Comparison of Three Fluid Solutions for Resuscitation in Dengue Shock Syndrome

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ABSTRACT

BACKGROUND

Dengue shock syndrome is characterized by severe vascular leakage and disordered hemostasis and progresses to death in 1 to 5 percent of cases. Although volume replacement is recognized as the critical therapeutic intervention, World Health Organization management guidelines remain empirical rather than evidence-based.

METHODS

We performed a double-blind, randomized comparison of three fluids for initial resuscitation of Vietnamese children with dengue shock syndrome. We randomly assigned 383 children with moderately severe shock to receive Ringer's lactate, 6 percent dextran 70 (a colloid), or 6 percent hydroxyethyl starch (a colloid) and 129 children with severe shock to receive one of the colloids. The primary outcome measure was requirement for rescue colloid at any time after administration of the study fluid.

RESULTS

Only one patient died (<0.2 percent mortality). The primary outcome measure — requirement for rescue colloid — was similar for the different fluids in the two severity groups. The relative risk of requirement for rescue colloid was 1.08 (95 percent confidence interval, 0.78 to 1.47; P=0.65) among children with moderate shock who received Ringer's lactate as compared with either of the colloid solutions, 1.13 (95 percent confidence interval, 0.74 to 1.74; P=0.59) among children who received dextran as compared with starch in the group with severe shock, and 0.88 (95 percent confidence interval, 0.66 to 1.17; P=0.38) among children who received dextran as compared with starch in the combined analysis. Although treatment with Ringer's lactate resulted in less rapid improvement in the hematocrit and a marginally longer time to initial recovery than did treatment with either of the colloid solutions, there were no differences in all other measures of treatment response. Only minor differences in efficacy were detected between the two colloids, but significantly more recipients of dextran than of starch had adverse reactions. Bleeding manifestations, coagulation derangements, and severity of fluid overload were similar for all fluid-treatment groups.

CONCLUSIONS

Initial resuscitation with Ringer's lactate is indicated for children with moderately severe dengue shock syndrome. Dextran 70 and 6 percent hydroxyethyl starch perform similarly in children with severe shock, but given the adverse reactions associated with the use of dextran, starch may be preferable for this group.

DENGUE SHOCK SYNDROME IS THE most serious manifestation of dengue hemorrhagic fever, a relatively new disease entity that has spread progressively throughout Asia and South America since its first appearance in Bangkok, Thailand, in the 1950s.[1] Dengue hemorrhagic fever is characterized by systemic vascular leakage and disordered hemostasis and may develop after infection with any of four dengue viral serotypes.[2,3] Between 250,000 and 500,000 cases of dengue hemorrhagic fever, mainly in children, are reported to the World Health Organization (WHO) annually, with mortality rates of 1 to 5 percent among patients with shock.[1,4] The pathophysiological mechanisms underlying the vascular leakage and coagulopathy are poorly understood, and no specific treatment is available.

Prompt restoration of the volume of circulating plasma is the cornerstone of therapy for dengue shock syndrome. WHO management guidelines, first proposed in 1975, recommend replacement of plasma losses with crystalloid solutions initially, followed by boluses of colloid for patients with recurrent or refractory shock.[5] Although the recommendations were initially invaluable in focusing attention on the need for volume replacement, they have not been updated to any appreciable degree since 1975.[6] During this time there has been considerable debate in the medical literature regarding the use of crystalloids versus colloids for volume replacement in critically ill patients.[7-9] Theoretically, colloid solutions offer advantages in patients with increased vascular permeability,[10] although in clinical practice a clear benefit has not been demonstrated. Conversely, most colloid solutions have adverse effects on hemostasis,[11] an important consideration in patients with dengue.

Only two randomized and blinded trials have investigated the effect of different crystalloid and colloid fluid regimens on the outcome from dengue shock syndrome. The first, a pilot study in which 50 children received one of four fluids (6 percent dextran 70, 3 percent gelatin, Ringer's lactate, or 0.9 percent saline) over a two-hour period for initial resuscitation, showed that there were significantly greater improvements in cardiac index, hematocrit, and blood pressure at the end of the infusion of the study fluid among children who had received a colloid solution than among those who had received a crystalloid solution.[12] All the children recovered, but differences in sustained effects among the four fluids were not examined.

This was followed by a one-year study of 230 children with dengue shock syndrome who received treatment with similar fluids. The study focused on sustained as well as immediate treatment effects.[13] The study showed no clear advantages among the fluids in terms of the time to recover from the initial episode of shock, the time to achieve final cardiovascular stability, or the requirement for rescue colloid. The most significant factor determining clinical response was the pulse pressure (i.e., the difference between the systolic and diastolic pressures) at presentation with shock. Dengue is unusual in that a slow leak occurs over several days, permitting compensatory mechanisms to operate. Before the development of overt cardiovascular collapse, the diastolic pressure rises to meet the systolic pressure, and the pulse pressure narrows; thus the pulse pressure is a marker of the severity of vascular leakage. According to WHO guidelines, a patient with dengue hemorrhagic fever is considered to have dengue shock syndrome once the pulse pressure narrows to 20 mm Hg or less. Post hoc analysis of the one-year study suggested that early treatment with a colloid solution hastened recovery in children with a pulse pressure of 10 mm Hg or less at presentation (i.e., the group with profound cardiovascular compromise).[13]

Many synthetic colloid preparations are now available, each with unique physicochemical characteristics that determine their likely efficacy and side-effect profiles.[11] However, if colloid resuscitation does confer a true benefit in children with dengue shock syndrome, it is not clear which preparation would be most appropriate. Pathophysiological studies indicate that there is preferential leakage of relatively small plasma proteins (e.g., albumin) as compared with larger molecules (e.g., IgG),[14] which implies that resuscitation with colloid preparations of larger molecular weights may offer therapeutic advantages.

