was expressed by hazard ratio (HR) and 95% confidence interval (95% CI). A *P* value <0.05 was considered significant.

Results

Comparison of general data between the two groups

Results in **Tables 1**, **2** showed that before matching, there were certain differences in indicators such as age and BMI between the GBE group (86 cases) and the GBE-URK group (54 cases) (standardized mean difference SMD>0.1). After 1:1 nearest neighbor matching (with a caliper value of 0.02), 54 patients were included in each group, and the baseline data were balanced and comparable. After matching, there were no significant differences between the two groups in general clinical characteristics such as age, BMI, and disease duration; disease-related indicators such as smoking rate, distribution of Rutherford classification, and affected side; and comorbidities such as hypertension, coronary heart disease, or migratory superficial phlebitis (all indicators with SMD<0.1 and all *P*>0.05). These results suggest that the two groups had good comparability for subsequent efficacy analysis.

Comparison of pain scores between the two groups before and after surgery

Data in **Table 3** showed that there was no statistically significant difference in pain scores between the GBE group and the GBE-URK group before surgery (*P* = 0.169). At 7 days, 30 days, and 90 days after surgery, the pain scores in both groups were significantly lower than those before surgery, and the scores in the GBE-URK group at each time point were significantly lower than those in the GBE group (all *P*<0.001). Results of repeated measures analysis of variance showed that the main effects of group, time, and their interaction effect were all significant (F = 94.03, 462.20, 19.103; all *P*<0.001), suggesting that the combined therapy had a better effect in relieving pain and the improvement persisted over time.

Table 1. Baseline covariates before and after matching

Variable	Level	Before Matching			After Matching		
		GBE group	GBE-URK group	SMD	GBE group	GBE-URK group	SMD
n		86	54		54	54	
Age, years		49.84±10.39	45.39±7.87	-0.565	45.35±8.21	45.39±7.87	0.005
BMI, kg/m^2		21.13±4.13	22.99±3.50	0.533	22.59±3.77	22.99±3.50	0.115
Disease duration, years		9.94±4.70	10.24±4.52	0.066	10.69±4.38	10.24±4.52	-0.098
Smoker, n (%)	No	16 (18.6)	8 (14.8)	-0.107	7 (13.0)	8 (14.8)	0.052
	Yes	70 (81.4)	46 (85.2)	0.107	47 (87.0)	46 (85.2)	-0.052
Rutherford category, n (%)	2	41 (41.7)	25 (46.3)	-0.028	26 (48.1)	25 (46.3)	-0.037
	3	18 (20.9)	17 (31.5)	0.227	14 (25.9)	17 (31.5)	0.120
	4	27 (31.4)	12 (22.2)	-0.221	14 (25.9)	12 (22.2)	-0.089
TAO affected side	Left	49 (57.0)	24 (44.4)	-0.252	27 (50.00)	24 (44.4)	-0.112
	Right	37 (43.0)	30 (55.6)	0.252	27 (50.00)	30 (55.6)	0.112
Hypertension	No	68 (79.1)	41 (31.5)	-0.074	41 (31.5)	41 (31.5)	0.000
	Yes	18 (20.9)	13 (22.2)	0.074	13 (22.2)	13 (22.2)	0.000
Coronary heart disease	No	76 (88.4)	48 (88.9)	0.016	48 (88.9)	48 (88.9)	0.000
	Yes	10 (11.6)	6 (11.1)	-0.016	6 (11.1)	6 (11.1)	0.000
Migratory superficial phlebitis	No	50 (58.1)	30 (55.6)	-0.052	31 (57.4)	30 (55.6)	-0.037
	Yes	36 (41.9)	24 (44.4)	0.052	23 (42.6)	24 (44.4)	0.037

Note: TAO: Thromboangiitis Obliterans; GBE: Ginkgo Biloba Extract; GBE-URK: Ginkgo Biloba Extract combined with Urokinase; SMD: Standardized Mean Difference.

