Efficacy and Safety of Thrombectomy Combined with Intracoronary Administration of Tirofiban in ST-segment Elevation Myocardial Infarction (STEMI)

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Source of support: Departmental sources

Background: No/slow reflow gives rise to serious complications in STEMI patients undergoing PCI, and can lead to worse outcomes. Several measures are used to prevent no/slow reflow, including thrombus removal processes and intensive use of anticoagulant agents. Our study was designed to evaluate the efficacy and safety of thrombectomy and intracoronary administration of GPIIb/IIIa inhibitors in STEMI patients undergoing PPCI.

Material/Methods: We randomly assigned 240 STEMI patients into 3 groups. Before PPCI, patients in group A received thrombectomy and intracoronary administration of tirofiban. Patients in group B received thrombectomy, and patients in group C neither of these 2 treatments. Their demographic data and coronary angiography results were recorded. TIMI grade flow was used to evaluate the effect. After the follow-up, major adverse cardiac events were regarded as study endpoints in evaluating the safety of the combined therapy.

Results: We found no significant differences among the 3 groups in demographic and clinical characteristics (p>0.05). Patients in group A had better TIMI grade classifications and ST-segment elevation (p=0.005), and lower incidence of no/slow reflow (p=0.031) and MACE. During 6-month follow-up, the MACE rate was lower in group A than in groups B and C (p=0.038).

Conclusions: The use of thrombectomy combined with intracoronary administration of tirofiban is relatively effective and safe in STEMI patients undergoing PPCI.

MeSH Keywords: Anticoagulants • Myocardial Infarction • No-Reflow Phenomenon • Thrombectomy

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/896703
Primary percutaneous coronary intervention (PPCI) has been proved to be the most effective treatment strategy to open the infarct-related artery in ST-segment elevation myocardial infarction (STEMI) patients [1]. STEMI usually leads to a serious thrombus burden in infarct-related arteries. During PPCI, the management of a thrombus lesion may lead to distal embolization, no-reflow, and slow-reflow, which are found in 20–40% of STEMI patients [2,3]. Distal embolization and thrombotic material with subsequent microvascular injury and flow impairment are associated with more extensive myocardial damage [4]. No-reflow is considered a dynamic process characterized by multiple pathogenetic components [5]. Compared to similar patients with adequate reflow, those with distal embolization, no-reflow, and slow-reflow have a higher incidence of death and heart failure and worse clinical prognosis [6].

To decrease the incidence of no/slow reflow, several measures have been recommended, including thrombus removal processes and intensive anticoagulant therapy [7]. The TAPAS study revealed thrombectomy can reduce thrombus burden in the culprit artery [8]. Adjunctive thrombectomy during primary PCI can increase myocardial reperfusion, reduce mortality, and improve the prognosis [9,10]. Unfortunately, the procedure cannot remove the thrombus completely [11]. Apart from oral dual-antiplatelet therapy, the intravenous administration of glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors has also been shown to be effective in reducing thrombus burden and preventing platelet re-accumulation [1,12]. Intracoronary (IC) administration of GPIIb/IIIa inhibitors may also have benefits for patients with serious thrombus burden. However, the effect of GP IIb/IIIa inhibition combined with thrombectomy could not be determined based on the currently available data. Given these considerations, we were interested in the effect of thrombectomy plus IC administration of tirofiban in PPCI. The present study was designed to evaluate the efficacy and safety of this combined treatment in STEMI patients undergoing PPCI.

