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Original Article

Rescue therapy with intravenous immunoglobulin in severe refractory dengue: A pilot study

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ABSTRACT

Background: Severe dengue causes more than 22,000 deaths annually worldwide. Complicated dengue has high mortality of 44–72%. Disordered immune system with capillary leak and thrombocytopenia are hallmark of complicated dengue. Intravenous immunoglobulin (IV Ig) therapy has shown to be effective in complicated dengue in pediatric age group with refractory shock, but studies in adults are lacking. Its immunoresuscitative role is not yet fully explored in critically ill patients with severe dengue.

Methods: This is retrospective observational study of patients with complicated dengue fever who were administered IV Ig therapy in a tertiary care hospital of southern India from 01 Jan 2018 to 31 Dec 2019.

Results: A total of 999 patients with dengue were admitted; 754 (75.47%) were males, and 245 (24.53%) were females. A total of 402 (40.24%) patients presented with warning signs. Bleeding was seen in 121 patients (12.11%); 102 (10.21%) had shock; 29 (2.90%) had acute kidney injury and 24 (2.40%) had adult respiratory distress syndrome. Overall, four people died (mortality rate: 0.40%). IV Ig in the dose of 0.4 g/kg for 5 days was used in 13 critically ill patients where standard therapy failed, 9 patients with refractory shock (which included three with myocarditis with refractory shock), 2 with encephalitis, 2 in hemophagocytic lymphohistiocytosis. Two patients died, one with myocarditis with refractory shock and another with refractory shock.

Conclusion: IV Ig therapy in critically ill patients with complicated dengue can be used as a rescue therapy.

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Introduction

Dengue fever is a mosquito-borne viral infection transmitted by the bite of *Aedes aegypti* mosquito and is responsible for more than 22,000 deaths annually.[1,2] As a result of early identifications of complications and effective supportive therapy, the mortality reduced to less than 1%.[3] However, there is no specific therapy for dengue and critically ill patients with complicated dengue viz dengue shock syndrome, organ involvement have a high mortality of 44–72% as reported by Vietnam studies.[4,5] A recent Indian study showed mortality at ICU-admitted patients to be 21.6%.[6] It is a monophasic illness with no chronic complications, and all efforts should be made to salvage the seriously ill patients. Dengue manifests with a wide spectrum from a simple febrile illness to severe haemorrhage, intractable shock and organ failure.[5]

Death in dengue is due to severe progressive shock with multiorgan failure. No specific therapy is currently available to prevent or treat the development of shock and multiorgan failure. One of the novel therapies tried to treat complicated dengue is IV Ig (intravenous immunoglobulin). The possible beneficial effects of IV Ig on vascular leakage and dengue shock, which is probably the most important cause of mortality, has not been studied till now. Its immunoresuscitative role in not fully explored in critically ill adults patients with severe dengue although various case series reveal its use in encephalitis, refractory thrombocytopenia and hemophagocytic lymphohistiocytosis (HLH). There is no study in adults regarding the use of IV Ig in dengue refractory shock.

The present study was undertaken to assess the clinical efficacy of IV Ig in complicated critically ill dengue patients who otherwise would have had a high mortality. The study was carried out in a tertiary care hospital in Southern India.

Materials and Methods

This is a prospectoretrospective observational study on patients diagnosed with dengue fever admitted to tertiary care hospital in Southern India from 01 Jan 2018 to 31 Dec 2019. This study was by the department of Internal Medicine. The study was approved by the ethics committee of the hospital, and informed consent was obtained from all the subjects.

Inclusion criteria

1. Age 16 years or more
2. Confirmed dengue with severe complications not responding to standard supportive therapy

Exclusion criteria

1. Coinfection with other infections such as confirmed cases of malaria, typhoid, rickettsial infections and chikungunya were excluded from the study

