More complications in patients with septic shock treated with dextran compared with crystalloids

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ABSTRACT

INTRODUCTION: In recent years, the safety-profile of synthetic colloids has been questioned. The purpose of the present study was to elucidate the safety-profile of the colloid dextran-70 in relation to acute kidney injury (AKI) and death.

METHODS: We conducted a retrospective, observational study of patients admitted to our intensive care unit with septic shock and treated with dextran-70 in the period from 1 January 2009 to 31 December 2009. The controls were included from 1 March 2012 to 28 February 2013 when dextran-70 was replaced with crystalloids.

RESULTS: There were 91 patients in the dextran group and 150 patients in the non-dextran group. The urinary output was 17.93 ml/kg/24 h in the dextran group and 27.87 in the non-dextran group ($p < 0.05$). Continuous renal replacement therapy (CRRT) was used in 48% in the dextran group and in 23% in the non-dextran group ($p < 0.05$). Major bleeding episodes occurred in 32% in the dextran group compared with 15% in the control group ($p < 0.05$). The 90-day mortality was 42% in the dextran group and 35% in the non-dextran group ($p = 0.08$).

CONCLUSION: Patients in the dextran group had significantly more bleeding episodes, a higher need for CRRT and a l ower urinary output than patients in the non-dextran group. Due to study design, it cannot be concluded that the use of dextran-70 is causally related to the development of AKI.

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The incidence of sepsis in Denmark is estimated to approx. two per 1,000 inhabitants. The mortality from sepsis is around 20%, which corresponds to approx. 1,000 annual deaths in Denmark [1]. Sepsis is the second leading cause of death in the intensive care unit (ICU), only exceeded by cardiac disease [2].

Since 2001, early goal-directed therapy [3] has been the standard for the treatment of patients with sepsis in most ICUs. This standard is recommended in the Surviving Sepsis Campaign (SSC) [4]. One of the cornerstones of the SSC is early, aggressive fluid therapy with crystalloids or synthetic colloids in doses of 500 ml. Synthetic colloids are a heterogeneous group of substances, which, among others, includes hydroxyethyl starch (HES), dextrans and succinylated gelatins. For several years, colloids have been used to achieve a quick and lasting effect on the haemodynamics in patients with shock, but in recent years the safety of colloids has been questioned by several randomised clinical trials (RCTs) and meta-analyses [5-10]. Most of the current evidence is based on studies on HES.

A study by Hvidt & Perner reported a significant difference in the number of major bleedings in patients treated with Dextran-70 compared with saline [11]. Bleeding is a serious complication in patients because it increases both mortality and length of stay in the ICU. The purpose of the present observational and retrospective study was to investigate the effect of the colloid dextran-70 on mortality and renal function in patients with septic shock. We investigated whether there was a difference in bleeding, mortality and renal function in patients admitted with septic shock and treated with dextran-70 compared with patients treated with crystalloids. We hypothesised that treatment with dextran-70 had a negative effect on 90-day mortality, bleeding and renal function compared with treatment with crystalloids only.

METHODS

Based on the above-mentioned trials, the ICU at Odense University Hospital stopped all use of dextran-70 in March 2012.

Data were collected retrospectively in the 25-bed mixed ICU at Odense University Hospital. All patients admitted with septic shock in the period from 1 January 2009 to 31 December 2009 were included in the dextran group. All patients with septic shock admitted to the same department in the period from 01 March 2012 to 28 February 2013 were included in the non-dextran group. Patients were identified by diagnostic codes given by the clinician as stated in the department's documentation system (Critical Information System (CIS) Daintel ApS, Copenhagen, Denmark). The inclusion critria were ICU admission with septic shock during the study period. To ensure that all patients with septic shock were included in the study, we identified all patients with the following diagnostic codes: sepsis, severe sepsis or septic shock. Each patient was then followed for the first 14 days of their ICU stay or until discharge or death. Each patient's medical record was reviewed and

