Cell Biochem Biophys (2014) 68:201–206
DOI 10.1007/s12013-013-9690-9

TRANSLATIONAL BIOMEDICAL RESEARCH

Safety and Effectiveness of Nitroprusside in Preventing No-Reflow During Percutaneous Coronary Intervention: A Systematic Review

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Published online: 8 June 2013

Abstract The objective of this study was to evaluate the clinical efficacy and safety of nitroprusside injection for preventing the slow-flow/no-reflow phenomenon after percutaneous coronary intervention (PCI). We searched the Cochrane Central Register of Controlled Trials (Issue 2, 2011), PubMed, EMbase, and Google Scholar for data. Two reviewers independently evaluated the quality of the included studies and extracted the data. A meta-analysis was performed using RevMan 5.0 software. Four randomized controlled trials (RCTs) involving 319 patients were included. The results of the meta-analyses showed that intracoronary nitroprusside is beneficial in preventing no-reflow/slow-flow, in reducing corrected TIMI frame count, and in improving left ventricular ejection fraction. It also likely reduces adverse reactions in patients after PCI and rehospitalization due to cardiovascular events. However, we must caution that in this review, there is a moderate possibility of bias with regard to patient selection, performance, and publication because of the small number of included studies. A larger sample size and high-quality RCTs are needed for a more reassuring analysis.

Keywords No-reflow · Percutaneous coronary intervention · Nitroprusside · Randomized controlled trial · Systematic review

Introduction

Percutaneous coronary intervention (PCI) is the most pivotal means of reperfusion for acute myocardial infarction (AMI) patients. The application of PCI has significantly improved the short- and long-term prognosis of AMI patients [1]. However, numerous studies have indicated that despite the opening of the epicardial coronary vessels, in some AMI patients, ischemic myocardia cannot be effectively reperfused. It expresses as limited microcirculation blood flow, stagnation of contrast agent flow, persistent elevated ST segment in ECG, and persistent chest pain, a phenomenon known as no-reflow [2]. Some reports suggested that in AMI patients undergoing PCI, the incidence of no-flow is about 25 % in the saphenous vein grafts (SVGs) and this no-flow is independently associated with sudden cardiac death and cardiac events [3, 4]. Nitroprusside is a strong vasodilator and its activity relies on the direct formation of nitric oxide which plays a powerful role in relaxation of vascular smooth muscle [5]. Therefore, the application of sodium nitroprusside in preventing no-flow is a very important and effective method. Although some clinical trials studied the effect of nitroprusside in preventing no-reflow after PCI, the efficacy and clinical applications of nitroprusside are still controversial. There are no standardized clinical guidelines for the application of nitroprusside, leading to a lack of standardized treatment of no-flow after PCI in AMI patients. In order to provide a scientific basis for clinical use of nitroprusside, it is necessary to evaluate the drug efficacy and safety in preventing no-flow using the method of the Cochrane systematic review.

Materials and Methods

Criteria of Ruling In and Ruling Out

Study Type

Randomized controlled trials of the effect of nitroprusside in preventing no-flow after PCI, regardless of blinding or not, were chosen.

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Rule in Criteria

Patients with AMI, in line with the WHO diagnostic criteria for the diagnosis of AMI, who underwent PCI were chosen. Patients with AMI combined with old myocardial infarction, ischemic cardiomyopathy, severe heart failure, moderate to severe liver and kidney dysfunction, left coronary disease, and with contraindication of anticoagulant were excluded.

Interventions

We chose nitroprusside versus placebo (including the blank control, saline, and nitroglycerin), requiring drugs to be administered by intracoronary injection.

Indicator Measurement

Primary indicators: corrected TIMI frame count (CTFC), thrombolysis in myocardial infarction trial (TIMI) <grade 3; secondary indicators: adverse cardiac events (MACE, including heart failure, target vessel revascularization, myocardial reinfarction, postoperative death) rate, readmission rates due to cardiac causes, left ventricular ejection fraction, ST segment regression, the final infarct size.

Search Strategy

The Cochrane Library of Controlled Trials databases (2011 No. 2), PubMed (1966 $\sim$ 2011.4), EMbase (1900 $\sim$ 2011.4), and Google Scholar were searched. Searching key words included slow-flow/no-reflow, PCI, nitroprusside, etc.

