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Early intervention of 5% albumin shown superior control of vascular integrity and function compared to ringer's lactatein hospitalized adult with grade I & II Dengue hemorrhagic fever: a multicenter randomized controlled trial in Indonesia

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Abstract

Background Dengue virus remains a major public health problem with one of the hallmark pathologies is the vascular leakage caused by endothelial dysfunction which can lead to Dengue Hemorrhagic Fever (DHF) manifestation. In the status quo, no specific therapy has been discovered but rather heavily relies on judicious and frequent monitoring of intravenous fluids administration. The current guideline has discussed the roles of fluid therapy during the Dengue Shock Syndrome (DSS) stage, however, administration of early fluid intervention for DHF grade I and II remains uncharted territory. In addition, the choice and timing of colloid administration remains underexplored. As one of the widely available colloids, 5% albumin has known physiological properties that potentially minimize plasma leakage. Therefore, this study aimed to evaluate the benefit of early intervention of 5% albumin in adults with DHF in the hope of preventing the lethal progression to DSS and further, shorten the length of stay (LOS) for patients.

Methods We conducted a multicenter, open-labeled, randomized controlled trial in Jakarta and Banten to compare the effect of early intervention with 5% albumin in adult patients with DHF compared to Ringer's Lactate (RL). Statistical analyses were conducted using unpaired t-test and Mann-Whitney for normally and abnormally distributed data respectively.

Results Adult patients with a diagnosis of DHF grade I and II that being hospitalized to receive the early intervention of 5% albumin had significantly lower levels of hemoconcentration 4, 12, and 24 h ($p=0.002$, 0.001, 0.003, respectively), higher platelet counts 4 h ($p=0.036$), higher serum albumin levels 48 h ($p=0.036$), lower proteinuria 24

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and 48 h post-albumin administration ($p < 0.001$, < 0.001, respectively), and shorter LOS ($p < 0.001$) when compared to the RL group.

Conclusion Early intervention of 5% albumin showed better control on vascular integrity and function compared to ringer lactate in hospitalized adults with grade I & II DHF, thus halting the progression of DHF into DSS and other related complications which leads to faster recovery and shorter length of stay.

Trial registration The study was registered to www.clinicaltrial.gov with trial registration number NCT04076254, and registration date October 31st 2016.

Keywords Dengue Hemorrhagic Fever, Albumin, Plasma leakage, Ringer lactate, Hemoconcentration, Colloid

Background

Dengue fever, a devastating disease caused by the dengue virus (DENV) remains a serious worldwide problem and a major burden in Indonesia [1]. Based on a global study, it was recorded that 400 million cases of dengue fever with over 22.000 deaths occurred annually, and further dengue infection becomes established both as epidemic and endemic transmission cycles [2]. The dramatic climate changes, high humidity especially in the equatorial region, and widespread urbanization all over the nation made the environment more suitable for Aedes aegypti, the host for DENV [3]. DENV is classified into the genus Flavivirus, and belongs to the Flaviviridae family, with its main characteristic being a positive-stranded ribonucleic acid (RNA) genetic material. Four strains of DENV have been discovered (DENV-1,2,3,4) and currently a new serotype, DENV-5 reported from Malaysia back in 2007 [4].

According to the worldwide epidemiology study, Indonesia has the second-highest prevalence of dengue fever among 30 dengue-endemic countries [5]. In addition, although the case fatality rate of DHF has changed significantly the number of incidences has been varying if not the trend tends to increase as a result of climate change and urbanization in Indonesia [6]. Dengue fever has a spectrum of clinical manifestations, that includes from asymptomatic, unspecified mild fever to severe DHF and DSS [7]. Although, the human immunity system can provide long-lasting protection after dengue fever infection specified into one serotype, it only gives partial and temporary effects toward other serotypes which can cause recurrence and multitude complications [8].

To date, there is no specific treatment for dengue, and it mostly relies on judicious and frequent monitoring of fluid administration with no available practical guideline changes since the release of the 1997 World Health Organization (WHO) guidelines. It was suggested that colloids can be administered if the patient remains unresponsive to crystalloid administration that is being given to manage the increase of hemoconcentration above 20% as the primary hallmark of vascular leakage [6, 7]. Patients with DHF and DSS can be treated with a variety of colloids, including 5% albumin. Albumin is a non-synthetic colloid that, due to its oncotic properties, is potent as a volume replacement. It has multiple physiological capabilities including an antioxidant, an anticoagulant, an anti-inflammatory agent, along a potent maintainer of vascular integrity [9]. Furthermore, non-synthetic colloids are known to have fewer side effects than synthetic colloids [10].

