Accepted June 2014

REVIEW

Postoperative renal replacement therapy after hydroxyethyl starch infusion: a meta-analysis of randomised trials

M.M. Wilkes, R.J. Navickis

Hygeia Associates, Grass Valley, California, USA

Correspondence

M.M. Wilkes – e-mail: mwilkes@hygeiaassociates.com

Keywords – **Hydroxyethyl starch, surgery, acute kidney injury, renal replacement therapy, randomized trials, meta-analysis**

Abstract

Background: Hydroxyethyl starch (HES) solutions are used for perioperative fluid management. However, robust renal safety data in surgical patients are lacking.

Methods: A meta-analysis was performed of randomised clinical trials comparing HES with non-HES control fluid in adult surgical patients. The endpoint was recourse to renal replacement therapy (RRT). Eligible trials were identified by multiple methods including computer database searches.

Results: Fifteen randomised trials with a total of 4409 surgical patients were included. The Crystalloid versus Hydroxyethyl Starch Trial (CHEST) was the source for 65.1% of the included surgical patients. Eighty-three of the 2157 patients assigned to HES (3.8%) underwent RRT versus 56 of 2252 control patients (2.5%). HES significantly increased recourse to RRT, with a pooled relative risk (RR) of 1.44 and 95% confidence interval (95% CI) of 1.04-2.01. The absolute risk increase in recourse to RRT attributable to HES was 1.2% (95% CI: 0.1-2.2%), indicating a number needed to treat with HES of 85 to prompt RRT in one additional patient. In a subset of trials comparing HES 130/0.4 with crystalloid, the pooled RR for recourse to RRT (1.47; 95% CI: 1.02-2.12) coincided closely with the overall pooled RR of 1.44. In a subgroup analysis of data from CHEST, the RR for RRT was higher in surgical than non-surgical patients (ratio of RR: 1.19; 95% CI: 0.77-1.83); however, the difference was not significant (p = 0.43).

Conclusions: HES increased recourse to RRT among surgical patients. There was no evidence that surgical patients are at lower risk for HES-induced acute kidney injury than non-surgical patients.

Introduction

Colloids have long been a common choice for perioperative volume expansion. In a 2010 survey of 391 intensive care units (ICUs) in 25 countries, colloids were administered to 67.3% of patients admitted from the operating room after elective surgery and 67.8% of those after emergency surgery.[1] In the prospective observational Sepsis Occurrence in Acutely ill Patients (SOAP) study at 198 European ICUs, 33.6% of elective surgery patients received the artificial colloid hydroxyethyl starch (HES) in the ICU; in patients undergoing emergency surgery this proportion was 20.7%.[2] Exposure to HES often commences in the operating room. In a prospective sequential analysis of perioperative fluid therapy in cardiopulmonary bypass surgery at one centre, all 6478 patients received HES intraoperatively to prime the extracorporeal circuit.[3]

Perioperative fluid management practices may now be in flux, however, because of safety concerns about HES solutions, most notably their potential to cause postoperative acute kidney injury (AKI).[3-6] In a survey of 80 German ICUs treating patients after cardiothoracic surgery, the proportion of respondents favouring HES as the first choice for volume therapy declined from 65.3 to 38.7% in the wake of emerging evidence about HES-related AKI.[7] Data implicating exposure to HES solutions as a cause of AKI have accumulated from rigorous large-scale randomised trials[8-10] and from meta-analyses of randomised trials.[11,12] While it had been speculated that the renal safety profiles of various HES solutions might differ, such differences could not be confirmed in meta-analyses,[11,12] and an expert panel convened by the US Food and Drug Administration (FDA) concluded that AKI is a class effect of HES solutions.[13]

The European Society of Intensive Care has recommended against the routine use of HES solutions in patients with severe sepsis and other ICU patients at increased risk for AKI.[14] Evidence of AKI and excess mortality attributable to HES has also prompted regulatory actions. Both the FDA[15] and the European Medicines Agency[16] (EMA) have determined that HES should no longer be used in critically ill patients, including those with sepsis. With the implementation of new risk minimisation procedures, including monitoring of renal function for 90 days after HES exposure, the perioperative administration of HES will still be permitted, although such continued HES use is controversial.[17,18]

EMA has concluded that there is 'a lack of robust long-term safety data in patients undergoing surgical procedures'.[16] In this meta-analysis of randomised trials, we sought to assemble the most robust dataset currently available in order to address a single focused clinical question: do HES solutions increase recourse to renal replacement therapy (RRT) in surgical patients?

