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Administration of erythropoietin in patients with myocardial infarction: does it make sense? An updated and comprehensive meta-analysis and systematic review

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ABSTRACT

This systematic review with meta-analysis sought to determine protective effects of erythropoietin on clinical outcomes following percutaneous coronary intervention (PCI). Medline, Embase, Elsevier and Sciences online database as well as Google scholar literature were used for selecting appropriate studies with randomized controlled design. The effect sizes measured were odds ratio (OR) for categorical variables and weighted mean difference (WMD) with 95% confidence interval for calculating differences between mean values of duration of hospitalization in intervention and control groups. Values of $P < 0.1$ for Q test or $I^2 > 50\%$ indicated significant heterogeneity between the studies. The literature searches of all major databases retrieved 973 studies. After screening, a total of 15 trials that reported outcomes were identified. Pooled analysis was performed on left ventricular ejection fraction (WMD of −0.047; 95% CI: −0.912 to 0.819; $P = 0.9$), left ventricular end diastolic volume (WMD of −0.363; 95% CI: −3.902 to 3.175; $P = 0.8$), left ventricular end systolic volume (WMD of 0.346; 95% CI: −2.533 to 3.226; $P = 0.8$), infarct size (WMD of −0.446; 95% CI: −2.352 to −1.460; $P = 0.6$), stroke (OR of 2.1; 95% CI: 0.58 to 7.54; $P = 0.2$), re-myocardial infarction (OR of 1.06; 95% CI: 0.52 to 2.185; $P = 0.8$), heart failure (OR of 0.53; 95% CI: 0.259 to 1.105; $P = 0.09$), mortality (OR of 0.56; 95% CI: 0.27 to 1.19; $P = 0.13$), thrombosis (OR of 0.774; 95% CI: 0.41 to 1.45; $P = 0.4$), major adverse cardiovascular events (OR of 0.926; 95% CI: 0.63 to 1.35; $P = 0.6$). Short-term administration of EPO in patients with myocardial infarction (MI) undergoing PCI does not result in improvement in cardiac function, reduction of infarct size and all-cause mortality. Low dose EPO therapy may not be the choice of treatment for the patients with MI, while higher doses might be more effective.

1. Introduction

Cardiovascular disease is the leading cause of death worldwide [1,2]. Coronary revascularization is associated with a high success rate of recanalization, contributing to decrease in prevalence of cardiac events and improvement of ventricular contractility and survival prognosis [1,2]. Rapid reperfusion of ischemic myocardium remains the best treatment for limiting infarct size and further complications [3]. Although additional therapies have been reported for cardioprotection after myocardial infarction (MI), left ventricular remodeling after MI is complicated by cardiac failure accompanying enlargement of left ventricular chamber and worsening long-term prognosis [4–6]. Erythropoietin (EPO) is commonly known as an effective treatment for anemia, partially caused by an inadequate production of endogenous EPO in patients with chronic renal impairment [7,8]. EPO is a 165 amino acid glycoprotein with a molecular weight of 34000, and is produced by the kidney in response to hypoxic stimulation. EPO promotes maturation of red blood cells in the bone marrow by binding to receptors coupled to anti-apoptotic Akt and JAK-STAT signaling pathway in erythroid precursors [7–10]. A functional EPO receptor was found in the cardiovascular system including endothelial cells and cardiomyocytes [10–13]. Animal model studies have reported that EPO may have cardioprotective effects including attenuating ischemic reperfusion injury, reducing infarct size, and improving LV function [11–15]. In recent years, several randomized controlled trails have investigated EPO in patients with MI. However, the findings of these trials are controversial. Some studies observed cardioprotective effects with EPO whereas others failed to exhibit any benefit.

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This systematic review with meta-analysis sought to determine the strength of evidence for effects of EPO on clinical outcome, echocardiographic and cardiac magnetic resonance imaging results and serum level of creatine kinase in patients with MI undergoing percutaneous coronary intervention (PCI).

2. Methods and materials

2.1. Literature search

A comprehensive literature search was conducted in major electronic databases (Medline/Pubmed, Embase, Elsevier, Web of Knowledge, Sciences online database and Google Scholar) from their inception through July 15, 2014 to identify RCT reporting the effects of EPO on clinical outcome in patients with MI undergoing PCI. Predefined search terms included: "erythropoietin", "Epoetin", "EPO", "darbepoetin", and "myocardial infarction", "MI", "ST-segment myocardial infarction", "STEMI", and "percutaneous coronary intervention", "PCI". No language restrictions were applied. All references of the included RCTs were also reviewed to determine additional studies not indexed in common databases. Studies were included into the analysis when they met following criteria: 1) RCT, 2) reporting at least one of the outcomes of interest including: heart failure, re-MI, stroke, thrombosis, major adverse cardiovascular events, mortality, echocardiographic and cardiac magnetic resonance imaging results and serum level of creatine kinase. Abstracts without peer-review publications of manuscripts, duplicate reports and ongoing RCTs were not included.