Despite years of advancements, the timing and indication for using colloid over another fluid therapy in DHF patients have not been fully elucidated. Currently, only four randomized clinical trials have explored different options of fluid therapies in DHF and DSS, but none of these trials have compared colloids such as 5% albumin specifically to crystalloids in exploring their full potency in improving vascular integrity and function in DHF patients. In addition, most trials focused on administering fluid therapy in severe DHF or DSS patients only in which widespread plasma leakage has occurred, thus limiting the benefit of fluid therapy to some extent [9–14]. This highlights that no research has tried different approaches by administering fluid therapy such as 5% albumin as an early intervention despite its various physiological potency. Thus, we conducted a first, open-labeled, multi-centered, randomized controlled trial in Jakarta and Banten, Indonesia that sought to investigate the effectiveness of early intervention of 5% albumin compared with ringer lactate as standard treatment in dengue patients' vascular integrity and function, in an attempt to prevent further progression of the hospitalized DHF grade I and grade II patients that would subsequently lead to shortening the length of stay and optimal treatment.

Methods

Aims

This study aims to evaluate the effect of early intervention of 5% albumin in comparison with RL as standard fluid therapy in dengue patients to prevent plasma leakage and its complications. This study assesses several outcomes relating to vascular integrity and function including hemoconcentration, thrombocyte level, albumin level, and proteinuria of patients that signify the progression of DHF. Further, this study also assesses the

difference in length of stay (LOS) between intervention and control populations.

Study design

This study was conducted as an open-labeled, multicenter, randomized controlled trial (RCT) using the concealment procedure. The study protocol has obtained ethical clearance from the ethics committee of *Fakultas Kedokteran Universitas Indonesia-Rumah Sakit Ciptomangunkusumo* (No.211/UN2.F1/ETIK/2016) and the study was registered to www.clinicaltrial.gov (NCT04076254).

Location, setting, and period of the study

This multicenter study was conducted in several Indonesian governments and private hospitals located in Jakarta and Banten provinces. The hospitals were as follows: Tangerang Selatan District Hospital, Hermina Ciputat Hospital, Cengkareng District Hospital, Taman Sari District Hospital, Kembangan District Hospital, and Royal Taruma Hospital. Each hospital included in our study was nationally accredited by the Indonesia Ministry of Health standard that ensures the quality of care and standard facilities for the patients. The list of hospitals included provide internal medicine specialty service and standardized laboratory examination. In addition, this research performed routine laboratories such as complete peripheral blood, urea, creatinine, lactate, and albumin that already frequently performed in this hospital.

Recruitment of patients started from January 2018 to February 2019. Grade I and II DHF patients were recruited from the emergency room or the ward by internists who were enrolled in the study team. All recruited patients are observed and managed according to medical standards, namely, hemodynamic examination, physical examination, and laboratory tests.

The population of the study

The target population of this study is hospitalized adult grade I and II DHF patients according WHO Classification of Dengue Infections and Grading of Severity of DHF 2011.

Eligibility criteria

This study included hospitalized grade I and II DHF patients between the ages of 18 and 60 who had fever within 5 days and were diagnosed with dengue infection based on positive non-structural protein-1 (NS1) and/or serological tests, and the evidence of early plasma leakage by an increased more than 10% hematocrit from baseline, with or without hypoalbuminemia.

The exclusion criteria were pregnancy confirmed by the presence of β-Human chorionic gonadotropin (β-HCG) in urine, patients in their menstrual period, patients with any of the following conditions: metabolic syndrome, hypertension, coronary heart disease, cirrhosis, sepsis, kidney failure, anemia, and malnutrition, and patients who declined to participate. List of definition are such as follows:

