

Effects of prostaglandin E1 on reperfusion injury patients

A meta-analysis of randomized controlled trials

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Abstract

Background: Prostaglandin E1 (PGE1) is widely used as a pretreatment for myocardial reperfusion injury in animal experiments. However, the cardioprotective effects of PGE1 in patients have not been established. We performed a meta-analysis to investigate whether PGE1 is cardioprotective, based on the reduction of correlative reperfusion injury events (CRIE), major adverse cardiac events (MACE), and biomarker release in patients with ischemia reperfusion injury.

Methods: The Medline, EMBASE, and Cochrane databases were searched for randomized clinical trials confirming the effects of PGE1. Two investigators independently selected suitable trials, assessed trial quality, and extracted data.

Results: Six studies in patients undergoing percutaneous coronary intervention (4 studies) and cardiac surgery (2 studies), comprising a total of 445 patients, were included in this review. The results showed that PGE1 reduced the incidence of CRIE (relative ratio 0.4 [95% confidence interval 0.43, 0.95]), the incidence of MACE (0.35 [0.17, 0.70]), and the level of troponin T (standardized mean difference 20.28 [20.47, 20.09]), creatine kinase-MB (−1.74 [−3.21, −0.27]), interleukin-6 (−1.37 [−2.69, −0.04]), and interleukin-8 (−2.05 [−2.75, −1.34]).

Conclusion: PGE1 may have beneficial effects on myocardial reperfusion injury in the clinic.

Abbreviations: CABG = coronary artery bypass grafting, CK-MB = creatine kinase-MB, CRIE = correlative reperfusion injury events, HF = heart failure, IHD = ischemic heart disease, IL-6 = interleukin-6, IL-8 = interleukin-8, IRI = ischemic reperfusion injury, MACE = major adverse cardiac events, PCI = percutaneous coronary intervention, PGE1 = prostaglandin E1, RCT = randomized controlled trial, RI = reperfusion injury, RR = relative ratio, SMD = standardized mean difference, TIMI = thrombolysis in myocardial infarction, TNT = troponin T, TVR = target vessel revascularization.

Keywords: correlative reperfusion injury events, major adverse cardiac events, Prostaglandin E1, reperfusion injury

1. Introduction

Ischemic heart disease (IHD) is a common cardiovascular disease, both in developed and developing countries. In 2011, a total of 7 million people died of IHD globally and it has become the

leading cause of mortality according to a report by the World Health Organization.^[1] The primary objective in the treatment of IHD is to restore blood perfusion to ensure adequate supply of tissue oxygen and nutrients and then to prevent ischemic injury. However, several clinical and animal studies have found that, when low tissue perfusion after ischemia is addressed, not only does ischemic tissue damage fail to resolve but also the injury is aggravated.^[2–8] This phenomenon, first described by Jennings et al^[9] in 1960, is defined as ischemic reperfusion injury (IRI). Myocardial IRI is often found in patients undergoing procedures involving ischemia reperfusion such as percutaneous coronary intervention (PCI), thrombolysis, coronary artery bypass grafting (CABG), and valve replacement, and its primary clinical manifestations are ventricular arrhythmia, lack of reflow phenomenon, and distal embolization.^[10–12] During reperfusion, inflammatory, and oxidative stress injury causes white blood cells to release inflammatory mediators such as interleukins and to activate complement, leading to myocardial injury, and endothelial injury activates platelet resulting in microvasculature blockage.^[13,14] Moreover, ventricular fibrillation or heart failure (HF) also arises from inner cell membrane instability.^[15]

Prostaglandin E1 (PGE1), also known as alprostadil, has many physiological and pharmacological properties which may contribute to IRI. In recent decades, some animal and clinical studies have shown that PGE1 can improve reperfusion injury (RI) in several biological systems.^[16–19] However, it is difficult to conclude that PGE1 has a beneficial effect in myocardial RI because of the limited numbers of patients included in these

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HZ and XX contributed equally to this study.

