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RESEARCH PAPER

Effects of Tirofiban and Nicorandil on Effective Reperfusion and the Levels of IL-4 and sICAM-1 After PCI for Chronic Coronary Total Occlusion

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Abstract

Aim: The effects of tirofiban combined with nicorandil on effective reperfusion, and the levels of interleukin-4 (IL-4) and soluble intercellular adhesion molecule-1 (sICAM-1) after percutaneous coronary intervention (PCI) for chronic coronary total occlusion (CTO) were investigated.

Method: From January 1, 2017, to June 31, 2019, a total of 40 patients with CTO receiving PCI in Shandong Qianfoshan Hospital were randomly divided into a control group (treated with single tirofiban) and a cocktail group (treated with nicorandil combined with tirofiban). Effective reperfusion was compared between groups. In addition, differences in coronary serum IL-4 and sICAM-1 levels before and 10 min after the operation were compared between groups, and the incidence rates of adverse reactions were observed. Finally, patient follow-up occurred at 1 month and 6 months, and the total incidence rates of adverse cardiac events in both groups were assessed.

Results: The levels of IL-4 and sICAM-1 in the cocktail group significantly decreased after the operation ($P < 0.05$). In addition, after the operation, significantly greater decreases in the IL-4 and sICAM-1 levels were observed in the cocktail group than the control group ($P < 0.05$). The Seattle Angina Scale (SAQ) score of the cocktail group, compared with the control group, showed a significant improvement after vessel opening in the patients with CTO. At the 1-month follow-up, the SAQ score of the cocktail group, compared with the control group, indicated further improvements in terms of angina attack frequency. No significant differences were observed in the incidence rates of adverse reactions between groups ($P > 0.05$).

Conclusion: The treatment of patients with CTO undergoing PCI with nicorandil and tirofiban alleviated the inflammatory response, improved the SAQ scores, and decreased the occurrence of angina pectoris in patients. Moreover, this treatment is safe and reliable, and has important clinical significance.

Keywords: Chronic coronary total occlusions (CTOs); effective reperfusion; tirofiban; nicorandil IL-4; sICAM-1

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Introduction

Chronic coronary total occlusions (CTOs) are generally defined as complete interruptions of antegrade blood flow, as detected with angiography, within a period of >3 months [1]. CTO, which occurs in as many as 30% of patients with coronary diseases, is the end stage of coronary artery atherosclerosis [2]. Percutaneous coronary intervention (PCI) is a treatment method for CTO that is relatively simple, safe, and nonpainful; thus, it is widely used in clinical practice. Despite remarkable advances in PCI for CTO, the low rate of effective reperfusion remains a clinical issue. The aim of this study was to identify auxiliary drugs to increase the rate of effective reperfusion in PCI, which is key to recanalization of the heart. Clinical and epidemiological studies have indicated a relationship between circulating inflammatory factors and coronary diseases. Inflammatory cells (expressing IL-4) and sICAM-1 are key factors in the progression of coronary diseases [3, 4]. However, limited data are available regarding the correlations among IL-4, sICAM-1, and effective reperfusion in CTO.

Tirofiban is a highly specific nonpeptide platelet GPIIb/IIIa receptor antagonist that effectively blocks the common pathway of platelet activation and aggregation [5], and alters coronary reflow [6]. Nicorandil is a new vasodilator drug type that has been used in PCI patients in emergent settings but is not used in patients with CTO [7]. In the present study, we evaluated the ability of tirofiban and nicorandil treatment to enhance effective reperfusion in patients with CTO receiving PCI. We detected the coronary serum levels of IL-4 and sICAM-1, evaluated the patients' subjective symptoms with the Seattle Angina Questionnaire (SAQ) score, and observed major adverse cardiac events in both groups.

Materials and Methods

General Data

A total of 40 patients with CTO treated at Qianfoshan Hospital (Shandong, China) between January 1, 2017 and June 31, 2019 were selected. The inclusion criteria were as follows: i) patients meeting the diagnostic criteria for CTO; ii) patients with clear evidence of ischemia affecting their quality of life; and iii) patients who provided signed informed consent. The exclusion criteria were as follows: i) patients who previously received CTO in-stent; ii) patients with mental disease or cognitive dysfunction together with a malignant tumor; iii) patients with any history of adverse reactions to tirofiban or nicorandil; and iv) patients with severe disease who could not tolerate surgery. The patients were divided into two groups: a control group (n = 20) and a cocktail group (n = 20). Informed consent forms were signed by the patients. The study was approved by the Ethics Committee of Qianfoshan Hospital (Shandong, China).

