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A Systematic Review Incorporating Meta-Analysis on the Effectiveness of Intravenous Immunoglobulin Versus Corticosteroids in the Treatment of Pediatric Myocarditis

Ahmed Mahmoud Abdelhaleem Ali[1], Mohamed EA Abdelrahim[2]*

[1]Department of Pharmaceutics and Industrial Pharmacy, College of Pharmacy, Taif University, P.O. Box 11099 Taif, 21944, Saudi Arabia

[2]Department of Clinical Pharmacy, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt

***Corresponding author:** Mohamed EA Abdelrahim, mohamedemam9@yahoo.com

Abstract: *Background:* Concerns have been raised about the efficacy of intravenous immunoglobulin and corticosteroids in pediatric myocarditis; however, the relationship between the risk and efficacy of these two therapies in children with myocarditis varies. *Methods:* A systematic review on seventeen studies was conducted in July 2020, which included 1,960 subjects at the baseline, with 788 receiving intravenous immunoglobulin and 142 receiving corticosteroids. The mean difference (MD) or odds ratio (OR) with 95% confidence intervals (CIs) was calculated to assess the prognostic role of both treatments using dichotomous and continuous methods with random or fixed-effect models. *Results:* The use of intravenous immunoglobulin was significantly associated with a lower mortality rate or heart transplantation in children with myocarditis (OR, 0.55; 95% CI, 0.40-0.77, $p < 0.001$) compared with the control group. However, corticosteroids were not significantly associated with the same parameters (OR, 0.72; 95% CI, 0.31-1.63, $p = 0.43$). The use of intravenous immunoglobulin was not significantly related to improving left ventricular ejection in children with myocarditis (OR, 2.30; 95% CI, -9.65-14.25, $p = 0.71$) and so were corticosteroids (MD, 5.17; 95% CI, -0.26-10.60, $p = 0.06$). *Conclusion:* The use of intravenous immunoglobulin might have an independent risk relationship with a lower mortality rate or heart transplantation and is recommended in children with myocarditis to prevent complications.

Keywords: Intravenous immunoglobulin; Corticosteroids; Pediatric myocarditis; Left ventricular ejection fraction; Mortality rate; Heart transplantation

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1. Background

Myocarditis is commonly known as an inflammatory infiltrate of the myocardium and is followed by non-ischemic cardiomyocyte necrosis [1,2]. It has different clinical appearances [3]. The incidence of pediatric myocarditis is uncertain [1]. However, the annual incidence of myocarditis among adults in the United States is 10-20 in every 100,000, and 1-2 occurrences per 100,000 children [4]. Although myocarditis is not

prevalent in children, it can cause serious illness and even death [1]. In myocarditis, injury to the myocardium could be the result of immunological mechanisms and not a direct effect of viruses [5]. Myocarditis is commonly assumed to be caused by viral infection. Its pathophysiology involves myocardial injury from several factors. A long-lasting immune reaction linked to molecular imitation might lead to chronic dilated cardiomyopathy, and sometimes with no indication of viral persistence [3,6]. Immunosuppressives, such as corticosteroids, are used in such patients. In a previous study, intravenous immunoglobulin has been reported to have immunomodulatory and antiviral properties [1,2]. The efficacy of intravenous immunoglobulin and corticosteroids is conflicting. Only a few studies have involved children, and they have varying outcomes. High-dose intravenous immunoglobulin is frequently used to treat myocarditis because of its immunosuppressant, antibacterial, and antiviral properties. In a previous study, 41 patients had better survival with intravenous immunoglobulin. However, in another study, intravenous immunoglobulin had no significant effect on left ventricular ejection fraction or the survival rate of patients [7]. The management of myocarditis in children is still confecting, and the benefits of intravenous immunoglobulin or corticosteroids are unsatisfying because of inadequate data [8]. A previous study showed no relationship between intravenous immunoglobulin or corticosteroids with neither left ventricle normalization nor survival [9]. Meanwhile, other studies have reported that the use of intravenous immunoglobulin could improve left ventricular ejection fraction [10-12] and is favorable for survival in children [13-15]. Even with these inconsistencies, intravenous immunoglobulin is often used in current clinical practice to treat myocarditis [4]. Therefore, a meta-analysis was conducted to estimate the effectiveness of intravenous immunoglobulin and corticosteroids in treating myocarditis in children.

2. Methods

The current study was based on a meta-analysis of epidemiological studies [16], which followed a set of guidelines.