Material and Methods

Patient population

From September 2013 to February 2015 a total of 240 patients diagnosed with STEMI for the first time and treated with emergency PPCI were enrolled in this study. All the patients were randomly assigned to 1 of 3 groups: Group A received thrombectomy combined with intracoronary injection of tirofiban before PPCI; Group B received thrombectomy before PPCI; and group C received PPCI only. Balloon dilatation was done as necessary in all 3 groups. All the participants were encoded using a random coding table composed of the letters A, B, and C. Patients who had a confirmed diagnosis of STEMI and received emergency PPCI were eligible to participate in this study if: 1) the age was 18–80 years; 2) the patients were able to understand the study content and provide consent; and 3) the patients were willing to accept the necessary follow-up, therapy, and laboratory examinations. The exclusion criteria were: 1) patients diagnosed as having non-ST elevation myocardial infarction; 2) patients with renal failure or severe liver disease; 3) patients with a life expectancy of ≤12 months; 4) pregnant and lactating women; 5) patients who were unable to understand the study content or to provide consent; and 6) patients who were currently participating in other medical studies. The diagnosis of STEMI was defined according to the World Health Organization definition of myocardial infarction (2008-09 revision) [13]. The criteria are: persistent chest pain suggestive of myocardial ischemia for at least 30 min; ST elevation >2 mm in ≥2 precordial leads, ST elevation >1 mm in ≥2 limb leads, or a new-onset left bundle branch block on electrocardiogram; and a concomitant increase in cardiac troponin T (cTnT) and creatine kinase (CK)-MB.

The institutional ethics committee of Tianjin Nankai Hospital approved the study and all the participants gave written informed consent.

Treatments

All the patients were treated with antiplatelet drugs before PPCI, including a loading dose of aspirin (300 mg) and clopidogrel (300 mg). Routine coronary angiography was performed to show the infarct-related artery (IRA) and thrombus burden lesions. Then, thrombectomy was carried out with a guiding catheter and thrombosis aspiration catheter. Aspiration was terminated when the thrombus disappeared or was reduced. After thrombectomy, the patients in group A received an intracoronary injection of tirofiban (Wuhan Grand Pharmaceutical Group, Wuhan, China). Patients in group B received only thrombectomy without intracoronary injection. In group C, patients received neither thrombectomy nor tirofiban intracoronary injection before stenting. Then, stenting and balloon dilatation, as necessary, were performed in all patients. Intravenous infusion of tirofiban was routinely maintained for 48 h. According to their individual conditions, patients were treated with dual-antiplatelet therapy, statin, and anti-remodelling therapy during hospitalization.

Data source and follow-up

Demographic data and risk factors for coronary heart disease (aging, sex, hypertension, smoking, diabetes mellitus, and hyperlipidemia) were documented. Echocardiographic findings, especially left ventricular ejection fraction (LVEF), were collected to evaluate cardiac function. The Killip classes and the peak
level of cardiomyocyte injury markers were tested to judge the severity of infarction. Coronary angiography data were recorded, including the door-to-balloon time, infarcted artery, balloon dilatation, coronary lesions, and the Thrombolysis in Myocardial Infarction Trial (TIMI) grade before and after PCI. In addition, no/slow reflow phenomenon was regarded as an endpoint to evaluate the efficacy of combined treatment. An electrocardiogram (ECG) was taken before and 90 min after angiography to calculate the ST-segment resolution (STR). During hospitalization, we focused on Major Adverse Cardiovascular Events (MACE) to assess the cardiovascular risk. Bleeding complications were recorded to analyze the risk of hemorrhage. All the patients were followed up for 6 months after discharge. Echocardiography was performed again to compare the cardiac function. The incidence of MACE was collected as the most important endpoint in our study.

**Definitions**

TIMI flow is defined as follows: TIMI 0 flow (no perfusion) refers to the absence of any antegrade flow beyond a coronary occlusion. TIMI 1 flow (penetration without perfusion) is faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed. TIMI 2 flow (partial reperfusion) is delayed or sluggish antegrade flow with complete filling of the distal territory. TIMI 3 is normal flow which fills the distal coronary bed completely. MACE consisted of a composite of: 1) cardiac death; 2) a recurrent nonfatal myocardial infarction; and 3) clinically driven target lesion revascularization (TLR) or target vessel revascularization (TVR). No-reflow was defined as the final TIMI grade 0 and slow-reflow was defined as grade 1 and 2. The degree of elevation and resolution were calculated for all patients. STR was classified as: 1) complete STR (CR): ≥70% resolution; 2) partial STR (PR): ≥30% but <70% resolution; or 3) no STR (NR): <30% resolution.

