Impact of Intra-Aortic Balloon Counterpulsation on Prognosis of Patients with Acute Myocardial Infarction: A Meta-Analysis

Zhi-Wei Gao, Ying-Zi Huang, Hong-Mei Zhao, Qing-Song Sun, Man Luo, Li-Qun Pang and Hong Sun

Background: This study aimed to evaluate the impact of intra-aortic balloon counterpulsation (IABP) on the prognosis of patients with acute myocardial infarction (AMI).

Methods: We identified and included in this study AMI cases treated with IABP from January 1970 to May 2014. For statistical analysis, we utilized RevMan 5.0 software.

Results: Fourteen RCTs with a total population of 2538 were included in this study. The in-hospital and 30-day mortality rate in the IABP group was not significantly lower than those in the non-IABP group. Subgroup analysis according to the type of revascularization, OR values of TT subgroup, PCI subgroup, and CABG subgroup were 0.64 (95% CI 0.25-1.61, p = 0.34), 0.85 (95% CI 0.65-1.11, p = 0.23) and 0.46 (95% CI 0.13-1.63, p = 0.23). And OR values of AMI patients in the before and after PCI subgroup were 0.43 (95% CI 0.21-0.91, p = 0.03) and 1.36 (95% CI 0.76-2.41, p = 0.30). The 6-month mortality in the IABP group was not significantly lower than that in the non-IABP group. And OR values of 6-month mortalities of the before and after PCI subgroup were 0.47 (95% CI 0.26-0.86, p = 0.01) and 1.40 (95% CI 0.57-3.45, p = 0.47).

Conclusions: IABP did not reduce the in-hospital and 30-day mortality of AMI patients, and did not reduce the 6-month mortality. But IABP used in AMI patients before PCI was associated not only with reduced in-hospital and 30-day mortality, but also reduced 6-month mortality.

Key Words: AMI • IABP • Meta-analysis • Mortality

INTRODUCTION

The mortality rate of acute myocardial infarction (AMI) remains high. Although coronary revascularization, including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), has been widely used in clinical practice, the mortality for AMI with cardiogenic shock (CS) is still 40%-50%. Intra-aortic balloon counterpulsation (IABP) is the main circulatory assist device used in high-risk PCI, CABG, or AMI with CS, and can increase coronary blood flow, reduce left ventricular afterload, and improve cardiac function.

The impact of IABP on the prognosis of AMI patients is controversial. Many previous clinical randomized controlled trials (RCTs) had shown that IABP plus PCI or CABG could help improve the prognosis of AMI patients, and reduce in-hospital mortality. Romeo reported that IABP could significantly reduce the mortality of AMI with CS. With further in-depth studies, the impact of IABP on the prognosis of AMI patients was called into question. The results of a large-scale RCT published recently were in contrast with the above
findings, and indicated that IABP did not reduce 30-day and 1-year mortality in AMI patients with CS.12,13 More than half of the studies in the meta-analysis by Romeo were observational, which might bias the results. Because RCTs can be used as the gold standard to assess the effectiveness of treatment,14 the present study conducted a meta-analysis of RCTs in AMI patients treated with IABP, aiming to further clarify the impact on prognosis in AMI.

MATERIALS AND METHODS

Data sources and search strategy
The Medline, EMBASE, and Cochrane databases, and other related websites were searched online without restriction by publication date or publication status. The search keywords included intra-aortic balloon counterpulsation, intra-aortic balloon pump, acute coronary syndrome, acute myocardial infarction, IABP, IABC, and ACS. The last search was conducted on May 30, 2014.

Selection criteria
To ensure the quality of the meta-analysis, the following selection and exclusion criteria were applied to assess the RCTs that were retrieved during the searches. Only published RCTs that enrolled AMI patients treated with drugs, PCI, or CABG were eligible. Only studies of IABP as an intervention for circulatory support were included. This study was conducted in accordance with the Declaration of Helsinki, and with approval from the Ethics Committee of Nanjing Medical University. Written informed consent was obtained from all participants.

Inclusion criteria for this study were as follows: 1) RCTs; 2) the study subjects were adult AMI patients; 3) the control group received conventional standard treatment, and the experiment group received standard treatment-based IABP; 4) the sample sizes of the experiment group and the control group were clear and comparable at the baseline level; 5) the prognostic indicator was in-hospital and 30-day mortality.