2.1. Eligibility

This study included any human studies in English that focused on measuring the potential effectiveness of intravenous immunoglobulin and corticosteroids in treating pediatric myocarditis. The assessment of the efficacy of both intravenous immunoglobulin and corticosteroids in children with myocarditis compared with conventional management (control group) was extracted to formulate a summary. The inclusion was not limited by the study type or study size. Commentaries, studies that did not deliver a level of relationship, and review articles were excluded from this study.

2.2. Screening

The data from the studies were reduced to a uniform arrangement on the basis of study-associated and subject-associated features: last name of the first author, time of the study, year and country of publication, region under study, and the design of the study; type of population, sample size, demographic data, as well as the clinical and treatment features; qualitative, categories, and quantitative techniques of assessment, source of information, as well as result assessment; statistical analysis [18]. Given that a study met the aforementioned criteria for inclusion, relevant data were collected individually by two authors. Any discrepancies occurring between the authors, the corresponding author was to render the final decision. When there were different data in a single study, the data were extracted separately.

2.3. Literature search

A systematic review was conducted using Embase, PubMed, Google Scholar, and Cochrane databases in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [16] and

MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines [17]. A combination of keywords and comparable words were used, including intravenous immunoglobulin, corticosteroids, pediatric myocarditis, left ventricular ejection, mortality rate, and heart transplantation. All identified studies were collected up to July 2020 in EndNote; replicas were rejected, and the title and abstracts were examined to exclude studies that did not show any association between the effectiveness of intravenous immunoglobulin and corticosteroids in treating pediatric myocarditis. The remaining studies were further examined for associated information. **Figure 1** shows the literature search process.

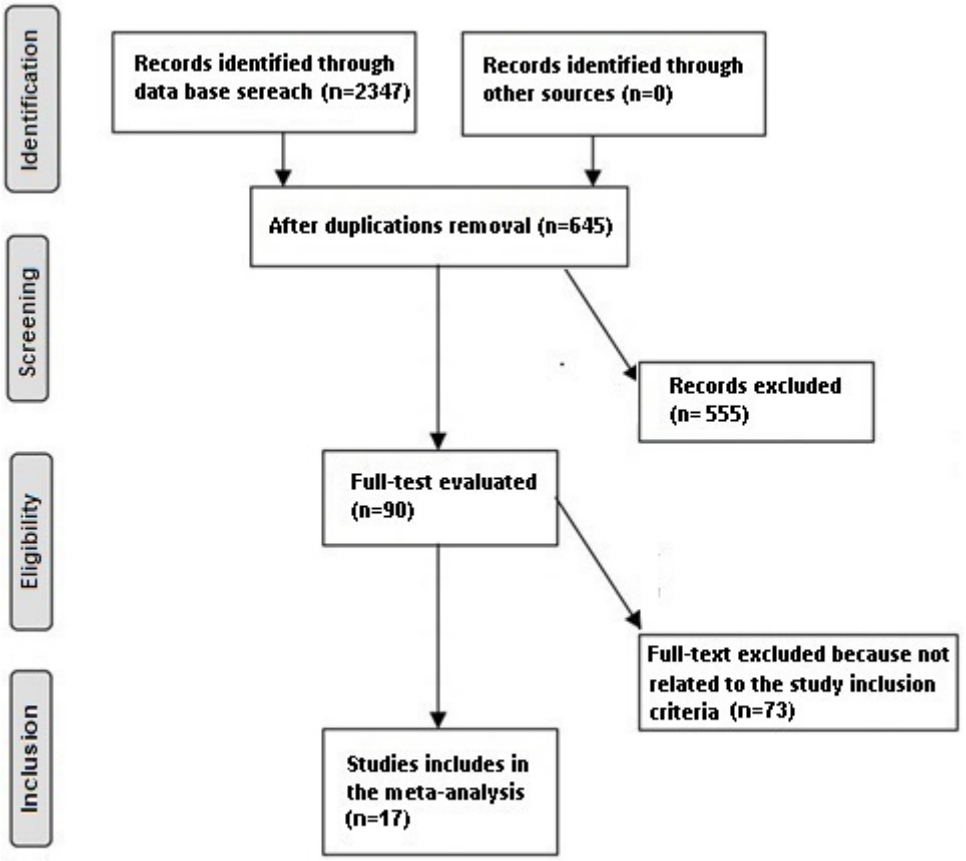

Figure 1. An illustration diagram of the literature search

2.4. Risk of bias

The reviewed Cochrane risk-of-bias tool for randomized clinical trials was utilized to estimate the methodological quality [19]. In terms of the evaluation criteria, each study was assessed and assigned to one of the subsequent three risks of bias as follows: if all quality criteria were met, the study was deemed to have a low risk of bias; if one or more of the quality criteria were incompletely met or unclear, the study was deemed to have a moderate risk of bias; if one or more of the criteria were not met or accounted for, the study was deemed to have a high risk of bias. Inconsistencies were addressed by a re-evaluation of the original article.