Table 2. Patient demographics and baseline characteristics

Characteristic	Before Matching				After Matching			
	GBE group N = 86[1]	GBE-URK Group N = 54[1]	t/χ^2	*P*-value	GBE group N = 54[1]	GBE-URK Group N = 54[1]	t/χ^2	*P*-value
Age, years	49.8±10.4	45.4±7.9	2.832	0.005	45.4±8.2	45.4±7.9	-0.024	0.981
BMI, kg/m^2	21.1±4.1	23.0±3.5	-2.820	0.006	22.6±3.8	23.0±3.5	-0.574	0.567
Disease duration, years	9.9±4.7	10.2±4.5	-0.374	0.708	10.7±4.4	10.2±4.5	0.519	0.605
Smoker			0.335	0.562			0.077	0.781
no	16 (18.6)	8 (14.8)			7 (13.0)	8 (14.8)		
yes	70 (81.4)	46 (85.2)			47 (87.0)	46 (85.2)		
Rutherford category			0.703	0.704			0.464	0.793
2	41 (41.7)	25 (46.3)			26 (48.1)	25 (46.3)		
3	18 (20.9)	17 (31.5)			14 (25.9)	17 (31.5)		
4	27 (31.4)	12 (22.2)			14 (25.9)	12 (22.2)		
TAO affected side			2.088	0.148			0.334	0.563
left	49 (57.0)	24 (44.4)			27 (50.00)	24 (44.4)		
right	37 (43.0)	30 (55.6)			27 (50.00)	30 (55.6)		
Hypertension			0.190	0.663			0.000	1.000
no	68 (79.1)	41 (31.5)			41 (31.5)	41 (31.5)		
yes	18 (20.9)	13 (22.2)			13 (22.2)	13 (22.2)		
Coronary heart disease			0.009	0.925			0.000	1.000
no	76 (88.37)	48 (88.9)			48 (88.9)	48 (88.9)		
yes	10 (11.6)	6 (11.1)			6 (11.1)	6 (11.1)		

Migratory superficial phlebitis			0.090	0.764			0.038	0.846
no	50 (58.1)	30 (55.6)			31 (57.4)	30 (55.6)		
yes	36 (41.9)	24 (44.4)			23 (42.6)	24 (44.4)		

[1]n (%). Note: TAO: Thromboangiitis Obliterans; GBE: Ginkgo Biloba Extract; GBE-URK: Ginkgo Biloba Extract combined with Urokinase; SMD: Standardized Mean Difference.

Table 3. Comparison of pain scores between the two groups before and after surgery (x ± s)

Time Point	GBE group (n = 54)	GBE Intragroup (Pre-op vs Post-op)		GBE-URK Group (n = 54)	GBE-URK Intragroup (Pre-op vs Post-op)		Inter-group t-value	Inter-group *P*-value
		t-value	*P-value*		*t-value*	*P-value*		
Before surgery	5.30±0.90	-	-	5.54±0.91	-	-	-1.383	0.169
7 d after surgery	3.93±0.43	10.093	<0.001	3.06±0.53	17.305	<0.001	9.400	<0.001
30 d after surgery	3.00±0.51	16.339	<0.001	2.00±0.51	24.937	<0.001	8.916	<0.001
90 d after surgery	2.74±0.48	18.443	<0.001	1.89±0.84	21.658	<0.001	6.464	<0.001

Note: Intragroup (Pre-op vs Post-op) refers to the comparison between the postoperative value and the preoperative value within the same group; Inter-group refers to the comparison between GBE Group and GBE-URK Group at the same time point. GBE: Ginkgo Biloba Extract; GBE-URK: Ginkgo Biloba Extract combined with Urokinase.

Table 4. Comparison of intermittent claudication distance scores between the two groups before and after surgery (*x* ± s)

Time	GBE group (n = 54)	GBE Intragroup (Pre-op vs Post-op)		GBE-URK Group (n = 54)	*GBE-URK Intragroup (Pre-op vs Post-op)*		Inter-group t-value	Inter-group *P*-value
		t-value	*P-value*		*t-value*	*P-value*		
Before surgery	3.76±0.43	-	-	3.80±0.41	-	-	-0.459	0.647
7 d after surgery	3.52±0.72	2.103	0.038	2.83±0.54	10.513	<0.001	5.591	<0.001
30 d after surgery	2.70±0.46	12.370	<0.001	2.07±0.47	20.383	<0.001	7.029	<0.001
90 d after surgery	1.69±0.61	20.382	<0.001	1.00±0.55	29.994	<0.001	6.139	<0.001

Note: Intragroup (Pre-op vs Post-op) refers to the comparison between the postoperative value and the preoperative value within the same group; "Inter-group" refers to the comparison between GBE Group and GBE-URK Group at the same time point. GBE: Ginkgo Biloba Extract; GBE-URK: Ginkgo Biloba Extract combined with Urokinase.

Comparison of intermittent claudication distance scores between the two groups before and after surgery

Table 4 shows no significant difference in the intermittent claudication distance scores between the two groups before surgery (*P*> 0.05). At 7 days, 30 days, and 90 days after surgery, the scores in both groups were significantly lower than those before surgery, and the improvement amplitude in the GBE-URK group was significantly better than that of the GBE group (all *P*<0.001). Repeated measures analysis of variance showed that the main effects of group, time, and their interaction effect were all significant (*F* = 104.769, 405.239, 11.382; all *P*<0.001), indicating that the combined therapy had a more significant effect on improving intermittent claudication.

