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Original Article

Comparison of the efficacy and safety of hydroxyethyl starch 130/0.4 and Ringer's lactate in children with grade III dengue hemorrhagic fever

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Abstract

Background Theoretically hydroxyethyl starch (HES) will give more rapid recovery from shock, including in dengue shock syndrome (DSS) and currently gained popularity for its less deleterious effects on renal function and blood coagulation.

Objectives To compare the efficacy and safety of HES 130/0.4 and Ringer's lactate (RL) for shock recovery in children with DSS.

Methods A randomized controlled study was performed on 39 children admitted with DSS at Dr. Soetomo Hospital, Surabaya, between March and May 2007. Children were grouped into grade III (n=25) and grade IV (n=14) dengue hemorrhagic fever (DHF) according to the WHO criteria. Within each group, subjects were randomly assigned to receive initial fluid resuscitation with either HES 130/0.4 (n=9 in the DHF grade III group, 10 in the DHF grade IV) or RL (n=16 in the DHF grade III group, 4 in the DHF grade IV). Clinical and laboratory data were collected to determine improvements in shock recovery and adverse reactions.

Results In both the grades III and IV DHF, HES 130/0.4 significantly decreased hemoglobin and hematocrit levels. Clinical improvements in pulse pressure and pulse rate were seen after treatment with HES 130/0.4 although these were statistically insignificant if compared to the RL group. No differences in fluid requirement and recurrent shock episodes were noted between the RL and HES groups. No adverse reactions were found during the study.

Conclusion HES 130/0.4 administration is effective and safe in children with DSS. **[Paediatr Indones. 2009;49:97-103]**.

Keywords*: dengue shock syndrome, children, hydroxyethyl starch 130/0.4, efficacy, safety*

Dengue shock syndrome (DSS) is the most serious manifestation of dengue hemorrhagic fever (DHF), a disease that has spread progressively throughout Asia and South America since its first appearance in Bangkok, Thailand, in the 1950s.[1,2] Dengue fever is the most widely distributed mosquito-borne viral infection in humans, and is currently the leading cause of hospital admission and death among children in Southeast Asia.[3-5] The incidence of DSS, as reported by Indonesian hospitals in 1996, was 16-40% with a relatively high mortality rate. By 1990, mortality rates in Indonesia were 60% in Pirngadi Hospital, Medan, 20-26% in Dr. Cipto Mangunkusumo Hospital, Jakarta and 16-20% in Dr. Soetomo Hospital, Surabaya.[1,6] Early detection of shock has been shown to increase the quality of monitoring and management of fluid therapy so that the mortality rate of DSS could be

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reduced from 26% in 1996 to 12% in 2002.[5]

Theoretically hydroxyethyl starch (HES) gives more rapid recovery from shock, including in dengue shock syndrome (DSS) and currently gained popularity for its less deleterious effects on renal function and blood coagulation. We compared the efficacy and safety of HES 130/0.4 and RL in DSS patients in terms of clinical, laboratory, and adverse reactions.

Methods

This randomized clinical trial was conducted between March and May 2007 at Dr. Soetomo Hospital, Surabaya, Indonesia. The study protocol was reviewed and approved by the Medical Research Ethics Committee at Dr. Soetomo Hospital. Children aged 1 to 13 years old admitted for DHF grade III or IV were included in the study, provided they had not received any fluid therapy and had obtained a parent or guardian's informed consent. Children were diagnosed with grade III or grade IV DHF according to WHO criteria. Subjects in each group were randomly assigned to either receive initial fluid resuscitation with either HES 130/0.4 or RL. We excluded patients with heart disease (congenital, rheumatic, myocarditis, and heart failure), lung disease (bronchopneumonia, bronchiolitis, and bronchial asthma), liver disorders and renal disease (nephrotic syndrome), malnutrition (defined as severe malnutrition with less than 70% of ideal body weight appropriate to age according to the CDC growth chart), morbid obesity (defined as a body mass index of more than the 97th percentile according to the CDC growth chart), and agonal patients.

