REVIEW ARTICLE

Fluid Replacement With Hydroxyethyl Starch in Critical Care—a Reassessment

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SUMMARY

Background: Hydroxyethyl starch (HES) is used for fluid replacement in millions of patients around the world every year, yet it has been found to have adverse effects that have a negative impact on patient survival. Recent clinical trials with a modern HES solution (HES 130) and meta-analyses now enable a reassessment of its risks and benefits.

Methods: On the basis of a selective literature search focusing on reports of the use of HES 130/0.4 and HES 130/0.42 in sepsis, trauma, and intensive care medicine, data from randomized controlled trials (RCTs) are presented, and up-to-date meta-analyses and reviews are discussed. Moreover, the authors conducted an independent meta-analysis of HES 130 in comparison to crystalloids or albumin in intensive care medicine, sepsis, and trauma.

Results: Seven RCTs were evaluated, involving a total of 7838 patients treated for sepsis or trauma, or in intensive care. HES 130 was associated with a higher cumulative risk of death (relative risk [RR] 1.10, 95% confidence interval [CI] 1.01–1.20), more frequent need for a renal replacement procedure (RR 1.26, 95% CI 1.08–1.46), and more frequent need for blood transfusion (RR 1.22, 95% CI 1.08–1.37). There was no patient-relevant benefit. Four recent meta-analyses of data from a total of more than 10 000 patients confirmed these concerns about the safety of HES in general and, in particular, of low-molecular-weight HES 130 for patients in intensive care. The safety of 6% HES 130 in the immediate perioperative period has not been adequately demonstrated.

Discussion: Because of safety concerns, fluid replacement with HES in critically ill patients cannot be recommended. Evidence for its superior efficacy, safety and cost effectiveness in preoperative use is also lacking.

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Fluid replacement therapy is used millions of times a day around the world (1); it is one of the most frequently employed therapeutic interventions in surgical patients and in emergency and intensive care units. For this reason, even small differences between the risks, benefits, and costs of the various volume replacement fluids can have major effects overall (2). Colloid solutions in the form of hydroxyethyl starch (HES), human albumin, or gelatin are preferred in many countries. The modern HES solutions (6% HES 130/0.4 and 130/0.42) are the colloid fluids most often used in intensive care in Germany and all over the world (2).

Although crystalloid solutions cost less, colloids are often preferred in order to achieve hemodynamic stabilization faster and in a more volume-efficient way (3, 4). However, for a long time there were no reliable clinical data on the safety and clinical benefits of volume replacement fluids, because all the colloid and crystalloid fluids in common use today, including HES, were already on the market before the laws regulating the approval of medical drugs were enacted during the 1970s (5).

Meta-analyses by the Cochrane Collaboration and other groups (4, 6–8) indicated without exception that patient survival was not improved by the use of colloids. For HES—as for other synthetic colloids—a number of undesired effects are known, such as an increased tendency to bleed, renal damage, tissue uptake in the reticuloendothelial system with organ damage to liver, lungs, spleen, and bone marrow, and refractory pruritus (9). In the past, the occurrence of a higher incidence of renal failure (10–12) or bleeding complications in patients treated with HES fluids was believed to be associated with the use of older HES solutions of a higher or intermediate molecular weight (450 or 200 kD), a higher degree of molar substitution (proportion of hydroxylated glucose units in relation to the total number of glucose units in the solution) of 0.5 to 0.7, or with exceeding the recommended daily dose limit. Modern HES solutions of the so-called third generation with a mean molecular weight of only 130 kD and a molar substitution degree of 0.4 were regarded as safer (13).

