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Restrictive versus Liberal Fluid Resuscitation in Children with Dengue Shock Syndrome: the differences in Clinical Outcomes and Hemodynamic Parameters

*Saptadi Yuliarto[1], Kurniawan Taufiq Kadafi[1], Dessy Anitasari[2]

[1]Department of Pediatrics, Division of Pediatric Emergency and Intensive Care, Saiful Anwar General Hospital, University of Brawijaya, Malang, East of Java, Indonesia.
[2]Department of Pediatrics, Saiful Anwar General Hospital, University of Brawijaya, Malang, East of Java, Indonesia.

Abstract

Background:
Fluid resuscitation is the mainstay of treatment to counteract massive plasma leakage in dengue shock syndrome. We aimed to determine the differences in clinical outcomes and hemodynamic parameters of children with dengue shock syndrome post restrictive and liberal fluid resuscitation.

Materials and Methods: A retrospective observational study of pediatric patients who were between one month to 18 years old, presented with clinical criteria for dengue hemorrhagic fever (DHF) grade III and IV based on WHO classification of dengue fever in 2011, and admitted to the Saiful Anwar General Hospital, Malang- Indonesia, from January 2016 to December 2016. Patients were divided in two groups: resuscitated with either <40 ml/kg body weight [BW] (restrictive group) or > 40ml/kg BW (liberal group) solutions; then we analyzed the clinical outcomes and hemodynamic parameters between two groups.

Results
Among 100 patients, 92 patients were classified as DHF grade III and 8 patients were DHF grade IV. 74 patients were in the restrictive group and 24 patients were in the liberal group. Median age at diagnosis was 6 years old, and 56% of patients were female. No significant differences were observed between length of stay in pediatric intensive care unit (P=0.09), and duration of ventilator use (P=0.68). The restrictive group had 53% lower mortality compared to the liberal group (P=0.18). This study also showed that there were no significant differences in hemodynamic parameters between two groups based on measurement with USCOM which were preload component (SVV) (P=0.89), inotropy components (SMII) (P=0.07), SVRI (P=0.85) as well as the cardiac index (P=0.66).

Conclusion
This study showed that there is no difference in clinical outcomes (length of mechanical ventilation and length of PICU stay), and hemodynamic parameters (preload, inotropy, afterload, and cardiac index) in Dengue Shock Syndrome patients who receive restrictive or liberal fluid resuscitation.

Key Words: Children, Dengue Shock Syndrome, Liberal, Fluid resuscitation, Restrictive.

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Corresponding Author:

Saptadi Yuliarto, Pediatric Intensivist, Address: Saiful Anwar General Hospital, JA Suprapto street 2, Malang, East Java, Indonesia. Postal code 65111; Fax: +62-341-564-755

Email: : dr.saptadiyuliarto@gmail.com

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1- INTRODUCTION

The World Health Organization (WHO) estimates that between 50 and 100 million people are infected with the dengue virus each year, whereas 500,000 cases of dengue hemorrhagic fever (DHF) require hospitalization, and ninety percent of mortalities occur in children less than 15 years of age (1,2). Dengue Shock Syndrome (DSS) is one of dangerous clinical manifestations of dengue infection characterized by severe plasma leakage due to increased vascular permeability leading to rapid and progressive intravascular volume reduction. DSS generally occurs in a time of fever defervescence or 4-5 days of fever and is often preceded by a warning sign (3).

The most common complications of dengue infection are plasma leakage, instead of massive bleeding and organ dysfunction; those are still the main cause of death for children. Current guideline recommends fluid resuscitation as a mainstay therapy, based on clinical sign and hematocrit level. The majority of children with DSS can be treated successfully with crystalloid solutions, however, if shock persists, colloid is considered effective for resuscitation. Moreover, blood transfusion is also needed in patient with severe bleeding condition. Unfortunately, the guideline does not provide the next step of management if fluid and blood transfusion fail (2).

