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ORIGINAL ARTICLE

Safety and efficacy of 6% hydroxyethyl starch in patients undergoing major surgery

The randomised controlled PHOENICS trial

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BACKGROUND Hydroxyethyl starch (HES) is often used for maintaining vascular volume during major surgery. Long-term high-dose HES in septic patients promotes renal injury, whereas meta-analyses of current HES products in surgical patients do not show such effects.

OBJECTIVE We studied if the peri-operative use of HES is noninferior to crystalloids in terms of acute kidney injury. Secondary outcome was the noninferiority of HES on worsening of renal injury and/or the incidence of a composite endpoint of major complications and mortality until postoperative day 90.

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DESIGN Randomised double-blind trial in patients undergoing elective abdominal surgery with expected blood loss at least 500 ml.

SETTING Multicentre trial at 53 study sites in 10 European countries.

PATIENTS One thousand nine hundred and eighty-five (HES 977, crystalloid-only 981) patients aged 40 to 85 years with ASA status II-III.

INTERVENTION Either 6% HES 130/0.4 or a crystalloid solution. Dosing was guided by mean arterial pressure and/or routine haemodynamic variables.

MAIN OUTCOME MEASURE Change from pre-operative to lowest cystatin C-based eGFR during the first 3 postoperative days. Key secondary outcome was a composite endpoint of mortality and major postoperative complications after 90 days.

RESULTS Mean change in eGFR from baseline to minimum was -3.4 ± 17.7 ml min^{-1} 1.73 m^{-2} in HES patients and -1.0 ± 17.1 ml min^{-1} 1.73 m^{-2} in crystalloid-only patients ($P < 0.001$ for noninferiority). The key secondary endpoint occurred in 35% of patients in each group. There were no clinically relevant differences in any safety endpoint including 90-day renal function. Any cause mortality-difference until the end of 1-year follow-up was not significantly different (8.6% in HES and 10.1% in crystalloid patients).

CONCLUSION Peri-operative use of HES was noninferior to crystalloids in short-term renal function or a composite of mortality and major complications at 90 days. PHOENICS provides robust evidence that peri-operative in-label use of HES is well tolerated.

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KEY POINTS

- PHOENICS is the largest prospective, randomised, double-blind study of HES vs. crystalloid in major surgery.
- Regarding the primary endpoint of early postoperative renal function, measured as cystatin C based eGFR, HES was noninferior.
- For the composite of mortality and major postoperative complications (including renal) at 90 days, also noninferiority was demonstrated.
- Overall mortality after 1 year was comparable for HES and crystalloid.
- Net fluid balance, decrease in mean arterial pressure and need for vasoactive/inotropic drugs showed favourable results for HES.

Introduction

Surgical patients are given intravenous fluids to maintain adequate vascular volume and organ perfusion. In most patients, saline or balanced crystalloid solutions are used. In case of significant blood loss and subsequent haemodynamic instability, higher volumes are required, and blood products and/or colloid solutions are infused, as they remain intravascular for a longer period. This approach improves blood pressure and organ perfusion.[1] Albumin is the ideal colloid in many situations; however, it is expensive, and availability is limited. Artificial colloidal solutions are also widely used including hydroxyethyl starch (HES) and gelatine solutions.[2]

High-dose HES solutions given over prolonged periods reportedly provoke acute kidney injury (AKI) in septic patients.[3,4] In surgical patients with acute blood loss, colloid solutions are mainly used during the intra-operative and early postoperative period. The available evidence indicates that intra-operative HES administration does not worsen acute or long-term renal function compared to crystalloids.[5] However, until now, controlled trials have been underpowered to draw a definite conclusion. Therefore, the European Medicines Agency (EMA) concluded in 2013 that there were insufficient long-term safety data in surgical patients with acute blood loss and the use of synthetic colloids. After receiving scientific and methodological advice from EMA, we conducted a Phase IV trial to re-evaluate the safety of 6% HES 130/0.4 colloid solution in surgical patients.

We tested the primary hypothesis that peri-operative use of HES does not result in an increased incidence of AKI compared with crystalloid solutions. Second, we tested the assumption that HES is noninferior in terms of renal injury or increase the incidence of major complications and mortality until postoperative day 90. Other secondary outcome parameters included measures of coagulation, inflammation, haemodynamic parameters, intravenous fluid volume, fluid balance, and rate and amount of blood transfusion. On an exploratory basis, we evaluated the effect of HES on the use of vasoactive medication as an indirect indicator of haemodynamic (in)stability.

Materials and methods

PHOENICS was a randomised, double-blind, parallel-group, multicentre trial conducted at 53 study sites in 10 European countries. The study protocol was co-designed with the scientific advice of the EMA, published[6] and registered at ClinicalTrials.gov before enrolling the first patient (NCT03278548). The study was conducted in compliance with International Conference on Harmonization

(ICH) guidelines for Good Clinical Practice (GCP), the most recent version of the Declaration of Helsinki, and was monitored by a data and safety monitoring board. The trial was approved by the responsible ethics committees at each site, and written consent was obtained from all participants.