The basic data for all enrolled patients were recorded, including their sex, age, history of hypertension, diabetes status, family history of coronary heart disease, smoking history, and left ventricular ejection fraction (LVEF) at admission. Biochemical indicators included total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), serum creatinine, hemoglobin, and platelets. For secondary prevention of coronary heart disease, according to the patient diagnosis, the experimental treatment was combined with other drugs to control blood sugar, blood pressure, and other risk factors.

Methods

Medication

Before the operation, the patients were treated with 300 mg aspirin enteric-coated tablets and 300 mg clopidogrel tablets. After the operation, the patients took aspirin (100 mg/d) and clopidogrel (75 mg/d) for 1 year. In patients in the control group, after the guide wire was passed through the CTO segment and percutaneous transluminal coronary angioplasty was performed, 10 μg/kg of tirofiban was injected through the microcatheter in 30 s, and then the patients received a standard intravenous drip of 0.15 μg/(kg/min) tirofiban for 24 h. On the basis of the treatment of the control patients, the patients in the cocktail group were treated with 3 mg of nicorandil after the opening of the target lesions and

then received a standard intravenous drip of 2 mg/h nicorandil for 24 h.

Sample Collection

After the guide wire was successfully passed through the lesion and was confirmed to be in the true lumen, 3 mL of coronary artery blood was collected immediately before balloon dilation. Three milliliters of coronary blood were collected within 5–10 min after successful PCI. The plasma was collected before and after the centrifugation of coronary blood. Then the supernatant was collected and stored at −80 °C.

ELISA

The levels of IL-4 and sICAM-1 in the samples were measured at the end of the experiment. All indexes were detected with enzyme-linked immunosorbent assay (ELISA; Omnimabs, Alhambra, CA, USA) according to the manufacturer's protocol. The serum IL-4 and sICAM-1 levels in the two groups were detected via ELISA before and after the operation.

Evaluation Criteria

TIMI Blood Flow Classification Standards

Level 0: no blood flow visualization (no perfusion) at the distal end of the diseased vessel; level 1: the blood flow at the distal end of the diseased blood vessel did not completely fill the entire blood vessel (permeation without perfusion); level 2: the blood flow filled the blood vessels, but more than three cardiac cycles (partial reperfusion) were required; level 3: the contrast agent filled the distal end of the blood vessel within three cardiac cycles (complete reperfusion). A blood flow velocity TIMI grade ≤2 was considered to indicate no reflow.

Surgical Success Criteria

Coronary angiography confirmed that the target lesion residual stenosis was <30%, the distal blood flow was TIMI grade 3, and no serious coronary events occurred within 24 hours after surgery (including acute stent thrombosis, emergency coronary bypass transplantation/CABG, and all-cause death).

Major Adverse Cardiac Events

Adverse events were investigated in patients during the perioperative period. Patients in both groups were followed for 6 months, and the incidence rates of major adverse cardiac events were compared, including 1) cardiogenic death; (2) nonfatal myocardial infarction; (3) target blood vessel revascularization; (4) recurrent angina; (5) congestive heart failure; and (6) life-threatening arrhythmia (ventricular tachycardia and ventricular fibrillation).

Seattle Angina Scale Ratings

Patients were followed before and 1 month after the operation. The SAQ scale designed by Spetus et al. was used to evaluate patient quality of life and body function status.

Statistical Analysis

SPSS 22.0 statistical software (SPSS, IL, USA) was used for data analysis. The measurement data are presented as the mean ± standard deviation. For data with a normal distribution, independent samples t-test was used for comparisons between groups, and paired samples t-test was used for within-group comparisons. For data not normally distributed, the Mann-Whitney U test was used to compare groups, and the Wilcoxon test was used for comparisons between groups. $P < 0.05$ was considered statistically significant.

Results

Comparison of Basic Patient Characteristics Between Groups

There was no variation in age between the control group and cocktail group. In addition, there was no statistically significant difference in risk factors (familial history of smoking, diabetes, hypertension, and coronary heart disease) between groups. The LVEF before surgery and the serum levels of all indexes (LDL-C, TG, TC, hemoglobin, platelets, and serum creatinine) did not differ significantly between the control group and the cocktail group (Table 1).

Table 1 Basic Patient Characteristics.