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studies. Therefore, the purpose of the present study was to identify and combine all relevant published clinical randomized controlled trials (RCTs) to investigate the effects of PGE1 on myocardial RI.

2. Methods

2.1. Data sources

The Medline, EMBASE, Cochrane, and databases and the lists of references found in original and review articles were searched independently by 2 reviewers (Zhu, Xu) using medical subject heading terms, key words, titles, and abstracts. The search keywords were “myocardial reperfusion injury,” “myocardial injury,” “reperfusion injury,” and “myocardial reperfusion” paired with “alprostadil,” “prostaglandin E1,” and “PGE1.” All historical literature was searched up until December 2016, and the search was not limited to the English language.

2.2. Study selection

An initial eligibility screen of all retrieved titles and abstracts was conducted, and original studies were included in our meta-analysis if they met the following criteria: (1) included human subjects; (2) included patients with myocardial ischemia who were randomly assigned to receive either PGE1 or placebo; (3) PGE1 was administered after ischemia and before reperfusion; (4) included sufficient data on correlative reperfusion injury events (CRIE), major adverse cardiac events (MACE) or relevant biomarkers (data at baseline and at the end of the study and/or data on change in standardized mean difference (SMD) from baseline or appropriate data estimation). Full manuscripts were obtained for all selected articles based on the assessment of abstracts. Only fully published trials were included (abstracts and congress presentations were not included). Primary outcome was the combined endpoint, divided into 2 subgroups: (1) CRIE, including no-reflow phenomenon, acute thrombus formation, and thrombolysis in myocardial infarction (TIMI) flow < 3; and (2) MACE, including recurrent angina, myocardial infarction, HF, and target vessel revascularization (TVR). Troponin T (TNT), creatine kinase-MB (CK-MB), interleukin-6 (IL-6), and interleukin-8 (IL-8) were defined as secondary outcome parameters. Trials not reporting any of these parameters were excluded from the review. Two investigators independently reviewed all full-text articles that could possibly meet the inclusion criteria according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement^[20] and the Cochrane Handbook guidelines.^[21] In the case of disagreement, consensus was obtained by discussion with a third author (Huang).

2.3. Data extraction

All selected papers were reviewed by 2 reviewers (Zhu, Xu), who independently extracted data to a data sheet. Data extraction included year of publication, study design, sample size, patient characteristics, inclusion and exclusion criteria, control and intervention protocol, randomization, blinding, and follow-up, as well as the outcome parameters described previously. Where the timing of when events took place differed, the primary outcome was divided into 2 subgroups: (1) CRIE during surgery and (2) MACE during hospitalization and after discharge. With respect to biomarker data, we used the peak values as reported in the paper. The SMD was used for analysis as detection times and

unit differed. Where data were presented in a graph but not in the text, we request the data from the corresponding author of the paper. If the data were not provided, we extrapolated them from the graph using a charting digital tool (GetData Graph Digitizer, <http://getdata-graph-digitizer.com>). Following the extraction of relevant data by the 2 authors, data were examined for possible inconsistencies which were then resolved by discussion, and if consensus could not be reached, a third author was consulted (Huang). Studies were not conducted directly on humans and ethical approval was therefore not necessary.

2.4. Quality assessment

Two authors used the 5 domains of the Cochrane risk of bias tool to evaluate the quality of the included studies, using the following criteria: randomization sequence generation, concealment of randomization sequence, blinding of intervention, blinding of outcome assessment, and incomplete outcome reporting, and studies were classified as having low risk, high risk, or unclear risk of bias for each item, as suggested in the Cochrane Handbook.^[21]