The demographic data, clinical profile, coexisting morbidities, complications and their outcomes were collected. Dengue cases were confirmed based on the presence of NS1 antigen and/or Ig M antibody demonstration serological test by rapid ICT and ELISA.[7] Relevant investigations were performed as per the clinical indications and as per WHO guidelines. All the patients who received IV Ig were critically ill and hence managed in the ICU. The warning signs of dengue, clinical fluid accumulation and haemoconcentration were defined as per WHO criteria.[7] Severe dengue was diagnosed by any one of severe plasma leakages leading to shock or fluid accumulation with respiratory distress, severe haemor rhage and severe organ involvement.[7] Severe organ involvement was indicated if there was impaired consciousness, severe hepatitis, acute kidney injury (AKI), acute respiratory failure, rhabdomyolysis, myocarditis, disseminated intravascular coagulopathy and haemophagocytosis.[7] Severe hepatitis was considered when liver enzymes (serum alanine aminotransferase and/or aspartate aminotransferase) levels were more than 1000 U/L.[8] Severe gastrointestinal (GI) bleeding was considered when GI bleed with hypotension (systolic blood pressure <90 mm Hg) and/or a sharp fall in haemoglobin concentration to 10 g/dL or less within 48 h.[9] AKI was considered when the raise of serum creatinine level by 0.3 mg/dL or more within 48 h. AKI was also defined if baseline creatinine was elevated by 1.5-fold or more.[10] Haemophagocytosis was defined as fever, splenomegaly, pancytopenia, hypertriglyceridemia, hyperferritinemia and tissue haemophagocytosis in the bone marrow or peripheral smear and increasingly being diagnosed using H score.[11] Cardiac dysfunction/myocarditis was considered if pro BNP (pro-brain natriuretic peptide) was more than 450 ng/L (age <50 years), more than 900 ng/L (age 50–75 years) and more than 1800 ng/L (age > 75 years).[12] Diagnosis of dengue encephalitis was based on criteria proposed by Soares and Marzia, which requires the demonstration of dengue viral antigens/antibodies in CSF with exclusion of other causes of encephalitis.[13]

The management as per WHO guidelines included oral fluids in haemodynamically stable patients.[7] In case of hypotensive dengue shock IV fluid boluses (20 ml/kg over 15 min) followed by maintenance fluids till hemodynamic improvement. Crystalloids, blood products for resuscitation, were used depending on the guidelines.[7] Platelet concentrates were given to patients with thrombocytopenia who had significant bleeding.[7] Respiratory support, vasopressors and organ support were provided whenever indicated.[7] IV Ig was used in critically ill patients with refractory hypotensive shock not responding to standard therapy, that is, after 20 ml/kg bolus crystalloids, 10–20 ml/kg colloids and after maximum dose of vasopressors. IV Ig was also used in patients with established complications not responding to standard therapy as per WHO guidelines such as HLH.[7] The dose of IV Ig used was 0.4 g/kg per day for 5 days. All treatments done at the hospital was free including IVIg. Secondary infections were treated with antibiotics initially empirically and later modified as per culture report. Comorbidities if present were treated appropriately. The outcome of the all patients with dengue were recorded.

Statistical analysis

All the data were entered in the Microsoft Excel sheet, and descriptive analysis was done using SPSS 23 software.

Results

A total of 999 patients diagnosed with dengue fever were admitted during the study period from 01 Jan 2018 to 31 Dec 2019. The detailed demographic profile has been shown in table (Table 1). Out of 999 patients, 402 (40.24%) patients presented with warning signs (Table 2). Shock at admission and during hospitalization was seen in 102 (10.21%) patients (Table 2). Bleeding diathesis with thrombocytopenia requiring platelet transfusions was seen in 121 (12.11%) patients.

There were a total of four fatal cases (mortality rate: 0.40%). Two of the mortality were due to severe plasma leakage with refractory shock, and other two mortality were due to intracranial haemorrhages; one subarachnoid haemorrhage and another with sudden intraventricular haemorrhage.

Among those patients, a total of 13 patients received IV Ig therapy. Nine patients had plasma leakage with refractory shock, two patients had encephalitis with refractory shock and two had HLH. The two patients with encephalitis and refractory shock presented with refractory shock and altered sensorium. Their sensorium did not improve despite resolution of shock and hence was evaluated with imaging of the brain and CSF analysis, which confirmed encephalitis.[13] Out of 13 patients, 11 survived and 2 expired. The details of patients who received IV Ig are given in (Table 3).

Table 1 – Demographic data of patients.