Comparison of hemodynamic indexes between the two groups before and after surgery

Data in **Table 5** showed no significant differences in ABI or TBI between the GBE group and the GBE-URK group before surgery (all *P*>0.05). At 7 days, 30 days, and 90 days after surgery, ABI and TBI in both groups were significantly higher than those before surgery, and the improvement amplitude of the indicators in the GBE-URK group at each time point was significantly better than that of the GBE group (all *P*<0.001). Results of repeated measures analysis of variance showed that for the ABI indicator, the main effects of group, time, and their interaction effect were all significant (*F* = 103.859, 121.409, 13.770; all *P*<0.001); for the TBI indicator, the main effects of group, time, and their interaction effect were also all

Table 5. Comparison of hemodynamic indexes between the two groups before and after surgery ($x \pm s$)

Variable	Time	GBE group (n = 54)	GBE Intragroup (Pre-op vs Post-op)		GBE-URK Group (n = 54)	GBE-URK Intragroup (Pre-op vs Post-op)		Inter-group t-value	Inter-group *P*-value
			t-value	*P-value*		*t-value*	*P-value*		
ABI	Before surgery	0.54±0.16	-	-	0.56±0.18	-	-	-0.732	0.466
	7d after surgery	0.77±0.21	-6.402	<0.001	0.94±0.17	-11.278	<0.001	-4.528	<0.001
	30 d after surgery	0.82±0.16	-9.093	<0.001	1.14±0.22	-14.994	<0.001	-8.611	<0.001
	90 d after surgery	0.88±0.19	-10.58	<0.001	1.23±0.35	-12.510	<0.001	-6.493	<0.001
TBI	Before surgery	0.35±0.15	-	-	0.34±0.19	-	-	0.449	0.655
	7 d after surgery	0.53±0.20	-5.291	<0.001	0.88±0.23	-13.301	<0.001	-8.586	<0.001
	30 d after surgery	0.76±0.26	-10.037	<0.001	1.09±0.30	-15.520	<0.001	-6.109	<0.001
	90 d after surgery	0.82±0.31	-10.029	<0.001	1.20±0.33	-16.596	<0.001	-6.097	<0.001

Note: ABI: Ankle-Brachial Index; TBI: Toe-Brachial Index; GBE: Ginkgo Biloba Extract; GBE-URK: Ginkgo Biloba Extract combined with Urokinase.

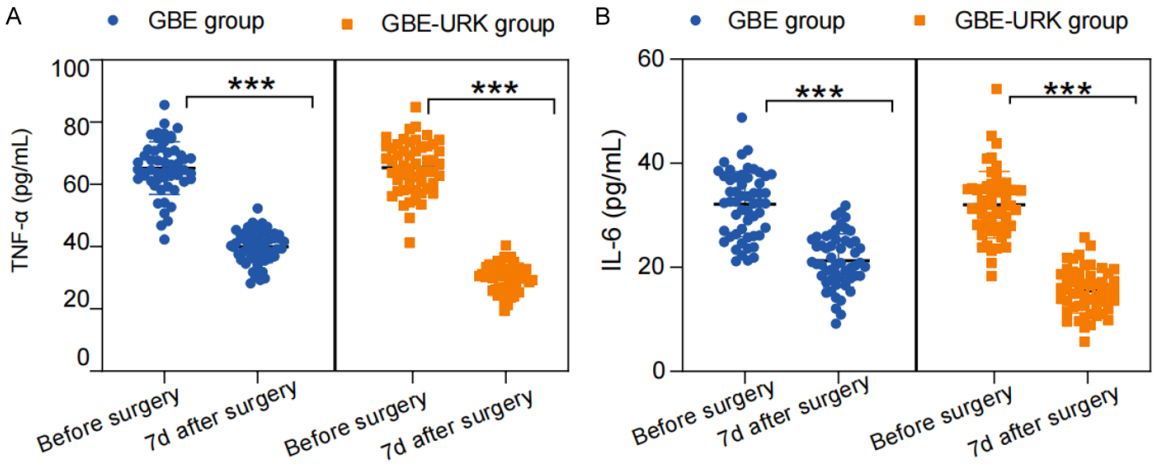

Figure 2. Scatter plot of inflammatory factor level distribution before and after surgery in the two groups. *P<0.05, **P<0.01, ***P<0.001. TNF-α: tumor necrosis factor-α; IL-6: interleukin-6; GBE: Ginkgo Biloba Extract; GBE-URK: Ginkgo Biloba Extract combined with Urokinase.

significant (F = 103.198, 153.397, 15.010; all P<0.001). These results suggest that target artery infusion of GBE combined with URK can more effectively improve lower extremity hemodynamics, and the effect improves over time.