**Statistical analysis**

Results are expressed as mean ± standard deviation (SD) for continuous variables and frequencies for categorical variables. Differences among groups were examined by nonparametric test and chi-square test for continuous and categorical variables, respectively. An alpha value of 0.05, corresponding to a
**Results**

All 240 patients completed the treatment and received a period of follow-up. The mean age of the 240 enrolled patients was 63.37±8.35 years. There were 111 males and 129 females. The data analysis for demographic comparison, including those related to complications among groups, showed no significant difference (Table 1). Due to the effects of β-blockers and ACEI/ARBs on the protection of cardiac structure and function, we also recorded the service condition for further analysis. Compared with group C, the differences between the usages of β-blockers and ACEI/ARBs were not significant (p>0.05). In addition, the Killip classes were also recorded to compare participant cardiac function. Results showed no significant differences in the grades (Table 1). During the hospital stay, we measured the serum level of troponin I and creatine kinase MB at different time-points and recorded the peak level to

|                | Group A (n=80) | Group B (n=80) | Group C (n=80) | P value |
|----------------|---------------|---------------|---------------|---------|
| **Multivessel lesions (%,** | 42            | 36            | 32            | 0.625   |
| **Infarcted-related artery** |               |               |               |         |
| LM             | 0             | 0             | 0             | –       |
| LAD            | 38            | 30            | 31            | 0.671   |
| LCX            | 16            | 18            | 12            | 0.597   |
| RCA            | 36            | 32            | 37            | 0.869   |
| **Door-to-balloon time (h)** | 1.9±0.3       | 1.8±0.5       | 2.0±0.8       | 0.532   |
| **Onset-to-balloon time (h)** | 6.7±0.8       | 5.0±1.0       | 5.5±0.9       | 0.756   |
| Preprocedural TIMI-grade flow (n) |               |               |               |         |
| 0              | 52            | 46            | 40            | 0.608   |
| 1              | 23            | 28            | 32            | 0.577   |
| 2              | 5             | 6             | 8             | 0.712   |
| 3              | 0             | 0             | 0             |         |
| Balloon dilatation (n) | 71            | 74            | 76            | 0.956   |
| Postprocedural TIMI-grade flow (n) |               |               |               |         |
| 0              | 0             | 1             | 2             | 0.101   |
| 1              | 1             | 1             | 5             | 0.112   |
| 2              | 1             | 2             | 5             | 0.211   |
| 3              | 78            | 76            | 67            | 0.791   |
| **ST-segment resolution (n)** |               |               |               |         |
| CR             | 70            | 68            | 48            | 0.242   |
| PR             | 8             | 8             | 24            | 0.005** |
| NR             | 2             | 4             | 8             | 0.154   |
| No-reflow (%,** | 0.0 (0)       | 1.2 (1)       | 3.7 (3)       | 0.181   |
| Slow-reflow (%,** | 5.0 (2)**     | 3.7 (3)       | 28.7 (10)     | 0.031*  |

LM – left main coronary artery; LAD – left anterior descending; LCX – left circumflex artery; RCA – right coronary artery; CR – complete ST-segment resolution; PR – partial ST-segment resolution; NR – no ST-segment resolution. * p<0.05; ** p<0.01.

p value <0.05, served as the criterion for establishing statistical significance. Analysis was performed using SPSS for Windows (SPSS Inc., Version 19.0, Chicago, IL) and STATA (Version 12.0).
estimate the area and severity of infarction. Compared with groups B and C, the peak serum levels were a little higher in group A (p>0.05).