Age and sex-wise distributions	Total No. (n = 999)	Percentage (%)
Sex	Total No. (n = 999)	Percentage (%)
Male	754	75.42
Female	245	24.53
Age in years	Total No. (n = 999)	
Mean age	29.64	SD = 10.28
Median age	28	Range: 16–69

Discussion

The hallmarks of severe dengue are dysfunctional immune system with vascular endothelial injury with capillary leak (plasma leak) and thrombocytopenia. There may be liver damage, muscle injury, neurological, myocardial involvement and direct organ damage, which are due to dysfunction of endothelial cells caused by cytokines including TNF-α[14] (tumour necrosis factor-α), IL-1 (interleukin −1) and IL-6 (interleukin −6) and IFN γ (interferon gamma), which causes plasma leakage in the presence of enhancing antibody,[14] and recent study has shown that NS1 (non-structural protein 1) contributes to endothelial leakage by multiple mechanisms through binding to the TLR4 of leukocytes (toll-like receptor 4).[15] In our study, all patients with severe dengue had plasma leakage, and most of dengue patients with shock improved with fluid therapy and supportive therapy. Only 13 patients received IV Ig therapy. Among these, nine patients had refractory shock, and three among them had evidence of myocarditis and one had nonimmune haemolytic anaemia. All of them received IV Ig. Two succumbed to illness, and remaining seven improved dramatically. IV Ig interacts with IgG Fc gamma receptors, thereby suppressing the dengue-virus-induced cytokine cascade and induces the production of anti-inflammatory cytokine IL-1 receptor antagonist (IL-1ra).[16,17] It prevents the generation of the complement membrane attack complex (C5b-9) by scavenging activated complements, and these immune-modulatory actions of IVIg may have beneficial effects in altering the disordered immunity in severe dengue.[17–20]

Table 2 – Severity of dengue cases (n = 999).

	Symptoms	Number N = 999	Percentage (%)
1	Dengue without warning signs	597	59.76
2	Dengue with warning signs	402	40.24
3	Dengue with complications. Severe dengue		
a.	Bleeding requiring transfusions	121	12.11
b.	Shock	102	10.21
c.	Acute kidney injury	29	2.90
d.	Severe hepatitis	19	2.26
e.	Lung/ARDS	24	2.40
f.	Myocarditis	10	1.00
g.	Hemophagocytic lymphohistiocytosis	02	0.20
h.	Intravascular haemolysis	01	0.10
i.	Encephalitis	04	0.40
j.	Cardiac tamponade	01	0.10
k.	Pulmonary thromboembolism	02	0.20
l.	Cortical venous thrombosis	01	0.10
4	Mortality	04	0.4
	Causes of mortality		
a.	Intracranial haemorrhage (intraventricular haemorrhage)	01	
b.	Myocarditis with severe plasma leakage refractory shock	01	
c.	Subarachnoid haemorrhage and severe plasma leakage with refractory shock	01	
d.	Severe plasma leakage, refractory shock and ARDS	01	

Table 3 – Clinical characteristics of patients receiving IV Ig (n = 13).

