Effects of fluid resuscitation with synthetic colloids or crystalloids alone on shock reversal, fluid balance, and patient outcomes in patients with severe sepsis: A prospective sequential analysis*

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Objective: **To assess shock reversal and required fluid volumes in patients with septic shock.**

Design: **Prospective before and after study comparing three different treatment periods.**

Setting: **Fifty-bed single-center surgical intensive care unit.**

Patients: **Consecutive patients with severe sepsis.**

Interventions: **Fluid therapy directed at preset hemodynamic goals with hydroxyethyl starch (predominantly 6% hydroxyethyl starch 130/0.4) in the first period, 4% gelatin in the second period, and only crystalloids in the third period.**

Measurements and Main Results: **Main outcome was time to shock reversal (serum lactate <2.2 mmol/L and discontinuation of vasopressor use). Hemodynamic goals were mean arterial pressure >70 mm Hg; $ScvO_2$ <70%; central venous pressure >8 mm Hg. Safety outcomes were acute kidney injury defined by Risk, Injury, Failure, Loss, and End-stage kidney disease criteria and new need for renal replacement therapy. Hemodynamic measures, serum lactate, and creatinine were comparable at baseline in all study periods (hydroxyethyl starch n = 360, gelatin n = 352, only crystalloids n = 334). Severity scores, hospital length of stay, and intensive care unit or hospital mortality did not differ significantly among groups. All groups showed similar time to shock reversal. More fluid was needed over the first 4 days in the crystalloid group (fluid ratios 1.4:1 [crystalloids to hydroxyethyl starch] and 1.1:1 [crystalloids to gelatin]). After day 5, fluid balance was more negative in the crystalloid group. Hydroxyethyl starch and gelatin were independent risk factors for acute kidney injury (odds ratio, 95% confidence interval 2.55, 1.76–3.69 and 1.85, 1.31–2.62, respectively). Patients receiving synthetic colloids received significantly more allogeneic blood products.**

Conclusions: **Shock reversal was achieved equally fast with synthetic colloids or crystalloids. Use of colloids resulted in only marginally lower required volumes of resuscitation fluid. Both low molecular weight hydroxyethyl starch and gelatin may impair renal function. (Crit Care Med 2012; 40:2543–2551)**

Key Words: acute kidney injury; coagulopathy; colloids; crystalloids; plasma volume expanders; shock

There is considerable controversy regarding the best choice of asanguineous fluid in hypovolemia and shock. Colloids are preferred in many countries despite potential risks and higher costs (1) because of data suggesting that they improve cardiac performance more effectively in patients with hypovolemia (2–4) and were associated with a three to four times lower resuscitation volumes than crystalloids (2, 5) – a compelling observation, considering that higher fluid balances are associated with worsened patient outcomes (6).

Tissue hypoxia is the hallmark of early septic shock (7) and elevated lactate levels, and increased oxygen extraction are indicators of impaired tissue oxygenation (8). Fluid resuscitation restores the intravascular volume with the aim to improve tissue perfusion, lactate clearance, and central venous oxygen saturation ($ScvO_2$), and to reduce the need for vasopressors (7–10).

However, recent evidence questions these conclusions. Larger studies that observed patients for longer periods were unable to show a lasting hemodynamic benefit (11) or improved patient survival with the use of albumin, gelatin, or hydroxyethyl starch (HES)

***See also p. 2709.**

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(12–15), and a lack of colloid superiority was repeatedly confirmed in meta-analyses (16, 17). Furthermore, the ratio of administered crystalloids to colloids in large randomized controlled trials in critically ill or septic patients was only 1.4:1 (12, 13). In addition, synthetic colloids have been shown to be potentially harmful, as reflected in dose-related side effects including renal impairment (13, 18–20), increased bleeding (21, 22), and tissue accumulation with organ damage (23, 24).

Triggered by the finding of starch nephrotoxicity in severe sepsis patients (13, 25), we undertook sequential changes in our approach to fluid therapy, and serially documented the consequences on patient outcomes. We first replaced starches with 4% gelatin. However, because rates of renal adverse events (26) remained high, we switched to the use of crystalloids alone (20). We used our electronic database of patients from these three sequential treatment periods between 2004 and 2010 to investigate whether the type of fluid has an impact on the time to shock reversal and achievement of preset hemodynamic goals.

MATERIALS AND METHODS

Setting

A 50-bed interdisciplinary surgical intensive care unit (ICU) of a university hospital.

Patients

We recruited consecutive patients who fulfilled the criteria for severe sepsis or septic shock (27) on the day of admission (supplemental Methods, Supplemental Digital Content 1, http://links.lww.com/CCM/A469).

Study Groups

Participants were grouped into different fluid groups according to the period in which they received fluid therapy: the *HES period* (January 1, 2004 to January 31, 2006, predominantly 6% HES 130/0.4 and crystalloids), the *Gelatin period* (March 1, 2006 to March 31, 2008, 4% gelatin and crystalloids), and the *Crystalloid period* (May 1, 2008 to April 8, 2010, where only crystalloids were given); (see details in the supplemental Method section, Supplemental Digital Content 1, http://links.lww.com/CCM/A469). The treatment periods were separated by a washout period of 1 month to allow sufficient implementation of the new standard fluid.