Although the main mechanism of DSS occurrence is a hypovolemic shock, many studies have reported that myocardial dysfunction or cardiomyopathies also played a role in hemodynamic instability and had the potential to cause recurrence of shock (4); while fluid responsiveness depends on the inotropy or contractility level, massive fluid resuscitation might be harmful in cardiomyopathies -associated DSS. Previous observational study revealed that most children with shock had low inotropy level, therefore fluid refractory occurred after 40 ml/kg body weight (BW) of fluid resuscitation (5). In this study, we hypothesized that clinical outcomes and hemodynamic parameters are different between patients who received fluid resuscitation ≤ 40 ml/kg BW, and > 40 ml/kg BW. We aimed to determine the differences in clinical outcomes and hemodynamic parameters of children with DSS post restrictive and liberal fluid resuscitation.

2- MATERIALS AND METHODS

2-1. Study design and population

This study was a retrospective observational study. All pediatric patients who presented with clinical criteria for dengue hemorrhagic fever grade III and IV based on WHO classification of dengue fever in 2011, and were admitted to a pediatric intensive care unit (PICU), pediatric wards, and emergency room at a Saiful Anwar General Hospital, Malang, Indonesia from January 2016 to December 2016 were included in this study.

2-2. Methods

We collected the following data from the medical records: patient age, gender, body weight, body height, nutritional status, final diagnosis, length of stay in PICU, duration of mechanical ventilation, and mortality event. We classified patients into two groups: restrictive and liberal fluid resuscitation. Restrictive fluid resuscitation group was defined as patients who received bolus infusion ≤ 40 ml/kg BW, whereas liberal group received bolus infusion > 40 ml/kg BW (5, 6). Patients were resuscitated with either crystalloid or colloid solutions. Initial fluid resuscitation was measured and documented since patients were diagnosed with dengue hemorrhagic fever.

2-3. Measuring tools

Hemodynamic parameters were measured by ultrasonic cardiac output monitor

(USCOM 1A, USCOM PVT Ltd, Coffs Harbor, NSW, Australia). The measured parameters included stroke volume variation (SVV), Smith-Madigan Inotropy Index (SMII), potential for kinetic ratio (PKR), stroke volume index (SVI), cardiac index (CI), and systemic vascular resistance index (SVRI). We measured aortic valve (AV) diameter by using patient's age, weight, and height. We also used Doppler to measured velocity time integral (VTI). We obtained stroke volume (SV) using available AV diameter and VTI. In context of preload; SVV is defined as stroke volume which is variation by respiratory cycle. We can measure CI by incorporating heart rate with SV. Afterload in the form of SVR and SVRI can be computed with the input of blood pressure. Inotropy in the form of SMII was calculated using a purpose-written computer program based on Smith-Madigan formula given with the input of SV. SVV ≤30% was defined as fluid-refractory shock, and >30% as fluid-responsive shock. Each of the parameters SMII, PKR, and SVI was divided into 3 levels; that is: low, normal, and high, based on the respective normal value for age (7). In addition, normal CI and SVRI were 3.3-6.0 L/min/m^2 and 800-1600 dyne.sec.cm^{-5} m^{-2}, respectively; a below-normal value was categorized as a low, while an above normal as high (8). A pediatric emergency and intensive care consultant or trained-senior resident performed all measurements.

2-4. Hospital protocol

The hospital protocol recommends fluid bolus 20 ml/kg for 5-15 minutes in case of DSS, and can be repeated until 40 ml/kg to achieve the therapeutic goals (normal heart/pulse rate and blood pressure according to age, normal perfusion [CRT, urine output, mental status], cardiac index [CI] 3.3-6.0 L/min/m^2, and systemic vascular resistance [SVRI] 800-1600 d.s/cm^5/m^2). Fluid bolus must be discontinued if therapeutic goals are achieved or total fluid amount is 40 ml/kg, or patient reveals sign of fluid overload (liver enlargement or rales). In case of persistent shock following ≥40 ml/kg of fluid bolus or fluid overload, diuretics and vasoactive agents are administered based on CI and SVRI level. Inotropes (dopamine 5-10 mcg/kg/min, dobutamine 5-20 mcg/kg/min, or epinephrine 0.05-0.3 mcg/kg/min) are given in low CI – high SVRI case, and can be combined with vasodilator (milrinone 0.5-0.75 mcg/kg/min) if blood pressure is normal. Vasopressor (norepinephrine 0.05 mcg/kg/min-1 mcg/kg/min or epinephrine >0.3 mcg/kg/min) is given in high CI – low SVRI case. Combination of inotropes and vasopressor are given in low CI- low SVRI case.

