Review Article
The efficacy of metformin treatment for myocardial infarction: a meta-analysis of randomized controlled trials

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Abstract: Introduction: The efficacy of metformin treatment for myocardial infarction remains controversial. We conduct a systematic review and meta-analysis to explore the impact of metformin versus placebo on myocardial infarction. Methods: We searched PubMed, EMBase, Web of science, EBSCO, and Cochrane library databases until July 2018 for randomized controlled trials (RCTs) assessing the effect of metformin versus placebo on myocardial infarction. This meta-analysis is performed using the random-effects model. Results: Six RCTs involving 1138 patients are included in this meta-analysis. Overall, compared with the control group of myocardial infarction, metformin treatment had no important impact on major adverse cardiac events (RR = 2.06; 95% CI = 0.90 to 4.74; P = 0.09), reinfarction (RR = 1.60; 95% CI = 0.67 to 3.85; P = 0.29), LVEF (MD = 1.25; 95% CI = -1.51 to 4.01; P = 0.38), NT-proBNP (MD = 0; 95% CI = -0.14 to 0.14; P = 1.0), glucose (MD = 0.05; 95% CI = -0.05 to 0.15; P = 0.31) and HbA1c (MD = 0; 95% CI = -0.02 to 0.02; P = 1.0), but results in the increase in LVEDV (MD = 0.50; 95% CI = 0.43 to 0.57; P < 0.00001) and LVESV were significant (MD = 3.80; 95% CI = 3.75 to 3.86; P < 0.00001). Conclusions: Metformin treatment may not provide significant benefits to patients with myocardial infarction.

Keywords: Metformin, myocardial infarction, major adverse cardiac events, randomized controlled trials, meta-analysis

Introduction

Myocardial infarction has spread wide throughout the world, with high mortality [1-3]. Patients with ST-segment elevation myocardial infarction need immediate treatment with antithrombotic agents and primary percutaneous intervention to restore coronary blood flow [2, 4]. Myocardial damage and the risk of developing left ventricular dysfunction can be substantially reduced by timely reperfusion [5-8], but there are as many as 50% of patients presenting left ventricular dysfunction, and approximately 20% to 40% of patients having heart failure [9-11].

The dimethylbiguanide metformin is known as a first-line treatment in patients with type II diabetes mellitus, and shows some cardioprotective effects in myocardial infarction irrespective of glucose-lowering abilities [12, 13]. Metformin treatment prior to reperfusion is reported to reduce infarct size in patients with diabetes mellitus [14]. Reduced N-terminal pro-brain natriuretic peptide (NT pro-BNP) levels are found after metformin treatment in patients with type II diabetes mellitus, which supports a potential beneficial effect on the risk of heart failure [15]. Metformin treatment during reperfusion can result in the improvement of left ventricular ejection fraction (LVEF) in non-diabetic mice undergoing permanent coronary artery ligation [12].

However, the efficacy of metformin treatment on myocardial infarction has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting [16-18]. With accumulating evidence, we therefore performed a systematic review and meta-analysis of RCTs to investigate the efficacy of metformin treatment versus placebo for myocardial infarction.
Materials and methods

Ethical approval and patient consent are not required because this is a systematic review and meta-analysis of previously published studies. This systematic review and meta-analysis are conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [19].

Search strategy and study selection

Two investigators independently searched the following databases (from inception to July 2018): PubMed, EMBase, Web of science, EBSCO, and Cochrane library databases. The electronic search strategy was conducted using the following keywords: metformin, and myocardial infarction. We also checked the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria are as follows: (i) population: patients with myocardial infarction; (ii) intervention: metformin treatment; (iii) comparison: placebo; (iv) study design: RCT. Patients with known diabetes, previous myocardial infarction, and severe renal dysfunction are excluded.

Data extraction and outcome measures

We have extracted the following information: author, number of patients, age, gender, body mass index, diabetes, and detailed methods in each group etc. Data have been extracted independently by two investigators, and discrepancies are resolved by consensus. We also contacted the corresponding authors to obtain any data when necessary.

The primary outcomes are major adverse cardiac events and reinfarction. Secondary outcomes include left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), NT-proBNP, glucose, and glycated hemoglobin (HbA1c).