Up until 2011 the debate was marked by controversy because of the absence of sufficient clinical data on HES (14, 15). Now, however, several high-quality studies on the modern 6% HES 130 solutions used in intensive care (16) and in patients with sepsis (17) have

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provided data that have been included in recent meta-analyses (18–20). These data have triggered an international debate on the safety of HES (3), which has been taken up by the public media. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have reassessed the risk–benefit profile of HES (21, 22). Based on an analysis of the existing evidence of benefit and risk of infusion solutions containing HES, the EMA expert committee responsible for drug safety (Pharmacovigilance Risk Assessment Committee [PRAC]) reached the conclusion that the benefits no longer outweigh the risks. PRAC has therefore recommended that the EMA should revoke the relevant approvals for marketing (22).

This review aims to discuss the most important clinical studies and meta-analyses underlying this recommendation.

Method

The selective literature search on which this review is based focused on studies of HES 130 and on systematic reviews and meta-analyses of HES in sepsis, trauma, and intensive care that were carried out or updated after the publication of the large studies by Myburgh et al. (16) and Perner et al. (17). This research was carried out in our own literature database, which is based on several systematic literature searches for systematic analyses and international consensus recommendations (23), supplemented with searching PubMed for 2012 and 2013 using the search term “hydroxyethyl starch,” and with the reference lists of the meta-analyses published in 2013. The final publication date for articles to be included in this study was 1 March 2013.

To summarize the published evidence for the HES user in a way that relates it to appropriate comparison fluids and clinically relevant end points, we performed our own meta-analysis. Our analysis therefore included all randomized controlled trials (RCTs) that

- were carried out in patients with sepsis, trauma patients, and those in intensive care,
- compared HES 130/0.4 or HES 130/0.42 with crystalloid fluids or human albumin
- implemented the above-mentioned fluid replacement for more than 24 hours, and
- reported patient-relevant outcomes.

For our meta-analysis we used the statistical program R (24) with the meta add-on package (25). The studies were summarized using the Mantel–Haenszel method in a fixed or random effects model, as appropriate. A test for heterogeneity was carried out first and the I^2 heterogeneity measure was calculated.

Results

Seven RCTs with a total of 7838 trauma patients, patients with sepsis, and patients in intensive care units (16, 17, 26–30) (Table 1), and 8 meta-analyses (Table 2) were included in our investigation. The two largest studies (CHEST and 6S) are described in more detail below.

CHEST study

This double-blind study (16) of 7000 intensive care patients compared 6% HES 130/0.4 with 0.9% NaCl. There was no statistically significant difference in 90-day mortality (18% versus 17%). In the HES arm, renal replacement therapy was needed significantly more often (7% versus 5.8%, $p = 0.04$), and the use of blood products was significantly higher (78 ± 250 mL versus 60 ± 190 mL, $p < 0.001$). Overall, the rate of adverse effects was significantly higher in the HES group (5.3% versus 2.8%; $p < 0.001$); pruritus was seen about twice as often in the HES group (4% versus 2.2%).

The CHEST study (16) showed HES effects that could be interpreted positively. These include more rapid hemodynamic stabilization—using a score that reflected the dosage of vasopressors—and the achievement of significantly higher central venous pressure than in the NaCl group. Normalization of the serum lactate value, however, which is taken as an indirect marker of the severity of circulatory failure, was achieved within the same time in both groups. Heart rate and blood pressure also showed the same behavior in both groups. The above-mentioned positive hemodynamic effects were not reflected in patient-relevant or cost-relevant factors such as duration of mechanical ventilation or hemodialysis, or length of stay in the intensive care unit or in hospital (16). New-onset cardiovascular organ failure was recorded less often in the HES group, but on the other hand the incidence of liver failure was higher. Whether these effects were of outcome-related relevance to patients is doubtful.

At first sight, the effect of HES on so-called RIFLE criteria also seemed paradoxical (31) (“RIFLE” stands for “risk—injury—[organ] failure—loss [of renal function]—end-stage renal disease”). Paradoxically, in the CHEST study more patients in the NaCl group fulfilled criteria of the early risk and injury category. This can be explained by the fact that the RIFLE score is calculated on the basis of changes in creatinine values and urine output (31). In the CHEST study, the creatinine values in the HES group over the first 6 days were significantly higher and urine output significantly lower than in the comparison group (16).