STEMI was confirmed by coronary angiography in all enrolled patients. Data on coronary lesions and the infarcted-related artery were recorded. Fortunately, no left main coronary artery lesion occurred in participants, and the distribution of lesions was equal in the 3 groups (Table 2). As important indicators in the rescue of STEMI, door-to-balloon time and onset-to-PCI time were noted. It was obvious that the differences in time were not significant in the 3 groups. However, we also found that the door-to-balloon time in our study was too long, according to the STEMI guideline. To exclude the effect of balloon dilatation, we compared the rate of balloon dilatation among groups. We found that almost all the patients received balloon dilatation before PCI, and the difference among the 3 groups was not significant (p=0.956). Preoperative and postoperative TIMI grade flow was calculated by the surgeons to evaluate the effect. According to the CAG results, the number of patients with TIMI grade 0 was higher in group A and group B before PCI, but the result was not significantly different from group C (p>0.05). However, the rates of TIMI grade 3 in group A and B after PCI were higher than the rate in group C (97.5% and 95.0% vs. 83.7%). We also compared the incidence of no-reflow and slow-reflow. Although the difference in no-reflow was not significant among groups, the incidences of slow-reflow in group A and B were significantly different from group C (p=0.031). Next, we measured the ST-segment elevation before and after PCI. Before the operation, the elevation of ST-segment was similar in the 3 groups. STR was calculated according to the degree of elevation. The differences in CR and NR were not significantly different from group C, but the difference in PR was obvious (p=0.005) Table 2. Although the advantage was not significant, the result also demonstrated the efficacy of our treatments. As one of the most important endpoints, we also recorded whether MACE occurred in patients before discharge. There were no major adverse cardiovascular events in group A, only 1 cardiac death in group B, but there were 3 adverse events in group C. Bleeding complications were not significantly different among the 3 groups (Table 2). There was 1 hemorrhagia and stool OB in group A, 1 stool OB in group B, and no bleeding in group C. No massive hemorrhage (e.g., intracranial hemorrhage and hematemesis) occurred in our study.

In general, although the differences between group A and B were not significant, patients in group A had better postoperative TIMI grade flow and ST-segment resolution, and fewer major adverse cardiovascular events, and they had no major bleeding events.

All the patients were followed up for approximately 6 months after discharge. As with hospitalization, echocardiography was performed to assess cardiac function. LEVF within 16 h of PPCI in the combined therapy group was better than in the thrombectomy group (40.1±5.5% vs. 39.1±6.2%), but this tendency disappeared at the 6-month follow-up (47.9±4.3% vs. 47.4±5.3%). Table 3 clearly shows that the same happened in left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD). Compared with the echocardiography report after the operation, the improvements in LEVF were all notable. At the end of follow-up, we counted the incidence of MACE again. There was 1 (a recurrent infarction target lesion revascularization) in group A, 4 (2 cardiac deaths, 2 cardiac deaths, 1 cardiac death, and 1 hemorrhagia and stool OB) in group B, and 9 (3 cardiac deaths, 1 hemorrhagia and stool OB, 8 no bleeding) in group C. The difference in incidence of MACE again was significant (p=0.038*) between group A and group B.

Table 3. Echocardiography and endpoints.

|                  | Group A (n=80) | Group B (n=80) | Group C (n=80) | P value |
|------------------|---------------|---------------|---------------|---------|
| MACE             | 0             | 1             | 3             | 0.925   |
| Bleeding         | 2             | 1             | 0             | 0.668   |
| LVEF (%)         | 40.1±5.5      | 39.1±6.2      | 39.5±6.0      | 0.693   |
| LVESD (mm)       | 29.5±4.7      | 29.8±4.5      | 30.7±4.3      | 0.878   |
| LVEDD (mm)       | 46.5±4.7      | 48.1±4.7      | 47.4±4.3      | 0.914   |
| Follow-up        |               |               |               |         |
| MACE             | 1             | 4             | 9             | 0.038*  |
| LVEF (%)         | 47.9±4.3      | 47.4±5.3      | 46.1±5.1      | 0.867   |
| LVESD (mm)       | 25.7±4.7      | 26.4±4.4      | 26.9±3.9      | 0.656   |
| LVEDD (mm)       | 43.4±4.6      | 44.4±3.9      | 44.1±4.3      | 0.734   |

MACE – major adverse cardiovascular events; LVEF – left ventricular ejection fraction; LVESD – left ventricular end systolic diameter; LVEDD – left ventricular end diastolic diameter. * p<0.05.
Several studies have evaluated the feasibility of thrombectomy in STEMI. Postoperative TIMI grade flow can reflect the reperfusion level. Because of microvascular obstruction, poor reperfusion at the myocardial level still appears in some patients with sufficient forward flow. Microvascular obstruction arises from atheromatous and thrombotic embolization, neutrophil plugging, edema, or vasospasm [2]. Therefore, enhanced thrombus removal processes, like thrombectomy and intensive anticoagulant therapy, have been suggested as optional therapy during PCI to obtain better reperfusion in myocardial levels. The TAPAS study demonstrated that mechanical clot aspiration was associated with improved myocardial perfusion and lower mortality at 1 year [8]. Although the TOTAL study showed that, in patients with STEMI who were undergoing PCI, routine manual thrombectomy, as compared with PCI alone, did not reduce the risk of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or NYHA class IV heart failure within 180 days, but was associated with an increased rate of stroke within 30 days [14].