2.5. Statistical analysis

The study factors comprised of statistical methods of relationship (odds ratio [OR], mean difference [MD], rate ratio, or relative risk, with 95% confidence interval [CI]), measuring the potential effectiveness of intravenous immunoglobulin and corticosteroids in the treatment of myocarditis in children.

The dichotomous technique with a random or fixed-effect model was used to calculate odds ratio (OR) or mean difference (MD) and the 95% confidence interval (CI). The I_2 index was calculated, and its results were between 0% to 100%. 0%, 25%, 50%, and 75% I_2 index were classified as no, low, moderate, and high heterogeneity, respectively [20]. An I_2 of more than 50% rendered the use of the random-effect model, while that of less than 50% rendered the use of the fixed-effect model. The unique evaluation was stratified as per outcome classes as detailed before performing subgroup analysis. Variances between the subcategories were referred to as statistically significant at *p* value less than 0.05. Publication bias was assessed quantitatively by using Egger's regression test (the presence of publication bias was indicated by $p \geq 0.05$) and qualitatively by visually investigating the funnel plots of the logarithm of the odds ratios against their standard errors [18]. All *p* values were calculated via the two-tailed test. All graphs and calculations were completed using Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Sensitivity analyses were restricted only to studies showing association between the effectiveness of intravenous immunoglobulin and corticosteroids in treating pediatric myocarditis. For subcategory and sensitivity analyses, we compared intravenous immunoglobulin to corticosteroids in children with myocarditis.

3. Results

Among the 2,347 recognized studies, 17 studies [4,7,10-15,21-29], from 1994 to 2020, satisfied the inclusion criteria and were incorporated in the meta-analysis.

The 17 studies included 1,960 subjects at the baseline, with 788 receiving intravenous immunoglobulin and 142 receiving corticosteroids. The study size was between 25 to 514 subjects, and the patients were followed for any risks of the effectiveness of intravenous immunoglobulin and corticosteroids in the treatment of pediatric myocarditis, as shown in **Table 1**. Fourteen studies reported data stratified by intravenous immunoglobulin use associated with its efficacy in children with myocarditis, while four studies reported data stratified by corticosteroid use associated with its efficacy in children with myocarditis. The risks of the efficacy of intravenous immunoglobulin and corticosteroids in treating myocarditis in children were observed in all populations studied.

Table 1. Characteristics of the selected studies for the meta-analysis

Study	Country	Total	Intravenous immunoglobulin	Corticosteroids
Drucker, 1994 [10]	USA	46	21	
Camargo, 1995 [27]	Brazil	68		16
McNamara, 2001 [7]	USA	62	33	
English, 2004 [26]	USA	41		16
Haque, 2009 [15]	Pakistan	25	13	
Aziz, 2010 [28]	Pakistan	173		49
Kim, 2010 [21]	South Korea	33	23	
Klugman, 2010 [20]	USA	216	98	
Ghelani, 2012 [23]	USA	514	317	
Bhatt, 2012 [13]	India	83	26	
Atiq, 2014 [25]	Pakistan	36	16	
Prasad, 2014 [11]	India	28	12	
Kishimoto, 2014 [24]	Japan	41	15	

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Study	Country	Total	Intravenous immunoglobulin	Corticosteroids
Yen, 2015 [14]	Taiwan	67	41	
Matsuura, 2016 [4]	Japan	221	143	61
Butts, 2017 [22]	USA	212	9	
Heidendael, 2018 [12]	Netherlands	94	21	
Total		1960	788	142

The use of intravenous immunoglobulin was significantly associated with a lower mortality rate or heart transplantation in children with myocarditis (OR, 0.55; 95% CI, 0.40-0.77, $p < 0.001$) and has moderate heterogeneity ($I_2 = 35\%$) compared to the control group, as shown in **Figure 2(a)**.

However, the use of corticosteroids was not significantly associated with a lower mortality rate or heart transplantation in children with myocarditis (OR, 0.72; 95% CI, 0.31-1.63, $p = 0.43$) and has no heterogeneity ($I_2 = 0\%$) compared to the control group, as shown in **Figure 2(b)**.

