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ORIGINAL ARTICLE

Combined Intracoronary Prourokinase Thrombolysis on Myocardial Perfusion and Vascular Endothelial Function in STEMI

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SUMMARY

Background: **This study aimed to investigate the effects of intracoronary prourokinase thrombolysis combined with emergency percutaneous coronary intervention (PCI) on myocardial perfusion and vascular endothelial function in patients with acute ST-segment elevation myocardial infarction (STEMI).**
Methods: **A total of 104 patients with STEMI were collected from August 2020 to August 2022, and were divided into control group and observation group in a random manner. The control group received PCI directly, and the observation group received intracoronary prourokinase thrombolytic therapy before PCI. The treatment effects were evaluated by measuring the cardiac function indexes, including left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and left ventricular ejection fraction (LVEF), the TIMI myocardial perfusion grade, the vascular endothelial indexes, including soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1), the von Willebrand factor (vWF), the myocardial injury indexes, including cardiac troponin I (cTnI), creatine kinase isoenzyme MB (CK-MB), and lactate dehydrogenase (LDH), and the inflammatory factors, including myeloperoxidase (MPO), C-reactive protein (CRP), and interleukin-6 (IL-6). Furthermore, the treatment safety was assessed by recording the incidence of major MACE events, 6 months after the operation.**
Results: **After treatment, LVEDD and LVESD were lower in the observation group than in the control group, and LVEF was higher ($p < 0.05$). The TIMI myocardial perfusion grade in the observation group was higher than in the control group, after treatment ($p < 0.05$). The levels of sICAM-1, sVCAM-1, and vWF were higher in the observation group than in the control group ($p < 0.05$). The levels of cTnI, CK-MB, and LDH in the observation group were lower than those in the control group, 24 hours after surgery. At 3 days after surgery, MPO was lower in the observation group than in the control group, and CRP and IL-6 were higher ($p < 0.05$). The incidence of major MACE events in the observation group was lower than that in the control group, 6 months after surgery ($p < 0.05$). There was 1 case of puncture site bleeding in the observation group, 1 case of puncture site bleeding and 1 case of subcutaneous ecchymosis in the control group, but no serious bleeding events, such as internal bleeding or cerebral hemorrhage, in the two groups.**
Conclusions: **Intracoronary prourokinase thrombolytic therapy combined with emergency PCI can promote the recovery of cardiac function, improve myocardial perfusion and vascular endothelial function, and reduce inflammation and the incidence of major postoperative MACE events in acute STEMI patients.**
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KEYWORDS

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INTRODUCTION

Acute ST-segment elevation myocardial infarction (STEMI) is a common clinical and critical condition with a high risk of disability and death. Percutaneous coronary intervention (PCI) is the main means of treatment of the disease, which can achieve early revascularization and promote the recanalization of blocked blood vessels [1]. However, after coronary artery occlusion, capillaries and tiny arteries will be damaged, and microcirculation disorders may still occur in the distal ischemic area of the coronary artery, even after an effective treatment [2]. Clinical data show that these patients are prone to recurrent myocardial infarction after surgery, which affects their prognosis [3]. As a plasminogen activator, prourokinase can be lysed into double-stranded urokinase in the human body, which mainly acts on the fibrin at the site of a thrombus. After entering the blood, it can bind to and dissolve the fibrin adsorbed on the fibrin of the thrombus, thus it can restore myocardial blood perfusion [4]. At present, there are relatively few clinical reports on the combined application of recombinant human prourokinase thrombolytic scheme and PCI, so it is very important to explore the feasibility of the combined application of the two methods and the impact on the prognosis of patients with acute STEMI. Based on this, the purpose of this study was to investigate the effects of intracoronary prourokinase thrombolytic therapy combined with emergency PCI on myocardial perfusion and vascular endothelial function in acute STEMI patients, hoping to support its application in the clinical practice.

MATERIALS AND METHODS

Clinical data

A total of 104 patients with STEMI were collected from August 2020 to August 2022, and were divided into control group and observation group in a random manner. There was no significant difference in the clinical data between the two groups ($p > 0.05$) (Table 1).

Inclusion criteria

1) Patients had to meet the diagnostic criteria of STEMI [5]; 2) age ≤ 75 years; 3) continuous chest pain lasting ≥ 20 minutes, ST-segment elevation of ≥ 2 mm in at least 2 contiguous precordial leads, ST-segment Elevation of ≥ 1 mm (0.1 mV) in at least 2 inferior leads, or new left bundle branch block; 4) all patients or their family members signed informed consent; 5) all patients exhibit a duration of less than 12 hours from the onset of their symptoms to their first medical contact (FMC). In the case of patients undergoing direct PCI, the time interval from FMC to the administration of PCI is less than 2 hours [6]; patients who received thrombolysis prior to PCI experienced a duration exceeding 2 hours from FMC to PCI [6]; 6) the administration of PCI occurred within a timeframe ranging from 2 to 24 hours subsequent to thrombolysis [7].

