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Original Article

Comparison of gelatin and HES 130/0.4 solution for fluid resuscitation in children with dengue shock syndrome

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Abstract

Background Dengue shock syndrome (DSS) is characterized by severe vascular leakage and hemostasis disorder, which causes death in 1-5% of cases. World Health Organization management guidelines for fluid resuscitation in DSS remain empirical, rather than evidence-based.

Objective To assess the efficacy of gelatin compared to hydroxyethyl starch (HES) 130/0.4 solution for fluid resuscitation in children with DSS.

Methods We performed a multi-centered, randomized study to compare gelatin and HES 130/0.4 solution for resuscitation of children with DSS. We randomly assigned 25 children with DSS to receive gelatin fluid and 25 children to receive HES 130/0.4. Statistical analyses were performed using Chi-square and Mann-Whitney tests.

Results More rapid increase in pulse pressure was noted in subjects treated with HES 130/0.4 compared to those treated with gelatin at 8 hours and 28 hours of therapy (P=0.037 and P=0.048). The decrease in hematocrit in subjects treated with HES 130/0.4 was faster than that of gelatin at 4 hours of therapy (P=0.001). One patient died due to an unusual manifestation of DSS. Respiratory rate decreased faster in subjects treated with HES 130/0.4 than those treated with gelatin at 4 hours and 8 hours of therapy (P<0.05). Body temperature remained higher in subjects treated with gelatin than HES 130/0.4 at 36 hours and 48 hours of therapy (P<0.05). However, the decrease in platelet counts in subjects treated with HES 130/0.4 was more than that of gelatin (P=0.018).

Conclusion HES 130/0.4 solution may be better for volume replacement compared to gelatin and is safe for fluid resuscitation in children with DSS. **[Paediatr Indones. 2013;53:328-33.]**

Keywords: *dengue shock syndrome, resuscitation, gelatin, HES 130/0.4*

Dengue shock syndrome (DSS) is a severe manifestation of dengue hemorrhagic fever (DHF). According to World Health Organization (WHO) recommendations, fluid resuscitation in DSS should be with crystalloids, followed by colloids.[1-3] The advantage of blood plasma is the similarity of its composition with intravascular body fluid. However, the disadvantages of blood plasma are disease transmission, allergic reactions, and the need for the Indonesian Red Cross to provide it.[4] Therefore, replacement fluids must be considered, such as synthetic colloids.

Synthetic colloid fluid has the desired effect of fluid resuscitation in children with DSS. Colloids may replace lost fluid and have oncotic effect, because they have greater molecular weight than crystalloids. As such, colloids may sustain longer intravascular fluid volume during the period of plasma leakage. Additionally, synthetic colloids are easily obtained at a lower price, do not require donors and the supply process in particular, and do not transmit any disease. How-

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ever, colloidal liquids may cause some adverse effects, such as anaphylactic reactions, coagulation disorders, kidney and liver disorders, and accumulation of fluid in the tissues.[3-5]

Gelatin and HES solutions are frequently used for fluid resuscitation in hypovolemic shock. Recent studies compared dextran and gelatin, as well as HES 200/0.6 and dextran. Good effects were observed in terms of intravascular volume, shorter duration to overcome shock, and reduced mortality.[6-9] In Indonesia, a study found that HES 130/0.4 was effective and safe.[10] To date, no study has determined the superior colloid for resuscitation of DSS patients, and no study has compared gelatin to HES 130/0.4 for resuscitation. We aimed to compare the effectiveness of gelatin to HES 130/0.4 solution in DSS.

Methods

We conducted a multi-centered, randomized study, to compare gelatin with HES 130/0.4 solution for fluid resuscitation in children with DSS, in the pediatric intensive care unit (PICU) from December 2011 to April 2012 at the R.D. Kandou Hospital, Pancaran Kasih Hospital, and Robert Wolter Monginsidi Hospital in Manado. Inclusion criteria were all patients diagnosed as DSS based on WHO criteria (1997) and with positive NS1 or anti-dengue immunoglobulin (Ig) M and/or IgG. Subjects' parents provided informed consent. Patients who had a history of hypersensitivity to gelatin or HES 130/0.4 solution, or who had been given fluid resuscitation with crystalloids and/or colloids before hospital admission were excluded. The study protocol was approved by the Ethics Committee of the hospitals.

The patients were randomly assigned to receive either gelatin or HES 130/0.4 solution. At the beginning of study, we recorded subjects' demographic data, history (duration of fever, bleeding manifestations, vomiting, and abdominal pain), physical examination findings (blood pressure, pulse pressure, pulse rate, respiratory rate, and body temperature), laboratory findings (hematocrit, platelet count, IgM and IgG by Rapid Strip Test and/or NS1).