Quality assessment in individual studies

Methodological quality of the included studies is independently evaluated using the modified Jadad scale [20]. There are 3 items for Jadad scale: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. If the Jadad score ≥ 3, the study is thought to be of high quality [21].

Statistical analysis

We estimate the mean difference (MD) with 95% confidence interval (CI) for continuous outcomes (LVEF, LVEDV, LVESV, NT-proBNP, glucose, and HbA1c) and risk ratio (RR) with 95% CIs for dichotomous outcomes (major adverse cardiac events and reinfarction). A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the $I^2$ statistic, and $I^2 > 50\%$ indicates significant heterogeneity [22]. Whenever significant heterogeneity is present, we search for potential sources of heterogeneity via omitting one study in turn for the meta-analysis or performing subgroup analysis. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).
Results

Literature search, study characteristics and quality assessment

A detailed flowchart of the search and selection results is shown in Figure 1. Four hundred thirty-four potentially relevant articles are identified initially. Finally, 5 RCTs that meet our inclusion criteria are included in the meta-analysis [16-18, 23, 24].

The baseline characteristics of the 5 eligible RCTs in the meta-analysis are summarized in Table 1. The 5 studies were published between 2014 and 2017, and sample sizes range from 152 to 379 with a total of 1138. Two RCTs report the patient sample with different follow-up times [16, 24], and the follow-up time in the included RCTs range from 24 h to 2 years. Four RCTs involve metformin given at 500 mg, twice daily [16-18, 24], while the remaining one RCT involve 250 mg of metformin given 3 times a day [23].

Among the 5 studies included here, 2 studies report major adverse cardiac events [16, 24], 3 studies report reinfarction [16, 23, 24], 3 studies report LVEF [17, 18, 24], 2 studies report LVEDV and LVESV [17, 18], 2 studies report NT-proBNP, glucose and HbA1c [17, 24]. Jadad scores of the 5 included studies vary from 3 to 5, and all 5 studies are considered to be high-quality according to quality assessment.

Primary outcomes: major adverse cardiac events and reinfarction

These outcome data are analyzed with the random-effects model, and the pooled estimate of the 2 included RCTs suggested that compared to the control group with myocardial infarction, metformin treatment shows no significant impact on major adverse cardiac events (RR = 2.06; 95% CI = 0.90 to 4.74; P = 0.09) with no heterogeneity among the studies ($I^2 = 0\%$, heterogeneity P = 0.60) (Figure 2), and reinfarction (RR = 1.60; 95% CI = 0.67 to 3.85; P = 0.29) with no heterogeneity among the studies ($I^2 = 5\%$, heterogeneity P = 0.31) (Figure 3).

Sensitivity analysis

No heterogeneity is observed among the included studies for the primary outcomes. Thus we do not perform a sensitivity analysis via omitting one study in turn or a subgroup analysis to detect the heterogeneity.

Secondary outcomes

Metformin treatment shows no substantial influence on LVEF (MD = 1.25; 95% CI = -1.51 to 4.01; P = 0.38; Figure 4) compared to placebo in patients with myocardial infarction. Although LVEDV (MD = 0.50; 95% CI = 0.43 to 0.57; P < 0.00001; Figure 5) and LVESV (MD = 3.80; 95% CI = 3.75 to 3.86; P < 0.00001; Figure 6) in the metformin group are found to be higher than placebo intervention. In addition, there is no significant difference of NT-proBNP (MD = 0; 95% CI = -0.14 to 0.14; P = 1.0; Figure 7), glucose (MD = 0.05; 95% CI = -0.05 to 0.15; P = 0.31; Figure 8) and HbA1c (MD = 0; 95% CI = -0.02 to 0.02; P = 1.0; Figure 9) between the two groups.

Publication bias

No significant publication bias is observed (P > 0.05) based on Begg's test and Egger's regression test.

Discussion

Many studies on the effects of metformin on myocardial infarction in animal experimental and human data are inconsistent. Some studies reveal a decrease in myocardial infarct size after metformin treatment [14]. Metformin shows the important ability to prevent the restenosis [25]. Patients with myocardial infarction and diabetes show reduced 30-day all-cause mortality in metformin intervention group compared to control intervention, but there is not a significant difference of 12-month all-cause mortality and LVEF between the two groups [26]. In an open-label randomized controlled clinical trial, 750 mg metformin pretreatment leads to less cardiac biomarker release and a favorable outcome at 1-year follow-up in patients with metabolic syndrome undergoing elective percutaneous coronary intervention [23].