Exclusion criteria

1) Patients with prior craniocerebral tumor disease; 2) patients with a history of cerebral hemorrhage; 3) patients with a history of ischemic stroke within 6 months before the enrollment; 4) patients with active bleeding; 5) patients with an allergic constitution; 6) patients with an abnormal coagulation function; 7) patients with an extremely poorly controlled or not well-controlled hypertension that cannot be effectively controlled, with uncontrolled diabetes or when accompanied by other serious diseases of the system; 8) patients with continuous cardiopulmonary resuscitation ≥ 10 minutes within 1 month; 9) patients with large vascular puncture, who could not compress the hemostatic site.

Treatment methods

Before operation, all patients were given 300 mg of aspirin effervescent tablets (AstraZeneca 0.5 x 10 tablets, national drug approval number: H32026201) and 180 mg of ticagrlor (AstraZenecaAB 90 mg, national drug approval number: H20120486). PCI was performed directly, in the control group, and PCI was performed in the observation group after treatment with 10 mg of recombinant human prourokinase for Injection (Shanghai Tasly Pharmaceutical Co., Ltd., specification: 5 mg (500,000 IU)/piece, national drug approval number: S20110003).

Outcome indicators

1) Cardiac function indicators: Acuson-Sequoia model 512 echocardiography system was used for the assessment of the left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and left ventricular ejection fraction (LVEF) in patients, both prior to and 7 days following treatment.

2) Myocardial perfusion: it was classified into grades 0 - 3, according to TIMI myocardial perfusion grading criteria [8]. Grade 0: no contrast agent or very little contrast agent into the myocardium. Grade 1: the contrast agent entered the myocardia slowly, the microvascular myocardial staining was ground glass, or the contrast agent staining remained in the myocardia, dominated by infarct-related vessels in the next sequence. Grade 2: the entry and clearance time of the contrast agent was prolonged, the myocardial contrast agent was ground-glass-like, the myocardial area, dominated by infarct-related vessels, was high-density, and the contrast agent was not cleared or the density of a small part of the myocardium decreased for 3 cardiac cycles. Grade 3: the con-

trast agent enters the myocardium normally and is quickly cleared without residue.
3) Vascular endothelial indices: soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), and the von Willebrand factor (vWF) were determined by ELISA, using the Denley Dragon automatic enzyme marker.
4) Indexes of myocardial injury: the level of cardiac troponin I (cTnI), before and 24 hours after surgery, was detected by implementing the chemiluminescence method, while that of creatine kinase isoenzyme MB (CK-MB) and lactate dehydrogenase (LDH) was measured by colorimetry.
5) Inflammatory factors: the levels of myeloperoxidase (MPO), C-reactive Protein (CRP), and Interleukin-6 (IL-6), before and after surgery, were detected by ELISA.
6) Incidence of major MACE events: the incidence of MACE events, 6 months after surgery, was analyzed in the two groups, including cardiac death, non-fatal myocardial infarction, and revascularization (target vessel revascularization and non-target vessel revascularization).

Statistical analysis
All the data were processed by using the SPSS 22.0 software (IBM Corp., Armonk, NY, USA). The categorical values were expressed as frequency and compared with the chi-squared test or Fisher's exact test. The measurement data were expressed by $\bar{x} \pm s$ and examined by using Student´s *t* test. A two-factor analysis of variance (ANOVA) was employed to examine the effects of the treatment method and the time on each parameter, followed by the application of the Bonferroni multiple comparison test to assess the significance of the obtained p-values. Grade data were evaluated by Z test. The dependent variable, the MACE events, was utilized in the analysis with a significance level of $\alpha = 0.05$. Individual variables underwent screening by using a univariate Cox risk regression, followed by the identification of risk factors for MACE through a multivariate Cox risk regression. $p < 0.05$ meant the difference was statistically significant.

RESULTS

Cardiac function indexes
Preoperative LVEDD, LVESD, and LVEF indicated no significant differences between the two groups ($p > 0.05$). LVEDD and LVESD after treatment were lower than before treatment, and they were lower in the observation group than in the control group ($p < 0.05$). LVEF in the two groups was higher after treatment than before treatment, and this elevation was more significant in the observation group ($p < 0.05$) (Figure 1).

Myocardial perfusion indexes
No significant difference was recorded in TIMI myocardial perfusion grading between the two groups before treatment ($p > 0.05$). TIMI myocardial perfusion grade after treatment was higher in both groups than before treatment, especially in the observation group ($p < 0.05$) (Table 2).

