Choice of Colloidal Solutions in Dengue Hemorrhagic Fever Patients

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Background: *DHF is characterized by plasma leakage and abnormal hemostasis. About 20% of DHF patients do require colloidal solution in addition to conventional crystalloid solution for the treatment. There is only one colloidal solution, 10% Dextran-40 in NSS that proved to be effective for this group of DHF patients.*
Objective: *To compare 10% dextran-40 in NSS with 10% Haes-steril in NSS in the management of DHF cases with severe plasma leakage for their effectiveness and impact on renal function, hemostasis, disease severity, and complications.*
Material and Method: *DHF patients admitted to Dengue Unit, QSNICH, who do not respond to conventional crystalloid solution, are randomly assigned to receive either dextran or haes-steril. Clinical and laboratory comparison are recorded and analyzed using SPSS for Window version 14.0.*
Results: *There are 104 DHF patients enrolled in the study; 57 are assigned in dextran and 47 in haes-steril group. The mean ages are 8.6 $\pm$ 3.9 years. About half of the patients in both groups require one dose of colloidal solution and 25% require 2 and 3 doses ($p = 0.138$). The average amount of IV fluid infused in dextran and haes-steril group are 119.4 and 129.3 ml ($p = 0.227$). The average drop in Hct after the bolus dose of both colloid are 7.9 and 8.5% ($p = 0.381$). About 80% of the patients in each group have shock ($p = 0.843$). The mean elevation of AST are 598 and 822 U ($p = 0.548$) while ALT elevation are 182 and 306 U ($p = 0.265$) in dextran and haes-steril group, respectively. BUN and creatinine are within normal limits and are decreased after the use of colloidal solutions. The amount of urine on day 1, 2 and 3 after the use of both colloidal solutions are not different. Coagulogram studies (PT, PTT and TT) in both groups are not different. Patients with significant bleeding and who require blood transfusions are 15.8 and 19.2% in dextran and haes-steril group ($p = 0.423$).The incidence of fluid overload in dextran and haes-steril group are 35.1 and 40.4% ($p = 0.360$). Other complications are not different between dextran and haes-steril group as follows: hypocalcaemia, hyponatremia, hypokalemia and acidosis. The overall severity and complications in both groups of patients are much higher than in DHF patients who respond to conventional crystalloid solution. No allergic reaction was found after the use of both colloidal solutions.*
Conclusion: *10% Haes-steril is as effective as 10% dextran-40 in the treatment of DHF patients who have severe plasma leakage. There are no differences in DHF disease severity and complications in both groups but the disease severity and complications, especially fluid overload are observed to be more comparative with admitted DHF patients. Both colloidal solutions are safe in DHF patients with no allergic reaction observed and no interference in renal functions and hemostasis.*

Keywords: *DHF, Severe plasma leakage, Colloidal solution, Fluid overload*

J Med Assoc Thai 2008; 91 (Suppl 3): S97-103
Full text. e-Journal: *http://www.medassocthai.org/journal*

Dengue is the most prevalent mosquito-borne viral infection worldwide. Around 100 million cases of dengue fever (DF) and half a million cases of dengue hemorrhagic fever (DHF) are estimated to occur annually[1,2]. DHF is the most serious manifestation of dengue infection with the 2 distinct disease hallmarks of plasma leakage and abnormal hemostasis which makes it different from DF. During febrile phase, DF

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and DHF patients present with high continuous fever and non-specific signs and symptoms and we cannot differentiate each other. DF patients may have more complaints of severe headache, retro-orbital pain, muscle and bone pain. The treatment is symptomatic during this phase and no need for intravenous fluid administration except in a few cases with severe vomiting and dehydration. At the end of febrile phase, thrombocytopenia (platelet count d $\leq$ 100,000 cells/cumm.) begins concomitantly with plasma leakage in DHF patients while DF patients recover spontaneously and uneventfully especially in children. Adult DF patients may have prolonged fatigue with loss of appetite for quite a period 2 weeks to 1-3 months[2-5].

Most DHF cases present with minor bleeding manifestations, *e.g.* skin bleeding, epistaxis, gum bleeding, coffee-ground vomiting, hematemesis and melena. Severe bleeding usually accompanies prolonged shock due to underlying diseases (peptic ulcer) or drug ingestion (aspirin, ibuprofen, steroid). Plasma leakage is the main problem in most DHF cases and the management is intravenous (IV) fluid for those patients who cannot have adequate oral intake. Isotonic salt solution, a crystalloid solution is the main choice for most DHF patients during this critical period. The total amount of IV fluid resuscitation and replacement during this critical period of 24-48 hours is limited to maintenance about +5% deficits, since the plasma selectively leaked into the pleural and abdominal spaces. If more fluid is given, the patients may have respiratory distress/failure due to massive pleural effusion and ascites[6-8].

