

## Original Article

# Clinical efficacy of triple antiplatelet therapy with tirofiban in elderly patients with acute coronary syndrome

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**Abstract:** Objective: To delve into the clinical efficacy of triple antiplatelet therapy (TAT) with tirofiban in treatment of elderly patients with acute coronary syndrome (ACS). Methods: From April 2015 to March 2017, a total of 100 elderly patients with ACS treated in our hospital were recruited in this study. They were randomly subdivided into the experiment group and the control group. The patients in the control group received dual antiplatelet therapy (DAT) with aspirin plus clopidogrel, while those in the experiment group were given TAT containing tirofiban, aspirin and clopidogrel. The clinical efficacy, platelet counts, coagulation function, platelet function, the rates of major adverse cardiac events (MACE) and the incidence of adverse reactions were compared between the two groups. Results: The patients in the experiment group had a greater improvement in the clinical efficiency after TAT compared with those in the control group ( $P=0.031$ ). No significant differences were observed in platelet counts and coagulation function between the two groups (Both  $P>0.05$ ), but the TXB<sub>2</sub>, GMP-140 and P-selectin levels (markers for platelet function measurements) were remarkably lower in the experiment group ( $P=0.029$ ,  $0.036$ ,  $0.032$ , respectively). The differences in the rates of MACE between the two groups were significant at 24 h and 30 days (4% vs 18%, 12% vs 28%,  $P=0.020$ ; 12% vs 28%,  $P=0.046$ ); but the incidence of adverse reactions differed mildly ( $P>0.05$ ). Conclusion: TAT of tirofiban-aspirin-clopidogrel was effective in the treatment of elderly patients with ACS, and the combination therapy was associated with more potent antiplatelet function, a lower rate of MACE and milder adverse reactions.

**Keywords:** Tirofiban, acute coronary syndrome, elderly population, antiplatelet agent, major adverse cardiac event

## Introduction

Acute coronary syndrome (ACS) is a set of clinical syndromes pathologically characterized by rupture or invasion of coronary atherosclerotic plaques, secondary to incomplete or complete occlusive thrombosis [1]. In recent years, the incidence of ACS is increasing on a yearly basis among the older patients [2]. Antiplatelet therapy is crucial in the treatment of ACS [3]. Clinically, conventional antiplatelet agents including aspirin and clopidogrel only partly affect the course of platelet aggregation [4]. Platelets may still be activated through other pathways. Additionally, as the physical functioning of elderly patients is hypercoagulable, the outcomes of DAT are poor in elderly patients with ACS. Therefore, it is of great implication to find the optimum administration of antiplatelet agents in elderly patients with ACS.

Tirofiban, a platelet glycoprotein GP IIb/IIIa receptor antagonist, plays an inhibitory role in the

final common pathway of platelet aggregation, and has a great effect on platelet aggregation [5, 6]. Some researchers have recommended triple antiplatelet therapy (TAT) combining tirofiban with aspirin and clopidogrel be used for intensive anticoagulation in elderly patients with ACS [7, 8]; but others argue that the antiplatelet regimen may result in higher risk for bleeding in elderly patients [9]. Currently, the clinical efficacy and safety of TAT with tirofiban remain uncertain in treating elderly patients with ACS. As a result, this study comparing the efficacy of TAT and that of DAT in elderly patients with ACS was to explore the clinical implication of tirofiban in treatment of elderly patients with ACS.

## Materials and methods

### General data

This study obtained approval from the Hospital Ethics Committee and all patients provided

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written informed consent. From April 2015 to March 2017, a total of 100 elderly patients with ACS admitted to our hospital were recruited as subjects in this study.

Patients older than 60 years old were eligible for this study if they had initial onset of ACS, met the American Heart Association (AHA)/American College of Cardiology (ACC) Guidelines for the Management of Patients with Acute Coronary Syndromes, and were able to comply with the follow-ups. Patients were excluded if they were resistant or sensitive to antiplatelet agents; had severe disease in the liver or the kidney, or combined with hemorrhagic stroke, intracranial hemorrhage, gastrointestinal bleeding or active ulcer; had a history of recent trauma or major surgery; had rheumatic cardiac disease, congenital heart disease or heart failure, or met the indications to emergent percutaneous transluminal coronary angioplasty (PTCA).

Eligible patients were assigned to the experiment group (n=50) or the control group (n=50) in terms of a random number table. The patients in the control group were given antiplatelet therapy containing oral aspirin (100 mg/d, once daily) plus oral clopidogrel (75 mg/d, once daily) in addition to standard care for one month. The standard care included bed rest, oxygen inhalation, oral betaloc for the ventricular rate control, oral lipitor for blood lipid regulation and atherosclerotic plaque stability, oral norvasc or other drugs for blood pressure control in patients complicated with hypertension, oral metformin or other drugs for glucose control in patients with diabetes. In addition to the same regimen administered to the control group, the patients in the experiment group were also administered intravenous tirofiban with an initial loading dose of 0.4 µg/kg/min for 30 min, followed by a consecutive infuse at a maintenance dose of 0.1 µg/kg/min for 48 h.