The following exclusion criteria applied: 1) non-English language literature; 2) overlapping reports, with poor quality, little information, or data that could not be used; 3) treatment prognosis not considered.

Quality assessment of included RCTs
Two reviewers independently performed quality assessments, and extracted study method information, IABP timing, treatment duration, and prognostic indicators. The results were then cross-checked, and any difference was resolved by further discussion or third-party arbitration. The included RCTs used the GRADE approach for the strength of evidence.

Statistical analysis
The data were analyzed using Review Manager 5.1 program. Endpoints were treated as dichotomous outcomes, and odds ratios (ORs) with 95% confidence intervals (CIs) were used as a statistical indicator of the curative effect and safety of IABP in AMI. When the event of interest did not occur, the treatment effect of that study was treated as not estimable.

The Breslow-Day χ² test (p < 0.1) and the I² statistic were used to test the heterogeneity of the 14 included studies, with an I² less than 25% considered to be low; 25% < I² < 50% as moderate, p > 0.1; and I² > 50% to be a high degree of heterogeneity.15 When I² was < 50%, a fixed-effects Mantel-Haenszel model was used to analyze the data; when I² was > 50%, the DerSimonian and Laird random-effects model was found to be better than the Mantel-Haenszel model. Then, a sensitivity analysis was also conducted, in which 1 study at a time was removed and the others analyzed to estimate whether the results could have been affected markedly by a single study. Publication bias was evaluated using funnel plots.16

RESULTS

Literature retrieval
A total of 950 English articles were preliminarily retrieved based upon the use of the above keywords; retrieval condition was then limited to RCTs, and 427 duplicates were excluded. Thereafter, 523 remaining articles were then screened for further retrieval. Finally, a total of 14 RCTS on IABP in AMI met the inclusion criteria (Figure 1).

Characteristics of the included RCTs
Among the 14 included RCTs, nine were multi-center studies.12,17-29 A total of 2538 patients were included,
including 1258 in the IABP group and 1280 in the non-IABP group. All patients included had AMI with or without CS. The treatment measure of the IABP group was need for further IABP based on the control group (thrombolysis, PCI, or CABG). The treatment timing and duration of IABP in different studies showed significant differences (Table 1). The quality of the included RCTs assessed by GRADE approach was low.

### Impact of IABP on prognosis in AMI patients

For in-hospital and 30-day mortality, the heterogeneity among the included 14 RCTs was mild ($p = 0.29$, $I^2 = 15\%$). The in-hospital and 30-day mortality rates of the IABP and non-IABP groups were 16.2% and 18.1%, respectively, OR = 0.85 (95% CI 0.67-1.08, $p = 0.19$), indicating that IABP did not improve mortality (Figure 2A).

