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CRITICAL CARE

Effects of hydroxyethyl starch administration on renal function in critically ill patients[†‡]

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Background. The influence of hydroxyethyl starch (HES) solutions on renal function is controversial. We investigated the effect of HES administration on renal function in critically ill patients enrolled in a large multicentre observational European study.

Methods. All adult patients admitted to the 198 participating intensive care units (ICUs) during a 15-day period were enrolled. Prospectively collected data included daily fluid administration, urine output, sequential organ failure assessment (SOFA) score, serum creatinine levels, and the need for renal replacement therapy (RRT) during the ICU stay.

Results. Of 3147 patients, 1075 (34%) received HES. Patients who received HES were older [mean (SD): 62 (SD 17) *vs* 60 (18) years, $P=0.022$], more likely to be surgical admissions, had a higher incidence of haematological malignancy and heart failure, higher SAPS II [40.0 (17.0) *vs* 34.7 (16.9), $P<0.001$] and SOFA [6.2 (3.7) *vs* 5.0 (3.9), $P<0.001$] scores, and less likely to be receiving RRT (2 *vs* 4%, $P<0.001$) than those who did not receive HES. The renal SOFA score increased significantly over the ICU stay independent of the type of fluid administered. Although more patients who received HES needed RRT than non-HES patients (11 *vs* 9%, $P=0.006$), HES administration was not associated with an increased risk for subsequent RRT in a multivariable analysis [odds ratio (OR): 0.417, 95% confidence interval (CI): 0.05–3.27, $P=0.406$]. Sepsis (OR: 2.03, 95% CI: 1.37–3.02, $P<0.001$), cardiovascular failure (OR: 6.88, 95% CI: 4.49–10.56, $P<0.001$), haematological cancer (OR: 2.83, 95% CI: 1.28–6.25, $P=0.01$), and baseline renal SOFA scores>1 ($P<0.01$ for renal SOFA 2, 3, and 4 with renal SOFA=0 as a reference) were all associated with a higher need for RRT.

Conclusions. In this observational study, haematological cancer, the presence of sepsis, cardiovascular failure, and baseline renal function as assessed by the SOFA score were independent risk factors for the subsequent need for RRT in the ICU. The administration of HES had no influence on renal function or the need for RRT in the ICU.

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Hydroxyethyl starch (HES) solutions are synthetic colloids with pharmacological properties that are closest to natural colloids.[1] Apart from being a pure volume expander, the use of HES in the context of sepsis has been associated with a reduction in the circulating levels of adhesion molecules,[2] thus potentially reducing endothelial activation and damage. Additionally, HES may exert useful

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effects on the microvascular coagulation cascade by elevating levels of protein C and protein S.[3] Numerous HES preparations are available with different combinations of concentration, weight-averaged mean molecular weight, and hydroxyethylation patterns.[1]

The high cost of albumin has promoted the more widespread use of HES solutions. However, there is continuing concern regarding the possible adverse effects of HES including coagulopathy, anaphylactoid reactions,[4] and renal impairment. Cases of acute renal failure or osmotic nephrosis-like lesions in biopsy specimens have been reported and were thought to be related to HES use.[5–8] Several small studies[9–16] have yielded conflicting results, some implicating HES use in the deterioration of renal function, and others refuting this relationship.

We investigated the effect of HES administration on renal function in patients included in a large European database of 3147 critically ill patients from the Sepsis Occurrence in Acutely ill Patients (SOAP) study.[17]

Methods

The SOAP study was a prospective, multicentre, observational study designed to evaluate the epidemiology of sepsis as well as other characteristics of intensive care unit (ICU) patients in European countries. Recruitment, data collection, and management are detailed elsewhere.[17] Briefly, all patients >15 yr old admitted to one of the 198 participating centres (see Appendix 1 for a list of participating countries and centres) between May 1 and May 15, 2002 were included. We excluded patients who stayed in the ICU for less than 24 h for routine postoperative observation. Patients were followed up until death, hospital discharge, or for 60 days. Owing to the observational nature of the study, institutional review board approval was either waived or expedited in participating institutions and informed consent was not required. Data were collected prospectively using pre-printed case report forms. Data collection on admission included demographic data and comorbidities. Clinical and laboratory data for the simplified acute physiology (SAPS) II score[18] were reported as the worst value within 24 h after admission. Microbiological and clinical infections were reported daily as well as the antibiotics administered. A daily evaluation of organ function according to the sequential organ failure assessment (SOFA) score (Appendix 2, Table A1),[19] was performed, with the most abnormal value for each of the six organ systems (respiratory, renal, cardiovascular, hepatic, coagulation, and neurological) being collected on admission and every 24 h thereafter.