### *Outcome measures*

Primary outcome was the efficacy of the treatment at 2 weeks. The efficacy was compared between the two groups at the end of 2 weeks. The criteria for clinical response included more than 50% reduction and even disappearance in angina symptoms, more than 50% reduction in the consumption of nitroglycerin, over 1.5 mm elevation of ST segments or T wave inversion

returned to normal sequence on the electrocardiograms.

The rates of major adverse cardiac events (MACE) were compared between the two groups at 24 h after treatment and 30 d after follow-up, respectively. MACE was defined as newly-diagnosed sudden cardiac death, myocardial infarction, and refractory angina.

Secondary outcomes included platelet counts, blood coagulation and platelet function. The measurements of platelet counts, blood coagulation and platelet function before treatment were within the normal range in both groups and basically similar between the two groups. The same measurements after treatment were also compared between the two groups. A blood sample (8 mL) was drawn from the elbow vein of each patient at 12 h after fasting. Platelet counts and coagulation function of the patients were examined with the use of automatic coagulation analyzers; thromboxane B<sub>2</sub>, platelet P-selectin and platelet α-granular membrane protein-140 (GMP-140) were detected using the Enzyme-Linked Immunosorbent Assay (R&D Systems, US).

Adverse reactions of the patients were compared between the two groups. The number of cases of subcutaneous ecchymosis, intracranial hemorrhage, epistaxis, gingival bleeding, upper gastrointestinal bleeding, hematuria and other adverse events within one month after follow-up were documented and the incidences of adverse reactions were calculated.

### *Statistical analysis*

All the data were analyzed with the use of SPSS statistical software, version 20.0. Count data were expressed as rates; the chi-square tests were used for comparisons between groups. Measurement data were described as mean ± standard deviation; the independent samples t-tests were applied in comparisons between the two groups. A *P* value of less than 0.05 was considered statistically significant.

## **Results**

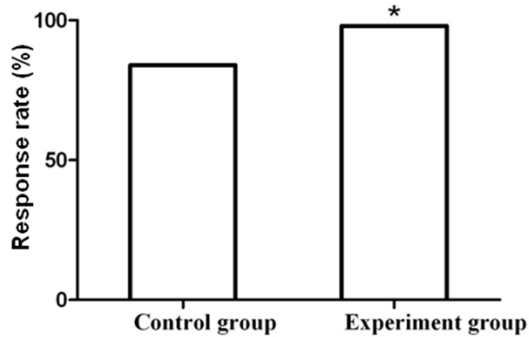
### *Basic data of the patients*

Age, sex, comorbidity, body mass index (BMI), left ventricular ejection fractions (LVEF) and

**Table 1.** Comparison of the basic data of patients between the two groups

| Variable                 | Control  | Experiment | t/ $\chi^2$ | P     |
|--------------------------|----------|------------|-------------|-------|
| Case                     | 50       | 50         |             |       |
| Age (n)                  | 67.5±7.6 | 68.3±8.1   | 0.125       | 0.907 |
| Female/Male (n)          | 31/19    | 29/21      | 0.167       | 0.683 |
| Comorbidity (n, %)       |          |            |             |       |
| Hypertension             | 22 (44)  | 23 (46)    | 0.040       | 0.841 |
| Diabetes mellitus        | 12 (24)  | 15 (30)    | 0.457       | 0.499 |
| Hyperlipidemia           | 35 (70)  | 37 (74)    | 0.198       | 0.656 |
| BMI (kg/m <sup>2</sup> ) | 22.8±1.4 | 23.2±1.7   | 0.315       | 0.769 |
| LVEF (%)                 | 55.4±3.2 | 55.8±3.5   | 0.146       | 0.891 |
| ACS subtype (n, %)       |          |            |             |       |
| Myocardial infarction    | 27       | 25         | 0.160       | 0.689 |
| Unstable angina          | 23       | 25         |             |       |

Note: ACS denotes acute coronary syndrome.



**Figure 1.** Comparison of the response rate between the two groups. Compared with the control group, \*P<0.05.

ACS subtypes were generally well-matched between the two groups (All P>0.05; **Table 1**).

#### Efficacy

In the control group, 8 patients had no response after treatment, but 42 had response, with a response rate of 84%. In the experimental group, 1 patient had no response after treatment, but 49 had response, with a response rate of 98%; the differences in the response rates were substantial between the two groups ( $\chi^2=6.737$ , P=0.031; **Figure 1**).

