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Efficacy and safety of early versus late glycoprotein IIb/IIIa inhibitors for PCI

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ABSTRACT

Background: Glycoprotein (Gp) IIb/IIIa inhibitors are beneficial for patients with ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI). However, optimal drug timing remains inconclusive. Therefore, this study was to perform a meta-analysis of the clinical efficiency and safety of early versus late GpIIb/IIIa inhibitors in STEMI patients undergoing PCI.

Methods: A comprehensive search was to identify randomized trials of early versus late GpIIb/IIIa inhibitors in STEMI patients undergoing PCI. The GpIIb/IIIa inhibitors were abciximab and small-molecular Gp inhibitors (SMGP) namely eptifibatide and tirofiban. The efficacy endpoints included pre-procedural Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow, post-procedural TIMI 3 flow, complete ST-segment resolution, left ventricle ejection fraction (LVEF), and mortality. The safety endpoint was the occurrence of major bleeding complications.

Results: Nineteen trials were included in the meta-analysis, involving 4209 patients (early 2124 versus late 2085). Early GpIIb/IIIa inhibitors significantly improved pre-procedural TIMI 3 flow, while early abciximab, but not SMGP, further enhanced post-procedural TIMI 3 flow, complete ST-segment resolution, LVEF, and reduced six-month mortality. In addition to clopidogrel loading, only early abciximab improved pre-procedural TIMI 3 flow and complete ST-segment resolution. The rate of major bleeding complications was not increased in early GpIIb/IIIa inhibitors with/without clopidogrel loading.

Conclusions: Early GpIIb/IIIa inhibitors improved pre-procedural TIMI 3 flow and early abciximab provided favorable clinical outcomes in STEMI patients undergoing PCI. On the basis of clopidogrel loading, early abciximab enhanced pre-procedural TIMI 3 flow and ST-segment resolution. These beneficial effects were achieved without increased risks of major bleeding complications.

1. Introduction

ST-segment elevation myocardial infarction (STEMI) results from a ruptured atherosclerotic plaque, leading to thrombosis and occlusion of an infracted-related artery (IRA). If antegrade coronary blood flow is not reestablished quickly, total occlusion epicardial IRA could result in irreversible myocardial necrosis, permanently impairing heart contractile function, potentially leading to death. The principal goals of initial STEMI treatment are to achieve rapid reperfusion of IRA and enhance myocardial microvascular reperfusion, limiting myocardial ischemic necrosis and preserving heart function, thereby reducing mortality [1–3]. Effective and prompt reperfusion can be accomplished using fibrinolytic therapy or PCI. Clinical trials have demonstrated that combined antiplatelet therapy offers additional clinical benefits.

Primary PCI is superior to fibrinolytic therapy in improving clinical outcomes and reducing overall mortality in STEMI patients [4,5]. Nevertheless, a small number of STEMI patients present directly to a PCI center, while most present initially to their local hospital and then require transportation to a tertiary care center for PCI availability. The time delay to treatment represents a major drawback of PCI and may result in worse outcomes, particularly in high-risk patients [6]. The risk of one year mortality is increased by 7.5% for each 30-minute delay [6].

Preprocedural Thrombolysis in Myocardial Infarction (TIMI) flow is an independent predictor of STEMI patient survival, suggesting that pharmacological pretreatment can restore antegrade flow soon after transportation. Therefore, combination therapy including pharmacological therapy and PCI for STEMI is currently an area of great interest. Adjunctive glycoprotein (Gp) IIb/IIIa inhibitors reduce recurrent myocardial infarction (MI) and mortality in STEMI patients undergoing PCI [7,8]. Several randomized trials have shown that timing is important for the administration of Gp IIb/IIIa inhibitors in patients undergoing PCI, indicating that early Gp IIb/IIIa inhibitors are more attractive for the benefits from early recanalization, particularly if the patient has to travel long distances [9–11]. Nonetheless, debates over the clinical efficiency and safety of early versus late GpIIb/IIIa inhibitors in patients undergoing PCI exist.