Sepsis was defined according to the consensus conference definitions.[20] Organ failure was defined as a SOFA score >2 for the organ in question.[21] Severe sepsis was defined by sepsis plus at least one organ failure. Daily fluid balance was calculated as the total fluid balance during the ICU stay divided by the duration of the ICU stay in days. Renal replacement therapy (RRT) was defined as any form of haemodialysis or haemofiltration alone or in combination. The 'subsequent need for RRT' was defined as the initiation of RRT in the ICU at least 24 h after HES administration or 24 h after admission in patients who did not receive HES.

Statistical methods

Data were analysed using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics were computed for all study variables. The Kolmogorov–Smirnov test was used to verify the normality of distribution of continuous variables. Non-parametric tests of comparison were used for variables evaluated as not normally distributed. Difference testing between groups was performed using the two-tailed *t*-test, Mann–Whitney *U*-test, χ^2-test, and Fisher exact test as appropriate. The Wilcoxon test was used to compare initial renal SOFA scores and maximum renal SOFA scores according to the type of fluid administered. The Kruskal–Wallis test was used to compare the change in renal SOFA score according to the type of fluid used. The Friedman test was used to compare the serum creatinine levels and urine output over the first week of administration of the corresponding fluid.

To identify the factors associated with an increased risk of subsequent need for RRT, we performed a multivariable logistic regression analysis, forward stepwise, with the need for RRT as the dependent factor in patients with an ICU length of stay (LOS) >24 h (n=1970), and age, sex, co-morbidities on admission, SAPS II score on admission, use of blood products (red blood cells, fresh frozen plasma), and the daily fluid balance as independent factors. The degree of organ failure assessed by the SOFA score, procedures (mechanical ventilation and pulmonary artery catheter), and the presence of sepsis syndromes on admission in patients who did not receive HES and at onset of HES administration in those who did, were also included as independent variables. Co-variates were selected and entered in the model if they attained $P<0.2$ on a univariate basis. Colinearity between variables was tested prior to modelling by computing the correlation of estimates, with a $R^2>0.7$ considered to be significant. A Hosmer and Lemeshow goodness-of-fit test was performed, and OR (95% CI) were computed. The amount and type of colloid administered (HES, gelatin, albumin, and dextran) was introduced in the model in a forward stepwise fashion. Administration of HES was forced in the final model as a dichotomous variable. Continuous data are presented as mean (SD) and categorical as number (%), unless otherwise indicated. All statistics were two-tailed and a $P<0.05$ was considered to be statistically significant.

Results

Characteristics of the study groups

Of the 3147 patients included in the SOAP study, 1075 (34%, 63% male) received HES during the ICU stay

(HES group), 932 (87%) within 48 h following admission. The median amount administered was 555 [interquartile range (IQ)=500–1000] ml day^{-1}, and the maximum amount 750 [500–1000] ml day^{-1}. The total amount per patient was 1000 (500–2250) ml in 2 (1–3) days per patient. On admission, patients who received HES were older, more likely to be surgical admissions, whether for elective, emergency or post-traumatic surgery, and had a higher incidence of haematological malignancy and heart failure. They also had higher SAPS II and SOFA scores, and fewer were receiving RRT than those who were not given HES (Table 1). During the ICU stay, the HES group was more likely to receive other colloids, such as gelatin, albumin 5%, albumin 20%, red blood cell transfusions, and fresh frozen plasma. They were also more likely to receive mechanical ventilation and RRT, and to have a pulmonary artery catheter inserted (Table 2).