Methods

Selection criteria

Published and unpublished randomised trials comparing HES with a non-HES control fluid in adult surgical patients were eligible. Trials of hypertonic saline/HES were not considered. Control fluids could consist of other volume expanders such as crystalloid, albumin or gelatin, but not haemoglobin substitutes. Recourse to RRT was the endpoint of the meta-analysis, and RRT data must have been available for a trial to be included. No limitations were placed on the time period of the trial or reporting language. Trials were excluded due to confounding if the control group received concomitant HES, for instance for postoperative volume expansion in a trial comparing intraoperative fluids. Trials reported by Boldt and colleagues were ineligible because of unreliability.[19]

Search methods

Eligible trials were identified by multiple methods, including computer searches of: Medline; Embase; the Cochrane Library; ClinicalTrials.gov; the FDA and EMA web sites; abstract databases for major conferences in surgery, anaesthesiology and intensive care; and Google. The search strategy for trials of HES was similar to that described by Mutter et al.[11] and encompassed the search terms hydroxyethyl starch; HES; hetastarch; pentastarch; tetrastarch; and commercial names of individual HES products. Searches were narrowed to randomised trials assessing renal function in surgical patients by filtering for additional terms and their variants including: randomised controlled trial; random allocation; surgery; operation; transplantation; cardiopulmonary bypass; coronary artery bypass; abdominal aortic; aortic aneurysm; valve; ascending aorta; abdominal; colorectal; hepatectomy; nephrectomy; renal replacement therapy; renal support; renal failure; kidney injury; dialysis; haemodialysis; haemofiltration; haemodiafiltration; and nephrotoxicity. Investigators involved in fluid management for surgical patients and manufacturers of volume expander products used in those patients were consulted to identify eligible trials. Reference lists of primary research papers and review articles were examined, and hard copies or online contents of selected journals were perused.

Data extraction

Working independently, both investigators determined trial eligibility and extracted data. Differences in interpretation were discussed until consensus was reached. The investigators, patients and methods in all trial reports were scrutinised to avoid duplication. Data were extracted on: the total number of patients in each group and the numbers undergoing RRT; age; type of surgery; fluids compared; and trial quality parameters. When clarification or supplementary data were needed, the randomised trial investigators were contacted. Requests under the Freedom of Information Act were submitted to secure eligible trial data on file at US government agencies.

Statistical analysis

The primary outcome measure of the meta-analysis was the relative risk (RR) of recourse to RRT. Since RR is undefined for trials with zero events in both groups, the absolute risk difference was also calculated. Data within separate trial arms evaluating different HES solutions were pooled for analysis as were data from arms evaluating different control fluids. However, a subset analysis was planned *a priori* of trials comparing HES 130/0.4 with crystalloid, and in that analysis only the data pertaining to those fluids were used without pooling. Heterogeneity was assessed by Cochran Q test and the I^2 statistic.[20] If no significant heterogeneity was present, trial results were combined under a fixed effects model. Publication bias was assessed by the method of Egger et al.[21] Subgroup difference was analysed by test of interaction.[22]

A level of 0.05 was the basis for judging statistical significance. Trial quality was evaluated by three validated criteria: randomisation method, allocation concealment and blinding.[23] All analyses were performed using R version 3.0.2 (The R Foundation for Statistical Computing, Vienna, Austria) statistical software.

Results

Included trials

The process of randomised trial selection is outlined in *figure 1*. Seventy-eighty candidate trial reports were identified, of which 25 were excluded after screening, most often because of an ineligible control fluid such as another HES solution. After detailed review another 38 reports were excluded, usually because no RRT data were available. Fifteen randomised trials with a total of 4409 surgical patients reported from 1989 to 2014 were included in the meta-analysis (*figure 1*).[10,24-37]