In an attempt to optimize management and address some of these unresolved issues, we conducted a trial comparing three resuscitation fluids, a crystalloid and two synthetic colloids, for primary resuscitation of children with dengue shock syndrome. Since our pediatric intensive care unit consistently achieves mortality rates of less than 1 percent for dengue shock syndrome, many thousands of children would need to be enrolled to examine effects on mortality. Instead, we used the established WHO format of primary resuscitation with an initial infusion of a specific volume of fluid fol-

lowed by rescue colloid treatment as necessary, and we tested the hypothesis that there is no difference in the requirement for treatment with rescue colloid after initial resuscitation with Ringer's lactate, 6 percent dextran 70, or 6 percent hydroxyethyl starch (each at 25 ml per kilogram of body weight) among Vietnamese children with dengue shock syndrome.

METHODS

STUDY DESIGN

The trial was a single-center, randomized, double-blind comparison of an isotonic crystalloid solution (Ringer's lactate) and two isotonic colloid solutions (6 percent dextran 70 [dextran] and 6 percent hydroxyethyl starch 200/0.5 [starch]) for emergency resuscitation of children with dengue shock syndrome. The children were stratified according to pulse pressure at admission, a marker of the severity of the vascular leak.[13] No children in the group with severe shock received a crystalloid because of concerns about the potential development of critical fluid overload without access to advanced respiratory support. The study took place in the pediatric intensive care unit at the Hospital for Tropical Diseases in Ho Chi Minh City, Vietnam. The ethics and science committee of the hospital approved the protocol.

STUDY POPULATION AND CLINICAL METHODS

Children 2 to 15 years of age presenting directly to the hospital with clinical dengue shock syndrome were eligible for enrollment provided a parent or guardian gave written informed consent. WHO guidelines were used for the diagnosis of dengue shock syndrome.[6] At study entry we recorded demographic data, history, and examination findings, and we obtained citrated plasma samples for coagulation screening and serum samples for the diagnosis of dengue. Patients were enrolled in one of two groups according to the pulse pressure at admission. Children with shock of moderate severity (pulse pressure, >10 and ≤20 mm Hg) constituted group 1 and were randomly assigned to receive Ringer's lactate, dextran, or starch. Group 2 consisted of those with severe shock (pulse pressure, ≤10 mm Hg); these children were randomly assigned to receive either dextran or starch. Each child received 15 ml per kilogram of body weight of the allocated fluid over a one-hour period, followed by 10 ml per kilogram over the second hour.

Treatment allocation was determined in advance with the use of computer-generated random numbers. To ensure prerandomization concealment as well as blinding, treatment packs comprising three 500-ml bottles of study fluid, sealed inside specially prepared cardboard containers and identified only by a study number, were supplied to the ward for each patient. Treatment packs for at least the next five patients in each severity group were kept on the ward at any time. Both the computer-generated randomization process and preparation of the treatment packs were carried out by independent research staff not involved in clinical care. A sealed envelope containing the identity of the study fluid was attached to the study file for each child in case of emergency.

After the infusion of the study fluid, the children received a standard schedule of Ringer's lactate that involved a reduction at specific time intervals to maintenance levels after eight hours. Pulse, blood pressure, and peripheral perfusion were monitored at least hourly until they were stable for a minimum of 24 hours, and then every 4 hours until discharge. The capillary hematocrit was measured at baseline, 2 and 6 hours after study entry, and then approximately every 12 hours or in the event of cardiovascular deterioration. Additional citrated plasma samples for coagulation screening were obtained on study days 2 and 4, together with a second serum sample for serologic testing for dengue infection at discharge. An ultrasound scan of the chest and abdomen was carried out on study day 3 by one of two trained observers with the use of a standardized protocol to measure the depth of any pleural effusions and assess the severity of ascites.

Patients whose cardiovascular status did not improve after administration of the study fluid (i.e., those who had further narrowing or no response in pulse pressure, together with persisting or worsening peripheral shutdown, a rising hematocrit, or both) received infusions of 5 to 10 ml per kilogram of rescue colloid (usually dextran) at the discretion of the clinician. Similarly, if after an initial favorable response, the pulse pressure subsequently narrowed again to 20 mm Hg or less with peripheral vasoconstriction, a rising hematocrit, or both, rescue colloid could be given. It was not possible to fix absolute criteria for the use of rescue colloid, but the same core group of clinicians was responsible for patient care throughout the study, and the general policy of the pediatric intensive care unit for intervention after initial resuscitation is conservative.

Patients received inotropes, blood transfusions, diuretics, and other therapy at the discretion of the treating clinician.

LABORATORY PROCEDURES

A diagnosis of dengue infection was made with the use of Dengue Duo IgM capture and IgG capture enzyme-linked immunosorbent assay kits (PanBio) on paired serum samples. Coagulation screening was performed with the use of kits obtained from Diagnostica Stago; tests included those for prothrombin time, activated partial-thromboplastin time, and fibrinogen level and a semiquantitative assay for fibrin-degradation products. Only results of samples separated within 12 hours of venipuncture and without visible hemolysis or clot formation were included in the analysis.

OUTCOME MEASURES

The primary outcome measure was the requirement for supplemental intervention with rescue colloid at any time after the infusion of the study fluid. The following secondary outcome measures were examined: the time taken to achieve initial cardiovascular stability (defined as the time in hours from study entry until the pulse pressure reached and was maintained at ≥25 mm Hg with a systolic pressure of ≥80 mm Hg for a minimum of two hours), the time taken to achieve sustained cardiovascular stability (defined as the time in hours from study entry to reach and maintain these cardiovascular indexes indefinitely without further intervention), the volumes of rescue colloid and total parenteral fluid required, the pattern of change in the hematocrit, and the number of days in the hospital. A single observer not involved in clinical management calculated all recovery times and fluid volumes. In addition, the following four possible adverse effects of the various fluids were investigated: clinical bleeding; laboratory evidence of coagulopathy; the severity of vascular leakage as assessed clinically, by ultrasonography, and by the requirement for diuretic therapy; and the incidence of allergic-type reactions.