6S study

The 6S study (17), which enrolled around 800 patients with sepsis, studied 6% HES 130/0.42 in comparison to Ringer’s acetate. In the HES group, significantly more patients had died at the end of 90 days (51% versus 43%; $p = 0.03$) and renal replacement therapy was required more frequently (22% versus 16%, $p = 0.04$). More patients in the HES group received blood products (RR: 1.20; 95% CI: 1.07 to 1.36; $p = 0.002$). The cumulative dose was 44 mL/kg body weight over the whole study period, and was thus below the maximum daily dose of 50 mL/kg recommended by the manufacturer.

Present meta-analysis

Our own meta-analysis (7 RCTs, 7838 sepsis, trauma, or intensive care patients) showed significantly

TABLE 1

Features of clinical studies of hydroxyethyl starch (HES) 130

Authors	Year	n	Setting	Multi-center	Double-blind	Patient population	HES	Control	Mortality reported	Renal replacement therapy reported	Transfusion requirement reported	Pruritus reported
Myburgh et al. (16)	2012	7000	ICU	Yes	Yes	Intensive care	HES 130/0.4	0.9% NaCl	90 days	Yes	Yes	Yes
Perner et al. (17)	2012	804	ICU	Yes	Yes	Severe sepsis	HES 130/0.42	Ringer's acetate	90 days	Yes	Yes	No
James et al. (26)	2011	115	ICU	No	Yes	Trauma	HES 130/0.4	0.9% NaCl	90 days	Yes	No	Yes
Guidet et al. (27)	2012	196	ICU	Yes	Yes	Severe sepsis	HES 130/0.4	0.9% NaCl	90 days	Yes	Yes	Yes
Dolecek et al. (28)	2009	56	ICU	No	No	Severe sepsis	HES 130/0.4	20% albumin	28 days	No	No	No
Dubin et al. (29)	2010	25	ICU	Yes	No	Septic shock	HES 130/0.4	0.9% NaCl	ICU*	No	Yes	No
Palumbo et al. (30)	2006	20	ICU	No	No	Severe sepsis	HES 130/0.4	20% albumin	ICU*	No	No	No

Inclusion criteria for study selection: randomized controlled trials of patients in intensive care, trauma patients, or patients with sepsis in whom fluid replacement was carried out for at least 24 hours using either HES 130 or crystalloids or albumin.

*ICU mortality relates to length of stay in the ICU (intensive care unit) and is therefore variable. HES, hydroxyethyl starch

increased risks of death of the patient (RR: 1.10; 95% CI: 1.01 to 1.19; $n = 7838$), need for renal replacement therapy (RR: 1.26; 95% CI: 1.08 to 1.46; $n = 7830$), and transfusion requirements (RR: 1.22; 95% CI: 1.08 to 1.37; $n = 972$; fixed effects model) in the HES 130 groups (Table 3).

Other recent meta-analyses

The meta-analyses are presented in Table 2. Some of these meta-analyses will be discussed in more detail.

Meta-analyses in mixed populations—Zarychanski et al. (18) included 38 RCTs in which critically ill adult patients in emergency or intensive care who needed fluid replacement had been given either HES fluids of varying molecular weight and substitution degree or other volume replacement fluids (crystalloid, gelatin, or human albumin). Most of the studies were heterogeneous and had a large or hard-to-define risk of their results being influenced by this lack of balance (study bias).

As to mortality risk, data for 10 880 patients were evaluable and showed a slightly increased risk of mortality in the HES group. After the exclusion of seven studies with a total of 590 patients published by a German author whose later studies had to be withdrawn on grounds of scientific misconduct, the association between receiving HES and mortality in the remaining 10 290 patients showed clear statistical significance (RR: 1.09; 95% CI: 1.02 to 1.17). There was also a significant correlation between need for renal replacement therapy and the use of HES in 9258 patients (RR: 1.32; 95% CI: 1.15 to 1.50; [Table 2]). The authors conclude that, because of serious safety concerns, HES should not be used (18).