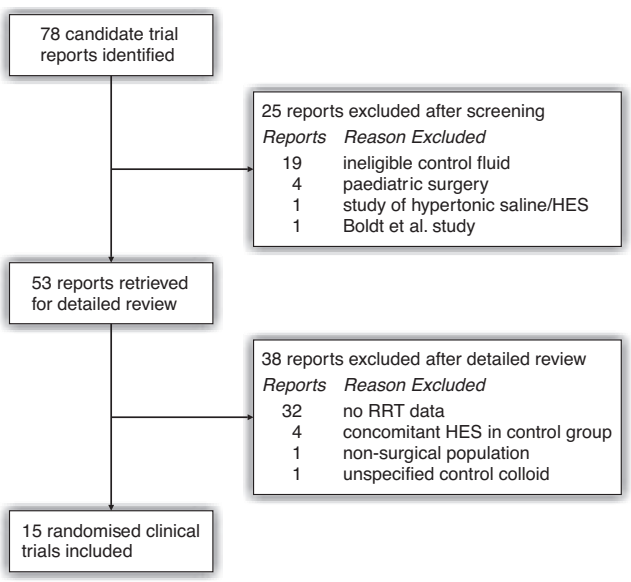
All 15 included trials were published. One trial was reported in abstract form only,[26] and a full draft manuscript, data, statistical reports and other documentation for the trial were obtained from the US Office for Human Research Protections in response to a Freedom of Information Act request.

The characteristics of the included trials are summarised in *table 1*. Thirteen trials (86.7%) were reported after 2000 and seven (46.7%) after 2010. A single trial, the Crystalloid versus Hydroxyethyl Starch Trial (CHEST) of HES 130/0.4 vs. normal saline, was the source for 2872 surgical patients comprising

65.1% of the total in the meta-analysis.[10] CHEST was a trial with a total of 7000 ICU patients at 32 adult medical-surgical ICUs in Australia and New Zealand. The patients from that trial included in the meta-analysis had been admitted from the operating room after elective or emergency surgery. CHEST patients could have received up to 1000 ml HES outside the ICU within the 24 hours before randomisation.

Twelve included trials were limited to elective surgical procedures. Eligibility of elective vs. emergency procedures was not specified for two trials.[24,25] In CHEST, reported results were not stratified according to elective vs. emergency procedures.

Figure 1. Randomised trial selection process. HES = hydroxyethyl starch; RRT = renal replacement therapy.



In 13 trials with 4156 patients (94.3%), postoperative care was rendered in the ICU, while the setting of such care was unspecified for the remaining two trials. In three of those 13 trials,[26,34,35] patients did not receive any study fluid after transfer to the ICU.

The mean patient age ranged from 44-73 years. In ten trials (66.7%), the mean age exceeded 60 years. Coronary artery bypass grafting was the type of surgery in six trials (40.0%), more than any other surgical procedure.

Patients with sepsis were excluded from one trial.[25] In CHEST, sepsis patients comprised 28.8% of the overall population; however, it was not reported how many, if any, of the surgical patients were septic. Inclusion of sepsis patients was not specified for the other 13 trials.

A single HES solution was evaluated in 14 trials (93.3%). Two different HES solutions were compared with gelatin in one trial. By far the most frequent HES solution was HES 130/0.4, which was evaluated in 11 trials (73.3%). HES 200/0.62 was a test HES solution in two trials and HES 70/0.5, HES 200/0.5 and HES 450/0.7 in one trial each. The most common control fluid was crystalloid, which was compared with HES in nine trials (60.0%). Albumin and gelatin were control fluids in four trials (26.7%) each. Study fluids were administered during the intraoperative period in only four trials, exclusively postoperatively in four and both in seven trials

Trial quality

An adequate method of randomisation, usually computer generation of random numbers, was reported for eight trials (53.3%), while the randomisation method was unspecified for the remaining seven trials (46.7%). Allocation concealment was adequate for five trials (33.3%) and unspecified for ten trials (66.7%). Nine trials (60.0%) were blinded and two (13.3%)

Table 1. Included trials.