STATISTICAL ANALYSIS

A sample size of 360 patients (120 in each fluid group) was calculated for the main study to give 80 percent power to detect a 50 percent reduction in the requirement for rescue colloid at a 5 percent significance level, taking as baseline the findings of an earlier study, in which approximately 30 percent of children with dengue shock syndrome required rescue colloid.[13] Parallel recruitment to the study comparing use of the two colloids in children with severe shock was expected at a ratio of approximately three patients with moderately severe shock to one patient with severe shock.

A statistician who was not involved in the design or execution of the study performed all analyses with the use of Stata (version 8.0) or StatsDirect statistical software. A preplanned interim analysis was carried out approximately halfway through the study, and the results were reviewed by the data and safety monitoring committee. After a series of adverse reactions, a second analysis, focusing on safety, was carried out after 440 children had been recruited; the committee recommended that the trial continue. All analyses were performed on an intention-to-treat basis. Patient characteristics and treatment effects of the various fluids were compared with the use of the chi-square or Fisher's exact test for categorical variables and the Mann–Whitney or Kruskal–Wallis test for continuous variables. Cardiovascular recovery times were compared with the use of the log-rank test, and the estimated probability of recovery is presented as Kaplan–Meier curves. Dextran was compared with starch across the categories of pulse pressure; comparisons were carried out with the use of the Mantel–Haenszel test for categorical outcomes, with conditional logistic regression used to test fluid association with continuous outcomes. Comparisons of event rates among the various fluid-treatment groups are presented as relative risks, focusing on comparisons between the crystalloid and either of the colloid groups, or between the dextran and the starch groups. We used Koopman's method for the ratio of binomials to determine 95 percent confidence intervals.

RESULTS

The profile of the trial is presented in Figure 1. A total of 512 children were recruited into the study between August 1999 and March 2004, and all received their designated study fluid. Of the 512 patients, 476 (93 percent) had confirmed dengue, were correctly enrolled and randomly assigned to receive a fluid, and received the assigned fluid to within 10 percent of the intended volume of 25 ml per kilogram over two hours for initial resuscitation. Treat-

Figure 1. Profile of the Trial.
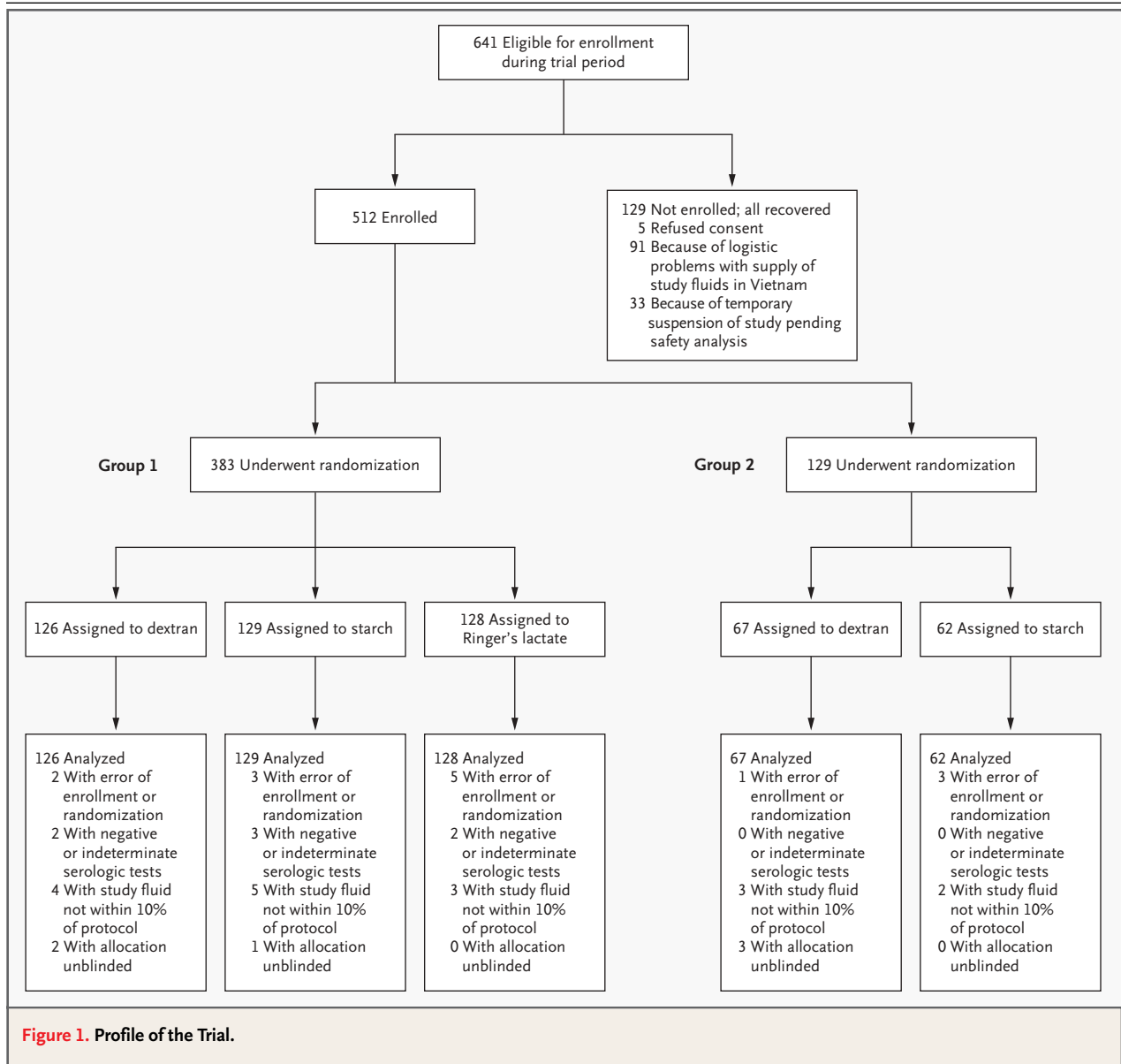
ment allocation was unblinded in six patients (five receiving dextran, and one receiving starch) after a severe allergic-type reaction to the study fluid, in order to permit decisions to be made about which colloid to use for subsequent rescue therapy. All baseline characteristics were similar among the fluid-treatment groups for the 383 children with moderately severe shock (group 1) and for the 129 children with severe shock (group 2) (Table 1). One child (a recipient of starch) died of profound shock and gastrointestinal bleeding. The remaining study patients recovered fully. Outcome data reported here are for all 512 children, except where indicated.

