Intra-Aortic Balloon Pump May Grant No Benefit to Improve the Mortality of Patients With Acute Myocardial Infarction in Short and Long Term

An Updated Meta-Analysis

Dan Su, MD, Bin Yan, MD, Litao Guo, MD, Livuan Peng, MD, Xue Wang, MD, Lingfang Zeng, PhD, HeanYee Ong, MRCP, and Gang Wang, MD, PhD

Abstract: Intra-aortic balloon pump (IABP) has been extensively used in clinical practice as a circulatory-assist device. However, current literature demonstrated significantly varied indications for IABP application and prognosis.

The objective of the study was to assess the potential benefits or risks of IABP treatment for acute myocardial infarction (AMI) complicated with or without cardiogenic shock.

MEDLINE and EMBASE database were systematically searched until November 2014, using the terms as follows: IABP, IABC (intra-aortic balloon counterpulsation), AMI, heart infarction, coronary artery disease, ischemic heart disease, and acute coronary syndrome. Only randomized controlled trials (RCTs) that compared the use of IABP or non-IABP support in AMI with or without cardiogenic shock were included. Two researchers performed data extraction independently, and at the mean time, the risk of bias among those RCTs was also assessed.

Of 3026 citations, 17 studies (n = 3226) met the inclusion criteria. There is no significant difference between IABP group and control group on the short-term mortality (relative risk [RR], 0.90; 95% confidence interval [CI], 0.77–1.06; P = 0.214) and long-term mortality (RR, 0.91; 95% CI, 0.79–1.04; P = 0.155) in AMI patients with or without cardiogenic shock. These results were consistent when the analysis was performed on studies that only included patients with cardiogenic shock, both on short-term mortality (RR, 0.91; 95% CI, 0.77–1.08; P = 0.293) and long-term mortality (RR, 0.95; 95% CI, 0.83–1.10; P = 0.492). Similar result was also observed in AMI patients without cardiogenic shock. Furthermore, the risks of hemorrhage (RR, 1.49; 95% CI, 1.09–2.04; P = 0.013) and recurrent ischemia (RR 0.54, 95% CI 0.37 to 0.79; P = 0.002) were significantly higher in IABP group compared with control group.

We did not observe substantial benefit from IABP application in reducing the short- and long-term mortality, while it might promote the risks of hemorrhage and recurrent ischemia. Therefore, IABP may be not an optimal therapy in AMI with or without cardiogenic shock until more elaborate classification is used for selecting appropriate patients.

Abbreviations: AMI = acute myocardial infarction, APACHE = Acute Physiology and Chronic Health Evaluation, CABG = coronary artery bypass grafting, CI = confidence interval, IABC = intra-aortic balloon counterpulsation, IABP = intra-aortic balloon pump, LVAD = left ventricular assist device, MODS = multi-organ dysfunction syndrome, PCI = percutaneous coronary intervention, RCT = randomized controlled trial, SIRS = systemic inflammatory response syndrome.

INTRODUCTION

Cardiogenic shock is the most common cause of death in patients with acute myocardial infarction (AMI), even following early revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Intra-aortic balloon pump (IABP) counterpulsation can increase coronary blood supply while at the same time support patients with cardiogenic shock by maintaining cardiac output hemodynamically. However, the efficacy of IABP has been controversial since its first application during the early 1960s. Current literature demonstrates wide inconsistency of the indications for IABP utilization and outcomes. A meta-analysis by Sjauw et al found conflicting outcomes when randomized studies, cohort studies, and observational data were pooled and analyzed. Consistent with another meta-analysis carried out in 2013, Sjauw et al also demonstrated the benefit of IABP may vary due to the adjunctive therapies, thrombolysis or PCI.