Data Extraction and Quality Assessment

Using a pre-designed data extraction form, two independent researchers extracted the following information: (a) the basic information of experiments and patients; (b) Interventions, outcome indicators, and loss of follow-up; (c) Methodology quality. If the information in clinical trials was incomplete, the original author was contacted. In case of different opinions held by the two researchers, third-party arbitration was applied. The methodological quality was evaluated using a cochrane collaboration recommended method; (d) Prevention of selection bias: if random was complete or if the allocation concealment was complete; (e) Prevention of the implementation of bias: if patients and investigators were blinded; (f) Prevention of the attrition bias: if the patient withdrawals and loss of follow-up were completely described and if intention to treat analysis (ITT) was applied; and (g) Prevention of the measurement bias: if the blinded measurement was applied.

Statistical Analysis

The Cochrane Collaboration's RevMan 5.0 software was used in the meta-analysis. In the enumeration data, risk ratio (RR) was used for the efficacy analysis of statistics; in the measurement data, mean difference (MD) was used. The effects of volume are expressed with 95 % CI. The heterogeneity of the results was measured using χ^2 test. When the studies were statistically homogeneous ($P > 0.1$, $I^2 < 50$ %), the fixed effects model was applied; otherwise, a random effects model was applied.

Results

Search Results

In the primary search, 178 publications were selected, in which 21 were from PubMed, 56 from EMbase, 7 from Cochrane Library, and 94 from Google Scholar. After reading the titles and abstracts, we excluded 174 studies: 87 publications were reviews and animal experiments, 36 reports did not meet the criteria, and 51 publications were repetitions of earlier literature. Ultimately, only 4 studies were included in our study [5–8] including 319 cases of patients. The basic information of these 4 studies is given in Table 1.

Quality Assessment of the Methodology

In all 4 studies, random methods were employed. However, only 2 RCTs [6, 8] reported the specific random methods. In one study [6], a random number table was used. In another study [8], a block random was applied. In none of the 4 studies were the allocation concealments described in detail. In two studies [7, 8], blinded methods were used. Of these two studies, a single-blind study was applied [7] in one and a double-blind study [8] was used in the other. Detailed methods are given in Table 2.

Statistical Analysis

TIMI Flow

Three studies [6–8] reported the incidence of no-reflow/slow-flow by coronary artery injection of sodium nitroprusside after coronary stent placement. There is no significant heterogeneity among these studies. So, the fixed effects model was applied for the Meta-analysis. The results showed that the differences were statistically significant [RR = 0.49, 95 % CI (0.25, 0.95)] (Fig. 1).

Table 1 Characteristics of included studies

Study	Age Exptl/Ctrl	Participants Exptl/Ctrl	Administration	Interventions trail/control		Outcomes
Pan et al. [6]	52 ± 11/ 54 ± 13	46/46	Intracoronary	100 μg Nitroprusside (diluted to 20 μg/ml)	100 μg Nitroglycerin	CTFC; final TIMI flow grade of <3; rehospitalization due to cardiovascular events; MACE
Hendler et al. [7]	60/63	10/10	Intracoronary	Nitroprusside (100–500 μg)	Nitroglycerin, (200–400 μg)	CTFC; final TIMI flow grade of <3; left ventricular ejection fraction
Amit et al. [8]	62 ± 11/ 62 ± 12	48/50	Intracoronary	60 μg of nitroprusside diluted in saline solution as a 5-mL bolus	Identical volume of saline solution	CTFC; final TIMI flow grade of <3; ST segment elevation resolution; rehospitalization due to cardiovascular events; MACE
Sakamoto et al. [9]	–	56/53	Intracoronary	Nitroprusside (50–150 μg)	No treatment	CTFC; final infarct size

Table 2 Assessment of methodological Quality of included studies

Study	Randomized method	Allocation concealment	Blinding	Withdrawals and loss of follow-up	Intent-to-treat (ITT) analysis
Pan et al. [6]	Random number table	Unclear	Unclear	No	No
Hendler et al. [7]	Unclear	Unclear	Single blind	No	No
Amit et al. [8]	Randomized block design	Unclear	Double blind	No	No
Sakamoto et al. [9]	Unclear	Unclear	Unclear	No	No