#### Platelet counts, coagulation function and platelet function after treatment

The platelet counts, prothrombin time (PT), activated partial thromboplastin time (APTT), and fecal indicator bacteria (FIB) levels of pa-

tients after treatment were similar between the experiment groups and the control group (All P>0.05); nevertheless, the markers for platelet function including TXB<sub>2</sub>, GMP-140 and P-selectin of patients after treatment were significantly lower in the experiment group (All P<0.05; **Table 2**).

#### Major adverse cardiac events

MACEs occurred in 4% of the patients in the experiment group at 24 h, including 1 case of myocardial infarction

and 1 case of refractory angina, whereas MACEs occurred in 18% of the patients in the control group, with 1 case of sudden cardiac death, 3 cases of myocardial infarction and 5 cases of refractory angina; the rate of MACE at 24 h was considerably different between the two groups ( $\chi^2=5.369$ , P=0.020). At 30-day follow-up, myocardial infarction occurred in 3 patients and refractory angina occurred in 3 patients in the experimental group, with a MACE rate of 12%; sudden cardiac death occurred in 2 patients, myocardial infarction occurred in 5 patients and refractory angina in 7 patients in the control group, with a MACE rate of 28%. Markedly differences were noted in the rates of MACE at 30 d between the two groups ( $\chi^2=4.000$ , P=0.046; **Figure 2**).

#### Adverse reaction

Adverse reactions including subcutaneous ecchymosis, intracranial hemorrhage, epistaxis, gingival bleeding, upper gastrointestinal bleeding and hematuria of patients were generally similar between the two groups (All P>0.05, **Table 3**). The renal and hepatic functions of the patients were normal in both groups.

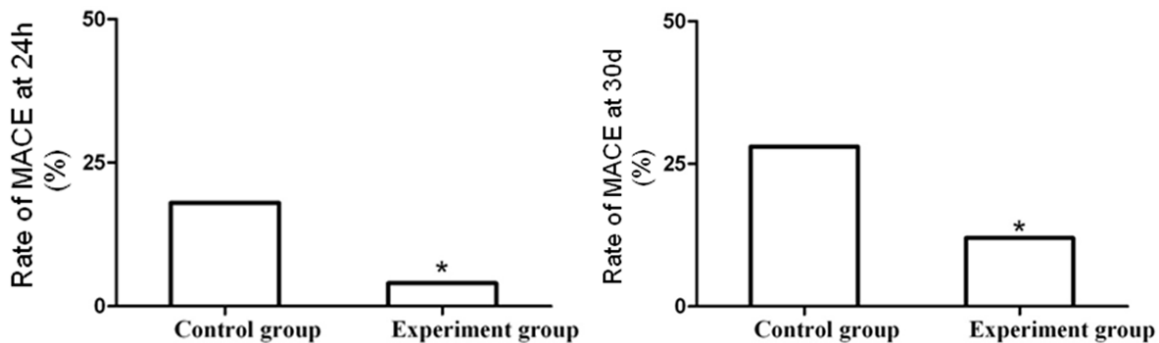
#### Discussion

Clinically, ACS is one of the most common cardiovascular diseases. The mortality of ACS in elderly patients is significantly higher than that in young patients [10, 11]. The pathogenesis of ACS is that coronary artery is partially or com-

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**Table 2.** Comparison of platelet counts, coagulation function and platelet function of patients after treatment between the two groups

| Variable    | Case | Platelet count ( $\times 10^9/L$ ) | Coagulation function |                |                | Platelet function |                |                          |
|-------------|------|------------------------------------|----------------------|----------------|----------------|-------------------|----------------|--------------------------|
|             |      |                                    | PT (s)               | APTT (s)       | FIB (g/L)      | TXB2 (pg/mL)      | GMP-140 (%)    | P-selectin ( $\mu g/L$ ) |
| Control     | 50   | 21.7 $\pm$ 5.2                     | 19.8 $\pm$ 6.1       | 24.9 $\pm$ 5.9 | 27.9 $\pm$ 7.1 | 101.6 $\pm$ 18.2  | 17.2 $\pm$ 5.6 | 11.7 $\pm$ 3.1           |
| Experiment  | 50   | 20.5 $\pm$ 4.9                     | 18.2 $\pm$ 6.5       | 23.8 $\pm$ 5.5 | 28.7 $\pm$ 6.9 | 89.5 $\pm$ 15.7   | 13.1 $\pm$ 4.9 | 9.3 $\pm$ 2.9            |
| t/ $\chi^2$ |      | 0.291                              | 0.311                | 0.236          | 0.140          | 2.307             | 2.238          | 2.297                    |
| P           |      | 0.786                              | 0.771                | 0.825          | 0.895          | 0.029             | 0.036          | 0.032                    |



**Figure 2.** Comparison of the rates of MACE of patients between the two groups. Compared with the control group, \*P<0.05.