Trial	n	Age† (y)	Type of surgery	Fluids compared
London et al., 1989[24]	94	63.5 (7.0)	CABG and/or valve	10% HES 200/0.5 vs. 5% albumin
Cittanova et al., 1996[25]	47	44.0 (11.0)	Renal transplantation	6% HES 200/0.62 vs. 3% succinylated gelatin
Bennett-Guerrero et al., 2001[26]	200	67.0 (10.8)	First-time CABG and/or valve	6% HES 450/0.7 vs. 5% albumin or RL
Mahmood et al., 2007[27]	62	72.3 (7.3)	Aortic aneurysm	6% HES 130/0.4 or 6% HES 200/0.62 vs. 4% succinylated gelatin
Ando et al., 2008[28]	21	68.6 (10.5)	Abdominal	6% HES 70/0.5 vs. Ringer's acetate
Godet et al., 2008[29]	65	73.0 (7.9)	Abdominal aortic	6% HES 130/0.4 vs. 3% succinylated gelatin
Mukhtar et al., 2009[30]	40	53.0 (5.9)	Liver transplantation	6% HES 130/0.4 vs. 5% albumin
Ooi et al., 2009[31]	90	58.0 (9.9)	CABG	6% HES 130/0.4 vs. 4% succinylated gelatin
Lee et al., 2011[32]	106	64.0 (8.5)	Off-pump CABG	6% HES 130/0.4 vs. balanced isotonic electrolyte
Yang et al., 2011[33]	90	49.6 (12.2)	Partial hepatectomy	6% HES 130/0.4 vs. 20% albumin or RL
Hung et al., 2012[34]	80	49.2 (9.8)	Major abdominal	6% HES 130/0.4 vs. RL
Myburgh et al., 2012[10]	2872	63.0 (16.9)	Elective or emergency	6% HES 130/0.4 vs. 0.9% NaCl
Gurbuz et al., 2013[35]	200	61.7 (9.7)	Isolated CABG	6% HES 130/0.4 vs. balanced multielectrolyte
Skhirtladze et al., 2014[36]	236	66.7 (13.6)	CABG, valve or ascending aorta	6% HES 130/0.4 vs. 5% albumin or RL
Yates et al., 2014[37]	206	71.0 (6.3)	Colorectal	6% HES 130/0.4 vs. Hartmann's solution

CABG = coronary artery bypass graft; HES = hydroxyethyl starch; RL = Ringer's lactate. †Mean (standard deviation).

unblinded. Blinding was unspecified for the remaining four trials (26.7%). In three trials, including CHEST, blinding and adequate randomisation method and allocation concealment were all implemented.

RRT

A total of 139 patients in ten trials underwent RRT, of which 106 (76.3%) were in CHEST (*figure 2*). In five trials with a total of 481 patients, no patients underwent RRT. Unpublished RRT data included in the meta-analysis were provided upon request by the investigators of four trials, including CHEST.[10,34,35,37]

RRT was administered in 83 of 2157 patients assigned to HES (3.8%) vs. 56 of 2252 control patients (2.5%). The pooled RR for RRT among the ten trials with at least one patient undergoing RRT was 1.44 with a 95% confidence interval (95% CI) of 1.04-2.01, signifying a 44% increase in RR for recourse to RRT attributable to HES (p = 0.029). There was no evidence of significant heterogeneity (p = 0.54) or publication bias (p = 0.93). The absolute risk increase in recourse to RRT attributable to HES, based on the data from all 15 trials, was 1.2% (95% CI: 0.1-2.2%; p = 0.030). On the basis of that absolute increase, the number needed to treat with HES to prompt RRT in one additional patient is 85.