Vascular endothelial function indexes
There were no significant differences in the sICAM-1, sVCAM-1, and vWF levels between the two groups before and after treatment ($p > 0.05$). Both treatment methods increased the sICAM-1, sVCAM-1, and vWF levels, and combined intracoronary prourokinase thrombolytic therapy had a better effect ($p < 0.05$) (Figure 2).

Myocardial injury indexes
There were no significant differences in preoperative cTnI, CK-MB, and LDH between the two groups ($p > 0.05$). The levels of cTnI, CK-MB, and LDH in both groups 24 hours after surgery were lower than those before surgery, and were the lowest in the observation group ($p < 0.05$) (Figure 3).

Inflammatory factors
Preoperative inflammatory factors showed no significant difference between the two groups ($p > 0.05$). MPO of 3 days after surgery was lower than before surgery, and that in the observation group was lower than in the control group ($p < 0.05$). The levels of CRP and IL-6 at 3 days after surgery were higher than before surgery, and were higher in the observation group than in the control group ($p < 0.05$) (Figure 4).

Incidence of major MACE events
The incidence of major MACE events 6 months after surgery was lower in the observation group than in the control group ($p < 0.05$) (Table 3). As shown in Table 4, after adjusting factors such as gender, age, medical history, and smoking history, STEMI patients have a 1.17 times higher risk of developing MACE events after direct percutaneous coronary intervention compared to percutaneous coronary intervention after thrombolysis.

Incidence of bleeding events
In total, 1 case of puncture site bleeding occurred in the observation group and 1 case of puncture site bleeding and 1 case of subcutaneous ecchymosis occurred in the control group. No serious bleeding events, such as internal bleeding or cerebral hemorrhage, occurred in the two groups.

DISCUSSION

Acute STEMI is a common heart disease based on acute coronary artery occlusion. Currently, it is believed that the key to the treatment of this disease is to open blood vessels as soon as possible to complete the reconstruc-

Table 1. Comparison of the clinical data between the two groups.

Classification	Observation group (n = 52)	Control group (n = 52)	χ^2/t	p
Gender (cases)			0.158	0.691
Male	31	29		
Female	21	23		
Age (years)				
Co-underlying disease (cases)	59.06 ± 5.58	60.13 ± 6.05	0.937	0.351
Hypertension	11	9	0.248	0.619
Diabetes	8	7	0.078	0.780
Hyperlipemia	13	15	0.195	0.658
Smoking history (cases)	9	7	0.295	0.587
Drinking history	11	8	0.580	0.446
Number of vessels involved (cases)			0.353	0.838
Single	9	10		
Double	24	21		
Multiple	19	21		
Time from SO-to-FMC (mins)	233.35 ± 36.05	216.58 ± 47.62	0.624	0.052

The categorical variable is denoted as n and was analyzed by using either the chi-squared test or the Fisher's exact test. The continuous variable is expressed as mean ± SD, and its significance is assessed by using the student *t*-test. p < 0.05 meant the difference was statistically significant. SO-to-FMC, symptom onset to first medical contact.

Table 2. Comparison of the myocardial perfusion indexes, before and after treatment, between the two groups.

Groups	Time	Grade 0	Grade 1	Grade 2	Grade 3	*Z*	p
Observation group	before treatment	5	10	12	25	14.962	< 0.001
	after treatment	0	3	6	43		
Control group	before treatment	4	13	11	24	5.648	0.017
	after treatment	0	7	11	34		

The incidence rate of TIMI myocardial perfusion grade was tested by using the Z-test, $\alpha = 0.05$. p < 0.05 meant the difference was statistically significant.

Table 3. Incidence of major MACE events in the two groups (e.g., %).

Groups	n	Heart failure	Cardiac death	Nonfatal myocardial infarction	Revascularization	Total incidence (%)
Observation group	52	1	0	2	1	7.69
Control group	52	4	1	3	4	23.08
χ^2						4.727
p						0.03

The incidence rate of MACE events was tested with the chi-squared test. p < 0.05 meant the difference was statistically significant.

Table 4. Cox risk regression analysis of events affecting the MACE occurrence.

Univariate Cox regression	OR	95% CI	p
Gender (Female)	2.32	0.36 - 10.52	0.285
Age (> 60)	0.76	0.63 - 3.25	0.732
Hypertension	1.66	0.93 - 6.89	0.822
Diabetes	2.54	1.25 - 3.63	0.159
Hyperlipemia	1.098	0.26 - 2.65	0.352
Smoking history (yes)	1.25	0.48 - 3.25	0.268
Drinking history	2.35	0.65 - 2.65	0.752
Number of vessels involved (≥ 2)	1.85	0.58 - 4.36	0.585
Time from SO-to-FMC	1.26	1.06 - 2.12	0.026
Treatment method (directly PCI)	1.94	1.32 - 5.25	< 0.001
Multivariate Cox regression	**HR**	**95% CI**	**p**
Time from SO-to-FMC	1.02	0.68 - 2.01	0.256
Treatment method (directly PCI)	1.17	1.08 - 2.12	0.035

HR - risk ratio, CI - confidence interval.