Case	Age Sex	Clinical course	Lab parameters	Rx	Complications	Day of IV Ig	Outcome
01	26 yr Male No co-morbidity	Presented with persistent fever of 7 days diarrhoea, abdominal pain, dyspnoea and prostration of 2 days clinically BP- unrecordable. Heart rate 140/min Resp. rate 30/mi Temp. 98 °F	Hb – 11.4 g% TLC – 2000/μL, platelets 25,000/μL LFT Bil- 12.3 mg%, AST/ALT- 891/271 U/L, INR 1.87 Sr creat- 4.5 mg% Lactate – 18.4 meq/L BNP >9000 pg/ml Ultrasonographic evaluation – ascites, gall bladder wall oedema and bilateral pleural effusion.	Initially, the patient was given IV fluids 20 ml/kg and started on vasopressors. His respiratory distress worsened. He was intubated and respiratory support given. Empirical antibiotics given. Renal support (continuous renal replacement therapy; CRRT) given.	Myocarditis with severe plasma leakage refractory shock MODS (AKI, thrombocytopenia, respiratory failure)	7 th day	Expired after 48 h
02	26 yr Male No co-morbidity	Presented with fever 3 days diarrhoea and dyspnoea h/o decreased urine output. Examination BP – 80/60 mm Hg Heart rate 132/min Resp rate 28/min Temp 98 °F	Hb – 12.1 g% TLC – 2100/μL, platelets 20,000/μL INR 2.16 LFT Bil- 2.8 mg%, AST/ALT- 1668/2003 U/L Sr creat – 2.8 mg% Lactate – 15.85 meq/L Ultrasonographic evaluation – ascites, gall bladder wall oedema and bilateral pleural effusion. Chest X ray s/o ARDS	Initially, the patient was given IV fluids 20 ml/kg and started on vasopressors as hypotension persisted. His respiratory distress worsened. He was intubated and respiratory support given. IV Ig started, empirical antibiotics given.	Severe plasma leakage with refractory shock and MODS (renal failure, ARDS with respiratory failure, hepatitis, thrombocytopenia, ARDS)	5th day	Expired after 72 h
03	63 yr Female with Diabetes mellitus and hypertension	Presented with fever 4 days associated with dyspnoea, severe prostration Received multiple platelets transfusion from other hospital. Clinical examination Pulse-128/min BP 80/66 mm Hg Resp rate-30/cmm Temp 98 °F. Spo2 at admission- 86%	Hb – 11.5 g% TLC – 2600/μL, platelets 18,000/μL INR 1.9 Blood sugar random 287 mg%. LFT Bil- 2.3 mg%, AST/ALT-346/310 U/L Sr creat – 2.8 mg% Lactate-9.6 meq/L BNP >9000 pg/ml Ultrasonographic evaluation – ascites, gall bladder wall oedema and bilateral pleural effusion. Chest X ray suggestive of ARDS	Initially, the patient was given IV fluids 20 ml/kg. Her respiratory distress worsened. Hypotension persisted and vasopressors started. Non-invasive respiratory support given. Insulin infusion used for controlling blood sugar. Empirical antibiotics given. Vasopressors tapered over 24 h	Plasma leakage with refractory shock MODS (renal failure, ARDS, respiratory failure, myocarditis, hepatitis, thrombocytopenia)	4th day	Survived

(*continued on next page*)

Table 3 – (*continued*)

Case	Age Sex	Clinical course	Lab parameters	Rx	Complications	Day of IV Ig	Outcome
04	21 males. No co-morbidity	Presented with fever and headache 3 days and altered sensorium of 1 day. Clinically at admission Pulse – 124/min BP 84/70 mm Hg Resp rate 22/min Temp 98 °F Neurological examination-Stuperous with no localizing deficits. GCS E3M5V3	Hb – 11.3 g% TLC – 1600/μL, platelets 58,000/μL INR 1.24 CSF- Proteins 70 mg%, cells 18 pred lymphocytes, sugar 80 mg %, LFT 0.8 mg%, AST/ALT-246/154 U/L Blood sugar – 114 mg%. creat – 1.1 mg% Lactate – 3.6 meq/L CECT head Normal, MRI brain – normal, ultrasonographic evaluation revealed mild ascites. CXR- Normal	Initially, the patient was given IV fluids 20 ml/kg an addition of 10 ml/kg fluid given. His blood pressure improved partially, but there was no improvement in sensorium. He was intubated and respiratory support was given. IV Ig given. Empirical antibiotics given. He improved over 4 days.	Encephalitis Plasma leakage	5th day	Survived
05	20-year-old male. No co-morbidity	Fever headache 3 days, altered sensorium of 1 day. Clinically at admission Pulse – 124/min BP 84/70 mm Hg Resp rate 22/min Temp 98 °F Neurological examination – drowsy no localizing deficits. GCS E3M5V3	Hb – 13.3 g% TLC – 2600/μL, platelets 85,000/μL INR 1.0 CSF- Proteins 85 mg%, cells 10 pred lymphocytes, sugar 90 mg %, LFT 0.8 mg%, AST/ALT-187/172 U/L Creatinine – 1.1 mg% Lactate-2.6 meq/L MRI Brain- Normal, Ultrasonographic evaluation revealed mild ascites, and Right pleural effusion CXR – normal	Initially, the patient was given IV fluids 20 ml/kg and no improvement in sensorium. Blood pressure improved to 94/70 mm Hg. IV Ig given. Empiricalantibiotics given. He recovered over 7 days.	Encephalitis Plasma leakage	6th day	Survived
06	22 Male No co-morbidity	Presented with fever for 4 days ass with dyspnoea and decreased urine output. Clinical examination Pulse-110min BP 84/60 mm Hg Resp rate-26/min Temp 98 °F	Hb – 13.4 g% TLC – 2400/μL, platelets 55,000/μL INR 1.00 LFT 2.3 mg%, AST/ALT-284/146 U/L Creatinine – 1.4 mg% Lactate – 5.4 meq/L BNP >9000 pg/ml Ultrasonographic evaluation revealed ascites, gall bladder wall oedema and bilateral pleural effusion. Chest X ray suggestive of ARDS	Initially, the patient was given IV fluids 20 ml/kg and started Blood pressure did not improve, and his respiratory distress worsened. He was started on vasopressors. IV Ig started. He was given non-invasive respiratory support and empirical antibiotics.	Myocarditis with severe plasma leakage refractory shock and ARDS	6th day	Survived

