CORONARY ARTERY DISEASE

Effect of Intracoronary Nitroprusside in Preventing No Reflow Phenomenon during Primary Percutaneous Coronary Intervention: A Meta-Analysis

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Background: Adjunctive therapy with intracoronary nitroprusside (NTP) in primary percutaneous coronary intervention (PPCI) had controversial benefits in patients with ST segment elevation myocardial infarction (STEMI).

Objectives: To evaluate the effect of intracoronary NTP on no reflow phenomenon (NR) and clinical outcomes in STEMI patients undergoing PPCI.

Methods: We searched the following databases without language or time limitation in January 2014: PubMed, EMBASE, CENTRAL, ISI Web of Science, and CNKI. Trials compared the effect of intracoronary NTP with control group (placebo or no NTP treatment) on NR in STEMI patients undergoing PPCI enrolled for analyzing.

Results: A total of 7 trials involving 781 patients were included into this meta-analysis. Intracoronary NTP significantly reduced the incidence of thrombolysis in myocardial infarction (TIMI) flow grade (TFG) \( \leq 2 \) (RR: 0.47, 95% CI: 0.30–0.73, \( P = 0.001 \)); the corrected TIMI frame count (CTFC) (WMD: –5.28, 95% CI: –6.79 to 3.78, \( P = 0.000 \)) increased the events of myocardial blush grade (MBG) \( \geq 2 \) (RR: 1.12, 95% CI: 1.01–1.24, \( P = 0.038 \)), and reduced the incidence of major adverse cardiac events (MACE) (RR: 0.43, 95% CI: 0.27–0.70, \( P = 0.001 \)). Although the events of the complete ST segment resolution (STR) did not reach statistical significance, there was a trend indicating improvement in the intracoronary NTP group (RR: 1.143, 95% CI: 0.97–1.34, \( P = 0.101 \)).

Conclusions: Intracoronary NTP can significantly reduce the incidence of angiographic NR during PPCI, as well as the incidence of MACE. It seems to be a promising adjunctive therapy for NR during PPCI.

Introduction

Primary percutaneous coronary intervention (PPCI) is the preferred treatment for ST segment elevation myocardial infarction (STEMI). However, even after successful PPCI for STEMI, adequate myocardial reperfusion is not achieved in up to 50% of cases.\(^1\) This phenomenon of inadequate myocardial perfusion of a given coronary segment without angiographic evidence of mechanical vessel obstruction is termed no reflow phenomenon (NR), and is associated with poor in-hospital and long-term prognosis.\(^2\) Nitroprusside (NTP) is a direct donor of nitric oxide,\(^3\) which can strongly dilate the resistance arterioles and plays a significant role in coronary blood flow through the microcirculation.\(^4,5\) Intracoronary NTP was used for the treatment of NR during PPCI in several clinical trials; however, its efficacy and clinical outcomes are still controversial. In order to provide a scientific basis for clinical use of NTP, we performed this meta-analysis to evaluate the effects of intracoronary NTP on NR and clinical outcomes in patients who underwent PPCI for STEMI.

Methods

Search Strategy. We identified all published studies, including full-text, and abstract, which compared the effect of intracoronary NTP with control...
group (placebo or no NTP treatment) in STEMI patients undergoing PPCI by searching PubMed, EMBASE, CENTRAL, ISI Web of Science, and CNKI in January 2014 using the search terms “no reflow,” “percutaneous coronary intervention,” “nitroprusside,” and “STEMI.” The search was performed without language or time limitation. The types of articles such as comments, letters, and the works that were not original reports were excluded.