Gattas et al. (32) evaluated 35 studies in which HES 130 was used (Table 2). A notable element was that 22 of the 35 studies were in the operative or perioperative setting. The three largest of these studies were homogeneous, carried little risk of study bias, and included 77% of all the patients. In the HES group, the cumulative risk for both death of the patient and need for renal replacement therapy was significantly higher, even though in 14 of the 25 studies included in the cumulative analysis, other synthetic colloids served as comparison fluids, such as higher-molecular-weight HES solutions ($n = 11$) or gelatin ($n = 5$), which have potential renal toxicity (32). For gelatin, a greater extent of renal damage has been shown both clinically and experimentally than with crystalloids, comparable to that of HES 130 (33, 34).

Meta-analyses of HES 130 in sepsis—Haase et al. (19) compared the influence of HES 130/0.4 or 130/0.42 with that of crystalloids. Including all studies that gave information about mortality ($n = 8$; 3414 patients), no statistically significant association between HES and mortality risk was shown (Table 2). Studies with a low risk of bias ($n = 3$) showed an increased mortality risk of 1.11 (95% CI: 1.00 to 1.23). The need for renal replacement therapy and the frequency of transfusion were significantly higher in the HES group (19).

Patel et al. (20) evaluated six RCTs with a total of 3033 patients with sepsis. They compared 6% HES 130/0.4 or 130/0.42 fluids with non-HES fluids (Table 2). Although case numbers were low, the authors were unable to find any differences between potato-derived and maize-derived starch.

TABLE 2

Recent meta-analyses and systematic reviews

Authors	Population	Setting	HES solutions	Comparison	Number of studies	Number of patients	Mortality* ¹	Renal replacement therapy* ¹	Transfusion* ¹
Perel 2013* ² (4)	Critically ill with hypovolemia, including patients with trauma, burns, surgical interventions, and sepsis	ICU, operative, emergency	All HES fluids	Isotonic or hypertonic crystalloids	25	9147	RR: 1.10 (1.02–1.19) N = 9147	n.d.	n.d.
Haase 2013 (19)	Sepsis	ICU	HES 130	Crystalloids or albumin	9	3456	RR: 1.04 (0.89–1.22) N = 3414	RR: 1.36 (1.08–1.72) N = 1311	RR: 1.29 (1.13–1.48) N = 973
Patel 2013* ^{2, 3} (20)	Sepsis	ICU	HES 130/0.4 (maize starch) and HES 130/0.42 (potato starch)	Non-HES fluids	6	3033	RR: 1.13 (1.02–1.25) N = 2913		
Zarychanski 2013* ² (18)	Critically ill	ICU, emergency	All HES fluids	Crystalloids, albumin or gelatin	31	10 290	RR: 1.09 (1.02–1.17) N = 10 290	RR: 1.32 (1.15–1.50) N = 9258	RR: 1.42 (1.15–1.74) N = 1482
Gattas 2013 (32)	Acutely ill with hypovolemia	ICU, peri-operative, operative	HES 130	Crystalloids, albumin, gelatin, dextran or HES fluids	35	10 391	RR: 1.08 (1.00–1.17) N = 9411	RR: 1.25 (1.08–1.44) N = 8496	n.d.
Wiedermann 2013 (e8)	Acutely ill with hypovolemia	ICU, peri-operative, operative	HES 130	Crystalloids, albumin, gelatin, dextran or HES fluids	15	8580	RR: 1.10 (1.02–1.19) N = 8580	n.d.	n.d.
Martin 2013 (36)	Surgical patients	Peri-operative	HES 130/0.4 (maize starch)	Crystalloids, albumin, gelatin, dextran or HES fluids other than HES 130	17	1230	n.d.	Risk reduction* ⁴ -0.003 (-0.028–0.022) N = 531	n.d.
van der Linden 2013 (35)	Surgical patients, trauma patients, and healthy volunteers	Peri-operative	HES 130	Crystalloids, albumin, gelatin, dextran, HES and MP4OX* ⁵	59	4529	OR: 0.51 (0.24–1.05) N = 1918	OR: 0.60 (0.23–1.53) N = 790	OR: 0.73 (0.61–0.87) N = 2151