07	26 Male No co-morbidity	Presented with fever of 5 days ass with dyspnoea Clinical examination Pulse-130min BP 84/70 mm Hg Resp rate-28/cmm Temp 98 °F	Hb – 12.4 g% TLC – 2000/μL, platelets 24,000/μL INR 1.87 LFT Bil 2.3 mg%, AST/ALT-421/356 U/L creat-3.4 mg% Lactate-7.8 meq/L Ultrasonographic evaluation revealed ascites, gall bladder wall oedema and bilateral pleural effusion consistent with dengue capillary leak syndrome. Chest X ray s/o ARDS	Initially, the patient was given IV fluids 20 ml/kg and additional 10 ml/kg fluids and started on vasopressors as blood pressure did not improve. His respiratory distress worsened. He was managed with non-invasive ventilation. IV Ig started. No renal support was required. Empirical antibiotics given	Plasma leakage with Refractory shock with MODS (Renal failure, ARDS, respiratory failure, hepatitis, thrombocytopenia	5th day	
08	28 Male No co-morbidity	Presented with fever of 6 days, diarrhoea 3 days associated with headache Clinical examination Pulse-118/min BP 70/52 mm Hg Resp rate-24/cmm Temp 98 °F.	Hb – 14.1 g% TLC – 2600/μL, platelets 42,000/μL INR 1.16 LFT Bil 1.4 mg%, AST/ALT-246/184 U/L Creatinine – 1.5 mg% Lactate – 7.2 meq/L Ultrasonographic evaluation-ascites, gall bladder wall edema and bilateral pleural effusion.	Initially, the patient was given IV fluids 20 ml/kg and additional 10 ml/kg and started on vasopressors as hypotension persisted. IV Ig started. He was given other supportive therapy. Empirical antibiotics given	Severe plasma leakage, Refractory shock	6th day	Survived
09	25 Male No co-morbidity	Presented with fever of 5 days, Diarrhoea 2 days Clinical examination Pulse – 128/min BP 74/52 mm Hg Resp rate-24/cmm Temp 98 °F	Hb – 14.6 g% TLC – 2800/μL, platelets 62,000/μL INR 1.20 LFT Bil 1.2 mg%, AST/ALT-282/168 U/L creat – 1.4 mg% Lactate – 6.4 meq/L Ultrasonographic evaluation revealed ascites, and bilateral pleural effusion	Initially, the patient was given IV fluids 20 ml/kg and additional 10 ml/kg and started on vasopressors as hypotension persisted. IV Ig started. He was given other supportive therapy Empirical antibiotics given	Severe plasma leakage, Refractory shock	5th day	Survived
10	32 female No co-morbidity	Presented with fever of 5 days diarrhoea of 3 days and abdominal distention of 1 day. Clinical examination Pulse-128/min BP 76/54 mm Hg Resp rate-24/cmm Temp 98 °F	Hb – 11.4 g% TLC – 2400/μL, platelets 36,000/μL INR 1.16 LFT Bil 3.0 mg%, AST/ALT-465/384 IU/L Creatinine – 2.0 mg% Lactate – 6.8 meq/L Ultrasonographic evaluation revealed moderate ascites and bilateral pleural effusion	Initially, the patient was given IV fluids 20 ml/kg and additional 10 ml/kg and started on vasopressors as hypotension persisted. IV Ig started. He was given other supportive therapy Renal functions improved without need of Renal replacement therapy. Empirical antibiotics given	Severe plasma leakage, refractory shock AKI	5th day	Survived

(*continued on next page*)

