High dosage of dextran 70 is associated with severe bleeding in patients admitted to the intensive care unit for septic shock

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ABSTRACT

INTRODUCTION: Synthetic colloids are frequently used in fluid resuscitation of septic patients. Despite this, little is known about the potential side effects including the risk of renal failure and bleeding. As practice has changed, we performed a before-and-after study of fluid resuscitation and outcome in patients with septic shock.

MATERIAL AND METHODS: We retrospectively assessed all adult patients with septic shock admitted to a general intensive care unit (ICU) at a tertiary hospital in the years 2006 and 2008. Data on patient characteristics, resuscitation fluids in the ICU and outcome were collected from electronic databases and patient files.

RESULTS: A total of 332 patients with septic shock were included: 171 in 2006 and 161 in 2008. The use of mainly dextran 70 in 2006 (median 3.5 (interquartile range 1.9-7.1) versus 1.5 (0.5-3.0) l, $p < 0.0001$; 44 (24-86) versus 18 (8-42) ml/kg, $p < 0.0001$) had changed to mainly crystalloids (Ringer's lactate 0 (0.0-0.3) versus 1.1 (0.0-3.0) l, $p < 0.0001$) and albumin (5%, 0.0 (0.0-1.0) versus 0.8 (0.0-1.5) l, $p < 0.0001$; 20%, 0.0 (0.0-0.3) versus 0.1 (0.0-0.4) l, $p < 0.0001$) in 2008. There were no differences in rates of renal replacement therapy or 90-day mortality, but more patients experienced severe bleeding in 2006 than in 2008 (30 versus 19%, $p = 0.03$). Also more red blood cells, plasma and platelets were given in 2006 than in 2008 ($p < 0.01$ for all).

CONCLUSION: In patients with septic shock, fluid treatment had changed from mainly dextran 70 in 2006 to crystalloids and albumin in 2008. The administration of high-dosage dextran 70 was associated with more patients experiencing severe bleeding.

FUNDING: not relevant.

TRIAL REGISTRATION: not relevant.

In severe sepsis, fluid resuscitation is essential for restoring the circulating blood volume and avoiding sepsis-related organ failure and death.

The present guidelines for management of patients with severe sepsis and circulatory failure recommend fluid resuscitation with either natural or synthetic colloids or crystalloids [1].

There is no evidence to support one type of fluid over another [2, 3], and the advantages and disadvantages of resuscitation with synthetic colloids versus crystalloids remain heavily debated.

Serious adverse effects of colloids have been reported including acute kidney injury (AKI) [4, 5], bleeding [6] and increased mortality [7]. The newly published 6S trial demonstrated an increased risk of death at 90 days and an increase in the need for renal replacement therapy when HES 130/0.42 was used in severe sepsis [8]. Comparable results were observed in a study of HES 200/0.5 [4].

Dextran 70 is a synthetic colloid of glucopolysaccharides which is still being used in the resuscitation of septic patients in Scandinavia, but to a lesser extent than other colloid solutions [9]. Dextran 70, however, is largely unstudied in adult patients with sepsis.

With a view to collecting data on any side effects of dextran 70, we performed a retrospective study on fluid administration and outcome in patients with septic shock in two time periods. We assumed that the use of colloids was likely to have changed between the two years, and our hypothesis was that this might be associated with differences in AKI rates, bleeding and mortality.

MATERIAL AND METHODS

Retrospective data were collected on all adult (aged more than 18 years) patients with septic shock admitted to the general Intensive Care Unit (ICU), Rigshospitalet, in 2006 and 2008.

Patients were identified from the Unit's clinical and administrative database (Critical Information System (CIS) Daintel, Copenhagen), where data were entered prospectively by the treating intensivist.

Inclusion criteria were "diagnostic code septic shock" and "admission date > 31.12.2005 < 01.01.2007" or "admission date > 31.12.2007 < 01.01.2009". All patients below the age of 18 years were excluded.

Basic characteristics

Baseline characteristics were registered including age, gender, weight, type of admission (surgical/medical), Simplified Acute Physiology Score (SAPS) II, the maximum Sequential Organ Failure Assessment (SOFA-max) score during ICU admission, and if the patient had hae-

ORIGINAL ARTICLE

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Dan Med J 2012;59(11):A4531

TABLE 1

Characteristics of intensive care unit patients with septic shock.