2.5. Statistical analysis

The verified data were analyzed using Stata software (version 13.0; Stata Corporation, College Station, TX) and REVMAN software (version 5.2; Cochrane Collaboration, Oxford, UK). Zhu entered the data and Xu verified data entry. The secondary outcome of this meta-analysis was the percentage change in biomarkers between the baseline and the final level in response to PGE1 administration. The relative ratio (RR) and SMD, and their corresponding 95% confidence intervals (CI), were calculated for dichotomous or continuous outcome data, respectively. A fixed effects model was used to analyze data with values higher than 0.10 by heterogeneity testing (χ^2 -based *Q*-test), whereas a random effects model was used when values were less than 0.10. The magnitude of heterogeneity was assessed by *I*² test (*I*²=0–25%, no heterogeneity; *I*²=25–50%, moderate heterogeneity; *I*²=50–75%, large heterogeneity; *I*²=75–100%, extreme heterogeneity). An intervention was assumed to have had a significant if the 95% CI did not include the value 1 for RR or 0 for SMD. In the analysis for small-study effects, publication bias was assessed using funnel plot techniques and Harbord’s test.^[22]

3. Results

3.1. Literature search

The literature search identified 109 records of clinical trials in Medline, 212 records in EMBASE, and 22 records in the Cochrane databases (Fig. 1), as well as 9 additional abstracts identified from the reference lists of relevant papers. After checking for duplicates, 81 unique references remained and 73 of them were excluded for reasons such as irrelevance to myocardial reperfusion injury or describing a nonclinical trial; the remaining 8 full texts underwent further evaluation. Among these, 2 articles^[23,24] were excluded as they did not provide the necessary data for our meta-analysis.

3.2. Surgical procedures in selected studies

Of the 6 included studies, 3 involved patients receiving elective PCI,^[25–27] 1 involved primary PCI,^[28] 1 involved elective mitral valve surgery,^[29] and 1 involved elective CABG or valve surgery^[30] (Table 1).

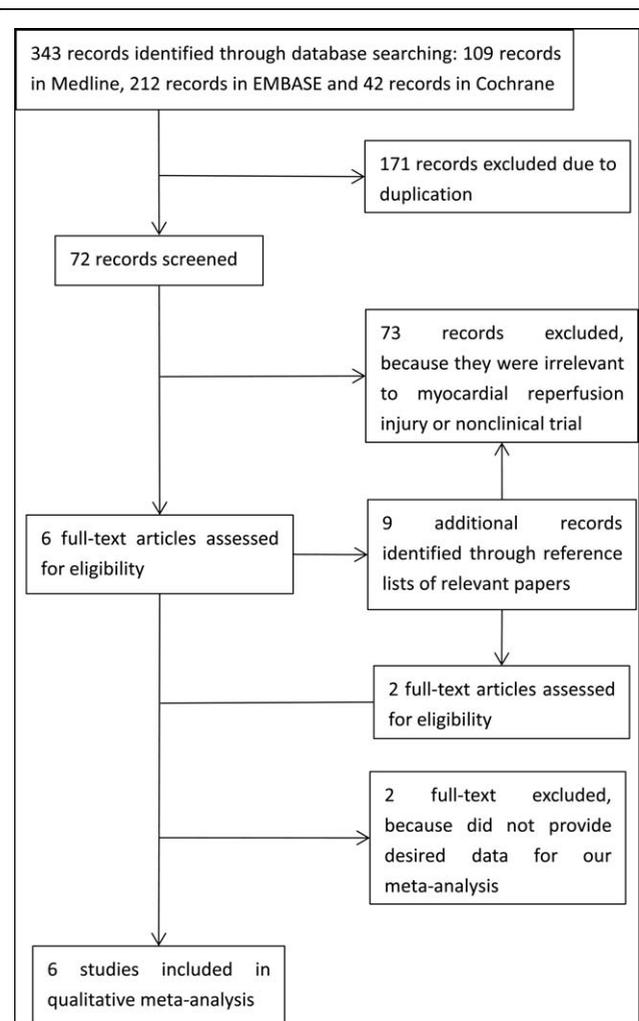


Figure 1. Flow diagram of study search and selection.