Trial participants

Eligible patients were between 40 and 85 years old, scheduled for elective abdominal surgery with an expected blood loss of at least 500 ml, and were designated American Society of Anaesthesiologists (ASA) physical status II-III. Screening was performed by the investigator within one week before surgery. We excluded patients with contraindications to HES, sepsis, burns, acute or chronic renal impairment, intracranial haemorrhage, pulmonary oedema, dehydration, electrolyte disturbances, severely impaired hepatic function, congestive heart failure, severe coagulopathy, previous organ transplants and patients who were critically ill. We also excluded patients with body weight at least 140 kg and those who were pregnant.

Randomisation and treatment

Anaesthetic and surgical care were per routine. Patients were randomised 1 : 1 based on computer-generated codes stratified by trial site. Randomisation was concealed until shortly before surgery (maximal 1 day before surgery) by a central interactive response system.

Patients were assigned to intravenous volume replacement with either 6% HES 130/0.4 in a balanced electrolyte solution (Volulyte, Fresenius Kabi, Bad Homburg, Germany) at a maximum dose of 30 ml kg^{-1} body weight or to the identical balanced electrolyte solution only (Ionolyte, Fresenius Kabi, Bad Homburg, Germany), given intra-operatively and up to a maximum of 24 h afterwards. The trial solutions were identical in appearance and packaging. Consequently, physicians, patients and outcome assessors were blinded to the treatment. Dosing was guided by a volume algorithm based on mean arterial pressure (MAP) and advanced haemodynamic parameters[6] (Supplemental File, http://links.lww.com/EJA/B213). All patients received basic crystalloid solutions following local practice.

Trial procedures

The study schedule is provided in the Supplemental File (Table S1, http://links.lww.com/EJA/B213). Serum for cystatin C concentrations was obtained at baseline, end of surgery, postoperative day (POD)1–10 (once daily), POD 28 and POD 90. Cystatin C analyses for all sites were performed by a central laboratory (Bioscientia Institut für Medizinische Diagnostik GmbH, Ingelheim, Germany). All other measurements and assessments were done per routine at trial sites. Serum cystatin C based estimation of eGFR is provided in the Supplemental File, http://links.lww.com/EJA/B213.

Outcomes

We estimated cystatin C based eGFR with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation developed by Inker *et al.*[7] Our primary outcome was the change in glomerular filtration from pre-operative baseline to the lowest recorded value during the initial 3 postoperative days. The noninferiority margin was defined together with EMA at 8.1 ml min^{-1} 1.73 m^{-2}, representing a 9% relative reduction from 90 ml min^{-1} 1.73 m^{-2} being the lower limit of the normal range,[8] as 10% or more reduction was considered clinically relevant.[9,10] The noninferiority margin for the composite of mortality and major postoperative complications was set at 7.5%, again after discussion with the EMA. The key secondary outcome was a composite endpoint of mortality and major postoperative complications (including renal) after 90 days.[11] As per protocol, postoperative complications must have been graded moderate or severe to be considered major.[6] Other secondary and exploratory endpoints included coagulation status, inflammation, haemodynamic parameters, intravenous fluid volume, fluid balance, transfusions, serious adverse events, in-hospital mortality and major postoperative complications.

Statistical analysis

All analyses were defined in a Statistical Analysis Plan before the study was unblinded. No interim analyses affecting the sample size or other features of the study were planned or conducted. Estimates were generated with SAS version 9.4. Variance is presented as ±SDs or 95% confidence intervals (95% CIs).

The planned sample size was 909 evaluable patients per group, which provided 90% power for analysis of covariance (ANCOVA) of the primary study hypothesis. Our estimate was based on noninferiority of the primary endpoint given a type-I-error-rate of 2.5% with a one-sided margin of $\Delta = 8.1$ ml min^{-1} 1.73 m^{-2} assuming a treatment difference of 0 and a standard deviation of 52.4 ml min^{-1} 1.73 m^{-2} under the alternative hypothesis. Our planned sample size also provided over 90% power for the key secondary endpoint. Details on the analysis sets are provided in the Supplemental File, http://links.lww.com/EJA/B213.

Our primary outcome was evaluated with ANCOVA with trial site as a fixed factor and baseline eGFR as covariate. The noninferiority of HES compared to crystalloid-only was derived from the noninclusion of the NI margin in the 95% CI of least-square mean difference between treatment groups and the respective *P* value from the ANCOVA. Testing on the per-protocol and full analysis sets was considered co-primary at an alpha level of 0.025.

The key secondary endpoint was analysed by the 'common treatment group risk difference' with a two-sided 95% CI, controlled for the eight possible combinations of the factors age (≤ or >median), sex and ASA physical status (≤II vs. ≥III) according to the method of Miettinen-Nurminen.[6,12] The secondary endpoint hypothesis of noninferiority of HES was derived from the noninclusion of the NI margin in the 95% CI of the common treatment group risk difference.

Other secondary or exploratory endpoints were compared between treatment groups by the following statistical tests depending on the type of variable. Continuous variables were compared with *t*-tests or (when the baseline was measured) ANCOVA with baseline covariate including least-square mean treatment difference (with 95% CI). Categorical variables were compared with chi square test and dichotomous variables with risk differences (with 95% CI).