- Metabolic syndrome: as per the National Cholesterol Education Program Adult Treatment Panel III (NCEP AT) III guidelines that becomes the worldwide most used criteria in which metabolic syndrome is diagnosed when at least three of the following five criteria are met: waist circumference exceeding 40 inches for men or 35 inches for women, blood pressure above 130/85 mmHg, fasting triglyceride (TG) level over 150 mg/dl, fasting high-density lipoprotein (HDL) cholesterol level below 40 mg/dl for men or 50 mg/dl for women, and fasting blood sugar greater than 100 mg/dl [15].
- Hypertension: following the International Society of Hypertension (ISH) guidelines for Hypertension in 2020 similar with other major guidelines in which hypertension should be diagnosed when a person's systolic blood pressure (SBP) in a clinical setting is 140 mm Hg or higher and/or their diastolic blood pressure (DBP) is 90 mm Hg or higher after repeated measurements to all adults over 18 years old [16].
- Coronary Heart Disease (CHD): according to American Heart Association (AHA), CHD, also known as coronary artery disease (CAD), is characterized by the buildup of plaque within the coronary arteries, which supply blood to the heart muscle. This plaque buildup, known as atherosclerosis, can lead to reduced blood flow and oxygen to the heart, resulting in chest pain (angina), heart attacks (myocardial infarction), or other serious heart conditions. The diagnostic criteria encompasses clinical evaluation, stress testing, and imaging tests such as echocardiography, coronary angiography, and blood tests [17].
- Cirrhosis: The American Association for the Study of Liver Diseases (AASLD) defines cirrhosis as a consequence of chronic liver disease characterized by replacement of liver tissue by fibrosis, scar tissue, and regenerative nodules leading to progressive loss of liver function. Diagnosis is often based on a combination of clinical, laboratory, imaging, and histological findings [18].
- Sepsis: according to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), sepsis is defined as a life-threatening condition resulting from organ dysfunction caused by an abnormal response of the body to an infection. Clinically, this can be identified by an increase of 2 points or more in the Sequential [Sepsis-

related] Organ Failure Assessment (SOFA) score, which correlates with an in-hospital mortality rate exceeding 10% [19].

- Kidney Failure: according to Kidney Disease: Improving Global Outcomes (KDIGO), kidney failure can be divided into Acute Kidney Injury (AKI) and Chronic Kidney Disease (CKD). CKD is a condition characterized by a gradual loss of kidney function over time. Kidney failure in CKD is defined as a glomerular filtration rate (GFR) of less than 15 mL/min/1.73 m^2 or the need for initiation of kidney replacement therapy (dialysis or transplantation) irrespective of GFR. Meanwhile, Acute Kidney Injury (AKI) is defined as a sudden decrease in kidney function, often reversible. AKI stages range from mild to severe, with severe AKI [20].
- Anemia: is defined by WHO as a hemoglobin concentration below 110 g/L for children under 5 years old and pregnant women at sea level, and below 120 g/L for non-pregnant women. Anemia is characterized by a hemoglobin concentration that falls below a certain threshold, which varies based on factors such as age, gender, physiological status, smoking habits, and the altitude of the population being assessed [21].
- Malnutrition: the WHO defines malnutrition broadly and provides specific criteria for different forms including undernutrition (wasting, stunting, underweight) micronutrient deficiencies, overweight, and obesity. Wasting is defined as low weight-for-height, indicating recent and severe weight loss while stunting is defined as low height-for-age, indicating chronic malnutrition. In addition, underweight refers to low weight-for-age, a composite measure reflecting both acute and chronic malnutrition. Micronutrient Deficiencies are defined as deficiencies in essential vitamins and minerals, such as iron, iodine, vitamin A, and zinc. Lastly, overweight and obesity are defined as excess weight-for-height (overweight) or high body mass index (BMI) for age (obesity) [22].

Randomization

Random allocation using the block randomization method was generated by utilizing WINPEPI software, with an equal number of subjects in each block. The type of block that was chosen was a block of two in which each block was represented with at least one treatment and one control patient to ensure every block was represented proportionally.

Concealment procedure

The randomization results were encased in a non-transparent envelope. The recruitment number was written on the outside of the envelope. In the envelope was inserted a piece of paper with the coded information of which fluid therapy was administered to the subject. The envelope was opened by the investigator when the patient was about to receive the fluid therapy. The investigator, the pharmacist, and the patient were all unblinded.

Recruitment procedure

The study used a consecutive sampling of patients who met the eligibility criteria. The attending physicians recruited the potential patients. The physicians then requested the patient's informed consent to participate in this study. If the patient agreed, they were asked to sign an informed consent form. This study used grade classification by WHO in 2011. Based on WHO, the criteria for diagnosing dengue fever include (1) acute or continuous fever for 2 to 7 days; (2) manifestation of thrombocytopenia (100,000 cells/mm3); (3) hemoconcentration (increased hematocrit > 20% of the basic hematocrit value), as well as a picture of plasma leakage. Further, dengue fever is divided into two main categories which are Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF). Dengue Fever (DF) is characterized by the following symptoms such as the sudden onset of high fever, severe headache, pain behind the eyes (retro-orbital pain), severe muscle and joint pains (often referred to as "breakbone fever"), nausea and vomiting, and rash. Meanwhile, DHF is a more severe form of the disease and is divided into four grades (I to IV) based on severity. Grade I is characterized by a fever accompanied by non-specific symptoms with the only hemorrhagic manifestation being a positive tourniquet test. Grade II showed spontaneous bleeding in addition to the manifestations of Grade I. Grade III manifests several signs of circulatory failure, such as a rapid and weak pulse, narrowing of pulse pressure, or hypotension. Grade IV is signaled by a profound shock with undetectable blood pressure and pulse. Therefore, through serial multiple laboratory examinations for hematocrit level in a day, the researcher was able to group patients with grade I and II DHF and give early albumin intervention to prevent exacerbation of plasma leakage.