GpIIb/IIIa inhibitors and clopidogrel are utilized as antiplatelet agents to optimize the treatment of STEMI. Clopidogel selectively inhibits adenosine diphosphate (ADP)-mediated binding of fibrinogen

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to the GpIIb/IIIa receptor, substantially decreasing the activation and aggregation of platelets. Clopidogrel, in combination with fibrinolytic therapy, has been shown to improve the patency of IRA and to reduce ischemic complications, with no associated increase in major bleeding [12]. GpIIb/IIIa inhibitors depress fibrinogen binding to GpIIb/IIIa receptors on the platelet surface, which is the final common pathway for platelet aggregation [13]. Consequently, GpIIb/IIIa inhibitors may act synergistically with clopidogel due to their distinct and complementary mechanisms of action. The adjunctive GpIIb/IIIa inhibitors on top of clopidogel loading provide the most sustained platelet inhibition and the lowest incidence of recurrent MI, as evidenced by the lowest myocardial necrosis [14–17]. Moreover, some patients have poor responses to clopidogrel and patients carrying two CYP2C19 (clopidogrel metabolism gene) loss-of-function variants have a higher rate of ischemic cardiovascular events following PCI [18]. Adjunctive GpIIb/IIIa inhibitor in addition to clopidogel administration is currently recommended for the prevention of atherothrombotic events following PCI in the American College of Cardiology/American Heart Association practice guidelines [17]. However, clinical efficacy and bleeding risk of early versus late GpIIb/IIIa inhibitor with adequate clopidogel loading have not been clarified and several clinical trials have been too small to deduce meaningful conclusions [19–21].

Currently, three intravenous GpIIb/IIIa inhibitors are available: the monoclonal abciximab and the small-molecule glycoprotein IIb/IIIa inhibitors (SMGP), namely eptifibatide and tirofiban. Abciximab is structurally and pharmacologically different from the SMGPs. Firstly, the affinity of abciximab for the GpIIb/IIIa receptor is higher than that of SMGP, resulting in nearly the entire drug adhering to platelets. Secondly, abciximab may bind to more sites within the GpIIb/IIIa complex than SMGP. Thirdly, abciximab binds to other molecules including the vitronectin receptor and Mac-1, whereas SMGIP is specific for GpIIb/IIIa. Significant differences exist between the clinical outcome of abciximab and SMGP following PCI procedures [22]. Therefore, the meta-analysis of pre-specified subgroups was performed according to abciximab and SMGP administration.

2. Materials and methods

2.1. Eligibility and search strategy

We identified all randomized trials comparing pharmacological facilitation using an early versus late administration of GpIIb/IIIa inhibitors in STEMI patients undergoing primary PCI according to Cochrane systematic review guidelines [23]. The literature was scanned using formal searches of Pubmed from 1966 to December 2010, Embase from 1974 to December 2010, Cochrane Central Register of Controlled Trials (The Cochrane Library 2010, Issue 11), and the Chinese Medical Journal Network from 1978 to December 2010. In addition, we searched the following websites: http://opensigle.inist.fr/ and http://clinicaltrials.gov/, and abstracts presented at major cardiovascular conferences. Finally, the appropriate trials were hand searched. Key words were used as follows: myocardial infarction, acute coronary syndrome; abciximab, tirofiban, eptifibatide, facilitated PCI, facilitated angioplasty, glycoprotein IIb/IIIa inhibitors, and Gp IIb/IIIa inhibitors. English or Chinese publications were identified using these searches.

2.2. Study selection

The randomized clinical trials were enrolled into our meta-analysis according to the following inclusion criteria: 1) the object of investigation was a STEMI patient undergoing primary PCI. 2) Interventional procedures were early administration of Gp IIb/IIIa inhibitors, which occurred en route to the hospital (e.g., in the ambulance) in the community hospital prior to or during transportation to the cardiac catheterization laboratory, or in the emergency room. 3) Late administration of Gp IIb/IIIa inhibitors just prior to PCI as control. 4) The endpoints included angiographic outcomes, electrocardiogram (ECG) changes, or clinical outcomes. The following clinical trials were excluded from this meta-analysis: 1) the randomized trials were performed between early Gp IIb/IIIa inhibitor administration and placebo control. 2) The randomized trials were designed to investigate the efficacy and safety of the addition of Gp IIb/IIIa inhibitors to fibrinolytic therapy. 3) The randomized trials compared the early conventional administration with the late bailout use of Gp IIb/IIIa inhibitors.

