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Original Article

Efficacy and safety of intracoronary thrombolysis versus PCI in myocardial infarction patients

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Abstract: Objective: To investigate the clinical efficacy and safety of an infarction-related coronary artery injection of recombinant human prourokinase in patients diagnosed with acute ST-segment elevation myocardial infarction (STEMI). Methods: This study was a randomized prospective study. From January 2018 to October 2020, 148 STEMI patients who agreed to undergo emergency percutaneous coronary intervention (PCI) or coronary angiography within 12 hours of stroke onset were enrolled; patients received either a targeted coronary artery injection of 20 mg of recombinant human prourokinase (experimental group) or underwent conventional PCI (control group). The recovery of thrombolysis in myocardial infarction (TIMI) blood flow in infarction-related arteries, cardiac function, incidence of major adverse cardiovascular events (MACEs), and bleeding rate of the two groups were observed. The efficacy and safety of the targeted intracoronary injection of recombinant human prourokinase were assessed for the treatment of STEMI patients. Results: There was no statistically significant difference in TIMI blood flow recovery, MACE incidence during hospitalization, or bleeding events between the recombinant human prourokinase intracoronary injection group and the conventional PCI group. However, the rate of severe bleeding in the PCI group was 1.4%, and there was no severe bleeding in the intracoronary thrombolysis group. The incidence of cardiogenic shock was higher in the PCI group, and the difference was statistically significant. Conclusion: The therapeutic effect of a recombinant human prourokinase infusion into the proximal infarction-related blood vessel target lesion through a microcatheter is equivalent to that of emergency PCI and does not increase the incidence of bleeding events.

Keywords: Acute ST-segment elevation myocardial infarction, recombinant human prourokinase, emergency PCI, intracoronary thrombolysis

Introduction

Acute ST-segment elevation myocardial infarction (STEMI) is one of the leading causes of mortality worldwide, and the key to treatment is reperfusion as soon as possible. In the reperfusion treatment of STEMI, the use of intravenous thrombolysis and emergency percutaneous coronary intervention (PCI) technology is well established. The main thrombolytic drugs include nonspecific plasminogen activators and specific plasminogen activators. Nonspecific plasminogen activators, such as urokinase and streptokinase, have low thrombolytic recanalization rates and high bleeding rates, and their use is inconvenient, so they are not recommended. Specific plasminogen activators have certain characteristics, such as high thrombolysis rates and a low incidence of cerebral hemorrhage, and are recommended based on current guidelines [1]. Recombinant human prourokinase is the precursor of urokinase. After entering the circulation, it can be adsorbed on the surface of the thrombus and converted into urokinase so that the thrombus can be dissolved quickly. Its role in the recanalization of acute myocardial infarction (AMI) has been reported in a large number of domestic and international studies, and its use is very important in the thrombolytic treatment of AMI [2-7]. However, the bleeding risk associated with intravenous thrombolysis is high. PCI is not commonly used in some countries and regions, which may be related to inadequate education

and technology, the limited acceptance of the utilized stents, the expense of the stents, a lack of PCI technology at the hospital or insufficient experience in handling these complex lesions. The latest study found that most emergency patients mainly have thrombosis. However, some patients have less severe stenosis, and stent implantation is not necessarily needed. Improper thrombus management and direct stenting implantation during catheterization have been confirmed to result in distal embolization, causing a second strike to the coronary microvascular circulation and cardiomyocytes [8-10]. Therefore, direct stenting is not recommended for STEMI patients with a high thrombus burden. In addition, the positive therapeutic effect of intracoronary thrombolysis has been investigated in patients with stent thrombosis, left main thrombus, Kawasaki disease, failed aspiration, and other complex circumstances [11-13]. In addition, some patients with STEMI who are undergoing emergency PCI have no reflow. Studies have shown that an intracoronary injection of prourokinase in the treatment of STEMI with emergency PCI (without reflow) can effectively restore coronary blood flow and myocardial reperfusion [14, 15]. Recently, intracoronary-targeted thrombolysis has become popular and efficient for handling coronary thrombotic lesions, but there are few international studies comparing intracoronary thrombolysis and PCI [16, 17]. The purpose of this study was to compare PCI and target vessel microcatheter injection of prourokinase in the treatment of STEMI, to provide patients with more suitable treatment options.

