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Advances in the Application of Fondaparinux in Acute Coronary Syndrome

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Abstract

Acute Coronary Syndrome (ACS) is one of the major causes of death worldwide, including unstable angina, ST-segment elevation myocardial infarction and NST-segment elevation myocardial infarction. ACS refers to a series of life-threatening heart diseases, which is caused by rupturing coronary plaque and releasing thrombin activation. Then thrombin is activated and generates plaque and thrombosis, which increases the risk of cardiac death and myocardial infarction. Aggressive and conservative treatment is available in clinic practice. Anticoagulant therapy is usually the first choice for conservative treatment and used in combination with dual antiplatelet drugs, which plays an important role in the treatment of acute coronary syndrome. Fondaparinux as a commonly used anticoagulant drug is both antithrombotic effectively and can reduce the risk of bleeding and coronary microvascular dysfunction in the pathogenesis of ischemic heart disease. However, it increased the rate of bleeding. People pay more attention to the role of long-term prognosis. Domestic and foreign researches contrast outcomes of acute coronary syndrome of fondaparinux and low molecular weight heparin.

Keywords

Fondaparinux Sodium, Acute Coronary Syndrome, Heparin

1. Introduction

Acute coronary syndrome is still a serious challenge to the clinical practice [1] [2] [3] [4]. Each person experiences a coronary event every 40 seconds, which increases the number of recurrent myocardial infarction by more than 600,000 and 200,000 per year [5] [6]. Although great progress has been made in the treatment of ACS in recent years, the survival rate has been improved. The mor-

tality rate of cardiovascular diseases is still relatively high [4].

As an anti-Xa factor drug, fondaparinux sodium has complete bioavailability [5]. It can be administered once a day through renal metabolism. To assure the safety of the patient's medication and inhibit the formation of thrombin, early venous anticoagulation is the prime therapy for patients with acute coronary syndromes. It antagonizes ongoing coronary thrombosis and promotes percutaneous coronary intervention to reduce mortality and acute stent thrombosis [7]. Although it can increase the blood clots, but not affect antithrombin of thrombin II inhibition of a factor. In addition, fondaparinux sodium does not interact with platelets, which does not affect the duration of bleeding. In recent years, a number of large trials abroad have proved that it is safe and effective for non-ST-segment elevation myocardial infarction with acute coronary syndrome [8] [9], which is superior to ordinary heparin or low molecular heparin significantly reducing bleeding and complications [10]. However, its efficacy and safety have not been proved for ST-segment elevation myocardial infarction patients [9]. In this paper, the research progress of fondaparinux sodium in acute coronary syndrome is reviewed and flow chart of literature screening as **Figure 1**.

2. The Clinical Research of Fondaparinux on ST Segment Elevation Myocardial Infarction

Tjeerd [11] researched the safety ang efficacy of fondaparinux compared to control according to 12,092 patients with ST-segment elevation myocardial infarction in the OASIS-6 trial. OASIS-6 is a controlled, randomized, double-blind trial, which is comparing fondaparinux to control (placebo or UFH).Myocardial infarction or death rates were reduced by fondaparinux at age 56 years (4.5% vs 4.8%); at age 56 - 68 years (7.9% vs 9.7%); at age ≥ 69 years(17.2% vs 19.8%). Severe hemorrhage rates were reduced at age 56 years (0.5% vs 0.6%), at age 56 -

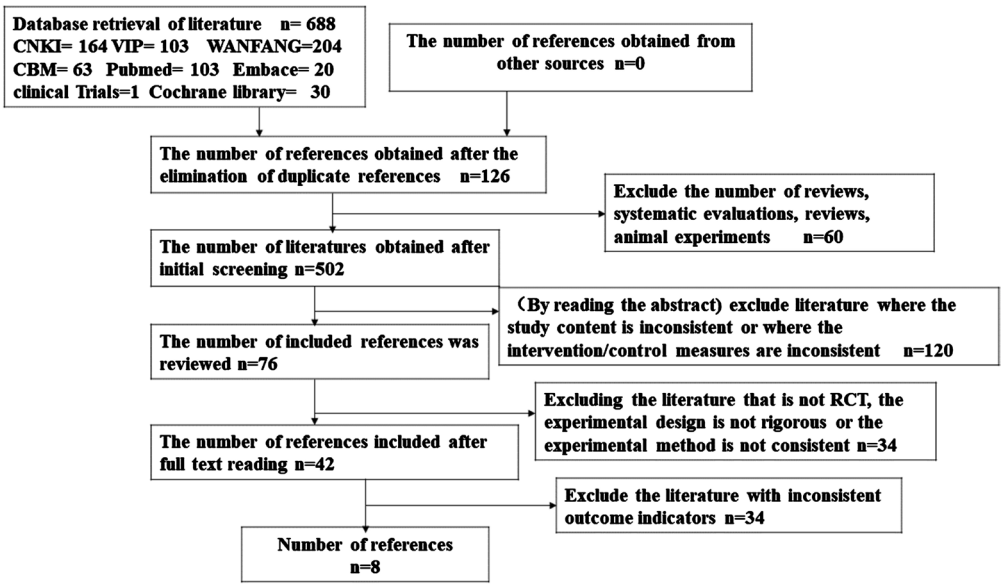

Figure 1. The flow chart of literature screening.