3.3. PGE1 protocols

PGE1 was administrated by intravenous injection in all studies (Table 1). In 2 studies,^[29,30] patients were administered PGE1 at a dose of 0.02 to 0.05 μg/kg/min from the beginning of surgery to the end of the study. In 2 other studies,^[2,5,26] patients were

administered 20 μg/day PGE1 starting at least 48 hours before PCI and continuing for 5 days or starting 3 days before PCI and continuing for 4 days after PCI, respectively. Moreover, one^[28] study described the administration of 20 μg PGE1 immediately after coronary angiography and another^[27] administered 0.005 to 0.03 μg/kg/min PGE1, starting at least 2 hours before PCI and continuing for 24 hours.

3.4. Patient characteristics

The mean ages of included patients ranged from 58.1 to 65.8 years (Table 2), the percentages of males varied from 54.4% to 80.0%, and the percentages of smokers ranged from 40.5% to 53.9%. Moreover, the percentages varied from 33.3% to 77.9%, 13.3% to 37.4%, and 13.3% to 35.4% for patients with hypertension, diabetes, and hyperlipidemia, respectively.

3.5. Primary outcome

The primary outcome included 2 subgroups: CRIE and MACE. The PGE1 group had a reduced incidence of CRIE (RR 0.40 [95%CI 0.43, 0.95]) (Fig. 2) compared with control, as reported in 3 studies,^[24,25,27] and there was no evidence for statistical heterogeneity ($\chi^2=2.91$, $I^2=0\%$, and $P_{\text{heterogeneity}}=.878$). MACE was reported in 3 studies^[24,26,27] and the results suggested that PGE1 reduced the incidence of MACE compared with placebo (0.35 [0.17, 0.70]), with no statistical heterogeneity ($\chi^2=1.24$, $I^2=0\%$, and $P_{\text{heterogeneity}}=.978$). Overall effects also showed that PGE1 was associated with lower risk of the primary outcome (0.53 [0.36,0.79]), and no statistical heterogeneity was found ($\chi^2=5.53$, $I^2=0\%$, and $P_{\text{heterogeneity}}=.954$).

3.6. Secondary outcome

TNT was the most widely reported biomarker of myocardial injury and was significantly reduced by PGE1 treatment (SMD -1.74 [95%CI -3.21, -0.27]) (Fig. 3) compared with control, although significant statistical heterogeneity was observed ($\chi^2=16.27$, $I^2=89\%$, and $P_{\text{heterogeneity}}=0$). The levels of CK-MB in 3 studies also showed significant differences between the groups (-1.64 [-3.00, -0.28]), and statistical heterogeneity was observed ($\chi^2=14.42$, $I^2=86\%$, and $P_{\text{heterogeneity}}=0$).

Regarding the expression of inflammatory response markers, IL-6 was reported in 3 studies and IL-8 in 2, and both markers

Table 1 Study design characteristics.

Study	Year	Design	Participants	Adminstrating method	Dosage
Fan et al ^[25]	2015	Prospective, monocentric, randomized, controlled, single-blind	Patients with UAP receiving elective PCI	Intravenous injection over 5 min starting 3 d before PCI and continuing for 4 d after PCI	20 μg/d
Wei et al ^[28]	2015	Prospective, monocentric, randomized, controlled	Patients with STEMI receiving primary PCI	Intravenous injection after coronary angiography immediately	20 μg
Luo ^[26]	2011	Prospective, monocentric, randomized, controlled, single-blind	Patients with AP receiving elective PCI	Intravenous injection starting at least 48 h before PCI and continuing for 5 d	20 μg/d
He and Li ^[29]	2004	Prospective, monocentric, randomized, controlled	Patients accepting elective mitral valve surgery	Intravenous injection from the beginning of surgery to the end of study	0.04 μg/kg/min
Kawamura et al ^[30]	2000	Prospective, monocentric, randomized, controlled, open-label	Patients undergoing elective CABG or valve surgery	Intravenous injection from the beginning of surgery to the end of study	0.02–0.05 μg/kg/min
Shechter et al ^[27]	1997	Prospective, monocentric, randomized, controlled, single-blind	Patients with AP receiving elective PCI	Intravenous injection starting at least 2 h before PTCA and continuing for 24 h	0.005–0.03 μg/kg/min