Inclusion criteria for study selection: all meta-analyses and systematic reviews of hydroxyethyl starch (HES) 130 carried out or updated after publication of the large studies by Myburgh et al. (16) and Perner et al. (17)

*¹ Represented as cumulative effects

*² The results of these two meta-analyses include studies by an author whose work was later withdrawn in part, on grounds of scientific fraud, and regarded overall as dubious. In the meta-analysis by Perel et al., no difference is shown when these studies are excluded. If the 7 studies with 590 patients by this author are included in the meta-analysis by Perel et al., a barely significant relative risk of dying is shown (RR: 1.07; 95% CI: 1.00 to 1.14; n = 38 studies; 10 880 patients).

*³ Primary end point was 90-day mortality

*⁴ Risk reduction = normally the difference between the risks of an event in two groups. A risk reduction of -0.003 (-0.028 to 0.022) means an absolute difference in the frequency of the event of 0.3% in favor of HES. The 95% confidence interval for the studies masks the effect of a reduction of 2.8% and an increase of 2.2%. The authors give no information as to whether an absolute risk difference was in fact calculated.

*⁵ MP4OX is a hemoglobin-based blood substitute currently approved for use only in South Africa and Russia.

ICU, intensive care unit; RR, relative risk; OR, odds ratio; 95% confidence interval in parentheses; N, total number of patients included; n.d., no data

TABLE 3

Meta-analysis
Studies of HES 130/0.4 or HES 130/0.42 in comparison to crystalloid fluids or human albumin in intensive care patients and patients with sepsis or trauma

Study	HES 130		Control		Relative risk	RR	95% CI	
	Event	Total	Event	Total				
Mortality								
Palumbo 2006 (30)	4	10	3	10		1.33	(0.40–4.49)	
Dubin 2010 (29)	1	9	5	11		0.24	(0.03–1.73)	
Dolecek 2009 (28)	6	20	4	26		1.95	(0.63–5.99)	
James 2011 (e1)	12	56	6	53		1.89	(0.77–4.68)	
Guidet 2012 (27)	40	99	32	95		1.20	(0.83–1.74)	
Perner 2012 (17)	201	398	172	400		1.17	(1.01–1.36)	
Myburgh 2012 (16)	597	3315	566	3336		1.06	(0.96–1.18)	
Fixed effects model	861	3907	788	3931	1.10	(1.01–1.19)		
<i>Heterogeneity: I² = 2.5%; Q = 6.2, df = 6, p = 0.4059</i>								
Renal replacement therapy								
Perner 2012 (17)	87	398	65	400		1.35	(1.01–1.80)	
Myburgh 2012 (16)	235	3352	196	3375		1.21	(1.00–1.45)	
James 2011 (26)	2	56	3	53		0.63	(0.11–3.63)	
Guidet 2012 (27)	21	100	11	96		1.83	(0.93–3.59)	
Fixed effects model	345	3906	275	3924		1.26	(1.08–1.46)	
<i>Heterogeneity: I² = 0%; Q = 2.2, df = 3, p = 0.533</i>								
Transfusion								
Dubin 2010 (29)	2	9	2	11		1.22	(0.21–7.04)	
Guidet 2012 (27)	29	100	20	96		1.39	(0.85–2.29)	
Perner 2012 (17)	243	376	204	380		1.20	(1.07–1.36)	
Fixed effects model	274	485	226	487		1.22	(1.08–1.37)	
<i>Heterogeneity: I² = 0%; Q = 0.3, df = 2, p = 0.8513</i>								
Pruritus								
Guidet 2012 (27)	3	99	3	95		0.96	(0.20–4.64)	
James 2011 (26)	2	56	5	53		0.38	(0.08–1.87)	
Myburgh 2012 (16)	137	3416	73	3358		1.84	(1.39–2.44)	
Fixed effects model	142	3571	81	3506		1.72	(1.31–2.25)	
Random effects model						1.13	(0.45–2.88)	
<i>Heterogeneity: I² = 52.6%; Q = 4.2, df = 2, p = 0.1211</i>								