DIFFERENCES IN EFFECTS OF FLUID TREATMENT
There was no significant difference among the fluids in terms of the overall proportion of children requiring rescue colloid in either severity group (Table 2). The relative risk of a requirement for rescue colloid was 1.08 (95 percent confidence interval, 0.78 to 1.47; P=0.65) among children with moderate shock who received Ringer's lactate as compared with either of the colloid solutions, 1.13 (95 percent confidence interval, 0.74 to 1.74; P=0.59) among children who received dextran as compared with starch in the severe shock group, and 0.88 (95 confidence interval, 0.66 to 1.17; P=0.38)

Characteristic	Group 1			Group 2	
	Dextran (N=126)	Starch (N=129)	Ringer's Lactate (N=128)	Dextran (N=67)	Starch (N=62)
Age — yr					
Median	10	10	10	9	9
90% range	6–14	4.5–14	5–14	4–13	5–14
Male sex — no. (%)	57 (45)	70 (54)	66 (52)	29 (43)	33 (53)
Day of illness at shock — no. (%)					
≤4	38 (30)	45 (35)	42 (33)	25 (37)	24 (39)
5–6	60 (48)	48 (37)	54 (42)	25 (37)	22 (35)
≥7	28 (22)	36 (28)	32 (25)	17 (25)	16 (26)
Fluid treatment before study entry — no. (%)					
None	64 (51)	65 (50)	53 (41)	45 (67)	43 (69)
Maintenance only	62 (49)	61 (47)	72 (56)	21 (31)	18 (29)
More than maintenance	0	3 (2)	3 (2)	1 (1)	1 (2)
Weight — kg					
Median	25	25	25	24	22
90% range	15–43	14–40	15–42	14–40	14–41
Temperature — °C					
Median	37.0	37.0	37.0	37.0	37.0
90% range	37.0–38.1	37.0–38.4	37.0–38.7	37.0–38.0	37.0–38.4
Pulse rate — beats/min†					
Median	110	110	120	120	120
90% range	80–140	80–130	90–140	80–140	83–142
Systolic blood pressure — mm Hg‡					
Median	90	90	90	90	90
90% range	75–110	80–110	72–113	80–106	70–110
Diastolic blood pressure — mm Hg§					
Median	75	75	75	80	80
90% range	57–90	60–90	55–95	66–94	59–100
Respiratory rate — breaths/min					
Median	24	24	24	26	28
90% range	20–29	20–31	20–32	20–32	20–32
Bleeding manifestations — no. (%)					
None	25 (20)	25 (19)	18 (14)	9 (13)	12 (19)
Skin only	79 (63)	78 (60)	87 (68)	43 (64)	40 (65)
Mucosal	17 (13)	26 (20)	21 (16)	12 (18)	8 (13)
Missing data	5 (4)	0	2 (2)	3 (4)	2 (3)
Liver size — cm					
Median	2.0	2.0	2.0	2.0	2.0
90% range	0–4.0	0–3.6	0.3–4.0	0–3.0	0–3.0
Hematocrit — %					
Median	48	47	48	51	51
90% range	42–54	41–55	42–54	45–56	43–58

Table 1. Baseline Characteristics of the Patients.*

Table 1. (Continued.)					
Characteristic		Group 1			Group 2	
	Dextran (N=126)	Starch (N=129)	Ringer's Lactate (N=128)	Dextran (N=67)	Starch (N=62)
Platelet count — per mm³					
Median	48,000	56,000	50,000	48,000	53,000
90% range	16,000–150,000	18,000–152,000	19,000–141,000	15,000–143,000	14,000–159,000
Prothrombin time — sec¶‖					
Median	12.8	13.0	13.1	13.7	14.1
90% range	11.8–16.2	11.8–21.7	11.9–19.2	11.9–18.6	11.7–22.4
Activated partial-thromboplastin time — sec¶**					
Median	39.4	42.1	41.4	43.9	51.9
90% range	31.7–54.1	32.6–74.6	32.0–70.8	31.4–69.6	33.2–76.2
Fibrinogen — g/liter¶‖					
Median	2.2	2.1	2.0	2.3	1.9
90% range	1.5–3.3	0.8–3.7	1.1–3.0	0.9–3.7	1.1–2.4
Fibrin-degradation products — no. (%)¶‖					
Negative	29 (63)	22 (61)	30 (68)	18 (82)	11 (52)
Weakly positive	9 (20)	8 (22)	10 (23)	4 (18)	7 (33)
Strongly positive	8 (17)	6 (17)	4 (9)	0	3 (14)
Study fluid volume received — ml/kg					
Median	25.0	25.0	25.0	25.0	25.0
90% range	24.0–25.8	22.8–25.6	23.8–25.7	22.8–25.5	23.8–25.5

* Patients in group 1 had a pulse pressure greater than 10 mm Hg and less than or equal to 20 mm Hg. Patients in group 2 had a pulse pressure of 10 mm Hg or less. Percentages may not sum to 100 because of rounding.