2-5. Ethical consideration

This study was approved by Ethical Commission of Medical/Health Researches, Faculty of Medicine, University of Brawijaya, Saiful Anwar Hospital (letter no. 400/28/K.3/302/2018). All participants' parent or guardian provided informed written consent.

2-6. Inclusion and exclusion criteria

In this study, DSS children with age from 1 month to 18 years old who were admitted to pediatric intensive care unit (PICU), pediatric wards, and emergency room at a Saiful Anwar General Hospital from January 2016 to December 2016 were included. The exclusion criteria were children with congenital heart diseases, immunodeficiency disorders, autoimmune diseases, pulmonary diseases, hematology diseases, and renal diseases.

2-7. Data Analyses

Data were analyzed using SPSS for Windows 20.0 (IBM Corp., Chicago, IL). Continuous variables were expressed as mean and standard deviation (SD). Variables with non-normal distributions were summarized with medians and interquartile ranges (IQR), as appropriate. The two independent groups were compared using Mann-Whitney test. Categorical variables were expressed as frequencies and percentages and analyzed with Chi-square tests or Fisher's exact tests, as appropriate. Level of statistical significance was declared at p- value < 0.05 levels.

3- RESULTS

3-1. Baseline characteristics

As shown in **Table.1**, one hundred patients enrolled and were analyzed (74 and 26 subjects in the restrictive and liberal groups, respectively). Of the 100 patients, 56 (56%) patients were female. The median age and gender distribution were similar between the restrictive and liberal groups. Median age at restrictive group was 6.0 years old whereas median age at liberal group was 5.5 years old. Among the 100 cases, 92 (92%) patients were classified as DHF grade III and 8 (8%) patients were DHF grade IV. In the restrictive group, the majority of DSS patients 42 (56.8%) had a normal nutritional status, while 16 patients (21.6%) had an underweight nutritional status and 16 patients (21.6%) had an overweight nutritional status. In the liberal group, among 26 patients, 15 (57.7%) patients had a normal nutritional status, while 7 (26.9%) patients had an overweight nutritional status and 4 (15.4%) patients had an underweight nutritional status.

Table-1: Comparison of baseline characteristics between restrictive and liberal groups

Baseline characteristics	Restrictive group (n=74)	Percent	Liberal group (n=26)	Percent
Age (years), median (IQR)	6.0 (0.33-13)		5.5 (0.42-13)	
Gender, n	36	48.6	8	30.7
Male	38	51.4	18	69.3
Female				
Nutritional status, n	16	21.6	4	15.4
Underweight	42	56.8	15	57.7
Normal	16	21.6	7	26.9
Overweight				
Diagnosis, n	70	94.6	22	84.6
DHF grade III	4	5.4	4	15.4
DHF grade IV				

Values are presented as number (%) or median (interquartile range [IQR]); DHF: dengue hemorrhagic fever; P-value was considered significant if P-value < 0.05.

3-2. Clinical outcomes

There was no statistically difference was found in clinical outcomes in both groups as shown in **Table.2** (P>0.05). The median (range) length of stay in PICU was similar in the two groups: 3 (2-18) days in restrictive group versus 4 (2-19) days in liberal groups (P=0.09). The median duration of mechanical ventilation in restrictive group was 4 (1-18) days, while in liberal group was 5 (2-18) days. Although the duration of mechanical ventilation was slightly longer for liberal group, no significant difference was found between two groups for patients who received less fluid resuscitation (P=0.68). The mortality rate for overall hospital stay was less in restrictive group (11.1% in restrictive group versus 23% in liberal group). Although the difference was not statistically significant (P=0.18), the restrictive group had absolute reduction risk (ARR) 12% and relative reduction risk

(RRR) 53% of mortality compared to liberal group. The number needed to treat (NNT) for mortality rate was 8.1, thus it means for every 8 patients in restrictive group, there would be 1 additional survivor.

