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ORIGINAL ARTICLE

Use of Intravenous Immunoglobulin Compared With Standard Therapy is Associated With Improved Clinical Outcomes in Children With Acute Encephalitis Syndrome Complicated by Myocarditis

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Abstract Although an autoimmune mechanism has been postulated for acute encephalitis syndrome (AES) complicated by myocarditis, immunomodulatory treatment strategies are still under investigation. To study the role of intravenous immunoglobulin (IVIG) in AES complicated by myocarditis in children age 2–12 years. This nonrandomized study was conducted in a tertiary care teaching hospital from July 2008 to January 2010. A total of 83 consecutive children with AES complicated by myocarditis were enrolled. Diagnosis of myocarditis was based on clinical, electrocardiogram, and echocardiogram findings. Patients were allocated to the two groups based on the days of the week: Those presenting on Monday and Friday were allocated to IVIG treatment (group I), and those presenting on the other days of the week to standard care (group II). Group I ($n = 26$) patients received IVIG at a dose of 400 mg/kg/day for 5 days in addition to standard care. All baseline and outcome data were recorded prospectively in a prestructured performa. The primary outcomes were mortality and improvement of left-ventricular dysfunction. A total of 83 children were studied: 26 in group I and 57 in group II. The mean (SD) age of the enrolled children was 4.6 years (3.1). The baseline characteristics were comparable between the two groups. A viral etiology could be established in 14 children, with the 2 most common agents isolated being Coxackie virus and enterovirus. Mortality was lower in the IVIG group [$n = 1$ (3.8 %)] patients compared with the standard care group [$n = 13$ (22.8 %)] with a relative risk of 0.17 (95 % CI = 0.02, 1.22). The difference in mortality reached borderline significance ($p = 0.05$). At discharge, mean (SD) ejection fraction improved from 32.8 % (6.31 %) to 49.5 % (9.04 %) in group I patients, which was significantly greater than that of group II ($p = 0.001$). Use of IVIG seemed to have a beneficial effect in terms of improved clinical outcomes in children with AES complicated by myocarditis. Our findings need further validation before IVIG can be incorporated into the treatment protocol of these children.

Keywords Encephalitis · Intravenous immunoglobulins · Myocarditis

Introduction

Viruses, especially enteroviruses (EVs), which are members of picornoviridae family, are common viruses associated with manifestation ranging from mild respiratory symptoms to serious conditions, including aseptic meningitis, encephalitis, myocarditis, neonatal sepsis, and acute flaccid paralysis [18, 34]. Several case reports have implicated viruses as a cause of encephalitis and myocarditis [14, 21, 29]. EVs may be responsible for 25–35 % of cases of myocarditis diagnosed on the basis of serological study, nucleic acid hybridization, and polymerase chain reaction (PCR)-based studies of endomyocardial biopsy and autopsy specimens [11, 27].

Clinically, a case of acute encephalitis syndrome (AES) is defined as a person of any age, at any time of the year,

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with an acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk), and/or new-onset seizures (excluding simple febrile seizures) [38]. Recently, many studies have implicated EVs as a common cause of acute viral encephalitis [5, 10, 20]. Myocarditis is an inflammatory disorder of myocardium with necrosis of myocytes and associated inflammatory infiltrate that is categorized into four major types: acute, fulminant, chronic active, and chronic persistent [4]. Although an autoimmune mechanism has been postulated for myocarditis and encephalitis, immunomodulatory treatment strategies are still under investigation**.** There are few case reports on the association of AES with myocarditis [14, 21, 29].

There have been reports of improved outcomes with the use of IVIG for treatment of myocarditis in pediatric age group [1, 7, 26]. Similarly, treatment of EV 71 mediated hand foot and mouth disease with IVIG has shown improved outcomes [10, 36]. Given this background, we hypothesized that IVIG therapy would be beneficial in children with myocarditis associated with AES. Accordingly, our objective was to see the effect of IVIG on the outcomes of children with AES complicated by myocarditis as an adjunct to the symptomatic treatment that is routinely given to these patients.

Material and Methods

This prospective nonrandomized study included 83 consecutive children age 2 months to 12 years who were admitted to a tertiary care teaching hospital from July 2008 to January 2010. All children with AES characterized by pleocytosis, an absence of bacteria on culture of cerebrospinal fluid (CSF), and some or all of the following features: fever; sensorium changes (such as confusion, disorientation, drowsiness, stupor, coma, convulsions, abnormal behavior), ataxia, limb paralysis, hemiplegia, and specific cranial nerve dysfunction [38]. Clinical and echocardiographic criteria adapted from the criteria proposed by Liberman et al. in 1991 [23] were used to define myocarditis. According to this, the diagnosis of acute myocarditis was made if a child had (1) a history suggestive of viral infection with fever of <2 weeks' duration, (2) developed acute and severe heart failure after this illness, (3) evidence of left-ventricular dysfunction on echocardiography (ejection fraction <40 %), and (4) no previous or family history of cardiomyopathy.