Results

Patients were enrolled between September 2017 and April 2022. Among 2346 patients screened, 2289 were randomised and 1958 received the study solution(s): 977 received HES and 981 received crystalloid-only (Fig. 1, Supplemental File Table S2, http://links.lww.com/EJA/B213). The main reason for not treating randomised patients was the lack of clinical need for volume infusion

Fig. 1 Consort diagram.

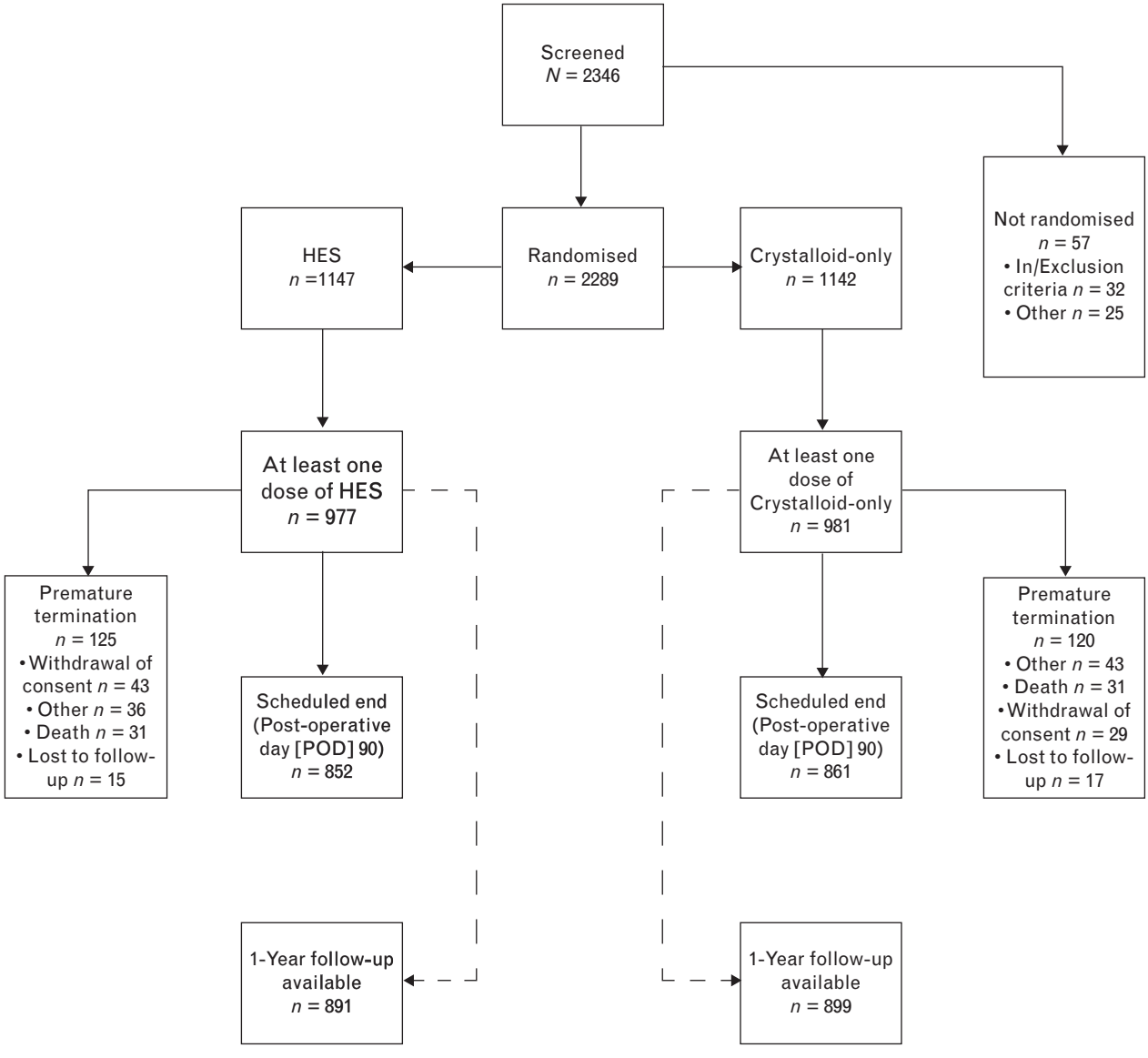


Table 1 Demographics and baseline characteristics

Variable	HES ($N = 977$)	Crystalloid-only ($N = 981$)	Standardised differences of means
Age (years)			
Mean	65 ± 9.5	65 ± 9.9	0.002
Median	66 [41 to 85]	66 [40 to 85]	
Height (cm)[a]			
Mean	170 ± 9.8	170 ± 9.6	0.068
Median	170 [143.0 to 198.0]	170 [140.0 to 199.0]	
Weight (kg)[a]			
Mean	77 ± 16.0	77 ± 16.1	0.022
Median	76 [38.0 to 135.0]	76 [38.0 to 138.0]	
BMI ($kg\,m^{-2}$)[a]			
Mean	26.6 ± 4.5	26.7 ± 4.8	−0.024
Median	26.2 [16.3 to 46.1]	26.1 [14.9 to 46.3]	
Sex			
Male	625 (64.0)	609 (62.1)	
Female	352 (36.0)	372 (37.9)	
Albumin/No albumin			
No Albumin	865 (88.5)	861 (87.8)	
Albumin	112 (11.5)	120 (12.2)	
ASA Score[b]			
II	560 (57.3)	565 (57.6)	
≥III	417 (42.7)	416 (42.4)	
Cystatin C based eGFR ($ml\,min^{-1}\,1.73\,m^{-2}$)			
Mean	87.9 ± 21.6	87.3 ± 21.9	0.031
Median	89.4 [26.3 to 176.7]	90.2 [21.5 to 189.0]	
Serum creatinine based eGFR ($ml\,min^{-1}\,1.73\,m^{-2}$)			
Mean	88.8 ± 15.1	88.7 ± 16.0	0.008
Median	90.4 [35.5 to 125.9]	90.3 [29.2 to 152.9]	
Haemodynamic parameter used to guide volume administration			
Mean arterial pressure	600 (61.4)	597 (60.9)	
Combined parameters	131 (13.4)	129 (13.1)	
Pulse pressure variation	118 (12.1)	124 (12.6)	
Stroke volume	67 (6.9)	67 (6.8)	
Stroke volume variation	60 (6.1)	63 (6.4)	
Stroke volume index	1 (0.1)	1 (0.1)	
Type of surgery in >5% of patients[c]			
General (Intestinal)	201 (20.6)	201 (20.5)	
Urological (Prostate)	176 (18.0)	165 (16.8)	
General (Pancreatic)	131 (13.4)	133 (13.6)	
General (Liver)	119 (12.2)	121 (12.3)	
Gynaecological	117 (12.0)	105 (10.7)	
Urological (Bladder)	63 (6.4)	67 (6.8)	
Urological (Renal)	62 (6.3)	65 (6.6)	
Duration of surgery (h)			
Mean	4.17 ± 2.16	4.17 ± 2.03	0.004
Median	3.83 [0.0 to 14.3]	3.83 [0.0 to 15.8]	
Estimated intra-operative blood loss (ml)			
Mean	823.8 ± 783.4	760.5 ± 780.6	0.081
Median	600.0 [0 to 11 600]	600.0 [0 to 16 500]	