If the patients have massive plasma leakage, additional colloidal solution is needed in its capacity to hold the plasma volume better. This colloidal solution should be in the plasma expander group, for which its osmolarity is more than plasma, not in the plasma substitute group, which is iso-osmolarity to plasma[6-8]. From our past experience, about 15-20% of admitted DHF patients do need this colloidal solution[6,9,10]. At the present time, only 10% Dextran-40 in normal saline solution is used nationwide as it is easily available, proved to be effective and recommended in the Thai Ministry of Public Health Guidelines for Dengue Case Management 2003 and other dengue recommendation guidelines[6-8].

Material and Method

Study design

The trial is a single-center, randomized, single-blind comparison of 10% Dextran-40 and 10% Haes-steril use in DHF patients who have indications fulfilled for using colloidal solution.

Study population

All DHF patients admitted to the Dengue Ward, Queen Sirikit National Institute of Child Health (QSNICH) are eligible for enrollment provided a parent or guardian gives informed consent. The Ministry of Public Health (MOPH), Thailand Guidelines for Dengue Case Management 2003[7] is used for the management. The author, one of the DHF patients' care team participates in the management of all study patients. DHF disease severity is classified according to the WHO classification[2]. The study was performed in Dengue Unit, QSNICH, Bangkok, Thailand.

Enrollment criteria

DHF patients who have received IV fluid (5% DAR or 0.9% NSS) resuscitation/replacement and have the following indications for using colloidal solution[6-8]:

- Have signs or symptoms of fluid overload: swollen eyelids, dyspnea, tachypnea, distended abdomen, positive lung signs; crepitation, rhonchi and wheezing,
- Shock and no response to conventional IV fluid resuscitation according to the above MOPH Guidelines
- Have received too much crystalloid solution (> maintenance + 5% deficit at that point of time) and still have high Hct or unstable vital signs

Exclusion criteria

- DHF patients who have underlying diseases
- No parental or guardian informed consent

Clinical methods

At study entry, demographic data, history and physical examinations are recorded.

Colloidal solution

The colloidal solutions used in this study are in the group of plasma expander which is effective in holding the intravascular volume in DHF patients:

10% Dextran-40 in normal saline solution (NSS) is polysaccharide which has molecular weight of 40,000 Daltons; osmolarity 330 mosm/l; expanded volume is 130-300% in normal subject; half life of 6-12 hours; 70% appears in urine within 24 hours.

10% Haes-steril in NSS is a penta-starch (hydroxyethyl starch) which has average molecular

weight 200,000 Daltons; osmolarity 309 mosm/l; expanded volume is 140% in normal subject; half life of 16-24 hours; 70% appears in urine within 24 hours.

Both colloidal solutions will be given in a bolus dose, 10 ml/kg/hr at a time, interrupt with the conventional IV fluid (5% Dextrose in Acetate Ringer-5%DAR). Doses of colloidal solutions are repeated if there are indications. The maximum dose is 30 ml/kg/day with few exceptions if the patients really need the 4th dose of colloidal solution[6-8]. Monitoring of clinical findings (at least twice a day), vital signs (at least every 1-2 hours), Hct (at least every 4-6 hours), and urine output (at least every 8 hours) are done by the same DHF patients' care team.

Laboratory procedures

All patients will have serologic and virologic verification for dengue virus infections done by Armed Forced Research Institute of Medical Sciences (AFRIMS) which is a WHO reference laboratory.

Hct will be done before and after every dose of colloidal solution. In addition to routine laboratory investigation for DHF patients at QSNICH (CBC, LFT and coagulogram: prothrombin time-PT, partial thromboplastin time - PTT and thrombin time - TT), BUN and creatinine are done 2 times; at the time of enrollment, *i.e.* before giving the first colloidal solution and at discharge. Additional laboratory investigations will be done in some patients if necessary.

Outcome measures

The primary outcome measure is the effectiveness of the colloidal solution in the degree of reduction of Hct after each bolus dose and the total amount usage compare between both colloidal solutions. The following secondary outcome measures are examined: the severity of DHF illness, the impact on renal function (amount of urine, BUN, creatinine) and the coagulogram study (PT, PTT and TT) and other complications especially fluid overload.