Improvements after treatment were defined as a pulse pressure of >20 mmHg, a strong and regular peripheral pulse rate between the 5th and the 95th percentile, and a 20% decrement of serum hemoglobin and hematocrit. We considered treatment failure if prolonged shock occurred and showed no improvement after two resuscitation cycles, meaning that the subject required further treatment with a blood transfusion or inotropic drugs. Subjects who had severe adverse reactions, those who were discharged upon request, or had insufficient data were removed from the study.

A minimum sample size of 36 patients was required. Chi-squared test, Fisher exact test and independent t-test were used to analyze the data as appropriate using SPSS for Windows version 13.0 software. A P value of less than 0.05 considered significant.

Table 1. Baseline clinical characteristics of dengue shock syndrome patients prior to fluid administration

Characteristic	Grade of DSS	Groups	
		HES 130/0.4 (n=19)	RL (n=20)
Age (years)	DHF grade III	7.6 (3.3)	7.6 (3.6)
	DHF grade IV	7.3 (2.6)	6.0 (3.8)
Gender ‡**	DHF grade III	Male 5 Female 4	Male 10 Female 6
	DHF grade IV	Male 6 Female 4	Male 1 Female 3
Body weight (kg)	DHF grade III	22.8 (11.1)	25.6 (11.1)
	DHF grade IV	22.2 (11.3)	23.9 (15.7)
Day of illness	DHF grade III	4.8 (0.8)	5.0 (0.7)
	DHF grade IV	4.3 (0.7)	4.7 (0.9)
Pulse pressure (mmHg)	DHF grade III	17.8 (6.7)	18.7 (3.4)
	DHF grade IV	0	0
Pulse (beats per minute)	DHF grade III	121.3 (14.3)	134.0 (20.7)
	DHF grade IV	0	0

Data were presented as mean (SD) except where marked‡ to indicate number of subjects (%)

Table 2. Baseline laboratory characteristics of dengue subjects

Characteristic	DSS grade	Treatment groups	
		HES 130/0.4 (n=19)	RL (n=20)
Hemoglobin (g/dl)	DHF grade III	15.1 (1.5)	15.8 (1.5)
	DHF grade IV	16.2 (1.4)	16.7 (1.9)
Hematocrit (%)	DHF grade III	45.91 (3.9)	46.5 (4.7)
	DHF grade IV	48.0 (7.4)	51.1 (5.5)
PPT difference (second)	DHF grade III	1.0 (0.7)	2.5 (2.1)
	DHF grade IV	1.8 (2.7)	2.4 (1.4)
APTT difference (second)	DHF grade III	12.2 (5.5)	17.7 (21.1)
	DHF grade IV	21.2 (25.1)	10.4 (6.7)
	DHF grade IV	73.5 (50.7)	66.7 (27.5)
Potassium (mEq/l)	DHF grade III	4.1 (0.9)	4.2 (0.6)
	DHF grade IV	4.5 (0.9)	4.9 (0.9)
Sodium (mEq/l)	DHF grade III	129.16 (11.3)	134.2 (6.4)
	DHF grade IV	134.0 (13.8)	128.5 (6.8)

Data is presented as mean (SD)

Results

Thirty-nine patients were studied over a three-month period; 25 of these had DHF grade III and the remaining 14 had DHF grade IV. Of the 25 patients with DHF grade III, 9 received HES 130/0.4 and 16 received RL by random allocation. Of the 14 patients with DHF grade IV, 10 received HES 130/0.4 and 4 received RL by random allocation. All patients recovered without serious complications.

Demographic information, clinical features at presentation, and preliminary laboratory data for all subjects is shown in **Tables 1** and **2**. The number of subjects in each group was similar in terms of age, gender, body weight, day of illness, pulse pressure, and pulse rate (**Table 1**), while similar laboratory data were seen in **Table 2**.

Analysis of clinical improvements i.e. pulse pressure increase and pulse rate decrease revealed that all subjects with grade III DHF were clinically improved within the first 20 minutes of fluid resuscitation when they were given either HES 130/0.4 or RL (**Table 3**). In the grade IV DHF group, more patients in the HES group were clinically improved within 20 minutes compared to the RL group, although this was statistically insignificant. Pulse rate improvement in 20 minutes was reached by all patients in HES 130/0.4 group (**Table 3**). These results indicate that RL and HES 130/0.4 were similarly effective to overcome shock in DHF grade III and IV patients.

