Safety and efficacy study of prourokinase injection during primary percutaneous coronary intervention in acute ST-segment elevation myocardial infarction

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Objectives **To evaluate the efficacy and safety of intracoronary administration of prourokinase via balloon catheter during primary percutaneous coronary interventions in patients with acute ST-segment elevation myocardial infarction.**

Methods **Acute ST-segment elevation myocardial infarction patients underwent primary percutaneous coronary interventions were randomly divided into two groups: intracoronary prourokinase group (n = 125) and control group (n = 135). During primary percutaneous coronary interventions, prourokinase or saline was injected to the distal end of the culprit lesion via balloon catheter after balloon catheter dilatation. Demographic and clinical characteristics, infarct size, myocardial reperfusion, and cardiac functions were evaluated and compared between two groups. Hemorrhagic complications and major averse cardiovascular events (MACE) occurred in the 6-months follow-up were recorded.**

Results **No significant differences were observed between two groups with respect to baseline demographic, clinical, and thrombolysis in myocardial infarction grade ($P > 0.05$). In the intracoronary prourokinase group, more patients had ST-segment resolution (>50%) compared with control group ($P < 0.05$). Patients in the intracoronary prourokinase group showed lower levels of serum CK, creatine kinase-MB fraction, and troponin I than those in control group ($P < 0.05$). No significant differences in bleeding complications were observed between the two groups ($P > 0.05$). At 6-months follow-up, there was no statistically different of MACE between the two groups ($P > 0.05$).**

Conclusions **Intracoronary administration of prourokinase via balloon catheter during primary percutaneous coronary interventions effectively improved myocardial perfusion and no increased bleeding in ST-segment elevation myocardial infarction patients.**
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Introduction

Acute ST-elevation myocardial infarction (STEMI) is a common cause of morbidity and mortality worldwide[1], which usually results from occlusive thrombus formation following coronary plaque rupture. Now primary percutaneous coronary intervention (PCI) remains the best reperfusion therapy which can successfully improve the survival and reduce combined clinical endpoints in the treatment of STEMI. However, some STEMI patients will suffer severe cardiovascular complications and adverse clinical prognosis even with thrombolysis in myocardial infarction (TIMI) 3 blood flow in epicardial coronary artery. It has been estimated that no/slow reflow events might occur during primary PCI for STEMI. During the process of PCI, thrombus and vascular debris may embolize and cause plugging of the microvasculature and eventually lead to myocardial necrosis. It was reported that despite the restoration of a good epicardial flow with PCI, myocardial perfusion at the cellular level remains impaired in nearly 50% of STEMI patients [1], which may attribute to the embolization of the coronary thrombus into the distal vasculature, producing microvascular plugging, vasospasm, interstitial edema, and cellular injury [2]. It is needful to identify effective and safe strategies to improve myocardial perfusion after primary PCI. Recombinant human prourokinase is a fibrin-specific plasminogen activator that has structural similarities to tissue-plasminogen activator but has a different mechanism of action [3]. In this study, we aimed to investigate the efficacy and safety of intracoronary administration of prourokinase on myocardial reperfusion in STEMI patients undergoing primary PCI.

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Methods

We conducted a single-center prospective randomized clinical trial on STEMI patients undergoing primary PCI in Shenzhen Yantian People's Hospital from July 2017 to December 2019. This study has been registered at Shenzhen City Health Commission (SZXJ2018009) and Shenzhen Yantian District Science and Technology Bureau (20170202). This study has been supported by Hu Dayi Three Engineering. This study was approved by the ethics committee of Shenzhen Yantian People's Hospital and was conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from each subject.

Patient enrollment

From July 2017 to December 2019, consecutive patients (aged 18–75 years) presented with STEMI within 12 hours of symptom onset undergoing primary PCI were enrolled. Exclusion criteria were history of intracranial hemorrhage; ischemic cerebral stroke within 3 months; suspicion of aortic dissection; active hemorrhage or hemorrhagic risk (including menstruation); severe or uncontrolled hypertension (≥180/110 mmHg); severe trauma; major operation within 3 weeks; vascular puncture that could not be controlled by compression; malignant tumor; severe hepatic or renal dysfunction; pregnancy or lactation; allergy to or contraindication of prourokinase; post coronary artery bypass graft status; participating in other clinical trials simultaneously.