Interventions

All recruited subjects were observed and treated according to the standard of care of DHF management. This standard of care includes routine laboratory tests such as complete blood count, alanine transaminase, aspartate aminotransferase, and albumin. Additional laboratory examinations performed for this study include creatinine, urine, blood glucose, and urine β-HCG. All these

laboratory examinations were performed at the respective hospital that was chosen as the site of a clinical trial.

The fluid therapy was administered to the recruited subjects according to the randomization that had been initially performed. The intervention group received 5% albumin while the control group received ringer's lactate (RL). Other than the fluid therapy from the trial, both groups receive fluid therapy and other interventions in line with the WHO 1997 guidelines. The researcher, study subject, and the attending physician were not blinded in giving a fluid therapy regimen.

After the patient was enrolled in the study, RL was administered at a rate of 3–5 mL per kilogram body weight (BW) (1500–2000 mL/day) for the control group, and 5% albumin 250 mL was administered 4 h intravenously for the intervention group. Further intravenous fluid therapy was administered according to the WHO guidelines. During treatment with 5% albumin, the patient's albumin level was continuously monitored by the research team through serial laboratory measurements that were conducted twice or thrice a day and reviewed by the internist in charge who also checked the patients 'condition regularly. No significant side effects were reported during treatment. The participants of the study were observed for signs of hypovolemic shock and bleeding. Hypovolemic shock and bleeding in the study subjects were treated according to WHO guidelines.

All the study subjects were observed for their clinical conditions as well as serial laboratory examinations that included complete blood count 4,12-, and 24-hours post-intervention. The levels of serum albumin level and quantitative urine protein were measured 24- and 48-hours post-intervention. An experienced clinical pathologist supervised all these laboratory tests. A radiologist performed an abdominal ultrasonography (USG) four to five days after the patient's fever began to look for signs of further plasma leakage in the form of pleural effusion or ascites. The USG operator printed and/or wrote the abdominal USG results in the medical record.

Outcomes

The primary outcome of this study was the mean of delta hemoconcentration. This value was obtained by subtracting the highest hematocrit value and the lowest hematocrit value and then multiplied by 100% at 4,12, and 24 h post-intervention using automatic hematologic analysis Sysmex XN-1000.

The secondary outcomes of this study were delta platelets, serum albumin, proteinuria, and the length of stay. Delta platelets were defined as the thrombocyte count 4,12, and 24 h post-intervention subtracted by the baseline thrombocyte value. Serum albumin was defined as the total amount of albumin (in grams) in 100mL of serum, analyzed by using bromocresol green via Architect Plus C 8000, Abbot, or Cobas C111. Proteinuria was defined as urine protein of more than 150 mg in 24 h. Length of stay (LOS) was defined as the total number of days the patient was hospitalized, starting with the admission to the hospital until the patient was discharged by the attending physician.

The investigators entered the data into a case report form and monitored for adverse events (AE) and severe adverse events (SAE). All AE and SAE were reported to the ethics committee of each respective site. Bleeding was an expected AE, due to the pathophysiology of DHF and shock was a possible SAE as there is the possibility of disease progression from DHF to DSS.

Management of samples

As many as 6 ml of venous blood was drawn in the ER or the ward (according to the location of the study subject). As many as 3 mL of venous blood from each subject was used for the complete blood count test and another 3 mL was used for the blood chemistry test. A urine sample for quantitative protein analysis was stored in a urine container filled with toluene for 24 h. Each site's laboratory received a complete blood count, albumin, biochemistry, and urine sample.

Variables

The independent variable was the fluid therapy, which was either 5% albumin for the intervention group or RL for the control group. The dependent variables were hematocrit, platelet count, serum albumin, urine protein, and length of stay.

Statistical analysis

The data collected in this study were recorded in a case record form, clarified, and analyzed descriptively to show the baseline characteristics of the subjects. The Kolmogorov-Smirnov test was used to assess whether the data were normally distributed. The mean differences between groups were analyzed using an unpaired t-test for normally distributed data, and Mann–Whitney test for abnormally distributed data. Additional, adjusted, and subgroup analyses were not performed in this study.