Exclusion criteria in our study were as follows: encephalitis caused by nonviral pathogens cultured in CSF (e.g., bacteria, mycobacterium, fungus parasites); altered sensorium caused by factors other than infections (e.g., hypoglycemia, hemorrhage, infarction, and other metabolic causes); pre-existing cardiac illness (congenital or acquired); conditions known to be associated with acute congestive heart failure (e.g., sepsis, metabolic disorder, human immunodeficiency [HIV] infection, Kawasaki disease, primary arrhythmia, structural heart disease, rheumatic heart disease, or any other nonviral etiology), and incomplete treatment [≤1 g/Kg IVIG].

Our primary objective was to study the effect of IVIG therapy on the mortality and left-ventricular (LV) function in children with AES complicated by myocarditis. Accordingly, the primary outcomes assessed were mortality and improvement of LV dysfunction on echocardiography at discharge, whereas the secondary outcomes assessed were duration of hospital stay, duration of inotrope therapy, inotrope score (IS), need for mechanical ventilation, and neurologic sequelae at discharge. We used the following definitions to define these outcomes: *mortality* was defined as death during hospitalization; *LV dysfunction* was defined as ejection fraction <40 % on echocardiography and was assessed at admission and at discharge; *duration of hospital stay* was defined as the number of days the child was hospitalized; and *duration of inotrope therapy* was defined as the total number of hours the patient received inotropes. IS used in our study was calculated as described by Wernovsky [37]. The score was based on the dose, type, and duration of inotropic medications. The score was obtained by summing the dose of inotrope while correcting for potency multiplied by the number of hours delivered. For example if a patient received dobutamine and epinephrine at different infusion rates and for different time periods, the IS was calculated as follows: [(dobutamine dose μg/kg/min × 1) × number of hours delivered] + [(epinephrine dose μg/kg/min × 100) × number of hours delivered]. Thus, a 10 kg child receiving 20 μg/kg/min dobutamine for 6 h and 1 μg/kg/min epinephrine for 4 h and then 5 μg/kg/min dobutamine for 12 h and 0.1 μg/kg/min epinephrine for 8 h, his or her IS would be (20 × 1 × 6) + (1 × 100 × 4) + (5 × 1 × 12) + (0.1 × 100 × 8) = 660. *Need for mechanical ventilation* was defined as the need for invasive mechanical ventilation during the intensive care unit (ICU) stay, and *neurologic sequelae* were defined as presence of any neurologic deficit/abnormality at the time of discharge.

The study was approved by the Institutional Ethical Committee. After obtaining informed consent from parents, enrolled patients were transferred to the pediatric ICU (PICU). The admitted patients were given supportive and symptomatic care, including management of increased intracranial pressure and congestive heart failure per standard recommendations. Furthermore, on the basis of the type of intervention, patients were divided into the following two groups:

Study Group (Group I)

Patients having AES with myocarditis admitted on specified days of the week (i.e., Monday and Friday) were given IVIG as an adjunct to conservative treatment. Per hospital policy, IVIG could be procured only on specific days of the week (i.e., Monday and Friday); therefore, patients presenting on these days were enrolled in the study group for convenience. We used one of the commonly recommended regimens of administering IVIG. Accordingly IVIG was administered during five consecutive days by slow infusion at dosage of 400 mg/kg/day [28].

Comparison Group (Group II)

Patients admitted on the remaining days of the week were managed conservatively and did not receive IVIG. The second group acted as the control. In the PICU, details of the patient's history and clinical examination were recorded in a structured proforma by the principal investigator on a daily basis. The echocardiography examination was used to evaluate valvular regurgitation, cardiac contractility, and pericardial effusion, among other parameters. In all cases, bacterial cultures from the blood, urine, or throat were performed, and antibody titres for cardiotropic viruses, such as Coxackie and EV, were performed. Stool and nasopharyngeal specimens were sent for virus isolation. CSF was sent for reverse transcriptase polymerase for EV, Japanese-B encephalitis virus, and Chandipura virus. Troponin T/I levels could not be estimated because this is not routinely performed in our institution due to logistic reasons.