However in a prospective Metformin in Coronary Artery Bypass Graft (MetCAB), pretreatment of metformin in 100 patients has no decrease in periprocedural myocardial injury based on Troponin I levels [27]. The analyses of GIPS-III study found no beneficial effects of 4 months of metformin treatment on long-term clinical...
<table>
<thead>
<tr>
<th>NO.</th>
<th>Author, year and country</th>
<th>Number</th>
<th>Age (years)</th>
<th>Male (n)</th>
<th>Body mass index (kg/m²)</th>
<th>Diabetes (n)</th>
<th>Methods</th>
<th>Follow up time</th>
<th>Jada scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hartman 2017, Netherlands</td>
<td>191</td>
<td>58.7 ± 11.8</td>
<td>144</td>
<td>26.9 ± 3.8</td>
<td>0</td>
<td>Metformin hydrochloride (500 mg) twice daily for 4 months.</td>
<td>2 years</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Eppinga 2016, Netherlands</td>
<td>185</td>
<td>58.8 ± 11.82</td>
<td>139</td>
<td>27.0 ± 3.8</td>
<td>0</td>
<td>Metformin (500 mg bid) during 4 months after primary percutaneous coronary intervention</td>
<td>4 months</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Al Ali 2016, Netherlands</td>
<td>118</td>
<td>57.9 ± 11.4</td>
<td>95</td>
<td>26.7 ± 3.7</td>
<td>-</td>
<td>Metformin 500mg twice daily initiated directly after PCI</td>
<td>4 months</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>Li 2014, China</td>
<td>76</td>
<td>62.4 ± 11.0</td>
<td>52</td>
<td>-</td>
<td>26</td>
<td>250 mg of metformin 3 times a day</td>
<td>24 h</td>
<td>3</td>
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<tr>
<td>5</td>
<td>Lexis 2014, Netherlands</td>
<td>191</td>
<td>58.7 ± 11.8</td>
<td>144</td>
<td>26.9 ± 3.8</td>
<td>0</td>
<td>Metformin hydrochloride (500 mg) twice daily for 4 months</td>
<td>4 months</td>
<td>5</td>
</tr>
</tbody>
</table>
Metformin for myocardial infarction

Our meta-analysis suggests that compared to control intervention for myocardial infarction, metformin intervention shows no significant influence on major adverse cardiac events, reinfarction, LVEF, NT-proBNP, glucose and HbA1c, but with an increase in LVEDV and LVESV.

Several factors should be considered for the efficacy of metformin treatment for myocardial infarction. The timing, duration and doses of...
Metformin treatment may have a crucial role in its potential cardioprotective effects. Metformin administration before or during reperfusion may be preferred in the experimental and observational data [14]. In the GIPS-III trial, metformin is administered directly after percutaneous coronary intervention and effective plasma levels may be achieved hours later, which reduces the time window to modify ischemia-reperfusion injury. Ischemic reperfusion injury can contribute up to 50% to the final size of myocardial infarction [28]. Metformin given at 500 mg twice daily for four months was insufficient in the GIPS-III trial, one year treatment with metformin dosed at 850 mg twice daily decreases the reduction in LDL particle concentration, small-sized low-density lipoprotein particles and improves insulin sensitivity in subjects with impaired glucose tolerance [29]. The efficacy of metformin may be determined by sex-dependent differences in the metabolic and functional response [30]. Metformin therapy can decrease fatty acid clearance and increase fatty acid plasma levels and myocardial fatty acid utilization and oxidation in men, but acts in the opposite in women [31].

This meta-analysis has several potential limitations. First, our analysis is based on only 5 RCTs, and more RCTs with larger samples should be conducted to confirm this issue. Next, the time, duration and doses of metformin treatment in the included RCTs are different, which may have an influence on the pooling results. Finally, the dose of 500 mg twice daily may not be sufficient for patients with myocardial infarction.

Conclusions

Metformin treatment did not show important beneficial effects for myocardial infarction in this study.

Disclosure of conflict of interest

None.

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References


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