Statistical analysis

All analysis is using SPSS for window version 14. Patients' characteristic and treatment effects are compared using chi-square or Fisher's exact test for categorical variables and paired t-test or ANOVA for continuous variables.

Results

There are 57 and 47 DHF patients enrolled in dextran and haes-steril group. There are 6 DHF grade I, 15 DHF grade II, 66 DHF grade III and 17 DHF grade IV in both groups. The male to female ratio is 1: 1.06 and the mean age is 7.8 $\pm$ 3.9 years old. The majority, 90.4% of DHF patients have secondary dengue infection while 5.8% have primary dengue infection. The majority of cases, 53.8% are caused by Dengue 1 while 27.9, 3.8 and 13.5% are caused by dengue 2, 3 and 4 viruses. There are no differences in the demographic data and degree of severity among these 2 groups of patients (Table 1).

About half of the patients receive only one dose, while 25% receive 2 or 3 doses of colloidal solution (p = 0.138). Two patients need 4 doses of colloidal solution and both are assigned in dextran group (Table 2).

The mean Hct drops after bolus dose of both colloidal solutions is 7.8% while in dextran and haes-steril groups are 7.5 and 8.1%, respectively (p = 0.381). The mean Hct drop after the first, second, third and fourth doses of dextran are 8, 7.7, 5.8 and 10.5

Table 1. Demographic data

	Dextran (n = 57)	Haes-steril (n = 47)	Total (n = 104)	p-value
Male / Female	30/27	20/27	50/54	0.204
Mean age (yr)	8.3$\pm$3.9	7.2$\pm$3.9	8.6$\pm$3.9	0.163
DHF grade I	3	3	6	0.843
DHF grade II	8	7	15	
DHF grade III	35	31	66	
DHF grade IV	11	6	17	
DEN 1	26	20	46	0.805
DEN 2	16	13	29	
DEN 3	3	1	4	
DEN 4	8	6	14	
Not isolate	4	7	11	
Primary	4	2	6	0.071
Secondary	53	41	94	
Indeterminate	0	4	4	

Table 2. Dose of colloid received

	Dextran (n = 57)	Haes-steril (n = 47)	Total (n = 104)	p-value
1 dose	30	23	53	0.138
2 doses	11	13	24	
3 doses	14	11	25	
4 doses	2	0	2	
Total	57	47	104	

respectively while in haes-steril group are 8.7, 7.3 and 7.4%, respectively (Fig. 1, 2).

The total IV fluid receive in dextran group (119.4 ml/kg) is less than in haes-steril group (128.3 ml/kg) (p = 0.227). The total IV fluid in both groups is less in non-shock (DHF grade I & II) compared with shock group (DHF grade III & IV) (p = 0.843) (Fig. 3). About 16% of patients in dextran group received blood transfusions while 19.15% of patients in haes-steril group receive transfusions (p = 0.423).

The value of BUN and creatinine are decreased after using both colloidal solutions and all values are within normal range (Table 3). The amount of urine is observed to be more in dextran group compared with haes-steril group in day 1 - 53.2 vs. 29.0 ml/kg (p = 0.050), day 2 - 45.4 vs. 30.3 ml/kg (p = 0.385) and day 3 - 42.8 vs. 43.9 ml/kg (p = 0.917) after the first use of colloidal solution (Table 4).

Coagulogram studies in dextran and haes-steril group are as follows: INR > 1.3-16.4 vs. 15.2% (p = 0.548), prolonged PTT - 38.3 vs. 54.8% (p = 0.090), prolonged TT - 9.3 vs. 5.0 (p = 0.359) (Table 5).

Complications of fluid overload are found in 35.1 and 40.4% of patients in dextran and haes-steril group (p = 0.360), while furosemide are given in 52.6 and 48.9% of dextran and haes-steril group (p = 0.429). The following signs and symptoms of fluid overload are shown in Fig. 4.