Materials and methods

Research patients

From January 2018 to October 2020, 148 STEMI patients admitted to the People's Hospital of Nanchuan, Chongqing, Beibei Traditional Chinese Medical Hospital, and Chongqing University Three Gorges Hospital were selected for inclusion in this cohort. According to the reperfusion treatment strategy, they were divided into a target intracoronary thrombolysis group (experimental group, n=75) and a conventional PCI group (control group, n=73). The enrollment criteria were in accordance with the American Heart Association diagnostic criteria for AMI [18] as follows: an ECG showing that the ST-segment elevation of two adjacent leads exceeded 0.1 cm, or the symmetry inversion of the T wave or dynamic changes, or the presence of a new left bundle branch block; confirmed by myocardial enzymology. Further inclusion criteria included patients who had undergone emergency PCI, those with persistent chest pain for >0.5 h, and those with a time from onset to a PCI operation of <12 h, and those had to have indications for PCI; coronary angiography showing that at least one main coronary artery was acutely completely occluded and a target vessel diameter ≥2.5 mm. All of the included patients had complete clinical and follow-up data. The exclusion criteria were as follows: ① preoperative cardiogenic shock; ② AMI with mechanical complications such as ventricular septal perforation or papillary muscle rupture; ③ a history of intracranial hemorrhage or a history of ischemic stroke within 3 months; ④ recent trauma or a history of major surgery; ⑤ a bleeding disease or coagulopathy; ⑥ prehospital thrombolysis for salvage PCI; ⑦ complications of severe liver and kidney dysfunction; ⑧ suspected aortic dissection; ⑨ hypersensitivity to contrast agents or thrombolytic agents; and ⑩ coronary artery bypass after transplantation. This study was registered with the hospital ethics committee and was reviewed and approved.

Research methods

According to the current STEMI diagnosis and treatment guidelines, all of the selected patients took aspirin enteric-coated tablets (300 mg) + ticagrelor (180 mg) or clopidogrel bisulfate (300 mg) before emergency PCI surgery. After admission, the patients in the experimental group underwent surgery where the proximal end of the infarction-related blood vessel (IRA) target lesion was entered via a microcatheter, and recombinant human prourokinase (trade name: Puyouke, Tianshili Biopharmaceutical Co., Ltd., National Standard No. s2011-0003; lot number: 20180601; 5 mg per tube, with a 20 mg + NS 10 ml mixed solution) was infused. Routine postoperative drug treatment included oral aspirin enteric-coated tablets (100 mg/d), clopidogrel tablets (75 mg/d) or ticagrelor tablets (90 mg/bid), and atorvastatin calcium tablets (20 mg/d). The patients in the control group underwent conventional PCI. On the basis of a patient's blood pressure and heart rate, we used β-receptor blockers and angiotensin-converting enzyme inhibitors when

necessary. Patients with hypertension, hyperlipidemia, diabetes and other diseases also received the appropriate treatments.

Observation indicators

Main outcomes: TIMI blood flow grade and major adverse cardiovascular events. Secondary outcomes: cardiac function and bleeding events.

Thrombolysis in myocardial infarction (TIMI) blood flow grade: The TIMI blood flow grade was assessed before and after surgery as follows: grade 0 - no perfusion, no forward blood flow at the distal end of the vascular occlusion; grade 1 - permeation without blood perfusion, the contrast agent passes through the occlusion site but cannot fill the distal vessels; grade 2 - partial perfusion, the occlusion of the distal angiogram is filled with the contrast medium, but the filling and clearance rate of the contrast medium is slower than that of the normal coronary artery; and grade 3 - complete myocardial perfusion, the distal blood vessels can fill quickly, and the contrast agent is completely cleared. TIMI grades 0 and 1 indicate that the coronary artery has not been opened, whereas TIMI grades 2-3 indicate that the coronary artery has been recanalized.