Results

In total, 126 subjects were recruited in the study from January 2018 until February 2019. Out of 126 patients, only 84 patients underwent randomization due to the exclusion criteria and insurance issues. After randomization, 42 patients were assigned to the RL group and 42 patients were assigned to the 5% albumin group. There was no significant difference in patient characteristics or baseline values between the RL and the 5% albumin groups (See Fig. 1).

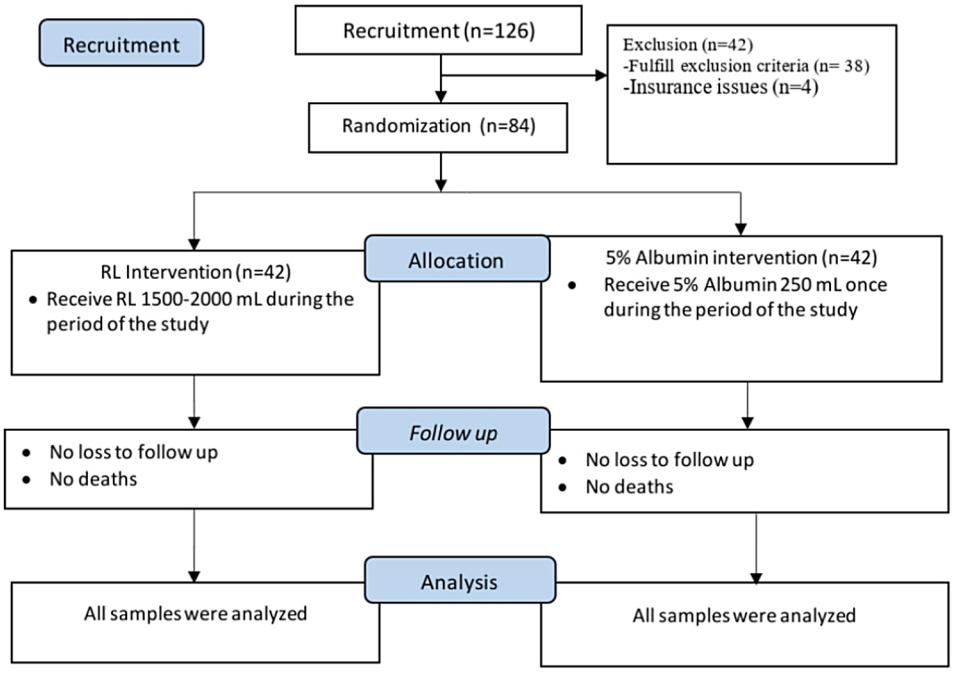

Fig. 1 The flow of the trial

Table 1 Baseline characteristics of subjects receiving early intervention with 5% albumin compared with standard care (RL)

Variable	Group	
	RL (*n* = 42)	Albumin 5% (*n* = 42)
Sex, n (%)		
Males	27 (64.3)	20 (47.6)
Females	15 (35.7)	22 (52.4)
Age (years), median (IQR)	32 (23–39)	31 (21–36)
Fever (days), median (IQR)	3 (3–4)	3 (3–4)
DHF Grade		
I	36 (85.7)	38 (90.5)
II	6 (14.3)	4 (9.5)
Infection		
Primary	13 (31.0)	6 (14.3)
Secondary	29 (69.0)	36 (85.7)
Urea (mg/dL), median (IQR)	22 (18.5–27.25)	23.5 (18.25–29.25)
Creatinine (mg/dL), median (IQR)	0.84 (0.6–1.07)	0.90 (0.70–1.17)
Baseline serum Albumin (g/dL), median (IQR)	3.72 (3.4–4.10)	3.93 (3.67–4.12)
Baseline platelet (10^3/µL), mean (SD)	113166.6 (17266.6)	110,642 (18,834)
Baseline hemoglobin (g/dL), mean (SD)	14.33 (SD 1.46)	13.94 (SD 1.52)
Baseline hematocrit (%), mean (SD)	40.50 (SD 4.38)	40.52 (SD 4.53)

Table 1 shows serial platelet counts and hematocrit values were measured every 4, 12, and 24 h post-intervention. Early intervention with 5% albumin significantly decreased the elevation of hematocrit compared to the RL group.