Synthesizing the results of studies comparing HES 130 to non-synthetic colloids shows that patient-relevant end points such as mortality, need for renal replacement therapy, or requirement for transfusion of allogenic blood products are significantly higher. For pruritus, because of the heterogeneity of the studies included (I^2 52.6%), a random effects model was also used, and with this the result was no longer significant. The studies are described in detail in Table 1. With the exception of the small studies by Dolecek and Palumbo et al., the only comparison fluids used were crystalloids. The proportion of studies where albumin was used was very low (0.8%, or 66 of a total of 7838 patients).
RR, relative risk; 95% CI, 95% confidence interval; HES, hydroxyethyl starch

Recent systematic reviews in surgical patients—There are no large multicenter studies of surgical patients with long-term follow-up. For this reason, after the two large studies by Perner et al. and Myburgh et al. in the intensive care setting were published (16, 17), two new reviews were carried out concentrating on patients undergoing surgery (35, 36). An earlier sys-

tematic literature review on HES 130 from 2011, which included studies of surgical patients, came to the conclusion that most studies in this area of medicine are limited by short follow-up periods of up to 24 hours and by the use of other HES fluids for comparison (15). It is known that the differences in mortality between HES and crystalloid groups only become visible after at

least 20 days (12, 16), and the statistical significance is highest after 90 days (17).

The analysis by van der Linden et al. (35) (*Table 2*) has serious deficiencies (37). Two thirds of the studies used inappropriate control fluids, including experimental hemoglobin solutions that were never approved for market because of serious adverse effects including excess mortality (38). The data of 19 patients who died were left out of the cumulative mortality calculation, even though one of the co-authors of the meta-analysis was the first author of the trauma study concerned (26). These limitations could explain why the odds ratios for mortality, renal replacement therapy, and transfusion trended in favor of HES 130 (35).

In one recently published study, the first to record 90-day mortality in the perioperative setting and which was not included in the above-mentioned meta-analysis, 5 of 24 patients in the HES 130 group died, in comparison to 0 of 24 patients in the crystalloid group (39).

The conclusion of van der Linden et al., that using HES 130 in the immediately postoperative period was not associated with adverse effects of HES, and that carrying out large randomized studies to investigate the safety of this substance were therefore not required (35), is in contradiction to other meta-analyses of studies in the surgical and intensive care settings (18, 32).

Another meta-analysis, by Martin et al. (36), evaluated 17 studies in which surgical patients received maize-derived 6% HES 130/0.4 or crystalloid or non-HES colloid fluids. The authors found no significant differences in maximum creatinine values, need for renal replacement therapy, or the length of stay in the hospital or intensive care unit. They therefore concluded that in surgical patients there is no evidence of adverse effects after maize-derived 6% HES 130/0.4. However, half of the studies used inappropriate control fluids (9). In addition, even in the perioperative setting there are indications of an increased need for renal replacement therapy (40), increased bleeding complications (26), and trends towards increased 90-day mortality after HES 130 (39, e1). The assumption that there are clinically relevant differences in risk profile between maize-derived and potato-derived HES fluids cannot be drawn on the basis of existing data (20). In patients with sepsis of comparable severity, the relative risks for 90-day mortality were of the same order of magnitude (20), at 1.20 (95% confidence interval [CI]: 0.83 to 1.74) after maize starch (27) and 1.17 (95% CI: 1.1 to 1.36) after potato starch (17).