	2006 (N = 171)	2008 (N = 161)	p-value
Age, median (25-75 percentiles), years	62 (52-71)	63 (56-72)	0.30
Gender, F/M, n	57/104	57/114	0.73
Body weight, median (25-75 percentiles), kg	80 (70-90)	75 (60-90)	0.10
Surgical admission, n/N (%)	105/171 (61)	86/161 (53)	0.14
SAPS II, median (25-75 percentiles)	56 (43-68)[a]	51 (41-62)[b]	0.04
SOFA-max in ICU, median (25-75 percentiles)	12 (10-16)[a]	12 (10-16)[b]	0.50
Haematological malignancy, n/N (%)	29/171 (17%)	22/161 (14%)	0.41
Time in the ICU, median (25-75 percentiles), days	9 (5-17)	8 (4-13)	0.02
Time in shock in the ICU[c], median (25-75 percentiles), days	4 (2-7)	4 (2-8)	0.51

F = female; ICU = intensive care unit; M = male; SAPS II = Simplified Acute Physiology Score II; SOFA-max = Maximum Sequential Organ Failure Assessment.
a) n = 165; b) n = 147; c) Registered as days of vasopressor therapy with infusion of either noradrenalin, adrenalin or dopamine.

TABLE 2

Cumulative doses of resuscitation fluids and blood products given to intensive care unit patients with septic shock. The values are medians (25-75 percentiles).

	2006 (n = 171)	2008 (n = 161)	p-value
Resuscitation fluids			
Total volume, l	6.12 (3.3-10.7)	5.90 (3.2-10.3)	0.67
NaCl 0.9%, l	1.0 (0.1-2.5)	1.0 (0.0-3.0)	0.79
Ringer's lactate, l	0.0 (0.0-0.3)	1.1 (0.0-3.0)	< 0.0001
Dextran 70 6%, l	3.5 (1.9-7.1)	1.5 (0.5-3.0)	< 0.0001
Dextran 70 6%, ml/kg	44 (24-86)	18 (8-42)	< 0.0001
HES 130/0.4, l	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.23
HA 5%, l	0.0 (0.0-1.0)	0.8 (0.0-1.5)	< 0.0001
HA 20%, l	0.0 (0.0-0.2)	0.1 (0.0-0.4)	< 0.0001
Blood products			
SAGM, l	2.0 (0.6-4.7)	0.8 (0.3-2.3)	< 0.0001
FFP, l	1.1 (0-2.4)	0.0 (0-0.5)	0.003
TC, l	0.7 (0-2.3)	0.0 (0-1.3)	0.01

FFP = fresh-frozen plasma; HA = human albumin; HES = hydroxyethyl starch; SAGM = erythrocyte suspension in saline with adenine, glucose and mannitol; TC = thrombocyte concentrate.

matological malignancy. Length of shock and number of ICU days were collected from patient files. Days of shock were defined as days during which vasopressor therapy was needed as registered infusion of noradrenalin, adrenalin or dopamine. This definition was used for practical reasons even though it does not adhere fully to the international definition of shock.

Thus, patients with septic shock were identified through diagnostic coding and length of vasopressor treatment.

Fluids and blood products

The total amount of resuscitation fluids (0.9% NaCl, Ringer's and colloid solutions) and blood products given during days of shock were summed up from ICU charts.

Complications and outcome

The use of acute renal replacement therapy (RRT) in the ICU was regiw stered from procedure coding (CIS) and by electronic search in the patient files (CIS). Patients who had received any form of RRT at another hospital or department before ICU admission were not included.

Patients with one or more major bleeding events were included. Major bleeding events were defined as a minimum of one day of administered erythrocyte suspension in saline with adenine, glucose and mannitol (SAGM) exceeding three units (> 735 ml) AND clinical bleeding reported in patient files [8].

Mortality rates during ICU admission and at 90 days were collected from the Danish hospital admission database (GS Open).

Statistics

Frequencies were reported as percentages and differences were tested with Fisher's exact test. Numerical values were reported as medians with 25th and 75th percentiles and analysed using the Mann Whitney U test. p values < 0.05 were considered statistically significant. All statistical analyses were performed with GraphPad Prism 5 for Windows.

Trial registration: not relevant.

RESULTS

A total of 361 patients were registered with septic shock in 2006 and 2008.

Twenty-nine patients were excluded; three patients received no vasopressor therapy, and the ICU charts of 26 patients were missing. Patients for whom only few data were missing were included in the analyses: for 11 patients data corresponding to a single day were missing, for two patients missing data for two days were missing, and for another two patients data corresponding to more than two days were missing. Thus, 332 patients were included in the analyses: 171 in 2006 and 161 in 2008.

The SAPS II and SOFA-max scores could not be described for six patients in 2006 and for 14 patients in 2008 because they had been admitted to the ICU for less than 24 hours.

Most patient characteristics did not differ between the two years, but SAPS II and days in ICU were higher in 2006 than in 2008 (**Table 1**).