### Table 1. General clinical conditions of the AMI patients selected for IABP

<table>
<thead>
<tr>
<th>Literature source</th>
<th>Research institute</th>
<th>Main diagnosis</th>
<th>Main treatment measure</th>
<th>IABP timing</th>
<th>IABP duration</th>
<th>Jadad scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Rourke et al., 1981</td>
<td>Multi-center</td>
<td>AMI plus heart failure</td>
<td>IABP Standard treatment</td>
<td>Chest pain within 4.5 d [1-11]</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Flaherty et al., 1985</td>
<td>Single center</td>
<td>Non-CS accompanied AMI</td>
<td>IABP+thrombolysis</td>
<td>7.1 h [4.8-13.7]</td>
<td>4.6 d ± 1.9</td>
<td>5</td>
</tr>
<tr>
<td>Waksman et al., 1993</td>
<td>Multi-center</td>
<td>AMI plus CS</td>
<td>IABP+PTCA/CABG PTCA/CABG</td>
<td>After PCI</td>
<td>48 h [43,51]</td>
<td>5</td>
</tr>
<tr>
<td>Ohman et al., 1994</td>
<td>Multi-center</td>
<td>Non-CS accompanied AMI</td>
<td>IABP+PCI</td>
<td>After PCI</td>
<td>48 h</td>
<td>3</td>
</tr>
<tr>
<td>Kono et al., 1996</td>
<td>Single center</td>
<td>Non-CS accompanied AMI</td>
<td>IABP+thrombolysis</td>
<td>1.9 h ± 1.1 after nitroglycerin pumping</td>
<td>48 h</td>
<td>3</td>
</tr>
<tr>
<td>Stone et al., 1997</td>
<td>Multi-center</td>
<td>Non-CS accompanied AMI</td>
<td>IABP+PTCA</td>
<td>After the failure of thrombolysis</td>
<td>47.9 h ± 28.0</td>
<td>3</td>
</tr>
<tr>
<td>Van't Hof et al., 1999</td>
<td>Single center</td>
<td>AMI</td>
<td>IABP+PTCA PTCA</td>
<td>After PTCA</td>
<td>56 h [14-216]</td>
<td>5</td>
</tr>
<tr>
<td>Ohman et al., 2005</td>
<td>Multi-center</td>
<td>AMI plus CS</td>
<td>IABP+thrombolysis</td>
<td>After thrombolysis</td>
<td>34 h [24-68]</td>
<td>5</td>
</tr>
<tr>
<td>Prondzinsky et al., 2010</td>
<td>Single center</td>
<td>AMI plus CS</td>
<td>IABP+thrombolysis IABP+PCI</td>
<td>After PCI</td>
<td>48 h</td>
<td>5</td>
</tr>
<tr>
<td>Perera et al., 2010</td>
<td>Multi-center</td>
<td>Non-CS accompanied AMI</td>
<td>IABP+PCI PCI</td>
<td>Before PCI</td>
<td>4-24 h</td>
<td>5</td>
</tr>
<tr>
<td>Gu et al., 2011</td>
<td>Multi-center</td>
<td>Non-CS accompanied AMI</td>
<td>IABP+PCI PCI</td>
<td>Before PCI</td>
<td>52 h ± 17</td>
<td>3</td>
</tr>
<tr>
<td>Patel et al., 2011</td>
<td>Multi-center</td>
<td>Non-CS accompanied AMI</td>
<td>IABP+PCI PCI</td>
<td>Before PCI</td>
<td>22.1 h</td>
<td>5</td>
</tr>
<tr>
<td>Thiele et al., 2012</td>
<td>Multi-center</td>
<td>AMI plus CS</td>
<td>IABP+PCI PCI</td>
<td>Before or after PCI</td>
<td>3 d [2-4]</td>
<td>5</td>
</tr>
<tr>
<td>Ranucci et al., 2013</td>
<td>Single center</td>
<td>Non-CS accompanied AMI</td>
<td>IABP+CABG CABG</td>
<td>Before CABG</td>
<td>Not reported</td>
<td>5</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CS, cardiogenic shock; IABP, intra-aortic balloon counterpulsation; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty.
Figure 2. Impacts of IABP on the in-hospital and 30-day mortality (A), and 6-month mortality (B) in the AMI patients accompanied with CS or not. AMI, acute myocardial infarction; CS, cardiogenic shock; 95% CI, 95% confidence interval.
The funnel diagram was proximally symmetrical, which indicated no publication bias (Supplement Figure S1).

The patients were then divided into two subgroups according to whether or not they had CS. The results showed the heterogeneity of these two RCT subgroups was mild ($I^2 = 22\%$ and 19\%, respectively); the OR values were 0.87 (95\% CI 0.65-1.16, $p = 0.33$) and 0.70 (95\% CI 0.43-1.15, $p = 0.16$), respectively, indicating that IABP did not reduce the in-hospital and 30-day mortality rate (Figure 2A).

Upon further analysis of 6-month mortality, the heterogeneity of the included seven RCTs was moderate ($p = 0.19$, $I^2 = 30\%$), and the 6-month mortality rates of the IABP and non-IABP groups were 27.0\% and 30.1\%, respectively, with OR = 0.78 (95\% CI 0.60-1.01, $p = 0.06$), indicating that IABP did not improve the 6-month mortality (Figure 2B). The funnel diagram was not symmetrical, which indicated existing publication bias (Supplement Figure S2).