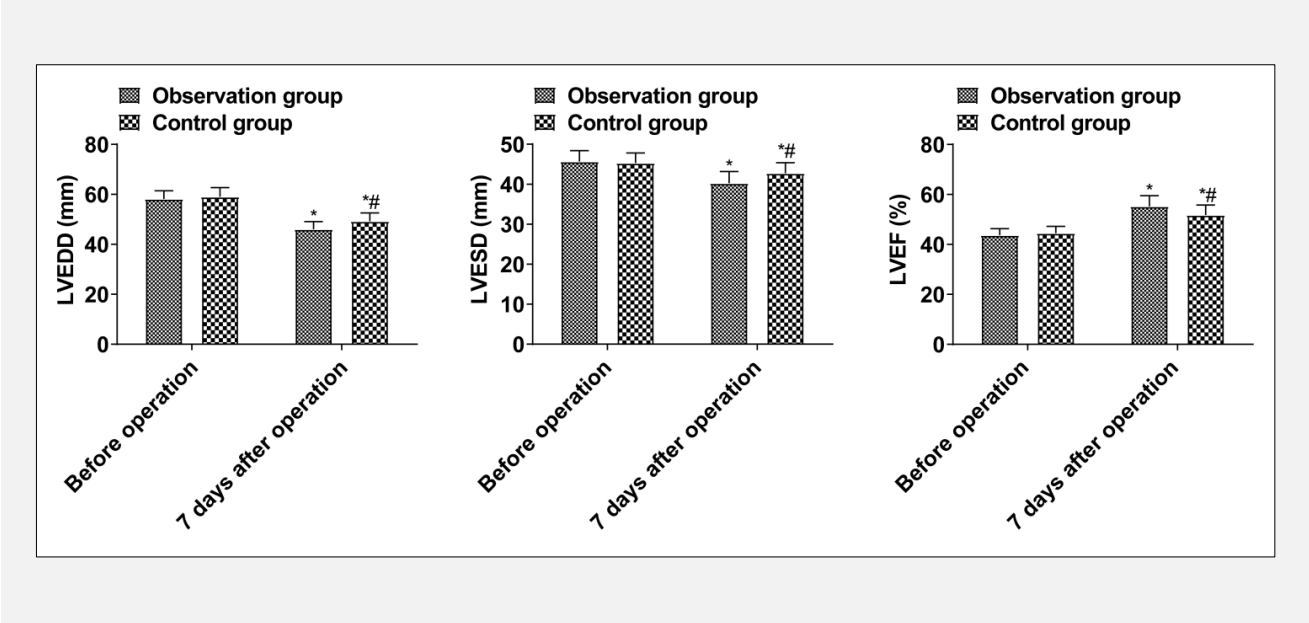

Figure 1. Comparison of cardiac function indexes.

Before vs. after treatment, * - p < 0.05; observation group vs. control group after treatment, *# - p < 0.05.

tion of blood circulation in the lesion area and to ensure a myocardial perfusion [9,10]. PCI is the preferred treatment method for this disease, which can directly intervene in occlusive blood vessels and effectively open infarct-related arteries, thus improve the patients' quality of life and prognosis [11]. No reflow is a common complication during PCI, which can increase the incidence of arrhythmia and heart failure after myocardial infarction, and thus increase mortality. It has been reported that combined treatment with recombinant human prourokinase can effectively prevent no reflow [12]. Recombinant human prourokinase is a precursor of uroki-