Study protocol and measures

All patients with STEMI as candidates for primary PCI were given 300 mg aspirin and 180 mg ticagrelor before coronary angiography. By using a computer-generated random-allocation system, patients eligible for the study were randomized into two groups: intracoronary prourokinase (IP) group (n=125), in which an additional bolus of prourokinase (10 mg diluted in 10 mL of saline within 3 minutes; Shanghai Tasly Pharmaceutical Co, Ltd.) was administered directly through the balloon catheter to the distal end of the culprit lesion; control group (n=135), in which saline (10 ml within 3 minutes) was administered by the same way. Coronary angiography and PCI were performed via radial or femoral access route using a 6F arterial sheath. After the access, 3000 U of heparin was injected through the sheath. Coronary angiography was performed using a 5F TIG multi-functional angiographic catheter. ECG and invasive blood pressure were continuously monitored during the operation. For PCI, total heparin (100 U/kg) was routinely given through arterial sheath, a guiding catheter was deployed at the ostium of coronary artery, and the guidewire was delivered to the distal segment of occlusive coronary artery. A balloon catheter was sent to the lesion, and the balloon was inflated. Then the balloon was withdrawn, and the balloon membrane was punctured with a needle to get a micropore. The punctured balloon was sent to the distal end of occlusive artery, and prourokinase (10 mg dissolved in 10 mL of saline, and injected within 3 minutes) or saline (10 mL, injected within 3 minutes) was gradually injected through the balloon. During the injection, changes of blood pressure and heart rate/rhythm were closely observed. After the injection, coronary angiography was performed, and stent was implanted if there was more than 75% residual stenosis. After the procedure, all patients were given a maintenance dosage of 100 mg aspirin daily and 90 mg ticagrelor twice a day. Other medications like statins, β-receptor blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, glycoprotein IIb/IIIa inhibitor, unfractionated heparin were applied according to guideline recommendations, if not contraindicated. The patients were given oxygen inhalation after the operation, and standard monitors of blood pressure, ECG, and blood oxygen saturation were applied.

Angiographic analysis

Coronary angiography of the target lesion was performed before and after primary PCI at the identical projections, which allowed optimal evaluation of the TIMI flow grades of the infarct related artery (IRA). Visual assessment was made by the same interventional cardiologists. TIMI grading criteria are described in Table 1.

Myocardial marker analysis and ST-segment resolution

Blood samples were obtained from each patient at 6, 12, 18, and 24 hours after the completion of PCI. Serum concentration of creatine kinase (CK) and creatine kinase-MB fraction (CK-MB) were measured by Vitros analyzer (Johnson and Johnson, Rochester, NY) using standard protocols by the manufacturer. Cardiac troponin I (TnI) was measured using a Biosite Triage (r) meter (Biosite Inc., San Diego, CA). Peak levels of CK, CK-MB, and TnI were used to estimate infarct size. The 12-lead ECG recorded the changes of ST segment 2 hours after PCI and at onset. The reduction rate of ST segment was used as an indicator, and the reduction of more than 50% was considered as myocardial reperfusion after PCI.

Cardiac functions

Indicators of cardiac functions, such as left ventricular ejection fraction (LVEF) and left ventricular end-diastolic dimension (LVEDd), were measured by echocardiography and recorded 1, 4, and 24 weeks after PCI.

Follow-up

Follow-up was completed by an interview of patients in cardiac clinic or by telephone conversation with patients

Table 1 Thrombolysis in myocardial infarction grading criteria

Level	Evaluation criteria
Level 0	No more than the anterior flow at the occlusion
Level I	Slightly more than the anterior flow of the occlusion
Level II	Slow or delayed forward flow can completely fill the distal vascular
Level III	The forward flow is normal, filling the distal vascular bed completely

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every 8 weeks after discharge and continued for 24 weeks. major adverse cardiovascular events (MACE), including stent thrombosis, recurrent myocardial infarction, congestive heart failure, post-infarction angina pectoris, and cardiac death, was recorded at 24 weeks. Hemorrhagic complications, including cerebral hemorrhage, gastrointestinal hemorrhage, urologic hemorrhage, hemoptysis, and oral bleeding, were recorded at 24 weeks.