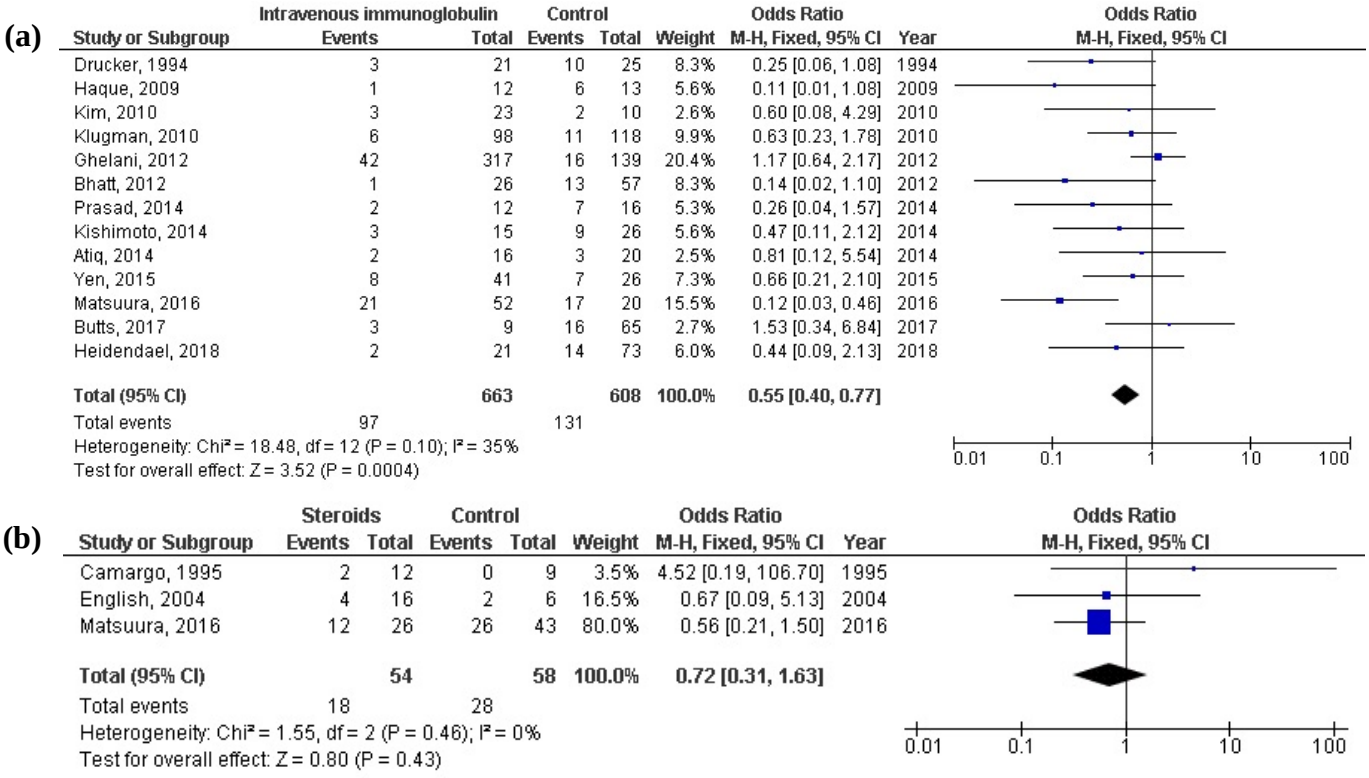

Figure 2. Forest plot of **(a)** intravenous immunoglobulin versus control in relation to rate of death or heart transplantation in children with myocarditis and **(b)** corticosteroids versus control in relation to rate of death or heart transplantation in children with myocarditis

Other than that, the use of intravenous immunoglobulin was not significantly related to improving left ventricular ejection fraction in children with myocarditis (OR, 2.30; 95% CI, -9.65-14.25, $p = 0.71$) and has high heterogeneity ($I_2 = 92\%$); the use of corticosteroids was also not significantly related to improving left ventricular ejection fraction in children with myocarditis (MD, 5.17; 95% CI, -0.26-10.60, $p = 0.06$) and has no heterogeneity ($I_2 = 0\%$) compared to the control group, as shown in **Figure 3(a)** and **Figure 3(b)**.