Data are presented as mean ± SD, median [range] and *n* (%). The standardised difference of means is calculated as the difference between means of treatment groups (HES − Crystalloid-only) divided by the pooled standard deviation. ASA, American Society of Anesthesiologists; $N_{missing}$, Number of missing observations. [a] Weight was missing in one patient in the HES group, Height and BMI were missing in two patients of the HES group and in three patients in the crystalloid group. [b] Two patients had ASA score IV at study inclusion. [c] Further details are provided in Supplemental Table S10, http://links.lww.com/EJA/B213. Analysis Set: Safety Set/Full Analysis Set-Efficacy.

per attending physicians. No patients received intravenous HES, dextran, or gelatine within 24 h before surgery. Pre-operative albumin was given in 11.5% of patients of the HES group and 12.2% in crystalloid-only patients.

Baseline characteristics (Table 1), types of surgery and anaesthesia, main surgical diagnoses, concomitant diseases and prior medications were comparable between the treatment groups (Supplemental File Tables S3-S7, http://links.lww.com/EJA/B213). Patients assigned to HES were given 1.2 ± 0.7 l of study fluid, whereas those assigned to crystalloid-only were given 1.4 ± 0.8 l ($P < 0.0001$) (Table 2).

Main results

The primary endpoint until 3 days after surgery was analysed in 922 patients of the HES-group and 935 patients assigned to crystalloid-only solution. The mean change in eGFR from baseline to minimum eGFR in the

Table 2 Study drug administration

Statistics	HES ($N = 977$)	Crystalloid-only ($N = 981$)	Mean treatment difference (95% CI)	P
Total administered fluid (ml)				
$N_{missing}$	0	1		
Median	1000.0 [500 to 1650]	1250 [750 to 2000]		
Range	[250 to 4000]	[250 to 4000]		
Mean	1161.61 ± 711.80	1355.90 ± 764.24	−194.28 (−259.76 to −128.81)	<0.0001
Fluid volume (ml kg^{-1})				
$N_{missing}$	1	1		
Mean	15.34 ± 9.09	17.97 ± 9.70	−2.63 (−3.46 to −1.80)	<0.0001
Duration of fluid treatment (h)				
$N_{missing}$	6	7		
Mean	3.63 ± 4.89	3.20 ± 4.11	0.43 (0.03 to 0.83)	0.0366

Data are presented as mean ± SD, Median [IQR], and mean difference (95% confidence interval). CI, confidence interval; IP, investigational product; $N_{missing}$, number of missing observations. 95% CI and P value calculated by t-test with Satterthwaite method.

first 3 postoperative days was -3.4 ± 17.7 ml min^{-1} 1.73 m^{-2} in patients assigned to HES and -1.0 ± 17.1 ml min^{-1} 1.73 m^{-2} in patients randomised to crystalloid-only ($P < 0.001$ for noninferiority). Comparable results were obtained for the respective sensitivity analysis (Table 3, Supplemental Figure 2, http://links.lww.com/EJA/B213).

