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Use of Anti-D (Rh0-D) Immune Globulin in Patients with Severe Dengue: A Case Series

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Abstract

Severe dengue fever (SDF) is a potentially fatal disorder with bleeding being a common cause of mortality. Bleeding in these patients is generally secondary to thrombocytopenia, which is a common complication of SDF. Intravenous anti-D is an approved therapeutic option in improving platelet counts in the management of idiopathic thrzzombocytopenic purpura (ITP). It has also been tried in patients with SDF for improving thrombocytopenia. Here we report a series of eight patients with SDF who showed remarkable improvement after administration of anti-D.

Keywords: *Dengue; Case series; Critical care*

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Introduction

Dengue fever still remains a cause for significant health concern in tropical countries like India. World health organization (WHO) has recognized SDF on the basis of presence of severe plasma leakage leading to shock (DSS) or fluid accumulation with respiratory distress or presence of severe bleeding or severe organ dysfunction. [1]

SDF is a potentially fatal disorder with bleeding and multi-organ failure (MOF) being common causes of mortality. Bleeding is generally secondary to thrombocytopenia, which is a common finding in patients with SDF. Intravenous anti-D is an accepted therapeutic option for improving platelet counts in the management of ITP. Anti-D has also been used in patients with SDF in hope of improving thrombocytopenia. [2, 4]Here we report a series of eight patients with SDF who showed remarkable improvement after administration of anti-D.

Case Seriest

Patient characteristics and hospital course is given in Tables 1 and 2, respectively.

Patient 1

A 31-years-old female with a history of fever, weakness, shortness of breath (SOB), and vomiting of five days duration. On day three, she was shifted to intensive care unit (ICU) with progressive dyspnea and increasing oxygen requirement. She was given NIV support, failing which she was intubated on day four requiring high FiO2 of 80% and high PEEP of 12 mmHg. She was hypotensive,

but responded to fluid resuscitation. Anti-D was given in view of progressive deterioration of clinical condition and evidence of multi organ failure (MOF). She showed signs of gradual improvement and could be extubated on day seven.

Patient 2

A 36-years-old female was admitted to high dependency unit (HDU) with fever of eight days, abdominal pain, distension and respiratory distress of four days duration. She also had a history of epistaxis and increased menstrual bleeding. Patient had an episode of generalized seizures and was shifted to ICU. She had to be intubated in view of respiratory distress, high FiO2 requirement and low GCS. She required high PEEP and FiO2 support. There was evidence of intrapulmonary bleed as endotracheal secretions were blood stained and CXR showed bilateral fluffy shadows. She was hypotensive and required vasopressor support. There was no coagulation abnormality and she was initially given one unit single donor platelet (SDP) and 2 units PRBC. Anti-D was given in view of MOF, active bleeding and thrombocytopenia. NCCT head did not show any abnormality. The patient's condition responded to therapy and was extubated on day five and shifted out of ICU on day seventh.

Patient 3

A 24-years-old female with a history of fever, nausea and body ache of four days and blackish discoloration of stools for two days duration was admitted in wards where she received two units of SDP over two days because of thrombocytopenia and gastrointestinal bleed. On day three, she developed hematemesis for which she was shifted to ICU. She was given Anti-D in view of active gastrointestinal bleed and persistent thrombocytopenia. She showed gradual improvement in platelet levels and gastrointestinal bleed.

Patient 4

A 52-years-old female was admitted in ICU with complaints of fever, body ache, and vomiting of seven days duration. Patient was referred from another hospital in view of progressive breathlessness and persistent hypotension. On examination, patient was hypotensive (106/56 mmHg, on noradrenalin and dopamine), tachypnic (RR – 36/min) and had tachycardia (HR – 155, in atrial fibrillation). She also had respiratory distress and required NIV support. She had ascities and bilateral pleural effusion. She was given Anti-D in view of thrombocytopenia and MOF. She showed gradual improvement in oxygenation and became hemodynamically stable by day three when she was shifted out of ICU.

Patient 5

An 18-year-old male was admitted in wards with complaints of fever, abdominal pain and vomiting of four days duration. He continued to have severe thrombocytopenia and on day four, he developed rash all over the body and became hypotensive with a systolic blood pressure (BP) of 70 mmHg. Hence, he was shifted to ICU. He was given Anti-D in view of persistent thrombocytopenia and worsening of clinical condition. He showed gradual improvement in platelet counts and was shifted out of ICU on day seven.