2.2. Data extraction and outcome measures

Three investigators (S.A-H-S., P.M. and M.T.) extracted data independently, and discrepancies were resolved via a consensus standardized abstraction check-list used for recording data in each study. Data retrieved from trials included: author's name, study design, country, type of controls (placebo or not), details of therapeutic regimens, clinical scenario, sample size, mean age and gender. For each group the following data were recorded: incidences of heart failure, re-MI, stroke, thrombosis, major adverse cardiovascular events, mortality, echocardiographic results such as left ventricular ejection fraction, left ventricular end diastolic and systolic volumes, and other variables such as infarct size measured by cardiac magnetic resonance imaging, and serum level of creatine kinase. For exploration of heterogeneity among trials a subgroup analysis of disparities in the patients' characteristics was performed for: (1) follow-up (≤30 days vs. >30 days), (2) dose of EPO (low vs. high), (3) time of administration (before PCI vs. after PCI), (4) number of administration (single vs. multiple).

2.3. Definitions

Mortality was considered as all-cause mortality occurring up to 30 days postoperatively or before hospital discharge. The length of hospital stay was measured in days. Ventricular arrhythmias and the composite of other serious cardiovascular events (such as cardiac death, recurrent MI, additional coronary revascularization procedures, and stroke) were considered as major adverse cardiovascular events. Doses of EPO were measured in IU (low dose: <30000 IU and high dose: ≥30000 IU).

2.4. Statistical analysis, publication bias and quality assessment

Data were analyzed by STATA version 11.0 utilizing METAN and METABIAS modules. The effect sizes measured were odds ratio (OR) with 95% confidence interval (CI) for categorical variables. Regarding non-categorical data, the standard mean difference (WMD) with 95% CI was used for calculating differences in continuous outcomes between intervention and control groups. OR < 1 favored EPO and OR > 1 favored control. RCTs with no events in the 2 arms were discarded from pooled analysis. Forest plots were created for each outcome. A value of $P < 0.1$ for Q test or $I^2 > 50\%$ indicated significant heterogeneity among the studies. Heterogeneity among trials was assessed by applying a random effect model when indicated. The presence of publication bias was evaluated using Begg and Egger tests. Quality assessment of RCTs was performed using the Jadad score. The Jadad score assesses 3 items including randomization (0–2 points), blinding of study (0–2 points), and withdrawals and dropouts (0–1 points). Higher scores indicate better reporting ("high" quality: 5; "good" quality: 3–4; "poor" quality: 0–2). Results were considered statistically significant at P-values <0.05.

3. Results

3.1. Literature search strategy and included trials

Literature search retrieved 973 studies from the screened databases of which 846 (86.9%) were excluded after initial review. Of 127 primary included studies, 112 were excluded after detailed evaluation due to insufficient reporting of endpoints of interest. The final analysis included 15 RCTs.

3.2. Study characteristics and effect measures and clinical outcomes

3.2.1. Left ventricular ejection fraction

A total of 1336 patients were included from 10 RCTs reporting data on LVEF. Patient populations from RCTs ranged from 20 to 529 patients (Table 1). From 1336 patients, 662 were allocated to EPO and 674 to the control group. Mean LVEF for all trials were 51.39 ± 9.97 with 51.82 ± 9.52 for EPO and 50.97 ± 10.43 for the control group (Table 2). Applying a random effect model, pooled analysis revealed that EPO therapy failed to increase ejection fraction with a WMD of −0.047 (95% CI: −0.912 to 0.819; $P = 0.9$) (Fig. 1). There was mild heterogeneity among studies (chi-squared = 17.81, $I^2 = 49.5\%$) (Table 3).

3.2.2. Left ventricular end diastolic and systolic volume

A total of 525 cases were included from 5 RCTs reporting data on LVEDV and LVESV. Patient population of RCTs ranged from 36 to 138 patients. From all patients, 261 were allocated to EPO and 264 to the control group (Table 1). The mean LVEDV for all trials was 88.7 ± 22.2 with 88.9 ± 19.3 for EPO and 88.5 ± 25.1 for the control group, and the mean LVESV for all RCTs was 43.4 ± 21.1 with 43.3 ± 20.3 for EPO and 43.6 ± 21.8 for the control group (Table 2). Applying a random effect model, pooled analysis reported that EPO therapy could not change LVEDV (WMD of −0.363; 95% CI: −3.902 to 3.175; $P = 0.8$) and LVESV (WMD of 0.346; 95% CI: −2.533 to 3.226; $P = 0.8$) (Supplementary Fig. 1A for LVEDV and 1-b for LVESV). There was no heterogeneity among the studies for LVEF and LVESV analyses ($I^2 = 0.0\%$ for both) (Table 3).

3.2.3. Infarct size

Mean size of infarction for all trials was 24.5 ± 12.9% for LV with 23.7 ± 12.7 for EPO and 25.2 ± 13.2 for the control group (Tables 1–2). Pooled analysis revealed that EPO therapy did not impact the size of myocardial infarction with a WMD of −0.446 (95% CI: −2.352 to −1.460; $P = 0.6$) (Fig. 2). No significant heterogeneity was observed between the RCTs (chi-squared = 4.82, $I^2 = 0.0\%$).

3.2.4. Incidence of stroke

A total of 1592 patients were included from 7 RCTs reporting data on the incidence of stroke. After removing RCTs with no events in 2 arms, a total of 1431 patients from 5 studies were included in the meta-analysis. Patient population of RCTs ranged from 57 to 529 patients. From 1431 cases, 721 were allocated to EPO and 710 to the control group (Table 1). The overall incidence of stroke was 0.55% ranging from 0.37% to 1.75%. Stroke occurred in 0.83% in CS group and 0.28% in control