68 years (0.9% vs 1.5%), at age ≥ 69 years (2.1% vs 2.4%). Myocardial infarction, Death or severe bleeding rates were reduced at age 56 years (4.8% vs 5.0%), at age 56 - 68 years (8.1% vs 10.1%), at age ≥ 69 years (17.6% vs 20.4%). The benefits and risks of fondaparinux is coincident across every age level, supporting that fondaparinux's use across every age level of patients with ST segment elevation myocardial infarction who don't undergo primary percutaneous coronary intervention.

Alexandre de Matos Soeiro [12] study is a multicenter retrospective observational study. The study includes 2282 patients, which were divided into two groups (1947 in the enoxaparin group; 335 in the fondaparinux group). Firstly outcome was all-causes mortality. Secondary outcome was combined with reinfarction, cardiogenic shock, death, bleeding and stroke. Comparison was done through Chi-Square test and T test between the groups. With regards to treatment, the performance of a percutaneous coronary intervention in 35.1% in the enoxaparin group ($p = 0.13$) and in 40.2% in the fondaparinux group. In the multivariate analysis, study respectively showed significant differences between two groups in relation to bleeding (2.3% vs. 5.2%) and combined these events (13.8% vs. 22%). According to recently published international literature proved fondaparinux is superior to enoxaparin and can reduce the combined events and bleeding.

3. The Clinical Research of Fondaparinux on NST Segment Elevation Myocardial Infarction

Yusuf S [13] study 20,078 patients with acute coronary syndromes to receive either enoxaparin (1 mg/kg twice daily) or fondaparinux (2.5 mg daily) and assessed death, refractory ischemia, or myocardial infarction in nine days; major bleeding; and their combination. The period of Patient's following is six months. The primary-outcome events were similar in the enoxaparin and fondaparinux groups (579 with 573 with enoxaparin [5.7 percent] vs. fondaparinux [5.8 percent]). The events of meeting this combined outcome indicated a non-significant difference in the fondaparinux group at 30 days (805 vs. 864) and in the ending of the research (1222 vs. 1308). The rate of major bleeding in nine days was observably higher enoxaparin than with fondaparinux (412 events [4.1 percent] vs. 217 events [2.2 percent]). The all outcome and major bleeding at nine days supported fondaparinux (7.3 percent vs. 9.0 percent). Fondaparinux was showed a significantly reduction of deaths at 30 days (295 vs. 352) and at 180 days (574 vs. 638). Fondaparinux compared with enoxaparin in reducing the rate of ischemic events at nine days. However, fondaparinux can reduces major bleeding and improves long term morbidity and mortality.

Yan HB [14] studied 300 patients with NST segment elevation Acute Coronary Syndrome who were randomized to accepted either nadroparin (n = 150, 0.1 ml/10 kg q12 h) or fondaparinux (n = 150, 2.5 mg/d) for a mean of 4 days, which is a randomized, prospective, single center, open-label study. The prime

safety end-point was the events of major or minor bleeding in 9 days, which was not associated with coronary artery bypass grafting (CABG). The prime efficacy end-points contained myocardial infarction, death, or recurrent ischemia in 9 days. All patients were followed up 180-day. There was a non-significant 28% relative risk decrease in the prime safety end-point in fondaparinux group compared with group nadroparin (4.7% vs. 6.7%). The prime efficacy end-point was 8.0% vs 10.0% in the group fondaparinux and nadroparin. The efficacy and safety end-points at 9 days (10.0% vs. 16.0%), 30 days (14.0% vs. 17.9%), or 180 days (18.7% vs. 27.3%) indicated a non-significant trend about a lower value in group fondaparinux. Fondaparinux showed a non-significant risk decrease in patients with NST segment elevation acute coronary syndrome in ischaemic both and bleeding events during short- and long-term follow-up comparing with nadroparin.

Coussement PK [15] study a total of 7 studies including 9618 patients (mainly non-ST-elevation myocardial infarction) were included. Analysis showed that the mortality of enoxaparin and fondaparinux sodium was similar (OR 1.05, 95% CI 0.67-1.63, P = 0.84).There was no significant difference between myocardial infarction and stroke at different follow-up periods. However, the risk of total bleeding was significantly reduced in the fondaparinux heparin group (OR 0.47, 95% CI 0.37 - 0.60, P = 0.00001); during the 10-day follow-up, P = 0.00001). The risk of bleeding was still lower than that of enoxaparin at 30 days of follow-up or at the middle follow-up.