Table-2: Comparison of clinical outcomes between restrictive and liberal groups

Clinical Outcomes	Restrictive group, (n=74)	Liberal group, (n=26)	P-value	ARR	RRR	NNT
Length of PICU stay (day), median (IQR)	3 (2-18)	4 (2-19)	0.09			
Length of mechanical ventilation time (day), median (IQR)	4 (1-18)	5 (2-18)	0.68			
Mortality rate (%)	11.1	23.0	0.18	12%	53%	8.1

Values are presented as number (%) or median (interquartile range); P-value was considered significant if P-value < 0.05; ARR: absolute risk reduction; NTT: number needed to treat; RRR: relative risk reduction.

3-3. Hemodynamic parameters

Regarding the hemodynamic parameters of the study patients (**Table.3**), no significant difference was observed among two groups (P>0.05). The mean SVV was similar in two groups: 29.0 ± 10.7% in restrictive group and 29,5 ± 12,2% in liberal groups (P=0.89). Patients in restrictive groups had similar SMII compared with liberal groups (1 W/m^2 versus 1.2 W/m^2) (P=0.07); however, SMII level in both groups was lower than normal value according to age. Mean SVRI in restrictive group was 1490.7 ± 355.6 d.s/cm^5 for 0-2 years age group, 2071.2 ± 712.4 d.s/cm^5 for 3-4 years group, while median SVRI for 5-18 years old was 1959 d.s/cm^5. In comparison, the mean SVRI in liberal group was 1526.7 ± 244.0 d.s/cm^5 for 0-2 years age group, 2097.1 ± 715.1 d.s/cm^5 for 3-4 years old, while median SVRI for 5-18 years old was 1970 d.s/cm^5. There were no significant differences in SVRI between two groups (P>0.05), yet the level was higher than normal value, especially in >3 years old group. Cardiac index was similar in both groups (P>0.05). Mean cardiac index for 3-4 years old group in restrictive group and liberal group was 3.48 ± 0.73 L/min/m^2 and 3.00 ± 0.88 L/min/m^2, respectively (P=0.66).

Table-3: Comparison of hemodynamic parameters between restrictive and liberal groups

Hemodynamic parameters	Restrictive group, (n=74)	Liberal group, (n=26)	P-value
Preload			
Stroke volume variation (%), mean ± SD	29,0 ± 10,7	29,5 ± 12,2	0,89
Inotropy			
SMII (W/m^2), median (IQR)			
Afterload	1.0 (0.19-1.90)	1.2 (0.70-2.60)	0,07
SVRI (d.s/cm^5/m^2)			
0–2 years (mean ± SD)			
3-4 years (mean ± SD)	1490.7 ± 355.6	1526.7 ± 244.0	0.85
5-18 years, median (IQR)	2071.2 ± 712.4	2097.1 ± 715.1	0.94
Cardiac index	1959 (586-5817)	1970 (1227-3838)	0.95
0–2 years (mean ± SD)			
3-4 years (mean ± SD)	3.56 ± 0.94	3.32 ± 0.27	0,66
5-18 years (mean ± SD)	3.48 ± 0.73	3.00 ± 0.88	0.22
	3.39 ± 1.06	3.50 ± 0.69	0.72

Values are presented as mean± standard deviation (SD) or median and interquartile ranges (IQR); SVRI: SMII: P-value was considered significant if P-value < 0.05.

4- DISCUSSION

This study aimed to determine the differences in clinical outcomes and hemodynamic parameters of children with dengue shock syndrome post restrictive and liberal fluid resuscitation. This study revealed that mortality was reduced by 12% during fluid resuscitation ≤ 40 ml/kg BW in dengue shock syndrome patients. Thus, the restrictive group had 53% lower mortality compared to the liberal group. There were no differences in length of mechanical ventilation and length of PICU stay. Additionally, the hemodynamic parameters (preload, inotropy, afterload, and cardiac index) was similar between two groups. The clinical presentation of dengue varies from a nonspecific febrile illness to severe forms, including dengue shock syndrome, a form of hypovolemic shock resulting from excessive plasma leakage due to a transient increase in systemic vascular permeability (9-11).