Statistical analysis

Before the launch of this study, sample size was calculated. The MACE incidence was assumed to be 20% in control group and 10% in IP group within 24 weeks, the values of power (1-β) and significance level α (two-sided) were set as 80% and 0.05, it was calculated that 108 subjects were needed for each group. Considering the loss of follow-up of 5%, each group would need more than 114 patients. SPSS19.0 software (SPSS, Chicago, IL) was used for statistical analysis. The continuous variables with normal distributions were presented as means±SD, continuous variables with non-normal distribution were presented as median and interquartile range. The categorical variables were presented as absolute values and percentages. Comparisons between two groups were performed by Student's *t*-test for normally distributed values or Mann–Whitney *U* test for non-normally distributed values. Categorical variables were compared using the chi-square test or Fisher's exact test. $P < 0.05$ (2-tailed) was considered as statistically significant.

Table 2 Demographic, clinical, and angiographic characteristics of the subjects

Variables	IP group (n = 125)	Control group (n = 135)	*P* value
Age (years)	53.87 ± 6.61	55.08 ± 6.77	0.147
Male (n [%])	77	88	0.549
Hypertension (n [%])	62	69	0.808
Diabetes (n [%])	32	35	0.952
Hyperlipidemia [n (%)]	39	44	0.810
Smoking (n [%])	69	77	0.766
Killip (n [%])			0.693
I	65	74	
II	40	35	
III	17	21	
IV	3	5	
Time from symptom onset to balloon dilatation (h)	5.10 ± 1.40	4.78 ± 1.33	0.057
Post-PCI TIMI grade [n (%)]			0.359
0	0	0	
1	0	1	
2	2	5	
3	123	130	
No/slow reflow after PCI (n [%])	2	6	0.284
Number of implanted stents [n (%)]			0.434
PTCA	10	11	
1-stent	103	104	
2-stent	12	20	
Infarction related artery (n [%])			0.957
LM	2	2	
LAD	66	69	
LCX	13	17	
RCA	44	47	
Applied IABP (n [%])	7	7	0.882
Temporary pacemaker (n [%])	5	5	0.901
Applied aspiration catheter (n [%])	10	8	0.510

IP, intracoronary prourokinase; IABP, intra-aortic balloon pump; LCX, left circumflex artery; LM, left main stem; PTCA, percutaneous transluminal coronary angioplasty; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

Results

Baseline demographic, clinical, and angiographic characteristics

In total, 260 enrolled STEMI patients completed this study with 125 patients in IP group and 135 patients in control group. Demographic, clinical, and angiographic characteristics of the subjects at baseline are described in Table 2. No significant differences were observed between two groups with respect to baseline demographic, clinical, and angiographic characteristics ($P > 0.05$).

Cardiac markers and myocardial reperfusion

Infarct size was estimated by cardiac markers, including serum CK, CK-MB, and TnI. Peak levels of serum CK, CK-MB, and TnI were significantly lower in the IP group than in the control group ($P < 0.05$) (Table 3). Myocardial reperfusion was estimated by the rates of ST-segment resolution, and results showed that in IP group, more patients had ST-segment resolution (>50%) compared with control group ($P < 0.05$) (Table 3).

Cardiac functions

The values of LVEF and LVEDd, 1, 4, and 24 weeks after PCI were measured to estimate the cardiac functions. At 1, 4, and 24 weeks after the PCI, the values of LVEF and LVEDd were all much better in IP group than in the control group ($P < 0.05$) (Table 4).

Hemorrhagic complications and MACE during the follow-up

During the follow-up, no intracranial hemorrhage was found in both groups. The numbers of bleeding complications in two groups were listed in Table 5. There were nine bleeding complications (including 2 gastrointestinal

Table 3 Markers of infarct size and myocardial reperfusion

Variables	IP group (n = 125)	Control group (n = 135)	*P* value
CK peak value (U/L)	2797.03 ± 631.69	3063.91 ± 984.98	0.010
CK-MB peak value (U/L)	349.19 ± 78.17	370.73 ± 73.42	0.023
TnI peak value (ng/L)	22.88 ± 5.42	24.30 ± 6.00	0.038
ST-segment resolution (>50%)	114	109	0.016

Decline rate of ST segment, subtracting ST elevation of infarction related artery from that before operation, and then dividing the ST-elevation before operation.
CK, creatine kinase; CK-MB, creatine kinase isoenzyme-MB; IP, intracoronary prourokinase; TnI, troponin I.