Table 3. BUN and creatinine change

	Dextran (n = 57)	Haes-steril (n = 47)	Total (n = 104)	p-value
BUN before	17.00	15.30	14.09	0.885
BUN after	10.80	11.80	9.60	0.737
Creatinine before	0.72	0.83	0.65	0.970
Creatinine after	0.56	0.68	0.59	0.174

Table 4. Urine output

	Dextran (n = 57)	Haes-steril (n = 47)	Total (n = 104)	p-value
Urine amount (ml/kg) Day1	53.2	29.0	40.0	0.050
Urine amount (ml/kg) Day2	45.4	30.3	37.9	0.385
Urine amount (ml/kg) Day3	42.8	43.9	43.2	0.917

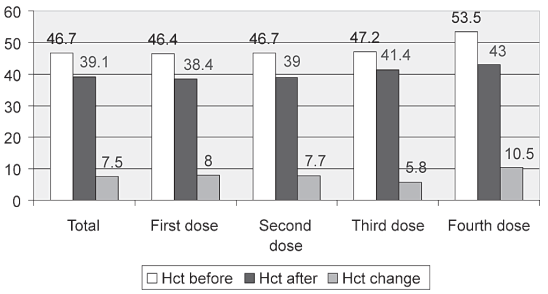

Fig. 1 Hematocrit change - dextran

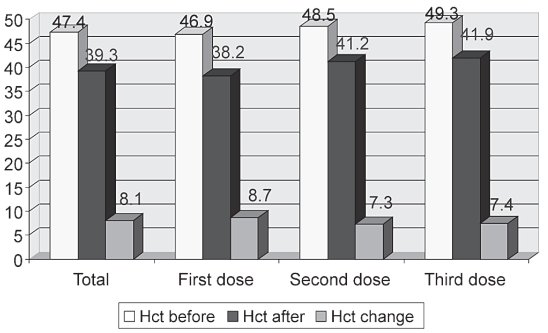

Fig. 2 Hematocrit change - haes-steril

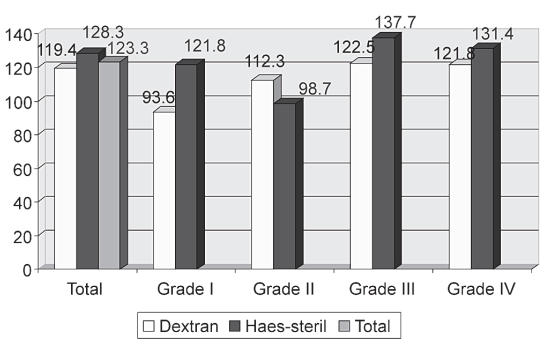

Fig. 3 Amount of IV fluid (ml/kg)

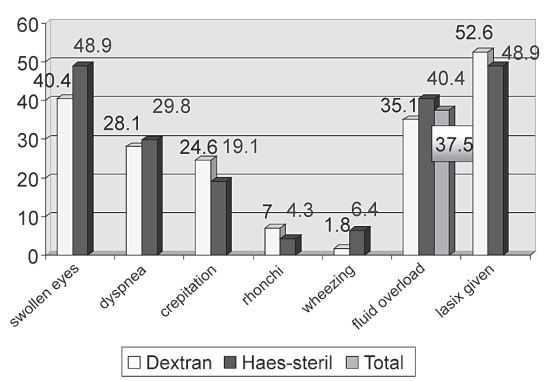

Fig. 4 Sign of fluid overload

Table 5. Coagulogram

	Dextran (n = 57)	Haes-steril (n = 47)	Total (n = 104)	p-value
INR (PT) abnormal (%)	16.4	15.2	15.8	0.548
PTT prolonged (%)	38.3	54.8	46.1	0.090
TT prolonged (%)	9.3	5.0	7.4	0.359
Blood transfusion (%)	15.8	19.2	17.3	0.423

Table 6. Laboratory values

	Dextran (n = 57)	Haes-steril (n = 47)	Total (n = 104)	p-value
Mean nadir plt (cells/cumm)	40,495	43,406	41,634	0.865
Mean hemoconcentration (%)	33.2	33.9	33.7	0.733
Mean min albumin (gm%)	2.60	2.39	2.52	0.368
Mean albumin change (gm%)	1.26	1.32	1.29	0.776
Mean max AST (U)	598	822	699	0.548
Mean max ALT (U)	182	306	238	0.265
Hypocalcemia (%)	90.0	88.2	89.4	0.603
Hypocalcemia (ionized) (%)	70.0	83.3	75.0	0.344
Hyponatremia (%)	52.6	54.2	53.2	0.557
Hypokalemia (%)	23.7	12.5	19.4	0.228
Acidosis (%)	8.3	8.3	8.3	0.689
LOS	4.6	4.4	4.5	0.623

The severity of DHF as measured by platelet count, percent hemoconcentration, level of serum albumin, AST and ALT elevations and other complications; hypocalcemia, hyponatremia, hypokalemia and acidosis in both groups of patients are not different and are shown in Table 6.