Sorosh [2] study showed low molecular weight heparin versus fondaparinux increase the risk of perioperative bleeding in patients who accepting coronary artery bypass. All acute coronary syndrome patients from the European multicenter registry, prospective on coronary artery bypass grafting preoperatively were treated with low-molecular weight heparin or fondaparinux. The prime outcome measure was major bleeding defined by the Universal Definition of Perioperative Bleeding stratified by P2Y₁₂ inhibitor quit. Secondary outcome measures contained 3 other definitions of major bleeding, which was available in cardiac surgery trials. Bias score matching was performed to adjust for differences in preoperative and perioperative covariates, 1525 patients were included, of whom 1249 (81.9%) low-molecular weight heparin and 276 (18.1%) received fondaparinux preoperatively. In cohorts matched by propensity score (245 pairs), the risk of massive bleeding was similar between the fondaparinux and low-molecular weight heparin groups, which was based on the general definition of perioperative severe or massive bleeding (11.8% vs 9.0%) and the other three major bleeding definitions. In summary, preoperative treatment with fondaparinux and low-molecular weight heparin was similar to perioperative bleeding in patients who with acute coronary syndromes undergoing coronary artery bypass grafting.

A recent study showed that non-ST patients were treated with fondaparinux and low molecular weight heparin in segmental elevation acute coronary syn-

dromes in 15 d group recurrence of angina pain, Q wave myocardial infarction, emergency coronary intervention, death and bleeding cases. There was no significant difference between the molecular heparin group ($P > 0.05$). This indicates that the therapeutic effect of fondaparinux on non - ST - segment elevation acute coronary syndrome is obvious [16].

However, PENTUA [17] study showed that the incidence of death, myocardial infarction or recurrent ischemia in subcutaneous injection of fondaparinux (and enoxaparin nine days) was 27.9% and 35.7%. There was no difference in bleeding risk between the two groups ($P < 0.05$). The Fondaparinux efficacy and safety of enoxaparin may be similar. The role of fondaparinux in acute coronary syndrome remains to be further studied [18].

Fondaparinux has been compared with low molecular weight heparins (LMWH) for Non-ST-Segment Acute Coronary Syndromes. We selected three random study information to systematically review the trials comparing the efficacy and safety of fondaparinux and LMWH for Non-ST-Segment Acute Coronary Syndromes (**Table 1**).

4. Conclusion

Acute coronary syndrome is characterized by acute onset, critical condition and high mortality, which need early anticoagulation intervention. The anticoagulant therapy is not only antithrombotic but also does not increase the risk of bleeding [19]. In terms of therapeutic drugs, the widely used antiplatelet drugs the anticoagulant and aspirin have gradually become routine treatment drugs [20]. The combination of antiplatelet agents and anticoagulants observably decreases the events of severe cardiovascular diseases and mortality. But the side-effect of anticoagulant drugs is also caused by an observably increase in various bleeding [7]. The consequences of serious threating to the patient's life and health are increasing at the same time. A large number of clinical studies have been conducted on fondaparinux by researchers, which showed that fondaparinux can decrease the risk of mortality, bleeding and morbidity for non-ST-segment elevation acute coronary syndrome. Fondaparinux may be the better choice, and this result is mainly applicable to patients with non-ST-segment elevation acute coronary syndrome [21]. But fondaparinux is III class international guidelines

Table 1. Three large random studies on non-ST-segment elevation acute coronary syndromes.

Characteristics of Included Studies				Medication Time		Doses of Medication		Number of Patients	
Study	Year	N	Clinical Trail Setting	Fondaparinux	LMWH	Fondaparinux	LMWH	Fondaparinux	LMWH
OASIS-5	2006	20078	Multicentered, double blind RCT	8 Day	2 - 8 Day	2.5 mg qd	1 mg/kg bid	10021	10057
PENTUA	2004	459	Multicentered, double blind RCT	3 - 7 Day	3 - 7 Day	2.5 mg qd	1 mg/kg bid	229	230
Yan	2011	300	prospective, open-label, and single center study, RCT	4 Day	4 Day	2.5 mg qd	0.01 ml/kg q12	150	150

that recommend not advocating using for ST-segment elevation acute coronary syndrome patients. However, the limitation number of patients with analysis that needs further large randomized trials will be confirmed. It is difficult to completely avoid clinical therapy. The influence of subjective choice on the results of the study was further evaluated. Large randomized controlled studies are needed to study the safety and efficacy of fondaparinux.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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