Evaluation of cardiac function: One week after the operation, the left ventricular ejection fraction (LVEF) was measured by ultrasonic cardiogram to evaluate cardiac function.

The incidence of bleeding events and major adverse cardiovascular events (MACEs): The incidence of bleeding complications and MACEs 30 days after the operation was recorded for the two groups. The degree of bleeding was divided into mild, moderate, and fatal bleeding according to the TIMI bleeding classification standard [19]. Fatal bleeding was defined as intracranial hemorrhage or bleeding with a severe hemodynamic impairment that required treatment; moderate bleeding was defined as macroscopic blood loss or a decrease in hemoglobin requiring a blood transfusion; and mild bleeding was defined as bleeding that did not require blood transfusion or other bleeding that did not cause hemodynamic impairment. The lowest hematocrit level during hospitalization was recorded. The MACEs included nonfatal recurring myocardial infarction, revascularization of target vessels, severe heart failure, arrhythmia (frequent ventricular premature beats, ventricular tachycardia, atrioventricular block of degree II and above), cardiogenic shock, and all-cause death.

Statistical analysis

SPSS 22.0 software was used for the statistical analysis. Continuous variables were tested for normal distribution using Kolmogorov-Smirnov's test. Normally distributed data were presented as mean ± SD and were compared by Student's t-test. Non-normally distributed data were presented as a median (first quartile, third quartile) and compared by Mann-Whitney U-test. Categorical variables were reported as a percentage and compared using χ^2 or Fisher's exact test. The significance level was set at $P<0.05$.

Results

Comparison of the baseline data between the two groups

The baseline data of the two groups included sex, age, underlying diseases, the number of lesions, and TIMI blood flow grading. There was no statistically significant difference in the demographic data between the groups ($P>0.05$, **Table 1**). There were differences in the number of left circumflex artery infarcts, but no differences in other arteries.

Comparison of the postoperative TIMI blood flow classification between the two groups

There was no statistically significant difference between the two groups in terms of the postoperative TIMI blood flow classification ($P>0.05$) (**Table 2**).

Comparison of the cardiac function indices between the two groups at 30 days after surgery

The ejection fraction (EF) of the two groups of patients was detected by ultrasonic cardiogram 30 days after surgery. The results showed that the LVEF of the PCI group was higher than that of the intracoronary thrombolysis group 30 days after surgery, but the difference between the two groups was not statistically significant ($P>0.05$) (**Table 3** and **Figure 1**).

Comparison of the incidence of bleeding events and MACEs between the two groups

There was no statistically significant difference in the incidence of MACEs 30 days postopera-

Table 1. Baseline clinical characteristics

	Intracoronary thrombolysis group (n=75)	PCI group (n=73)	χ^2/t	*P*
gender			0.945	0.331
Male (n)	50	54		
Female (n)	25	19		
Age (years)	65±12.4	64±12	0.404	0.687
Risk factors				
Hypertension (n (%))	44 (58.7%)	32 (43.8%)	3.257	0.071
Diabetes mellitus (n (%))	26 (34.7%)	17 (23.3%)	2.324	0.127
Risk factors				
LAD (n (%))	37 (49.3%)	34 (46.6%)	0.113	0.737
LCX (n (%))	28 (37.3%)	9 (12.3%)	12.336	0.0004
RCA (n (%))	43 (57.3%)	35 (47.9%)	1.308	0.253

LAD, left anterior descending branch; LCX, left circumflex; RCA, right coronary artery.