Several studies have demonstrated a greater risk for vascular leakage and development of DSS among children compared to adults (7, 12-13). The endothelial glycocalyx layer (EGL) has been recognized as a key regulator of vascular permeability and helps to regulate proper vascular function (10). Recently, one report revealed that a secreted protein from dengue virus infected cells, non-structural protein 1 (NS1) can trigger increased fluid leakage by disrupting the integrity of EGL (15). Disruption of this layer may further edema, inflammation, hypercoagulability, platelet aggregation, and sepsis syndrome including capillary leak (16, 17). Further, other evidence indicated that over-aggressive fluid resuscitation in condition with disruption of EGL, such as in septic shock, was associated with increased morbidity and mortality (18); while previous randomized clinical trial (RCT) revealed similar mortality rates in pediatric septic shock who received fluid resuscitation >40 ml/kg and ≤40 ml/kg (cumulative survival rate 72.5% vs. 77.6%; P=0.71, respectively) (19); our study showed opposing results. The mortality rate of fluid-restrictive group was 53% lower than liberal group. Restricting fluid resuscitation to maximum 40 ml/kg reduced mortality rate by 12%. Moreover, massive fluid resuscitation could increase extravascular lung water (EVLW) which is the amount of fluid that is accumulated in the interstitial and alveolar spaces. Increased EVLW is always potentially life-threatening, mainly because it impairs gas exchange and reduces lung compliance (20). Previous study also revealed that the initial bolus infusion of hypertonic sodium lactate solution (5ml/kg BW) was as effective as the initial bolus infusion of ringer lactate (20 ml/kg BW) for the acute shock management in dengue shock syndrome (21). For another case such as major surgery, a restrictive fluid regimen leads to reduced complications and improved disability-free (22, 23).

Thus, recognition and early intervention in potentially severe cases represent one of the principal strategies for reducing case fatality (1, 24), in particular, judicious use of parenteral fluid therapy to counteract plasma leakage (25). Although cardiac manifestations specific to dengue are rare, acute reversible myocardial dysfunction is the most commonly documented heart disorder in dengue and myocardial depression is fairly common in cases with shock (24). Impairment of cardiac function in patients with DHF/DSS and the proportion of patients with cardiac dysfunction was larger in patients with higher clinical severity of the disease (8, 26, 27). Thus we measured Smith-Madigan Inotropy Index (SMII) which represents a new approach to the problem of measuring inotropy degrees quickly and accurately (28). We found that the results of SMII were similar in both groups (P=0.07), and lower compared to SMII value in normal children (Smith BE). The lower value of SMII in both groups demonstrated the presence of myocardial depression in some children with DSS even though the cause of cardiac dysfunction in DSS is still unknown (29). Although fluid administration was aimed at increasing intravascular volume to a certain extent, and could increase myocardial muscle fiber resulting in increased strength of myocardial contraction (29), another study mentioned that excessive fluid resuscitation could also cause cardiac dysfunction in patients with increased vascular permeability by causing myocardial edema (30). Moreover, one study stated that almost 58% of children with shock are refractory shock that required vasoactive drugs which indicated a disruption of myocardial function (5). Therefore, our result showed that inotropy index correlated negatively with the amount of intravenous fluid resuscitation (Table.3).