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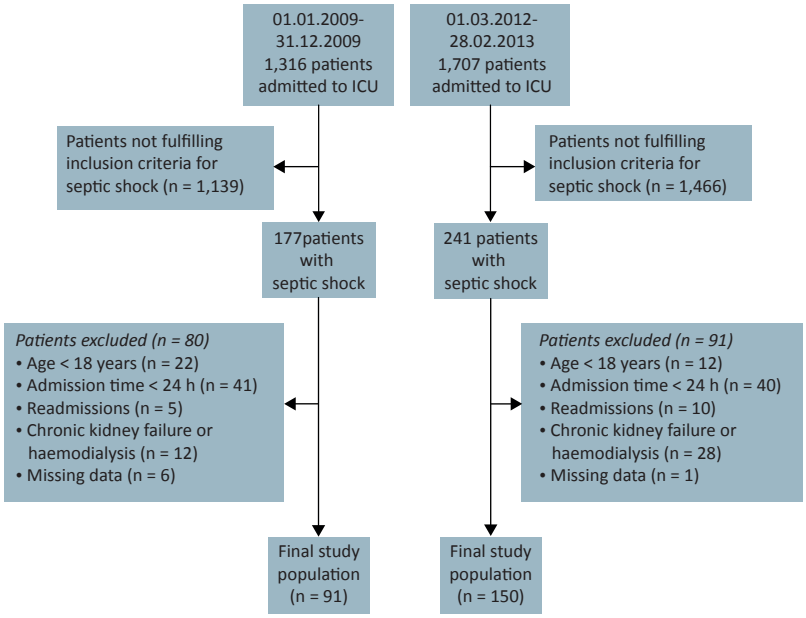
FIGURE 1

CONSORT diagram showing number of included and excluded patients.



ICU = intensive care unit.

assessed in order to identify septic shock and any presence of clinical infection. Any treatment with one of the following vassopressors was recorded: norepinephrine, epinephrine or dopamine. Patients were registered as being in shock if they had a systolic blood pressure (BP) measured invasively or non-invasively below 90 mmHg for more than 1 hour without any external cause.

The following patients were excluded: patients hospitalised for less than 24 hours, readmissions, patients younger than 18 years of age, patients on chronic haemodialysis and patients suffering from preexisting renal disease with the following laboratory renal parameters on the day of admission to the ICU: creatinine > 300 µmol/l, urea > 35 mmol/l or an estimated glomerular filtration rate (eGFR) < 20 (**Figure 1**).

Baseline characteristics.

The following baseline characteristics were collected from the patient records: age, sex, weight on the day of admission, the Acute Physiology and Chronic Health Evaluation II score (APACHE II score) on day 1 of the patient's hospitalisation in the ICU and the Simplified Acute Physiology Score II (SAPS II) also on day 1 of hospitalisation in the ICU. Furthermore, the number of days in the ICU was recorded.

Fluids and blood products

The daily amount of the following fluids and blood products was recorded. The following crystalloids were recorded: NaCl 0.9% and Ringer's acetate. Synthetic colloids and blood products: HES 130/0.38-0.45 (Voluven 60 g/l sodium chloride), dextran-70 (Macrodex 60 g/l sodium chloride), packed red blood cells in SAGM solution (SAGM: saline, adenosine, glucose, mannitol), frozen plasma, platelet concentrate, human albumin 5% and human albumin 20%. In this study, only fluids received in the ICU were registered, whereas fluids given in the ward and emergency room were not.

Outcome measures

The primary outcome was 90-day mortality. Deaths in the ICU were collected from medical records, whereas data on deaths after admission to the ICU or outside the hospital were extracted from the Funen County Patient Administration System (FPAS) that receives information from the Danish Central Person Register (the CPR). Our secondary outcome was renal function assessed by urinary output and startup of continuous renal replacement therapy (CRRT). Data on the daily urinary output and startup of CRRT were collected from the medical records.

Patients transferred from another ICU during CRRT treatment were registered as having a preexisting kidney disease and were therefore excluded from the study. The number of major bleeding events during the ICU stay was also recorded. A major bleeding was defined as a need for ≥ 900 ml of packed red blood cells during one day.

Data processing and statistics

Data were entered into Microsoft Access (Microsoft Corporation, Redmond, USA). Numerical variables were reported as medians by 50, 25 and 75 percentiles and tested with the Mann-Whitney U test. Frequencies were reported in percentages and tested with Pearson's chi-square test. Differences in survival were tested with Cox regression and Kaplan-Meier estimates. P-values < 0.05 were considered statistically significant. All statistical calculations were made using STATA 12 (StataCorp LP, Texas, USA).

Trial registration: not relevant.

RESULTS

Figure 1 shows that 1,316 patients were admitted to the ICU in 2009 and therefore might have been treated with dextran-70. A total of 1,707 patients admitted to the ICU in 2012. In 2009, 177 patients had septic shock compared with 241 in 2012. Thus, the total for both years was 418 patients. Of these, 171 patients were excluded: 34 patients were under 18 years at the time of admission, 81 patients had a hospital stay of less than 24 hours, 15 admissions were readmissions and 40 had ei-

ther chronic renal failure or received haemodialysis in the period leading up to admission. For six patients in the dextran group and one in the non-dextran group, fluid schedules and/or intensive medical records could not be retrieved.