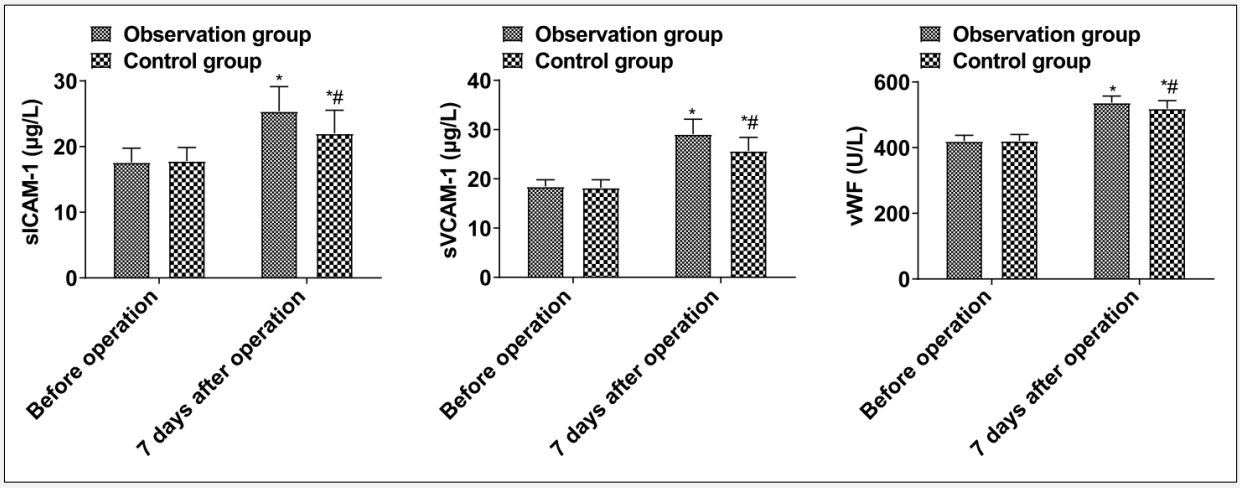

Figure 2. Comparison of vascular endothelial function indexes.

Before vs. after treatment, * - p < 0.05; observation group vs. control group after treatment, *# - p < 0.05.

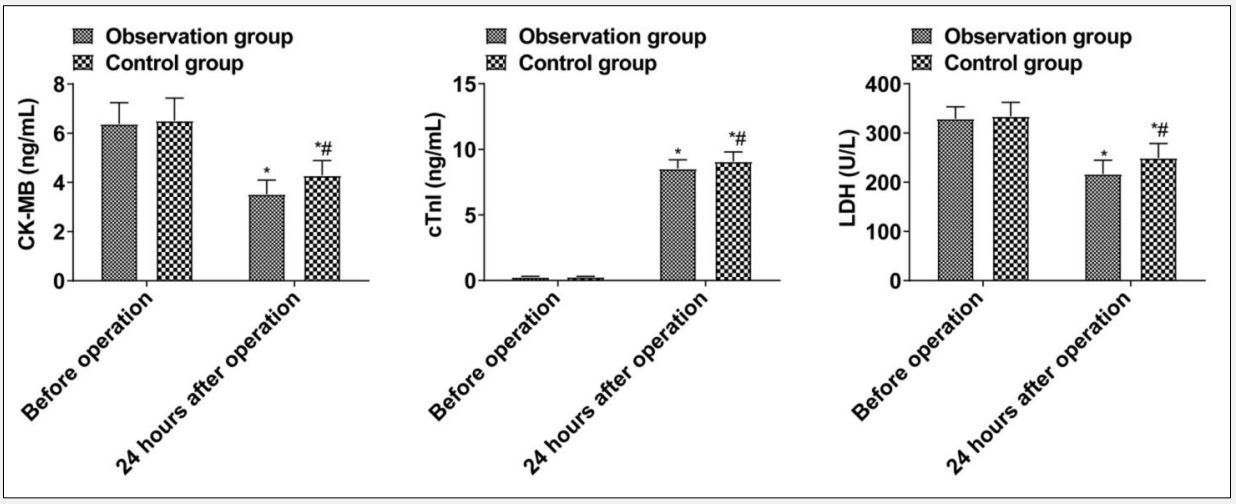

Figure 3. Comparison of myocardial injury indexes.

Before vs. after treatment, * - p < 0.05; observation group vs. control group after treatment, *# - p < 0.05.

nase, a fibrinolytic activator that has no pharmacological activity upon entry into the bloodstream, but its specific structure, double-chain urokinase, is 500 times more active. Double-chain urokinase acts on the thrombus, causing the plasminogen on its surface to become plasminase, which dissolves the thrombus fibrin and leaves it exposed. The original single-chain recombinant human prourokinase is used in this area and acts as a thrombolytic agent [13,14]. For patients diagnosed with STEMI, the prompt initiation of percutaneous coronary intervention (PCI) within a 2-hour timeframe from the first medical contact has been shown to yield