Parameter	Control group (n = 20)	Cocktail group (n = 20)	P
Age (years, $\bar{x} \pm s$)	65.6 ± 10.01	69.4 ± 8.27	0.14
Male [(%)]	15 (75.0%)	14 (70.0%)	0.27
Smoking [(%)]	12 (60%)	11 (55.0%)	0.23
Diabetes [(%)]	11 (55.0%)	13 (65.0%)	0.27
Hypertension [(%)]	15 (75.0%)	12 (60.0%)	0.43
Family history of coronary heart disease	3 (15.0%)	2 (10.0%)	0.49
LVEF (%, $\bar{x} \pm s$)	56.2 ± 11.88	57.4 ± 10.22	0.31
Blood biochemical index			
LDL-C [mmol/L, $\bar{x} \pm s$]	2.32 ± 0.73	2.34 ± 0.81	0.81
TG [mmol/L, $\bar{x} \pm s$]	3.92 ± 1.13	4.03 ± 1.21	0.31
TC [mmol/L, $\bar{x} \pm s$]	2.01 ± 1.22	2.04 ± 0.92	0.36
Hemoglobin (g/L, $\bar{x} \pm s$)	138.6 ± 13.2	138.9 ± 12.7	0.62
Platelets ($\times 10^9$/L, $\bar{x} \pm s$)	227 ± 51.5	231 ± 52.1	0.17
Serum creatinine (μmol/L, $\bar{x} \pm s$)	75.5 ± 17.5	78.2 ± 21.7	0.37

LVEF: left ventricular ejection fraction; TC: total cholesterol, TG: triglycerides, LDL-C: low-density lipoprotein cholesterol, SCr: serum creatinine

Comparison of TIMI Between Groups

The TIMI flow grading in the cocktail group after treatment was significantly greater than that in the control group ($P < 0.05$), and the surgical success rate was 90% (Table 2).

Comparison of IL-4 and s-ICAM-1 Levels at Different Time Points Between Groups (ng/mL)

Before treatment, no significant differences were observed in IL-4 or ICAM protein expression between groups ($P > 0.05$). After treatment, the levels of IL-4 and ICAM were significantly lower in the cocktail group than the control group ($P < 0.05$). An intragroup comparison indicated that, in the control group, the IL-4 and s-ICAM-1 protein levels did not significantly differ before and after tirofiban treatment ($P > 0.05$), whereas in the cocktail group, the levels of IL-4 and sICAM-1 were significantly lower after treatment ($P < 0.05$, Figures 1–2, Tables 3–4 In conclusion, the inflammation index indicating alleviation in the cocktail group compared with the control group.

Comparison of Adverse Events During the Perioperative Period Between Groups

No significant differences were observed in the incidence rates of adverse reactions between groups ($P > 0.05$) (Table 5).

Comparison of Major Adverse Cardiac Events Between Groups

At the 6-month follow-up, the number of major adverse cardiac events in the cocktail group was significantly lower than that in the control group ($P < 0.05$) (Table 6).

Table 2 Comparison of TIMI Between Groups.

	n	Grade 0	Grade 1	Grade 2	Grade 3
Control group	20	3	0	1	16
Cocktail group	20	0	0	0	20
z/t		–	–	–	–2.032
P		–	–	–	0.049

Red color indicates significant difference between two groups.

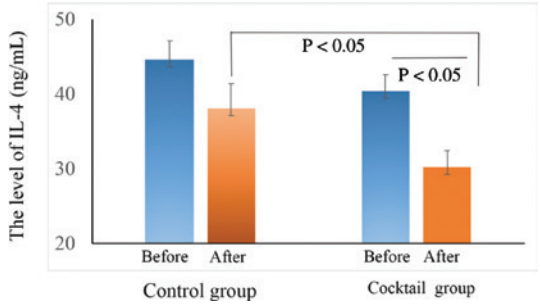

Figure 1 Comparison of IL-4 Levels Between Groups. After treatment, the levels of IL-4 were significantly lower in the cocktail group than the control group ($P < 0.05$). In the cocktail group, the level of IL-4 was significantly lower after treatment than before treatment ($P < 0.05$).