Comparison of inflammatory factor levels between the two groups before and after surgery

Before surgery, there were no significant differences in the levels of TNF-α and IL-6 between the GBE group and the GBE-URK group (TNF-α: 65.24±8.47 pg/mL vs 65.40±8.25 pg/mL, P = 0.920; IL-6: 32.13±6.24 pg/mL vs 32.04±6.39 pg/mL, P = 0.944). At 30 days after surgery, the levels of inflammatory factors in both groups were significantly lower than those before surgery, and the decrease in the GBE-URK group was significantly more (TNF-α: 29.99±4.27 pg/mL vs 39.99±5.14 pg/mL, P<0.001; IL-6: 15.46±4.24 pg/mL vs 21.29±5.12 pg/mL, P<0.001). These results suggest that the combined therapy had a better effect in inhibiting the inflammatory response of the vascular wall, as shown in **Figure 2**.

Comparison of vascular endothelial injury factor levels between the two groups before and after surgery

Before surgery, there were no significant differences in the levels of ET-1 or ICAM-1 between the GBE group and the GBE-URK group (ET-1: 165.14±25.38 pg/mL vs 169.59±27.44 pg/mL, P = 0.384; ICAM-1: 411.66±62.30 pg/mL vs 424.05±64.71 pg/mL, P = 0.313). At 30 days after surgery, the level of ET-1 in the GBE-URK group was significantly lower than that of the GBE group (268.17±37.44 pg/mL vs 189.85±19.20 pg/mL, P<0.001), and the level

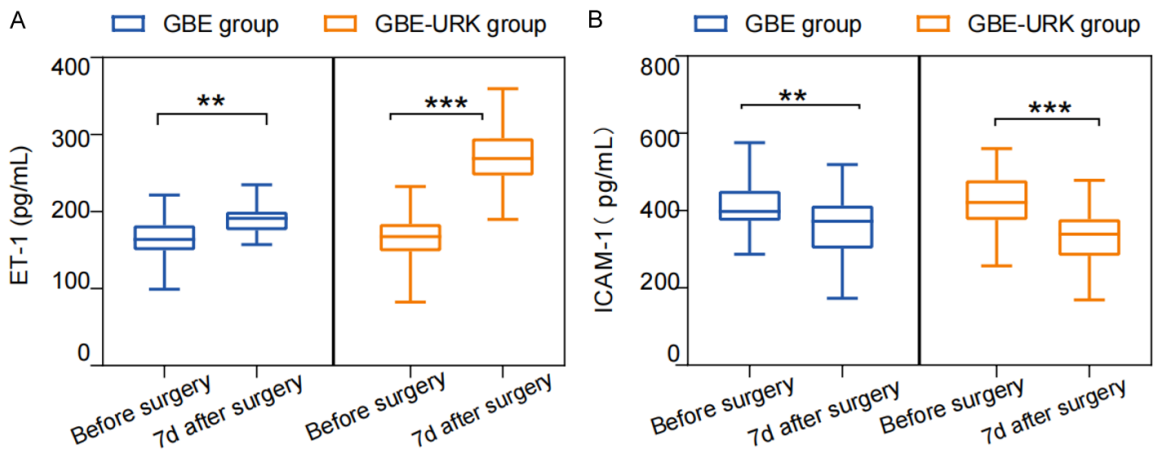

Figure 3. Vascular endothelial injury factor levels before and after surgery in the two groups. *P<0.05, **P<0.01, ***P<0.001. ET-1: endothelin-1; ICAM-1: intercellular adhesion molecule-1; GBE: Ginkgo Biloba Extract; GBE-URK: Ginkgo Biloba Extract combined with Urokinase.

Table 6. Adverse events [case (%)]

Event	GBE group (n = 54)	GBE-URK Group (n = 54)	χ^2-*value*	*P-value*
Dizziness	2 (3.70)			
Skin rashes	2 (3.70)	1 (1.85)		
Skin pruritus	4 (3.70)	3 (5.56)		
Puncture site bleeding	0	0		
Subcutaneous bleeding	0	0		
Total	8 (14.81)	4 (7.41)	1.500	0.221

Note: GBE: Ginkgo Biloba Extract; GBE-URK: Ginkgo Biloba Extract combined with Urokinase.

of ICAM-1 was also significantly lower than that in the GBE group (329.32±64.65 pg/mL vs 359.87±75.84 pg/mL, P = 0.026). These results indicate that the combined therapy can more effectively reduce vascular endothelial injury and protect vascular endothelial function, as shown in **Figure 3**.

Comparison of adverse reactions between the two groups before and after surgery

The surgical success rate was 100% in both groups. During the treatment period, 2 cases of dizziness, 2 cases of skin rashes, and 4 cases of skin pruritus occurred in the GBE group, with a total incidence of adverse reactions of 14.81% (8/54); in the GBE-URK group, 1 case of skin rash and 3 cases of skin pruritus occurred, with a total incidence of adverse reactions of 7.41% (4/54). No puncture site bleeding or subcutaneous bleeding was observed in either group. There was no significant difference in the total incidence of adverse reactions between the two groups (P> 0.05), as shown in **Table 6**.