2.3. Outcome measures

The primary endpoints included pre-procedural Thrombolysis in Myocardial Infarction Study (TIMI) grade 3 flow. Secondary endpoints included post-procedural TIMI 3 flow, complete ST-segment resolution, left ventricle ejection fraction (LVEF) and mortality. Safety endpoints included major bleeding complications. Complete ST-segment resolution was interpreted as recovery of the ST-segment >70%. Major bleeding complications were defined as retroperitoneal, intracranial bleeding, reduced in hemoglobin >5 g/dl, or an absolute drop in hematocrit >15%.

2.4. Data extraction

Two authors (Jian Yin and Qiang Xu) independently reviewed the trials according to the inclusion and exclusion criteria. Trial quality was scored using a quality assessment form based on Cochrane systematic review guidelines [23]. This scale assessed sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias. Extracted data were as follows: 1) baseline characteristics of included trials consisted of author, sample size, study design, endpoints, and follow-up duration. 2) Clinical features of patients included age, gender, hypertension, hyperlipemia, diabetes, smoking, and time duration from drug administration prior to the procedure. 3) Observation indicators comprised the number of incidences and total numbers of categorical variables, the mean ± standard deviation and the number of observations for continuous variables. In cases of incomplete or unclear data, authors were contacted whenever possible. Disagreements were resolved by discussion with the senior author (Dr. Liangyi Si).

2.5. Statistical analyses

Statistical analyses were performed using Review Manager 5.1 (The Cochrane Collaboration, Oxford, England) and SPSS 15.0 (SPSS Inc, Chicago, IL) statistical package. Risk ratio (RR) and 95% confidence interval (CI) for categorical variables were calculated using a fixed-effect model with the Mantel–Haenszel method. The DerSimonian and Laird random effect model was additionally applied to calculate RRs in cases of significant heterogeneity across studies. The mean difference (MD) and 95% CI were used for continuous variables with Inverse Variance Method. Heterogeneity across trials was analyzed using means of $I^2 = [(Q - df)/Q] \times 100\%$, where Q is the chi-square statistic, and df is the degrees of freedom. Potential publication bias was examined by constructing a funnel plot. Pre-specified subgroup analyses were performed according to abciximab and SMGP. The P value for significance of association and heterogeneity tests was set at 0.05, with $P<0.05$ considered statistically significant. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology: Shewan LG and Coats AJ. Ethics in the authorship and publishing of scientific articles. Int J Cardiol 2010;144:1–2.

3. Results

Of the 1367 potentially relevant articles initially screened, we initially included 938 from Pubmed, 992 from Embase, 237 from Cochrane Library, 17 from the Chinese Medical Journal Network, and two from other resources. Nineteen randomized trials were included in the final meta-analysis. Trial selection flow was outlined in Fig. 1. Eleven trials was conducted on abciximab (n = 2626, 62.4%) [11,20,21,24–31], six trials on tirofiban (n = 1165, 27.7%) [19,32–36] and two trials on eptifibatide (n = 418, 9.9%) [37,38]. Study characteristics are summarized in Table 1. A total 4209 patients were included, 2124 patients

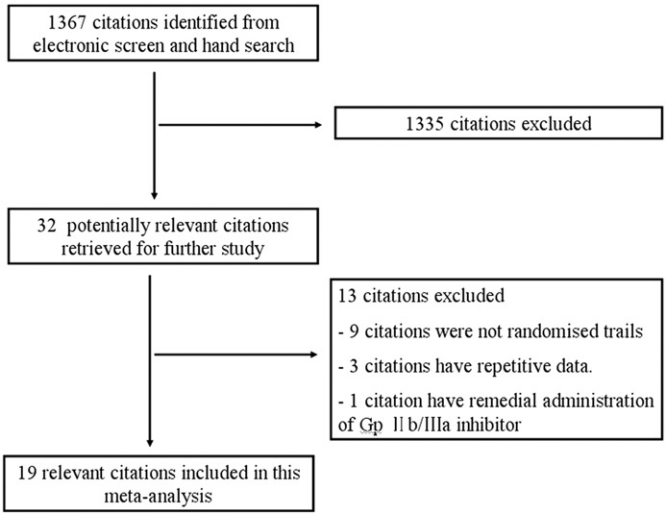

Fig. 1. Trial selection flow chart. Flow chart indicates processes performed for selecting relevant randomized clinical trials included in the current meta-analysis.