The patient was given 20 mL/kg BW Ringer's acetate (RA) immediately (maximum 30 minutes after arrival) until the patient was not in shock. The procedure was repeated once more if the patient was still in shock. After pulse pressure was ≥30 mmHg, we performed repeat physical examination (blood pressure, pulse pressure, pulse rate, respiratory rate, and body temperature) and laboratory examinations (hematocrit) before starting the colloid solution. Then each subject was given 20 mL/kg BW/hour of gelatin or HES 130/0.4 solution for a 1-hour period, followed by RA solution of 10mL/kg BW/hour until the subject was stable, for a maximum of 24 hours. Blood pressure, pulse pressure, pulse rate, respiratory rate, body temperature, and diuresis were monitored every hour for a minimum of 24 hours until the general condition was stable. Capillary hematocrit was measured every four hours after study entry or in the event of cardiovascular deterioration. Platelet counts were measured every 12 to 24 hours.

Fluid overload manifestations (palpebral edema, ascites, or ronchi in both lungs) were also monitored. If the patient was stable (systolic blood pressure ≥80 mmHg, pulse pressure ≥30 mmHg, diuresis ≥1 mL/kg BW/hour, and hematocrit ≤ 40%) for at least 8 hours, RA solution was decreased to 7 mL/kg BW/hour (4 hours minimum), then to 5 mL/kg BW/hour (4 hours minimum), then to 3 mL/kg BW/hour (4 hours minimum) and then decreased to 8 drips/minute. When subjects became unstable, gelatin or HES 130/0.4 at 10 mL/kg BW/hour (total maximum 30 mL/kg BW) was administered. Subjects who had repeat shock symptoms were given RA at 20mL/kg BW. Ionotropic drugs, blood transfusions, diuretics, and other therapy could also be given depending on the clinical condition.

All data was processed and analyzed with SPSS version 20.0 for Windows. To compare the general examination findings (systolic and diastolic blood pressures, pulse pressure, pulse rate, respiratory rate, body temperature, hematocrit, diuresis, platelet count, total fluid volume, and subjects' length of hospital stay) in the gelatin group to the HES 130/0.4 solution group of DSS patients, we used T-test or Mann-Whitney test. Data normality was initially assessed using the Kolmogorov-Smirnov test.

Results

During the study period, a total of 51 subjects were recruited, and all received their designated fluid. One

subject dropped out because of complications (dengue encephalopathy, pulmonary edema, and massive bleeding). Of the remaining 50 subjects, 25 received gelatin and 25 received HES 130/0.4 solution. All subjects recovered fully. Baseline characteristics of subjects by group are shown in **Table 1**.

The mean total fluid used by the gelatin group was 152.84 mL/kg BW and that used by the HES 130/0.4 group was 153.12 mL/kg BW **(Table 2)**. Administration of fluids resulted in significantly improved hemodynamic variables, such as systolic blood pressure, diastolic blood pressure, pulse pressure, respiratory rate, body temperature, and hematocrit for both groups. Mann-Whitney test revealed a significantly higher increase in pulse pressure in the HES 130/0.4 group than in the gelatin group at 8 hours and 28 hours of therapy (P=0.037 and P=0.048) **(Figure 1),** and remained stable until 48 hours treatment with no significant difference afterwards. In addition, subjects in the HES 130/0.4 group had a significantly lower respiratory rate compared to that of the gelatin group at 4 hours and 8 hours (P<0.05), but respiratory rates were not significantly different at the other times of evaluation (P≥0.05). Body temperature was significantly lower in the HES 130/0.4 group than in the gelatin group at 36 hours and 48 hours (P<0.05), but not significantly different at the other times of the evaluation (P≥0.05).

Mann-Whitney test also revealed a significantly more rapid decrease in hematocrit at 4 hours in the HES 130/0.4 group than in the gelatin group (P=0.001) (**Figure 2**).

Nevertheless, there were no significant differences between the HES 130/0.4 and gelatin solution groups for systolic blood pressure, diastolic blood pressure, pulse rate and diuresis using Mann-Whitney test and T-test (P>0.05).