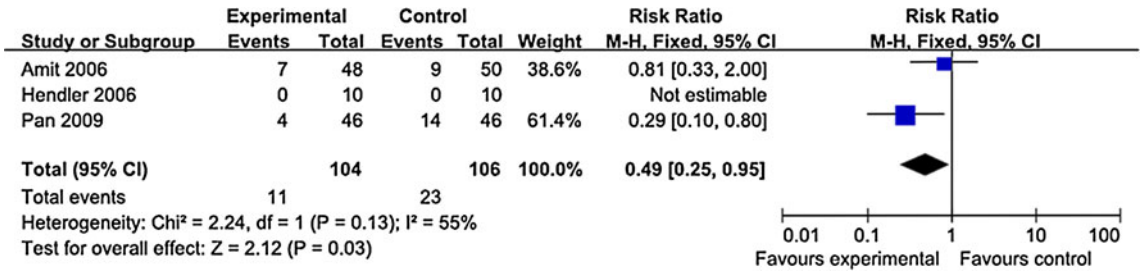

Fig. 1 Effect of nitroprusside and placebo on no-flow/slow-flow after PCI

Corrected TIMI Frame Count (CTFC)

Four studies [6–9] reported the CTFC of no-flow by injection of sodium nitroprusside. There are no statistical heterogeneities among these studies, so the fixed effects model was applied for the Meta-analysis. The results showed that the differences were statistically significant [MD = −4.24, 95 % CI (−6.40, −2.08)] (Fig. 2).

Final Infarct Size

One study [9] reported the infarct myocardial size after 3 months of coronary artery injection of sodium nitroprusside. The results showed that in comparison with the control group, there was no significant difference between the infarct sizes in the patient groups (16.7 ± 21.5 vs. 20.2 ± 19.3 %, $P = 0.403$).

Left Ventricular Ejection Fraction

One study [7] reported the LVEF 1 month after the coronary artery injection of sodium nitroprusside preventing no-reflow and the results showed that compared with the control group, the difference of the left ventricular ejection fractions was statistically significant ($P < 0.05$).

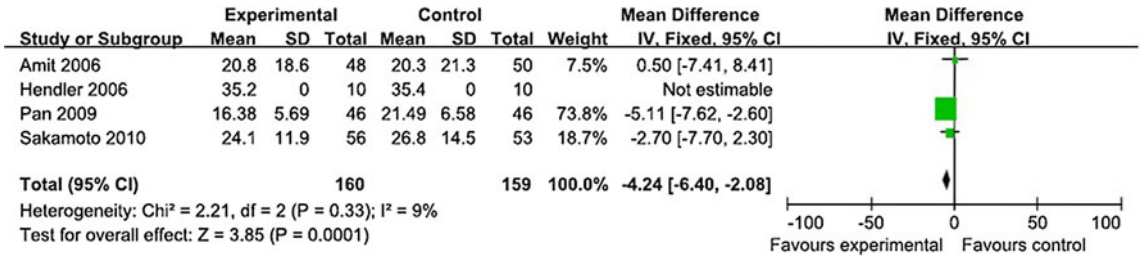

Fig. 2 Effect of nitroprusside and placebo on CTFC after PCI

ST Segment Regression

One study [8] reported the ST segment regression after the coronary artery injection of sodium nitroprusside preventing no-reflow and the results showed that compared with the control group, both in 1 and 24 h, there were no significant differences between the two groups ($P > 0.05$).

The Incidence of Adverse Cardiac Events

Two studies [6, 8] reported the incidence of adverse cardiac events after the injection of sodium nitroprusside. There was no statistical heterogeneity between the studies, so the fixed effects model was applied and Meta-analysis was performed. The results showed that the differences were statistically significant [RR = 0.27, 95 % CI (0.11, 0.63)] (Fig. 3).

Readmission Rates Due to Cardiac Causes

Two studies [6, 8] reported the rehospitalization rates due to the adverse cardiac events. There was no statistical heterogeneity between studies, so the fixed effects model was applied and Meta-analysis was performed. Results showed that the differences were statistically significant [RR = 0.44, 95 % CI (0.21, 0.91)] (Fig. 4).