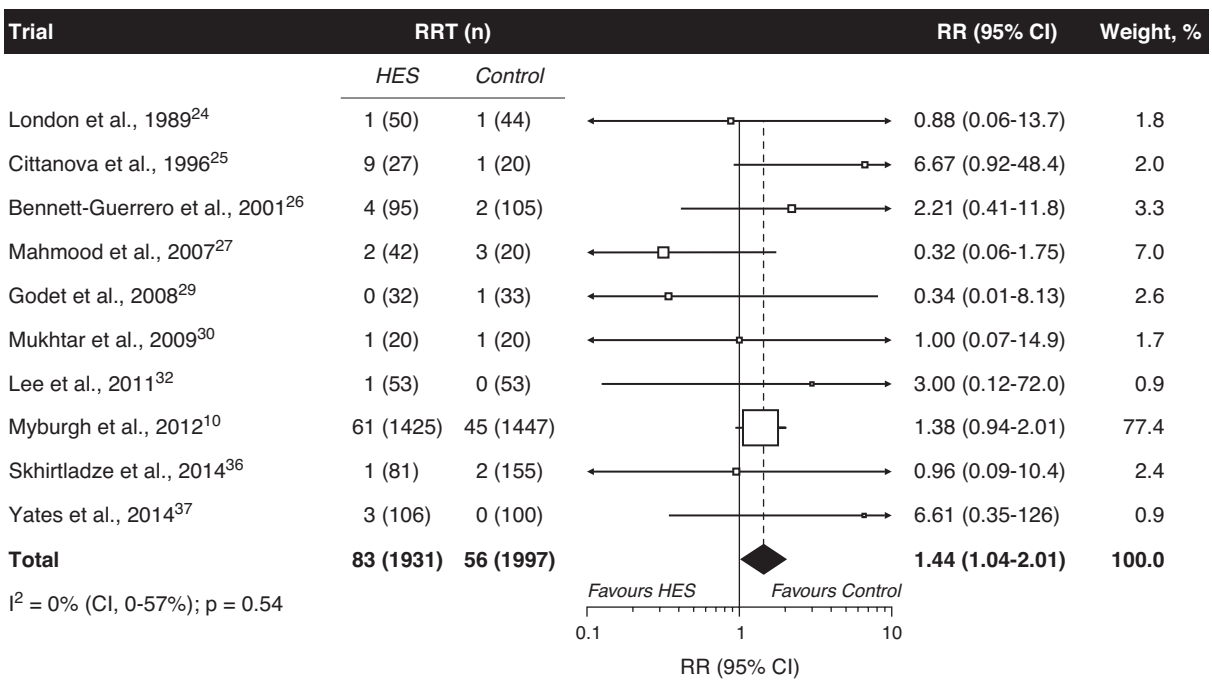
In a subset of four trials, including CHEST, HES 130/0.4 was compared with crystalloid, and at least one patient underwent RRT. In that subset the pooled RR for recourse to RRT (1.47; 95% CI: 1.02-2.12; p = 0.040) coincided closely with the overall pooled RR of 1.44.

Among trials in which study fluid was administered exclusively during the intraoperative period, the RR for RRT was higher than that of trials with postoperative study fluid administered (ratio of RR: 2.98; 95% CI: 0.81-10.94). The difference was not significant, however (p = 0.10).

CHEST subgroups

The above findings demonstrate that HES increases recourse to RRT in surgical patients, as has been shown previously in non-surgical patients. Comparison of the CHEST RRT data between the surgical and non-surgical subgroups of that trial allows an assessment of whether the magnitude of increased RRT risk differs between those subgroups. In CHEST, 61 of 1425 surgical patients assigned to HES (4.3%) and 45 of 1447 to saline (3.0%) underwent RRT (RR: 1.38; 95% CI: 0.94-2.01; *figure 2*), compared with 173 of 1919 non-surgical patients assigned to HES (9.0%) and 150 of 1925 to saline (7.8%), respectively (RR: 1.16; 95% CI: 0.94-1.43). Thus, the RR for recourse to RRT in CHEST was higher in surgical than nonsurgical patients, with a ratio of RR equalling 1.19 (95% CI: 0.77-1.83), although the difference was not statistically significant (p = 0.43). Hence, there was no evidence from CHEST that surgical patients might be less susceptible to HES-induced renal failure prompting RRT than their non-surgical counterparts.

Figure 2. RR for RRT. Error bars indicate 95% CI. Data points scaled according to meta-analytic weight.



CI = confidence interval; HES = hydroxyethyl starch; RR = relative risk; RRT = renal replacement therapy.

Discussion

This is the first meta-analysis to demonstrate increased recourse to RRT in surgical patients receiving HES. The subset analysis of trials comparing HES 130/0.4 with crystalloid provides further confirmation that AKI is a class effect of HES solutions.

The demonstration of a significant effect on RRT was made possible by the availability of data from CHEST, which furnished 77.4% of the meta-analytic weight (*figure 2*). On the other hand, the other trials included in the meta-analysis contributed important statistical power, since the RRT increase due to HES was not statistically significant within the CHEST surgical subgroup by itself (*figure 2*).

Some systematic reviews and meta-analyses have suggested a favourable renal safety profile of HES in surgical patients;[38-40] however, only relatively small studies were included and short follow-up in many of those studies and other confounding factors weaken safety inferences.[41-44]

Surgical admissions accounted for 26.2% of the total in the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) randomised trial of 2857 ICU patients.[45] There was no evidence of excess RRT attributable to colloid in that trial, although RRT results were not reported separately either for HES recipients or surgical patients. Also complicating the interpretation of that trial was the co-administration of albumin to 16.4% of the crystalloids control group.