† Data are for those patients with recordable values for cardiovascular characteristics at admission. In group 1, data are for 119 patients receiving dextran, 117 receiving starch, and 119 receiving Ringer's lactate. In group 2, data are for 39 patients receiving dextran and 34 receiving starch.

‡ Data are for those patients with recordable values for cardiovascular characteristics at admission. In group 1, data are for 125 patients receiving dextran and 127 receiving Ringer's lactate. In group 2, data are for 47 patients receiving dextran and 39 receiving starch.

§ Data are for those patients with recordable values for cardiovascular characteristics at admission. In group 1, data are for 125 patients receiving dextran and 127 receiving Ringer's lactate. In group 2, data are for 43 patients receiving dextran and 36 receiving starch.

¶ Data are for samples separated within 12 hours, with no hemolysis or visible clot formation.

‖ In group 1, data are for 46 patients receiving dextran, 36 receiving starch, and 44 receiving Ringer's lactate. In group 2, data are for 22 patients receiving dextran and 21 receiving starch.

** In group 1, data are for 45 patients receiving dextran, 35 receiving starch, and 44 receiving Ringer's lactate. In group 2, data are for 22 patients receiving dextran and 20 receiving starch.

among children who received dextran as compared with starch in the combined analysis. Children in group 1 who received Ringer's lactate for primary resuscitation took longer to achieve initial cardiovascular stability than patients receiving either of the colloids (Fig. 2A), but the degree of compromise during this period was generally not sufficient to warrant intervention with rescue colloid, and the time to final cardiovascular stability was not different among the fluid-treatment groups (Fig. 2B).

No child in group 1 who had received starch for primary resuscitation required rescue colloid to recover from this episode. Overall, significantly fewer recipients of starch than of dextran required rescue colloid at this early stage in either severity group; the relative risk of a requirement for rescue colloid for the initial episode of shock was 0.34 (95 percent confidence interval, 0.07 to 1.71; P=0.03) among starch recipients as compared with dextran recipients in the combined analysis. There was a corresponding minor advantage in initial cardiovascular recovery times in the recipients of starch as compared with the recipients of dextran in group 2 (median, one hour vs. two hours; P=0.03 by the log-rank test). However, the numbers involved were small and the effect was

Table 2. Primary and Secondary Outcome Measures.*

Outcome	Dextran	Starch	Ringer's Lactate	P Value†
Any rescue colloid — no. (%)				
Group 1	31 (25)	43 (33)	40 (31)	0.28
Group 2	28 (42)	23 (37)	—	0.59
Groups combined	59 (31)	66 (35)	—	0.38
Rescue colloid for initial resuscitation — no. (%)				
Group 1	5 (4)	0	4 (3)	0.05
Group 2	6 (9)	3 (5)	—	0.49
Groups combined	11 (6)	3 (2)	—	0.03
Rescue colloid required subsequently — no. (%)				
Group 1	29 (23)	43 (33)	38 (30)	0.18
Group 2	26 (39)	22 (35)	—	0.70
Groups combined	55 (28)	65 (34)	—	0.22
Total volume of rescue colloid — ml/kg				
Group 1				0.11
Median	0	0	0	
90% range	0–17	0–26	0–29	
Group 2				0.76
Median	0	0	—	
90% range	0–25	0–33	—	
Groups combined				0.16
Median	0	0	—	
90% range	0–22	0–28	—	
Total fluid volume — ml/kg				
Group 1				0.76
Median	100	100	100	
90% range	66–142	70–163	65–157	
Group 2				0.70
Median	104	106	—	
90% range	63–178	66–202	—	
Groups combined				0.17
Median	100	100	—	
90% range	64–152	70–166	—	
Percentage reduction in hematocrit at 2 hr‡				
Group 1				<0.001
Median	25	22	9	
90% range	10–35	7–31	1–19	
Group 2				<0.001
Median	28	25	—	
90% range	21–37	16–34	—	
Groups combined				<0.001
Median	26	22	—	
90% range	10–36	10–32	—	
Days in hospital				
All groups				0.81
Median	4	4	4	
90% range	4–7	4–7	4–7	

* In group 1, data are for 126 patients receiving dextran, 129 receiving starch, and 128 receiving Ringer's lactate. In group 2, data are for 67 patients receiving dextran and 62 receiving starch. In the groups combined, data are for 193 patients receiving dextran and 191 receiving starch. A dash denotes not applicable.

† The chi-square or Fisher's exact test was used for categorical variables, and the Mann–Whitney or Kruskal–Wallis test for continuous variables. Comparisons between the children receiving dextran and starch across the two severity groups were carried out with the use of the Mantel–Haenszel test for categorical outcomes, with conditional logistic regression used to test fluid association with continuous outcomes. P values are for three-way comparisons in group 1 and for two-way comparisons in group 2 and the combined group analyses. For the combined analyses, tests for heterogeneity were not significant in each instance.