**Studies Selection.** Two reviewers performed study selection independently, with disagreements solved through discussion and by the opinion of a third reviewer if necessary. Studies were considered potentially eligible for this meta-analysis if they met the following criteria: (1) RCT or retrospective study with reasonable design and outcome measurements about patients who suffered from STEMI and performed PPCI; (2) NTP was administered intracoronary and compared with control (placebo or no NTP treatment); and (3) the studies included at least one of the following interesting outcomes: final thrombolysis in myocardial infarction (TIMI) flow grade (TFG), corrected TIMI frame count (CTFC), myocardial blush grade (MBG), TIMI myocardial perfusion grade (TMPG), complete ST segment resolution (complete STR, defined as post-procedural resolution ≥70%), and major adverse cardiac events (MACE, including target vessel revascularization, myocardial reinfarction, postoperative death, etc.). Duplicated literature, reviews, nonclinical studies, and case observations were excluded in this study.

**Data Extraction.** Using a pre-designed data extraction form, 2 independent researchers extracted the following information: (1) the basic information of experiments and patients; (2) interventions, outcome indicators; and (3) methodology quality. The disagreements would be solved through discussion and by the opinion of a third reviewer if necessary.

**Statistical Analysis.** Statistical analysis was performed using STATA 12.0 software (STATA Corp., College Station, TX). We determined pooled weighted mean difference (WMD) and corresponding 95% confidence intervals (CIs) for continuous data as the outcome measurements in all trials used the same mean difference (WMD) and corresponding 95% confidence intervals (CI). The significance of the pooled estimate was determined using the Z-test. The appropriateness of pooling data across studies was assessed with the use of the I² test for heterogeneity. Data were pooled by use of a fixed effects (FE) model (Mantel–Haenszel method) if I² ≤ 50%. If I² > 50%, we tried to find clinical heterogeneity across studies first and addressed it by sensitivity analyses or subgroup analyses, and if significant heterogeneity remained, a random effects (RE) model would be used if appropriate. Funnel plots were used to assess publication bias, and Begg’s test were used to assess funnel plot asymmetries. All tests were 2-sided with a P value of <0.05 as statistically significant.

### Results

**Baseline Characteristics of Included Studies.** A total of 185 articles relevant to the searched keywords were initially identified. After browsing the title and, abstract, we identified 19 potentially relevant studies through electronic searches; after browsing the full text, 12 of these investigations were excluded. The remaining 7 studies, which were composed of 6 RCTs and 1 retrospective study, involved a total of 781 cases. The literature selection process is illustrated in Figure 1; detailed information regarding the examined studies is provided in Table 1.

**Quality Assessment.** The modified Jadad scale was scored by randomization, blinding method, withdrawals and dropouts, and allocation concealment. The Jadad scores ranged from 0 to 4 (Table 2), suggesting that the overall quality of the literature was lower. We evaluated the publication bias risk using a funnel plot in Figure 2 based on the outcome of final TFG ≤ 2.

**Statistical Analysis.**

**TFG.** Six studies reported the events of final TFG ≤ 2 after coronary reperfusion. There was no significant heterogeneity among these studies. So, the FE model was applied for the meta-analysis. The results showed that intracoronary use of NTP was associated with a significant reduction in the events of final TFG ≤ 2 (RR: 0.47, 95% CI: 0.30–0.73, P = 0.001; Fig. 3).

**CTFC.** Six studies reported the CTFC after intracoronary injection of NTP. There was no statistical heterogeneity among these studies, so the FE model was used for the meta-analysis. The results showed that CTFC was significant lower in NTP group compared with control group (WMD: −5.28, 95% CI: −6.79 to 3.78, P = 0.000; Fig. 4).

**Complete STR.** Three studies reported the events of complete STR after the coronary injection of NTP. There was no significant heterogeneity among
these studies, so the FE model was used. The results showed there was a trend indicating improvement in the intracoronary NTP group but did not reach statistical significance (RR: 1.143, 95% CI: 0.97–1.34, P = 0.101; Fig. 5).

**MBG.** Three studies\(^9,13,14\) reported the events of MBG ≥2 after intracoronary use of NTP. There was no significant heterogeneity among these studies, so the FE model was applied. The results showed that intracoronary use of NTP was associated with a significant increase in the events of MBG ≥2 (RR: 1.12, 95% CI: 1.01–1.24, P = 0.038; Fig. 6).