Variables

Shock reversal was defined as the first time a serum lactate level of <2.2 mmol/L or discontinuation of vasopressor use was achieved. Reaching of preset hemodynamic goals was defined as the first time the criteria for mean arterial pressure (MAP) >70 mm Hg, $ScvO_2$ > 70%, and central venous pressure (CVP) > 8 mm Hg were met. Patients with relapsing shock were not considered. Mean values of MAP, CVP, and $ScvO_2$ were used to describe response to treatment.

We defined study fluids as all hydroxyethyl starches, gelatin, and crystalloids that were administered as bolus infusions given at high flow rate to treat volume deficit, but not fluids given for maintenance or carrier fluids for medication. Total fluids were defined as all enteral and parenteral fluids including bolus and maintenance fluids, nutrition, drug administration, and blood products.

Fluid balance was calculated daily as the difference between total fluid intake and total fluid loss. Fluid loss included urine output, fluid removal by dialysis, drainage fluid, estimates of insensible losses, and oral and rectal secretions.

Acute kidney injury (AKI) was defined by the standardized Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) criteria or new occurrence of renal replacement therapy (RRT) (28) (see Supplemental Digital Content 1, http://links.lww.com/CCM/A469). AKI was defined by the most severe RIFLE criterion, which was reached during the ICU stay.

Data Sources and Measurement

Data were collected prospectively from an electronic patient data-management system (see supplemental Methods, Supplemental Digital Content 1, http://links.lww.com/CCM/A469).

To compare reversal of shock criteria within the first 4 days after admission, survival functions were estimated using the Kaplan-Meier estimator. The time to event was calculated using the mean values of MAP, $ScvO_2$, CVP, and lactate in consecutive 4-hr intervals. In patients presenting with abnormal hemodynamic or lactate values, time to achievement of preset hemodynamic goals or return to normal lactate values was calculated as the difference between admission time and the midpoint of the 4-hr interval when the respective goal was achieved. For patients receiving vasopressors at the time of admission, the time between admission time and the midpoint of the first 4-hr interval when patients were free from vasopressors was used. Log-rank tests were performed to test for group differences.

Statistical Analysis

All analyses were performed using SPSS version 18.0 (SPSS Inc, Cary, NC) and R version 2.11.1 (R Development Core Team 2010; R Foundation for Statistical Computing, Vienna, Austria). All reported p values are two-sided. For univariate analyses, we applied the t test or the Mann-Whitney test and Fisher's exact test for continuous and categorical variables, respectively.

Forward and backward stepwise multiple logistic regression analysis based on Akaike Information criterion was performed to identify risk factors for AKI and RRT. The resulting model was checked by the Hosmer-Lemeshow goodness-of-fit test as well as the area under the receiver-operating characteristic curve. In a second step, we added period effects of HES and gelatin as categorical variables with crystalloids as reference category.

RESULTS

Patients

We screened 24,326 surgical ICU patients. After excluding 23,280 patients who met exclusion criteria, a total of 1,046 patients with severe sepsis or septic shock remained, 360 patients in the HES period, 352 in the gelatin, and 334 patients in the crystalloid period (see details in Supplementary Fig. 1, Supplemental Digital Content 1, http://links.lww.com/CCM/A469).

Descriptive Data

Study groups were comparable at baseline regarding MAP, CVP, $ScvO_2$, and lactate levels, as well as the number of patients with septic shock (Table 1). Patients had similar exposure to a range of nephrotoxic drugs except for a higher use of diuretics in both synthetic colloid groups, a higher use of angiotensin-converting enzyme inhibitors in the gelatin group and a higher use of vancomycin and antimycotics in the crystalloid group in comparison to the gelatin group (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/A469). There were some imbalances at admission regarding comorbidities, surgical procedures, source of sepsis, procalcitonin levels, and baseline Simplified Acute Physiology II score (Table 1).

Clinical Course and Response to Treatment During icu Stay

Mean values of MAP, CVP, and $ScvO_2$ were similar over the first 48 hrs, and noradrenaline use was higher on day 0 in the crystalloid group (Supplemental