Table 1 Characteristics of the study group on admission stratified according to HES administration. *6 missing values, **5 missing values. COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus

	All patients ***n*=3147**	**No HES** ***n*=2072**	**HES** ***n*=1075**	***P*-value**
Age, yr, mean (range)	61 (19–99)	60 (15–99)	62 (15–94)	0.022
Sex, M, (%)**	1920 (62.0)	1244 (60.0)	676 (62.9)	0.169
Type of admission				
Medical	1628 (51.7)	1240 (59.8)	388 (36.1)	<0.001
Elective surgery	766 (24.3)	405 (19.5)	361 (33.6)	
Emergency surgery	507 (16.1)	284 (13.9)	223 (20.7)	
Trauma	246 (7.8)	143 (6.9)	103 (9.6)	
SAPS II score, mean (SD)	36.5 (17.1)	34.7 (16.9)	40.0 (17.0)	<0.001
SOFA score, mean (SD)	51.1 (3.8)	5.0 (3.9)	6.2 (3.7)	<0.001
Comorbidities, (%)				
Cancer	415 (13.2)	264 (12.7)	151 (14.0)	0.305
Haematological cancer	69 (2.2)	35 (1.7)	34 (3.2)	0.007
COPD	340 (10.8)	218 (10.5)	122 (11.3)	0.478
HIV infection	26 (0.8)	16 (0.8)	10 (0.9)	0.584
Cirrhosis	121 (3.8)	77 (3.7)	44 (4.1)	0.602
Heart failure	307 (9.8)	180 (8.7)	127 (11.8)	0.005
Diabetes	226 (7.2)	152 (7.3)	74 (6.9)	0.641
RRT, (%)	115 (3.7)	91 (4.4)	24 (2.2)	<0.001

Morbidity and mortality

Patients who received HES had a higher incidence of sepsis, severe sepsis, septic shock, and shock due to any cause. They had greater SOFA scores, higher ICU and hospital mortalities, and longer median ICU and hospital lengths of stay than patients who did not receive HES (Table 3).

Renal function and determinants of the need for RRT according to the type of colloid used

The most commonly used colloid solutions were HES (*n*=1075, 34%) and gelatin (*n*=962, 32%). Albumin 20/25% (*n*=237, 8%), albumin 4/5% (*n*=162, 5%), and dextran (*n*=155, 5%) were used less commonly. A total of 1287 patients (41%) received only crystalloids and 574 (18%) received more than one colloid in the ICU. The use of colloids varied markedly among the contributing countries (Figure 1). Neither serum creatinine levels nor daily urine output differed significantly regardless of the type of fluid used (Figure 2). The renal SOFA score increased significantly during the ICU stay, but this increase was independent of the type of fluid administered (*P*=NS) (Figure 3). Although more patients who received HES needed RRT, in a multivariable logistic regression analysis, with the need for RRT as the dependent factor in patients with ICU LOS >24 h (*n*=1970), HES administration was not associated with an increased risk for subsequent need for RRT, but the presence of sepsis, cardiovascular failure, haematological cancer, and baseline renal SOFA scores >1 (*P*<0.01 for renal SOFA 2, 3, and 4 with renal SOFA=0 as a reference) (Table 4) were. Similarly, in a subgroup of patients with severe sepsis and septic shock (*n*=822), HES administration was not associated with an increased risk for subsequent RRT. None of the other colloids was associated with a higher risk of subsequent need for RRT (*P*>0.2 for all).

Table 2 Fluid and blood product administration, and procedures during the ICU stay

	All patients ***n*=3147**	**No HES** ***n*=2072**	**HES** ***n*= 1075**	***P*-value**
Colloids, (%)				
Gelatin	962 (31.6)	607 (29.3)	355 (33.0)	0.031
Dextran	155 (4.9)	112 (5.4)	43 (4.0)	0.084
Albumin 5%	162 (5.1)	83 (4.0)	79 (7.3)	<0.001
Albumin 20%	237 (7.5)	84 (4.1)	153 (14.2)	<0.001
Blood products, (%)				
Red blood cell transfusion	1040 (33.0)	478 (23.1)	562 (52.3)	<0.001
Fresh frozen plasma	209 (6.6)	88 (4.2)	121 (11.3)	<0.001
Platelet	46 (1.5)	25 (1.2)	21 (2.0)	0.098
Daily fluid balance, litres, mean (SD)	0.2 (1.3)	0.1 (1.2)	0.2 (1.4)	0.072
Procedures, (%)				
Mechanical ventilation	2025 (64.3)	1122 (54.2)	903 (84.0)	<0.001
Pulmonary artery catheter	481 (15.3)	224 (10.8)	257 (23.9)	<0.001
RRT	306 (9.7)	192 (9.3)	114 (10.6)	0.006