Analysis of laboratory data revealed statistically significant decreases in hemoglobin and hematocrit levels after fluid resuscitation. These parameters are indicators for plasma leakage, and showed that faster recovery of plasma leakage occured in the HES compared to the RL group (**Table 4**). These results indicated that HES 130/0.4 could hasten vascular permeability improvement when used for initial fluid resuscitation.

Table 3. Clinical improvements after treatment with HES 130/0.4 and RL

Diagnosis	Groups	Number of patients reached clinical improvements					
		Pulse pressure			Pulse rate		
		In minute 20	In minute 40	P	In minute 20	In minute 40	P
DHF Grade III	HES 130/0.4 n	9	0	NA**	9	0	NA**
	RL n	16	0		16	0	
DHF Grade IV	HES 130/0.4 n	8	2	0.520	10	0	0.286
	RL n	2	2		3	1	

*Significant difference of Fisher test in P<0.05

**Not analyzed

Table 4. Laboratory tests used to indicate clinical improvements after HES 130/0.4 and RL is administered.

Diagnosis	Groups	Number of patients reached laboratory improvements							
		Hemoglobin				Hematocrit			
		In minute 20	In minute 40	In minute 60	P	In minute 20	In minute 40	In minute 60	P
DHF Grade III	HES 130/0.4 n	7	1	1	0.008	7	1	1	0.011
	RL n	3	1	12		3	2	11	
DHF Grade IV	HES 130/0.4 n	8	1	1	0.019	9	1	0	0.005
	RL n	0	1	3		0	2	2	

Table 5. Distribution of patients based on the amount of fluid resuscitation required to achieve clinical and laboratory improvements in subjects with dengue shock syndrome

Diagnosis	Groups	Number of patients		P
		1x20 ml (per kgBW)	2x20 ml (per kgBW)	
DHF grade III	HES 130/0.4 n (%)	9	0	1.000
	RL n (%)	15	1	
DHF grade IV	HES 130/0.4 n (%)	8	2	1.000
	RL n (%)	4	0	

Table 6. Mean amounts of fluid required to achieve clinical and laboratory improvements in subjects with dengue shock syndrome

Diagnosis	Amount of fluid required (ml/kgBW) to achieve clinical and laboratory improvements		P
	HES 130/0.4 Mean (SD)	RL Mean (SD)	
DHF grade III	20.0 (0.00)	21.3 (5.00)	0.465
DHF grade IV	24.0 (8.43)	20.0 (0.00)	0.168

In this study, two times the initial volume of resuscitation fluid (total of 40 ml/kgBW) was required to achieve clinical and laboratory improvements in two of 10 subjects in the DHF grade IV group who were given HES 130/0.4 group, and in one of 16 subjects in the DHF grade III group who were given RL. Based on the amount of fluid requirement, there were no significant differences in number of patients (**Table 5**).

Means of the amount of fluid required to achieve clinical and laboratory improvements in the grade III DHF group was 20.00 ml/kgBW for subjects given HES 130/0.4 and 21.25 ml/kgBW for patients given RL The difference was not statistically significant. Similarly, the fluid requirements for DHF grade IV did not show any significant difference between the HES and RL groups (**Table 6**).

In this study, one episode of recurrent shock occurred in four out of 39 subjects, i.e., 3 in RL group and 1 in HES 130/0.4 group. The number was too small for statistical analysis.

During intensive observation after recovery from initial shock, two DHF grade III subjects who were treated with RL suffered from recurrent shock less than 6 hours after treatment. None of the subjects treated with HES 130/0.4 in the same group suffered from recurrent shock. In DHF grade IV subjects, the episodes of recurrent shock occurred more than six hours after initial shock recovery.

Examination of subjects for adverse reactions to the treatments was carried out by looking at decreases in blood coagulation, impaired liver and renal functions, and acid-base equilibrium. No significant differences were found between the groups (data not shown).