Table 1. Patient baseline characteristics

	Hydroxyethyl Starch Period (n = 360)	Gelatin Period (n = 352)	Crystalloid Period (n = 334)
Age, years, median [interquartile range]	69.5 [57.8–76.8]	68.8 [57.7–76.3]	70.2 [58.6–77.6]
Male, n (%)	238 (66.1)	239 (67.9)	226 (67.7)
Comorbidities, n (%)			
Hypertension	169 (46.9)[a]	184 (52.3)[b]	200 (59.9)
Diabetes mellitus	99 (27.5)	109 (31.0)	96 (28.7)
Cancer	74 (20.6)[a]	101 (28.7)	116 (34.7)
Chronic renal failure	18 (5.0)	3 (0.9)	9 (2.7)
Liver cirrhosis	13 (3.6)[c]	27 (7.7)	32 (9.6)
Surgical procedures, n (%)			
Abdominal	122 (33.9)[c]	158 (44.9)	149 (44.6)
Cardiac/thoracic surgery	137 (38.1)[a]	103 (29.3)	87 (26.0)
Trauma	25 (6.9)[b]	13 (3.7)	10 (3.0)
Others[d]	67 (18.6)	57 (16.2)	63 (18.9)
No surgery	9 (2.5)[c]	21 (6.0)	25 (7.5)
Source of sepsis, n (%)			
Respiratory	184 (51.1)[a]	138 (39.2)	125 (37.4)
Abdominal	113 (31.4)[a]	158 (44.9)	162 (48.5)
Urogenital	10 (2.8)	7 (2.0)	6 (1.8)
Others[e]	53 (14.7)	49 (13.9)	41 (12.3)
Hemodynamic and laboratory values, median (interquartile range)			
Mean blood pressure, mm Hg	73 [67–80]	72 [67–78]	73 [67–78]
Heart rate, beats/min	97 [86–109]	99 [88–113][a]	93 [82–107]
Central venous pressure, mm Hg	9 [7–12]	10 [7–13]	9 [6–12]
Septic shock, n (%)	295 (81.9)	293 (83.2)	288 (86.2)
Procalcitonin, ng/mL	2.9 [0.8–10.1]	2.3 [0.7–6.7][b]	3.0 [0.8–10.4]
Serum lactate, mmol/L	2.3 [1.3–4.1]	2.1 [1.3–3.8]	1.8 [1.2–3.2]
Central venous oxygen saturation, %	71 [67–74]	70 [66–74]	71 [68–75]
Platelet count, $\times 10^3$/mL	167 [109–241]	141 [49–238][c]	159 [88–258]
Serum creatinine, µmol/L	101 [81–139]	96 [79–130]	96 [81–144]
Creatinine clearance, mL/min	62 [43–89]	66 [48–91]	62 [43–88]
Simplified Acute Physiology Score II score	50 [39–63][b]	52 [40–65]	53 [41–66]
Sequential Organ Failure Assessment score	8 [6–11]	8 [6–10]	8 [6–11]

p values were calculated with the *t* test or the Mann-Whitney *U* test and Fisher's exact test, as appropriate. Hydroxyethyl starch and gelatin group were compared with crystalloid group, respectively.

[a]$p < .001$; [b]$.01 < p < .05$, [c]$.001 < p < .01$; [d]includes neurosurgical, metabolic, renal urinary tract, and gynecological procedures; [e]includes catheter-related, wound, coagulase-negative staphylococci, blood stream infections, and endocarditis.

Fig. 2, Supplemental Digital Content 1, http://links.lww.com/CCM/A469). Thereafter, mean daily MAP values were significantly higher on most days in both colloid patient cohorts, and noradrenaline use was higher on days 3–8 in the crystalloid groups. CVP measurements did not differ significantly over the first 10 days, and $ScvO_2$ values differed significantly among groups only at day 2 (Supplemental Fig. 2, Supplemental Digital Content 1, http://links.lww.com/CCM/A469). Heart rate was slightly but significantly higher in the HES group over most of the study period (Supplemental Fig. 2, Supplemental Digital Content 1, http://links.lww.com/CCM/A469). Hemoglobin levels were modestly but significantly higher in the HES group compared with the crystalloid group on days 2 and 6 (Supplemental Fig. 2, Supplemental Digital Content 1, http://links.lww.com/CCM/A469). Daily procalcitonin levels were similar over the study duration (Supplemental Fig. 3, Supplemental Digital Content 1, http://links.lww.com/CCM/A469). Use of low-dose hydrocortisone and insulin is given in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/A469). Activated protein C was used in six and eight patients in the HES and gelatin periods, respectively. No patient in the crystalloid period received activated protein C.

Outcome Data

Shock Reversal. Patients who presented with abnormal serum lactate measurement at the time of admission, attained normal values equally rapidly despite the choice of fluid (Fig. 1*a*). Time to discontinuation of vasopressor use did not differ between fluid groups (Fig. 1*b*).

Reaching of Hemodynamic Goals. Time to reach preset values of MAP and $ScvO_2$ was similar in all groups (Fig. 2, *a* and *b*). Preset CVP values were reached less quickly in the crystalloid group (Fig. 2*c*).

Fluid Intake and Fluid Balance. Patients in the colloid groups received more crystalloid than colloid fluids during the first 4 days as well as over the whole treatment period. During the first 4 days, the volume of resuscitation fluids (i.e., including bolus crystalloids in the colloid groups) in the crystalloid group was 1.4-fold higher than in the HES group, and 1.1-fold higher than in the gelatin period. Patients in the crystalloid period received 1.2-fold more total fluid volume than patients in the HES period and 1.1-fold more volume than patients in the gelatin period (Table 2). Over the entire ICU stay, cumulative fluid doses were higher in the synthetic colloid groups (Table 2).

Fluid intake was measured at two-hourly intervals in the first 24 hrs following admission. Intakes were highest in the crystalloid group and less so in the gelatin group, but only during the 12–16 hrs following admission (Fig. 3*a*). Fluid intake in the crystalloid group was significantly higher than in the HES group over the first 16 hrs and in the gelatin group only over the first 6 hrs and similar thereafter, respectively (Fig. 3*a*). Overall, mean fluid intake on day 0 and day 1 was significantly higher in the crystalloid groups, and overall fluid balance was significantly less positive on these days in the HES group. However, from day 5, fluid balance was more positive in the HES and gelatin groups (Fig. 3, *b* and *c*).