Table 2. Comparison of immediate TIMI blood flow grade between the two groups (n (%))

	Intracoronary thrombolysis group (n=75)	PCI group (n=73)	χ^2	*P*
TIMI flow grade			3.799	0.294
0	2 (2.7%)	2 (2.7%)		
1	0	2 (2.7%)		
2	4 (5.3%)	8 (11%)		
3	69 (92%)	61 (83.6%)		

TIMI, thrombolysis in myocardial infarction.

Table 3. Comparison of postoperative cardiac function indexes between the two groups

	Intracoronary thrombolysis group (n=75)	PCI group (n=73)	*t*	*P*
EF (%)	57±11.218	59.32±8.13	-1.09	0.279

EF, ejection fraction.

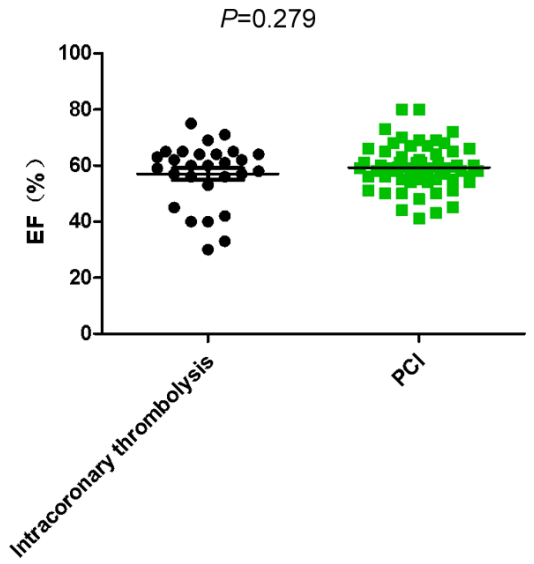

Figure 1. Comparison of cardiac function between the two groups at 30 days postoperatively, *P*>0.05, no statistical significance.

tively between the two groups (P>0.05) (**Tables 4**, **5**). However, the PCI group had more cardiogenic shock than the intracoronary thrombolysis group, and the difference was statistically significant.

Discussion

Emergency PCI and intravenous thrombolysis are the main treatment strategies for acute STEMI patients [20]. Improving the efficacy and safety of PCI and thrombolysis in STEMI patients has always been an important concern in clinical practice. Trials administering prourokinase to patients with myocardial infarction, including those with STEMI, have shown that prourokinase primarily acts on the fibrin of the thrombus and has good efficacy and safety [21, 22]. This study found that an intracoronary injection of recombinant human prourokinase through a microcatheter in the target vessel resulted in a recanalization rate of 97.3%

Table 4. Comparison of the incidence of short-term bleeding events between the two groups (n (%))

	Intracoronary thrombolysis group (n=75)	PCI group (n=73)	χ^2	*P*
bleeding events			4.574	0.116
mild	6 (8%)	1 (1.4%)		
moderate	0	0		
fatal	0	1 (1.4%)		

Table 5. Comparison of the incidence of short-term MACEs between the two groups (n (%))

	Intracoronary thrombolysis group (n=75)	PCI group (n=73)	χ^2	*P*
MACEs			1.715	0.19
Cardiogenic shock	0	4 (5.5%)		
Arrhythmia	20 (26.7%)	19 (26%)		
Heart failure	8 (10.7%)	13 (17.8%)		
death	4 (5.3%)	3 (4.1%)		

MACEs: Major Adverse Cardiovascular Events.

and a bleeding rate of 8%, and none of the patients experienced a major bleeding event. The 90-minute recanalization rate of intravenous thrombolysis was 53% for urokinase, 85% for recombinant human prourokinase (Puyoke), 79% for alteplase, 83% for reteplase, and 82% for tenecteplase [23]. Regarding the bleeding rate, there have been differences in the results of different clinical trials. A large sample study found that the bleeding rate associated with the use of urokinase was 10%-15%, and the bleeding rate of cerebral hemorrhage was 1%-2% [24]. A small research project conducted in China showed that the rate of cerebral hemorrhage associated with intravenous thrombolysis with reteplase was 0.9% [25, 26]. Therefore, targeted intracoronary injection of recombinant human prourokinase through a microcatheter increases the local drug concentration of the thrombus, increases the contact area between the drug and the thrombus, improves the recanalization of blood vessels, reduces the systemic dosage that patients receive, and reduces the risk of systemic bleeding [27].