Discussion

Shock in DSS is thought to be caused by leakage of plasma into the extravascular compartment, including fluid effusion to pleural and peritoneal cavities, hemoconcentration and hypovolemia and failure of homeostasis mechanisms.[3,4,7] In the majority of cases, capillary leakage resolves spontaneously by the sixth day of illness and is followed rapidly by full recovery. Fluid resuscitation is essential in the management of DSS, and hypovolemic shock must be rapidly overcome in order to maintain intravascular volume. This allows optimal oxygen transport to cells and tissues and decreases oxygen debt in tissues.[5,8] In DSS patients with more than 30% plasma leakage, prolonged shock occurs when the initial shock fails to resolve in the first two hours. In this condition, colloids (plasma or plasma expander) are required as initial therapy because their sealing effect will limit vascular leakage, and will help maintain intravascular volume and will allow plasma to remain in the intravascular system for longer.[9] WHO still recommends crystalloid solution (Ringer's lactate = RL) as a standard therapy for DSS. RL is isotonic and therefore can rapidly fill intravascular spaces; however, this solution also rapidly leaks into extravascular space so that episodes of recurrent shock and fluid overload causing cerebral edema may develop.[6,9]

Hydroxyethyl starch (HES) is a synthetic colloid solution that has been used and developed extensively as a volume expander in hypovolemic cases where it acts a sealant and maintains intravascular volume for. HES 130/0.4 is a new version of HES that has a molecular weight of 130,000 Daltons and a

molecular substitution of 0.4. This compound has been reported to be safer with respect to renal and blood coagulation functions than first generation HES.[5] However, this solution has a high level of chloride compared to plasma and this can lead to hyperchloremic acidosis, particularly in critically ill patients. Therefore, determination of acidosis through comparison of chloride and sodium levels is essential in the management of these patients too.[10-12]

Studies by Dung *et al*, Nhan *et al* and Setiati revealed that hemodynamic response and cardiovascular stability could be achieved better and faster with administration of colloids.[3-5] On the other hand Wills *et al*[2] showed that no significant differences were found in therapeutic response between RL and colloid groups. In addition, Setiati revealed significant improvements in mortality rates and duration of shock recovery when HES 200/0.5 was administered, although laboratory parameters were not studied.[16]

Ringer Lactate as the standard solution used for the management of DSS but it has disadvantages such as incidence of frequent recurrent shock, fluid overload and cerebral edema.[8] In grade IV DHF, prolonged shock occurs when treatment for initial shock fails to lead to improvement within 2 hours. This worsens the overall prognosis of the patient. In this situation, a colloid solution (plasma or plasma expander) is needed. Plasma is not usually readily available and it is more expensive.[8] HES is a synthetic colloid with sealing effect, able to maintain intravascular volume within 4-6 hours, have a better expansion effect and hindrance of molecular adhesion so that leukocyte activation and endothelial damage that lead to vascular leakage and failure of organ function can be prevented. Adverse reactions including disorders of renal function, blood coagulation and acid-base equilibrium is safer in HES 130/0.4.[5,10,11]

Analysis of preliminary clinical parameters of the subjects before treatment showed that the pulse pressure in grade III DHF cases was lower in the subjects that were assigned to receive HES 130/0.4 compared to those assigned to receive RL. Preliminary pulse rate was higher in the subjects assigned to be given RL than those assigned to be given HES 130/0.4 group. Descriptively, grade III DHF cases in subjects assigned to be given HES 130/0.4 group had a poorer initial condition compared to subjects assigned to be given RL, although this was statistically insignificant. In grade IV DHF cases, pulse pressure and pulse rate were all homogenically unmeasurable in both groups. Analysis of preliminary laboratory parameters before treatment showed abnormal coagulation profiles and increasing liver enzymes in both groups, although the difference was not statistically significant. Preliminary renal function, serum electrolyte and acid-base equilibrium were within normal limits in both groups.

Analysis of clinical improvements including increasing pulse pressure and pulse rate revealed that in grade III DHF cases, all subjects showed improvements by 20 minutes after treatment with either RL or HES 130/0.4, indicating that both treatments were similarly effective in clinical recovery of grade III DHF subjects. However, in grade IV DHF cases, more subjects treated with HES 130/0.4 improved during the 20 minutes after treatment compared to those treated with RL, although this difference was not statistically significant.