More blood products were used in the HES group, and more patients in the HES and the gelatin groups were exposed to allogeneic blood products (Table 2). More human albumin 20% was administered

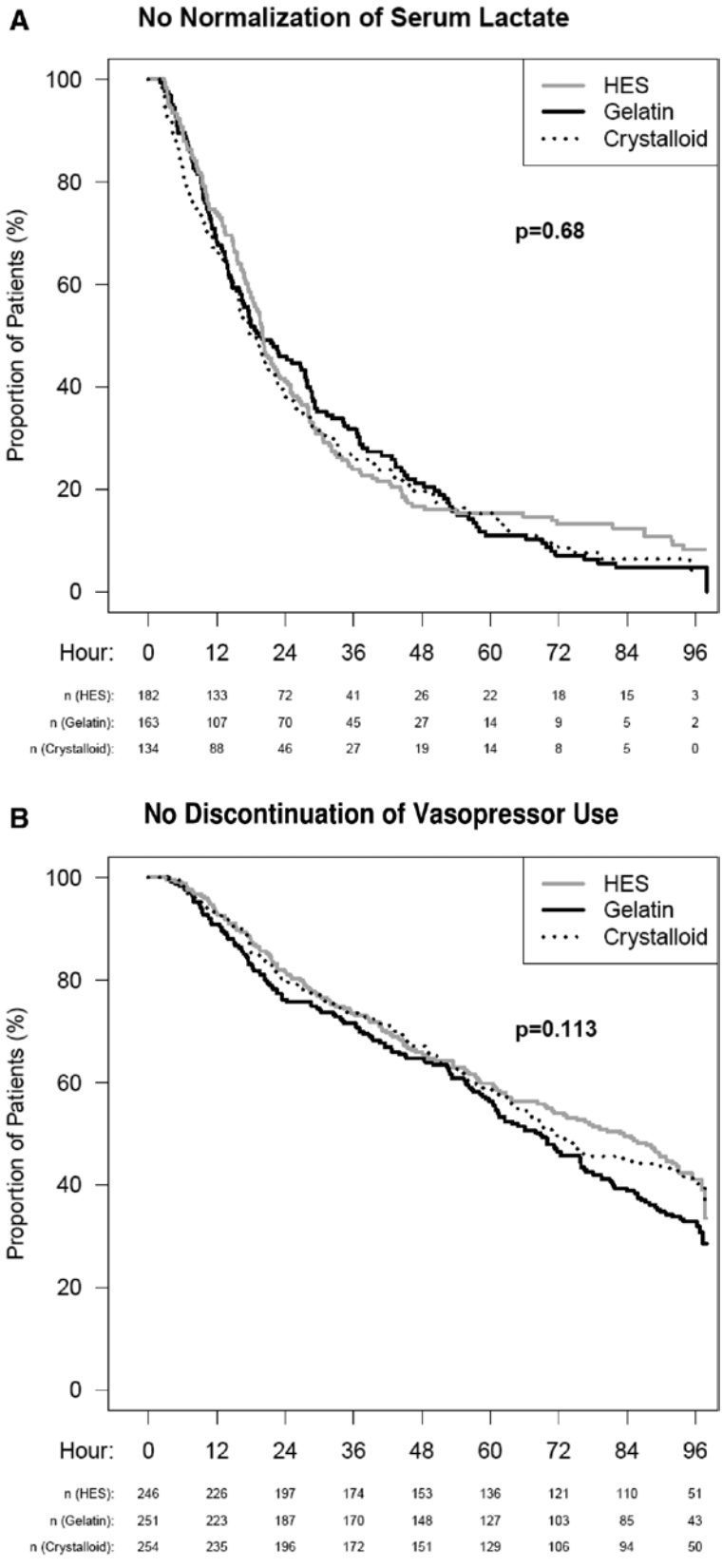

Figure 1. Shock reversal estimated by the Kaplan-Meier method. Time to normalization of serum lactate values (<2.2 mmol/L) and time to discontinuation of vasopressors in the hydroxyethyl starch (*HES*), gelatin and crystalloid study periods. Significance testing by log-rank tests. n denotes patients with predefined shock criteria.

to patients in the gelatin and crystalloid groups (Table 2).

Morbidity and Mortality

AKI occurred in 65.7% (687 of 1,046) of patients. RRT was initiated in 32.6% of patients (341 of 1,046), and both AKI and the decision to start RRT occurred more frequently in the HES and gelatin groups than in the crystalloid group (Table 3). Reasons to initiate RRT were similar between groups, and the median serum creatinine level was significantly higher in the HES group at the onset of RRT (Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/CCM/A469).

The majority of patients with AKI were classified as RIFLE class "failure", and more patients in the synthetic colloid groups achieved RIFLE class "failure" criteria than in the crystalloid group, this difference reaching significance in the HES group (42.5%, $p = .012$) but not in the gelatin group (40.1%, $p = .069$) vs. the crystalloid group (33.2%). The number of patients who fulfilled RIFLE classes "risk" and "injury" were lower and similar in all groups (Table 3).

Patients in both colloid groups spent a significantly longer period of time on the ventilator (Table 3). Severity scores, hospital length of stay, and ICU or hospital mortality rates did not differ significantly. ICU length of stay was significantly longer in both synthetic colloid groups (Table 3).

AKI Adjusted for Potential Confounding Factors

Multiple logistic regression analysis with AKI as a dependent binary variable showed that age, baseline creatinine, Simplified Acute Physiology II score, cardiothoracic surgery, liver cirrhosis, diabetes, vancomycin, iodinated contrast media, human albumin 20%, HES 6%, and gelatin 4% were independent risk factors (OR 2.55, 95% confidence interval 1.76, 3.69 and OR 1.85, 1.31, 2.62, respectively, Table 4). HES and gelatin were also independent risk factors for RRT (Supplemental Table 3, Supplemental Digital Content 1, http://links.lww.com/CCM/A469).