**MACE.** Five studies\(^8,9,12–14\) reported the incidence of adverse cardiac events after the coronary injection of NTP. There was no significant heterogeneity among these studies, so the FE model was applied for the meta-analysis. The results showed that the use of intracoronary NTP was associated with a significant reduction in the events of MACE (RR: 0.43, 95% CI: 0.27–0.70, P = 0.001; Fig. 7).

**Discussion**

NR could be defined as the persistence of reduced flow and regional myocardial dysfunction after the removal of an experimental epicardial coronary occlusion.\(^16\) So far, the exact mechanisms of NR have not been fully clarified. The most likely causes include spasms in resistant vessels, coagulation of platelets, activation of inflammatory cells, shower embolization, tissue edema, or a combination of these factors.\(^2,17\) However, of the several mechanisms that have been proposed to explain the NR phenomenon, microcirculatory dysfunction and vasospasm that occurs at the level of the resistance arterioles are considered the central mechanisms of NR in several studies.\(^1,16,18–20\) Nitrogen oxide (NO) is a potent vasodilator in the resistance arteriolar circulation and plays a significant role in coronary blood flow through the microcirculation,\(^4\) and it also has other multiple functions, such as anticoagulation of platelets and anti-inflammatory functions.\(^21\) NTP is a direct donor of NO and requires no intracellular metabolism to generate NO,\(^3\) so unlike nitroglycerin, intracoronary use of NTP was supposed to have a beneficial effect on the prevention of NR.

TFG is a classical indicator of reperfusion during PPCI\(^2,22,23\); however, successfully restoring epicardial flow does not always result in myocardial salvage.\(^24\) Although CTFC was developed to quantify distal coronary flow and can further risk-stratify patients with

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**Figure 1.** Flow diagram of study selection.
TGF 3 into lower- and higher-risk subgroups, both TFG and CTFC represent indirect measures of microvascular flow and patency that do not allow tissue perfusion assessment, which is the final goal of reperfusion therapy. MBG or the slightly different TMPG appears to assess myocardial tissue perfusion more accurately than CTFC does and may be an even better method of risk stratification. Though TFG, CTFC, MBG, and TMPG were all shown to be associated with improved clinical outcomes, it had been proved that in patients in whom TFG 3 was restored, survival was still strongly dependent on the myocardial perfusion grade. So, we think only use of TFG and CTFC as major indicators may underestimate the rate of NR events. In addition, it has been found that complete STR was also an independent predictor of long-term clinical outcome and could be used to describe the effectiveness of myocardial reperfusion, and unlike angiographic data, STR as ECG data seems to reflect also the myocardial involvement during reperfusion that needs time to appear.

In this study, using meta-analysis, we quantitatively analyzed the efficacy of intracoronary NTP injection in the prevention of NR in patients with STEMI undergoing PPCI. The present study, incorporating 781 patients, showed that intracoronary use of NTP had significantly improved the final TFG, CTFC, MBG, and the incidence of MACE, which reflected an enhanced myocardial reperfusion and greater myocardial salvage. Though the myocardial reperfusion assessed by STR did not reach statistical significance, there was a trend indicating improvement in the intracoronary NTP group. Furthermore, intracoronary use of NTP was well tolerated and free of any severe side effects in all enrolled studies. Some patients experienced transient hypotension for a short time, but prolonged hypotension was not noted, and the use of vasopressor or intra-aortic balloon pump (IABP) during the procedure was also similar in both groups. Compared with drugs such as adenosine, verapamil, and nicorandil that have not yet been proved to be associated with conclusive improvements in clinical outcome, NTP would be a more promising adjuvant drug in the treatment of NR, and the possible mechanisms partly due to intracoronary NTP could produce an equivalent but more prolonged coronary hyperemia than adenosine or other drugs. There are also some limitations in the present study. Firstly, among the 7 studies, we enrolled 1 retrospective cohort.
Table 2. Assessment of Methodological Quality of Included Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomization</th>
<th>Randomization Method</th>
<th>Blinding</th>
<th>Withdrawals/Dropouts</th>
<th>Allocation Concealment</th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhao et al.</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Niccoli et al.</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Nayel et al.</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Sakamoto et al.</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Pan et al.</td>
<td>Yes</td>
<td>Random number table</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>3</td>
</tr>
<tr>
<td>Shinozaki et al.</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Amit et al.</td>
<td>Yes</td>
<td>Randomized block design</td>
<td>Double blind</td>
<td>No</td>
<td>No</td>
<td>4</td>
</tr>
</tbody>
</table>

Figure 2. Funnel plot for the events of TIMI flow grade (TFG) ≤2.