Recourse to RRT is incorporated as an indicator of severe AKI under both the RIFLE[46] and AKIN[47] classification systems. Nevertheless, standardised criteria for instituting RRT have not been established, and disparate criteria may have been applied among the trials included in this meta-analysis. This limitation should have been at least partly mitigated by including randomised trials only. The same criteria for commencing RRT would have been applied in each randomised group of any particular randomised trial.

It has been proposed that surgical patients might be at lower risk of HES-mediated AKI.[48] The endothelial glycocalyx is presumed to be intact in surgical patients, whereas it is likely to be degraded in critically ill patients such as those with severe sepsis. Lack of an intact glycocalyx could permit extravasation of large molecules such as HES that might otherwise be retained within the intravascular space. The premise of this argument may be faulty, however, since there is evidence that glycocalyx disruption occurs after major surgery as well as in sepsis.[49] Furthermore, increased capillary permeability may not be an essential mechanism of HES-mediated AKI. There is evidence that such injury may result from uptake of filtered HES molecules on the luminal side of the renal tubules independent of a transvascular mechanism such as capillary leak.[50]

The potential of renal HES storage to mediate AKI is underscored by one of the trials included in this meta-analysis.[25] In that trial osmotic nephrosis, a characteristic histological manifestation of HES storage, developed in all biopsied recipients of transplanted kidneys exposed to HES but none of the control patients. In a recent systematic review of clinical studies on HES tissue storage with 635 patients, HES was found to be stored in kidney tissue to a greater extent than in other major organs and to persist there for as long as ten years.[51] Of all groups providing evidence of HES storage in the systematic review, surgical patients accounted for the highest share (45.9%).

EMA has announced that additional studies will be performed on HES in elective surgical patients.[16] Pending the results of those studies, current evidence assembled in this meta-analysis suggests that surgical patients may be at no less risk of HES-induced AKI than other groups.

Acknowledgment

The authors gratefully acknowledge the cooperation of Dr. Kuang-Cheng Chan, Dr. A. Baris Durukan, Dr. John A. Myburgh and Dr. David Yates in furnishing data from their trials.

References

1. Finfer S, Liu B, Taylor C, et al. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. Crit Care. 2010;14:R185.
2. Sakr Y, Payen D, Reinhart K, et al. Effects of hydroxyethyl starch administration on renal function in critically ill patients. Br J Anaesth. 2007;98:216-24.
3. Bayer O, Schwarzkopf D, Doenst T, et al. Perioperative fluid therapy with tetrastarch and gelatin in cardiac surgery—a prospective sequential analysis. Crit Care Med. 2013;41:2532-42.
4. Winkelmayer WC, Glynn RJ, Levin R, Avorn J. Hydroxyethyl starch and change in renal function in patients undergoing coronary artery bypass graft surgery. Kidney Int. 2003;64:1046-9.
5. Rioux JP, Lessard M, de Bortoli B, et al. Pentastarch 10% (250 kDa/0.45) is an independent risk factor of acute kidney injury following cardiac surgery. Crit Care Med. 2009;37:1293-8.
6. Patel M, Niemann C, Sally M, et al. The impact of hydroxyethyl starch use in organ donors after neurologic determination of death on the development of delayed graft function in kidney transplant recipients. Presented at the 85th Annual Meeting of the Pacific Coast Surgical Association, Dana Point, California, USA, 14-17 February 2014.
7. Kastrup M, Carl M, Spies C, Sander M, Markewitz A, Schirmer U. Clinical impact of the publication of S3 guidelines for intensive care in cardiac surgery patients in Germany: results from a postal survey. Acta Anaesthesiol Scand. 2013;57:206-13.
8. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358:125-39.
9. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.4 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367:124-34.
10. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367:1901-11.
11. Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database Syst Rev. 2013;7:CD007594.
12. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA. 2013;309:678-88.
13. Food and Drug Administration. 104th Meeting of the Blood Products Advisory Committee. 2012; www. fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/bloodvaccinesandotherbiologics/bloodproductsadvisorycommittee/ucm325690.pdf; accessed 2014-03-21.
14. Reinhart K, Perner A, Sprung CL, et al. Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. Intensive Care Med. 2012;38:368-83.

15. Food and Drug Administration. FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings. 2013; www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm358271.htm; accessed 2014-05-10.