Fluids and blood products

The total volume of fluid administered in 2006 and 2008 did not differ. There were, however, significant differences regarding the different fluid types given in 2006 and 2008. We found that significantly more dextran was used per patient in 2006 than in 2008 ($p < 0.0001$). Only

6% dextran 70 (Macrodex) and dextran 1 (Promiten) was administered. A volume larger than recommended (25 ml/kg/day) was given to five patients in 2006 and to 11 patients in 2008 (p = 0.10).

Significantly larger volumes of Ringer's lactate, 5% human albumin (HA) and 20% HA were used in 2008 and 2006, respectively, see Table 2. Also, higher volumes of SAGM, fresh-frozen plasma and thrombocyte concentrate were administered in 2006 than in 2008 (**Table 2**).

Complications and outcome

There were no differences in the rates of acute RRT, ICU mortality or 90-day mortality between 2006 and 2008 (**Table 3**). In contrast, the number of patients experiencing one or more severe bleeding episodes was significantly higher in 2006 than in 2008 (p = 0.03), see Table 3. Among the patients who received a dose exceeding the recommended daily dose, only two had a severe bleeding (12.5%; two in 2006, none in 2008).

Bleeding episodes also occurred in patients who received only a low dose of dextran. However, larger cumulative doses of dextran (ml/kg) were associated with an increasing rate of bleeding, see **Table 4**.

TABLE 3

Complications and outcome of ICU patients with septic shock.

	2006 (N = 171)	2008 (N = 161)	p-value
Renal replacement therapy[a], n_1/n_2 (%)	71/150 (47)	56/139 (40)	0.24
Patients with ≥ 1 major bleeding event[b], n/N (%)	51/171 (30)	31/161 (19)	0.03
ICU mortality, n/N (%)	47/171 (27)	47/161 (29)	0.81
90-day mortality, n/N (%)	77/171 (45)	83/161 (52)	0.27

ICU = intensive care unit; SAGM = Erythrocyte suspension in saline with adenine, glucose and mannitol; SAGM = erythrocyte suspension in saline with adenine, glucose and mannitol.
a) Renal replacement therapy in the ICU (92 patients in 2006, 78 patients in 2008). Patients who were dialysed before ICU admission were excluded (21 patients in 2006, 22 patients in 2008); b) Major bleeding event was defined as administration of more than three units of SAGM (> 735 ml) in one day AND registered bleeding in the patient's notes.

TABLE 4

Cumulative doses of dextran 70[a] and number of patients experiencing severe bleeding episodes[b].

Dosis, ml/kg	2006, n/N (%)	2008, n/N (%)
0-25	8/45 (17.8)	15/100 (15.0)
25-50	13/48 (27.1)	4/27 (14.8)
50-75	7/27 (26.0)	3/13 (23.1)
75-100	5/15 (33.3)	4/16 (25.0)
≥ 100	18/37 (48.6)	3/4 (75)

a) Cumulative doses of dextran 70: 10 ml/kg, 20 ml/kg, 50 ml/kg, 100 ml/kg or above 100 ml/kg; b) Percentage of bleeding episodes in the specific group was calculated as the number of patients with severe bleeding (n)/total number of patients (N).

DISCUSSION

The main findings of the present study were that fluid treatment of patients with septic shock had changed from 2006 to 2008 from mainly dextran 70 to crystalloids and albumin. More patients experienced severe bleeding in 2006 than in 2008 and, also, more blood products were given in 2006 than in 2008. However, there were no differences in the use of acute RRT or in ICU mortality rates or 90-day mortality between the two years.

Which is the better fluid for resuscitation of septic patients is heavily debated [2]. While some argue that colloids may lead to less oedema formation, others point out that the solutions will not be retained in the intravascular space in septic patients and therefore may generate an increased oncotic pressure in the interstitium which will lead to an increase in fluid accumulation. In the present study, we found no difference in the total volume of fluid administered in 2006 and 2008, which questions the notion that less fluid is needed when using colloid solutions.

Synthetic colloids may have harmful effects on renal function and cause AKI [4, 7, 8]. While older studies have shown an increased risk of AKI with the use of dextran 40 [10], studies of dextran 70 are still lacking, probably because of its limited use worldwide. Our results showed a tendency towards a higher use of RRT in 2006 than in 2008, although the 7% absolute difference was not statistically significant. This may be due to a type 2 error, but timing or indications for RRT may also have changed. Using a more detailed definition of AKI could have eliminated this last potential confounder. The RIFLE (risk, injury, failure, loss, end-stage renal disease) criteria include measures of serum creatinine and urinary output, and using this definition would most likely cause more patients to be categorised as AKI. From the present data, though, we cannot establish if dextran 70 increased the risk of AKI in septic shock. The rate of RRT found in the present study is somewhat higher than in the 6S trial. This may be explained by the differences between patient populations (severe sepsis versus septic shock and higher SAPS II and SOFA scores in the present study) or study design.

