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Original Article

Comparison of blood plasma and gelatin solution in resuscitation of children with dengue shock syndrome

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Abstract

Background Dengue shock syndrome (DSS) is characterized by severe vascular leakage and hemostasis disorder. It is the cause of death in 1 to 5 percent of cases. WHO management guidelines for resuscitation remain empirical rather than evidence-based.

Objective To find out the alternative fluids to replace plasma leakage in DSS.

Methods We performed a prospective study and randomized comparison of plasma and gelatin solution for resuscitation of Indonesian children with DSS. We randomly assigned 25 subjects with DSS to receive plasma and 25 children to receive gelatin fluid. Statistical analyse were performed using chi-square test, Fisher's exact test, t test, Mann-Whitney test.

Results The increment of pulse pressure width and the decrement of hematocrit in subjects treated with gelatin were higher than that of plasma at four-hour therapy ($P=0.002$ and $P=0.017$). Only one patient died caused by unusually manifestation of DSS. The increment of body temperature in subjects treated with plasma was higher than that of gelatin at four-hour therapy ($P=0.011$). The decrement of platelet count in subjects treated with gelatin were less than that of plasma ($P=0.018$). The increment of diuresis rate in subjects treated with gelatin was higher than that of plasma at twenty-hour therapy ($P<0.0001$). The decrement of respiratory rate in subjects treated with gelatin was higher than that of plasma at twenty-eight hour therapy ($P=0.018$). There was no difference in studied variables : total volume rate, blood pressure, pulse rate, re-shock rate, clinical fluid overload, allergy reactions, bleeding manifestations, and length of stay ($P>0.05$).

Conclusions Gelatin solution can be used as volume replacement in resuscitation of DSS if blood plasma is not available especially at four- hour therapy. **[Paediatr Indones. 2009;49:322-9]**

Keywords: *Dengue shock syndrome, resuscitation, gelatin, plasma.*

Diagnosis of dengue hemorrhagic fever (DHF) is based on diagnosis criterion of WHO (1997).[1] Dengue shock syndrome (DSS) is a severe manifestation of DHF. It is a health problem in tropical Asia and America which causes morbidity and mortality in children and DHF accompanied with shock is still an emergency problem in Indonesia and it is the main cause of death.[2-7] In Sardjito Hospital, there was 6.5% patient found death with DSS grade III and 18.2% patient with DSS grade IV since 1987 to 1989.[6] World Health Organization (WHO) reports the mortality rate of DSS among children was 1 to 5 percents.[8]

Prompt restoration of the volume plasma circulation is the cornerstone of DSS therapy due to the poorly understood of the pathophysiology and mechanisms underlying the vascular leakage, therefore no specific treatment is available.[4,8] WHO management guidelines, first proposed in 1975, recommend crystalloid solutions initially as a

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replacement of plasma loss, followed by boluses of colloid for patients with recurrent or refractory shock.[9] Theoretically, blood plasma therapy is ideal for the vascular leakage, but it has disadvantages such as transmitting diseases, allergic reactions, anaphylactic reactions, graft versus host disease. In addition to the limitation of Indonesian Red Cross (IRC) providing plasma, there is no IRC facilities provided in fringe areas.[6,10] On the other hand, nowadays, there are still difficulties to find proper donors in immediate time. Therefore, alternative solutions such as synthetic colloid, is needed. However, most colloid solutions have adverse effects on coagulation factor, renal, liver, and fluid accumulation.[6,10]

Gelatin solution is a plasma substitute which is a colloid that used to resuscitate patients with hypovolemic shock.[11] WHO use gelatin solution as one of colloids for DSS management.[12] Nhan et al reported that gelatin solution for DSS resuscitation in Southern Vietnam is better than Ringer lactate® and normal saline to recover pulse pressure.[13] Gelatin solution is better than Starch® and Dextran® solution base on anaphylactic reactions, coagulations effects, renal dysfunction, liver dysfunction or fluid accumulation.[10,12] Compare with plasma, gelatin has no adverse effects such as transmitting diseases, graft versus host disease. It is cheaper than plasma and easy to provide at anytime. We tested whether blood plasma could be replaced by gelatin solution if blood plasma was not available. However, we used the established WHO format with initial infusion with RL for primary resuscitation followed by colloid such as: gelatin solution or plasma among Indonesian children with DSS in R.D. Kandou Hospital in Manado, Indonesia.[1]