Statistical Analysis

Data were collected and analyzed using SPSS software (version 16; SPSS, Chicago, IL). Chi-square test, Fisher's exact test (used where expected frequency was <5), and Student t test (continuous data) were used for statistical analysis, and $p < 0.05$ was considered significant. Absolute risk reduction/difference of mean was also calculated.

Sample Size Estimation

Based on previous studies on mortality in patients with AES (83 %) with or without myocarditis [9] and assuming a power of 80 % and a two-sided alpha error of 5 %, we calculated that a sample size of 30 patients would be required in each group to detect an absolute decrease in mortality by 33 %.

Results

A total of 90 patients were eligible for the study: 30 in group I and 60 in group II. Four patients were excluded in group I (the parents refused to give consent), and 3 patients were excluded in group II (1 patient showed growth of bacteria in culture, and 2 patients had structural anomaly of heart). Therefore, 26 patients in group I and 57 patients in group II were studied. The mean (SD) age of group I patients was 4.4 years (3.2), whereas that of group II patients was 4.7 years (3.2). The majority were male in both groups and had similar baseline characteristics as listed in Table 1.

At admission, the most common presenting features were fever [$n = 83$ (100 %)] followed by altered sensorium, anasarca, difficulty breathing, and convulsions. The onset of heart failure symptoms was after the onset of encephalitis in all cases. The mean (SD) duration between the onset of encephalitis and myocarditis was 50 (15) h. At admission, patients had features of encephalitis (as described in Materials and Methods) along with signs of heart failure, such as tachycardia, tachypnea, hepatomegaly, and basal crepitations/rhonchi (Table 1).

Although an extensive search was made for the etiological agent in all patients in the two groups, only two

Table 1 Baseline characteristics of the study subjects

Variables	IVIG group ($n = 26$)[a]	Standard therapy group ($n = 57$)[a]	p
Clinical features			
Fever	26 (100)	57 (100)	
Change mental status	23 (88.4)	48 (84.2)	0.86
Convulsions	14 (53.8)	34 (59.6)	0.79
Edema	21 (80.7)	42 (73.7)	0.87
Difficulty in breathing	12 (46.1)	30 (52.6)	0.75
Hepatomegaly	23 (88.4)	48 (84.2)	0.83
Tachycardia	21 (80.7)	49 (85.9)	0.64
Gallop rhythm	2 (7.7)	06 (10.5)	0.76
Muffled heart sound	5 (19.2)	08 (14.0)	0.71
Plantar extensor	20 (76.9)	42 (73.66)	0.61
Laboratory features			
CSF pleocytosis (>10 cells/mm^3)	20 (76.9)	44 (77.2)	0.62
Mean (SD) CSF cell count	70.3 (57.8)	50.8 (46.2)	0.10
Increased SGPT	22 (84.6)	49 (85.9)	0.59
ECG changes			
Sinus tachycardia	09 (34.6)	19 (33.3)	0.81
Low voltage	08 (30.8)	18 (31.5)	0.87
rsr' pattern	03 (11.5)	07 (12.3)	0.89
ST T-wave change	26 (100)	57 (100)	
Echocardiography			
Ejection fraction (%) at presentation [mean (SD)]	32.8 (6.3)	33.2 (6.4)	0.78

SGPT serum glutamic pyruvate transaminase

[a] Values are represented as number (%) unless specified otherwise

patients in group I and five patients in group II showed significant increase in Coxackie B1 titers (four-fold increase) in serum samples. Stool PCR showed EV in two specimens in group I and in six specimens in group II.

The most common finding on electrocardiogram (ECG) was ST segment depression ($n = 65$). Ten children had paroxysmal supraventricular tachycardia, whereas atrial flutter was seen in 4 patients. Cardiac enzyme was increased in all patients with a mean (SD) of 110 (50) U/L. The liver enzymes, serum glutamic oxaloacetic transaminase and serum glutamic pyruvate transaminase (SGPT), were found to be increased in 35 and 71 patients, respectively. All except 5 patients had cardiomegaly with mean the cardiothoracic ratio of the subjects being 62 ± 5.8 (SD). Of those with cardiomegaly, 15 (18 %) patients had frank pulmonary edema on chest X-ray.

Echocardiography

At presentation the mean (SD) ejection fraction in group I and group II was 32.8 % (6.3) and 33.2 % (6.4), respectively. All of the children had valvular insufficiency with significant mitral regurgitation. Wall hypokinesia was present in 48 of these patients. The left ventricle was dilated in all of the children: The mean end diastolic diameter (EDD) adjusted to body surface area was 96 (27) mm/m^2, and the mean z-score for EDD was 4.41 (1.8) SD. Thirty nine children (47 %) had associated pericardial effusion, but none requiring any active intervention.