AP=angina pectoris, CABG=coronary artery bypass graf, PCI=percutaneous coronary intervention, PTCA=percutaneous transluminal coronary angioplasty, STEMI=ST-elevation myocardial infarction, UAP=unstable angina pectoris.

Table 2
Patient characteristics.

Study	Year	Number of subjects	Age	Male	Hypertension	Diabetes	Hyperlipidemia	Smoking
Fan et al ^[25]	2015	219	58.1 ± 11.31	74.0%	48.4%	37.4%	26.0%	53.9%
Wei et al ^[28]	2015	68	65.8 ± 7.9	54.4%	77.9%	35.3%	Not reported	48.5%
Luo ^[26]	2011	79	62.1 ± 10.3	78.5%	43.0%	34.2%	35.4%	40.5%
He and Li ^[29]	2004	30	Not reported	Not reported				
Kawamura et al ^[30]	2000	19	64.1 ± 12.3	73.7%	Not reported	Not reported	Not reported	Not reported
Shechter et al ^[27]	1997	30	57.0 ± 10.1	80.0%	33.3%	13.3%	13.3%	43.3%

were reduced with PGE1 treatment (−1.37 [−2.69, −0.04]; −2.05 [−2.75, −1.34], respectively). Overall effects also showed that PGE1 lowered the secondary outcome parameters compared with control (−1.59 [−2.14, −1.04]), but an obvious heterogeneity was observed ($\chi^2 = 63.98$, $I^2 = 85.8\%$, and $P_{\text{heterogeneity}} = 0$).

3.7. Quality of studies

In 4 studies, the process of sequence generation was correctly performed^[25,26,28,29] (Fig. 4), but in the other studies, the methods were not described in detail. In 2 studies concealment was achieved using a random number table,^[28,29] which was

defined as high risk of bias. One study used an open trial design, 3 adopted single blinding, and the other 2 studies did not describe the blinding method; none of the studies contained sufficient information to judge the risk of performance and detection bias. One study exhibited withdrawal bias,^[25] but missing data did not affect the analysis so this study was defined as low risk.

3.8. Publication bias

Funnel plots of the study were visually symmetric and a statistical analysis of funnel plots also suggested that no publication bias was present (Harbord’s test, $P = .34$) (Fig. 5).

