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Intracoronary injection of tirofiban prevents microcirculation dysfunction during delayed percutaneous coronary intervention in patients with acute myocardial infarction

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ABSTRACT

Objective: To determine whether tirofiban can prevent microcirculation dysfunction during delayed percutaneous coronary intervention (PCI) of spontaneously recanalized and severe narrowing coronary artery in patients with acute myocardial infarction.
Methods: 62 patients who have a single angiographically confirmed narrowing culprit coronary artery for more than 75% between 7 and 14 days after the onset of acute myocardial infarction were randomly divided into the tirofiban group (32 cases) and the placebo group (30 cases). All the patients received measurement of the index of microcirculatory resistance (IMR) before tirofiban/placebo administration and PCI. After PCI, IMR value was measured again.
Results: There was no significant variation between the two groups before PCI (11.67 ± 6.45 of placebo group vs. 14.65 ± 12.45 of tirofiban group, P = 0.158). After PCI, the IMR value of the tirofiban group is significantly lower than that of the placebo group (23.63 ± 9.91 of placebo group vs. 16.75 ± 9.98 of tirofiban group, P = 0.008).
Conclusions: Intracoronary injection of tirofiban can significantly prevent the abnormal increase of IMR value during delayed PCI in patients with acute myocardial infarction.

1. Introduction

It's reported that even after successful reperfusion by emergent percutaneous coronary intervention (PCI) in patients with acute myocardial infarction, the 28-day absolute mortality risk is still 12–18%, and the 5-year absolute mortality risk is even up to 53–58% [1]. The underlying mechanism is that the microcirculation remains a problem in spite of successful reperfusion by emergent PCI. Compared with the fractional flow reserve (FFR) of epicardial coronary, the widely accepted "gold standard" of coronary physiologic functional evaluation [2], the index of microcirculatory resistance (IMR) has not been so well known. The main reasons lie in a fact that the coronary microcirculation cannot be displayed by conventional imaging techniques including coronary angiography [3]. Fortunately, more and more evidences tend to indicate that IMR may be a better prognostic indicator for PCI therapy than FFR, especially in myocardial infarction patients [4]. With the development of researches in coronary microcirculation, IMR has been paid more and more attention to, especially in the area of acute coronary syndrome (ACS) [5]. However, the mechanisms on coronary microcirculation abnormality are still not clear. As far as the index of coronary microcirculation resistance is concerned, related research in acute myocardial infarction is the hottest area. For those patients with acute myocardial infarction, abnormal IMR value measured after emergent PCI therapy was often correlated with lesser clinical symptom improvement and poorer heart function recovery [6]. William F et al. [7] reported a research on the IMR value in 29 ST segment elevated acute myocardial infarction patients who accepted emergent PCI. The results show that IMR values were significantly correlated with creatine kinase (CK) peak (R = 0.61, P < 0.0005). In contrast, there was no correlation between CK peak and TIMG or CFR. The CK peak of patients with IMR over 32 U was higher than those with IMR below 32 U (3128 ± 1634 ng/ml vs. 1201 ± 911 ng/ml, P < 0.002), and the left ventricular wall motion score of patients with an IMR value over 32 U was also higher than those with an IMR value below 32 U (28 ± 7 vs. 20 ± 4, P < 0.001). This research proved that IMR can serve as an independent predictor for patients with myocardial infarction who accept emergent PCI therapy. And more recently, it's reported that [8] ADAMTS13 (disintegrin-like and metalloprotease with thrombospondin type I repeats 13), a von-Willebrand factor (VWF) targeted metalloprotease, can exert a thrombolytic effect in coronary microcirculation, which means that a von-Willebrand factor (VWF) targeted drug is a new prospective treatment to prevent micro thrombus-related IMR abnormality during emergent PCI in acute myocardial infarction. However, despite

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the numerous studies on IMR during emergent PCI in patients with acute myocardial infarction, research on IMR value during delayed PCI in patients with acute myocardial infarction has never been reported before.

The present research is a randomized, controlled, prospective clinical trial that manages to discover whether there are obvious changes in IMR value after delayed PCI of spontaneously recanalized and severe narrowing coronary artery (because IMR can only be measured in spontaneously recanalized coronary artery before PCI) in patients with acute myocardial infarction and whether tirofiban, a kind of VWF-targeted drug commonly used in clinical practice, can prevent the microcirculation dysfunction during delayed PCI or not.

Trail Registration: ClinicalTrials.gov ID: NCT01761656.

2. Study protocol

2.1. Patient population

62 patients who have a single angiographically confirmed narrowing culprit coronary artery for more than 75% between 7 and 14 days after the onset of acute myocardial infarction were enrolled at Xiangtan City cardiac disease center. All the enrolled patients met the following inclusion criteria: between 7 and 14 days after the onset of acute myocardial infarction; willing to accept further follow-up if necessary; age of 18–75 years old; having an angiography-confirmed spontaneously recanalized and more than 75% narrowing culprit coronary artery; and having signed an informed consent form. The exclusion criteria include: emergent PCI after acute myocardial infarction, ultrasound-measured LVEF less than 30%, estimated glomerular filtration rate less than 30 ml/min per 1.73 m^2, and abnormal liver function. The project was approved by the ethics committee of Xiangtan City Central Hospital. Sixty-two patients were randomly divided into the tirofiban group (32 cases) and the placebo group (30 cases).