The clinical improvements seen in patients treated with HES 130/0.4 were similar to those found by Nhan *et al* and Wills *et al* where delayed initial cardiovascular improvement was observed in subjects treated with RL group compared to those treated with a colloid solution.[2,4] Clinical improvements observed in our study were also similar to those observed by Dung *et al*, where an increase in pulse pressure was found after colloid administration (although this data was not statistically significant).[3] This indicates that HES 130/0.4 is able to improve and maintain clinical hemodynamic stabilization faster than crystalloid solution.[13-17]

Analysis of laboratory data, either in grade III DHF or grade IV cases, showed that hemoglobin and hematocrit levels decreased significantly in more subjects treated with HES 130/0.4 compared to those treated with RL. These findings are similar to those of Dung *et al,* Nhan *et al* and Wills *et al*, where significantly faster and greater reduction of hematocrit occurred after colloid administration compared to RL administration.[2,3,4] This supports the theory that HES 130/0.4 is able to improve plasma leakage in DSS patients, and thus reduce the risk of recurrent shock. Significant decrease in hematocrit levels 6-8 hours after administration is caused by hemodilutional effect of the increase of plasma volume. This would leads to decreased of blood viscosity, therefore improving

microcirculation in tissues.[15,17,18]

Studies by Dung *et al* and Wills *et al* which showed that only hematocrit levels had a significant difference with colloid administration compared to RL.[2,3] Results from these studies are still show controversy between crystalloid and colloid treatments in the management of DSS in children. Significant laboratory improvements were seen in groups treated with colloids in all trials, while clinical improvements were varied. A smaller amount of fluid was required to achieve clinical and laboratory improvements with HES 130/0.4 treatment compared to RL treatment, although the difference was statistically insignificant. Studies by Nhan *et al* and Wills *et al* showed no significant difference in the amount of fluid required between colloid and crystalloid treatments.[2,4] RL as crystalloid solution needs four times of assumed lost volume to maintain adequate intravascular volume, because 75% of the solution will be distributed into interstitial space rapidly.[17,18] HES 130/0.4 as a colloid solution has a great volume expansion effect to 100% that is maintained for 3-4 hours, no excessive amount of fluid are required to overcome hypovolemic shock, therefore reducing the risk of volume overload.[15]

Analysis of recurrent shock episodes showed that the frequency of recurrent shock was lower in subjects treated with HES 130/0.4, compared to those treated with RL, although the difference was not significant. These findings are similar to those of Nhan *et al.* [4] This indicates that in this study, HES 130/0.4 is able to reduce the risk of recurrent shock in DSS patients and thus is clinically more effective.[19] This is probably because HES 130/04 is maintained for longer than 3-4 hours, whereas RL stays in intravascular space only for 1-2 hours. This means that vascular leakage is minimized, leading to a decrease in the recurrence of shock.

Similar to the data of Wills *et al*[2], no adverse reactions, allergy or deaths occurred during this study. This indicates that HES 130/0.4 is safe and clinically effective to be used in DSS patients.[5,17] Haemorrhage due to dilution of coagulation factors usually does not occur during HES administration with recommended dose, especially in low molecular weight HES.[19,20] Liver dysfunction usually occurs only with repeated or long term use of HES.[21] In this study, HES was only administered over a short period. In some cases, administration of HES that is diluted in a physiological salt solution can increase the mortality rate of patients by causing hyperchloremic acidosis, decreasing base excess and SID.[11,22-24] In this study, no cases of hyperchloremic acidosis were found in subjects treated with HES 130/0.4.

In conclusion, most children with grade III DHF in this study responded well to standard treatment with isotonic crystalloid solution. Early intervention with colloid solution is more beneficial in children with grade IV DHF as indicated by clinical and laboratory improvements in subjects treated with HES 130/0.4. No adverse reactions were noted in this study, indicating a good safety profile for HES 130/0.4 in children with DSS. No differences were noted on resuscitation fluid requirement and recurrent shock episodes between HES and RL.

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