Methods

The study was a single-centered, randomized, comparison of blood plasma and gelatin solution for fluid resuscitation of children with DSS and it was conducted in the pediatric intensive care unit from February to May 2007 at the R.D. Kandou Hospital in Manado, Indonesia. Gelatin solution used was gelofusin solution and blood plasma was provided from the Indonesian Red Cross in Manado. Inclusion criteria were all patient diagnosed as DSS (DHF grade III & IV) based on WHO criteria (1997)[1], the parents agreed to join the study. Patients who had history of hypersensitivity of blood transfusion and gelatin solution, or who had been given fluid resuscitation with crystalloid and/or colloid before admitted to the hospital or rejected to participate in the study were excluded. The study protocol was approved by the Ethics Committee of the hospital.

Clinical procedures. The patients were randomly assigned to receive either plasma or gelatin solution. At the beginning of the study, we recorded demographic data, history (duration of fever, bleeding manifestation, vomits, abdominal pain, diarrhea, headache), examination findings (general condition, consciousness, blood pressure, pulse pressure, pulse rate, respiratory rate, body temperature, liver size), laboratory findings (hematocrit, platelet count, IgM and IgG Rapid Strip Test) and blood compatibility test (cross-match) was done to prepare blood plasma and whole blood for transfusion, and examined blood ureum and creatine.

The patient was given RL solution 20 ml/kg immediately (in 30 minute maximum) until the patient was not in shock (pulse pressure $\geq$ 30 mmHg) and could be repeated once more if the patient was still in shock. After pulse pressure $\geq$30 mmHg, we performed physical examination (general condition, consciousness, blood pressure, pulse pressure, pulse rate, respiratory rate, body temperature, liver size) and laboratory examination (hemotocrit) before starting to study the fluid (Ho). Then each subject was given 10 ml/kg/hour of blood plasma or gelatin solution for over one-hour period, followed by RL solution of 10 ml/kg/hour until the subject was stable, in 24 hours maximum. Blood pressure, pulse pressure, pulse rate, respiratory rate, body temperature, diuresis were monitored per hour for 24 hours minimum until the general condition stable. The capillary hematocrit was measured at every four-hour baseline after the study entry or in the event of cardiovascular deterioration. Platelet count was measured every 12 and 24 hours.

Fluid overload manifestation (palpebral edema, ascites, ronchii or wheezing on both lung) were also monitored every time. The patient was stable (systolic blood pressure $\geq$ 80 mmHg, pulse pressure $\geq$30 mmHg, diuresis $\geq$ 1 ml/kg/hour, and hematocrit $\leq$ 40%) for at least 8 hours, RL 10 ml/kg/hour decreased to 7 ml/kg/hour (1x4 hours minimum), then to 5 ml/kg/hour

(1x4 hours minimum), then to 3 ml/kg/hour (1x4 hours minimum) and decreased to 8 drips/ minute. Whenever subjects became unstable, blood plasma or gelatin 10 ml/kg/hour (total maximum 30 ml/kg) was administered. Subjects who had reshock were given RL 20 ml/kg immediately. Subjects who had severe anaphylactoid reactions must be excluded. Ionotrops, blood transfusions, diuretics and other therapy could be given depend on clinical condition.

Outcome measurements. Data were recorded since the subjects were admitted to the hospital, at that time subjects would have received RL 20 ml/kg, (subjects would receive either blood plasma or gelatin solution), while patients were receiving RL solution 10 ml/kg/hour, 7 ml/kg/hour, 5 ml/kg/hour, 3 ml/kg/hour, 8 drips/kg/hour, or whenever subjects complained about side effects and showed symptoms and sign.

Statistical analysis. All data were processed and analyzed with SPSS version 15.0 for Windows. To analyze the comparison between general examination such as; systolic blood pressure, diastolic blood pressure, pulse pressure, pulse rate, respiratory rate, body temperature, hematocrite, diuresis, decreased platelet count, total fluid volume, the subjects' length of stay in the hospital and blood plasma or gelatin solution in DSS patients, we used t-test or Mann-Whitney test. The first step was that we performed data normality test using Kolmogorov-Smirnov test.