Patient 6

A 16-years-old male was admitted to the ICU with fever of five days duration, and rash and abdominal pain of two days duration. On examination, he was tachypnic (RR – 35/min) and his BP was not recordable. He was started on vasopressors when his BP was not maintained even after fluid resuscitation. He continued to deteriorate with persistent thrombocytopenia and increasing FiO2 requirement. He was given Anti-D on day two, in view of persistent shock, persistent thrombocytopenia and severe hypoxemia. He showed signs of improvement with stabilization of BP and improved oxygenation and platelet counts. He was shifted out of ICU on day four and discharged on day five.

Patient 7

A 28-years-old male was admitted to ICU with a history of fever of four days and abdominal pain and vomiting of three days duration. On examination, he was hypotensive (BP – 90/50 mmHg), tachypnic (RR – 35/min), hypoxemic (saturation 87% on room air) and had tachycardia (HR – 110/min). His condition continued to deteriorate with increasing FiO2 requirement (on NIV support), persistent shock (increasing vasopressor requirement) and severe thrombocytopenia (in spite of three units of SDP transfusion). On day four, patient was intubated and started on invasive mechanical ventilation in view of severe hypoxemia and refractory shock. On day five,

Anti-D was given to the patient in view of persistent thrombocytopenia and worsening clinical condition with MOF (ARDS, hypotension, AKI). He showed gradual improvement with hemodynamic stabilization, improvement in platelet counts and reduction in oxygen requirement. He could be safely extubated on day 10 and was shifted out of ICU on day 13.

Patient 8

A 60-years-old male presented with complaints of fever of seven days, and malena, hematuria, and epistaxis of two days duration. On admission, he was hypotensive (BP – 80 mmHg systolic), tachypnic (RR – 38/min), hypoxemic (saturation 85% on room air) and had tachycardia (HR – 115/min). He also had anuria in spite of fluid resuscitation and had to be started on vasopressors because of persistent shock. He also required NIV support for persistent hypoxemia and renal replacement therapy in view of severe metabolic acidosis and anuria. He was transfused Anti-D in view of severe thrombocytopenia, ongoing bleeding and MOF. Even though his bleeding stopped and he became hemodynamically stable, on day three, he had to be intubated in view of severe hypoxemia and respiratory distress. He showed gradual improvement with improved oxygenation but thrombocytopenia and renal dysfunction persisted requiring intermittent hemodialysis. He could be extubated on day eight. By day thirteen, his platelet counts improved and he was discharged from hospital but he still required RRT.

Discussion

In the present case series, most of the patients (5/8, 62.5%), were admitted to ICU with evidence of multi-organ failure but only two patients were having symptoms of minor bleeding (epistaxis and malena). The diagnosis of dengue was confirmed by detection of NS1 antigen or by using dengue serology in all our patients. Mean platelet count was 29,000/mm3 before and 66,700, 93,500, and 1,16,000/mm3 after intravenous anti-D administration at 24, 48, and 72 hours, respectively (Table 3). Only one patient required SDP transfusion after anti-D injection. Anti-D was administered as a single dose of 250 IU/kg (50 mcg/kg) over five minutes. There were no adverse effects and the average drop in hemoglobin after 48 hours of administration of anti-D was 1.3 g/dL. All the eight patients showed significant clinical improvement with improved organ function and there was no mortality in our patient cohort.

Anti-D (Rh0-D) immune globulin (WinRho® SDF) is a freeze-dried gamma globulin (IgG) fraction of human plasma having antibodies to Rh0 (D), which is prepared by Cangene Corporation (Winnipeg, Canada). Apart from suppression of Rh iso-immunization, Anti-D is recommended in the treatment of ITP for thrombocytopenia. Its proposed mechanism of action is selective blockade of the Fc receptors in splenic macrophages and other sites of the reticulo-endothelial system. The anti-D attaches to the RBCs in Rh-positive (D-positive) patients and preferentially blocks platelet destruction by sacrificing the patient's RBCs. [5]

Reported complications are anaphylactic or severe systemic reaction to human immune globulin products. Hemolysis may occur and hence patients should be monitored for hematuria and hemoglobinuria for at least eight hours after administration along with development of signs and symptoms of intra-vascular hemolysis like backache, fever with chills, and discoloration of urine. We did not observe any adverse reaction associated with use of Anti-D, including hemolysis, in any of our patients which is consistent with earlier reports. [4]