Course During Hospitalization

The mean (SD) duration of hospital stay in group I and group II was 16.4 (5) and 18 (6) days, respectively. All of the patients were managed conservatively with decongestive therapy. Six patients in group I required inotropes, and two of them also required ventilatory support. Mean (SD) duration of mechanical ventilation was 29 (24) h. Fifteen patients in group II required inotropes, and 5 of these 15 patients required ventilator support for a mean (SD) duration of 27 (14) h. The maximum [mean (SD)] IS in group I and group II patients was 334.5 (192) and 361.2 (157) μg, respectively ($p = 0.74$), whereas the median (interquartile range) duration of inotropic support in groups I and II was 5.5 (1.5) and 7 (3) days, respectively. Four patients in group I and 9 patients in group II had cardiogenic shock requiring dopamine and dobutamine infusion; of them, all 4 patients in group I and 8 patients in group II required the maximum dose (i.e., 20 μg/kg/min) of one or both inotropes. During IVIG infusion, 1 patient developed mild rashes, and 1 patient had headache and tachycardia; however, these side effects did not prompt discontinuation of the IVIG infusion.

Table 2 Primary outcome of study patients

Primary outcomes	IVIG group ($n = 26$)	Standard therapy group ($n = 57$)	Risk difference (95 % CI)	p
No. (%) deaths	01 (3.8)	13 (22.8)	0.17 (0.02–1.22)	0.05
Mean ejection fraction (SD) at discharge	49.5 (9.04)	35.9 (19.6)	13.6 (5.13–22.06)	0.001

CI confidence interval; *IVIG* Intravenous immunoglobulin

Table 3 Secondary outcome of study patients

Outcome measures	IVIG group ($n = 26$)	Standard therapy group ($n = 57$)	p
Mean (SD) duration of hospital stay	16.4 (5)	18 (6)	0.239
No. (%) with neurologic sequelae at discharge	3 (11.5)	10 (17.5)	0.54
Duration (SD) of ventilation	29 (24)	27 (14)	0.634
Mean (SD) IS	334.5 (192)	361.2 (157)	0.74

SD Standard deviation; *IVIG* Intravenous immunoglobulin; *IS* Inotrope score

Immediate Outcomes

In group I, of 26 patients, only 1 died. The difference in mortality between the 2 groups reached borderline significance [$n = 1$ (3.8 % vs. $n = 13$, 22.8 %, $p = 0.05$)] with a relative risk of 0.17 (95 %, CI: 0.02, 1.22). The predominant causes of death were refractory congestive heart failure (CHF) in 5, refractory shock in 3, increased ICP with cerebral herniation in 2, arrhythmias in 2, and disseminated intravascular coagulation in 2 patients. At discharge, mean (SD) ejection fraction improved from 32.8 % (6.31) to 49.53 % (9.04) in group I at discharge and from 33.2 % (6.4) to 35.9 % (19.6) in group II at discharge ($p = 0.001$ between groups I and II (Table 2).

There was no significant difference between the two groups with respect to hospital stay, need for mechanical ventilation, and inotropic support (Table 3). At discharge, only two patients in group I had sequelae in the form of behavioral problems (excessive abuse and irrelevant talk), whereas one patient had hemiparesis. In group II, five patients had behavioral problems, two had dystonias, and three had hemiparesis ($p = 0.54$).

Discussion

Use of IVIG was associated with decreased mortality and improvement in LV function in our study. Previous studies

showed a benefit of IVIG in cases of AES without myocarditis [9, 24, 36]. Our study is therefore the first to show that this benefit can be extended to patients having AES with myocarditis.

For patients with infectious diseases, IVIG is administered with two aims: (1) to increase viral clearance due to antibody-dependent neutralization in immunodeficient patients (e.g., in cytomegalovirus-infected bone marrow transplant recipients or parvovirus-infected subjects with HIV infection) or in patients with specific infections (e.g., St. Louis encephalitis or West Nile virus infection) [2] and (2) to benefit patients with certain acute inflammatory diseases that have both viral and autoimmune causes (i.e., acute disseminated encephalomyelitis). However, in the latter case the mechanism of action is unclear.