Table 1. Baseline characteristics of study subjects

Characteristics	Plasma (N= 25)	Gelatin (N=25)
Age (yr)		
Mean	6.9	7.1
Male Sex	12	13
Body weight (kg)	22.06	22.71
Ab response		
Primary	0	0
Secondary	21	19
Day of illness at shock (day)		
Mean	5	4
Bleeding manifestation (mucous)		
Epistaxis	3	3
Hematemesis	0	0
Mean	0	4
Bleeding gum	2	0
Liver size (cm)		
Mean	2.0	2.0
Systolic blood pressure (mmHg)		
Mean before RL 20 ml/kg	90.00	90.00
Mean after RL 20 ml/kg	100.00	100.00
Diastolic blood pressure(mmHg)		
Mean before RL 20 ml/kg	76.67	76.75
Mean after RL 20 ml/kg	70.00	70.00
Hematocrit %		
Mean before RL 20 ml/kg	48	48
Mean after RL 20 ml/kg	42	41
Platelet count x10^3 /mm3		
Mean	69.48	67.00

Statistical analysis: [a]t-test, [b]chi-square test, [c]Fisher's exact test, [d]Mann-Whitn ey test

Results

During 1 February to 1 May 2007, a total of 51 subjects were recruited in the study, and all had received their designed study fluid. From 51 subjects, one subject dropped out of complications (dengue encephalopathy, pulmonary edema and massive bleeding). Out of 50 subjects, 25 of them received blood plasma and other 25 received gelatin solution and all of them fully recovered. Baseline characteristics of the subjects were well-balanced among the fluid treatment groups and there were no significant difference between plasma group and gelatin solution group (**Table 1**).

The median of total fluids used by plasma group was approximately 140 ml/kg. It was the same as those that were used by gelatin solution group (**Table2**).

Hemodynamic variables

Administration of all the fluid types showed significant improved hemodynamic variable, such as systolic blood pressure, diastolic blood pressure, pulse pressure, pulse rate, hematocrit and diuresis on both groups. For pulse pressure variable, t significant difference such as higher increament of the width of pulse pressure in subjects received gelatin than that of plasma at four-hour therapy, using Mann-Whitney test, P=0.002 (**Figure 1**) and remained stable until 48 hour

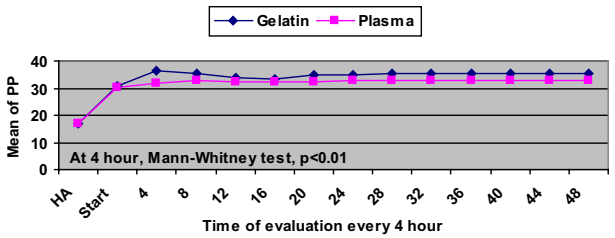

Figure 1 Curve of pulse pressure in gelatin group and plasma group during fluid

Table 2. Main Outcome Measurements

Characteristics	Plasma (N= 25)	Gelatin (N=25)	P
Total volume of iv fluid infusion (ml/kg)			
Mean	140	140	0.389[a]
Platelet count (x 10^3 cells/mm^3)			
Mean before fluids tretment	69.48	67.00	0.670[b]
Mean after treatment 12 hour	37.04	46.96	0.048[b]
Mean of decreased in 12 hour	32.44	20.12	0.018[b]
Re-shock state			
Number of reshock	1	0	1.000[c]
Average time to reshock (hour)	20	0	-----
Clinical fluid overloa	2	0	0.49[0c]
Allergic reactions			
Mild	1	1	1.000[c]
Severe	1	0	1.000[c]
Bleeding manifestation (mucous)			
Epistaxis	0	0	----
Hematemesis	0	0	----
Melena	3	2	0.235[c]
Bleeding gum	1	0	0.490[d]
Lengh of hospital stay (day)			
Mean	3.00	3.00	0.389[a]

Statistical analysis: [a]Mann-Whitney test, [b]t-test, [c]Fisher's exact test, [d]chi-square test,

treatment with no significant difference afterwards.

From the hematocrit variable, there was also significant difference in higher decreament of hematocrit, in subjects received gelatin than than that of plasma at four-hour therapy, using Mann-Whitney test, P=0.017 (**Figure 2**).

