Intravenous Immunoglobulin Therapy for Acute Myocarditis in Children and Adults

A Meta-Analysis

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Summary

The efficacy of intravenous immunoglobulin (IVIG) in the treatment of acute myocarditis remains controversial. The aim of this study was to conduct a meta-analysis to assess the efficacy of IVIG in children and adults with acute myocarditis.

We searched PubMed, Scopus, Embase, Medline, the Cochrane Library, Google Scholar, and the ClinicalTrials.gov website. Eligible studies were clinical trials of patients with acute myocarditis who received IVIG therapy. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate the outcomes.

Thirteen studies with 1534 cases were incorporated into our meta-analysis. Pooled results showed that IVIG therapy significantly reduced in-hospital mortality (OR: 0.44, 95% CI 0.17 to 0.71, \( P < 0.001 \)) and improved the left ventricular ejection fraction (LVEF) (OR: 1.73, 95% CI 1.34 to 2.13, \( P < 0.001 \)) in acute myocarditis patients. Furthermore, patients with acute fulminant myocarditis (AFM) exhibited a significantly higher survival rate (OR: 2.80, 95% CI 1.16 to 6.77, \( P = 0.022 \)) in the IVIG group.

IVIG therapy can not only result in lower in-hospital mortality and superior recovery of left ventricular function in patients with acute myocarditis, but also increase the survival rate of AFM patients. The present study provides some supportive evidence for IVIG therapy in acute myocarditis patients.

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Key words: Heart failure, Mortality, Immunoregulation, Literature search

Acute myocarditis (AMC) is defined as inflammation of the myocardium. Myocarditis is believed to be initiated by viral infection in most cases. Soon afterwards, a direct cytopathic effect of the cardiotropic virus can swiftly induce excessive immunologic activation.1) Direct viral invasion and indirect immunemediated myocardial injuries can both contribute to the development of myocarditis.2) Acute fulminant myocarditis (AFM) is characterized by abrupt onset of cardiogenic shock, severe arrhythmia, and heart failure, which may lead to acute cardiac death in both pediatric and adult populations.3,4) Despite modern advances in mechanical circulatory support, the in-hospital mortality of AFM remains high.5) Therefore, therapeutic options for AMC and AFM are warranted in order to decrease their in-hospital mortality.

Intravenous immunoglobulin (IVIG) has both antiviral and anti-inflammatory effects on myocarditis,6) but its efficacy at improving short-term or long-term outcomes remains controversial. A retrospective study indicated that applying IVIG to AFM patients may improve left ventricular function and reduce the incidence of fulminant arrhythmias.7) Nevertheless, another two randomized controlled trials (RCTs) in pediatric or adult patients reported inconsistent results.8,9) In those studies, no remarkable difference in survival rate was found, and there was no rigorous evidence indicating whether IVIG could amplify the improvement in left ventricular function. Therefore, we conducted a meta-analysis of all available studies to elucidate the efficacy of IVIG for patients with acute myocarditis.

Methods

Search strategy and selection criteria: We systematically searched PubMed, Scopus, Embase, Medline, the Cochrane Library, Google Scholar, and the ClinicalTrials.gov website up to March 31, 2018. A comprehensive search strategy was developed based on the following terms: (1) immunoglobulin, intravenous immunoglobulin, immunoglobulin, intravenous immunoglobulin,
IVIG, intravenous gamma globulin and (2) myocarditis, cardiomyopathy, myocardopathy, heart inflammation. We additionally hand-searched the references of relevant articles, and contacted investigators of certain studies when necessary. The language of the included articles was restricted to English.

Studies were taken into account when they satisfied the following inclusion criteria: (1) patients had a clinical diagnosis of acute myocarditis; and (2) patients treated with IVIG as the case group and patients without IVIG as the control group. Exclusion criteria were as follows: (1) studies not pertinent to IVIG or myocarditis; (2) no control groups; (3) similar studies from the same author as well as multiple duplicate data in different studies, and (4) animal experiments, case reports, correspondences, reviews, expert opinions, letters, talks, and effect estimates from conference abstracts when a full-published study was not available.