Recurrence of lower extremity vascular occlusion between the two groups before and after surgery

Results in **Figure 4** showed that the recurrence-free survival rates of the GBE group and the GBE-URK group presented different trends changing over time. The Log-rank test indicated a significant difference in the survival curves between the two groups (Log-rank P = 0.009). During the follow-up period (0-365 days), the overall recurrence-free survival rate of the GBE-URK group was higher than that of the GBE group, suggesting that the GBE-URK regimen may have better clinical effects than the GBE regimen in reducing the recurrence risk of lower extremity vascular occlusion. To further identify the independent factors affecting core outcomes (90-day pain score, 12-month recurrence), this study first performed univariable regression analysis to screen candidate variables, then conducted multivariable regression analysis, and its variable assignment and inclusion list are as follows: ① Dependent variables: 90-day postoperative Wong-Baker FPS-R score (continuous variable, using original scale scores directly), 12-month lower extremity vascular occlusion recurrence (binary variable: 1 = recurrence, 0 =

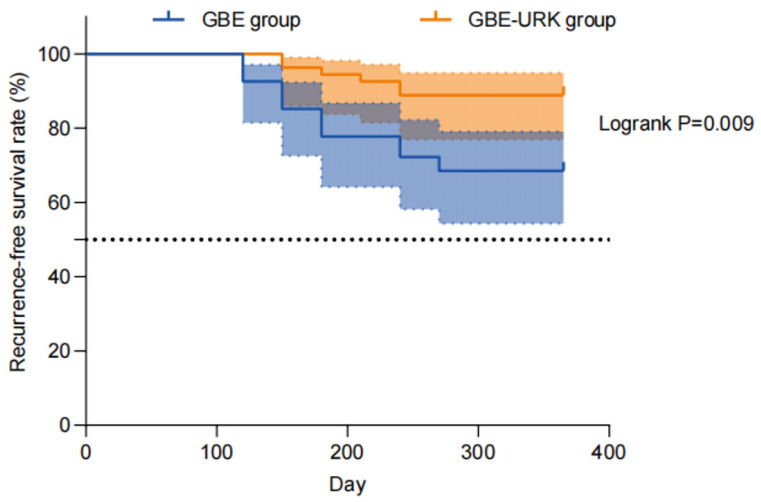

Figure 4. Kaplan-Meier survival analysis plot of recurrence of lower extremity vascular occlusion in the two groups. GBE: Ginkgo Biloba Extract; GBE-URK: Ginkgo Biloba Extract combined with Urokinase.

no recurrence); ② Core independent variable: treatment regimen (binary variable: 1 = GBE-URK combination group, 0 = GBE alone group); ③ Adjustment variables: age, BMI, disease duration, TAO affected side, Rutherford classification, smoking history, hypertension, coronary heart disease, and migratory superficial phlebitis (all potential confounders collected at baseline).

Univariable and multivariable regression analysis results

Univariable regression analysis was first performed to screen candidate variables associated with core outcomes (**Table 7**). The results showed that two variables were statistically significantly correlated with the outcomes: ① For the 90-day postoperative FPS-R score, only the treatment regimen was significant (β = -0.852, 95% CI: -1.113~-0.091, P<0.001); ② For the 12-month lower extremity vascular occlusion recurrence, both the treatment regimen (OR = 0.272, 95% CI: 0.098~0.758, P = 0.013) and Rutherford grade (OR = 3.111, 95% CI: 1.160~8.347, P = 0.024) were significant. No other baseline confounders (including age, BMI, disease duration, TAO affected side, smoking history, hypertension, coronary heart disease, and migratory superficial phlebitis) exhibited significant associations with the above outcomes (all P>0.05).

Multivariable regression analysis showed that after adjusting for potential confounders (age, BMI, disease duration, TAO affected side, Rutherford classification, smoking history, hypertension, coronary heart disease, migratory superficial phlebitis), the treatment regimen remained independently associated with core outcomes: ① For 90-day postoperative FPS-R score: The GBE-URK group had significantly lower scores than the GBE group (β = -0.816, 95% CI: -1.086 to -0.547, P<0.001), confirming the independent analgesic effect of the combined regimen; ② For 12-month lower extremity vascular occlusion recurrence: The GBE-URK group had significantly lower risk than the GBE group (OR = 0.247, 95% CI: 0.084 to 0.725, P = 0.011), verifying its independent protective effect on long-term prognosis.

None of the baseline confounders (e.g., age, disease duration, smoking history) showed significant impacts on the above outcomes (all P>0.05), further confirming the treatment regimen itself was key to improving symptoms and reducing recurrence risk, as shown in **Table 8**.