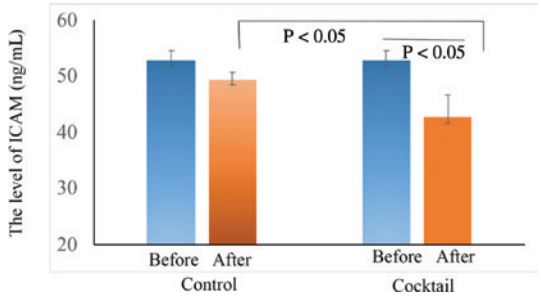

Figure 2 Comparison of ICAM Levels Between Groups. After treatment, the levels of ICAM were significantly lower in the cocktail group than the control group ($P < 0.05$). In the cocktail group, the levels of ICAM were significantly lower after treatment than before treatment ($P < 0.05$).

Comparison of SAQ Scores Before and After Operation in the Two Groups

After treatment, the frequency of angina pectoris was significantly lower in the cocktail group than the control group ($P < 0.05$, Table 7). An intragroup comparison indicated that, in the control group, the SAQ score significantly increased after tirofiban treatment ($P > 0.05$, Table 8), whereas in the cocktail group, the SAQ score significantly increased after treatment ($P < 0.05$, Table 9).

Discussion

Coronary artery disease is widely regarded as the most common disease endangering human health worldwide. With economic development, the incidence of coronary heart disease is rising each year, and CTO accounts for approximately 30% of cases, according to coronary angiography [1, 2]. Patients with CTO often have atrial fibrillation, arrhythmia, angina pectoris, and heart dysfunction. PCI can help restore the blood perfusion in the coronary arteries and the blood supply. However, the rate of effective reperfusion remains low and is closely associated with surgery, inflammation, stent thrombosis, and genetic factors [8, 9]. Therefore, PCI and early drug

Table 3 Comparison of IL-4 Levels Between Groups (ng/mL).

	n	IL-4 (before)	IL-4 (after)	z/t	P
Control group	20	44.66 ± 2.46	38.22 ± 2.25	1.634	0.114
Cocktail group	20	40.38 ± 3.23	30.29 ± 2.14	2.602	0.013
z/t		0.749	2.490		
P		0.459	0.018		

Red color indicates significant difference between two groups.

Table 4 Comparison of ICAM Levels Between Groups (ng/mL).

	n	ICAM (before)	ICAM (after)	z/t	P
Control group	20	52.94 ± 1.77	49.50 ± 1.70	1.399	0.171
Cocktail group	20	52.86 ± 1.37	42.74 ± 3.96	6.278	0.000
z/t		0.035	3.767		
P		0.972	0.001		

Red color indicates significant difference between two groups.

Table 5 Comparison of Adverse Events During the Perioperative Period.

	Control group (n = 20)	Cocktail group (n = 20)	P
Bleeding	2 (0.1)	2 (0.1)	>0.05
No reflow/slow blood flow	0	0	–
Pericardial tamponade	0	0	–
Malignant arrhythmia	0	0	–
Myocardial infarction	1 (0.05)	1 (0.05)	>0.05
Death	0	0	–

Table 6 Comparison of Major Adverse Cardiac Events (follow-up for 6 months).

	Control group (n = 20)	Cocktail group (n = 20)	P
Congestive heart failure	3 (0.15)	1 (0.05)	<0.05
Malignant arrhythmia	0	0	–
Myocardial infarction	2 (0.1)	1 (0.05)	<0.05
Target vessel reconstruction	0	0	–
Death	0	0	–

Table 7 Comparison of SAQ Scores in the Control Group.

SAQ	Preoperative score	Postoperative score	P
Degree of limitation of physical activity	42.31 ± 7.27	82.35 ± 9.30	<0.05
Angina stable state	49.12 ± 10.04	82.28 ± 7.43	<0.05
Frequency of angina pectoris	50.2 ± 7.11	78.12 ± 7.37	<0.05
Treatment satisfaction	43.17 ± 10.0	81.47 ± 8.34	<0.05
Disease awareness	48.26 ± 11.42	86.24 ± 7.54	<0.05

Table 8 Comparison of SAQ Scores in the Cocktail Group.

SAQ	Preoperative score	Postoperative score	P
Degree of limitation of physical activity	43.29 ± 7.14	84.18 ± 10.03	<0.05
Angina stable state	48.27 ± 9.15	87.24 ± 8.89	<0.05
Frequency of angina pectoris	49.27 ± 8.71	88.79 ± 8.24	<0.05
Treatment satisfaction	45.81 ± 9.70	87.56 ± 9.28	<0.05
Disease awareness	49.54 ± 6.92	84.29 ± 7.98	<0.05

Table 9 Comparison of SAQ Scores After the Operation Between Groups.