Table 3 Morbidity and mortality. *1 missing value, **45 missing values

	All patients $n=3147$	No HES $n=2072$	HES $n=1075$	*P*-value
Sepsis syndromes, (%)				
Sepsis	1177 (37.4)	662 (31.9)	515 (47.9)	<0.001
Severe sepsis	930 (29.6)	488 (23.6)	442 (41.1)	<0.001
Shock	462 (14.7)	205 (10.0)	257 (23.9)	<0.001
SOFA scores, mean (SD)				
SOFA max	6.5 (4.4)	5.8 (4.3)	8.2 (4.3)	<0.001
SOFA mean	4.5 (3.5)	4.0 (3.5)	5.5 (3.4)	<0.001
Shock due to any cause, (%)	960 (30.5)	454 (21.9)	506 (47.1)	<0.001
ICU mortality, (%)*	583 (18.5)	317 (15.3)	266 (24.7)	<0.001
Hospital mortality, (%)**	747 (23.7)	425 (20.5)	322 (30.0)	<0.001
ICU LOS, days, median [IQ]	3 [2–7]	3 [1–6]	5 [2–11]	<0.001
Hospital LOS, days, median [IQ]	11 [5–24]	11 [5–21]	13 [6–31]	<0.001

Discussion

This large observational study performed in 198 European ICUs indicates that the colloids most commonly used during the study period were HES and gelatin, with considerable variation among the contributing countries. Albumin and dextran were used less commonly. In this study, HES did not have a systematic adverse effect on renal function. A moderate increase in the renal component of the SOFA score occurred regardless of the type of fluid administered during the ICU stay. However, in a multivariable analysis, none of the colloids used was found to be associated independently with an increased risk of subsequent need for RRT in the ICU. Moreover, patients admitted to the ICU during the study period for routine non-complicated postoperative monitoring were excluded. Thus, only patients with a considerable degree of physiological derangement necessitating extended treatment in the ICU were included.

The higher need for RRT throughout the ICU stay and the increase in renal SOFA scores in patients who received HES can be explained by older age, higher incidence of co-morbidities, and greater severity state (as reflected by higher SAPS II and SOFA scores), than the patients who did not receive HES. Moreover, the incidence of sepsis syndromes and cardiovascular failure during the ICU stay was higher in the HES group compared with the non-HES group. All these confounding variables have been reported previously to be important predictors for the development of renal failure in the ICU.[12 22–26] The moderate deterioration in renal function observed during the ICU stay in all groups is also not surprising. Adjusting for all possible confounders by a multivariable analysis, we found that neither the use of HES nor the dose administered was associated with an increased risk of subsequent need for RRT.

The use of colloids may induce acute renal failure by raising the plasma colloid osmotic pressure.[27] Concerns

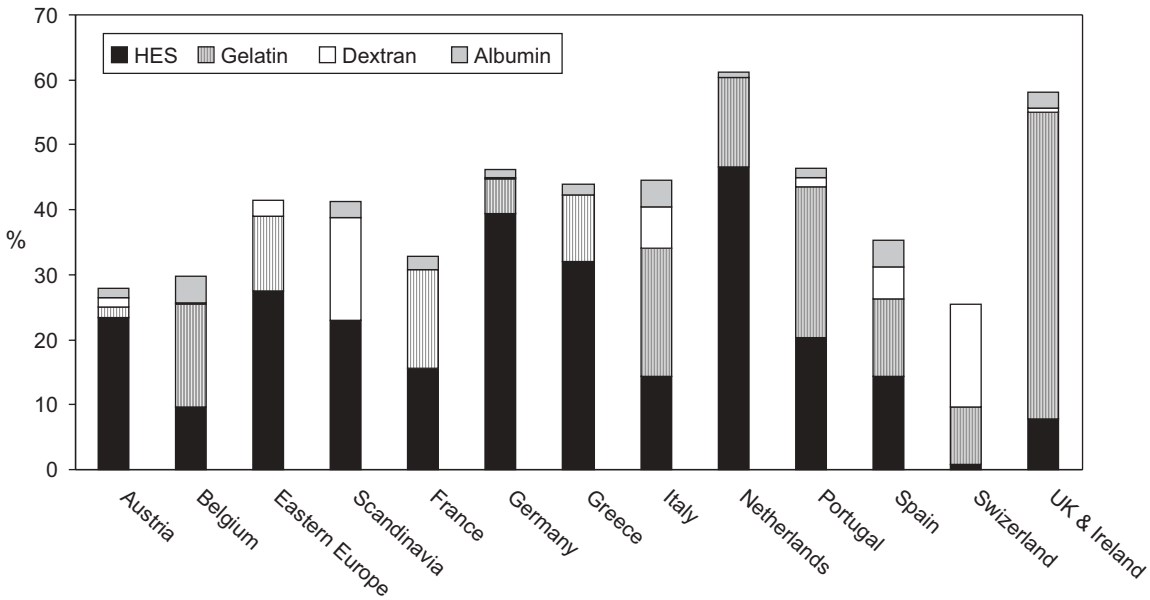

Fig 1 Bar chart demonstrating the use of various colloids in the contributing countries.