The use of IABP for high risk PCI was recommended as a class IIb (level of evidence C) indication in ACCF/AHA/SCAI guidelines. However, in a recent randomized trial (IABP-SHOCK II), IABP support did not reduce the 30-day mortality in patients with AMI and cardiogenic shock, compared with IABP support. In addition, the same study found that IABP did not reduce 6- and 12-month mortality rate compared with the control group, despite early revascularization and optimum medical therapy in both groups. Therefore, in the 2014 ESC/EACTS myocardial revascularization guidelines, IABP was only granted an IIIA recommendation and recommended

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From the Departments of Cardiology (DS) and Emergency Medicine (BY, LP, GW), the Second Affiliated Hospital; Intensive Care Unit, the First Affiliated Hospital, Xi’an Jiaotong University, Xi’an, China (LG, XW); Cardiovascular Division, King’s College London, British Heart Foundation Centre, London, United Kingdom (LZ); and Department of Cardiology, Khoo Teck Puat Hospital, Singapore (HYO).
Correspondence: A/Prof. Gang Wang, Department of Emergency Medicine, the Second Affiliated Hospital, Xi’an Jiaotong University, Xi’an, China (e-mail: gang_wang@mail.xjtu.edu.cn).
The first two authors contributed equally to this work.
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as a bridge to surgery for patients with mechanical complications. Our current updated meta-analysis has collected all published randomized trials to date, aiming to evaluate the potential short- or long-term benefits and risks of IABP therapy in AMI with or without cardiogenic shock.

**METHODS**

To identify all randomized controlled trials (RCTs) of IABP therapy, public databases including MEDLINE (1966–2014) and EMBASE (1980–2014) were searched. Keywords and medical subject headings are as follows: IABP, IABC (intra-aortic balloon counterpulsation), AMI, heart infarction, coronary artery disease, ischemic heart disease, and acute coronary syndrome. The search was restricted to human studies and clinical trials or RCTs only. In addition, we also manually searched bibliographies of identified studies if needed.

All RCTs were published before November 2014 on the treatment of AMI with IABP in either intensive care unit or coronary care unit settings. Studies were excluded if they were in abstract form only, not RCT, not on AMI patients, IABP in surgery or when other cardiac support devices, such as a left ventricular assist device (LVAD) or an extracorporeal membrane oxygenator, were used. Information on the surname of the first author, year of publication, average patient age, sample size, mean or medium IABP duration, inclusion criteria, exclusion criteria, and outcomes were extracted. Data from each study were collected in intention-to-treat categories rather than per-protocol categories to avoid bias towards excluding patient dropped-out, withdrew, or incompliance to the treatment. For assessment of the risk of bias, Cochrane risk of bias tool was used. Two authors independently collected information from all studies to obtained information on sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. We assigned “unclear” to an item with insufficient information.

**FIGURE 1.** Flowchart of the selection process in our study. IABP = intra-aortic balloon pump, RCT = randomized controlled trial.

**FIGURE 2.** The results of evaluation using Cochrane collaboration’s tool for assessing risk of bias. Each risk of bias item presented as percentages across all included studies.
All analyses were conducted using STATA 12.0 (StataCorp LP, College Station, TX). Relative risks (RRs) and 95% confidence intervals (CIs) were calculated for each study. Relative weights were assigned according to the contribution of each study to each analysis. Publication bias was assessed graphically using a funnel plot. Statistical significance was set as 0.05 on the basis of 2-way z tests and χ² tests.

RESULTS

Literature Search

Potentially relevant references were identified by the above stratagem. A total of 3026 references were identified (Pubmed: n = 1962, Embase: n = 1049, 15 records identified from other sources). Seventeen relevant studies with 3226 participants were enrolled after in-depth review. The selection strategy of our study is shown in Figure 1.

Study Characteristics

The baseline characteristics of the 17 studies included in the meta-analysis are summarized in Supplemental Digital Content-Table 1, http://links.lww.com/MD/A273. The risks of bias in all studies (measured by Cochrane risk of bias tool) are presented in Figures 2 and 3. The mean (or medium) duration of IABP support in the selected RCTs ranged from 24 hours to 11 days. All the patients in the trials received optimal medical therapy based on guidelines. We analyzed the impact of IABP management on short-term mortality in 14 trials (n = 2354), long-term mortality in 9 trials (n = 1743), risks of hemorrhage in 8 trials (n = 1296), reinfarction in 8 trials (n = 1371), recurrent ischemia in 4 trials (n = 964), and stroke in 4 trials (n = 684) during the study periods.