SAQ	Control group	Cocktail group	P
Degree of limitation of physical activity	82.35 ± 9.30	84.18 ± 10.03	0.57
Angina stable state	82.28 ± 7.43	87.24 ± 8.89	0.21
Frequency of angina pectoris	78.12 ± 7.37	88.79 ± 8.24	0.02
Treatment satisfaction	81.47 ± 8.34	87.56 ± 9.28	0.19
Disease awareness	86.24 ± 7.54	84.29 ± 7.98	0.23

therapy for patients with CTO are important for increasing effective reperfusion.

In patients with CTO, PCI may lead to tearing of the coronary artery intima, thereby activating platelets and resulting in a slow or no-flow phenomenon in ischemic vessels, as well as decreasing effective reperfusion [10]. The results of this study showed that after treatment, the TIMI flow grading in the cocktail group was significantly superior to that in the control group. The stent implantation stimulated blood vessels, thus causing microvascular reperfusion injury. The forward flow in infarction-related vessels triggered low reperfusion. We added a cocktail of drugs (tirofiban + nicorandil) to the traditional dual antiplatelet treatment. Tirofiban is a highly-specific non-peptide platelet GPIIb/IIIa receptor antagonist that effectively blocks the common pathway of platelet activation and aggregation. Nicorandil is a preparation with dual pharmacological functions as an opener of ATP-sensitive potassium (KATP) channels and as a source of nitrates. Nicorandil expands the aorta; decreases coronary resistance; increases coronary blood flow; expands blood vessels; and ultimately decreases the preload and afterload, and relieves symptoms of myocardial ischemia [11]. The synergistic effects of the above two drugs effectively improved myocardial tissue perfusion, thereby increasing effective reperfusion.

Atherosclerosis is a chronic inflammatory disease caused by the abnormal accumulation of macrophages, white blood cells, and lipids in the arterial wall [12]. IL-4, in addition to being an important member of the IL family, plays an important role in the development of arteriosclerosis [13]. This study showed that, only in the cocktail group, the levels of IL-4 significantly decreased after the operation. In addition, this decrease was greater in the cocktail group than in the control group ($P < 0.05$). The cocktail therapy effectively inhibited inflammation and decreased IL-4 levels. Tirofiban and nicorandil not only blocked platelet activation and the expanding aorta, but also inhibited the expression of inflammatory factors. That is, the intraoperative and postoperative administration of tirofiban and nicorandil alleviated the degree of inflammation in patients with CTO.

sICAM-1 is scarcely expressed in normal blood vessels, although it is abundantly expressed in the blood of patients with atherosclerosis [14]. Many clinical studies have examined the relationship between sICAMs and CAD manifestations [15]. Our study showed that the levels of sICAM-1 in the cocktail group significantly decreased after the operation ($P < 0.05$). Moreover, after the operation, the decrease was greater in the cocktail group than the control group ($P < 0.05$). The 6-month follow-up indicated that the total incidence rate of adverse cardiac events in the cocktail group was significantly lower than that in the control group ($P < 0.05$), because sICAM-1 is involved in the inflammatory response and adhesion reaction in patients after PCI, thus causing vasoconstriction and slowing the blood flow, and ultimately leading to cardiovascular events [16]. Tirofiban and nicorandil treatment inhibited the expression of inflammatory factors, thereby decreasing the level of sICAM-1, the frequency of angina pectoris, and the incidence rate of adverse cardiac events in patients.

Many clinical studies have compared PCI and optimal medical therapy (OMT) in patients with CTOs [9, 17–19]. However, little is known about the effects of a combination of OMT and PCI for CTO. Moreover, in-stent restenosis occurs in 15% of all CTO-PCIs [20]. Hence, timely OMT after PCI is crucial to achieve effective reperfusion in CTO.

This study revealed that a combination of OMT and PCI for CTO, that is, the treatment of patients with CTO undergoing PCI with tirofiban and nicorandil, is not only safe and reliable, but also is associated with fewer major adverse cardiac events, through decreasing the IL-4 inflammatory biomarker and sICAM-1 levels.

In conclusion, the treatment of patients with CTO undergoing PCI with tirofiban and nicorandil, which is safe and reliable, decreases IL-4 and sICAM-1 levels and elevates effective reperfusion. The small sample size in this study inevitably led to data bias; therefore, the sample size must be increased in future studies to observe the long-term efficacy.

Declaration

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Conflict of interest

The authors declare that they have no conflicts of interest.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Qian Foshan Hospital (Shandong, China). Informed consent forms were signed by the patients or their guardians.

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