Discussion

Although most admitted DHF patients recover very well with only crystalloid solution, about 10-20% have massive plasma leakage that need colloidal solution[6,9,10]. Previous experience revealed that iso-oncotic colloid, including plasma is not as effective as hyper-oncotic colloid[8]. This is likely due to the expander effect of hyper-oncotic colloid that can better hold the intravascular volume and lessen the degree of increased vascular permeability in DHF, as evidence by bringing the Hct down to about 6-10%. It's noted that to bring Hct down to this extent, both colloidal solutions have to be given in a bolus dose of 10 ml/kg/hr. Crystalloid solution and iso-oncotic colloid including plasma in a bolus dose can bring Hct down to only 2-3%[8]. Both dextran and haes-steril cannot be used as the initial fluid resuscitation in shock patients because of their hyper-oncotic, hyper-viscosity nature. Most doctors misunderstand that colloidal solution is used only in shock patients, but in fact the indications include those DHF patients with signs of fluid overload or persistent high Hct. In this study 79.8% of the patients have shock while 20.2% have no shock.

We found no renal impairment after the use of both colloidal solutions. Both the average values of BUN and creatinine are lower after the administration of both colloidal solutions. Even in 2 patients who received 4 doses of dextran have normal values of BUN and creatinine. The total amount of urine on day 1, 2 and 3 after the use of both colloidal solutions are much more than normal amount, 38-43 ml/kg, no matter the patients have received furosemide or not.

The percentage of abnormal PT, PTT and TT are not different between dextran and haes-steril group. The percentage of prolonged PT, PTT and TT are 15.8, 46.1 and 7.4% in the study group compared with 5.2-13%, 64.1-73%and 7.6-13.3% in the previous

Table 7. Disease severity compare with previous study

	This study both colloid groups	1995-1999
Mean Platelet counts (cells.cumm)	41,634	53,452-63,855
Mean albumin (mininmum) (gm%)	2.52	3.6-4.1
Mean AST (U)	699	192-423
Mean ALT (U)	238	88-159
Shock (%)	79.8	44
Total IV fluid (ml/kg)	123.3	56.1-95.2
Blood transfusion (%)	17.3	5.3-12.9
Fluid overload (%)	37.5	4

study[10]. Krishnamurti et al[11] showed that 33.3 and 54.6% of DHF patients had prolonged PT and PTT while Srichaikul et al[12] showed the evidence of DIC in 58% and 82% of DHF and DSS patients in the late 70's when there were more shock cases.

In conclusion, DHF patients from both groups are not different in disease severity and complications. Both colloidal solutions are equally effective in terms of amount, dosage use and the ability to hold the plasma volume as shown by degree of reduction in Hct. There are no serious side effects and no allergic reactions observed for both colloidal solutions. The study patients are more severe when compared with admitted DHF patients in the previous study[10] as shown in Table 7: lower platelet counts, lower mean albumin, higher mean AST and ALT, more patients with shock, more IV fluid and blood transfusions need and more complications of fluid overload.

Acknowledgement

The author would like to thank all the DHF patients' care team of Dengue Unit, QSNICH, especially Dr. Prim Thupvong who is interested and helped in initiating this study; Fresenius Kabi Thailand Ltd for supplying 10% Haes-steril in NSS for this study.

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การเลือกใช้สารคอลลอยด์ในผู้ป่วยโรคไข้เลือดออก

ศิริเพ็ญ กัลยาณรุจ

ภูมิหลัง: *พยาธิสรีรวิทยาที่เป็นลักษณะเฉพาะของโรคไข้เลือดออกคือการรั่วของพลาสมาและความผิดปกติของการแข็งตัวของเลือด มีผู้ป่วยประมาณร้อยละ 20 ที่นอกจากใช้สาร crystalloid แล้วต้องใช้สารคอลลอยด์ในการรักษาด้วย โดยในขณะนี้มีเพียง dextran-40 เท่านั้นที่พิสูจน์ว่าได้ผลดี*

วัตถุประสงค์: *เพื่อเปรียบเทียบประสิทธิภาพของ 10% dextran-40 และ10% haes-steril ในการรักษาผู้ป่วยไข้เลือดออกที่มีการรั่วของพลาสมามาก และผลต่อการทำงานของไต การแข็งตัวของเลือด ความรุนแรงของโรคและภาวะแทรกซ้อนในผู้ป่วย*