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Table 4 Indicators of cardiac functions

Variables	IP group (n = 125)	Control group (n = 135)	*P* value
7-day LVEF (%)	54.34 ± 5.72	52.68 ± 5.75	0.021
7-day LVEDd (cm)	4.91 ± 0.34	5.03 ± 0.42	0.008
1-month LVEF (%)	56.99 ± 6.06	54.90 ± 5.57	0.004
1-month LVEDd (cm)	4.87 ± 0.39	5.04 ± 0.47	0.002
6-month LVEF (%)	57.44 ± 5.36	55.79 ± 5.49	0.015
6-month LVEDd (cm)	4.83 ± 0.39	4.94 ± 0.44	0.032
6 minutes walking test(m)	485.63 ± 34.89	472.25 ± 43.06	0.007

IP, intracoronary prourokinase; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

Table 5 Hemorrhagic complications and MACE events during the follow-up

Variables	IP group (n = 125)	Control group (n = 135)	*P* value
Hemorrhagic complications (n [%])	9	8	0.678
Cerebral hemorrhage	0	0	
Gastrointestinal hemorrhage	2	1	
Urologic hemorrhage	2	2	
Hemoptysis	1	0	
Oral bleeding	4	5	
MACE 6 months after PCI (n [%])	8	13	0.340
Stent thrombosis	0	1	
Reinfarction	1	2	
Congestive heart failure	4	5	
Angina pectoris	3	4	
Cardiac death	0	1	

MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention.

hemorrhage, 2 urologic hemorrhage, 1 hemoptysis, and 4 oral bleeding) in IP group and 8 bleeding complications (including 1 gastrointestinal hemorrhage, 2 urologic hemorrhages, 0 hemoptysis, and 5 oral bleeding) in control group. All bleeding complications, no significant differences were observed between the two groups ($P > 0.05$). At 24 weeks, there was no difference in MACE rate between the two groups ($P > 0.05$).

Discussion

In STEMI, one of the most severe and critical cardiovascular emergencies, opening the IRA without delay to rescue surviving myocardium is the most important principle in therapeutics. Primary PCI can effectively dredge the infarcted coronary arteries and has been selected as the first-line treatment strategy for the clinical management of STEMI [4]. The recent investigation based on large samples inferred that primary PCI could establish blood flow in >90% IRA and restore TIMI to level 3, which reduced the mortality rate of acute myocardial infarction to as low as 3% to 4% [4]. However, the efficacy of primary PCI is counteracted with some severe side effects such as slow flow/no flow induced by I/R injuries. Slow flow/no flow is one of the risk factors influencing the prognosis of STEMI patients. Previous reports indicated that about 30%–50% STEMI patients cannot achieve effective myocardial reperfusion after PCI, even those with TIMI 3 blood flow [5,6]. Insufficient myocardial perfusion is associated with decreased myocardial salvage, increased left ventricular remodeling, and worse clinical outcomes. The mechanisms of no reflow may include cardiomyocyte edema; endothelial dysfunction; activation of exogenous coagulation; leukocyte aggregation; inflammatory reactions induced by oxygen radicals and inflammatory cytokines released from leukocytes; intraoperative use of devices including balloon and stent which may damage vascular endothelia and activate platelets; activation of platelets and complements; microembolus composed of thrombosis segment, dropped unstable plaque, and aggregated platelets [7–10]. Insufficient myocardial perfusion will lead to myocyte necrosis, expand myocardial infarct size, damage cardiac functions, result in malignant arrhythmia, increase incidence of MACE, and finally affect salvage quality of primary PCI. Gibson *et al.* [11] pointed out that insufficient myocardial perfusion is a risk factor of sudden cardiac death. Therefore, effective improvement of myocardial perfusion is a critical question in primary PCI. To improve the treatment outcomes of primary PCI, some agents, such as tirofiban and prourokinase, are being applied to ameliorate the coronary blood flow after primary PCI.

In this study, we aimed to improve myocardial perfusion by delivering prourokinase into the remote end of coronary lesion, placement of the catheter just proximal to the lesion would be essential, as drug may be significantly diluted due to the combined effects of pulsatility, vessel wall anomalies, and the multiphasic nature of blood flow [12]. The safety and cost of drug delivery were also important factors we concerned. We developed a simple, effective, and low-cost method to deliver prourokinase via a punctured balloon after the inflation of the balloon was finished. After the injection of prourokinase, the balloon was washed with saline to minimize drug residue.

