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Corticosteroid in Dengue Hemorrhagic Fever as Preventive Treatment of Severe Outcome: A Case Report

Nyoman Angga Santosa[1], Diah Pradnya Paramita[1], Made Wirama Diyana[2]

[1]General Practitioner, Department of Internal Medicine, Wangaya General Hospital, Denpasar, Bali, Indonesia

[2, 3]Internist, Department of Internal Medicine, Wangaya General Hospital, Denpasar, Bali, Indonesia

[1]Corresponding Author email: *anggasantosa6[at]gmail.com*

Abstract*: Dengue is known as the most common vector-borne viral infection between humans by Aedes genusmosquito. Dengue has a broad spectrum of disease, ranging from asymptomatic infection to a severe systemic plasma leakage syndrome. Pathogenesis of severe dengue stillpoorly understood, one factor that is thought to cause the dreaded shock syndrome is antibody-dependent enhancement. Despite of fluid replacement therapy as the main treatment, corticosteroids usage in order to suppress immune-mediated mechanisms in DHF also expected to prevent severe outcome. Since this is still controversial, further research is still very much needed.*

Keywords: dengue hemorrhagic fever, dengue shock, corticosteroids, preventive treatment

1. Introduction

Dengue is known as the most common vector-borne viral infection of humans, with around 50 million infections estimated to occur annually and some 2.5 billion people living in areas of risk.[1] It is a mosquito-borne acute febrile illness which is spread between humans by the *Aedes* genus (i.e., *Aedes aegypti* and *Aedes albopictus*) that carry a *flavivirus* wich has four distinct serotypes (DENV-1, 2, 3, 4).[1, 2] Dengue has a broad spectrum of disease, ranging from asymptomatic infection to a systemic plasma leakage syndrome typically accompanied by thrombocytopenia and coagulation derangements. The plasma leakage phenomenon might progress into a worse condition causing a life-threatening shock.[1, 3]

Studies stated that almost 4 billion people from at least 128 countries are under the risk and estimated 50 million dengue infections are occurring each year globally.1, [3]The World Health Organization (WHO) declared South Asia as an endemic area for the disease due to favorable dissemination environment of its vector.3 Dengue infection can incubates around 4-7 days before the symptom begin, the cases has been traditionally classified by WHO since 1997, which still relevant until nowadays, as Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS).4 DF characterized as acute fever which usually accompanied with at least two following features: ocular pain, headache, muscle and/or joint pain, dizziness.1, [4] Laboratory finding shows leukopenia and thrombocytopenia.4DHF is DF with bleeding manifestation and evidence of plasma leakage, i.e. increased hemoconcentration. While DSS is DHF with signs of impaired blood flow perfusion such as hypotension, tachycardia with weak pulse, low pulse pressure (< 20 mmHg), and/or altered consciousness.[1, 2, 4]

Pathogenesis of severe dengue is not fully understood yet, studies said that antibody-dependent enhancement is thought to be one cause of increasing viral replication which resulting shock syndrome, despite many other host and virus factors are thought to contribute.[1, 2]Much of the evidence points to severe manifestations of dengue having an immunological basis such as cytokine and chemical mediators, rather than being due to direct tissue damage by the virus, leading to vascular endothelial cell dysfunction in dengue.[2, 4]

Although fluid replacement therapy is still the main treatment due to blood plasma leakage process, only a limited number of studies were done to evaluate the effectiveness of corticosteroids in dengue hemorrhagic fever in order to suppress the immune response according to dengue pathology.[1, 4] We report a case of DHF patient with corticosteroid as adjunctive therapy to prevent severe outcome.

2. Case Report

A 42-year-old female patient came to Emergency Department in Wangaya General Hospital, Bali, Indonesia on December 2021 with complaints of fluctuating fever since 3 day before administration. The fever was around 37.5° to 38.2° Celsius and got treated by taking paracetamol tablets independently, but no improvement. She also felt dizziness, muscleache and abdominal pain since 1 day before. The patient felt light-headed especially when standing up or walking but no spinning sensation. Abdominal pain was come and go, mostly in central region and she threw up two times in the morning containing the food which have been eaten before. Complaints of sneezing, coughing, sore throat and shortness of breath were denied. She also said that some of her work colleagues were having fever as well. History of systemic disease, smoking or alcohol consumption habit were denied. She said that she used to has a low blood pressure around 90/60 mmHg to 100/70 mmHg.