Table 1. Baseline characteristics of study subjects

Characteristics	Gelatin group (n=25)	HES 130/0.4 group (n=25)
Gender, n		
Male	15	15
Female	10	10
Mean age (SD), years	6.76 (3.19)	7.72 (2.45)
Mean body weight (SD), kg	22.88 (9.87)	24.82 (8.62)
Mean length of fever before shock (SD), days	4.40 (0.86)	4.52 (0.71)
Clinical manifestations on admission, n		
Abdominal pain	15	22
Vomiting	8	22
Epistaxis	2	1
Primary infection, n	5	2
Secondary infection, n	20	23
Mean platelet count (SD), $x10^3/mm^3$	60,320 (24,304)	67,520 (24,634)
Mean hematocrit, %	48.00	46.00
Mean systolic blood pressure, mmHg	90.00	100.00
Mean diastolic blood pressure, mmHg	70.00	80.00

Table 2. Main outcomes measurements

Outcomes	Gelatin group (n=25)	HES 130/0.4 group (n=25)	P value
Mean total volume fluid, mL	152.84	153.12	0.323
Mean platelet count, $x10^3/mm^3$			
Before treatment	60,320	67,520	0.670
After treatment	52,080	47,800	0.048
Recurrent shock, n	2	1	0.466
Allergic reactions, n	0	0	
Bleeding manifestations, n	0	1	0.156
Mean length of hospital stay, days	4.52	4.48	0.405
Excessive fluid	2	0	

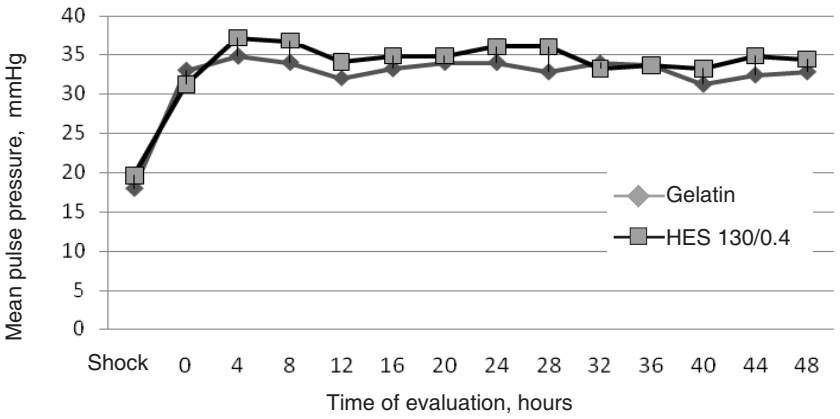

Figure 1. Curve of mean pulse pressure in the gelatin and HES 130/0.4 groups during fluid treatment

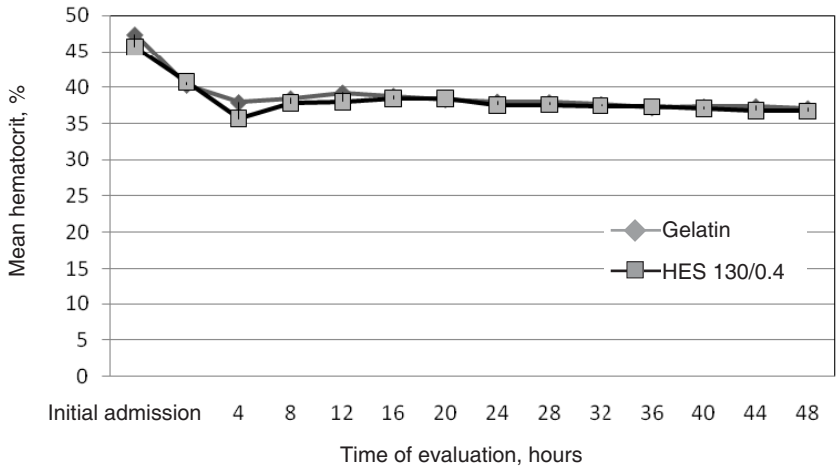

Figure 2. Curve of mean hematocrit in the gelatin and HES 130/0.4 groups during fluid treatment.

In the gelatin group, there were two patients who had recurrent shock at 4 and 12 hours, respectively, while in HES 130/0.4 group, there was one patient who had recurrent shock at 12 hours ($P \geq 0.05$) **(Table 2)**.

For the first 48 hours of treatment, we observed no allergic reactions in any of our 50 subjects. However, excess fluid was found in two subjects of the gelatin group and gastrointestinal bleeding was found one in subject in the HES 130/0.4 group **(Table 2)**. The mean lengths of hospital stay were not significantly different between the two groups **(Table 2)**.