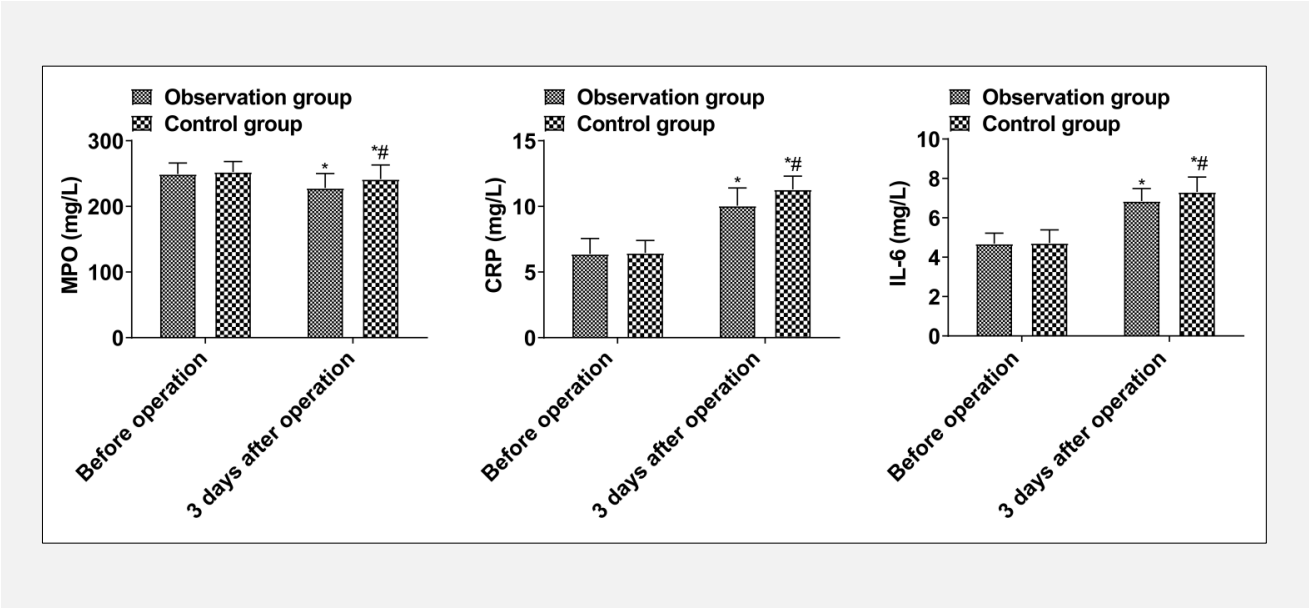

Figure 4. Comparison of inflammatory factors (mg/L).

Before vs. after treatment, * - p < 0.05; observation group vs. control group after 7 days of treatment, *# - p < 0.05.

improved treatment outcomes [15,16]. Nevertheless, it is important to acknowledge that not all healthcare institutions possess the necessary capabilities to perform PCI. In cases where STEMI patients require transfer, the administration of thrombolytic drugs should be promptly initiated within 10 minutes after the STEMI diagnosis, followed by PCI within a window of 2 to 24 hours subsequent to successful thrombolysis [17,7].In this study, LVEDD and LVESD after treatment were reduced in the observation group, LVEF was elevated, and the myocardial perfusion grade of TIMI was higher, suggesting that combined therapy can improve the cardiac function and the myocardial perfusion level in acute STEMI patients. The reason for this is that PCI is a simple physical method to stimulate thrombus rupture into microthrombus, so that the microthrombus is swallowed by macrophages at the distal end of the blood vessel. It is easy to block the microcirculation vessels, resulting in no reflow and slow blood flow phenomenon, affecting myocardial perfusion, while the combination of recombinant human prourokinase and PCI can open up the blood vessel occlusion by physical and chemical methods. The thrombolytic effect of recombinant human prourokinase can improve the blockage of microcirculation vessels and the absence of reflow, thus improve postoperative myocardial perfusion in patients [18,19].

Serum sICAM-1 and sVCAM-1 can reflect the vascular endothelial function of patients, regulate cell adhesion, cause vascular endothelial damage, enhance the activity of neutrophils in vivo, initiate patients' autoimmune response, induce endothelial cell apoptosis, further aggravate endothelial cell damage during surgery, promote the up-regulation of vascular endothelial cell expression, and make the adhesion molecules between cells and blood vessels and leukocyte adhesion molecules act on each other, aggravating the microcirculation disorder [18]. vWF is the synthesis and storage of vascular endothelial cells and megakaryocytes in the endodermal middle layer. Once endothelial cells are injured, they will be released into the blood and will then participate in the activation of platelets and coagulation process, which is considered a specific marker reflecting vascular endothelial injury [20]. The results of this study showed that the levels of sICAM-1, sVCAM-1, and vWF in the observation group were higher than those in the control group 7 days after surgery, suggesting that combination treatment could reduce the degree of microcirculation vessel blockage and improve myocardial perfusion. In addition, as a fibrinolytic reagent, prourokinase can play a catalytic role in the formation of fibrinase, which can improve the symptoms of thrombus, reduce the fibrinogen and fibrin clot, and can play a role in the dissolution of thrombus formation and inhibit platelet aggregation. Thus, vascular endothelial function of patients can be improved [1,21].