PCI is the safest and most effective treatment of choice for acute STEMI patients, but the degree of reversibility and extent of myocardial necrosis are both time dependent [28]. Because of the vast area of China, some districts and counties with a relative lack of medical resources cannot meet the equipment and technical requirements needed to perform this technique; some patients are resistant to proceeding with stenting due to the lack of medical knowledge; patients with STEMI combined with heart failure cannot tolerate prolonged surgery; and transferring patients for PCI takes a long time, and the optimal window for saving the heart muscle may be missed. Similarly, in a study of more than 20 countries, only approximately 32% of all patients who were treated with reperfusion underwent primary PCI [29]. Historical data from the US National Registry of Myocardial Infarction databases showed that only 4.2% of STEMI patients requiring referral for PCI had a total door-to-balloon time less than 90 minutes and 16.2% less than 120 minutes [30, 31]. Therefore, PCI is not yet widely performed in China and in other countries, and thrombolytic therapy, which has the same effect as PCI, is selected when patients do not have any contraindications, especially for patients with thrombolysis with an onset time of <3 hours. However, intravenous thrombolysis has a high risk of bleeding and is not adequately targeted. The local administration of thrombolytic drugs through a microcatheter into a target coronary artery not only meets the effectiveness needed for vascular recanalization but also reduces the risk of systemic hemorrhage, especially fatal hemorrhage [32].

Agents have been administered through multiple catheters, such as guide [33], aspiration [34-36] and dedicated [37, 38] catheters. A large abciximab intracoronary versus intravenous drug administration (AIDA) trial of 2,065 patients found that intracoronary abciximab had a 52% recanalization rate and may be associated with a reduction in congestive heart failure. However, this route of administration

had no clinical benefit on the composite endpoint of death, reinfarction, or congestive heart failure [39]. The intracoronary abciximab and aspiration thrombectomy for ST-segment elevation myocardial infarction (INFUSE-AMI) trial randomized 452 patients undergoing PCI with bivalirudin to the intracoronary abciximab group versus the no abciximab administration group. Intracoronary abciximab reduced the 30-day infarct size but did not improve the abnormal wall motion score, as assessed by magnetic resonance imaging [40].

This study evaluated the efficacy and safety of two different treatment options for acute STEMI (targeted intracoronary thrombolysis via a microcatheter and emergency PCI) in a multicenter clinical study. We show that targeted intracoronary thrombolysis via a microcatheter is feasible for STEMI patients and can be used as an alternative to emergency PCI. The findings of the study are as follows: 1) a targeted intracoronary injection of recombinant human pro-urokinase through a microcatheter showed no significant difference in vascular recanalization or the improvement in cardiac function; and 2) there was no difference between the two groups in the incidence of short-term bleeding events and MACEs. However, the severe bleeding rate was 1.4% in the PCI group, and there was no severe bleeding in the intracoronary thrombolysis group. The incidence of cardiogenic shock was higher in the PCI group, and the difference was statistically significant. The results of this study showed that intracoronary thrombolysis does not increase the risk of bleeding and MACEs and has good efficacy and safety, and the therapeutic effect is comparable to that of emergency PCI. Therefore, intracoronary thrombolysis has the potential to be widely used in areas where emergency PCI is not available. However, the study sample size was small, the follow-up time was short, and the content was not comprehensive. A multicenter, prospective, large sample study with a high degree of matching between the control and experimental groups needs to be carried out.

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Disclosure of conflict of interest

None.

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