DISCUSSION

We found that in patients with severe sepsis, normalization of the indicators

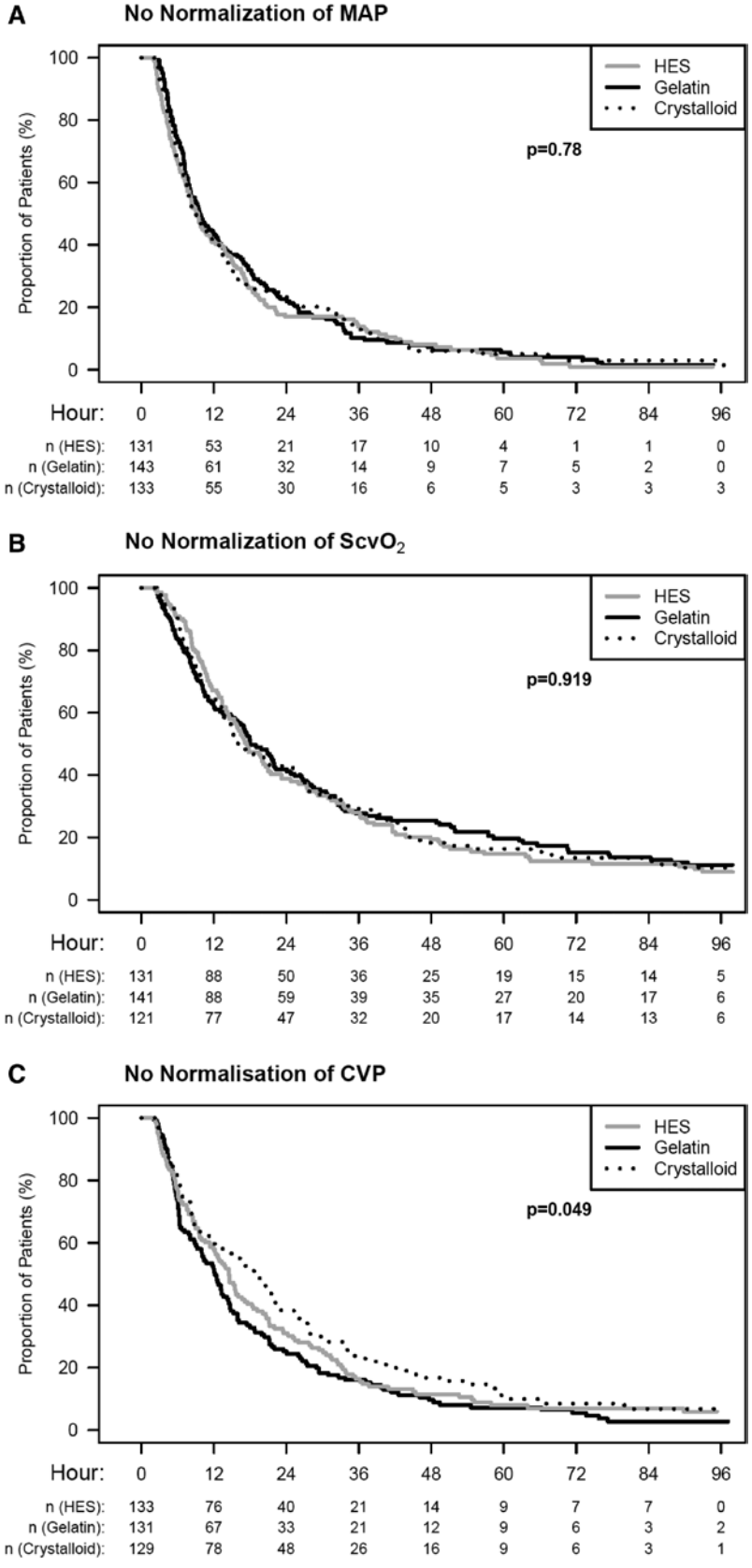

Figure 2. Reaching of hemodynamic goals estimated by the Kaplan-Meier method. Time to normalization of preset hemodynamic goals, including mean arterial pressure (*MAP*) of ≥70 mm Hg, central venous pressure (*CVP*) of ≥8 mm Hg, central venous oxygenation saturation ($ScvO_2$) of ≥70%. Significance testing by log-rank tests. n denotes patients not having reached hemodynamic goals at the respective time. *HES*, hydroxyethyl starch.

of shock (raised serum lactate and discontinuation of vasopressor use) occurred as quickly and effectively in patients resuscitated using only crystalloids as in those resuscitated using a combination of synthetic colloids and crystalloids. Response to treatment, measured by the time it took to achieve predefined hemodynamic goals, was similar regarding time to normalization of MAP and $ScvO_2$ values, whereas normal CVP values were achieved more slowly in the crystalloid group. Resuscitation with crystalloids alone required more fluid and vasopressor initially. Over the first 4 days, about 2.5 L more total fluid was given to patients in the crystalloid group, and mean daily fluid balances were more positive over the first 2 days. However, from day 5 on, the daily fluid balance became more negative in the crystalloid group.