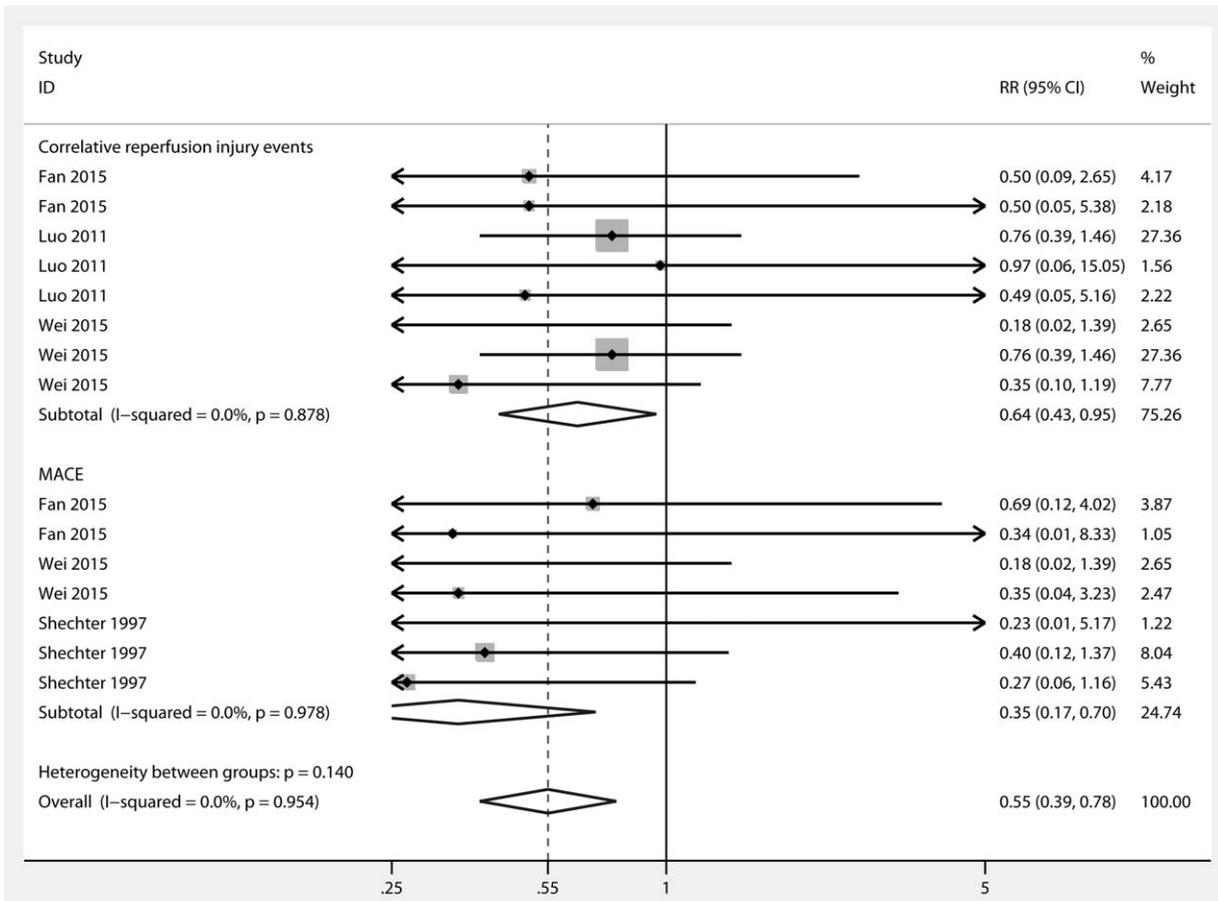


Figure 2. Forest plot showing the effects of PGE1 on incidence of correlative reperfusion injury events and MACE. A significant effect of PGE1 was assumed if the 95% CI did not include the value 1 for RR. CI = confidence interval, MACE = major adverse cardiac events, PGE1 = prostaglandin E1, RR = risk ratio.