Table 2 Mean difference in hematocrit values between the 5% albumin and the RL groups

Mean Differences of Hematocrit (%)	Group		*p**
	RL (*n* = 42)	Albumin (*n* = 42)	
4th hour, mean (SD)	-0.34 (2.29)	-2.26 (3.19)	0.002
12th hour, mean (SD)	-0.23 (2.72)	-2.38 (2.94)	0.001
24th hour, mean (SD)	-0.71 (3.04)	-2.67 (2.79)	0.003

*Unpaired T-test

Table 3 Mean differences in platelet count between the 5% albumin and the RL groups

Mean Differences of Platelet Count (10^3/µl)	Groups		*p**
	RL (*n* = 42)	Albumin 5% (*n* = 42)	
4th hour, mean (SD)	-34,976 (20689.92)	-30,350 (23846.84)	0.345
12th hour, mean (SD)	-41,833 (28952.37)	-33109.52 (32377.29)	0.197
24th hour, mean (SD)	-45,430 (36779.43)	-27095.23 (41931.30)	0.036

*Unpaired T-test

Serial platelet counts and hematocrit values were measured every 4, 12, and 24 h post-intervention. At all-time intervals after the intervention, Early intervention with 5% albumin significantly decreased the elevation of hematocrit compared to the RL group. (Table 2).

Table 3 shows the 5%- albumin group has a significant reduction in thrombocytopenia 24 h after the intervention. Intriguingly, there was no significant difference in

thrombocytopenia between the two groups at the 4th and 12th-hour post-intervention.

Table 4 shows at the 24th and 48th-hour post-intervention, serial serum albumin and quantitative urine protein levels were measured. We found no significant difference in mean differences of albumin levels at the 24th-hour post-intervention, but a significant decrease was obtained in the 5% albumin group at the 48th-hour post-intervention.

Table 5 shows, the 5% albumin group had a significant decrease in proteinuria at all-time points. In addition, a significant decrease in the median length of stay (median: 4, IQR: 3–5) compared to the RL group (median: 5, IQR: 4–6) with a p-value less than 0.001.

Table 4 Mean differences in serum albumin level between the 5% albumin and the RL groups

Mean Differences of Albumin Serum (g/dL)	Groups		*p**
	RL (*n* = 41)	Albumin 5% (*n* = 42)	
24th hour, mean (SD)	-0.27 (0.32)	-0.15 (0.38)	0.121
48th hour, mean (SD)	-0.25 (0.37)	-0.086 (0.32)	0.036

*Unpaired T-test

Table 5 Median and inter quartile range of in proteinuria between the 5% albumin and the RL groups

Quantitative Urine Protein (mg/dL)	Groups		*p***
	RL (*n* = 42)	Albumin 5% (*n* = 40)	
24th hour, median (IQR)	230.00 (27.00–1459.00)	93.00 (6.00–768.00)	<0.001
48th hour, median (IQR)	212.00 (0.00–1625.00)	68.00 (0.00–579.00)	<0.001

**Mann Whitney

Discussion

Adults with grade I and II DHF are at risk of developing grade III and IV DHF if there is a continuation of plasma leakage. The mechanism under this phenomenon is explained by the transient progression of vascular permeability which is caused by endothelial dysfunction that occurs in the severe stage such as in grade III and IV DHF. [23] Although the vascular leakage and its pathogenesis were not yet fully elucidated, it was known that the vascular permeability was associated with vascular leakage, further creating an accumulation of fluid both in peritoneal and pleural cavities, that subsequently led to a systematic decrease of blood and pulse pressure, ultimately lead to poor organ perfusion and mortality. [24] Deeper analysis investigating the molecular process finds that complex interaction between host endothelial cells, immune response, and virus along with serotype-cross antibodies and its mediators, contribute to disruption in the barrier integrity leading to non-functional endothelial cells that produce plasma leakage. [25] Hemoconcentration becomes one of the main processes that indicates the presence of plasma leakage, and this occurred almost always in the case of classic DHF and becomes even more prominent in patients with severe DHF and shock. [26]

A research conducted by Singhi et al. suggested that if there is an increase in hematocrit > 10% or the hematocrit level has reached 50% or more, clinicians need to be aware of plasma leakage. It was reported that plasma leakage already occurred at the early phase of the infection which can be observed when the hematocrit level increases 10% compared to normal parameters.1 In addition, according to WHO grade classification in 2011, the increase of hematocrit level reaching 20% above normal level signifies the impending dengue shock syndrome2 in which the purpose of early intervention cannot be achieved. Therefore, through serial multiple laboratory examinations for hematocrit level in a day, the researcher was able to group patients with grade I and II DHF and give early albumin intervention to prevent exacerbation of plasma leakage. [27]

In adults with grade I and II DHF, early intervention with albumin at 5% significantly reduces hemoconcentration at 4,12, and 24 h post-intervention compared to the RL group. This indicates that the administration of 5% albumin may prevent additional plasma leakage and show superior results compared to crystalloid in this case RL. This observation can be explained by the oncotic features of colloid, which is its capacity to generate plasma expansion by maintaining intravascular volume for an extended period while retracting previously extravasated fluid through exerting an increase of oncotic pressure. [9] In addition, the anti-inflammatory and antioxidant properties of albumin may mitigate the damage to the surface of vascular endothelial cells induced by cytokines, NS1-DENV, and the activation of complement factors. [8] This suggests that, while other colloids may be able to normalize hematocrit values rapidly, [9–12] the physiological function of albumin may provide advantages in DHF patients when compared to other commonly used colloids which also warrant further molecular investigation and clinical trial.