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The patient was well aware, vital signs examination showed the blood pressure showed 100/68 mmHg with pulse rate 88 bpm, respiratory rate 18 times per minute, axillary temperature 37.0° Celsius, oxygen saturation was 98% in room air. On physical examination, her lips looked dry, there were multiple petechiaes on extremities and her back, epigastric pain was also found. The remainder of physical examination was within normal limit. Laboratory finding showed leukopenia (1.32 x 10^3/uL), hematocrit level 37.8 %, and thrombocytopenia (39 x 10^3/uL), while other complete blood count finding was within normal limit. Biochemical evaluation showed elevated transaminases level (SGOT 213 U/L and SGPT 157 U/L). Sodium, potassium and chloride level were 135 mmol/L and 3.7 mmol/L while was 105 mmol/L sequentially. The chest x-ray was within normal limit. The RT-PCR test for SARS-CoV-2 was negative.

According to history of her symptoms, physical examination and laboratory finding, she was diagnosed with DHF grade II and Transaminitis. Patient was given intravenous fluid of Ringer Lactate with maintained drops, paracetamol tablets as antipyretic as well as other symptomatic treatment such as intravenous ondansetron and omeprazole. There was no specific treatment of transaminitis given to this patient. Complete blood count was planned to be routinely checked every 12 hours in the ward.

On the 1st day of in-ward hospitalization, which is 4 days since the patient's symptoms began, body temperature was fluctuating around 36.6° to 37° Celsius. Nausea and abdominal pain was getting better as well as the dizziness, the patient can eat well, muscle pain improved, no vomiting was found. The blood count monitoring results are shown in the table 2.

Table 1: Initial Laboratory Result on Admission

Lab Investigation	Result	Reference Range
White Blood Cells count (10^3/uL)	**1.32**	4.0 – 10.0
Red Blood Cells count (10^6/uL)	4.08	4.20 – 5.40
Hemoglobin (g/dL)	12.1	12.0 – 16.0
Hematocrit (%)	**37.8**	37.0 – 47.0
Platelet count (10^3/uL)	**39**	150 – 400
Neutrophil count (10^3/uL)	0.95	1.50 – 7.00
Lymphocytes count (10^3/uL)	0.25	1.00 – 3.70
Biochemical		
SGOT (U/L)	**213**	0 – 37
SGPT (U/L)	**157**	0 – 42
BUN (mg/dL)	19	10 – 50
Serum Creatinine (mg/dL)	0.9	0.3 – 1.2
Random Blood Glucose (mg/dL)	101	80 – 200
Electrolytes		
Na (mmol/L)	135	130 – 145
K (mmol/L)	3.7	3.5 – 5.5
Cl (mmol/L)	105	95 – 108

The petechiaes seemed extend to patient's chest and stomach, and her gums bleed when provoked by brushing teeth on 2nd day. An intravenous colloid fluid, Widahes (contains hydroxyethyl starches and sodium chloride), was added due to blood plasma leaked more according patent's clinical appearance and the laboratory result. The patient blood pressure was dropping to 84/52 mmHg in the night with pulse rate 78 bpm, body temperature was 36.7° Celsius. Hence, more intravenous fluid of Ringer Lactate drops were given. Blood pressure was showed improvement to 90/58 mmHg after vital sign monitoring 2 hours later. An addition of methylprednisolone was given 62.5 mg twice a day intravenously (body weight 61kg, height 162cm), and complete blood count checked every 8 hours on the next day.