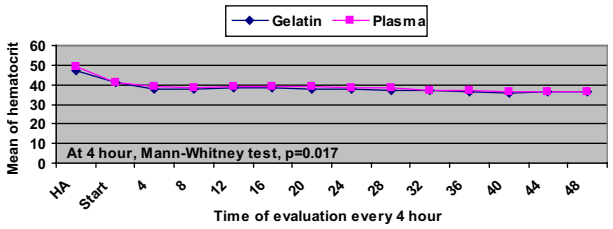

Figure 2. Curve of hematocrite in gelatin and plasma groups during fluids treatment

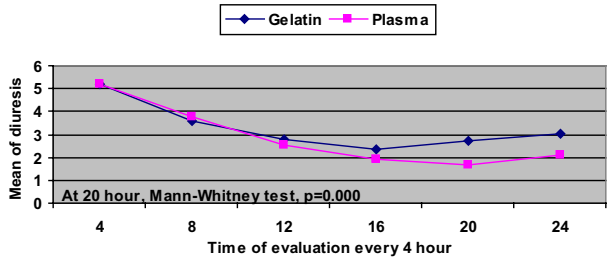

Figure 3. Curve of diuresis in gelatin and plasma groups during fluids treatment

Different from previous hemodynamic variables, diuresis variable was just significantly different after 16-hour therapy, and culminating at 20-hour therapy. Gelatin solution group had higher diuresis rate than that of plasma group in convalescent phase, using Mann-Whitney test, P<0.0001 (**Figure 3**).

Nevertheless, there was no significant difference between plasma and gelatin solution groups in systolic blood pressure variable (**Figure 4**), diastolic blood pressure (**Figure 5**) or pulse rate (**Figure 6**) using Mann-Whitney test and t-test, P>0.05.

Hematologic Variable

Out of 50 subjects with DSS, there were lower decreament of platelet count in gelatin solution group than that in plasma group (20,120/mm^3 and 32,440 / mm^3), using t-test, P=0.018 (**Tabel 2**).

Possible complications of fluid treatment

Recurrent shock was recorded only in one subject receiving blood plasma at 20-hour treatment. Clinical fluid overload were found in three subjects receiving blood plasma who were treated with furosemide. One of the sign of clinical fluid overload was the increment of respiratory rate. Decreased respiratory-rate during therapy indicated there were improvement of clinical