‡ In group 1, data are for 121 patients receiving dextran, 123 receiving starch, and 126 receiving Ringer's lactate. In group 2, data are for 62 patients receiving dextran and 60 receiving starch.
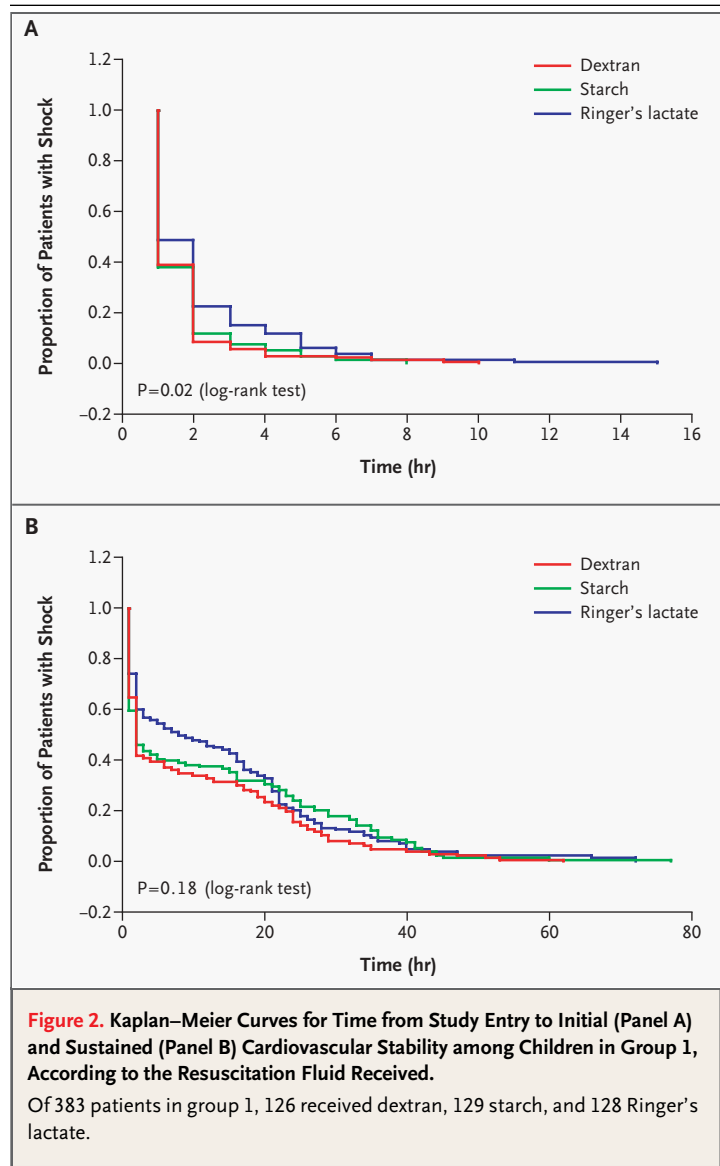
not sustained. Thus, there was no difference in either severity group in the requirement for colloid subsequent to the initial episode of shock, in the volumes of rescue colloid or total parenteral fluid administered, in the final recovery times, or in the number of days in the hospital.

Marked differences were noted among the fluids in their effects on the capillary hematocrit. Two hours after study entry, the median reduction in the hematocrit from baseline was 9 percent (90 percent range, 1 to 19 percent) for children in group 1 who received Ringer's lactate as compared with 25 percent (90 percent range, 10 to 35 percent) for those who received dextran and 22 percent (90 percent range, 7 to 31 percent) for those who received starch (P<0.001) (Table 2). However, the subsequent increase in the hematocrit between two and six hours was significantly greater for the two colloids than for the crystalloid. The median increase in the hematocrit during this period was 5 percent (90 percent range, −8 to 20 percent) for dextran and 5 percent (90 percent range, −10 to 21 percent) for starch as compared with 0 percent (90 percent range, −12 to 12 percent) for Ringer's lactate in group 1 (P<0.001), and 8 percent (90 percent range, −6 to 22 percent) and 5 percent (90 percent range, −9 to 21 percent) for dextran and starch, respectively, in group 2 (no statistical difference).

POSSIBLE COMPLICATIONS OF FLUID TREATMENT
There were no significant differences in any adverse effects of the various fluid treatments, except in the incidence of allergic-type reactions (Table 3). Fifteen of 193 patients (8 percent) receiving dextran had severe reactions (transient high fever and rigors without cardiorespiratory compromise) that occurred within six hours of commencing the study fluid. Bacterial cultures and tests for endotoxin contamination were negative, but ongoing investigations suggest contamination of certain batches with a nonendotoxin pyrogen (Dr. S. Poole, National Institute for Biological Standards and Control, London: personal communication). An urticarial rash without fever developed in one patient in the starch group at the end of the infusion. All patients responded to symptomatic treatment alone.

There were no differences among the fluid-treatment groups in the development of new bleeding manifestations, clinical fluid overload, objective measures of the overall severity of vascular leakage, or the use of furosemide (Table 3). The serial coagulation-screening tests revealed a mild coagulopathy at study entry in all groups of patients, as expected, that worsened slightly on study day 2 but improved again by study day 4 (Table 4). The only significant difference was between the absolute values for the partial-thromboplastin time in the children in group 2 who received dextran or starch on day 2. However, all the coagulation variables were slightly worse before study entry in the children in group 2 who received starch, and the day 2 results actually represented an improvement from day 1. All other comparisons showed no differences among the fluid-treatment groups, including comparisons of the percentage changes in each variable on the different days (data not shown).

Figure 2. Kaplan–Meier Curves for Time from Study Entry to Initial (Panel A) and Sustained (Panel B) Cardiovascular Stability among Children in Group 1, According to the Resuscitation Fluid Received.

Of 383 patients in group 1, 126 received dextran, 129 starch, and 128 Ringer's lactate.