Serum creatinine concentrations and eGFR were similar between groups on POD 1 to 3 (Fig. 2). Further, AKI, as assessed by RIFLE and AKIN scores, was comparable during the first postoperative days and on POD 28 and 90 (Supplemental File, http://links.lww.com/EJA/B213, Figure 1). No patient required pre-operative renal replacement therapy (RRT), and use of RRT posttreatment was similar after surgery [nine patients (0.9%) in HES and 10 patients (1.0%) in the crystalloid-only group, see Supplemental File, Table S8, http://links.lww.com/EJA/B213].

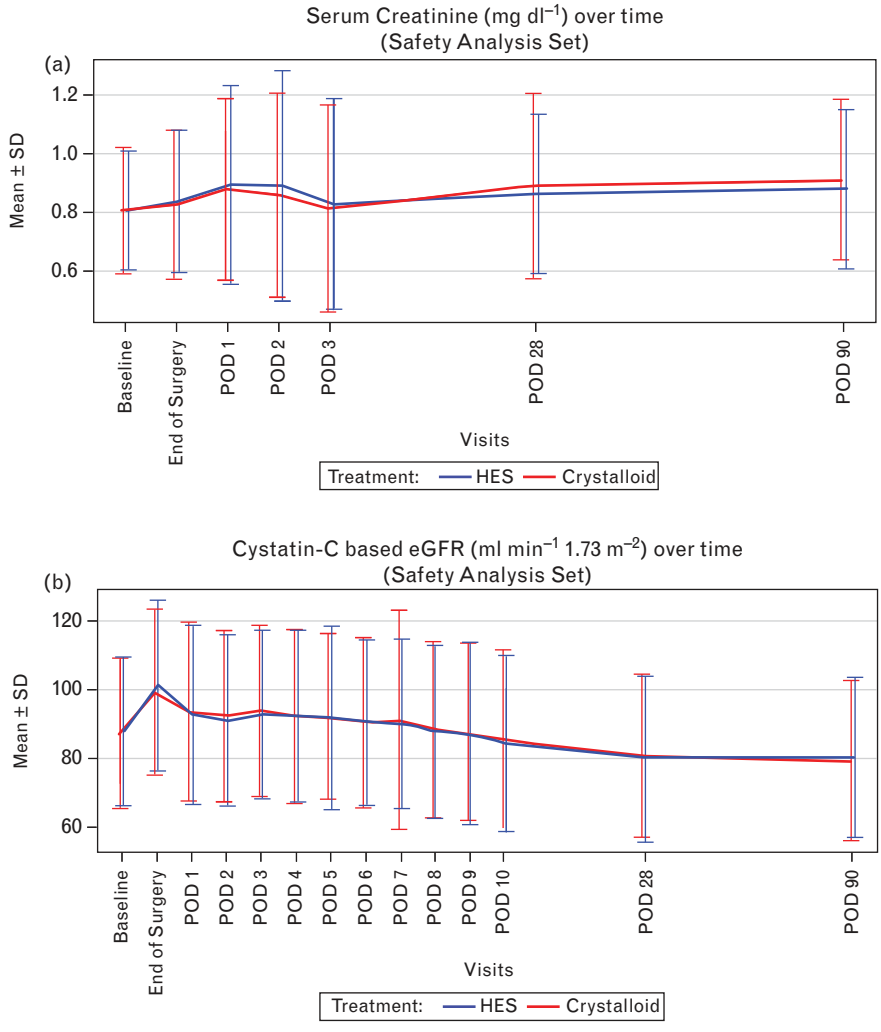
The key secondary endpoint (composite of mortality and major postoperative complications) until day 90 was reached in 35% of patients in both groups, resulting in noninferiority (risk difference 0.63%, 95% CI -3.83 to 5.09). Results were similar in the sensitivity analysis

Table 3 Descriptive statistics and ANCOVA-results for the change from pre-operative to minimal cystatin C based estimated glomerular filtration rate during the first 3 postoperative days