Table 3 – (*continued*)

Case	Age Sex	Clinical course	Lab parameters	Rx	Complications	Day of IV Ig	Outcome
11	20 y Male No co-morbidity	Presented with Fever of 2 days asso with Diarrhoea, abdominal distention and Hematochezia Clinical examination Pulse-128/min BP 90/54 mm Hg Resp rate-24/cmm Temp 102 °F	Hb – 9.4 g% TLC – 1800/μL, platelets 9000/μL INR 1.69 LFT Bil 9.0 mg%, AST/ALT-456/347 U/L creat- 1.4 mg% Lactate – 3.2 meq/L Ferritin- >24000 ng/ml TG-350 mg% Ultrasonographic evaluation revealed Hepatosplenomegaly ascites, gall bladder wall oedema and bilateral pleural effusion. Bone marrow-haemophagocytosis H score-280. NCCT Brain- Normal CSF was not done	Initially, the patient was given IV fluids 20 ml/kg. His Blood pressure improved. Platelets were transfused. However he persisted to have fever and on day 6 again went became hypotensive not responding to fluids requiring vasopressors. His sensorium worsened with GCS 8/15(E2M4V2) with respiratory distress. He was intubated and started on was given IVIg and Dexamethasone. Empirical antibiotics were given.	HLH, Encephalitis,Plasma leakage, GI Bleed	6th day	Survived
12	32 male No co-morbidity	Presented with Fever and diarrhoea x 3 days ass with prostration and headache Clinical examination Pulse – 108/min BP 100/74 mm Hg Resp rate-22/cmm Temp 101.5 °F	Hb – 10.6 g% TLC – 2600/μL, platelets 86,000/μL INR 1.37 LFT Bil 1.6 mg%, AST/ALT-243/206 IU/L Sr creat- 1.0 mg% Lactate – 3.8 meq/L Ferritin- 18540 ng/ml TG-268 mg% Ultrasonographic evaluation revealed hepatosplenomegaly, mild ascites. Bone marrow-haemophagocytosis. H score-234	Initially, the patient was given IV fluids 20 ml/kg. His Blood pressure improved. However he persisted to have fever and diarrhoea, persistent leukopenia and thrombocytopenia. He was started having hypotension unresponsive to fluids. Vasopressors were added. He was given IVIg. Empirical antibiotics were given.	HLH	7th day	Survived
13	18 yr Male No Co-morbidity	Presented with Fever of 3 days Haematuria on day 4 associated with Prostration Pulse 116/min BP- 86/60 mm Hg Temp 98 °F Systemic examination-Normal	Hb – 6.8 g% TLC – 2600/μL, platelets 85,000/πL INR 1.37 LFT Bil 4.6 mg%, AST/ALT-291/242 U/L Sr creat- 1.4 mg%. Lactate – 6.4 meq/L Ferritin-510 ng/ml Direct Coombs Test- Negative Ultrasonographic evaluation —Mild ascites. Peripheral blood smear- s/o haemolysis	Initially, the patient was given IV fluids 20 ml/kg and started. Blood pressure did not improve and another bolus of 10 ml/kg fluid was given, vasopressors were added. Shock and haematuria persisted. Now IV Ig started. Packed RBC were transfused. Empirical antibiotics given. Forced alkaline diuresis given once the blood pressure improved.	Intravascular Haemolysis (non-autoimmune haemolytic anaemia) Severe plasma leakage and refractory shock	4th day	Survived