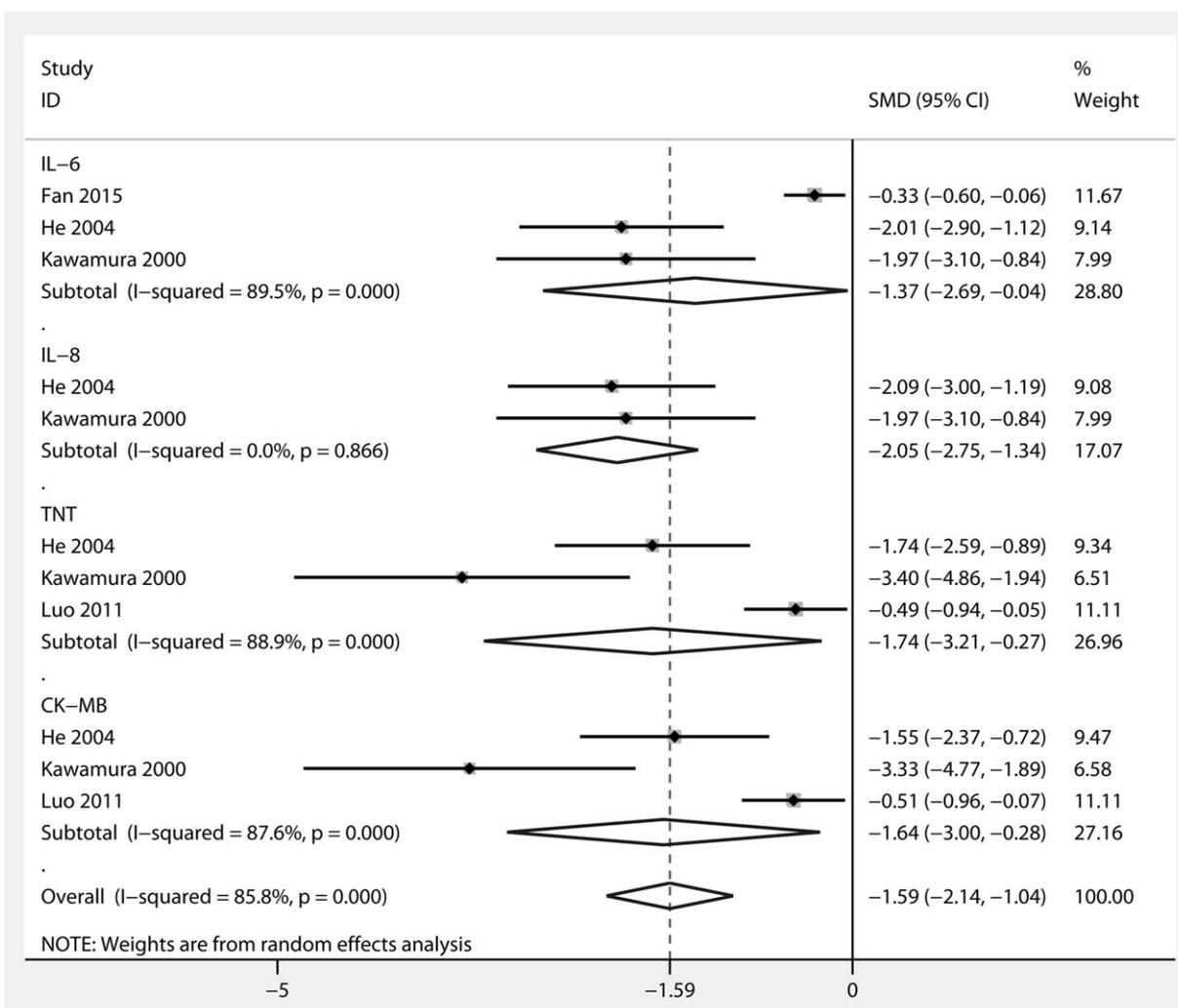


Figure 3. Forest plot showing the effect of PGE1 on changes in TNT, CK-MB, IL-6, and IL-8 levels. A significant effect of PGE1 was assumed if the 95% CI did not include the value 0 for SMD. CK-MB=creatin kinase-MB, IL-6=interleukin-6, IL-8=interleukin-8, PGE1 = prostaglandin E1, SMD=standardized mean difference, TNT=troponin T.

4. Discussion

We conducted a review of the protective effects of PGE1 on myocardial RI in the clinical setting using data from 6 RCTs comprising a total of 445 patients. To our knowledge, this meta-analysis is the first review of the effects of PGE1 on RI, although relatively few studies were included in our review. The objective of our study was to confirm whether PGE1 could protect the heart from myocardial RI by investigating the incidence of CRIE and MACE in the identified studies.

The main finding of this meta-analysis was that PGE1 treatment significantly reduced the incidence of CRIE and MACE. Moreover, the secondary outcome parameters TNT, CK-MB, IL-6, and IL-8 were also reduced by PGE1, although there were some limitations to these conclusions.