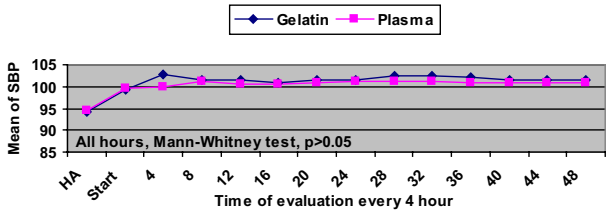

Figure 4. Curve of systolic blood pressure in gelatin and plasma groups

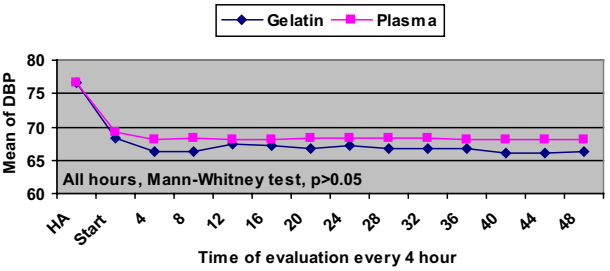

Figure 5. Curve of diastolic blood pressure in gelatin and plasma groups

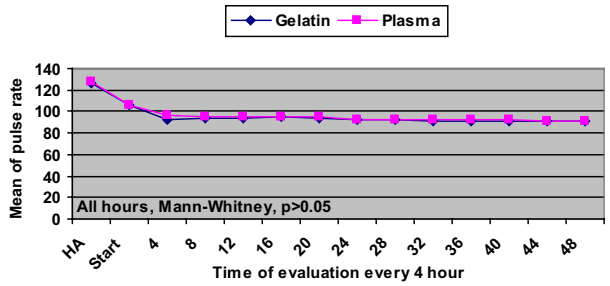

Figure 6. Curve of pulse rate in gelatin and plasma groups

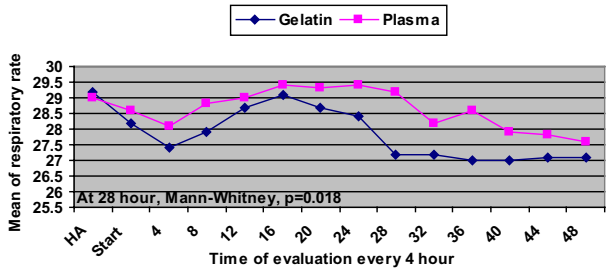

Figure 7. Curve of respiratory rate in gelatin and plasma groups

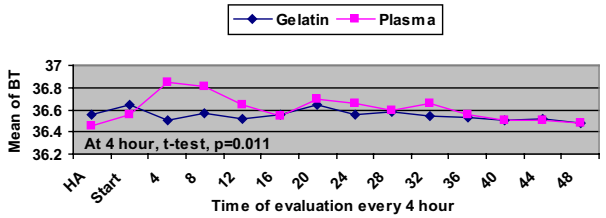

Figure 8. Curve of body temperature in gelatin and plasma groups

fluid overload. We found respiratory-rate decrement in gelatin group during therapy which was significantly higher than that in plasma group at 28 hours in convalescent phase (**Figure 7**).

There was significant difference (using Mann-Whitney tes, P=0.018). Three subjects in the study had allergic reaction. An urticarial rash without fever developed in one subject in each of both groups as mild allergic reaction and one subject had severe allergic reaction (urticarial rash, fever and dropped blood pressure after receiving blood plasma. All had been treated by oral anti-histamines for mild allergic reaction and diphenhydramine-HCl intravenously for severe allergic reaction (**Table 2**). During the study, an excess of febrile response occurred in plasma group. Increased body temperature in plasma-group was significantly higher than gelatin solution-group especially at four-hour treatment (**Figure 8**).

Out of 50 subjects with DSS during fluid treatment, we found three subjects had melena in plasma-group, two subjects in gelatin solution-group. Bleeding gum was recorded in one subject in plasma group. Epistaxis and hematemesis were not found in both groups (**Table 2**). However, there were no significant difference among the fluid treatment groups in the developing of new bleeding manifestation, clinical fluid overload, and allergic reaction, P>0.05 (**Table 2**).

Average length of hospital stay in gelatin-group was shorter than that in plasma-group, but both groups had the same mean number (3.00 and 3.00), and no significant difference, using Mann-Whitney test, P>0.05 (**Table 2**).

Discussion

The general introduction of intensive fluid treatment intravenously in DSS more than 25 years ago led to a marked reduction in the mortality rate in the best pediatric centers, from approximately 20% to 2%. However, there has been no consensus on which intravenous fluid should be used.[14]

Colloid solution is usually given to prevent plasma leakage and to have normal rebound hemodynamic in patient with DSS.[6,13,15] Re-shock state that occurred before six hours from the onset of the

disease has the worst of prognosis.[6] In this study we compared blood plasma as natural colloid and gelatin solution as synthetic colloid. We wanted to know the benefits and side effects of each fluids in the study. Indicators were used in the study were total fluids volume, hemodynamic variables, new bleeding manifestation development, clinical fluid overload, re-shock state, allergic reactions, length of hospital stay. From this study, we found increased systolic blood pressure, decreased diastolic blood pressure and increased width of pulse pressure in gelatin recipient which were higher than that of plasma recipient. Pulse pressure variable was significantly difference between both groups at four-hour treatment ($P<0.01$). There was an increment of mean pulse pressure to 10 mmHg, but afterwards no significant difference was noted. This fact was correlated with the half life of both substances. Gelatin has four hours of half life and plasma albumin has 3.5 to 4.5 hours.[15-16] From previous studies, Dung et al reported increased pulse pressure in gelatin recipient was 16.9 mmHg (range 10.7-23.2) after two-hour treatment. The difference of the value was caused by giving gelatin from the first hour of resuscitation.[14] Nhan et al[13] reported pulse pressure recovery-time in gelatin-group was the same as dextran and better than RL® and normal saline.

Pulse pressure is the most significant factor predicting the clinical response to resuscitation in DSS.[13] Decreased hematocrit in gelatin solution-group at four-hour treatment was 3.68% and plasma group was 2.58%. Decreased hematocrit in this study was less than reported by Nhan et al[13] at one-hour treatment (9.7%) and by Dung et al[14] at two-hour treatment (7.1%). Different methods in these studies caused different results in hematocrit decrements including our study. After four-hour of fluid treatment, mean of diuresis in gelatin solution-group continued to fall down until the 16th hour and then became relatively stable. In contrast, mean diuresis in plasma group continued to fall down until the 20th hours, causing significant difference to mean diuresis at the time. All these findings showed gelatin was better to improve hemodynamic in patients with DSS than plasma solutions.