Data extraction and quality assessment: Two investigators (XH, YFS) evaluated the eligibility of all retrieved studies and extracted the relevant data independently. Extracted databases were then cross-checked between the two authors to rule out any discrepancy. Disagreement was resolved by consulting with a third investigator (GHS). The following data of each collected study were extracted independently. The Cochrane Collaboration risk of bias tool was used to assess risk of bias. Our investigation process was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Statistical analysis: The statistical analyses were performed using the Review Manager (RevMan) software version 5.3 and STATA 14. Estimates were summarized as odds ratio (OR) with 95% confidence interval (CI) for each study. The between-study heterogeneity was assessed quantitatively using the I² statistic (< 25%, no heterogeneity; 25%-50%, moderate heterogeneity; > 50%, strong heterogeneity). When a significant heterogeneity existed across the included studies (I² > 50%), a random effects model was used for the analysis. Otherwise, the fixed effects model was used. Subgroup analyses were performed to detect the source of heterogeneity. We further conducted sensitivity analyses to substantiate the stability of results and detect the potential source of heterogeneity. Publication bias was evaluated qualitatively by inspecting funnel plots and quantitatively using the Begg’s test and Egger’s test. A two-tailed P-value < 0.05 implies a statistically significant publication bias.

Results

Study selection: A total of 3856 potential articles were identified from the search of databases (Figure 1). Among these articles, 3788 were excluded after title and abstract review and a further 55 articles were excluded after full-text review. Finally, 13 studies with a total of 1534 cases that met the inclusion criteria were included in this meta-analysis.

Study characteristics: Baseline characteristics of the included studies are presented in Table I. Among the 13 studies conducted between 1994 and 2017, two were randomized controlled trials, three were cohort studies, and the others were retrospective studies. The patients in these studies included both pediatric and adult populations, and the diseases involved were AMC and AFM. The median follow-up period ranged from 1 to 13.5 months. Moreover, the dose of IVIG administrated to patients mainly ranged from 1 to 2 g/kg in total/48 hours, which was defined as high dose. Additionally, the results included substantial differences in the baseline characteristics, laboratory tests, echocardiography, and complications between the IVIG and control groups (Supplemental Table).

Quality assessment: The quality assessment of each included publication was assessed by the Cochrane Collaboration risk of bias tool (Supplemental Figure 1). In summary, the involved articles were considered to have low risk of bias according to the Cochrane collaboration tool.

In-hospital mortality and survival rate: Compared with the control group, the in-hospital mortality decreased (OR: 0.44, 95% CI 0.17 to 0.71, P < 0.001) significantly in the IVIG group for AMC patients (Figure 2). The survival rate of AFM patients was significantly higher in the IVIG group than in the control group (OR: 2.80, 95% CI 1.16 to 6.77, P = 0.022). However, there was no difference in the survival rate of AMC patients between the IVIG group and control group (OR: 1.14, 95% CI 0.86 to 1.52, P = 0.255) (Figure 3).

Left ventricular ejection fraction: Eight studies reported on left ventricular ejection fraction (LVEF). The AMC patients who received IVIG therapy had a higher LVEF compared with the non-IVIG therapy patients (1 to 12 months subsequent to the treatment) (OR: 1.73, 95% CI 1.34 to 2.13, P < 0.001) (Figure 4).

Possible sources of heterogeneity and subgroup analysis: Subgroup analysis was conducted on the association between IVIG and in-hospital mortality (Table II). After being stratified by population, the pooled ORs of the adult group for in-hospital mortality were 0.38 (95% CI 0.11 to 0.74, P = 0.326, I² = 40.1%), while in the subgroup of children, the ORs were 0.12 (95% CI -0.05 to 0.29, P = 0.777, I² = 0.0%) and apparently less heterogeneity was present. When stratified by diseases, the association between IVIG and in-hospital mortality seemed to be strengthened in the subgroup of AFM (OR 0.11, 95% CI -0.07 to 0.29, P = 0.115, I² = 46.2%), while in the subgroup of AMC, the OR was 0.43 (95% CI 0.12 to 0.61, P = 0.918, I² = 0.0%) with less heterogeneity. Stratified analysis according to study design was also conducted. Whether the study design was RCT or not, similar results were found with respect to the association between IVIG and in-hospital mortality, and no heterogeneity (P = 0.721, I² = 0.0% for RCT; P = 0.734, I² = 0.0% for Non-RCT) was found among these subgroups.

Publication bias and sensitivity analysis: There was no obvious evidence of funnel plot asymmetry among the studies, demonstrating that no publication bias existed in this analysis (Supplemental Figure 2). No evidence of publication bias was observed from Begg’s funnel plot (P = 0.711 for in-hospital mortality, P = 1.000 for recovery of LVEF) (Supplemental Figure 3) and Egger’s test (P = 0.834 for in-hospital mortality, P = 0.617 for recovery of LVEF) (Supplemental Figure 4). To sum up, the possibil-
therapy, the plasma levels of interleukin (IL)-10, IL-1 receptor antagonist, and soluble tumor necrosis factor receptors (sTNF-Rs) were elevated crucially. Moreover, the reduction of oxidative stress by IVIG therapy was also observed. It is known that the negative inotropic effects result from the production of nitric oxide induced by diverse pro-inflammatory cytokines. Therefore, IVIG was supposed to relieve the negative inotropic effects by inhibiting the pro-inflammatory cytokines. Furthermore, levels of N-terminal pro-atrial natriuretic peptide (NT-proANP) continued to decrease during IVIG therapy.