Data from 241 patients were collected; 91 patients in the dextran-group and 150 patients in the non-dextran group. Data were collected for the first 14 days in the ICU. Baseline characteristics were similar between the two groups (**Table 1**).

The cumulative values of intravenous fluids throughout hospitalisation were calculated. As seen from **Table 2**, there was a difference between the fluids used in the dextran group and the non-dextran-group. On average, the dextrangroup received 5.56 ml/kg/24 h dextran-70 during their admission in the ICU, whereas the non-dextran-group did not receive any colloids. Accordingly, significantly more colloid was used in the dextran group than in the non-dextran group ($p < 0.00001$). In the non-dextran group, significantly more crystalloid was used than in the dextran group ($p < 0.00001$). In addition more erythrocytes ($p = 0.0014$), frozen plasma ($p = 0.0004$) and platelet concentrate ($p = 0.0003$) were used in the dextran group than in the non-dextran group. A lower use of human albumin in the dextran group than in the non-dextran group was observed.

In the dextran group, 42% of the patients died within 90 days compared with 35% in the control group (Table 2) ($p = 0.0769$). The 90-day mortality is also presented in a Kaplan-Meier plot (**Figure 2**). In the dextran group, a significant difference was seen in the use of CRRT compared with the non-dextran group. 48% of patients in the dextran group received CRRT, whereas only 23% in the non-dextran group received CRRT ($p = 0.004$).

Furthermore, a significantly lower urinary output was observed in the dextran group than in the non-dextran group. The dextran group had a median urinary output of 17.93 ml/kg/day compared with the non-dextran group where the median urinary output was 27.87 ml/kg/day ($p = 0.0004$). In the dextran group, 32% of the patients needed more than 900 ml of erythrocyte suspension during one day compared with 15% in the non-dextran group ($p = 0.002$).

TABLE 1

Baseline characteristics as medians (25-75 percentiles) except for sex.

	2009 (n = 91)	2012 (n = 150)	p-value
Age, yrs	65 (57-74)	69 (60-76)	0.062
Sex, men/female, n	63/28	85/65	0.052
Weight, kg	75 (60-85)	71.5 (62-80)	0.21
APACHE II	29 (22-33)	27 (24-33)	0.81
SAPS II	56 (47-68)	56 (44-71)	0.44

APACHE II = Acute Physiology and Chronic Health Evaluation II score; SAPS II = Simplified Acute Physiology Score II.

DISCUSSION

In this retrospective study, we found that more patients

TABLE 2

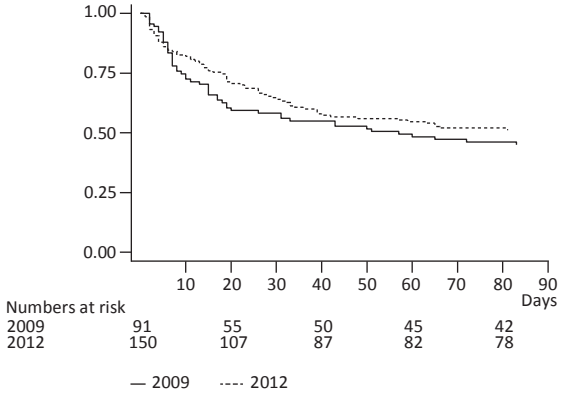
	2009 (n = 91)	2012 (n = 150)	p-value
Fluids and blood products, ml/kg/24 h, median (25-75 percentiles)			
Resuscitation fluids:			
NaCl 0.9%	10.68 (5.24-16.13)	4.42 (1.60-13.23)	< 0.00001
Ringer's acetate	2.65 (0.00-8.57)	19.14 (12.17-35.71)	< 0.00001
Crystalloid, pooled	14.52 (9.24-22.06)	25.62 (16.32-50.96)	< 0.00001
Blood products:			
Red packed cells	0.03 (0.01-0.07)	0.66 (0.00-2.22)	0.0014
Frozen plasma	1.43 (0.00-3.69)	0.00 (0.00-0.87)	0.0004
Platelet concentrate	0.00 (0.00-1.88)	0.00 (0.00-0.00)	0.0003
Other:			
Human albumin, 5%	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.039
Human albumin, 20%	0.24 (0.00-0.71)	0.00 (0.00-0.39)	0.0008
Human albumin, pooled	0.25 (0.00-0.83)	0.00 (0.00-0.81)	0.16
Outcome measures			
90-day mortality, dead/alive, n (%)	38/53 (42)	52/98 (35)	0.077
CRRT, yes/no, n (%)	44/47 (48)	35/115 (23)	< 0.0001
Urinary output, ml/kg/24 h, median (25-75 percentiles)	17.93 (3.40-32.11)	27.87 (17.43-39.97)	0.0004
Major bleeding episodes, yes/no, n (%)	29/62 (32)	23/127 (15)	0.002

CRRT = continuous renal replacement therapy.