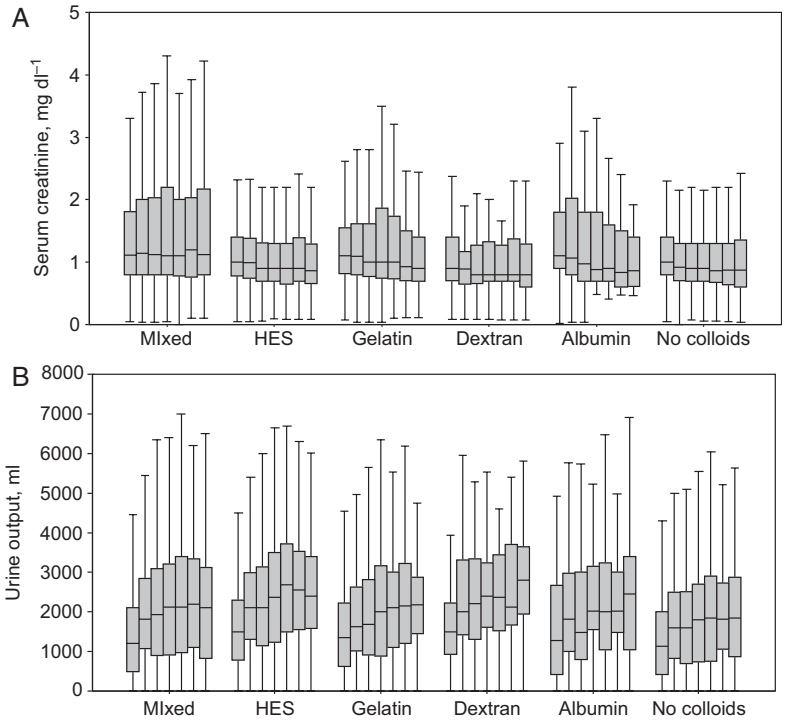

Fig 2 Box plot representing the evolution of serum creatinine (A) and urine output (B) over the first week of administration of the corresponding colloid. The first box in each cluster represents the first day the corresponding colloid was administered. Subsequent boxes represent the days following commencement of the corresponding colloid. $P<0.05$ in each group of fluid used over time.

about the adverse effects of HES on renal function were first raised by Legendre and colleagues,[10] who reported an association between HES exposure of organ donors and osmotic nephrosis-like lesions in the transplant recipients. These authors retrospectively compared 90 patients from a single institution for two distinct time periods: one before HES was made available for use in France and a subsequent period where HES was widely used. The appearance of osmotic nephrosis-like lesions involving proximal and distal tubules was observed more frequently during the later time period, but without obvious detriment in renal function in the recipients. This observation was limited by the retrospective nature of the study, the small sample size, and the absence of systematic adjustment for possible confounders. Similar histological lesions were subsequently reported after aggressive isovolemic haemodilution with HES in anaesthetized dogs[28] and have also been reported with other agents, including dextran, immunoglobulin, mannitol, and iodinated contrast agents.[29–32]

The first randomized trial exploring possible deleterious effects of HES administration on renal function was conducted by Cittanova and co-workers,[11] who compared HES (200 kDa/0·60) with gelatin and revealed that the use of HES solutions in brain-dead kidney donors was