MPO promotes cholesterol deposition and foam cell formation, which can aggravate the process of stent restenosis and atherosclerosis. IL-6 reflects the acute inflammatory response of the body and leads to restenosis in the scaffold through adhesion of inflammatory cells, aggregation of platelets, and proliferation of neointima, and can also increase the production of CRP. As a nonspecific inflammatory factor, CRP is a sensitive indica-

tor, regulated by IL-6 and other inflammatory factors, and plays a role in promoting the expression of local adhesion factors, thrombosis, and vascular inflammation [22,23]. The results demonstrated that cTnI, CK-MB, and LDH were lower 24 hours after surgery, MPO was lower 3 days after surgery, and CRP and IL-6 were higher in the observation group, indicating that combined treatment can reduce the degree of myocardial injury and body inflammation. This is mainly because the thrombolytic effect of recombinant human prourokinase can alleviate postoperative acute inflammation, and the mechanism of coagulation and bleeding will not be affected in the process of thrombolytic, so as to reduce the risk of bleeding, protect the damaged myocardial cells, and thus reduce the inflammatory response caused by myocardial injury. Prourokinase can prevent microthrombus formation, reduce the degree of myocardial cell damage, indirectly improve myocardial function, and thus reduce the inflammatory response of the body [24].

Clinical data show that PCI alone cannot completely avoid the occurrence of no reflow and MACE, intraoperative stent placement and balloon dilation are easy to stimulate the primary thrombus, and microthrombus formed after thrombus rupture will block microcirculation vessels, resulting in poor myocardial perfusion, and increase the rate of surgical failure and the incidence of poor prognosis [25]. In this study, the incidence of major MACE events was lower in the observation group than in the control group 6 months after surgery, indicating that combined therapy could reduce the incidence of major MACE events, which is mainly related to the improvement of myocardial perfusion and vascular endothelial function. All patients received care within a multidisciplinary setting, where all appropriate legal treatment plans were administered, ensuring that written informed consent was obtained prior to any interventions. Despite providing treatment plans to patients, subsequent treatment and echocardiography collection and analysis were conducted by physicians, who were kept in the dark about the treatment group. The primary objective of this study was to minimize bias from the treating physicians and the doctors responsible for collecting echocardiographic data.

Intracoronary prourokinase thrombolytic therapy combined with emergency PCI can promote the recovery of cardiac function, improve myocardial perfusion and vascular endothelial function, and reduce inflammation and the incidence of major postoperative MACE events in acute STEMI patients.

Availability of Data and Materials:

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Declaration of Interest:

The authors have no conflicts of interest to declare.

References:

1. De la Garza-Salazar F, Lankenau-Vela DL, Cadena-Nuñez B, González-Cantú A, Romero-Ibarguengoitia ME. The Effect of Functional and Intra-Coronary Imaging Techniques on Fluoroscopy Time, Radiation Dose and Contrast Volume during Coronary Angiography. Sci Rep 2020;10(1):6950. (PMID: 32332840)

2. Wu Y, Fu X, Feng Q, et al. Efficacy and safety of intracoronary prourokinase during percutaneous coronary intervention in treating ST-segment elevation myocardial infarction patients: a randomized, controlled study. BMC Cardiovasc Disord 2020;20(1): 308. (PMID: 32590944)

3. Chung J, Kumins NH, Smith J, et al. Physiologic risk factors increase risk of myocardial infarction with transcarotid artery revascularization in prospective trials. J Vasc Surg 2023;77(4): 1192-8. (PMID: 36563712)

4. Song H, Wang Y, Ma Q, et al. Efficacy and Safety of Recombinant Human Prourokinase in Acute Ischemic Stroke: A Phase IIa Randomized Clinical Trial. Transl Stroke Res 2022;13(6):995-1004. (PMID: 35505174)

5. van der Ende NAM, Roozenbeek B, Smagge LEM, et al. Dual thrombolytic therapy with mutant pro-urokinase and small bolus alteplase for ischemic stroke (DUMAS): study protocol for a multicenter randomized controlled phase II trial. Trials 2022;23(1): 641. (PMID: 35945566)

6. Joy ER, Kurian J, Gale CP. Comparative effectiveness of primary PCI versus fibrinolytic therapy for ST elevation myocardial infarction: a review of the literature. J Comp Eff Res 2016;5(2): 217-26. (PMID: 26946949)

7. Ibanez B, James S, Agewall S, et al; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment Elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39(2): 119-77. (PMID: 28886621)

8. Rambarat CA, Elgendy IY, Handberg EM, et al. Late sodium channel blockade improves angina and myocardial perfusion in patients with severe coronary microvascular dysfunction: Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction ancillary study. Int J Cardiol 2019;276:8-13. (PMID: 30293664)

9. Jiang W, Xiong X, Du X, Ma H, Li W, Cheng F. Safety and efficacy study of prourokinase injection during primary percutaneous coronary intervention in acute ST-segment elevation myocardial infarction. Coron Artery Dis 2021;32(1):25-30. (PMID: 32310850)