Despite the widespread utilization of IVIG in various inflammatory conditions, such as Kawasaki disease and chronic inflammatory demyelinating polyradiculoneuropathy, no rigorous evidence has indicated the efficacy of IVIG for myocarditis. Several studies have evaluated the effect of IVIG for myocarditis, the results of which were consistent with our findings. Drucker, et al. treated 21 children diagnosed with presumed AMC with high-dose IVIG (2 g/kg over 24 hours), which led to recovery of left ventricular function and better survival. Subsequently, there was a consistent improvement in left ventricular function.

Discussion

The present study revealed a significant association between IVIG treatment and in-hospital mortality, and improvement of LVEF in both children and adults with acute myocarditis. Moreover, AFM patients who received IVIG therapy had slightly better survival during follow-up. Our meta-analysis suggests that additional IVIG therapy, especially with a high dose, may be effective in the treatment of acute myocarditis. To our knowledge, this is the first meta-analysis to evaluate the association between IVIG therapy and acute myocarditis.

The immunomodulatory effects of IVIG are multifactorial. IVIG showed not only antiviral effects, but also anti-inflammatory effects by neutralizing pathogens and suppressing inflammatory cytokines. During IVIG therapy, the plasma levels of interleukin (IL)-10, IL-1 receptor antagonist, and soluble tumor necrosis factor receptors (sTNF-Rs) were elevated crucially. Moreover, the reduction of oxidative stress by IVIG therapy was also observed. It is known that the negative inotropic effects result from the production of nitric oxide induced by diverse pro-inflammatory cytokines. Therefore, IVIG was supposed to relieve the negative inotropic effects by inhibiting the pro-inflammatory cytokines. Furthermore, levels of N-terminal pro-atrial natriuretic peptide (NT-proANP) continued to decrease during IVIG therapy.

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Table I. Main Characteristics of Included Studies

| First author       | Year | Sample size | Study design       | Subjects | Population | Dose            | Regimen                      | Follow-up (months) |
|-------------------|------|-------------|-------------------|----------|------------|-----------------|------------------------------|--------------------|
| Isogai, et al.    | 2015 | 603         | Cohort study      | AFM      | adult      | ≥ 60.0 g for total| NA                          |                    |
| Yu, et al.        | 2014 | 58          | Retrospective study | AFM      | adult      | ≥ 60.0 g for total| NA                          |                    |
| Saji, et al.      | 2012 | 44          | Retrospective study | AFM, AMC | children   | 1-2 g/kg         | 1-2 g/kg/day for 24-48 hours| 12                 |
| Drucker, et al.   | 1994 | 46          | Retrospective study | AMC      | children   | 2 g/kg          | 2 g/kg over a maximum of 24 hours| 12                 |
| Prasad, et al.    | 2014 | 28          | Retrospective study | AMC or early DCM | children   | 2 g/kg       | 1 g/kg/day for 2 days       | 6                  |
| El-Saiedi, et al. | 2013 | 86          | RCT               | AMC or early DCM | children   | 2 g/kg       | 1 g/kg/day for 2 days       | 6                  |
| Atiq, et al.      | 2014 | 36          | Retrospective study | AFM      | children   | 2 g/kg         | NA                          | 12                 |
| Bhatt, et al.     | 2012 | 83          | RCT               | AMC      | children   | 2 g/kg         | 400 mg/kg/day for 5 days    | NA                 |
| Haque, et al.     | 2009 | 25          | Retrospective study | AFM      | children   | 2 g/kg         | 2 g/kg over 16-24 hours     | NA                 |
| Klugman, et al.   | 2009 | 216         | Nonconcurrent cohort study | AMC      | children   | NA            | NA                          | NA                 |
| Kim, et al.       | 2010 | 33          | Retrospective study | AMC      | children   | 2 g/kg         | 2 g/kg/day                  | 13.5               |
| Matsura, et al.   | 2016 | 221         | Retrospective study | AFM, AMC | children   | NA            | NA                          | NA                 |
| Butts, et al.     | 2017 | 55          | Contemporary multi-center cohort study | AMC | children | NA | NA | NA | NA |

RCT indicates randomized controlled trial; AFM, acute fulminant myocarditis; AMC, acute myocarditis; DCM, dilated cardiomyopathy; and NA, not available.