During the initial large outbreaks of EV71 in Asia, IVIG was used by clinicians in Sarawak and Taiwan on the presumptive basis that it would neutralize the virus and have nonspecific anti-inflammatory properties [31]. Analysis of cytokine profiles before and after IG treatment showed substantial decreases in concentrations of some proinflammatory cytokines in patients with EV71 if they had encephalitis with autonomic dysfunction [9, 24, 25, 30, 35, 36].

Ooi et al. [31] and Chang et al. [9], in their retrospective studies, suggested a benefit of IVIG in patients with AES if it was instituted early. Although a complete mechanism of IVIG action is still unknown, it is suggested that IVIG may achieve its therapeutic effect through multiple mechanisms of immunomodulation [17]. Wang et al. [36] showed that levels of interferon, INF-γ, interleukin (IL)-6, IL-8, IL-10, and IL-13 levels significantly decreased in patients with pulmonary edema after IVIG administration in EV-76-associated brain stem encephalitis. They also showed that plasma levels of IL-6 and IL-8 were significantly decreased in patients with autonomic nervous system dysregulation after administration of IVIG.

The role of IVIG in AES associated with viral myocarditis has not been previously reported. We found that ejection fraction at discharge had improved by almost 50 % compared with baseline values (49.5 vs. 32.8) in patients treated with IVIG during 2–3 weeks of therapy. Our findings are in concordance with previous reports on the beneficial use of IVIG in acute myocarditis in which myocardial function improved by almost 32 % (fractional shortening) and 125 % (ejection fraction) in two studies within 1 to 3 weeks of starting therapy [12, 15].

The reasons discussed previously on the mechanism of action of IVIG, such as neutralization of pathogens, antiviral effects, and anti-inflammatory effects, such as decrease of cytokines, could have probably played a role in improving myocardial dysfunction in the IVIG-treated group.

Numerous case reports and case series have reported on the beneficial effect of IVIG in cases of acute fulminant myocarditis without encephalitis [12, 15, 16, 19]. However, a recent meta-analysis from the Cochrane database, reviewed by Robinson et al. [33], suggested no benefit of IVIG regarding immediate or short-term outcomes. Therefore, larger adequately powered clinical trials would be required to validate our hypothesis that IVIG improves outcomes in children having myocarditis with or without AES. There was no significant difference regarding neurological sequelae, duration of hospital stay, or any of the other secondary outcomes between children receiving IVIG and those not receiving IVIG.

The therapeutic regimen of IVIG adopted in various immune mediated diseases is 400 mg/kg/day for 5 days; the same regimen was used in our study. However, high-dose IVIG at the dosage of 1 g/kg for 2 days or 2 g/kg for 24 h, has been successfully used by some investigators in the treatment of severe acute myocarditis [12, 16, 19].

The diagnosis of myocarditis in our study was largely based on the clinical, ECG, and echocardiographic characteristics. We did not have the provision to perform endomyocardial biopsy (EMB) for any of the patients. EMB, which is considered essential for histopathological confirmation of a myocarditis diagnosis, is not routinely performed in most centers due to the risks associated with the procedure, particularly in children with dilated hearts [32]. In the prospective pediatric studies published to date, only a few of them subjected all of the patients to biopsy because of the reasons mentioned previously [3]. Myocarditis can also be diagnosed with the help of newer radiologic techniques, such as contrast-enhanced magnetic resonance imaging, and immunodiagnostic tools, such as induction of major histocompatibility and intercellular adhesion molecules on cardiac myocytes, in addition to direct evidence of viral infection, such as PCR, antibody titres, and cell cultures [6, 8, 13, 22]. In view of these recent advances in the diagnosis of myocarditis, there may be a shift from invasive to noninvasive tests in the near future.

The strengths of our study are (1) it was a prospective nonrandomized study with adequate sample size and (2) it was the first study to investigate the role of IVIG on patients with encephalitis complicated by myocarditis.

Limitations

There are several limitations to our study. First, it is difficult to say whether these children had acute myocarditis or acute fulminant myocarditis because they had mixed features of both of these conditions, and biopsy could not be performed to differentiate between them. Biopsy could not be performed in these children because no expertise or

logistics were available to carry out this risky procedure in our hospital. Therefore, it may be appropriate to say that these children had myocarditis associated with/or secondary to encephalitis. Second, the viral yield was too low, and therefore the diagnosis of encephalitis was also mostly clinical. Finally, we did not have follow-up data for the children with persistent LV dysfunction to see how many improved completely and how many developed complications, such as dilated cardiomyopathy.

Conclusion

To conclude, the present study clearly showed a beneficial effect of IVIG on the survival of patients with AES complicated by myocarditis, probably of viral origin. Larger randomized control trials are required to further validate these findings.

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