<table>
<thead>
<tr>
<th>Study</th>
<th>Events, %</th>
<th>Events (%)</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhao et al. (2013)</td>
<td>7/82</td>
<td>12.41</td>
<td>0.88 (0.31, 2.50)</td>
<td>6/80</td>
</tr>
<tr>
<td>Niccoli et al. (2013)</td>
<td>8/80</td>
<td>14.35</td>
<td>1.00 (0.39, 2.53)</td>
<td>8/80</td>
</tr>
<tr>
<td>Nayel et al. (2013)</td>
<td>11/20</td>
<td>19.74</td>
<td>0.18 (0.05, 0.72)</td>
<td>2/20</td>
</tr>
<tr>
<td>Pan et al. (2009)</td>
<td>14/46</td>
<td>25.12</td>
<td>0.29 (0.10, 0.80)</td>
<td>4/46</td>
</tr>
<tr>
<td>Shinozaki et al. (2007)</td>
<td>7/60</td>
<td>12.56</td>
<td>0.14 (0.02, 1.13)</td>
<td>1/60</td>
</tr>
<tr>
<td>Amit et al. (2006)</td>
<td>9/50</td>
<td>15.82</td>
<td>0.58 (0.21, 1.60)</td>
<td>5/48</td>
</tr>
<tr>
<td>Overall (I-squared = 38.1%, p = 0.152)</td>
<td>56/338</td>
<td>100.00</td>
<td>0.47 (0.30, 0.73)</td>
<td>26/334</td>
</tr>
</tbody>
</table>

Figure 3. RR of the events of TIMI flow grade (TFG) ≤2.
Although the retrospective study was done with clear inclusion criteria and reasonable study design, it may still lead to the major limitation of the present study. And due to the limited study number and population size, the power of the analysis might be restricted. Secondly, since a majority of trials in this meta-analysis did not report random method and allocation concealment in detail, the quality scales of the enrolled trials were not high, so the bias should not be ignored. Thirdly, since there are no statistical heterogeneities among the studies for all indicators, we did not perform subgroup analyses and sensitivity analyses. As a consequence, this meta-analysis contained trials regardless of the condition of patients, the time and dosage of NTP, the routes of administration, the duration of follow-up, and the location of occlusion, which may also influence the outcomes. Finally, magnetic resonance imaging (MRI) and myocardial

**Figure 4.** Corrected TIMI frame count (CTFC) after PPCI.

**Figure 5.** RR of the events of complete ST segment resolution (STR).
contrast echocardiography (MCE) may be more accurate methods of evaluating myocardial perfusion and NR, but no study provided the relevant data. Similarly, we did not use TMPG as an indicator, for only 1 of the enrolled studies provided the data of TMPG. However, in that study, an enhanced TMPG 2–3 ratio was observed in the intracoronary NTP group ($P = 0.030$). Therefore, the results of the present study should be interpreted with caution and may warrant further investigation.

**Conclusions**

Intracoronary use of NTP can significantly improve the final TFG, CTFC, MBG, and the incidence of MACE in patients who suffered from STEMI undergoing PPCI. Although the myocardial reperfusion assessed by complete STR did not reach statistical significance, there was a trend indicating improvement in intracoronary NTP group. However, due to the methodological limitations of the selected studies,
additional high-quality RCTs with a longer follow-up duration are required to further assess the efficacy and safety of intracoronary NTP on NR during PPCI.

References