Pain-relief rate

Figure 5 presents the Kaplan-Meier analysis in which "pain relief" was defined as the first postoperative day on which the Wong-Baker FPS-R score decreased by ≥2 points from baseline (minimal clinically important difference). The cumulative probability of achieving this endpoint rose significantly faster in the GBE + URK group than in the GBE-alone group (log-rank P = 0.017). The median time to clinically meaningful pain relief was 7 days in the combination arm versus 30 days in the monotherapy arm. By post-operative day 30, 38.89% (21/54) of patients in the GBE + URK cohort had reached the endpoint, compared with 20.37% (11/54) in the GBE cohort (χ^2 = 4.441, P = 0.035). At the 90-day follow-up, 94.44% (51/54) of patients in the GBE + URK group had achieved a ≥2-point reduction, whereas 70.37% (38/54) of patients in the GBE group had done so (χ^2 = 10.794, P = 0.001). Thus, although both strategies ultimately provided adequate analgesia,

Table 7. Univariable regression analysis of factors associated with outcomes

Outcome Indicator	Independent Variable	β/OR	Std. Error	95% Confidence Interval	*P*-value
90-day FPS-R Score (Linear Regression)	Treatment regimen (1 = GBE-URK)	-0.852	0.132	-1.113–0.091	<0.001
	Age (years)	0.014	0.010	-0.006-0.033	0.170
	BMI (kg/m^2)	-0.025	0.022	-0.068-0.018	0.258
	Disease duration (years)	-0.031	0.017	-0.065-0.002	0.068
	TAO affected side (1 = right)	-0.273	0.153	0.578-0.031	0.078
	Rutherford grade (1 = III-IV)	0.199	0.155	-0.107-0.505	0.200
	Smoking history (1 = yes)	-0.022	0.209	-0.436-0.392	0.915
	Hypertension (1 = yes)	-0.045	0.184	-0.411-0.320	0.806
	Coronary heart disease (1 = yes)	0.254	0.238	-0.217-0.726	0.287
	Migratory superficial phlebitis (1 = yes)	-0.068	0.157	-0.379-0.243	0.667
12-month Recurrence (Logistic Regression)	Treatment regimen (1 = GBE-URK)	0.272	0.523	0.098-0.758	0.013
	Age (years)	0.972	0.030	0.917-1.030	0.330
	BMI (kg/m^2)	0.935	0.067	0.819-1.066	0.315
	Disease duration (years)	0.943	0.053	0.850-1.045	0.263
	TAO affected side (1 = right)	0.628	0.479	0.245-1.606	0.331
	Rutherford grade (1 = III-IV)	3.111	0.504	1.160-8.347	0.024
	Smoking history (1 = yes)	2.435	0.790	0.577-11.460	0.260
	Hypertension (1 = yes)	0.903	0.567	0.297-2.740	0.857
	Coronary heart disease (1 = yes)	0.641	0.807	0.132-3.119	0.581
	Migratory superficial phlebitis (1 = yes)	0.629	0.489	0.241-1.640	0.343

Note: TAO: Thromboangiitis Obliterans; BMI: Body Mass Index; OR: Odds Ratio; FPS-R: Wong-Baker Faces Pain Rating Scale; CI: Confidence Interval.

Table 8. Multivariable regression analysis of factors associated with outcomes

Outcome Indicator	Independent Variable	β/OR	Std. Error	95% Confidence Interval	*P*-value
90-day FPS-R Score (Linear Regression)	Treatment regimen (1 = GBE-URK)	-0.816	0.136	-1.086–0.547	<0.001
	Age (years)	0.012	0.009	-0.005-0.030	0.165
	BMI (kg/m^2)	-0.020	0.020	-0.058-0.019	0.316
	Disease duration (years)	0.002	0.016	-0.030-0.034	0.904
	TAO affected side (1 = right)	-0.134	0.141	-0.414-0.147	0.346
	Rutherford grade (1 = III-IV)	0.077	0.142	-0.204-0.359	0.585
	Smoking history (1 = yes)	0.051	0.189	-0.324-0.426	0.789
	Hypertension (1 = yes)	-0.052	0.174	-0.397-0.293	0.765
	Coronary heart disease (1 = yes)	0.199	0.211	-0.219-0.616	0.348
	Migratory superficial phlebitis (1 = yes)	-0.053	0.141	-0.332-0.226	0.705
12-month Recurrence (Logistic Regression)	Treatment regimen (1 = GBE-URK)	0.247	0.550	0.084-0.725	0.011
	Age (years)	0.965	0.033	0.905-1.028	0.266
	BMI (kg/m^2)	0.940	0.080	0.803-1.100	0.440
	Disease duration (years)	0.951	0.060	0.846-1.070	0.408
	TAO affected side (1 = right)	0.711	0.538	0.248-2.040	0.526
	Rutherford grade (1 = III-IV)	1.026	0.530	0.363-2.899	0.962
	Smoking history (1 = yes)	2.864	0.875	0.516-15.914	0.229
	Hypertension (1 = yes)	0.644	0.660	0.177-2.348	0.505
	Coronary heart disease (1 = yes)	0.686	0.882	0.122-3.865	0.669
	Migratory superficial phlebitis (1 = yes)	0.444	0.554	0.150-1.314	0.143

Note: TAO: Thromboangiitis Obliterans; BMI: Body Mass Index; OR: Odds Ratio; FPS-R: Wong-Baker Faces Pain Rating Scale; CI: Confidence Interval.