Current theories of microvasculer ultrafiltration support the basic Starling principle of a balanced equilibrium between opposing oncotic and hydrostatic pressure, but postulate the glycocalyx, rather than the endothelial cells, to be the major regulator of fluid flow. There is good evidence that plasma proteins, particularly albumin, absorbed to positive residues in the glycocalyx layer and restrict ultrafiltration.[8] Theoretically, one gram of albumin has an oncotic force to bind 18 water molecules and one gram of gelatin has oncotic force to bind 14 water molecules, it shows that oncotic force of plasma is stronger than gelatin.[15] However, oncotic force of blood plasma is different with synthetic albumin because the number of albumin in human blood plasma is only 3.5 to 5.0 mg/dl approximately and different for each individual.[17] It also means oncotic force of blood plasma in each individual is varied. Therefore blood plasma and gelatin solution may be equal in oncotic force for resuscitation in patient with DSS. These facts are supported by the study reported by Samsi et al. Samsi et al found that weight of the fluids molecule did not always correlate with size of the fluid molecule. They found that the size of gelatin molecule was the biggest among the others, as follows: gelatin 30.000Da, HES 200.000Da, HES 70.000Da, and Dextran 40.000Da. Although weight of HES molecule (200.000Da) was 6.7 times bigger than the weight of gelatin molecule (30.000Da), but the size of gelatin molecule was 100 times bigger than the size of HES molecule (200.000Da) out of its plate shape. Its shape causes sealing effect in the microvascular endothelial cell and reducing outward flux.[18] Its phenomena causes decreased of platelet cells consumptions in gelatin group which were less than plasma-group and explains why decreased platelet cells count in patients in gelatin solution-group were significantly lower than patients in plasma-group. As it is known that patient with DSS has increased platelet cells consumption.[6,19-20]

These are good evidences to explain why gelatin solution is better than blood plasma to stabilize hemodynamic variables in patients with DSS and may explain how gelatin solution remain longer in intravascular space in patients with DSS than that of plasma. The facts also may explain why patients with DSS in gelatin solution-group will need less total volume of fluids and fewer clinical overloads than that of plasma group. Thus frequency of respiratory rate rapidly fall down in gelatin recipient than in plasma recipient in convalescent phase and caused significant difference in respiratory-rate at 28 hour treatment.

During study, side effects of allergic reaction

occurred in both groups. One mild allergic reaction occurred in each group but there was also one severe allergic reaction in plasma group. Allergic reaction in plasma group was caused by protein intake as antigen and in gelatin group may occurred as allergic-type I reaction which histamin will play a role as mediator in anaphylactic reaction to gelatin urea linked and polygeline.[11,21] Darell et al[22] reported number of allergic reaction was 1%. In any previous literatures, allergic reaction was reported in gelatin group (0.38%)[16] and severe anaphylactic reaction was 0.038%. It was less than HES (0.058%).[11] Multicenter studies in Germany reported that incidence of allergic reaction in gelatin group was 0.115%.[23] Febrile response in plasma recipient might be caused by either bacterial or non endotoxin pyrogens.[12]

Gelatin costs approximately 150,000 IDR/bottle (500ml), while plasma costs approximately 150,000 IDR/ bag (150 ml). Thus gelatin is cheaper than plasma.

The limitation of this study was that the definitive diagnosis was only based on WHO criteria without DEN virus isolation. As we know, grade of virus virulency correlates with serotype of DEN virus.[6]

In conclusion, most of children with DSS respond well to judicious treatment with blood plasma and gelatin solution. Gelatin solution can be used as volume replacement in DSS resuscitation if blood plasma is not available, especially in the first four-hour treatment. On the other side, Gelatin is cheaper than plasma and it is relatively available at any time.