The case series by Ostronoff et al showed dramatic improvement in platelets in IV Ig-treated patients.[21] However, only RCT by Dimaano et al, which evaluated the effect of IVIG on thrombocytopenia, did not show benefit of IV Ig.[22] However, seriously ill patients and those with shock were excluded in this study. Another unpublished RCT from Philippines by Alejandria compared treatment with IVIG vs. placebo in children with dengue shock syndrome in which 205 patients with dengue shock syndrome were randomized to receive placebo or IV Ig at the dose of 0.4 g/kg for 3 days. A total of 103 children received IV Ig, and 102 received placebo. Overall mortality in the study was 21%. The mortality rate in those given IV Ig and placebo was 15% and 28%, respectively, which was significant ($p < 0.05$). The absolute risk reduction was 0.12 (CI 0.01,0.23), and the number needed to treat was 8 (CI of 4.33, 101.75).[23,24] One case report in renal transplant recipient with dengue shock syndrome benefitted dramatically with 5 days of IV Ig therapy.[25] IV Ig may also expand the intravascular oncotic pressure by physical property and may maintain intravascular fluid. On the contrary, our experience with IV albumin, a colloid, which is supposed to restore intravascular volume, was disappointing. The albumin passes through leaky endothelium and may aggravate the ARDS although albumin rescue therapy is shown to be beneficial in burns and septic shock.[26] IV Ig is especially useful in those with shock and ARDS/Lung involvement where fluid management is challenging. These patients are very sick and progress rapidly leading to fatal outcome within minutes if hemodynamic stability is not restored immediately. Those with hypotension may also have cardiac dysfunction/myocarditis, and IV Ig may be useful in such patients due to its immunomodulatory function. All patients who do not respond to fluid therapy should be evaluated for myocarditis. In an observational study of South India published in an unindexed journal in which 96 paediatric patients were given IV Ig for fluid unresponsive dengue shock. The mortality with IVIg therapy was 1.03% and 10% without IVIg therapy.[27] However, the authors did not mention the dose of IV Ig given in those children. We used highly selected adult patients of dengue shock patients unresponsive to fluids, that is, refractory dengue shock no study has ever been done on these patients.

The initial two patients in whom IV Ig was used had advanced acidosis and organ failure and hence may not have responded to IV Ig.

Two patients with HLH and two patients with encephalitis with refractory shock also responded to IV Ig. In the presence of persistent fever, cytopenias, one should suspect secondary HLH. The first-line treatment for secondary HLH is IV Ig, and there are several case reports of successful IV Ig therapy in dengue patients. Our first patient with HLH needed dexamethasone in addition to IV Ig. More than 74 dengue-associated paediatric and adult HLH cases have been described in the published literature since 1966 with a cumulative case-fatality rate of 9.5%.[28] Recent study from India on secondary HLH in which out 20 patients with HLH, 12 were due to dengue fever. Out of 12 patients with dengue HLH, 9 patients responded to therapy and 3 died. But in that study only two were treated with IV Ig and four were treated with steroids, but HLH was not confirmed by the bone marrow in that study.[29] IV Ig is especially useful if started early in the course of illness.

Encephalitis is one of the severe complications of dengue and is commonest neurological complication.[30] Treatment is mostly symptomatic with good outcome. In our study four patients had encephalitis and two received IV Ig therapy due to associated refractory shock. They responded to therapy.

The overall mortality rate in this study was 0.40%. Mortality in dengue shock varies from 21 to 72%. There is no study that studied mortality in refractory dengue shock. The mortality rate of dengue shock in our study was 1.96% (2 deaths out of 102 dengue shocks), whereas the mortality rate in refractory dengue shock with IV Ig use was 18.18% (2 deaths out of 11), which would have been very high without its use.

IVIg may be used in refractory shock after failure of fluid therapy early in the course of critical phase. IVIg not only acts as a colloid with high-molecular-weight antibodies to immediately increase oncotic pressure and expand intravascular volume, it also acts with its immunomodulatory and immune resuscitative action. Other colloids may aggravate the plasma leakage and ARDS, which is not seen with IV Ig.

Although IV Ig is effective, it was needed only in few patients, which supports the present standard therapy. The good response in IV Ig-treated patients may also be due to spontaneous recovery or by chance. IV Ig is costly and should be judicially used. The correct dose and duration and efficacy need a larger study with optimal inclusion criteria, which is very difficult given the dynamic nature of severe dengue. The main strength of the study is that this is first study in use of IV Ig in adults with severe dengue and refractory dengue shock. Another main strength of the study was to reinforce efficacy of standard supportive therapy in dengue management. The limitation of the study was a small sample size and no controlled arms, which would have given a conclusive evidence of role of IVIg.

Conclusion

The present study highlights the importance of standard supportive care in the management of dengue. The study nevertheless highlights the possible role of IVIg in complicated dengue that are unresponsive to standard therapy and are critically ill with usually fatal outcomes. IV Ig is a novel therapy in refractory dengue shock with a possible benefit, and its efficacy should be explored in future with adequately powered and well-controlled randomised studies.

Disclosure of competing interest

The authors have none to declare.

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