Table 3. Possible Adverse Effects of Fluid Treatment.*

Adverse Effect	Group 1			Group 2	
	Dextran (N=126)	Starch (N=129)	Ringer's Lactate (N=128)	Dextran (N=67)	Starch (N=62)
New bleeding after study entry — no. (%)					
None	103 (82)	106 (82)	108 (84)	58 (87)	52 (84)
Minor skin bleeding	16 (13)	17 (13)	12 (9)	5 (7)	5 (8)
Mucosal or major soft-tissue bleeding	6 (5)	5 (4)	5 (4)	2 (3)	4 (6)
Any bleeding requiring transfusion	1 (<1)	1 (<1)	3 (2)	2 (3)	1 (2)
Clinical fluid overload — no. (%)	44 (35)	39 (30)	39 (30)	27 (40)	24 (39)
Depth of right pleural effusion — cm†					
Median	4.4	4.6	4.3	4.8	4.9
90% range	0–7.2	0–7.7	0–7	2–6.8	2.1–8.5
Volume of ascites — no. (%)†					
None	7 (9)	5 (6)	3 (4)	0	0
Mild	21 (27)	20 (24)	27 (35)	12 (29)	10 (28)
Moderate	46 (59)	54 (66)	43 (56)	27 (66)	23 (64)
Severe	4 (5)	3 (4)	4 (5)	2 (5)	3 (8)
Diuretic therapy — no. (%)					
None	91 (72)	93 (72)	103 (80)	44 (66)	42 (68)
≤2 mg/kg furosemide, total dose	30 (24)	31 (24)	18 (14)	19 (28)	18 (29)
>2 mg/kg furosemide, total dose	5 (4)	5 (4)	7 (5)	4 (6)	2 (3)
Severe allergic-type reactions after infusion — no (%)‡	9 (7)	1 (<1)	0	6 (9)	0

* Percentages may not sum to 100 because of rounding.
† Data are for children for whom an ultrasound scan was performed 48 to 72 hours after study entry (i.e., in group 1, 78 patients receiving dextran, 82 receiving starch, and 77 receiving Ringer's lactate; and in group 2, 41 receiving dextran and 36 receiving starch). To assess the severity of leakage, the depth of fluid (in centimeters) in the right hemithorax posterior to the liver was measured with the patient lying flat and the probe placed at the costal margin in the mid-clavicular line.
‡ P<0.001 for group 1 and P=0.03 for group 2 by Fisher's exact test. All other statistical comparisons were not significant.

DISCUSSION

Although volume replacement is accepted as the mainstay of treatment for children with dengue shock syndrome, the two previous studies that investigated the efficacy of different fluids in this situation were not adequately powered with respect to a clinically relevant outcome to permit definitive comparisons between management with crystalloid and colloid solutions. This study, with requirement for rescue colloid as the outcome indicator, establishes that the cheapest and safest choice, Ringer's lactate, is as effective as either of the colloids for initial resuscitation of children with moderately severe shock. The recent publication of the Saline versus Albumin Fluid Evaluation (SAFE) Study findings,[15] indicating that albumin and normal saline were equally effective for fluid resuscitation in a large, heterogeneous population of patients in in-

tensive care units, has advanced considerably the general debate about crystalloids versus colloids. Our trial, focusing on a single disease entity for which fluid resuscitation is the essential and usually sole intervention required, indicates that even in patients with vascular leak, isotonic crystalloid solutions are as effective as colloid solutions for the majority of patients.

More patients with severe shock at presentation required rescue colloid than did patients with moderately severe shock, but only minor differences in efficacy were detected between the colloids in either severity group. Although minor benefits were seen among the recipients of starch during the initial resuscitation, the relatively large molecular size of starch as compared with dextran did not result in prolonged intravascular persistence or a more sustained volume-expanding effect. We found no evidence of adverse effects of either colloid on the

Table 4. Results of Serial Coagulation-Screening Tests According to Day of Shock.*

Variable	Day 1			Day 2			Day 4		
	Dextran	Starch	Ringer's Lactate	Dextran	Starch	Ringer's Lactate	Dextran	Starch	Ringer's Lactate
Group 1									
No. of patients	46	36	44	90	96	95	97	90	89
Prothrombin time — sec									
Median	12.8	13.0	13.1	13.3	13.1	13.1	12.2	12.2	12.1
90% range	11.8–16.2	11.8–21.7	11.9–19.2	11.9–19.4	11.9–18.5	11.9–18.5	11.1–14.7	11.0–15.1	11.2–14.5
Activated partial-thromboplastin time — sec									
Median	39.4	42.1	41.4	43.8	42.8	42.2	35.4	35.0	34.8
90% range	31.7–54.1	32.6–74.6	32.0–70.8	32.0–60.4	32.1–59.3	32.5–59.2	30.1–44.8	29.8–46.4	30.1–47.4
Fibrinogen — g/liter									
Median	2.2	2.1	2.0	1.6	1.5	1.7	2.1	2.3	2.3
90% range	1.5–3.3	0.8–3.7	1.1–3.0	0.8–3.1	0.7–2.7	0.7–2.9	1.1–3.3	1.5–3.2	1.1–3.4
Fibrin-degradation products — no. (%)									
Negative	29 (63)	22 (61)	30 (68)	67 (74)	74 (77)	75 (79)	62 (64)	56 (62)	55 (62)
Weakly positive	9 (20)	8 (22)	10 (23)	13 (14)	17 (18)	17 (18)	18 (19)	24 (27)	20 (22)
Strongly positive	8 (17)	6 (17)	4 (9)	10 (11)	5 (5)	3 (3)	17 (18)	10 (11)	14 (16)
Group 2									
No. of patients	22	21	—	48	44	—	52	48	—
Prothrombin time — sec									
Median	13.7	14.1	—	13.8	14.4	—	12.6	12.7	—
90% range	11.9–18.6	11.6–22.4	—	11.2–21.8	11.8–21.8	—	11.2–16.1	10.9–19.0	—
Activated partial-thromboplastin time — sec									
Median	43.9	51.9	—	42.2†	48.5†	—	35.5	36.8	—
90% range	31.4–69.6	33.2–76.2	—	32.1–62.3	34.3–63.1	—	30.7–51.1	31.7–53.8	—
Fibrinogen — g/liter									
Median	2.3	1.9	—	1.4	1.5	—	2.3	2.3	—
90% range	0.9–3.7	1.1–2.5	—	0.9–3.3	0.7–3.0	—	1.5–3.9	1.4–3.9	—
Fibrin-degradation products — no. (%)									
Negative	18 (82)	11 (52)	—	36 (73)	36 (82)	—	26 (50)	22 (46)	—
Weakly positive	4 (18)	7 (33)	—	10 (20)	6 (14)	—	16 (31)	14 (29)	—
Strongly positive	0	3 (14)	—	3 (6)	2 (5)	—	10 (19)	12 (25)	—

* The day of study entry is day 1. Data are for samples separated within 12 hours, with no hemolysis or visible clot formation. Dashes denote not applicable. Percentages may not sum to 100 because of rounding.