Thrombocytopenia has been shown to be an independent predictor of severity of dengue infection and mortality associated with it. [6, 7] Platelet counts tend to improve generally after 24 to 48 hours of administering Anti-D. [4] In our patient cohort, administration of Anti-D not only improved the thrombocytopenia, it also helped in improving the multi-organ dysfunction. Release of various inflammatory cytokines (cytokine tsunami), have been implicated in the causation of severe features, including bleeding and capillary leak, of dengue fever which may ultimately lead to MOF. [8] Even though there is no direct evidence of how Anti-D may improve MOF, we may postulate that by reducing platelet destruction and hence release of inflammatory cytokines, Anti-D may help in preventing or worsening of MOF.

In the recent years, several drugs like anti-malarials (chloroquine), steroids (prednisolone), statins (lovastatin) and anti-viral agents (celgosivir and balapiravir) have been tried in various trials for their efficacy in managing patients with dengue fever. However, none of these are presently approved for regular use. [9, 10] Even though there are a few case reports showing efficacy of anti-D in improving

platelet counts in patients with dengue fever, most of these reports are in pediatric patients [2, 3] and its efficacy in adult population is presently doubtful. [4] However, our data suggest that anti-D might prove to be a safe and viable therapeutic option in the management of adult patients with SDF and warrants further investigations.

Patient	Age (in years), sex	Relevant comorbidities	Reason for ICU admission	Admission APACHE II score	PDR%	SOFA Score	Platelets	Hemoglobin	Hematocrit	Outcome
1	31/F	No	Respiratory distress	10	11.3	5	18,000	12.8	37.4	Discharge
2	36/F	No	Epistaxis	8.0	8.7	12	40,000	9.9	27.9	Discharge
3	24/F	No	Melena	01	3.3	5	20,000	15.9	51.4	Discharge
4	52/F	HTN	Tachycardia, Low platelet, Dengue +ve	5.6	5.8	5	33,000	12.5	38	Discharge
5	18/M	No	Pain abdomen, Dengue, low platelet count	12	14.6	4	11,000	16.1	46	Discharge
6	15 /M	No	Hypotension	7	7.6	9	25,000	16.4	46.9	Discharge
7	28/M	No	Hypotension	2	3.8	9	9000	13.4	35.7	Discharge
8	60/M	No	Alter sensorium	24	49.7	10	10,000	5.9	17.3	Discharge

APACHE - Acute Physiology and Chronic Health Evaluation. CKD - chronic kidney disease. PDR - predicted death rate. SOFA - Sequential Organ Failure Assessment.

Table 1: *Baseline characteristics*

Patient No.	Admission Days after fever	Anti D given: Days after admission	Days in ICU	Days in Hospital	Need for Vasopressors	Days on vasopressors	Need for RRT	Days on RRT	Need for MV	Days on MV
1	5	Day 5	5	11	NO	--	NO	--	YES	4

2	8	Day 1	6	8	YES	4	NO	--	YES	4
3	4	Day 2	3	7	NO	--	NO	--	NO	--
4	7	Day 1	3	5	NO	--	NO	--	NO	--
5	4	Day 4	7	8	NO	--	NO	--	NO	--
6	5	Day 2	4	5	YES	3	NO	--	NO	--
7	4	Day 5	13	14	YES	12	NO	--	YES	9
8	7	Day 2	13	13	YES	3	YES	12	YES	5

RRT – renal replacement therapy, MV – mechanical ventilation

Table 2: *Hospital course*

Patient	Pre-anti-D		24 Hours		48 hours		72 hours	
	Platelets	Hemoglobin	Platelets	Hemoglobin	Platelets	Hemoglobin	Platelets	Hemoglobin
1	18	12.4	82	10.2	139	9.9	190	10.6
2	40	9.9	102	9.5	95	8.8	87	9.2
3	13	15.9	17	15.2	23	14.1	67	13.9
4	33	10.5	32	9.6	67	9.1	83	9.2
5	34	13.4	97	12.5	178	11.9	215	12.8
6	25	15.4	42	13.8	70	12.9	121	13.2
7	59	9.6	111	9.7	136	9.1	137	10.1
8	10	6.8	51	8.6	40	7.9	28	8.5

Table 3: *Platelet count and hemoglobin levels before and after giving Anti-D.*

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