The in-hospital and 30-day mortalities of the AMI patients in the thrombolytic therapy (TT), PCI, and CABG subgroups were evaluated according to revascularization type. There were three RCTs included in the TT subgroup, 18,21,24 OR = 0.64 (95\% CI 0.25-1.61, $p = 0.34$), eight RCTs were included in the PCI subgroup, 12,19,20,22,25,28 OR = 0.85 (95\% CI 0.65-1.11, $p = 0.23$), and only one RCT was about CABG therapy, 29 OR = 0.46 (95\% CI 0.13-1.63, $p = 0.23$) (Figure 3A). The funnel diagram was proximally symmetrical, which indicated no publication bias (Supplement Figure S3). The OR value of the 6-month mortalities of AMI patients in subgroups of TT and PCI were 0.79 (95\% CI 0.32-1.97, $p = 0.62$) and 0.78 (95\% CI 0.59-1.02, $p = 0.07$) (Figure 3B). The funnel diagram was not symmetrical, which indicated existing publication bias (Supplement Figure S4).

Further analysis of the PCI subgroup was performed to ascertain the impact of different IABP timing (i.e., before or after PCI) on the in-hospital and 30-day mortality in AMI patients. In the before-PCI subgroup, 26-28 OR = 0.43 (95\% CI 0.21-0.91, $p = 0.03$); in the after-PCI subgroup, 20,22,23,25 OR = 1.36 (95\% CI 0.76-2.41, $p = 0.30$) (Figure 4A). The funnel diagram was not symmetrical, which indicated existing publication bias (Supplement Figure S5). The OR value of 6-month mortalities of AMI patients in the before and after PCI subgroup were 0.47 (95\% CI 0.26-0.86, $p = 0.01$) and 1.40 (95\% CI 0.57-3.45, $p = 0.47$) (Figure 4B). The funnel diagram was not symmetrical, which indicated existing publication bias (Supplement Figure S6).

Bleeding events

The heterogeneity of the 11 included RCTs was mild ($p = 0.59$, $I^2 = 0\%$), and the OR value of the combined OR output from the fixed effects model was 1.36 (95\% CI 1.09-1.70, $p = 0.006$), indicating that the bleeding-related events in the IABP group were significantly more than those in the control group (Figure 5). The funnel diagram was not symmetrical, which indicated existing publication bias (Supplement Figure S7).

DISCUSSION

IABP is widely used in treating AMI patients. However, whether IABP can improve the prognosis of AMI patients remains controversial. The meta-analysis conducted by Sjauw showed that IABP significantly reduced hospital mortality in AMI. 30 But another recent meta-analysis by Ye showed that IABP did not improve the two-month mortality of AMI patients with or without CS. 31 The meta-analysis of this study showed that IABP did not reduce the in-hospital and 30-day mortality in AMI patients, and not reduce 6-month mortality.

The combination of different therapies, such as TT, PCI, or CABG might have different effects on IABP in AMI patients. The results of the prospective observational National Registry of Myocardial Infarction 2 study and ALKK-PCI showed no prognostic improvement in AMI pa-
Figure 3. Impacts of IABP on the in-hospital and 30-day mortality in the AMI patients accepting different revascularizations (A), and on the 6-month mortality in the AMI patients accepting different revascularizations (B). AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CS, cardiogenic shock; PCI, percutaneous coronary intervention; TT, thrombolysis; 95% CI, 95% confidence interval.
patients with CS treated by IABP combined with PCI. Numerous studies have shown that mortality in AMI patients receiving TT combined with IABP was significantly reduced. However, our meta-analysis indicated that IABP did not reduce the in-hospital and 30-day mortality in AMI patients receiving TT, possibly because most studies included in the meta-analyses of Sjauw and Romeo were observational studies instead of RCTs, which might bias the results. This meta-analysis only included three small-scale RCTs, and only 63 and 59 patients were included in the IABP and non-IABP groups, respectively. Therefore, large-scale RCTs are still needed to further confirm the impact of IABP on AMI patients received TT.

The implantation of IABP would delay PCI, which might be the cause of increased mortality in the IABP
group. IABP could help increase coronary perfusion and maintain hemodynamic stability, thus possibly reducing infarct size and improving the prognosis. However, the results of clinical RCTs concluded the opposite to the above speculation. The Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction study included a total of 337 AMI patients without CS, and randomly divided them into IABP (before PCI) and control (PCI) groups. The results suggested that IABP did not reduce AMI infarct size (42.1% vs. 37.5%, p = 0.06). This might be related to the fact that the preparation time for PCI in the IABP group was significantly longer than that in the control group (77 min vs. 68 min, p = 0.04).