† In group 2 on day 2, the activated partial-thromboplastin time was significantly prolonged in the children who received starch as compared with those who received dextran (P<0.001 by the Kruskal–Wallis test). All other comparisons for the absolute values and for the percentage changes in the variables at each time point showed no differences among the fluids.

intrinsic coagulopathy or clinical bleeding manifestations or on the severity of fluid overload.

The serial hematocrit measurements reflect a combination of the effects of fluid treatment and ongoing vascular leak. The hematocrit data indicate that the two colloids exert a dramatic immediate ef-

fect that is followed by a rebound increase in vascular leak a few hours later.

Current theories of microvascular ultrafiltration support the basic Starling principle of a balanced equilibrium between opposing oncotic and hydrostatic pressures but postulate that the glycocalyx,

rather than the endothelial cells themselves, is the major regulator of fluid flow.[16,17] There is good evidence that plasma proteins, particularly albumin, adsorb to positive residues in the glycocalyx layer and restrict ultrafiltration.[18-20] Albumin is probably washed out of this layer during dengue infections but may be replaced temporarily by the synthetic colloids, which are known to permeate the glycocalyx at different rates, depending on molecular size.[21] In this way, colloids may briefly alter the selective permeability of the endothelial barrier, reducing outward flux and permitting the low hydrostatic pressure of the capillaries to rise until the colloid molecules themselves are washed out and the net Starling forces again favor leakage but from a higher baseline hydrostatic pressure. In contrast, crystalloid solutions equilibrate rapidly throughout the intravascular and interstitial fluid spaces and appear to have no effect on the function of the endothelial barrier. The effects of colloids are transient, however, and despite the early rebound in the hematocrit seen in the children receiving colloids, we found no difference between the different fluids in the overall severity of fluid overload when it was assessed 48 to 72 hours after the study infusion.

During the study, an excess of febrile responses occurred in the recipients of dextran. Dextrans are produced by a process involving bacterial degradation, and despite purification, residual pyrogens may be sufficient to induce febrile responses. In the present study, febrile responses were associated with particular batches of fluids. The overall frequency and importance of this adverse effect in the management of dengue remain to be determined.

In addition to its relevance to dengue, major strengths of this large, randomized trial in the general debate about crystalloids versus colloids are the uniform nature of the underlying disease process and the fact that fluid resuscitation is the single most important therapeutic intervention. Subgroup analysis of the SAFE trial suggested a treatment effect favoring albumin in patients with severe sepsis of mixed underlying causes,[15] many of whom are likely to have had an associated vascular-leak syndrome. In our study, however, there was no clear benefit to the use of a colloid in children with moderately severe shock due to vascular-leak syndrome. Although the pathophysiological mechanism underlying the vascular leak associated with severe sepsis may well be different from that associated with the dengue virus, this group of children showed considerable cardiovascular compro-

mise, and yet most did well with Ringer's lactate alone.

Unlike the SAFE trial, the present trial did not examine mortality as an outcome; our primary outcome was an intervention based on the treating clinician's subjective assessment of need. However, our study took place in a single ward staffed by the same core group of doctors throughout and study treatment was concealed and blinded so that differences in the threshold for intervention are likely to have been distributed evenly across the groups of children receiving the various fluids. Although there is no proven relationship to mortality, colloid rescue is an integral part of the WHO management guidelines for resuscitation of dengue shock syndrome, and a substantial requirement for rescue colloid is considered by physicians in endemic areas to be a poor prognostic marker.

It is likely that the excellent overall outcome (one death among 641 children with dengue shock syndrome treated during the trial period) reflects meticulous overall medical and nursing care as much as the specific treatments used. Hourly observations, immediate access to ward-based hematocrit measurements, and a conservative intervention policy ensure that patients receive volumes of intravenous fluid that are titrated carefully to requirements, thus providing sufficient fluid to maintain vital functions during the period of systemic leakage without overfilling the intravascular space. Respiratory compromise secondary to fluid overload is a major contributor to mortality in settings with poor resources, few personnel, and limited equipment. In general, in the Southeast Asian region, mortality rates of 1 to 5 percent persist, and efforts to improve management must continue. For ethical reasons, we did not address the issue of the use of crystalloids for patients with profound or recurrent shock, two situations in which colloid solutions are thought to be beneficial, despite a lack of good supporting evidence. Further studies are needed that focus on these high-risk groups. The uniformly good outcome in children with shock of moderate severity who received the crystalloid in this study may help to provide reassurance for future studies. In addition, work to better define the pathophysiological mechanisms underlying the vascular-leak process will be useful to inform future studies.

In conclusion, most children with dengue shock syndrome respond well to judicious treatment with isotonic crystalloid solutions. Early intervention with colloid solutions is not indicated. The fluid

regimen of Ringer's lactate at 25 ml per kilogram over a period of two hours is now supported by strong prospective evidence and should be recommended for children with moderately severe shock. For those with severe shock, the situation is less clear-cut, and clinicians must continue to rely on personal experience, familiarity with particular products, local availability, and cost. Minor advantages in initial recovery were shown with starch, and significantly more adverse reactions were associated with dextran, so if the use of a colloid is considered necessary, starch may be the preferred option.

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