The cumulative values of intravenous fluids throughout hospitalization.

FIGURE 2

The 90-day mortality in a Kaplan-Meier plot.



in the dextran group than in the non-dextran group had significantly lowered urinary output. Significantly more patients in the dextran group received CRRT. Significantly more bleeding episodes were observed in the dextran group. We observed a trend towards a higher mortality in the dextran group.

The 2012 guidelines from the SSC stated that it was the individual clinician's choice to decide whether to use crystalloids or colloids [4]. Acute renal failure is common in critical illness and can have serious consequences for the individual patient, and it is associated with considerable health-care expenditure. AKI has also been shown to increase mortality [12].

There are relatively few studies on dextran, and the majority are based on dextran-40 used as an anticoagulant or plasma substitute in trauma patients. Although both trauma patients and patients with septic shock are critically ill, there is considerable variation in the physiology and the pathophysiology of these patients. Thus, only few studies have documented the adverse effects of dextran-70 in septic patients [11, 13].

The decreasing use of dextran-70 in the present study is consistent with the general trend towards the use of crystalloids instead of synthetic colloids. We observed a decrease in the use of HES 130/0.38-0.45. Several studies have shown a relationship between AKI and HES [5, 6] We found a trend towards an increased 90-day mortality in the dextran group compared with the non-dextran group. In another study, an increased frequency of bleeding, but no effect on mortality, was associated with the use of dextran-70 [11].

More patients in the dextran group than in the non-dextran group more frequently developed AKI that was treated with CRRT. Similarly, the CHEST-trial reported an increased frequency of AKI treated with CRRT. 7% of patients were treated with CRRT in the HES group compared with 5.8% in the non-dextran group [6]. The 6S-study also reported an increased use of CRRT in the group treated with HES [5]. In one study on dextran-70, the authors reported a trend towards more AKI treated with CRRT in patients receiving very large amounts of dextran-70 [11]. This is in accordance with the present study in which patients in the dextran group were treated significantly more often with CRRT than patients in the the non-dextran group.

The decision to start CRRT was up to the individual clinician. However, indications for CRRT have not changed in the two years that separate the two study periods [14]. Among the patients in the dextran group there was a significantly lower urinary output than among the patients who had not received dextran-70. Urinary output is strongly related to kidney function and is used in defining acute kidney injury according to the RIFLE criteria [15].

Dextran-70 has anticoagulant properties, and it is possible that large amounts of dextran-70 might increase the number of bleeding episodes. The present study showed that patients treated with dextran-70 have a larger number of major bleeding episodes. This is in accordance with a previous study by Hvidt & Perner [11].

Patients with known renal disease were excluded according to predefined values. However, we did not have pre-admission blood samples from all patients. Some patients might have had a reduced kidney function before their admission to the ICU and should therefore have been excluded from our study. However, this risk seems small and one would expect an even distribution between the two groups.

In this study, we did not register the amount and type of fluids that patients had received before their admission to the ICU. This entails a risk of underestimating the total amount and type of fluids that our patients received during their hospital admission. We believe that in the ICU, the largest amount of fluid is given to patients with septic shock which makes data on the amounts and kinds of fluid given before ICU admission less important.

An important limitation to this study was that all data were obtained retrospectively. It was therefore not possible to make any causal conclusions with respect to the use of dextran in critically ill patients. Furthermore, the 2-year time span between the two groups introduced a risk that some treatment modalities changed which could explain our findings. However, little has changed in the treatment of septic patients within the past four years according to the SSC 2008 versus 2012 [16].

CONCLUSION

The main findings of this study are that patients in septic shock who were treated with dextran had a significantly

higher frequency of bleeding episodes, a significantly higher occurrence of AKI treated with CRRT and a significantly lower urinary output than the non-dextran group. Since this was a retrospective observational study, we cannot determine any causal relationships between the use of dextran-70 and the development of AKI. A blinded, randomised, controlled trial (RCT) is necessary to rule out a causal relationship between Dextran-70 and AKI. Until such a RCT is implemented, we recommend using only crystalloids during fluid resuscitation of patients in septic shock.

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