Discussion

The general introduction of intensive intravenous fluid treatment for DSS more than 25 years ago led to a marked reduction in mortality rates in the best pediatric centers, from approximately 20% to 2%. However, there is still no consensus on which intravenous fluid should be used.[11]

Colloid solutions are usually given to prevent plasma leakage and to normalize the hemodynamics in patients with DSS.[3-5] Repeat state of shock that occurs before six hours from the onset of the disease has the worst prognosis.[3-5] From this study, we found

more rapid increase of pulse pressure in the HES 130/0.4 group compared to that of the gelatin group. Pulse pressure variables were significantly different between the groups at 8 hours and 28 hours of treatment ($P<0.05$). HES 130/0.4 is known to stay in the intravascular space longer (4-8 hours) even though the second half of this colloid as the 3-4 hours to achieve 100% volume expansion. Compared to other colloidal solutions, HES 130/0.4 has longer O_2 transport effects.[12] A previous study reported an increase in pulse pressure at 20 minutes after administration of HES 130/0.4,[10] although it was not statistically significant. In contrast, we gave HES 130/0.4 solution earlier in the resuscitation process and rapid pulse pressure observations were made in the 20 minutes and 40 minutes after treatment. Several studies have reported that HES 130/0.4 has a good effect on the microcirculation during shock, by increasing organ perfusion pressure and intravascular volume.[13-15]

Results showed a decrease in hematocrit values for both treatment groups, particularly after 4 hours of observation, after which the hematocrit values were relatively stable. This observation may be due to the effect of the second half of the colloidal fluid in the intravascular space, that is at 3-4 hours.[7] Decreased hematocrit values indicate that HES 130/0.4 is more durable in the intravascular space compared to liquid gelatin, and has the effect of hemodilution which may increase plasma volume, lower blood viscosity and improve microcirculation in the network so as to prevent recurrent shock in DSS patients.[7]

Differences in the total fluid required between groups is related to the oncotic pressure difference in the two types of fluids in maintaining hemodynamics in DSS patients. A study reported that differences in the hemodynamic variables for four types of fluids, dextran, gelatin, Ringer's lactate, and 0.9% NaCl, were directly proportional to the total amount of fluid used.[6]

Allergic reactions may occur in patients who receive gelatin or HES 130/0.4 solutions. However, gelatin more frequently causes allergic reactions than other colloidal fluids, ranging from skin redness and pyrexia to life-threatening anaphylaxis. Those reactions are associated with histamine release as a possible direct effect of gelatin on the mast cells. However, the frequency of any type of reaction is low (0.04%).[16] Like all other colloids, HES-associated anaphylactic reactions are mild, with a frequency of approximately 0.006%. Hydroxyethyl starch does not cause histamine release, as is the case of gelatin, but it may still cause anaphylactic reactions, as well as dextran.[16] In our study, we found no allergic reactions in either group of subjects.

In our study, we observed no bleeding in the gelatin group, but one patient in the HES 130/0.4 group experienced bleeding in form of melena. Bleeding occurs as a manifestation of DSS, not as an effect of HES. However, HES may dilute coagulation factors and large volumes may decrease levels of factor VIII. Although studies have reported increased bleeding tendency after the use of HES at 33 mL/kg BW, hemostasis is not usually affected. Nonetheless, the use of repeated small doses may cause coagulation disorders, hence, HES should be limited in dose and duration. Adverse effects of HES, especially with regards to the molecular weight and degree of substitution, are high. HES solution has a 130,000-dalton molecular weight and 0.4 degree of substitution, but was reported to not cause coagulation disorders at a maximum dose of 50mL/kg BW.[17]

Hematologic variables, namely mean platelet counts, were not significantly different between the gelatin and HES 130/0.4 groups (60,320/mm^3 and 67,520/mm^3, respectively) at baseline. However, after treatment there were significant differences in mean platelet counts between the two groups (52,080/mm^3 VS 47,800/mm^3, in the gelatin and HES130/0.04 groups, respectively. The HES 130/0.4 group may have increased consumption of platelets compared to that of the gelatin group, in order to overcome capillary endothelial leakage. One cause of thrombocytopenia on DSS due to increased platelet consumption occurs in the closed capillary endothelial vascular leakage.[5]

A limitation of our study was the experimental open-label design (open trial) with treatment done in parallel. Diagnosis of patients was made by DSS WHO 1997criteria and positive NS1 or anti-dengue IgM and/or IgG serology. Also, we did not perform viral isolations to determine the dengue serotypes in our subjects. As the four dengue serotypes are known to differ in virulence, we were not able to compare the effects of the colloids in our subjects based on serotype. In addition, synthetic colloid fluid administration may affect coagulation factors causing bleeding in

DSS patients. We only examined the coagulation factor if there was a bleeding manifestation. However, Wills *et al.* found no evidence of colloidal adverse side effects on the intrinsic coagulopathy or bleeding manifestations.[9]

In conclusion, efficacy of HES 130/0.4 fluid is better than liquid gelatin in the treatment of DSS in children, especially in terms of improving towards a normovolume intravascular state and lower hematocrit. HES 130/0.4 fluid do not cause any adverse side effects in our subjects, such as allergic reactions, bleeding, or excess fluid.

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