The given 5% albumin is unlikely to pass the transcellular and paracellular gap within the vascular endothelium due to its physiological role. Despite albumin having a net negative charge, its amphoteric properties allow it to bind closely to the glycocalyx. This binding effectively reduces hydraulic conductivity across the vascular barrier, protects against glycocalyx degradation (preventing shedding), and helps maintain vascular integrity and normal capillary permeability, as well as facilitating the transmission of shear stress. Thus, albumin can retain a longer time within endothelium to exhibit its function to maintain oncotic pressure within the vessel, subsequently

retaining the fluid and preventing leakage. [28] Further, albumin exerts immunomodulatory and anti-inflammatory effects by binding bacterial products, influencing the function of antigen-presenting cells, modulating cytokine production, and decreasing the expression of hypoxia-inducible factor-1α, which is typically upregulated in response to low oxygen levels. All these mechanisms subsequently help the recovery of patients. [29]

This study also found that early intervention with 5% albumin significantly reduced thrombocytopenia 24 h after intervention compared to the RL group. A prior study found no significant differences in mean platelet count during admission and after hospitalization. [11] While, other fluid resuscitation trials on DHF and DSS patients did not measure thrombocytopenia as an outcome. [10–14] The reduced platelet count can be explained by the effect of albumin on platelets. Albumin has anticoagulant and anti-aggregation properties. Albumin binds anti-thrombin, which increases the neutralization of coagulation factor Xa. Albumin also binds with platelet-aggregating molecules such as arachidonic acid, thromboxane A2, platelet-activating factor (PAF), and prostacyclin. [30] While thrombocytopenia may not be associated with bleeding events during the disease, [31] sequential platelet count was found as a significant predictor of progression to DSS in children. [32] This suggests that early intervention with 5% albumin may prevent DHF from progressing to DSS.

Early intervention with 5% albumin in DHF patients was also found to significantly decrease hypoalbuminemia compared to the RL group in 48 h post-albumin administration. Most dengue fluid therapy trials did not measure serum albumin post-intervention. In addition, only one study [10], found that serum albumin levels were not significantly different between groups on trial that used four different IV therapies which includes colloids (protein digest gelafundin 35,000 or dextran 70) or crystalloids (0.9%-weight/volume saline or Ringer's lactate). It should be remarked that in another study, instead of 5% albumin, hyperosmolar sodium lactate (HSL) was used in the intervention group. [12] Hyperosmolar sodium lactate and most colloids are not known to affect endothelial integrity, whereas albumin does. Albumin is one of the hallmarks of plasma leakage. It is well known that the transcapillary escape rate of albumin significantly increased 48 h after inflammation. [33] Interestingly, early intervention with 5% albumin significantly decreased hypoalbuminemia, implying that 5% albumin has a repairing effect on the endothelium through plasma expansion and decreasing the rate of transcapillary escape. [34]

Based on the observation, it shows that early intervention with 5% albumin significantly reduced proteinuria at 24- and 48 h post-intervention in Grade I and II DHF adult patients compared to the RL group. Current research has proposed that proteinuria can be used as a prognosticating adult dengue patient with a high level of sensitivity and specificity. [35] Proteinuria should be highlighted since it can predict the severity and likely development of DHF to DSS, as well as identify patients with DHF who require close monitoring. [36, 37] Despite this finding, proteinuria was not measured in the majority of DHF resuscitation fluid studies. [10–13] Proteinuria in DHF can be explained by the vascular endothelial glycocalyx dysfunction in the glomerulus and proximal tubules, as well as microvascular hypoxia caused by plasma leakage. [8] This suggests that early intervention with 5% albumin could possibly repair and maintain vascular integrity, thereby reducing plasma leakage. Therefore, early intervention with 5% albumin may prevent the progression of DHF to DSS, which is characterized by a decrease in proteinuria.