The use of a left ventricular assist device or more vasoactive drugs in some patients in the non-IABP group could increase cardiac output and improve tissue perfusion, thus affecting prognosis. Thiele reported no difference in the systemic inflammatory response index and the tissue perfusion index between the two groups; this was likely related to the significantly increased use of vasoactive agents in the control group. Additionally, 8.5% of the control group in the Perera study received IABP. The proportion of the above studies accounted largely for the proportion of our study, which might be the reason for no prognosis improvement in the IABP group.

The beneficial effects of IABP differed among AMI patients. The improvement in coronary blood flow depended on the severity of stenosis. The results of one study in 239 AMI patients who received IABP showed that those with sustained ischemia post-PCI or post-CABG benefited from IABP. Ramanathan’s study on the IABP effects in 499 AMI patients with CS demonstrated that the mortality in those with rapid systemic hypoperfusion reversal (after IABP treatment for 30 min) was significantly reduced. Further study is needed to verify more clinical indications to provide a reference for clinical practice.

IABP might possibly improve the long-term prognosis of some AMI patients. The SHOCK long-term prognosis study revealed that the 6-month mortality was significantly improved. Our study also confirmed that IABP could help reduce the 6-month mortality in AMI patients without CS. However, some recent studies showed that IABP did not improve 6-month or 12-month mortality in AMI patients, possibly because the AMI patients included in the above studies all had CS.

Our study shows that the in-hospital and 30-day mortality in the IABP-before-PCI subgroup was reduced, and also 6-month mortality, suggesting that the timing of IABP may be very important. Perera confirmed that IABP before PCI did not reduce 30-day mortality, which may be related to several factors, such as significantly increased procedural complications, 12% received rescue IABP, and longer IABP duration in the control group. Gu concluded that the explanation as to why IABP before PCI therapy did not reduce 6-month mortality was the small sample size. Thus, IABP inserted before PCI may help improve prognosis.

Our study had some limitations. The mortality in the IABP group was only 16.2%, significantly lower than the results (42%~48%) in other RCTs and observational studies; this might be related to the different disease severities among these AMI patients. Some funnel dia-

Figure 5. Forest plots of bleeding events of the IABP group and the non-IABP group.
grams were not symmetrical, indicating publication bias, which might influence the accuracy of these results. Most RCTs had relatively small sample size, and did not indicate whether the sample size was a minimum, which might affect the mortality in this meta-analysis.17,18

CONCLUSIONS

Although the use of IABP remains controversial, resulting in a reduced recommendation level in European and American guidelines, it is still too early to discount the benefit of IABP in AMI. Our results appear to confirm IABP did not improve the prognosis of AMI patients. However, IABP used in AMI patients before PCI was associated with not only reduced in-hospital and 30-day mortality, but also with reduced 6-month mortality. Future studies should focus on studying the impact of different combined treatments on the prognosis of AMI, by choosing appropriate AMI patients who might benefit from IABP, trying to reduce the IABP implantation time as much as possible, and restoring coronary blood flow as soon as possible.

CONFLICTS OF INTEREST

All of the authors declare that they have no conflicts of interest regarding this paper.

REFERENCES

18. Flaherty JT, Becker LC, Weiss JL, et al. Results of a randomized prospective trial of intraaortic balloon counterpulsation and intravenous nitroglycerin in patients with acute myocardial infarc-


**Figure S1.** Funnel plot of mortality within the hospital-stay or 30-day.
Intra-Aortic Balloon Counterpulsation in AMI

Figure S2. Funnel plot of mortality within 6-month.

Figure S3. Funnel plot of mortality within hospital-stay or 30-day mortality in the AMI patients accepting different revascularizations.

Figure S4. Funnel plot of mortality within 6-month mortality in the AMI patients accepting different revascularizations.

Figure S5. Funnel plot of mortality within hospital-stay or 30-day in the AMI patients of different PCI subgroups.

Figure S6. Funnel plot of mortality within the 6-month in the AMI patients of different PCI subgroups.

Figure S7. Funnel plot of bleeding events.