Synthetic colloids have been associated with haemostatic derangements through effects on blood coagulation factors and platelet function [11]. Dextran has been used in the prevention of venous thrombosis and its antithrombotic features have been compared to those of heparin [12]. Ex vivo studies using thromboelastography have shown prolonged clot formation time and weakened maximum clot strength by synthetic colloids [11, 13]. These interactions with haemostasis may cause an increased risk of bleeding with synthetic colloid solutions, but clinical data are limited [14]. In the present study, we found significantly more patients experiencing severe bleeding in 2006 when higher doses of dextran 70

Ringer's lactate and SAGM.

were used than in 2008. Also, more blood products were used in 2006 than in 2008. It is likely that the high use of dextran 70 in 2006 contributed to the observed high rate of severe bleeding, but this may not be explained by administration exceeding the recommended daily dose as the overdosed patients had no increased tendency to bleeding compared with the overall results. However, it may be that the risk of bleeding increases when the cumulative dose of dextran exceeds a certain level as observed for starch and gelatine and kidney failure in a study comparable to ours [15]. We found that higher cumulative doses of dextran were associated with an increased rate of bleeding. These data therefore challenge the concept of having recommended daily doses for synthetic colloids, but not recommended total doses.

The observed bleeding rate in 2008 was also higher than the 10% observed in the 6S trial cohort using the same definitions [8]. Whether this difference is due to continued use of dextran 70 in 2008 or to differences in study design or cohort characteristics, as described above, cannot be uncovered.

The association between dextran 70 and bleeding found in our study should ideally be investigated in a randomised clinical trial as this would minimise any effects of residual confounding. Randomised trials were performed of dextran versus crystalloids in dengue shock in children [16] and a small study in shocked, adult trauma patients [17]. Neither of these trials reported increased bleeding with dextran 70.

The strength of the present study is that it represents the daily clinical practice of one ICU, which increases the internal validity. Using identical electronic registration procedures make data reliable and comparable. In addition, the data of each patient were entered prospectively with few missing values. The study is limited by its retrospective nature, which precludes strong conclusions regarding cause and effect. We found significant changes in the use of dextran, but it was still used in 2008, which may have affected the results. There was a difference in SAPS II between the two years, which may have affected the outcome, even though maximum SOFA scores did not differ. We did not assess co-morbidities, admission diagnosis, underlying infections or biochemical markers of coagulation and kidney function. Instead, we assessed bleeding and use of RRT, which may be more meaningful than laboratory test results. We are not aware of any change in the transfusion pol-icy or other interventions in the two time periods. Changes may have happened as the Surviving Sepsis Campaign guidelines were updated in 2008. Lastly, the study only represents the practice of one ICU, which limits the external validity.

Which fluids should be used for resuscitation of patients with septic shock? The present study does not show better outcome on mortality, the need for RRT or the need for blood transfusion when using mainly dextran 70 in the resuscitation of septic shock patients. Furthermore, a larger cumulative dose of dextran was associated with more patients with severe bleeding. We therefore suggest that dextran 70 should be used with caution in septic shock in, particularly in patients with an increased risk of bleeding. Again, a randomised trial should test the safety and efficacy of dextran 70 in septic shock, but its limited use makes it unlikely that anyone would undertake such a trial.

It is difficult to defend the continuous use of synthetic colloids in patients with sepsis, especially if the ongoing CHEST trial [18] shows the same unfavourable results with HES 130/0.4 as the 6S trial [8]. On the other hand, a recent meta-analysis indicated favourable outcome with 4% or 5% albumin in septic patients [19], but most of the results originated from the subgroup analysis of the SAFE study [20]. These results should be confirmed in a large trial with a low risk of bias before albumin may be recommended for sepsis resuscitation, in particular as albumin is an expensive drug of limited availability.

CONCLUSION

In patients with septic shock, fluid treatment changed from mainly dextran 70 in 2006 to mainly crystalloids and albumin in 2008. This was not associated with significant differences in RRT rates or mortality. In contrast, the administration of higher doses of dextran 70 (mean

total dose 44 versus 18 ml/kg) was associated with more patients experiencing severe bleeding. We therefore recommend using dextran 70 with caution in patients with septic shock, in particular in those at risk of bleeding. If used, the total dose given should be limited.

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ACCEPTED: 19 September 2012

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk.

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