2.2. IMR measurement and intracoronary injection of tirofiban during PCI

Previous studies have proved that it is feasible to complete the measurement of the IMR value through a single pressure- and thermatic-sensitively guiding wire [9], so our study used a coronary pressure and temperature sensitive guide wire (St Jude Medical, Sweden) as both the PCI guide wire and the IMR-measuring wire. The guide wire was calibrated before used, equalized with aortic pressure at the tip of the guide catheter, and then sent to the distal endpoint of the culprit coronary artery. The index of microcirculation resistance (IMR) was defined as the product of distal coronary pressure (Pd) and mean transit time of three measurements (Tmn), and according to previous reports, the IMR formula is: IMR = Pd · Tmn [10,11], among which transit time is the time that 3 ml room temperature saline takes to flow from the ostial to the distal endpoint of the culprit coronary artery under the condition of maximal target coronary hyperemia. The hyperemia was established by 140 μg/kg·min ^{1} intravenous adenosine preceded by 200 μg nitrate by intracoronary bolus injection. After IMR measurement, the patients of the tirofiban group received intracoronary injection of tirofiban 10 μg/kg diluted in 10 ml saline, and the patients of the placebo group received intracoronary injection of 10 ml saline.

The pressure guide wire was also used for the following interventional therapy. After PCI, the IMR value was measured again with the tip of the guide wire at the same position as that before PCI. According to previous reports, PCI itself will not disturb the IMR value, because PCI itself can only change the FFR (Pd/Pa) value by elevating the distal coronary pressure (Pd), yet IMR is repeatable and independent of hemodynamic variations including FFR [12,13].

Table 1
Baseline characteristics of placebo group and tirofiban group.

Parameters	Placebo group	Tirofiban group	P
Age (years)	66.60 ± 9.42	67.40 ± 8.17	0.720
Sex (M/F)	18/12	24/8	0.279
BMI (kg/m^2)	23.95 ± 2.69	24.74 ± 2.37	0.222
Smoking (Y/N)	12/18	17/15	0.322
Diabetes (Y/N)	6/24	11/21	0.260
Hypertension (Y/N)	14/16	13/19	0.798
Hypercholesterolemia (Y/N)	3/27	1/31	0.346
Statins treating history (Y/N)	9/21	10/22	1.000
Systolic pressure (mm Hg)	139.37 ± 19.21	140.13 ± 19.89	0.879
Diastolic pressure (mm Hg)	81.17 ± 11.87	84.56 ± 14.37	0.316
eGFR (ml/min·1.73 m^2)	71.16 ± 42.99	72.70 ± 23.51	0.694
Stenosis (%)	85.97 ± 7.41	88.66 ± 7.04	0.148
FFR before PCI	0.64 ± 0.18	0.62 ± 0.15	0.604

Table 2
Comparison of IMR value before delayed PCI between tirofiban group and placebo group.

Groups	n	IMR (mm Hg·s^{-1})	t	P
Placebo group	30	11.67 ± 6.45	−1.44	0.158
Tirofiban group	32	14.65 ± 12.45		

2.3. Angiographic analyses

The angiographic measurement of coronary stenosis severity was analyzed by two other interventional cardiologists independent of the IMR analysts.

2.4. Statistical analyses

All the statistical analyses were performed by SPSS 21.0. Normality was assessed by the Shapiro–Wilk test. Means and SDs were used to summarize data normally distributed. Normal distributions were achieved by logarithmic transformation where necessary. All tests were two tailed, and the significance level was set as 0.05. Comparisons of continuous variables between groups were made with analysis of variance (ANOVA) and the Student t tests or Dunnett t tests. All the statistical tests took 95% confidence intervals (CIs), and a P value of below 0.05 was adopted for significance.

3. Results

3.1. Patient characteristics

From November 1, 2012 to November 1, 2013, 62 patients were randomly divided into two groups: the tirofiban group (32 cases) and the placebo group (30 cases). All of the baseline characteristics including age, sex, BMI, smoking, diabetes, hypertension, hypercholesterolemia, statin treating history, systolic pressure, diastolic pressure, eGFR (ml/min·1.73 m^2), stenosis severity and fractional flow reserve were all balancedly distributed in the two groups (Table 1).

3.2. IMR comparison between two groups and IMR changes during PCI

All the sixty-two patients accepted percutaneous transluminal coronary angioplasty (PTCA) and stenting, without any main accidents or complications. Immediately after the PTCA and stenting, IMR value measurement was completed with the tip of the guide wire in the same position as before.

Table 3
Comparison of IMR value after delayed PCI between tirofiban group and placebo group.

Groups	n	IMR (mm Hg·s^{-1})	t	P
Placebo group	30	23.63 ± 9.91	2.72	0.008
Tirofiban group	32	16.75 ± 9.98		