Intracoronary administration of GPIIb/IIIa inhibitors has been demonstrated to improve results in STEMI patients, supporting the advantage of intracoronary over intravenous administration in STEMI [15]. However, the efficacy of the intracoronary administration of tirofiban combined with thrombectomy is unknown. Theoretically, thrombectomy cannot aspirate the whole thrombus, and many small particles are left, even in arteries, which leads to distal microvascular embolization [11]. Highly localized intracoronary administration therapy can obviously increase the concentration in the peripheral artery and microcirculation. GPIIb/IIIa inhibitors have been proved effective in reducing thrombus burden and preventing platelet reaccumulation. Therefore, intracoronary administration of GPIIb/IIIa inhibitors may reduce the incidence of microvascular embolization caused by thrombectomy.

Several studies have evaluated the feasibility of thrombectomy combined with intracoronary administration of tirofiban. Zhou et al. showed that combined therapy could reduce the incidence of no-reflow after primary PCI [16]. Zhang et al. suggested that the combined therapy is associated with improved myocardial reperfusion without increasing bleeding complications or other adverse cardiovascular events [17]. Other studies also showed positive results [18]. In our study, patients in group A received intracoronary administration of tirofiban via aspiration catheter after thrombectomy. To demonstrate the efficacy of this combined therapy, we compared the incidence of no/slow reflow and MACE. Patients in group A had less no/slow reflow events than in the control group (p=0.031). In addition, results showed a notable difference in MACE at the end of follow-up (p=0.038). Although the other differences were small, the efficacy of combined therapy was superior to that in the control group. Broadly speaking, combined therapy is as effective as simple thrombectomy and has more advantages. A major clinical concern limiting the use of GP IIb/IIIa inhibitor is the increased bleeding risk, especially intracranial hemorrhage, hematemeses, and ecchymoses. We recorded no adverse bleeding events in our study, which demonstrates the safety of added intracoronary administration of tirofiban. In summary, the results of the present study demonstrate that intracoronary administration of tirofiban may augment thrombectomy therapy, and the combined therapy has a relatively good safety and efficacy profile in STEMI patients undergoing PCI.

Several limitations of this study must be mentioned. The sample size was small and the follow-up time was relatively short, which may have influenced the evaluation of long-term prognosis. Although the surgeons were all experienced, the influence of surgeon skill should be taken into account. We also need to refine the monitoring of microvascular perfusion. Although TIMI grade flow and STR are used to reflect myocardial reperfusion, a defect in sensitivity still exists. Despite of the limitations of our approach, the study strongly supports the effectiveness of thrombectomy combined with intracoronary administration of tirofiban in PCI.

Discussion

Primary PCI is now regarded as the most effective treatment for patients with STEMI. Postoperative TIMI grade flow can reflect the reperfusion level. Because of microvascular obstruction, poor reperfusion at the myocardial level still appears in some patients with sufficient forward flow. Microvascular obstruction arises from atheromatous and thrombotic embolization, neutrophil plugging, edema, or vasospasm [2]. Therefore, enhanced thrombus removal processes, like thrombectomy and intensive anticoagulant therapy, have been suggested as optional therapy during PCI to obtain better reperfusion in myocardial levels. The TAPAS study demonstrated that mechanical clot aspiration was associated with improved myocardial perfusion and lower mortality at 1 year [8]. Although the TOTAL study showed that, in patients with STEMI who were undergoing PCI, routine manual thrombectomy, as compared with PCI alone, did not reduce the risk of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or NYHA class IV heart failure within 180 days, but was associated with an increased rate of stroke within 30 days [14].

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Conclusions

The application of thrombectomy combined with intracoronary administration of tirofiban is relatively effective and safe in STEMI patients undergoing PCI.

Acknowledgements

We are grateful to all the co-workers and partners in our department. They provided us with great help and support during the study.
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