Discussion

Sodium nitroprusside (SNP) is an inorganic nitrite, which can dilate arteries and veins, relax vascular smooth muscle, reduce the pre- and after-loads of the heart, and decrease ventricular ejection resistance. SNP also increases cardiac output under the condition of low-oxygen consumption and therefore improves the heart function. As a direct nitric oxide donor, SNP plays a strong role in vasodilation by activating guanylate cyclase in vascular smooth muscle cells leading to the increase of cytoplastic cG cyclophosphamide [10, 11]. Meanwhile, SNP can primitively dilate the coronary microcirculation, improve the dysfunction of coronary small blood vessels and microvessels, and therefore effectively induce coronary hyperemia [12–14].

In this study, using Meta-analysis, we quantitatively analyzed the efficacy and safety of injection of SNP in the prevention of coronary no-reflow after PCI. The results show that the injection of SNP can significantly improve TIMI blood flow and CTFC and reduce the incidence of the no-reflow phenomenon. For adverse heart events, SNP can significantly reduce the incidence of adverse events and reduce the readmission rate caused by cardiac events.

Among the 4 RCTs included in this study, 2 RCTs [6, 8] illustrate the methods of randomization. All 4 do not describe the process of allocation concealment; therefore, the possibility cannot be ruled out that selection bias exists in some studies, although due to the specialty of PCI, it is impossible to blind doctors to avoid the effect of implementation bias. However, for the most subjective measurements, such as TIMI flow, CTFC, etc., it is necessary to measure personnel using a blinded method to avoid the effect of bias on the research results. However, only one study of the four RCTs included [8] a double-blind method for patients and researchers. One study [7] used a single-blind method for researchers. The others did not mention whether or not the

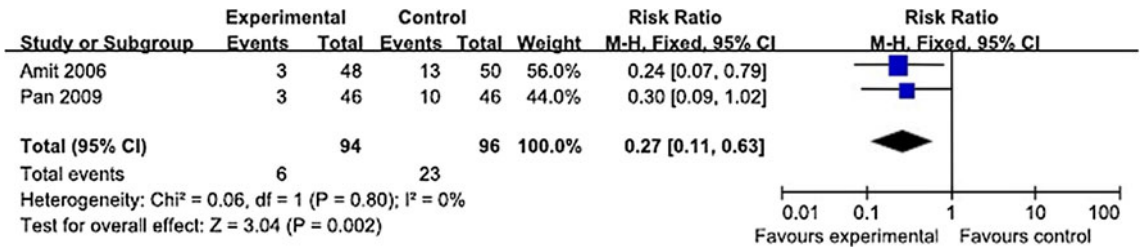

Fig. 3 Effect of nitroprusside and placebo on the incidence of adverse cardiac events

Fig. 4 Effect of nitroprusside and placebo on the rehospitalization rate after PCI

blind method was used. Therefore, in terms of the measurements of those subjective indicators, the possibility of measurement bias cannot be ruled out. In addition, due to the variety of the patient ages, there is some certain degree of heterogeneity among the studies. All of these will affect the research results.

Currently, many complementary medicines are considered to improve the treatment of AMI and the clinical outcomes of myocardial function [15]. Although the no-reflow phenomenon occurs only in a small proportion of patients, these patients are at a high risk of fatal complications and poor clinical prognosis. Therefore, prevention of microvascular dysfunction can reduce the number of such type of patients, but the significant effect cannot be reflected in the general population. Atrial natriuretic peptide (ANP) is a very good drug. It limits infarct size after myocardial infarction, improves left ventricular ejection fraction, and reduces the incidences of sudden cardiac death and heart failure. However, ANP does not improve the no-reflow phenomenon [16]. Although adenosine can reduce the incidence of no-reflow after initial PCI [17], it cannot improve the clinical outcome after myocardial infarction [18]. Compared with these drugs, SNP can both prevent the occurrence of no-reflow and improve cardiac function and clinical outcomes. Therefore, SNP would be a more promising adjuvant drug treatment.

In summary, intracoronary injection of SNP can improve TIMI flow and CTFC, serving to prevent no-reflow/slow-flow. In addition, SNP is also effective in increasing the left ventricular ejection fraction and reducing major adverse cardiovascular event occurrence. However, due to the methodological limitations in the ruled-in studies, we think that a larger number of samples and high-quality RCTs need to be performed to further demonstrate SNP's efficacy and safety.

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