10. Jiang C, Gao J, Luo D-L, Guo J-T. Effect of pharmacoinvasive therapy with half-dose prourokinase on adverse cardiovascular events during angiography or percutaneous coronary intervention. Asian J Surg 2022;45(3):890-1. (PMID: 35000847)

11. Vyas Y, Workneh E, Leibowitz JL, Sarkar R, Ghoreishi M, Toursavadkohi S. Evaluating the Safety of Transcarotid Artery Revascularization under Local Anesthesia Prior to Coronary Artery Bypass Grafting Surgery. Ann Vasc Surg 2023;91:176-81. (PMID: 36481672)

12. Fan G, Wu X-G, Jiao W-P, Zhang H-K, Guo D-L. Safety and efficacy of intracoronary recombinant human prourokinase administration in patients with acute myocardial infarction and ST-segment elevation: A meta-analysis of randomized controlled trials. Exp Ther Med 2022;25(1):40. (PMID: 36569445)

13. Wang LJ, Mohebali J, Goodney PP, et al. The effect of clinical coronary disease severity on outcomes of carotid endarterectomy with and without combined coronary bypass. J Vasc Surg 2020; 71(2):546-52. (PMID: 31401112)

14. Mcalister C, Samuel R, Alfadhel M, et al. TCT-21 Thrombolysis in Spontaneous Coronary Artery Dissection: Angiographic Findings and Clinical Outcomes 2021;78(19):B10. https://www.researchgate.net/publication/355833213_TCT-21_Thrombolysis_in_Spontaneous_Coronary_Artery_Dissection_Angiographic_Findings_and_Clinical_Outcomes

15. Thomas MP, Bates ER. Update on primary PCI for patients with STEMI. Trends Cardiovasc Med 2017;27(2):95-102. (PMID: 27450063)

16. Gevaert SA, De Bacquer D, Evrard P, et al. Gender, TIMI risk score and in-hospital mortality in STEMI patients undergoing primary PCI: results from the Belgian STEMI registry. EuroIntervention 2014;9(9):1095-101. (PMID: 24457280)

17. Alyamani M, Campbell S, Navarese E, Welsh RC, Bainey KR. Safety and Efficacy of Intracoronary Thrombolysis as Adjunctive Therapy to Primary PCI in STEMI: A Systematic Review and Meta-analysis. Can J Cardiol 2021;37(2):339-46. (PMID: 32739451)

18. Gibson CM, Kumar V, Gopalakrishnan L, et al.; TIMI & PERFUSE Study Group. Feasibility and Safety of Low-Dose Intra-Coronary Tenecteplase During Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction (ICE T-TIMI 49). Am J Cardiol 2020;125(4):485-90. (PMID: 31870492)

19. Lee Y, Kim E, Kim BK, Shin J-H. A case of successful reperfusion through a combination of intracoronary thrombolysis and aspiration thrombectomy in ST-segment elevation myocardial infarction associated with an ectatic coronary artery. BMC Cardiovasc Disord 2017;17(1):94. (PMID: 28381215)

20. Costa C, Durão D, Belo A, Domingues K, Santos B, Leal M; Investigators of the Portuguese Registry of Acute Coronary Syndromes. Coronary angiography after successful thrombolysis - Is the recommended time interval of 24h an important issue? Int J Cardiol 2016;222:515-20. (PMID: 27509219)

21. Patel DC, Gaba RC, Liu L, Lokken RP. Tissue plasminogen activator dose and pulmonary artery pressure reduction in catheter directed thrombolysis of submassive pulmonary embolism. PLoS One 2019;14(2):e0211701. (PMID: 30726288)

22. Wright SL, Jahangiri B, Smyth DW, et al. Successful intravenous thrombolysis for ischemic stroke as a complication of coronary intervention in patients with ticagrelor pretreatment. J Clin Neurosci 2020;71:283-6. (PMID: 31662237)

23. Mathias W, Tsutsui JM, Tavares BG, et al. Sonothrombolysis in ST-Segment Elevation Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention 2019;73(22):2832-42. (PMID: 30894317)

24. Cao M, Wang Z, Meng X, et al. Effects of intracoronary low-dose prourokinase administration on ST-segment elevation in patients with myocardial infarction and a high thrombus burden: a randomized controlled trial. J Int Med Res 2022;50(12):3000605221139723. (PMID: 36514961)

25. Eisen A, Cannon CP, Braunwald E, et al. Predictors of Nonuse of a High-Potency Statin After an Acute Coronary Syndrome: Insights From the Stabilization of Plaques Using Darapladib-Thrombolysis in Myocardial Infarction 52 (SOLID-TIMI 52) Trial. J Am Heart Assoc 2017;6(1): e004332. (PMID: 28077384)