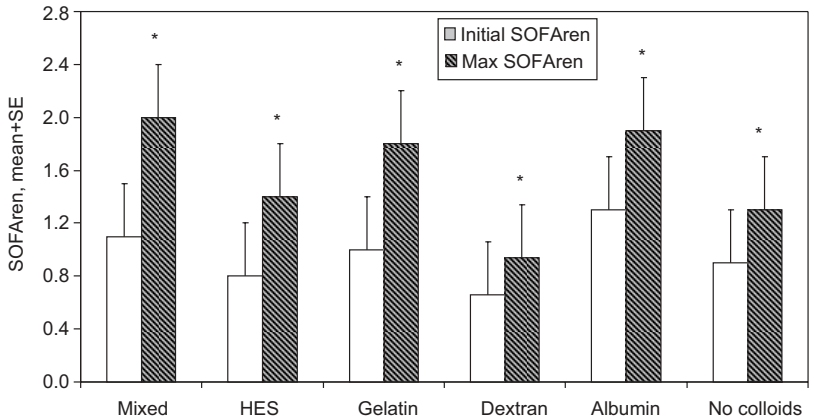

Fig 3 Bar chart representing the mean renal SOFA score (SOFAren) on the first day of administration of the corresponding fluid (initial) and the maximum (max) value recorded during the ICU stay thereafter. *$P<0.05$ compared with the initial value.

Table 4 Summary of multivariable logistic regression analysis, forward stepwise, with the need to initiate RRT during the ICU stay as the dependent factor in patients with ICU LOS >24 h* (n=1970) and a subgroup of patients with severe sepsis (including septic shock). *Excluding patients who were already receiving RRT on admission. **Forced in the final model

	All patients n=1970		**Severe sepsis n=822**	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Sepsis	2.03 (1.37–3.02)	<0.001	—	—
SOFA renal				
0	Reference		Reference	
1	1.46 (0.85–2.51)	0.167	1.15 (0.59–2.23)	0.676
2	2.67 (1.45–4.89)	0.002	2.26 (1.13–4.53)	0.002
3	5.0 (3.01–8.28)	<0.001	4.07 (2.31–7.18)	<0.001
4	27.33 (15.8–47–28)	<0.001	16.33 (8.53–31.28)	<0.001
Cardiovascular failure	6.88 (4.49–10.56)	<0.001	4.07 (2.31–7.18)	<0.001
Haematological cancer	2.83 (1.28–6.25)	0.01	—	—
HES administration**	0.417 (0.05–3.27)	0.406	1.08 (0.69–1.68)	0.718

followed by immediate impairment of renal function in the recipients with an increased rate of haemodialysis and higher serum creatinine concentrations. The use of an inferior preservation agent (Eurocollins) in this study was suggested as having aggravated the HES induced nephrotoxicity.[12] However, in a retrospective, multicentre analysis of kidney transplant recipients, Deman and colleagues[12] failed to confirm a deleterious effect of HES use on renal graft function, defined as the need for dialysis during the first post-transplant week. Likewise, Kumle and colleagues[13] reported no change in creatinine clearance in response to HES at different concentrations or to modified gelatin over 3 days of observation in elderly patients without preoperative renal dysfunction who were undergoing abdominal surgery. In cranio-cerebral trauma patients, Neff and colleagues[16] found no differences in renal function after repetitive large dose-infusion of 6% HES 130/0.4 or HES 200/0.5, although this was an observation study limited by the small number of patients. The debate regarding HES solutions was fuelled when a multicentre randomized study by Schortgen and colleagues,[14] comparing the effects of 6% HES (200/0.62) and fluid modified gelatin on renal function in 129 patients with severe sepsis, found that the frequencies of acute renal failure, oliguria, and serum creatinine concentrations were higher in the HES group than in the gelatin group. A limiting factor in that study was the better renal function at baseline in the gelatin group.[33–35] Likewise, Winkelmayer and colleagues[9] retrospectively studied 239 patients who underwent coronary artery bypass grafting surgery. The use of 6% HES (130/0.4) was independently associated with a modest reduction in glomerular filtration rate (GFR) on postoperative days 3 and 5, with GFR declining by 7.2 ml min^{-1} 1.73 m^{-2} on day 3 per unit of HES administered, and by 6.6 ml min^{-1} 1.73 m^{-2} on day 5. However, Boldt and colleagues[15] randomized 40 elderly (>70 yr) patients undergoing cardiac surgery using cardiopulmonary bypass to either 6% HES 130/0.4 or gelatin, and found an increase in kidney-specific proteins in the 40 patients, with no difference between HES and gelatin. None of the patients developed acute renal failure. Our results support the lack of deleterious effect of HES on renal function in a heterogeneous group of critically ill patients.