Because a causal relationship between cardiac dysfunction and the occurrence of shock cannot be determined from this study, we assumed cardiac dysfunction can also be the result of coronary hypoperfusion from low cardiac output. Thus, we measured cardiac output component in both groups. The Cardiac Index (CI) is one of the hemodynamic parameters on USCOM examination that represents the cardiac output component. Despite receiving different amounts of fluid resuscitation, we found that CI values were similar (P=0.66), and still within normal limits in both groups (31). Probably this result was due to compensation of increased heart rates for the poor blood circulation and tend to maintain mean arterial pressure (MAP) in DSS patients. CI was also low during the toxic stage due to decreased preload (low end-diastolic volume) and depressed left ventricular ejection fraction. CI also remained subnormal during convalescence due to sinus bradycardia (32). In critically ill children, adequate fluid resuscitation is a particular challenge for the physician since fluid hemostasis is maintained in a narrow range and physiological compensation of both hypervolemia and hypovolemia is limited (33). SVV is a reliable predictor in the assessment of fluid responsiveness in adult patients (34), and it is important to monitor the need for fluid resuscitation and optimize the number of preloads in critical children (32). We found that SVV in both groups has similar results (P=0.89), despite difference of fluid resuscitation volumes. SVV less than 30% was found in both groups which demonstrated patients with DSS had a refractory shock condition. These results were consistent with previous study which showed that most of refractory fluid conditions in children were reached after fluid administration ≤40 ml/kg BW (5).

Important changes in blood pressure also take place during DSS, including enhanced peripheral vascular resistance with diminished cardiac output and normal or low central venous pressure (35). Thus we measured SVRI which represented the resistance to blood flow offered by all the systemic vasculature. Our study showed there was an increased SVRI and similar results (P=0.94) in both groups compared to SVRI value in normal children (31). The elevated SVRI in DSS is likely to be affected by contracted intravascular volume. We evaluated the clinical outcomes after fluid resuscitation in both groups and found that the median length of stay in PICU, duration of mechanical ventilation, and fluid excess in both groups had no significant difference (P=0.09, P=0.68, P=0.83, respectively). These results are likely to be affected by our critical care management in DSS children which is based on our hospital protocol. In this study, the use of noninvasive hemodynamic monitoring, the restrictive fluid management, timely use of noninvasive mechanical ventilation and early implementation of diuretics and inotropic supports were carried out in patients with DSS. The use of advanced monitoring technique would be most useful in this regard, such as USCOM, since it is a tool for early detection of fluid leakage and could help us to adjust fluid administration for children with shock condition. Thus, in the restrictive group, we should refrain from giving treatment intervention outside the guidance provided whereby fluid boluses are administered only for fluid resuscitation. On the other hand, in the fluid liberal group, we use an advanced monitoring to allow for fluid boluses based on volume responsiveness and immediately stop giving fluid resuscitation when they are in a condition of fluid refractory and consider using inotropic and/or diuretics supports judiciously. Previous study also suggested that the use of cardiovascular monitoring and rational use of inotropic support and fluid removal strategies might decrease mortality and incidence of fluid overload in patients with DSS (6). Early diagnosis and optimal clinical management reduce fatalities in both children and adult patients (36). Current management of dengue infection does not have any specific treatment except cautious monitoring and appropriate fluid replacement therapy (2).

Further, the current guidelines for treatment of DHF published by the WHO do not mention the treatment after fluid resuscitation and the use of invasive or noninvasive hemodynamic monitoring or inotropic support in patients with DSS (2). Although dengue-related shock syndrome is primarily due to increased capillary permeability and the consequent hypovolemia, persistent hemodynamic instability after appropriate volume expansion requires evaluation and treatment of the associated ventricular dysfunction (37). Evaluation of cardiac dysfunctio using hemodynamic monitoring and/or management after fluid resuscitation using judicious inotropic supports in DSS children is yet to be defined and deserves further study.

4-1. Limitations of the study

There are several limitations to this study. First, this study was conducted in a single center with different samples and no matching sampling, which may limit its generalizability. Second, we did not check packed cell count (PCV) before or after fluid resuscitation as WHO guideline to detect plasma leakage, so we could not compare the hemodynamic parameters results in USCOM with PCV.

5- CONCLUSION

This study revealed that mortality was reduced by 12% during fluid resuscitation ≤ 40 ml/kg BW in dengue shock syndrome patients. Thus, the restrictive group had 53% lower mortality compared to the liberal group. There were no differences in length of mechanical ventilation and length of PICU stay. Additionally, the hemodynamic parameters (preload, inotropy, afterload, and cardiac index) were similar between two groups.

6- CONFLICT OF INTEREST: None.

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