Up until now, 5% albumin has not been investigated in many RCT. [10–13] According to a large-scale trial, 5% albumin and saline were both equally effective for intravascular volume resuscitation. However, it should be noted that this was a large-scale trial conducted in a heterogeneous population of Intensive Care Unit (ICU) patients, not specifically for DHF or DSS patients, and its effect to prevent further plasma leakage cannot be generalized from its outcome. [38] In addition, not only judicious reasoning between the usage of crystalloid or colloid is needed, but another conundrum arises in choosing between natural or synthetic colloid. Albumin is a natural colloid with various advantages over synthetic colloids like dextran, gelatin, and starch. Non-synthetic colloids have fewer side effects of pruritus, anaphylactoid responses, and coagulopathy. [39] Albumin also has anti-inflammatory, ligand-binding, and antioxidant properties. Therefore, albumin has potential advantages over other commonly used synthetic colloids due to its innate physiological properties. Albumin's function may allow it to be used not only as a symptomatic volume replacement but also as a preventive and curative approach to DHF patients.

Early intervention with 5% albumin significantly decreased the LOS in patients following early intervention with 5% albumin. Another problem relating to this scope of outcome is that most fluid resuscitation trials in dengue infection did not include the LOS as a study outcome. [10–13] One of the research found that DHF as a relatively high cost of illness that includes both direct and indirect costs, also further concludes that the correlation between the LOS in the cost of hospitalization was significant in DHF patients. [40] Therefore, LOS should be more highlighted as it possibly generates more cost-effective treatment for patients and hospitals.

Although Ringer Lactate still offers benefits in managing grade I and grade II DHF adult patients, the superior benefit of 5% albumin shown by this RCT should have its spotlight and be further taken into consideration. Despite these promising findings, 5% albumin is still not widely available in many healthcare facilities due to its high cost. It is important to note that Indonesia has one of the world's highest dengue infection economic burdens, with hospitalized care accounting for 90% of the cost. [41] This potential cost-effective treatment relies on the albumin's function in maintaining vascular integrity along with its physiological properties that enhance the recovery progress, prevent the lethal progression of DHF to DSS, and further reduce the number of administrations to the ICU subsequently cutting the need for intensive treatment. [30] Therefore, further research with a larger scale is warranted on how early intervention with 5% albumin can deliver cost-effective treatment to patients and hospitals, and be further implemented in guidelines.

To the best of our knowledge, this is the first RCT in Indonesia that uses 5% albumin as an early intervention in DHF. We conducted a multi-centered randomized controlled trial, in which the randomization was done using a computer, resulting in equal characteristics in both groups. The analysis was carried out using the Intention-to-Treat (ITT) technique, which is a pragmatic analysis technique used in clinical trials. The external assessment was also conducted objectively. Therefore, this study has good internal validity. However, it was not possible to conduct a double-blinded study. This was because the dosage form and the packaging of 5% albumin and ringer's lactate were different and the researcher could not alter the packaging as both fluids were already in a sterile condition. Hence, we conducted an open-labeled study. We recommend that future trial to be conducted in pediatric populations since the mortality rate of DENV infection and the prevalence of DSS is higher in children.

Conclusion

Early intervention with 5% albumin significantly decreased hemoconcentration, thrombocytopenia, proteinuria, and increased serum albumin levels, as well as the shortened length of stay in adult with grade I and II DHF, compared to RL. The findings suggest that the early intervention with albumin may aid in maintaining vascular integrity during plasma leakage and potentially preventing DHF from progressing to DSS.

Abbreviations

AE	Adverse events
β-HCG	β-Human chorionic gonadotropin
BW	Body Weight
DENV	Dengue Virus
DHF	Dengue Hemorrhagic Fever
DSS	Dengue Shock Syndrome
HSL	Hyperosmolar Sodium Lctate
ICU	Intensive Care Unit
ITT	Intention-to-Treat
LOS	Length of Stay
NS-1	Dengue Non-Structural Protein-1
PAF	Platelet-Activating Factor
RCT	Randomized Controlled Trial
RL	Ringer's Lactate
RNA	Ribonucleic Acid
SAE	Severe Adverse Events
USG	Ultrasonography
WHO	World Health Organization

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Author contributions

RB conveyed the whole trial and was involved in the protocol design, data collection, data interpretation, and the writing of this manuscript. SS was involved in the design of the study protocol and acted as the main advisor of the trial. HP was involved in the design and an acting supervisor of the trial. JP was involved in the data analysis of the trial. HAR was involved and the data collection and sample management of the trial. BED was involved in the design of the study protocol and acted as supervisor of the trial. MS was acting as supervisor of the trial. AR was an acting supervisor of the trial and was involved in the substantial revision of the manuscript. HY was an acting supervisor of the trial.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethics was approved by the ethics committee and the authors made sure the study was conducted by the principles listed in the Declaration of Helsinki and the authors made sure the study was conducted following the ICH Guidelines for Good Clinical Practice. All participants enrolled in this study gave their written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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