![Forest plot of in-hospital mortality](image)

**Figure 2.** Forest plot of in-hospital mortality.
**Figure 3.** Forest plot of survival rate for AFM or AMC. AFM indicates acute fulminant myocarditis; and AMC, acute myocarditis.

**Figure 4.** Forest plot of LVEF (%). LVEF indicates left ventricular ejection fraction.
function in adults based on the study of McNamara, et al.\textsuperscript{26} Likewise, IVIG was also shown to remarkably benefit children diagnosed with AFM.\textsuperscript{27-29} According to previous studies and our meta-analysis, IVIG is associated with better outcomes in both adult and pediatric patients suffering from AMC or AFM.

However, the promising results of IVIG were also challenged by some other reports. After reviewing adults in the Cochrane database, Robinson, et al.\textsuperscript{30} failed to detect overwhelming evidence of efficacy in IVIG over controls. Similarly, no improvement was demonstrated with IVIG alone or in combination with steroids as assessed by short-term or long-term outcomes, based on the study of English and coworkers.\textsuperscript{31} Moreover, no statistical differences in LVEF and survival of children receiving IVIG were observed by Kim and colleagues.\textsuperscript{6} Several factors may account for no beneficial effects of IVIG in these previous studies. Firstly, endomyocardial biopsy is strongly recommended for the diagnosis of biopsy-proven myocarditis. However, it is not routinely used yet due to its unavailability and its risk of procedure-related complications in some hospitals. Thus, no beneficial effect of IVIG was partly attributed to the distinction between clinical diagnosis and endomyocardial biopsy-proven myocarditis. Secondly, it is known that the early viral phase is the most effective period when using IVIG in children,\textsuperscript{6} who are more vulnerable than adults to the earlier inflammatory stage of myocarditis. Therefore, the neglect of a distinction between children and adults may lead to no efficacy of IVIG. Thirdly, the New York Heart Association (NYHA) functional class is a good predictor of outcome. When applying IVIG to patients in NYHA class III or IV with a poor prognosis, it may yield no efficacy in patients. Moreover, the baseline characteristics of subjects between the IVIG and control groups may not have been completely balanced. Subsequently, a lack of comparability at baseline between the two groups may account for the differing efficacy. Finally, the small sample size, the lack of randomization and blinding, and loss of follow-up may have contributed to the inconsistent results.

In an effort to obtain a better understanding of IVIG therapy among an enlarged population, 13 eligible clinical studies were ultimately incorporated in this meta-analysis. The results showed critical benefits of IVIG therapy for acute myocarditis. During this process, no heterogeneity or a moderate heterogeneity was detected. Further sensitivity analysis revealed that differences in patient enrollments, study design, disease types, drug administration, non-blinded-endpoint manner, and follow-up duration may be potential sources of inconsistency, although these factors ultimately did not alter the primary results of the present meta-analysis.

Study limitations: First, the effect of high-dose IVIG could not be assessed because the doses of IVIG administered to the IVIG group in all included studies were not uniformly predefined. Regardless of this limitation, our study provides greater insights into the efficacy of high-dose IVIG which was utilized in most studies included. Second, the component studies were predominantly retrospective studies with only two small sample-sized RCTs, which might result in a lack of statistical power. Third, our study demonstrated that the survival rate of AMC did not increase significantly, contrary to AFM. Due to the lack of published literature, it remains to be elucidated whether a different response to IVIG between AFM and AMC exists. Finally, the long-term effect of IVIG therapy cannot be confirmed due to the limited follow-up duration, which was between 6 months and 12 months mostly.

Conclusion

The present meta-analysis suggests that IVIG therapy is superior to conventional treatment in terms of reducing in-hospital mortality. Compared with conventional treatment, additional IVIG therapy for AMC is apparently associated with improved recovery of LVEF. Moreover, AFM patients who received IVIG therapy had slightly better survival during follow-up. Accordingly, IVIG seems to be a promising strategy in the treatment of AMC. Nevertheless, large-scale, multicenter, better-designed randomized controlled trials with a longer follow-up duration are warranted to further identify the benefits of IVIG therapy in AMC patients.

Disclosures

Conflicts of interest: The authors have no conflicts of interest to disclose.
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Supplemental Files
Supplemental Table
Supplementary Figures 1-5.
Please see supplemental files; https://doi.org/10.1536/ihj.18-299