	HES	Crystalloid- only	Treatment effect LS mean (95% CI)	P of non-inferiority Δ = -8.1 ml min^{-1} 1.73 m^{-2}
FAS-pEP (N_{valid})	*971*	*975*		
Baseline (after imputation)				
Mean	87.86 ± 21.62	87.33 ± 21.79		
Median	89.16 [72.76 to 103.67]	90.31 [72.20 to 103.69]		
Minimum				
Mean	84.37 ± 24.71	86.39 ± 25.06		
Median	87.96 [66.73 to 103.81]	90.13 [68.90 to 106.43]		
Change from baseline to minimum				
Mean	−3.48 ± 17.88	−0.93 ± 17.20		
Median	−0.88 [−12.13 to 7.78]	1.84 [−9.21 to 9.03]		
LS Mean change from Baseline	−1.886 (−3.40 to −0.37)	0.677 (−0.85 to 2.21)	−2.56 (−4.06 to −1.06)	< 0.0001
PPS-pEP (N_{valid})	*922*	*935*		
Baseline (after imputation)				
Mean	88.16 ± 21.60	87.49 ± 21.71		
Median	89.97 [73.13 to 104.05]	90.85 [72.44 to 103.73]		
Minimum				
Mean	84.78 ± 24.44	86.53 ± 24.89		
Median	88.26 [68.05 to 103.86]	90.23 [69.00 to 106.43]		
Change from baseline to minimum				
Mean	−3.38 ± 17.66	−0.96 ± 17.10		
Median	−0.88 [−12.00 to 7.70]	1.79 [−9.18 to 9.03]		
LS Mean change from baseline	−1.713 (−3.27 to −0.15)	0.667 (−0.91 to 2.24)	−2.38 (−3.90 to −0.86)	< 0.0001

Data are presented in mean ± SD, median [IQR] and LS mean (95% CI). If cystatin C based eGFR could not be calculated due to missing serum cystatin C value, then it was imputed by: 1. Serum creatinine-based eGFR if serum creatinine is non-missing at baseline. 2. Median value of SAF-patients that are in the same stratum, defined by the combination of sex, age category (≤ median age and > median age) and ASA physical status (stage ≤II and stage ≥III) pooled over both treatment arms at baseline. Since renal replacement therapy (RRT) has an impact on cystatin C based eGFR, cystatin C-based eGFR within the interval from start to 48 h after the end of RRT are not valid for the assessment of renal functioning and are removed from the computation. Treatment effect between treatments estimate is computed as HES minus Crystalloid. CI, confidence interval; FAS-pEP, full analysis set for the primary endpoint; LS Mean, least-square mean, that is, mean values for treatment group and mean difference between treatment groups adjusted for (potentially) confounding variables (in this analysis centre and eGFR at baseline); N, number of patients in analysis set; N_{valid}, number of valid and non-missing values; POD, postoperative day; PPS-pEP, per-protocol set for the primary endpoint; Δ = non-inferiority margin.

Fig. 2 Serum creatinine and cystatin C based eGFR.



(a) Mean serum creatinine levels until postoperative day (POD) 90. Error bars indicate standard deviations. (b) Mean cystatin C-based eGFR until postoperative day (POD) 90. Error bars indicate standard deviations. Renal replacement therapy (RRT) has a relevant effect on measurements. Hence, affected measurements within the interval from the start to 48 h after the end of renal replacement therapy (i.e. date of RRT +1 day until the date of RRT +2 days) were excluded.

(Supplemental File, Table S9, http://links.lww.com/EJA/B213). More specifically, the number of patients in each group with cumulative major postoperative complications was 33% in the HES and 32% in the crystalloid-only group (Supplemental File, Table S10, http://links.lww.com/EJA/B213). Mortality until day 90 was 3% in both groups ($P > 0.05$).

One-year follow-up data were analysed in 1790 patients (891 HES and 899 crystalloid-only patients). New RRT between postoperative day 90 and 1 year was required in one patient per group (Table 4). All-cause mortality between day 90 and 1-year follow-up was 5.1% in HES-treated and 6.9% in crystalloid-treated patients ($P > 0.05$). Overall mortality at 1 year did not differ significantly, being 8.6% in the HES patients and 10.1% in crystalloid-only patients.

Secondary efficacy and safety endpoints

Between anaesthesia induction and the first postoperative morning, patients assigned to the HES group received a total of 4.8 ± 2.6 l of fluids, and patients assigned to the crystalloid-only group received 5.1 ± 2.7 l, respectively. Urine output was similar (2.6 ± 1.8 vs. 2.6 ± 1.7 l). Thus, net fluid balance, calculated on basis of patients with nonmissing values for volumes of intravenous medication, fluid and urine output, was significantly lower in HES-treated patients (0.6 ± 2.9 vs. 1.2 ± 2.7 l, $P = 0.0002$, Supplemental File, Table S11, http://links.lww.com/EJA/B213).

Table 4 Mortality and RRT after late post treatment phase and overall

	HES ($N = 977$)	Crystalloid-only ($N = 981$)	Percent RD (95% CI)	P
Mortality after late post-treatment phase[a]				
$N_{missing}$	86	82		
No/or died until POD104	846 (94.9)	837 (93.1)		
Yes	45 (5.1)	62 (6.9)	−1.85 (−4.04 to 0.35)	0.0995
Overall mortality after IP start until end of 1-year follow-up				
$N_{missing}$	86	82		
No	814 (91.4)	808 (89.9)		
Yes	77 (8.6)	91 (10.1)	−1.48 (−4.18 to 1.22)	0.2829
New RRT after late post-treatment phase[a]				
$N_{missing}$	102	109		
No/or died until POD104	874 (99.9)	871 (99.9)		
Yes	1 (0.1)	1 (0.1)	0.00 (−0.32 to 0.32)	0.9981
Any RRT after IP start until end of 1-year follow-up				
$N_{missing}$	100	107		
No	868 (99.0)	863 (98.7)		
Yes	9 (1.0)	11 (1.3)	−0.23 (−1.23 to 0.76)	0.6473