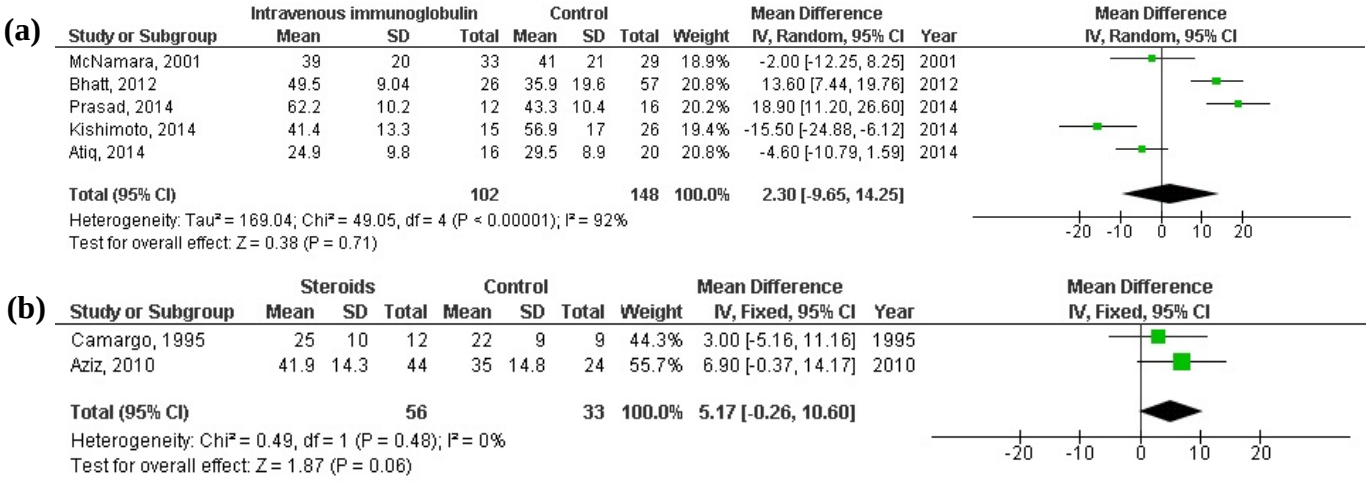

Figure 3. Forest plot of (**a**) Intravenous immunoglobulin versus control in relation to left ventricular ejection fraction in children with myocarditis and (**b**) corticosteroids versus control in relation to left ventricular ejection fraction in children with myocarditis

A stratified analysis of the studies on the use of intravenous immunoglobulin and corticosteroids in children with myocarditis in relation to age, ethnicity, and gender was not performed as none of these factors were described or studied in those papers.

Based on the visual examination of the funnel plot and the quantitative measurement using the Egger's regression test, there was no indication of publication bias ($p = 0.86$). However, most of the studies were considered to be of low methodological quality due to their small sample size. There was no selective reporting bias in any of the studies, and no articles had incomplete result data or selective reporting.

4. Discussion

This study investigated the use of intravenous immunoglobulin and corticosteroids in relation to their effectiveness in treating pediatric myocarditis with varying outcomes. Previous studies have reported the risks of the effectiveness of intravenous immunoglobulin and corticosteroids in treating myocarditis in children; however, their results were conflicting [4,7,10-15, 21-29].

From the 17 studies selected, only intravenous immunoglobulin use was significantly associated with a lower mortality rate or heart transplantation in children with myocarditis compared with the control group. However, the use of intravenous immunoglobulin was not significantly associated with improving left ventricular ejection fraction in children with myocarditis. Meanwhile, the use of corticosteroids was found to have no significant association with a lower mortality rate or heart transplantation in children with myocarditis compared with the control group as well as to improving left ventricular ejection fraction in these children. However, the *p* value obtained from the association between corticosteroid use and left ventricular ejection fraction in children with myocarditis compared with the control group was low and might have been influenced by other studies ($p = 0.06$). This influence was noticeable in all populations studied [4,7,10-15,21-29]. Therefore, this insignificant association is worth further evaluation.