วัสดุและวิธีการ: *ผู้ป่วยไข้เลือดออกที่รับไว้รักษาที่หอผู้ป่วยไข้เลือดออก สถาบันสุขภาพเด็กแห่งชาติมหาราชินีที่ไม่ตอบสนองต่อการรักษาด้วยสารคริสตัลลอยด์จะถูกสุ่มเลือกเพื่อให้ได้รับ dextran หรือ haes-steril อาการอาการแสดง และผลการตรวจทางห้องปฏิบัติการจะถูกบันทึกและวิเคราะห์เปรียบเทียบโดยใช้โปรแกรมสำเร็จรูป SPSS for Window version 14.0*

ผลการศึกษา: *มีผู้ป่วยทั้งหมด 104 ราย 57 ราย ได้รับ dextran และ 47 ราย ได้รับ haes-steril อายุเฉลี่ยของผู้ป่วยกลุ่ม dextran และ haes-steril เท่ากับ 8.6 $\pm$ 3.9 ปี ประมาณครึ่งหนึ่งของผู้ป่วยทั้ง 2 กลุ่มได้รับสารคอลลอยด์ 1 ครั้ง ร้อยละ 25 ได้รับ 2 และ 3 ครั้ง (p = 0.138) ปริมาณสารน้ำทั้งหมดที่ให้ผู้ป่วยกลุ่ม dextran และ haes-steril เท่ากับ 119.4 และ 129.3 มล. (p = 0.227) ค่าเฉลี่ยของ Hct ที่ลดลงเท่ากับ 7.9 และ 8.5% หลังการให้ dextran และ haes-steril (p = 0.381) ความรุนแรงของโรคไม่ต่างกันในผู้ป่วยทั้ง 2 กลุ่มโดยร้อยละ 80 ของผู้ป่วยมีอาการช็อก (p = 0.843) ค่าเฉลี่ยของ AST เพิ่มขึ้นในกลุ่ม dextran และ haes-steril เท่ากับ 598 และ 822 U (p = 0.548) ส่วน ALT เพิ่มขึ้นเป็น 182 และ 306 U (p = 0.265) ค่าเฉลี่ย BUN และ creatinine อยู่ในเกณฑ์ปกติในผู้ป่วยทั้ง 2 กลุ่มทุกรายและค่าเฉลี่ยหลังให้สารคอลลอยด์จะน้อยลง ปริมาณปัสสาวะหลังให้สารคอลลอยด์มีจำนวนมากและไม่ต่างกันทั้ง 2 กลุ่ม อุบัติการณ์ของภาวะน้ำเกินในกลุ่ม dextran และ haes-steril เท่ากับร้อยละ 35.1 และ 40.4 (p = 0.360) ภาวะแทรกซ้อนอื่น ๆ ที่พบในผู้ป่วยกลุ่ม dextran และ haes-steril ไม่แตกต่างกัน คือ hypocalcaemia, hyponatremia, hypokalemia และ acidosis ความรุนแรงและภาวะแทรกซ้อนทั้งหมดไม่ต่างกันทั้ง 2 กลุ่ม แต่มากกว่ากลุ่มผู้ป่วยไข้เลือดออกทั่วไปที่รับไว้ในโรงพยาบาล ไม่พบปฏิกิริยาภูมิแพ้ในผู้ป่วยทั้ง 2 กลุ่ม*

สรุป: *10% Haes-steril มีประสิทธิภาพเหมือนกับ dextran ในการรักษาผู้ป่วยไข้เลือดออกที่มีการรั่วของพลาสมามาก สารคอลลอยด์ทั้งสองชนิดสามารถใช้ได้อย่างปลอดภัยในผู้ป่วยไข้เลือดออก ไม่พบอาการแพ้ และไม่มีผลต่อการทำงานของไตและการแข็งตัวของเลือด ผู้ป่วยที่ได้รับสารคอลลอยด์ทั้งสองชนิดไม่มีความแตกต่างกันในแง่ของความรุนแรงของโรค และภาวะแทรกซ้อน แต่ผู้ป่วยทั้ง 2 กลุ่มนี้มีความรุนแรงของโรคและภาวะแทรกซ้อนโดยเฉพาะภาวะน้ำเกินมากกว่าผู้ป่วยไข้เลือดออกทั่วไปที่รับไว้รักษาในโรงพยาบาล*