Data are presented as *n*, *n* (%) and percentage risk difference (95% CI). Mortality after late post-treatment phase includes all patients that died between POD104 (the upper limit of the visit window for POD90 analyses) and POD395 (the upper limit of the visit window for the 1-year follow-up). *N*missing indicate patients who had (a) no 1-year follow-up or (b) were known to be alive when the follow-up was performed but were excluded because the follow-up was done earlier than POD335 (the lower visit window for the 1-year follow-up). Risk-difference between treatments estimate is computed as HES minus Crystalloid. CI, confidence interval; IP, investigational product (study fluid); *N*, number of patients in the statistical analysis set; *N*missing, number of missing observations; POD, postoperative day; RRT, renal replacement therapy. [a]Late post-treatment phase is defined from day after POD90 +14 days until end of 1-year follow-up. Analysis set: Safety set/Full analysis set-efficacy.

The decrease in MAP from baseline was lower in patients receiving HES than crystalloid-alone (−14 ± 18 vs. −16 ± 19 mmHg; $P = 0.0003$) (Supplemental File, Table S12, http://links.lww.com/EJA/B213). In a post hoc analysis, the proportion of patients who required vasoactive/inotropic drugs was significantly lower in the HES group compared to the crystalloid-only group (26 vs. 35%, $P < 0.0001$). Mean intra-operative blood loss was similar between groups and was approximately 0.81 (Supplemental File, Table S13, http://links.lww.com/EJA/B213).

There were 3088 adverse events which emerged after the start of treatment (TEAEs) in 689 patients (71%) in the HES group and 3018 TEAEs in 703 patients (72%) of the crystalloid-only group. Severe TEAEs were observed in 208 (21%) HES and 193 (20%) crystalloid-only patients. Overall, 55 adverse drug reactions (ADRs) were reported in 51 patients (5%) in HES-treated patients vs. 49 in 46 patients (5%) assigned to crystalloid-only (Supplemental File, Table S14, http://links.lww.com/EJA/B213). The most common ADR was AKI, which was reported in 4% of patients in each group. Serious ADRs occurred sporadically in both groups (four patients in the HES-only and two patients in the crystalloid-only group). Serious adverse events, irrespective of causality, were reported in 30% of the patients in each group.

Discussion

Early postoperative renal function and a composite of mortality and serious complications after major surgery were noninferior in patients randomised to HES vs. crystalloid solution. Further, renal outcomes at 90 days, mortality and the need for RRT were similar 1 year after surgery. The results of PHOENICS are consistent with a 1057-patient trial, which similarly showed that peri-operative colloid use does not worsen acute or long-term renal function, and is not associated with additional complications compared to crystalloid solutions.[5] The basis for PHOENICS was the authorities' concern about potential renal site effects of HES, primarily based on studies in septic patients in which high doses of HES were given over several days.[3,4] The VISEP trial ($N = 537$) used a hyper-oncotic HES solution (10% HES 200/0.5 in 0.9% saline) in doses of up to 250 ml kg^{-1}. This dose equals 417 ml kg^{-1} of a modern 6% HES solution and exceeds current maximum dose limits almost 14-fold. Remarkably, more than one-third of the patients assigned to HES were given amounts exceeding the licensed maximum at the time of the study by more than 10%.[3]

In a mixed critically ill population including septic and nonseptic patients, the CHEST trial ($N = 7000$) compared a saline-based HES 130 solution (an average of about 2 l) with saline 0.9%.[13] The primary outcome was death at day 90, for which no statistical difference was shown [relative risk (RR) 1.06, 95% CI 0.96 to 1.18, $P = 0.26$]. Fewer patients randomised to HES had RIFLE-R (RR 0.94, 95% CI 0.90 to 0.98, $P = 0.007$ or RIFLE-I (RR 0.91, 95% CI 0.85 to 0.97) grade renal injury, and the use of RRT was marginally and nonsignificantly increased in the HES group (7.0 vs. 5.8%, RR 1.21, 95% CI 1.00 to 1.45). After a year, there were no significant differences in mortality, quality of life or healthcare costs.[14]

Aside from one trial that used excessive doses of HES in septic patients, there is little evidence of harm from HES, even in critical care patients. Our trial, combined with previous work,[5,15] provides robust evidence that HES is well tolerated when used as intended in surgical patients.[2]

HES differs from crystalloids in remaining longer in the intravascular space, thus providing improved haemodynamic support. Even in patients with normal capillary

barrier integrity, only about 20% Ringer's lactate remains in the intravascular space. Thus, patients given HES combined with crystalloid require less total fluid than those assigned to crystalloid alone and require fewer intra-operative boluses (4 vs. 6) to maintain stroke volume.[16] Our results showed that patients assigned to HES required slightly less fluid, were closer to a neutral fluid balance at the end of surgery and needed less vasopressor support.