AKI and need for RRT occurred significantly more often in the HES and the gelatin period than in the crystalloid period, confirming previous findings (20, 26). More patients in the synthetic colloid groups were exposed to allogeneic transfusion, and these patients received more packed red blood cells. Patients from the HES period also received more fresh frozen plasma and platelet concentrates. Time on the ventilator was significantly longer in both synthetic colloid groups. ICU and hospital mortality rates remained similar despite the significant differences in AKI and use of RRT. The seeming absence of colloid-associated effects on mortality may be explained by the fact that ICU or hospital mortality rates are short-term parameters, whereas synthetic colloid effects may become apparent only after a longer interval, as was shown in the VISEP study after 30 days (13).

Overall fluid load was higher in the colloids groups, because these patients stayed longer on the ICU. If only the first four ICU days were considered, total fluid dose were *lower* in the colloid periods, achieving significance for patients treated in the HES period.

Colloids may adsorb to the glycocalyx layer and restrict ultrafiltration, whereas crystalloid solutions equilibrate rapidly between the intravascular and the interstitial fluid spaces (29). Initially therefore, colloids may be more effective expanders of intravascular volume, as seen in a study of children with Dengue shock syndrome (11). During the first 2 hrs, HES or dextran lowered the hematocrit significantly than Ringer's lactate. Thereafter,

Table 2. Total fluids, blood products, and human albumin administered from admission to day 4 and during intensive care unit stay

	Hydroxyethyl Starch Period(n = 360)	Gelatin Period (n = 352)	Crystalloid Period (n = 334)
Cumulative fluid dose, median [IQR] in mL/kg body weight			
Day 0–4			
Colloid bolus[d]	39 [20–55][c]	21 [12–33][c]	
Crystalloid bolus	50 [25–97][c]	92 [56–154][c]	124 [75–182]
Total resuscitation fluid[e]	89 [55–133][c]	116 [75–177]	124 [75–182]
Total fluids[f]	205 [156–267][b]	224 [176–305]	239 [171–314]
Intensive care unit stay			
Colloid bolus[g]	83 [39–158][c]	40 [19–70][c]	
Crystalloid bolus	97 [51–186][c]	178 [87–313]	178 [93–347]
Total resuscitation fluid[e]	194 [107–334]	229 [118–385][a]	178 [93–347]
Total fluids[f]	790 [355–1512][c]	631 [276–1091][c]	406 [205–918]
Use of blood products, median (IQR) in units			
Fresh frozen plasma	10 [4–22][a]	8 [4–14]	8 [4–12]
Platelet concentrates	4 [2–7][c]	3 [1–5]	2 [1–4]
Red blood cells	7 [3–13][c]	6 [2–11][a]	4 [2–8]
Exposure to allogeneic blood products, n (%)			
Fresh frozen plasma	205 (57)[c]	159 (45)[c]	105 (31)
Platelet concentrates	139 (39)[c]	87 (25)	64 (19)
Red blood cells	306 (85)	293 (83)	273 (82)
Human albumin 20%, median [IQR] in mL/kg body weight	8 [5–18]	12 [5–25][c]	7 [4–14]
Patient exposure to human albumin 20%, n (%)	82 (22.8)[c]	200 (56.8)	193 (57.8)

IQR, interquartile range.

p values were calculated with the Mann-Whitney *U* test. Hydroxyethyl starch (HES) and gelatin group were compared with crystalloid group. [a].01 < *p* < .05, [b].001 < *p* < .01, [c]*p* < .001; [d]336 patients received HES, 349 patients received gelatin, 333 patients received only crystalloids from day 0 to day 4; [e]total resuscitation fluid included all colloid and crystalloid boli in the colloid groups and crystalloid boli in the crystalloid group; [f]total fluid amount includes oral and parenteral administered fluids including nutrition, drug administration, blood products, albumin, and intravenous volume replacement; [g]357 patients received HES, 349 patients received gelatin, 333 patients received only crystalloids over the whole intensive care unit stay.

however, the hematocrit rebounded only in the colloid groups (11). The transience of this colloid effect may explain why only short-term volume challenge studies (2, 5) showed a requirement of three- to four-fold more volume of crystalloid than colloid fluid whereas we found a volume ratio of only 1.4 to 1 and 1.1 to 1 for 6% HES and 4% gelatin, respectively, which is similar to findings in other studies with longer observation periods (12, 13).

The higher prevalence of AKI and requirement for RRT and the increased exposure to allogeneic transfusion in the HES period is consistent with the observed impairment of renal function and increased transfusion requirements reported from other studies and meta-analyses (13, 19, 21, 25, 30). It has been postulated that 6% HES 130/0.4 when administered within the allowed dose limits and together with crystalloids is devoid of clinically relevant adverse effects (31), but as 88% of the HES preparations administered in this study were 6% HES 130/0.4 and the median cumulative HES dose during the first four study days was 39 mL/kg, thereby well below the recommended dose limit for 1 day (50 mL/kg), these findings do not support this claim. A recent multicenter observational study also found no differences between lower and higher molecular weight starches in respect to renal impairment (30). Gelatin is not commonly perceived as nephrotoxic, but may induce osmotic nephrosis-like lesions similar to starches (32, 33). Recent experimental data suggest that gelatin may damage kidney morphology and impair renal function (34) differing only by degrees from changes induced by 6% HES 130/0.4 and 10% HES 200/0.5 (35). In sepsis patients, 3% gelatin has resulted in less renal impairment than 6% HES maybe because of the difference in colloid concentration (25).