The evaluation between intravenous immunoglobulin and corticosteroids in the mortality rate or incidence of heart transplantation discloses a statistical advantage of the intravenous immunoglobulin regiment. Possible causes of myocarditis include infection, physical agents, toxins, drugs, auto-antigens, and others [30]. Viral and post-viral myocarditis are the main reasons for dilated cardiomyopathy [1,2]. The range of viruses differs from human herpesvirus, enteroviruses, Epstein-Barr virus, and adenovirus to hepatitis C, parvovirus B19, and cytomegalovirus [4]. The presentation of myocarditis varies in children from subclinical symptoms to chest pain, suggesting pericarditis or myocardial infarction; unexpected ventricular fibrillation or sudden cardiac death may even occur. Furthermore, heart failure symptoms may

appear when the disease progresses to dilated cardiomyopathy, which may result in death or a need for heart transplantation. For decades, researchers have been studying the mechanisms of injury in viral myocarditis. Molecular imitation is most likely crucial in this autoimmune response. In some cases, the patient recovers as viral titers decline, but in others, the disease progresses to chronic irreversible dilated cardiomyopathy. Infection of cardiac endothelial cells by parvovirus B19, for example, could result in myocarditis [1-3,6,31]. Conventional treatment includes optimum therapy for arrhythmia and heart failure. In patients with deteriorating conditions, mechanical circulatory support is required until heart transplantation or recovery. As an immunosuppressant, corticosteroids play an active role in the second pathological stage of myocarditis. Therefore, the use of corticosteroids must be based on an evaluation of the stage of myocarditis [32-35]. Intravenous immunoglobulin, on the other hand, can reduce inflammatory and immune responses without causing significant side effects. In cases where the patient has continuing infection, post-infectious inflammatory response, or non-infectious response, intravenous immunoglobulin may be beneficial [36]. However, more research on children in this field is required to further investigate the efficacy of intravenous immunoglobulin. Hypothetically, immunosuppressive regimen can cause side effects, such as infectious diseases, hypertension, edema, weight gain, and others [34]. Intravenous immunoglobulin regimen was found to have infusion-related side effects, but those were shown to be mild [36]. Since the drug aims at different stages of the pathology, a combination treatment may be a more active option. A large number of studies involving the use of intravenous immunoglobulin combined with corticosteroids as treatment for pediatric myocarditis have been discovered [27,37]. Many studies have found that combination management groups outperformed the control groups; however, others have reported no significant difference. Therefore, conducting more studies to evaluate the safety and effectiveness of combined management is crucial. The majority of previous meta-analyses on myocarditis management focused on adults [34,38], and most of these papers only involved the use of either intravenous immunoglobulin or corticosteroids. There was only one previous study that looked at both intravenous immunoglobulin and corticosteroids in children with myocarditis, and the results were almost identical [39]. The only difference was that intravenous immunoglobulin had a significant effect on improving left ventricular ejection fraction in children with myocarditis, whereas the present study did not. This could be attributable to the large number of studies included in this study, which found that intravenous immunoglobulin had no significant effect on improving left ventricular ejection fraction. The risks of the effectiveness of intravenous immunoglobulin and corticosteroids in treating pediatric myocarditis are likely to be multifactorial. Furthermore, no studies attuned for additional relationships, making it a challenge to draw out any of these multi-factor properties in relation to the risks of therapeutic effectiveness of intravenous immunoglobulin and corticosteroids in treating myocarditis in children. A stratified analysis of studies attuned for the use of intravenous immunoglobulin and corticosteroid in children with myocarditis associated with gender, age, and ethnicity was not conducted, as none of these studies attuned for these features, thereby no solid conclusions associated with these features have been drawn. From this study, the use of intravenous immunoglobulin in children with myocarditis is encouraged to prevent any possible complications.

5. Limitations

There might be data gathering bias in this meta-analysis as numerous studies were excluded from this study, in which the studies excluded did not satisfy the inclusion criteria of this meta-analysis. Furthermore, we were unable to determine if the results were associated with children's age or ethnicity and analyze other measures of the effect of using intravenous immunoglobulin and corticosteroids in children with myocarditis associated with age, ethnicity, and gender. Numerous variable values used for judging the effectiveness of the drugs were not included in the selected studies; therefore, we were not able to evaluate

them further. In addition, in biopsy-confirmed virus-negative children whose situation worsened even with optimum conventional treatment, immunosuppressive treatment was still administered after eliminating possible contraindications.

6. Conclusion

Depending on this meta-analysis, the use of intravenous immunoglobulin might have an independent risk relationship with a lower mortality rate or heart transplantation in children with myocarditis. However, the use of corticosteroids was not significantly associated with lower mortality rate or heart transplantation in children with myocarditis compared with the control group. Moreover, the use of both intravenous immunoglobulin and corticosteroids were not significantly related to improving left ventricular ejection fraction. These findings necessitate the use of intravenous immunoglobulin in children with myocarditis in order to prevent complications.

Disclosure statement

The authors declare no conflict of interest.

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