A consequence of colloids staying longer in the intravascular space is that different amounts of colloid and crystalloid are needed to maintain physiologically comparable intravascular volumes. We are aware of this potential limitation but defining a specific protocol ratio based on population averages is unsatisfactory because individual needs differ based on capillary permeability, oncotic pressure, and other factors. There were two practical approaches we could have used to guide fluid management: a goal-directed approach or one that relied on practical clinical judgement. Goal-directed fluid management relies on titrating vascular volume with either fluid to the same point on the Starling curve. One previous large study that compared peri-operative colloids and crystalloids used this approach in 1057 patients showed that patients randomised to crystalloids received about 15% more fluid than those assigned to HES.[5] Another trial in 775 patients used a goal-directed approach based on stroke volume index and showed no outcome differences.[17] However, in this study, patients at risk of kidney injury were included and thus the results are not comparable to the present study. In addition, both previous studies are not adequately powered to answer the relevant safety question.

We selected the second option, a pragmatic approach which allowed clinicians to give an amount of the designated fluid as clinically deemed necessary, which is less precise from a haemodynamic perspective but more practical and reflects how colloids are used in clinical practice. Interestingly, our results were comparable with earlier studies.[5,17] In our study population, patients in the crystalloid group received about 17 to 20% more fluid than those assigned to colloid. On a population basis, fluid management thus appears to have been appropriate.

We used cystatin C to estimate GFR as our primary endpoint because it better reflects renal function than creatinine-based assessments which can be influenced by various nonrenal factors.[7] Furthermore, the outcome is continuous rather than ordinal, and thus more sensitive to small degrees of impairment than categorical scales. The declines from baseline of cystatin C based eGFR in our patients were clinically irrelevant considering the non-inferiority margin. However, detecting small amounts of AKI is important because early impairment persists or worsens in about a third of postoperative patients.[18]

HES solutions potentially impair coagulation, with modern HES 130/0.4 showing the least influence.[19–21] Impairment is dose-dependent, though, and is negligible with intended peri-operative dosing. Consequently, no statistically significant or clinically meaningful effect on coagulation was observed in our patients (Supplemental File, Table S15, http://links.lww.com/EJA/B213).

The PHOENICS trial responded to previously published concerns about renal toxicity of HES. The protocol allowed all patients in line with the label and permitted the full dose of HES with unrestricted crystalloid use when needed. Our patients received doses of HES 130/0.4 up to 30 ml kg^{-1} for up to 24 h, with most of the volume given in the intra-operative period. All our patients had elective major surgery and PHOENICS comprised patients with a median age of 66 years, ASA score III in approximately 42%, actual mean estimated blood loss of approximately 0.8 l and identical postoperative complication rates of 35% in both groups, representing a consistently relevant study population, and thus, inclusion bias is considered unlikely. We excluded patients with contraindications to HES, especially renal dysfunction or RRT because of a higher risk of renal toxicity. Results might differ in such patients. Prolonged use, especially with doses outside the recommended range, might be harmful, as appears to be the case with long-term use in sepsis patients.[3,4]

We are aware of several limitations of PHOENICS. Due to differences in physiological efficacy in volume replacement between HES and crystalloids, the most formal approach would have been goal-directed guided fluid management to assure physiologically comparable vascular volumes. It remains possible that fluid management was sub-optimal in some individuals. Arguably, the lack of goal-directed fluid administration makes our results more generalisable, as goal-directed management remains uncommon. However, given comparable blood pressures, serious bias seems unlikely between the groups. Hence, there was no indication that the control group was inadequately treated, as both groups received treatment according to haemodynamic parameters in a blinded fashion and the incidence of cardiac adverse events was similar. Further, the composite key secondary endpoint comprises a variety of terms for serious complications as per ESA-ESCIM definition. Therefore, we included moderate to severe complications only to focus on clinically relevant events. The overall rate of such events appears high, but is comparable between the groups and consistent with published studies in this area. Another limitation is, that beside mortality, no other patient-centered outcomes such as WHODAS 2.0 were assessed, but at the time of study design, the focus was primarily on renal safety.

In conclusion, peri-operative use of HES was noninferior to crystalloid in short-term renal function or composite of mortality and major complications at 90 days.

Outcomes at 1 year were also similar. Our large trial therefore provides robust evidence that peri-operative in-label use of HES is well tolerated.

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WB: travel expenses and honoraria for medical writing from Fresenius Kabi and institutional payments as coordinating investigator, grants (EU Horizon, Zon MW, and Netherlands Cancer Foundation), honoraria for lectures/presentations and meetings from BD Diagnostics; MG: honoraria for lectures (CSL Behring, Edwards Lifesciences); GK: research grants from CSL Behring, consulting fees Takeda Development Center Americas Inc., honoraria for lectures EurAsia Heart Foundation, VFPM; SJ: payments from Fisher-Paykel, Mindray, Drafer, Medtronic, Baxter, meeting support from Fisher-Paykel, Mindray; DdeK: consulting fees from ESAIC for the study; MGdeA: consulting fees from Ambu Inc.; DZ: lecture fees from I-SEP; SS and SR are employees of B. Braun Melsungen AG; CG, MH (former), CJ, UN, and MW (former) were employees of Fresenius Kabi Deutschland GmbH. All other authors declare no conflicts of interest.

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