Limitations and Strengths of This Study

This was a single center convenience cohort study with post-hoc adjusted analyses and multivariate modeling. We cannot exclude the possibility that systematic differences between the two groups reflect non measured alterations in other aspects of therapy, or secular changes over time as a result of general improvements in the care of septic patients (25, 36). Lack of baseline differences does not preclude the presence of unidentified group differences because of the nonrandomized nature of the study. The colloid groups included more patients with pneumonia as the source of sepsis. However, multivariate analysis identified no association between source of sepsis and AKI, and the need for RRT was found to be significantly higher in patients with abdominal than pulmonary sepsis in a large European survey (37). We cannot rule out that uncontrolled changes in treatment patterns such as changes in end of life decisions may have contributed to the decreased length of stay on the ICU and reduced time on the ventilator over the three sequential study periods. However analysis of secular changes over each of the three study intervals failed to show any evidence of improving outcomes over time unrelated to different fluid management strategies. Several HES trials are currently ongoing in critically ill or septic patients (CHEST Clinicaltrials.gov NCT00935168, 6S NCT00962156, BaSES NCT00273728).

Some observations strengthen our findings. Disease severity at baseline and during the course of the disease were comparable, as were cardio-respiratory variables, vasopressor support over time, and ICU and hospital mortality, and finally the daily levels of the sepsis marker procalcitonin which closely reflects the severity of the host response (38) strengthen the hypothesis that the observed effects may be associated with the changes of our fluid regimen.

CONCLUSIONS

The results of this study question the paradigm that shock reversal occurs faster with use of colloids, and that large three- to four-fold volume saving occurs when colloids are used. Furthermore, the results from our study place serious doubt on the assumption that third-generation HES 130/0.4 and low molecular weight gelatin are innocuous regarding renal function.

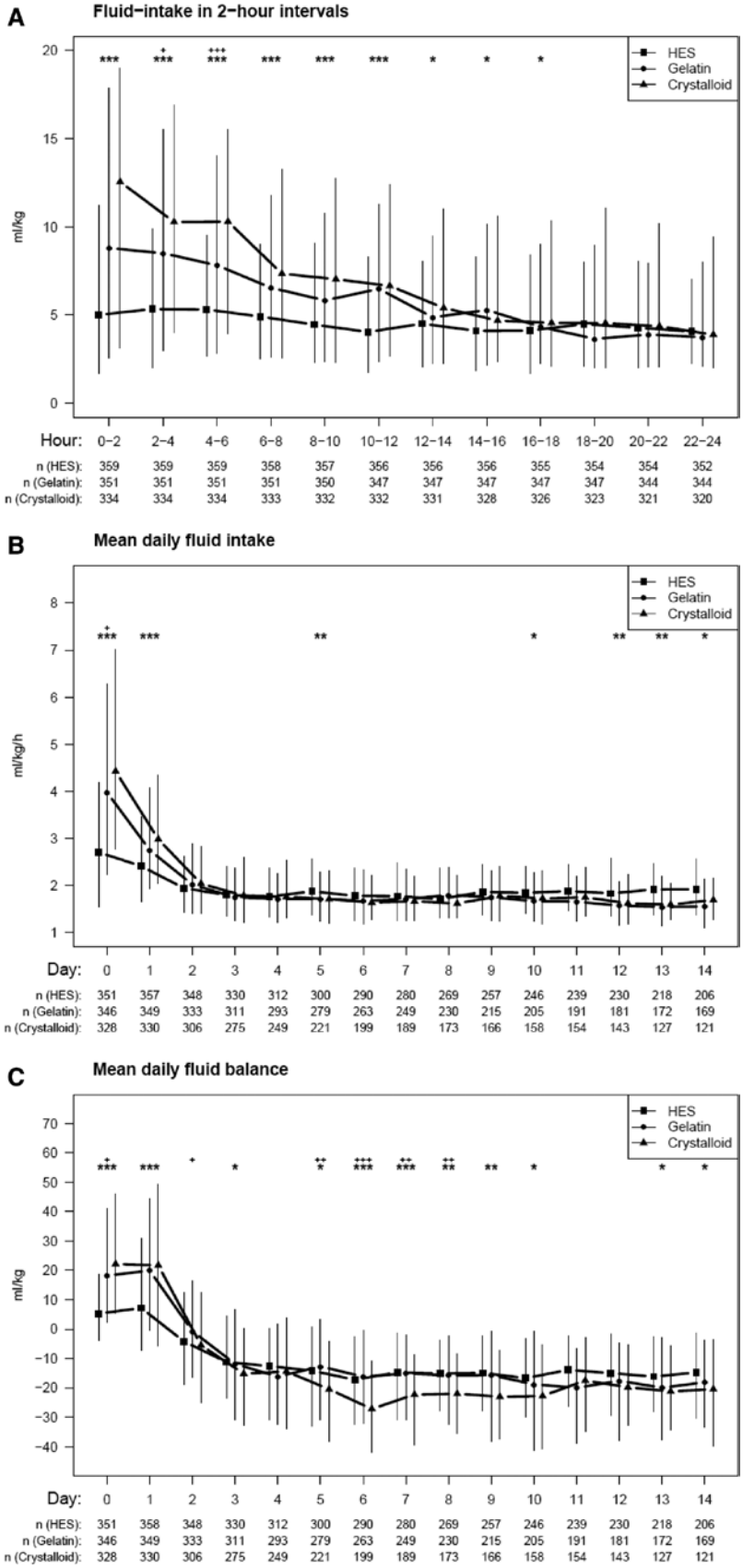

Figure 3. Fluid intake and fluid balance. Two-hourly intervals over the first 24 hrs (*a*), mean daily fluid intake (*b*), mean daily total fluid balance (*c*). Data presented as median and interquartile ranges. ***/+++ $p < .001$, **/++$p < .01$, */+$p < .05$ (*comparisons between hydroxyethyl starch (*HES*) and crystalloids groups; + between gelatin and crystalloid groups). n denotes patients with available data at each timepoint.