Summary

The recent studies and meta-analyses confirm the recommendations of national and international sepsis guidelines (e2, e3) and of the European Society of Intensive Care Medicine (ESICM) Task Force (23), and also the statements by the UK National Institute for Health and Clinical Excellence (e4) and the Cochrane group on the use of colloids (4).

Neither clinical studies nor the meta-analyses that include the available studies from all settings in which colloid fluids are used for fluid replacement provide evidence of either patient-relevant advantages or savings in the use of resources (length of hospital stay or other cost-relevant treatment factors). The widespread assumption that modern low-molecular-weight HES fluids are associated with a lower risk of kidney damage than are older HES fluids (13) is contradicted by the recent RCTs by Perner et al. (17) and Myburgh et al. (16), and by several meta-analyses (19, 20, 32).

It must likewise be doubted whether the use of HES in surgical patients is safe. No study in this setting has shown a patient-relevant advantage for HES, whereas once again studies do exist that show clear indications of HES-specific adverse effects such as, for example, negative effects of HES on coagulation (e5), renal function (32) or tissue uptake (e6), 90-day mortality (39), or pruritus in patients with sudden hearing loss (e7). Gattas et al. (32) doubt whether there could be a benefit not observed in their analysis—at least not in their study population—that would outweigh the observed risks. They therefore advise against the use of HES.

Patient-relevant adverse effects that have long been known for older-generation HES fluids have now also been shown for the modern balanced and unbalanced maize- and potato-derived HES 130 fluids. From a patient perspective, it may be doubted whether the intermittently reduced vasopressor requirement compensates for the increased use of renal replacement therapy and blood products seen with HES therapy in the CHEST study.

As to the use of HES 130 in surgical or trauma patients, there is neither sufficient safety evidence nor indications of any clinically relevant benefit. No reliable studies are available for the surgical setting, and recent meta-analyses have methodological deficiencies.

Furthermore, the fact that evidence of damage has not been proven does not allow the assumption that evidence of damage does not in fact exist. Because many of the studies used inappropriate control fluids, the recommendations of the ESICM Task Force (23) point out that studies investigating the safety and efficacy of synthetic colloids should use crystalloid fluids or human albumin as control fluids, since these substances themselves show no specific effects on the kidneys. Given the proven adverse effects of HES fluids used for other (i.e., non-surgical) indications, the relevant authorities, ethics committees, and expert commissions free of financial conflicts of interest have a duty to decide to what extent methodologically adequate studies in surgical patients can still be ethically justified, given that for these patients, too, crystalloids offer an available alternative to colloids.

Conflict of interest statement

Professor Reinhart has in the past (up to 2006) received financial support for carrying out the VISEP study and (up to 2008) speaker fees from B. Braun Melsungen AG.

Professor Welte has received financial support (third-party payment) from B. Braun Melsungen AG for carrying out the VISEP study.

Dr. Hartog and Professor Schlattmann declare that no conflict of interest exists.

KEY MESSAGES

- Reliable clinical studies and meta-analyses have provided no indications of any patient-relevant benefit from the use of HES fluids compared to alternative volume replacement fluids.
- The use of HES 130 in patients in intensive care and patients with sepsis is associated with increased mortality, an increased need for renal replacement therapy, and an increased transfusion requirement.
- Because of the lack of reliable studies in the surgical and immediately postoperative setting, the safety, benefit, and cost effectiveness of using HES 130 in surgical patients has not been adequately demonstrated.
- Since doubts also exist about the safety of other synthetic colloids such as gelatin, in accordance with international consensus recommendations crystalloids should be the first choice for fluid replacement in critically ill patients.
- In patients with severe sepsis and those with liver failure, in accordance with international consensus recommendations the use of human albumin may be considered.

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REVIEW ARTICLE

Fluid Replacement With Hydroxyethyl Starch in Critical Care—a Reassessment

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