IABP Failed to Improve the Short- and Long-Term Mortality

The short-term mortality was analyzed in 14 studies involving 2354 patients (5 trials in AMI with cardiogenic shock and 9 trials in AMI without cardiogenic shock). As shown in Figure 4, there was no significant difference on short-term mortality (<30-day mortality) between IABP on AMI patients with cardiogenic shock and control group (RR, 0.91; 95% CI, 0.77–1.08; P = 0.293). Similar result was also observed in AMI patients without cardiogenic shock (RR, 0.88; 95% CI, 0.60–1.29; P = 0.279). Taken together, our meta-analysis indicates that short-term mortality of patients with AMI with and without cardiogenic shock does not differ between IABP and control group (RR, 0.90; 95% CI, 0.77–1.06; P = 0.214).

Interestingly, further analysis of 2 subgroups in 9 studies (4 AMI trials with cardiogenic shock and 5 without cardiogenic shock) also demonstrated that IABP therapy was not associated with a significantly reduced risk of long-term mortality (6- and 12-month mortality) rate (RR, 0.91; 95% CI, 0.79–1.04; P = 0.155). This analysis covers 1743 patients, 866 patients in the IABP group and 877 in the control group. Moreover, the results remained the same when the analysis was performed on studies only either on patients with cardiogenic shock (RR, 0.95; 95% CI, 0.83–1.10; P = 0.492) or without cardiogenic shock (RR, 0.73; 95% CI, 0.49–1.09; P = 0.122) (Figure 5).

IABP May Increase the Risks of Hemorrhage and Recurrent Ischemia for AMI Patients During Mechanical Support

Furthermore, incidences of hemorrhage, reinfarction, recurrent ischemia, and stroke within IABP group and control group were also analyzed. We observed no significant differences in the risks of reinfarction (RR, 1.01, 95% CI 0.64–1.59; P = 0.954) and stroke (RR, 2.95, 95% CI 0.97–9.0; P = 0.057) between IABP and control groups. However, as shown in Figure 6, amongst 1296 patients (644 patients in the IABP
FIGURE 4. Forest plot of short-term mortality in acute myocardial infarction with or without cardiogenic shock. Solid lines denote CIs of effect size (ES) estimate for individual studies, boxes denote the study weighting, dashed line denotes the combined ES, and the diamonds denote the CI for the overall effect size. CI = confidence interval, RR = relative risk.

FIGURE 5. Forest plot of long-term mortality in myocardial infarction with or without cardiogenic shock. CI = confidence interval, RR = relative risk.
group and 652 in the control group) in the investigation, the risk of hemorrhage was significantly higher in IABP group than control group (RR, 1.49; 95% CI, 1.09–2.04; \( P = 0.013 \)). In addition, we also found that IABP treatment was associated with an increased risk for recurrent ischemia events (RR, 0.54, 95% CI 0.37–0.79; \( P = 0.002 \)) among 4 reports13,15–17 analyzed.

**DISCUSSION**

The aim of AMI management is to reduce the mortality by improving or restoring the coronary circulation. Thus far, even with rapidly emerging medical options available, mechanical circulatory support devices are still necessary to provide hemodynamic support when required. IABP has been shown to improve the outcomes of AMI patients with cardiogenic shock by increasing diastolic peak pressure and reducing afterload in the pre-PCI era.27 In addition, IABP was reported to maintain the hemodynamic stability in selective high-risk AMI individuals undergoing PCI during short term.28 The prophylactic IABP support in high-risk patients during selective PCI has also been thoroughly evaluated in a study with a total of 106 patients, suggesting IABP could reduce the level of C-reactive protein and short-term mortality following PCI.24

Before the IABP-Shock II Trial, which did not find improved 30-day, 6-month, or 12-month survival rate after the implantation of IABP,6,9 Prondzinsky et al23 showed that IABP support could reduce afterload, as measured by a significant reduction in BNP in 2010. However, they also revealed that mechanical support, such as IABP, failed to prevent the initiation and development of systemic inflammatory response syndrome (SIRS) and multi-organ dysfunction syndrome (MODS), which lead to the high mortality of AMI patients with cardiogenic shock as assessed using Acute Physiology and Chronic Health Evaluation (APACHE) II score.23 There was a meta-analysis from Bahekar et al32 supporting Prondzinsky et al in the importance of prognosis assessment in patients with AMI complicated with cardiogenic shock. Although APACHE II score was not applied in the meta-analysis, it reported a significant reduction of in-hospital mortality in AMI with cardiogenic shock, while AMI patients with high-risk and cardiogenic shock may not benefit from the use of IABP in terms of in-hospital mortality, rate of reinfarction, and recurrent angina.32 Nevertheless, this study might be inherent biased due to the combined analysis of RCTs, prospective and retrospective observational studies.