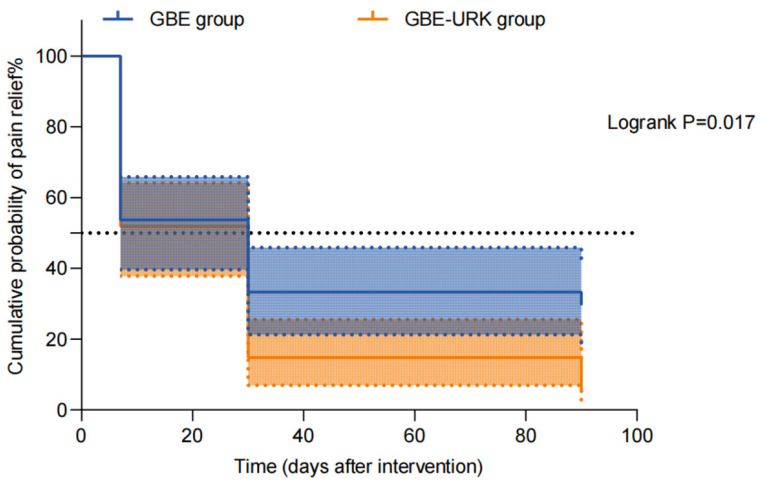

Figure 5. Kaplan-Meier curve showing the cumulative probability of pain relief (FPS-R decrease ≥2 points) over time. GBE: Ginkgo Biloba Extract; GBE-URK: Ginkgo Biloba Extract combined with Urokinase.

the combined thrombolytic-vasculo-protective regimen significantly shortened the onset time of clinically detectable pain reduction.

Discussion

The clinical treatment of TAO has long been limited by the constraints of existing methods. Studies have shown that even after standardized traditional treatment, more than half of patients with stage III TAO still fail to achieve symptom relief, and a single treatment modality often struggles to address the complex pathologic processes of the disease [16]. For example, single-drug therapy has limited effect on established thrombotic obstruction, while surgical treatment is unable to simultaneously control the chronic inflammation of the vascular wall [17]. As a local treatment approach, target artery perfusion can improve the contact efficiency between drugs and diseased vessels, but single GBE perfusion still has room for improvement in terms of enhancing hemodynamics and long-term efficacy [18]. Based on this, this study explored the therapeutic strategy of combined target artery perfusion of GBE and URK. As shown in the results, the GBE-URK combined regimen was significantly superior to the GBE monotherapy group in terms of postoperative pain relief, improvement in intermittent claudication, hemodynamic optimization, and 12-month recurrence-free survival rate. This finding not only provides a new strategy for the clinical treatment of thromboangiitis obliterans (TAO) but also verifies the scientific validity of the synergistic intervention between the thrombolytic effect of urokinase (URK) and the vascular protective effect of Ginkgo biloba extract (GBE).

Immunological and inflammatory injuries have been confirmed as the main pathological changes of TAO, with sustained upregulation of TNF-α, IL-1β and other cytokines exacerbating vascular injury and pain [19, 20] - this aligns with our findings that the GBE-URK group, which showed stronger inhibition of TNF-α and IL-6, also achieved better pain relief. This consistency verifies that our results are in line with the known pathological mechanism of TAO, enhancing the validity of the combined regimen's efficacy". In addition, a variety of autoantibodies have been found in TAO patients, including anti-endothelial cell antibodies, antibodies against vascular wall structures such as elastin and collagen, anti-cardiolipin antibodies and anti-neutrophil cytoplasmic antibodies, which further confirm that immune abnormalities are involved in the process of vascular injury [21, 22]. In addition, a variety of autoantibodies have been found in TAO patients, including anti-endothelial cell antibodies, antibodies against vascular wall structures such as elastin and collagen, anti-cardiolipin antibodies, and anti-neutrophil cytoplasmic antibodies, which further confirms that immune abnormalities are involved in the process of vascular injury.

In this study, the therapeutic advantage of the combined treatment group mainly stems from the synergistic effect of GBE and URK, and the target artery perfusion method further amplifies this synergistic effect. From the perspective of drug action mechanisms, the core value of GBE lies in vascular protection and anti-inflammation [23]. Its main component, ginkgo flavonoids, can exert antioxidant effects by scavenging free radicals and inhibiting lipid peroxidation [24, 25]. As a platelet-activating factor (PAF) receptor antagonist, terpenoid lactones can resist platelet aggregation and inhibit

inflammatory responses [26]. In addition, the quercetin component in GBE can reduce endothelial cell apoptosis caused by oxidative stress [27], and kaempferol can protect vascular endothelial integrity by regulating the SphK1/S1P/S1PR1/MLC2 signaling pathway [28]. These effects collectively improve vascular endothelial function, laying the foundation for unobstructed blood flow.