Four studies focused on the effect of PGE1 on biomarker and inflammatory factor levels, so short or long-term clinical outcomes were not the primary outcome. Some studies did not report on the occurrence of adverse events, such as death. Therefore, some low probability adverse events were zero in both the PGE1 and placebo groups, which required us to exclude these

events when calculating the RR. It is therefore inevitable that we may have over-estimated the possible effect because of the exclusion of patients with no events. Although our analysis suggested that PGE1 reduced the primary outcome, we used the definition applied by the investigators of the respective studies when examining the endpoint events. This means that different events could have been classified as identical, and we may have erroneously pooled these events in the meta-analysis. In addition, the results of the meta-analysis are largely driven by the study of Fan et al,^[25] which may have induced bias.

TNT and CK-MB are commonly used as biomarkers for myocardial injury, and IL-6 and IL-8 are also thought to be highly expressed in reperfusion injury.^[31-34] In this analysis, we therefore used these biomarkers as secondary endpoints to determine the molecular biological effects of PGE1 in RI. We selected the peak values of these biomarkers in their respective studies, but this nonetheless led to inevitable variance as the reported time-points differed between studies, even in comparable settings. Statistical heterogeneity was therefore observed for all biomarkers except IL-8. Although we intended to perform subgroup analysis to explore heterogeneity, the number of included studies was too few. Additionally, we included studies

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)
Fan 2015	+	?	?	?	+
He 2004	+	-	?	?	+
Kawamura 2000	?	?	?	?	+
Luo 2011	+	?	?	?	+
Shechter 1997	?	?	?	?	+
Wei 2015	+	-	?	?	+

Figure 4. Risk of bias summary. + = low risk, - = high risk, ? = unclear risk.

with significant clinical heterogeneity. Studies differed in setting, patient population, and extent of ischemia the patients were at risk for. Patients undergoing elective or primary PCI, CABG, and valve surgery were all pooled for the meta-analysis on the chosen outcome parameters. Because of the existence of clinical and statistical heterogeneity, we used a random effects model for the secondary endpoint. Since random effects models typically provide a broader confidence interval than fixed effects models, they may therefore draw a more conservative conclusion.^[35]

An important limitation of most of these studies was adequate blinding design, which is seemingly more difficult to achieve than in trials investigating a pharmacological agent. In the present meta-analysis, unfortunately, all included studies presented a risk of blinding bias.

Overall, our meta-analysis indicated that PGE1 treatment prior to myocardial reperfusion appeared to be superior to placebo in reducing CRIE, MACE, and the levels of related biomarkers. However, this conclusion is based on studies in a small group of patients, and this restriction in available data ensured that no

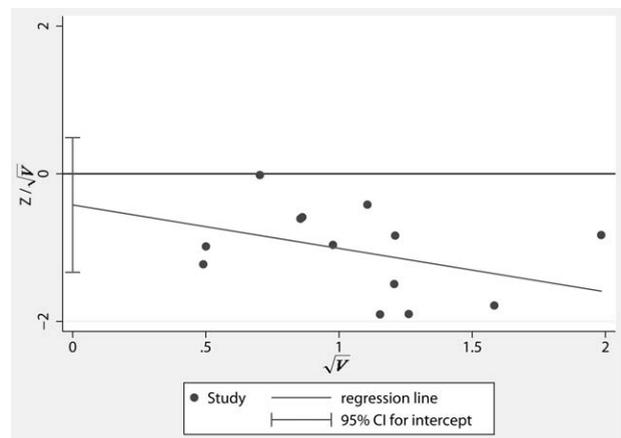


Figure 5. Harbord's funnel plot to evaluate publication bias in the effects of PGE1 on incidence of CRIE and MACE. CRIE = correlative reperfusion injury events, MACE = major adverse cardiac events, PGE1 = prostaglandin E1.

further subgroup analysis could be performed in patients with PCI, valve surgery, or CABG. Moreover, inadequate blinding design may also have led to false positives in the data. Therefore, additional, large RCTs are required to firmly establish the role of PGE1 in regulating myocardial reperfusion injury.

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