Although this is the largest analysis to date exploring the effects of HES on renal function, our study has some limitations. The retrospective nature of the analysis could be a limiting factor. However, the data were collected prospectively and were subjected to meticulous quality control measures.[17] The multivariable approach is limited by the variables included in the analysis, so that other unmeasured variables could have contributed to the final results. In addition, the indications for fluid therapy and for commencing RRT were not standardized. However, we considered a large number of variables related to the severity of illness, organ failure, associated comorbidities, and procedures in the ICU. The type of HES used was not reported specifically in our study; possibly the use of recent generation HES with a lesser potential for nephrotoxicity could have contributed to the favourable results. The median amount of HES administered in our study was below the maximal recommended dose;[1] however, the dose of HES, introduced as a variable in the multivariable analysis, was not found to contribute to the subsequent need for RRT. It was not possible to calculate the GFR as a specific measure of renal function from the collected data; however, the use of the SOFA score has been shown to be an effective indicator of renal function[21] and the need for RRT is a practical measure indicating clinically relevant renal impairment in the ICU. Although prospective randomized controlled trials are the best way to evaluate these factors, large observational studies can help to demonstrate the deleterious effects of interventions, as shown recently for aprotinin in patients undergoing cardiac surgery.[36]

Conclusion

In this large cohort, HES was the most frequently used colloid in the participating European ICUs with considerable

variations among the participating countries. Haematological cancer, the presence of sepsis, cardiovascular failure, and baseline renal function as assessed by the SOFA score, were independent risk factors for the subsequent need for RRT in the ICU. The administration of HES had no influence on renal function or the subsequent need for RRT in the ICU.

Acknowledgement

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Appendix 1

Participants by country (listed alphabetically)

Austria: University Hospital, Vienna (G. Delle Karth); LKH Steyr (V. Draxler); LKH-Deutschlandsberg (G. Filzwieser); Otto Wagner Spital, Vienna (W. Heindl); Krems, Donau (G. Kellner, T. Bauer); Barmherzige Bruede, Linz (K. Lenz); KH Floridsdorf, Vienna (E. Rossmann); University Hospital, Innsbruck (C. Wiedermann). Belgium: CHU, Charleroi (P. Biston); Hôpitaux Iris Sud, Brussels (D. Chochrad); Clinique Europe Site St Michel, Brussels (V. Collin); C.H.U., Liège (P. Damas); University Hospital Ghent (J. Decruyenaere, E. Hoste); CHU Brugmann, Brussels (J. Devriendt); Centre Hospitalier Jolimont-Lobbes, Haine St Paul (B. Espeel); CHR Citadelle, Liege (V. Fraipont); UCL Mont-Godinne, Yvoir (E. Installe); ACZA Campus Stuivenberg (M. Malbrain); OLV Ziekenhuis Aalst (G. Nollet); RHMS Ath-Baudour-Tournai (J.C. Preiser); AZ St Augustinus, Wilrijk (J. Raemaekers); CHU Saint-Pierre, Brussels (A. Roman); Cliniques du Sud-Luxembourg, Arlon (M. 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Appendix 2

Table A1 SOFA score 19. *Norepi, norepinephrine; Dop, dopamine; Epi, epinephrine; Dob, dobutamine; $F_{I_{O_2}}$, fraction, inspired oxygen. †Values are with respiratory support. ‡To convert bilirubin from mg dl^{-1} to μmol $litre^{-1}$, multiply by 17.1. §Adrenergic agents administered for at least 1 h (doses given are in μg kg^{-1} min). ¶To convert creatinine from mg dl^{-1} to μmol $litre^{-1}$, multiply by 88.4

Variables	SOFA score 0	1	2	3	4
Respiratory					
$P_{a_{O_2}}/F_{I_{O_2}}$, mmHg	>400	≤400	≤300	≤200†	≤100
Coagulation					
Platelets ($\times 10^3$ μl^{-1})‡	>150	≤150	≤100	≤50	≤20
Liver					
Bilirubin (mg dl^{-1})‡	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular					
Hypotension	No hypotension	Mean arterial pressure <70 mm Hg	Dop ≤5 or Dob (any dose)	Dop >5, Epi ≤0.1, or Norepi ≤0.1§	Dop >15, Epi >0.1, or Norepi >0.1§
Central nervous system					
Glasgow Coma Score	15	13–14	10–12	6–9	<6
Renal					
Creatinine (mg dl^{-1}) or urine output (ml day^{-1})	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 <500	>5.0 <200

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