URK directly relieves mechanical obstruction through thrombolysis. During the course of TAO, the formation of a large number of fibrotic microthrombi in blood vessels will aggravate blood supply disorders, while low-dose URK can effectively dissolve newly formed microthrombi, control thrombus progression, recanalize occluded vessels, and improve peripheral circulation [29]. The administration method of target artery perfusion further enhances the therapeutic effect. Compared to intravenous administration, target artery perfusion can increase the contact area between the drug and the diseased vascular endothelium as well as the local concentration, making the vascular protective effect of GBE and the thrombolytic effect of URK act more directly on the lesion [30]. This synergistic strategy, which relieves obstruction through thrombolysis and protects blood vessels through anti-inflammatory effects, not only solves the immediate ischemia problem but also curbs the inflammation-driven pathological progression, ultimately manifesting as comprehensive benefits such as pain relief, improvement of claudication, optimization of hemodynamics, and reduction of recurrence rate.

Compared to existing treatment methods, the combined regimen in this study shows unique advantages. Traditional single-drug therapy (such as single GBE perfusion) can improve vascular endothelial function to a certain extent, but it lacks direct thrombolytic effect and has limited effect on formed thrombi; while single surgical treatment (such as vascular reconstruction) can improve blood supply in the short term, but it is traumatic, has a narrow applicable population, and cannot control vascular inflammation simultaneously [31]. The combined regimen in this study achieves minimal invasiveness through local administration, which not only avoids surgical risks but also covers multiple links including thrombolysis, anti-inflammation, and vascular protection through the synergy of GBE and URK, thus responding to the complex pathology of TAO more comprehensively than single treatment.

Compared to other interventional therapies, the advantages of combined medication through targeted artery perfusion are obvious. For example, although endovascular treatment can relieve symptoms in the short term, its long-term patency rate is low [32]. However, the combined regimen in this study, through the immediate thrombolysis of URK and the long-term protection of vascular endothelium by GBE, not only achieves significant short-term symptom improvement but also has a higher long-term recurrence-free survival rate, making up for the limitation of single interventional therapy that can only relieve symptoms in the short term but is difficult to control pathological progression.

Smoking is a key risk factor for the onset and progression of TAO. In this study, 90 out of 108 patients had a definite smoking history, which further confirms the close association between the two. Components such as nitrosamines and benzopyrene in tobacco can directly damage vascular endothelium, inhibit the activity of endothelial nitric oxide synthase (eNOS), reduce the production of nitric oxide (NO), and impair vascular diastolic function [33]. Although smoking cessation can reduce the risk of adverse events such as amputation, it alone cannot relieve ischemic symptoms such as rest pain and claudication [34]. This result suggests that in clinical treatment, “strict smoking cessation” should be combined with “combined drug intervention”: smoking cessation serves as the basis to delay disease progression, while the combined perfusion of GBE and URK addresses existing ischemic symptoms by improving blood supply and controlling inflammation. Only the synergy of the two can maximize the improvement in patients’ prognosis.

This study has three specific limitations: first, it is a single-center retrospective study with a relatively small sample size (n = 108), which may restrict the external validity of the conclusions - future multi-center, large-cohort studies are needed to verify the efficacy of the combined regimen. Second, the follow-up duration was 12 months, and long-term outcomes such as vascular patency rate over 2 years and potential delayed adverse reactions (e.g., long-

term vascular endothelial function changes) were not observed. Third, the molecular mechanism exploration was insufficient: we did not investigate the regulatory effects of GBE and URK on key inflammatory pathways (e.g., NF-κB) or pain-related signaling molecules (e.g., substance P), which may have omitted part of the synergistic mechanism and requires supplementation with cellular and animal experiments.

For example, how GBE and URK specifically regulate inflammatory pathways such as NF-κB still needs in-depth analysis through cellular and animal experiments. Future research can proceed from three aspects: first, optimize the administration regimen, such as adjusting the dose of URK and the perfusion duration of GBE, to further improve safety and efficacy; second, combine radiomics technology to evaluate the association between target vessel morphology and efficacy, so as to achieve individualized treatment; third, explore the combined application with emerging technologies such as stem cell therapy to provide more options for patients with end-stage TAO.

Conclusion

Treatment of TAO with target artery perfusion of GBE combined with URK showed significant effects in relieving symptoms, optimizing blood flow, anti-inflammation, and protecting endothelium, providing a new strategy for clinical treatment. However, its long-term value and mechanism still need in-depth research and verification.

Disclosure of conflict of interest

None.

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