Most of current meta-analyses and recommendations for IABP application on AMI patients with or without cardiac shock since the 1990s. Although IABP results in a hemodynamic benefit on afterload reduction and coronary perfusion improvement, the effects on cardiac output are modest and not sufficient to reduce mortality.29,30 As shown in a recent meta-analysis, preoperative insertion of IABP reduced mortality in selective high-risk coronary artery bypass graft patients.31 IABP may play a role as a bridge or transition in short term but not on increasing long-term survival rate, which are also affected by subsequent physiopathologic progression and treatment following AMI.
difference on the short-term mortality regardless of whether IABP-SHOCK II trial was included or not, the long-term mortality was improved without IABP-SHOCK II trial. However, our results are consistent with another recently published meta-analysis, which also showed that IABP was not found to improve 30-day mortality among patients with AMI in RCTs, no matter patients had cardiogenic shock or not.33 As we know, cardiogenic shock is commonly rapidly progressive and usually fatal. Despite of the advances in coronary revascularization, cardiogenic shock as a complication of AMI still remains as a huge clinical challenge with high mortality. It eventually results in SIRS and MODS due to peripheral hyperperfusion with microcirculatory dysfunction of ischemia sensitive tissues and organs. This would happen in various percentage of patients with mild, moderate, or severe cardiogenic shock, which could preclude the statistical processing.34–36 Therefore, further studies should include hemodynamic measurements or laboratory inflammatory markers within a scoring system to divide AMI patients into more accurate subgroups.

In addition, safety is another important issue in consideration of IABP application. Although the sheathless catheter insertion technique and catheters with smaller profiles were developed, the use of IABP may produce a high rate of complications, such as hemorrhage, recurrent ischemia, stroke, and reinfarction. Although no differences regarding hemorrhage were observed in IABP-Shock II Trial,8 conflicting conclusions were reported in a meta-analysis, in which IABP was found to significantly increase the risk of moderate-to-severe bleeding.33 In our meta-analysis, we also found IABP was associated with an increased rate of bleeding, possibly associated with the use of multiple antithrombotic agents with aggressive anticoagulation regimen in acutely MI patients.37,38 Besides, the use of IABP was also the strongest independent predictor for major bleeding due to femoral artery cannulation and prolonged duration of IABP support, IABP-related thrombocytopenia and renal impairment, which were consistently demonstrated by other study populations, especially in patients who had developed or were anticipated to develop cardiogenic shock.39,40 Davidavicius et al further pointed out that IABP insertion in the urgent setting in response to intra-procedural hemodynamic instability confers a higher risk of bleeding compared with selective insertion for stable patients.31 In terms of other safety issues, we observed significantly increased risk for recurrent ischemia in IABP group than in the control group. Although it seems more closely related to the premorbid status of patients, our findings may add additional support on a more conservative strategy for using IABP in acute phase of MI with or without cardiogenic shock.

As mentioned earlier, AMI is not only associated with compromised cardiac contractile function, especially in patients with cardiogenic shock. Therefore, other than mortality, more comprehensive assessment of hemodynamic changes and inflammatory markers of patients with AMI may serve as better endpoint for IABP application. In addition, there were <10% of patients in control group accepting IABP or LVAD support in IABP-SHOCK II trial, which might interfere the analysis of mortality in our study.42,43 In terms of the timing of IABP insertion, it was too difficult to control in real clinical settings and to be included for analysis in most studies. Future RCTs with larger numbers of patients and rigorous design are required in the future.

In conclusion, the findings of this study suggest that IABP use in AMI patients with or without cardiogenic shock may not reduce the short-term and long-term mortality, and potentially promote the recurrent ischemia and hemorrhage events.

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