Table 3. Morbidity and mortality

	Hydroxyethyl Starch Period (n = 360)	*p*	Gelatin period (n = 352)	*p*	Crystalloid Period (n = 334)
RIFLE risk, n (%)	48 (13.3)	.648	49 (13.9)	.496	40 (12.0)
RIFLE injury, n (%)	53 (14.7)	.585	48 (13.6)	.911	44 (13.2)
RIFLE failure, n (%)	153 (42.5)	.012	141 (40.1)	.069	111 (33.2)
Acute kidney injury by RIFLE[a], n (%)	254 (70.6)	<.001	238 (67.6)	.014	195 (58.4)
Renal replacement therapy, n (%)	123 (34.2)	.085	125 (35.5)	.033	93 (27.8)
Maximum sequential organ failure score, median [IQR][b]	12 [10–14]	.662	12 [10–15]	.186	12 [9–14]
Mean Sequential Organ Failure Assessment score, median [IQR][b]	8 [6–11]	.690	8 [6–10]	.514	8 [6–11]
Time on ventilator, hrs,median [IQR]	214 [60–368]	<.001	146 [48–332]	.002	105 [15–280]
Duration of renal replacement therapy, days, median [IQR]	8 [4–18]	.003	6 [3–14]	.097	5 [3–9]
Intensive care unit mortality, n (%)	123 (34.2)	.192	107 (30.4)	.802	98 (29.3)
Hospital mortality, n (%)[c]	152 (42.2)	.383	151 (42.9)	.491	152 (45.5)
Intensive care unit length of stay, days, median [IQR]	18 [8–30]	<.001	13 [6–24]	<.001	10 [4–18]
Hospital length of stay, days, median [IQR][c]	31 [19–50]	.103	31 [19–51]	.088	29 [17–48]

IQR, interquartile range; RIFLE, Risk, Injury, Failure, Loss, and End-stage kidney disease.

p values vs. crystalloid (calculated with the Mann-Whitney *U* test and Fisher's exact test, as appropriate).

RIFLE risk: 1.5-fold increase in serum creatinine levels, acute increase in serum creatinine ≥26.2 μmol/L, urine output <0.5 mL/kg/hr for ≥24 hrs.

RIFLE injury: two-fold increase in serum creatinine levels, urine output <0.3 mL/kg/hr for ≥24 hr.

RIFLE failure: three-fold increase in serum creatinine levels and/or renal replacement therapy, serum creatinine ≥354 μmol/L with an acute rise of at least 44 μmol/L, urine output <4/70 mL/kg/hr for ≥ 24 hr.

[a]Defined by any RIFLE stage; [b]within 28 days of admission to the ICU; [c]missing data for one patient in the hydroxyethyl starch group.

Table 4. Multiple logistic regression analysis with acute kidney injury by Risk, Injury, Failure, Loss, and End-stage kidney disease as dependent binary variable

	n	Adjusted Odds Ratio (95% Confidence Interval)	*p*
Age (per year)	1024	1.02 (1.01, 1.03)	<.001
Baseline creatinine: (per μmol/L)	1024	1.0023 (1.0002, 1.0043)	.031
Baseline Simplified Acute Physiology Score-II: (per point)	1024	1.02 (1.01, 1.03)	<.001
Cardiac/thoracic surgery: yes vs. no	1024	1.70 (1.23, 2.75)	.001
Liver cirrhosis: yes vs. no	1024	2.30 (1.21, 4.38)	.011
Diabetes: yes vs. no	1024	1.43 (1.03, 1.99)	.030
Antimycotics: yes vs. no	1024	1.58 (0.97, 2.57)	.067
Vancomycin: yes vs. no	1024	1.96 (1.38, 2.78)	<.001
Iodinated contrast media: yes vs. no	1024	1.84 (1.23, 2.75)	.003
Human albumin 20%: yes vs. no	1024	1.54 (1.15, 2.08)	.004
Added after model selection			
Period effects			
Period: ref.=Crystalloids			
Gelatin 4%	1024	1.85 (1.31, 2.62)	<.001
Hydroxyethyl starch 6% (130/0.4)	1024	2.55 (1.76, 3.69)	<.001

Variables considered in the analysis: age, liver cirrhosis, diabetes, baseline creatinine, baseline Simplified Acute Physiology Score-II, cardiac/thoracic surgery, nonsteroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, aminoglycosides, antimycotics, vancomycin, iodinated contrast media, diuretics, human albumin 20%, study period using dummy coding. Forward and backward stepwise multiple logistic regression analysis based on Akaike Information Criterion was used to derive a multivariable model where the Hosmer-Lemeshow goodness-of-fit test (C test: $p = .589$, H test: $p = .155$) and region of area under curve analysis (area under curve = 0.66) indicate an acceptable fit and discrimination, respectively. *p* values were obtained by Wald's test. After model selection the period effect was studied. Data for 22 patients were missing.

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