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References

1. WHO. Dengue haemorrhagic fever: diagnosis, treatment, prevention and control. 2nd ed. Genewa:WHO; 1997.
2. Halstead SB. Epidemiology of dengue hemorrhagic fever. In: Gubler DJ, Kuno G, editors. Dengue and dengue haemorrhagic fever. Walingford, England: CAB International, 1997: p. 23-44.
3. Srisakul CK, Suchitra N, Ananda N, Donald SB. Evidence that maternal dengue antibodies are important in the development of dengue hemorrhagic fever in infant. Am J Trop Med Hyg. 1988;38:411-9.
4. Sumarmo. Demam berdarah dengue pada anak. [Dissertation]. Jakarta: UI Press, 1983.
5. Gubber DJ. Dengue and dengue hemorrhagic fever. Clin Microbiol Rev. 1998;11:1-14.
6. Sutaryo. Dengue. Yogyakarta : Medika FK UGM, 2004; p. 4,32,65-78,156-83,184-207.
7. Djoharman S, Samsi TK. Demam berdarah dengue berat dengan konfirmasi virologik. CDK edisi khusus. 1992;81:40-3.
8. Wills BA, Dung NM, Loan HT, Tam DTH, Thuy TTN, Minh LTT, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. N Engl J Med. 2005. [cited on 2006 Januari 22] 353:877-89. Available from http://nejm.org.
9. WHO. Technical guides for diagnosis, treatment, surveillance, prevention and control of dengue haemorrhagic fever. Technical advisory committee on dengue haemorrhagic fever for South-East Asian and Western Pacific Region; 1975.
10. Setiati TE. Pengelolaan syok pada demam berdarah dengue. In : Sutaryo, Pudjo HW, Mulatsih S. Tatalaksana syok dan perdarahan pada DBD. Yogyakarta : Medika FK UGM, 2004; p. 75-85.
11. Ong EL. A case of hypersensitivity to gelafundin. Singapore Med J. 2001;42:176-7.
12. WHO. Guidelines for treatment of dengue fever/dengue haemorrhagic fever in small hospital. New Delhi : WHO, Regional Office for South East Asia, 1999; p. 1-10.
13. Ngo NT, Cao XT, Kneen R, Wills B, Nguyen VM, Nguyen TQ, et al. Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. Clin Infect Dis. 2001:32:204-13.
14. Dung NM, Day NP, Tam DT, Loan HT, Chau HT, Minh LN, et al. Fluid replacement in dengue shock syndrome: a randomized, double-blind comparison of four intravenous-fluid regimens. Clin Infect Dis. 1999;29:787-94.
15. Putjiadi A. Koloid dan kristaloid. In :Trihono P, Purnawati S, Syarif DR. Hot topics in pediatrics II. Jakarta, 2002; p. 121-33.
16. Composition of colloid solutions and blood products. 2006. [cited on 2006 October 14]; 1:4. Available from : http://homepage.ed.ac.uk/asb/SHOA2/composition-of-colloid-solutions.htm.

17. Ganong WF. Buku ajar fisiologi kedokteran (translation). 17th ed. Philadelphia: WB Saunders, 1999; p. 523-4.
18. Samsi MK, Yang JS. Tidak adanya hubungan langsung berat molekul dengan besarnya ukuran molekul cairan koloid untuk resusitasi sindroma syok dengue. In: Sadjimin T, Juffrie M, Julia M, Wibowo T,editors. Abstract PIT IKA III,2007. Yogyakarta : PIT IKA III IDAI/Bagian IKA FK-UGM/Institut Kesehatan Anak RSUP Dr. Sarjito, 2007; p.17.
19. Sumarmo. Infeksi virus dengue. In : Sumarmo, Garna H, Hadinegoro SRS,editors. Buku ajar ilmu kesehatan anak. Jakarta :Bagian ilmu kesehatan anak FKUI, 2002; p.177-208.
20. Rampengan TH. Demam berdarah dengue. In : Rampengan TH, Laurents IR, editors. Penyakit infeksi tropik pada anak. Jakarta : EGC, 1992; p.135-55.
21. Dronen SC. Plasma and volume expanders. In : Barsan WG, Jastremski MS, Syverut SA, editors. Emergency drug therapy. Philadelphia : WB Saunders company, 1991; p. 50-68.
22. Darell J, Triulzi. Use and abuse of fresh frozen plasma. [cited on 1997 March]; 1-3. Available from: www.itxm.org/tmu1997/tmu3-97.htm.
23. Ring J, Laubenthal H, Mebmer K. Incidence and classification of adverse reactions to plasma substitutes. JMM. 2005:997-1002.