On 3rd day of in-ward hospitalization, patient's blood pressure was dropping again to 86/57 mmHg with pulse rate 98 bpm, capillary refill time was less than 2 seconds, patient's extremities were still warm and but she said she felt weak. Hence, intravenous fluid resuscitation of ringer lactate was given due to pre-shock condition. Blood pressure was increased to 93/68 mmHg, pulse rate decreased to 82 bpm after that. Vital signs monitoring was planned to be done every 4 hours in order to ensure no sign of shock happened. Fortunately, on following days the patient's condition getting better, no fever was found, neither nausea nor vomiting, petechiaes seemed decreasing in number. Vital signs were stable and blood count results were improved. Colloid fluid was stopped in the afternoon of 4th day in-ward hospitalization; it is same for corticosteroid treatment. Liver enzymes were rechecked and showed improvement without any specific treatment. Convalescence rash began to appear on day 5 of in-ward hospitalization. The patient was able to be discharged from hospital on the following day.

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Table 2: Blood Count Monitoring Since Day-1 in Ward

Lab Investigation	Day 1	Day 2	Day 3	Day 4	Day 5
WBC count (10^3/uL)	Morning – 0.98 Night – 1.31	Morning – 1.55 Night – 2.42	Morning – 4.93 Afternoon – 5.13 Night – 4.42	Morning – 4.21 Afternoon – 4.30 Night – 4.02	Morning – 4.10
RBC count (10^6/uL)	Morning – 4.16 Night – 4.43	Morning – 4.80 Night – 4.92	Morning – 4.71 Afternoon – 4.47 Night – 4.50	Morning – 4.42 Afternoon – 4.38 Night – 4.40	Morning – 4.22
Hemoglobin (g/dL)	Morning – 12.3 Night – 13.1	Morning – 13.9 Night – 14.4	Morning – 13.6 Afternoon – 13.1 Night – 13.3	Morning – 13.0 Afternoon – 13.1 Night – 13.3	Morning – 12.9
Hematocrit (%)	Morning – 38.0 Night – 38.1	Morning – 41.4 Night – 41.9	Morning – 40.0 Afternoon – 37.7 Night – 38.6	Morning – 38.4 Afternoon – 37.7 Night – 37.5	Morning – 37.3
Platelet count (10^3/uL)	Morning – 21 Night – 14	Morning – 11 Night – 8	Morning – 9 Afternoon – 4 Night – 11	Morning – 16 Afternoon – 33 Night – 45	Morning – 68
SGOT (U/L)	-	-	-	101	-
SGPT (U/L)	-	-	-	60	-

3. Discussion

We present a case of 42 years old woman diagnosed as DHF with warning sign, onset day-4. This patient had some symptoms related to dengue hemorrhagic fever with low blood pressure and no spontaneous bleeding manifestation. From the laboratory examination we revealed leukopenia, severe thrombocytopenia, hemoconcentration, and elevated liver enzymes. The patient experienced a decrease in platelet count since the first day of hospitalization. Steroid intravenous therapy was then initiated on the second day of hospitalization (DHF onset day-5), concurrently with volume expander (Widahes) fluid therapy and symptomatic medication. Several studies have been conducted regarding the administration of steroids in DHF, and their usefulness is still under debate.

Most of the beneficial results were seen with intravenous usage, with high doses and with multiple doses of methylprednisolone. At high concentrations glucocorticoid molecules intercalate into cell membrane and alter cellular functions resulting in reduced calcium and sodium cycling across the plasma membranes of immune cells. This is thought to contribute to rapid immunosuppression and a subsequent reduction of the inflammatory process when corticosteroids are used in high concentration. Low dose steroids may act via the genomic pathway of corticosteroids, whereas a high-dose of steroids may act through both genomic and non-genomic pathways.[5]