**Table 3.** Comparison of the adverse reactions between the two groups (n, %)

| Variable    | Case | SE    | IH    | Epistaxis | GB    | UGB    | Hematuria |
|-------------|------|-------|-------|-----------|-------|--------|-----------|
| Control     | 50   | 3 (6) | 2 (4) | 2 (4)     | 1 (2) | 5 (10) | 3 (6)     |
| Experiment  | 50   | 2 (4) | 1 (2) | 2 (4)     | 3 (6) | 6 (12) | 4 (8)     |
| t/ $\chi^2$ |      | 0.212 | 0.350 | 0.000     | 1.088 | 0.102  | 0.154     |
| P           |      | 0.645 | 0.554 | 1.000     | 0.617 | 0.749  | 0.695     |

Note: SE denotes subcutaneous ecchymosis, IH intracranial hemorrhage, GB gingival bleeding, UGB upper gastrointestinal bleeding.

pletely obstructed by thrombosis which results in myocardial ischemia, and an imbalance between myocardial oxygen supply and demand. Platelet activation, adhesion and aggregation play a crucial role in the initiation of thrombosis. Notably, antiplatelet therapy is essential to the treatment of ACS. Aspirin and clopidogrel are clinically common antiplatelet agents [12, 13]. The mechanism of antiplatelet aggregation is to inhibit the TXA pathway. Clopidogrel blocks the activation of platelets dependent on ADP by selectively inhibiting ADP receptor, hence leading to antiplatelet aggregation. Nevertheless, both aspirin and clopidogrel cannot completely block the pathway of platelet aggregation. In addition, elderly patients have viscous blood, high fibrinogen levels and significant isblood hypercoagulability, and they also tend to be complicated with underlying dis-

eases (eg. hypertension, hyperlipidemia and diabetes) inducing blood hypercoagulability. Therefore, it is essential to strengthen antiplatelet therapy in elderly patients with ACS. The results of our current study indicated that the efficacy of TAT with tirofiban is superior to that of dual antiplatelet

therapy in elderly patients with ACS, and the difference is statistically significant.

Tirofiban is a non-peptide GP IIb/IIIa receptor antagonist and a new generation of antiplatelet agent. It selectively combines with platelet fibrinogen and blocks the binding of platelet GP IIb/IIIa receptor to fibrinogen, thereby inhibiting platelet aggregation and thrombosis. Previous studies have indicated that tirofiban exerts a favorable effect on anti-platelet aggregation in ACS patients undergoing PCI [14, 15]. TXB2, GMP-140 and P-selectin are important markers of the activation and aggregation of platelets through various pathways. The results of the current study revealed that measurements of PT, APTT and FIB (markers for platelet counts and blood coagulation) were basically similar among all the elderly patients with ACS; how-

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ever, the TXB<sub>2</sub>, GMP-140 and P-selectin levels (markers for platelet function) in patients who had undergone TAT with tirofiban were remarkably lower than those of patients who had received dual antiplatelet therapy, and the findings were consistent with those reported by Kupó P et al [16]. This suggests that tirofiban is a potent antiplatelet agent, which can significantly improve the efficacy of dual antiplatelet agents and reduce thrombus events. Apart from platelet function, the addition of tirofiban to the therapy significantly reduces the rates of MACEs in ACS patients who had undergone dual antiplatelet therapy [17, 18]. According to another study, the rates of MACEs changed slightly among patients at moderate-to-high risk for ACS at 5 d after tirofiban therapy, but the rates were strikingly lower at 30 d [19]. Our current study demonstrated that tirofiban added to dual antiplatelet therapy significantly reduced the rates of MACEs in elderly patients with ACS, which were largely similar to the results of previous studies [20]. Of note, antiplatelet therapy with tironon was more effective in inhibiting thrombosis and reducing MACSSs.

Bleeding is a major adverse event of tirofiban. Increasing attention has been paid to the bleeding risk of tirofiban therapy in elderly patients with ACS. The results of our current study indicated that adverse reactions including subcutaneous ecchymosis, intracranial hemorrhage, epistaxis, gingival bleeding, upper gastrointestinal bleeding and hematuria were largely similar between the two study groups, suggesting that TAT with tirofiban is reliable in elderly patients with ACS.

In conclusion, the combination therapy with tirofiban plus aspirin and clopidogrel was effective in the treatment of elderly patients with ACS, laying experimental basis and providing evidence for reasonable use of antiplatelet therapy in clinical practice. However, as the follow-up period was short in this study, additional randomized controlled trials with larger sample size and longer follow-up are needed to further validate the long-term efficacy of tirofiban.

### Disclosure of conflict of interest

None.

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