Myocardial perfusion and cardiac functions were analyzed to evaluate the efficacy of prourokinase. Peak values of CK and CK-MB are closely related with infarction area [13]. In our study, peak values of myocardial enzymes in IP group were obviously lower than that in control group, suggesting that IP can reduce myocardial infarction area. Early resolution of ST segment in infarction related lead of ECG is a good indicator of effective myocardial reperfusion [14]. In this study, the amplitude of ST-segment elevation was declined immediately after primary PCI in both groups, however, in the IP group, more patients had ST-segment resolution (>50%) compared with control group, suggesting that IP could effectively improve myocardial reperfusion. With the improvement in myocardial reperfusion in IP group, the patients also showed better cardiac functions indicated by the values of LVEF and LVEDd. The myocardial function of the patients was also evaluated with ECG, and it was found that the change of ST-segment decline ratio in IP group was larger than that of control group. Previous study showed that the recovery of myocardial ischemia injuries was in positive relation

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to the restoration of sum-STR [11]. Combined with the larger change in LVEF in IP group, it was evident that prourokinase could also improve the myocardial function. Additionally, the current study also performed a 24 weeks follow-up after all the patients discharged from the hospital and the results showed that no significant difference was detected regarding parameters of hemorrhagic complications and MACE between the 2 groups, the results were representative of the safety of the application of prourokinase in clinic.

We assumed that prourokinase administration via balloon to the remote end of lesion during the primary PCI could increase local drug concentration at the thrombotic lesion, exert local thrombolytic effect, increase microcirculation, reduce the area of myocardial necrosis, improve cardiac function and might reduce hemorrhagic risks. In some of our cases, we even directly stabbed into the core area of thrombosis and performed a thrombolysis, resulting in rapid and effective disintegration and 'melting' of the heavy thrombus load. Intracoronary targeted injection can ablate not only the gross thrombosis in epicardial vessels but the thrombolytic particles can also readily reach the most microscopic parts of the structure of the coronary circulatory system, and then utterly melt down all micro thrombosis and debris. This characteristic may eventually achieve a permeating clearance to the thrombosis, extending from the conductive vessels to the arteriolar vessels. We chose prourokinase as our intracoronary thrombolytic medicine. Compared with the older generation thrombolytics, like urokinase and streptokinase, it does not conjugate with plasma prothrombin, which avoids the dose waste before contact with the thrombosis, and refrains from stimulating the coagulatory system to produce additional thrombus before performing its antithrombotic effect, as well as reducing the incident rate of bleeding events. Therefore, we selected this drug for its more effective thrombus ablation and higher safety profile.

In this study, there is less myocardial necrosis in IP group. At 6 months follow-up, the IP group had a less chance to have MACE events, although it was not statistically different. The lack of statistical difference in the outcome could probably due to the insufficient sample size. Before the launch of this study, sample size was estimated based on previous studies on early coronary intervention after thrombolysis in acute myocardial infarction (such as NORwegian study on DIstrict treatment of ST-Elevation Myocardial Infarction study [15], routine early angioplasty after fibrinolysis for acute myocardial infarction [16], long-term follow-up of early versus delayed invasive approach after fibrinolysis in acute myocardial infarction [17]) combined with experiences in our center, the MACE incidence was assumed to be 20% in control group and 10% in prourokinase group at 6 months. However, the actual results proved that it was an over-optimistic estimation as out of the 20% expected events at 6 months in the control group only 12.5% occurred. Studies with larger sample size are needed to verify the results, and our work may provide some experiences on sample size estimation and power calculation. Besides the insufficient sample size, there are other limitations that can be improved in any future study. In our work, all the patients in the IP group were given 10 mg prourokinase via the balloon catheter during primary PCI, which could significantly improve myocardial reperfusion. Take into consideration that different dosage and administration route of the drug may influence the efficacy and safety, future studies are needed to explore the most ideal dosage and route of prourokinase administration.

Conclusion

Prourokinase injection during primary PCI administration can improve myocardial perfusion and cardiac function in acute STEMI patients without increasing incidence of hemorrhagic complications and MACE events.

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We would like to declare that all authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors agree with the manuscript.

Conflicts of interest

There are no conflicts of interest.

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