Steroids act through several pathomechanisms: *1) Corticosteroids suppress cells involved in innate immunity*. Methylprednisolone usually increases antigen uptake and prevents dendritic cell differentiation and maturation as well as TNF-a, IL-6, and IL-12 production. By slowing the maturity of dendritic cells (DCs), it can reduce the replication of dengue virus in mature DCs. Methylprednisolone also reduces the ability of DCsto elicit a proliferative response and the production of matrix metalloproteinase, thereby prevent the vascular leakage in dengue. Corticosteroids exert a strong suppressive effect on human DCs thereby inhibit the induction of primary T and B cell responses so prevent dengue virus-induced immune dysfunction.[6] *2) Corticosteroids suppress T cells, B cells and antibody in dengue pathology*. Dengue virus infected cells secrete nonstructural protein 1 (NS1) glycoprotein which can be found bound to platelets, endothelial cells and cells in the lung and liver. Methylprednisolone suppresses IL-1[7] and IFN-γ, which are important immune molecules for an autoimmune role in dengue disease caused by anti-NS-1 antibodies. It indirectly reduces the cytotoxic effects of nitric oxide and tumor necrosis factor (TNF). This prevents anti-NS-1 antibody-induced intrinsic apoptosis and vital tissue damage, which can lead to organ failure and death in dengue. Corticosteroids inhibit cytokine-induced apoptosis by regulating anti-apoptotic genes and by suppressing humoral immunity via B cells to express lower numbers of IL-2 and IL-2 receptors, thereby decreasing antibody-induced immune pathology in dengue patients.[7, 8] *3) Corticosteroids suppress DEN virus induced complement activation*. In DHF found a large amount of C3a which functions to recruit monocytes, macrophages and dendritic cells that regulate vasodilation, increase the permeability of small blood vessels, disrupt vasculature and smooth muscle contraction.[9] It can induce oxidative burst and formation of cytotoxic oxygen radicals, mediate chemotaxis, inflammation and histamine release by basophils, neutrophils, eosinophil, and mast cells.[10] Methylprednisolone directly inhibits the alternative pathway and complement amplification. Steroids in higher doses can regulate membrane stabilization, complement inhibition, which helps stop or prevent histamine release, vascular permeability, and circulatory collapse.[11]

A research by Gomez, et al., found patients that had reduced pulse pressure as a warning sign treated with 1 mg/kg/day methylprednisolone had a faster recovery than those in the control group. It leads to the hypothesis that the uses of steroids shorten the time oflow blood pressure, so could prevent many of the severe complications than usually present with sudden onsetin this disease.[12] In our case, methylprednisolone was given at dose of almost 2 mg/kg/day (given every 12 hours) with close monitoring of vitals and warning signs. After the third dose of steroids administration, the patient's platelets had an upward trend, the patient felt less abdominal pain, the hemoconcentration and hemodynamics were also improved. Some studies stated a decreasing of viremia evidence and no significant side

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effects after the administration of low and high doses of oral corticosteroids and high doses of intravenous corticosteroids.[13]

It is suggested that different doses, roots of administration, and particular groups of steroids contribute to suppress immune pathology of dengue at different stages of dengue infection due to different pharmacological actions of corticosteroids at molecular and receptor levels.1[1]Beneficial therapeutic effects were seen in some studies, which used high doses or multiple doses of steroids. The effectiveness of corticosteroids in dengue is depended upon sustained therapeutic blood levels of corticosteroids for an adequate duration and using a steroid with higher receptor affinity.[13]Another researches found that the most beneficial effects of the steroids were seen in the intermediate stage. This may be because the immune-mediated mechanisms, cross-reacting antibodies, cytokines and chemokines are high during this period, which can be suppressed by adequate steroid use.[13]

4. Conclusion

We present a case of 42 years old woman diagnosed as DHF with warning sign who had low blood pressure, severe thrombocytopenia and hemoconcentration. Steroid therapy was initiated in this patient on 5thday of DHF. There was an improvement in hemodynamics and hemoconcentration also an upward trend of platelets after the third administration dose of intravenous methylprednisolone 1 mg/kg every 12 hours. Steroids believed to act through several pathomechanisms such as suppress cells involved in innate immunity, suppress T cells, B cells and antibody in dengue pathology, and suppress DEN virus induced complement activation. The use of steroids in cases of DHF is still debated. Research has been carried out, but different results have been obtained. Further research is still very much needed.

5. Conflict of Interest

The authors declare no conflicts of interest.

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