16. European Medicines Agency. Hydroxyethyl-starch solutions (HES) no longer to be used in patients with sepsis or burn injuries or in critically ill patients. HES will be available in restricted patient populations. 2013; www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Solutions_for_infusion_containing_hydroxyethyl_starch/European_Commission_final_decision/WC500162361.pdf; accessed 2014-03-21.

17. Bellomo R, Bion J, Finfer S, Myburgh J, Perner A, Reinhart K. Open letter to the Executive Director of the European Medicines Agency concerning the licensing of hydroxyethyl starch solutions for fluid resuscitation. Br J Anaesth. 2014;112:595-600.

18. Bion J, Bellomo R, Myburgh J, Perner A, Reinhart K, Finfer S. Hydroxyethyl starch: putting patient safety first. Intensive Care Med. 2014;40:256-9.

19. Wilkes MM, Navickis RJ. The Boldt affair: a quandary for meta-analysts. Anesthesiol News. 2013;39:8-9.

20. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539-58.

21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J. 1997;315:629-34.

22. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. Br Med J. 2003;326:219.

23. Jüni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. Br Med J. 2001;323:42-6.

24. London MJ, Ho JS, Triedman JK, et al. A randomized clinical trial of 10% pentastarch (low molecular weight hydroxyethyl starch) versus 5% albumin for plasma volume expansion after cardiac operations. J Thorac Cardiovasc Surg. 1989;97:785-97.

25. Cittanova ML, Leblanc I, Legendre C, Mouquet C, Riou B, Coriat P. Effect of hydroxyethyl starch in brain dead kidney donors on renal function in kidney-transplant recipients. Lancet. 1996;348:1620-2.

26. Bennett-Guerrero E, Frumento RJ, Mets B, Manspeizer HE, Hirsh AL. Impact of normal saline based versus balanced-salt intravenous fluid replacement on clinical outcomes: a randomized blinded clinical trial. Anesthesiology. 2001;95:A147.

27. Mahmood A, Gosling P, Vohra RK. Randomized clinical trial comparing the effects on renal function of hydroxyethyl starch or gelatine during aortic aneurysm surgery. Br J Surg. 2007;94:427-33.

28. Ando Y, Terao Y, Fukusaki M, et al. Influence of low-molecular-weight hydroxyethyl starch on microvascular permeability in patients undergoing abdominal surgery: comparison with crystalloid. J Anesth. 2008;22:391-6.

29. Godet G, Lehot J-J, Janvier G, Steib A, de Castro V, Coriat P. Safety of HES 130/0.4 (Voluven®) in patients with preoperative renal dysfunction undergoing abdominal aortic surgery: a prospective, randomized, controlled, parallel-group multicentre trial. Eur J Anaesthesiol. 2008;25:986-94.

30. Mukhtar A, Aboulfetouh F, Obayah G, et al. The safety of modern hydroxyethyl starch in living donor liver transplantation: a comparison with human albumin. Anesth Analg. 2009;109:924-30.

31. Ooi JS, Ramzisham AR, Zamrin MD. Is 6% hydroxyethyl starch 130/0.4 safe in coronary artery bypass graft surgery? Asian Cardiovasc Thorac Ann. 2009;17:368-72.

32. Lee JS, Ahn SW, Song JW, Shim JK, Yoo KJ, Kwak YL. Effect of hydroxyethyl starch 130/0.4 on blood loss and coagulation in patients with recent exposure to dual antiplatelet therapy undergoing off-pump coronary artery bypass graft surgery. Circ J. 2011;75:2397-402.

33. Yang J, Wang W-T, Yan L-N, Xu M-Q, Yang J-Y. Alternatives to albumin administration in hepatocellular carcinoma patients undergoing hepatectomy: an open, randomized clinical trial of efficacy and safety. Chin Med J (Engl). 2011;124:1458-64.

34. Hung M-H, Zou C, Lin F-S, Lin C-J, Chan K-C, Chen Y. New 6% hydroxyethyl starch 130/0.4 does not increase blood loss during major abdominal surgery—a randomized, controlled trial. J Formos Med Assoc. 2012;http://dx.doi.org/10.1016/j.jfma.2012.08.002.

35. Gurbuz HA, Durukan AB, Salman N, et al. Hydroxyethyl starch 6%, 130/0.4 vs. a balanced crystalloid solution in cardiopulmonary bypass priming: a randomized, prospective study. J Cardiothorac Surg. 2013;8:71-6.

36. Skhirtladze K, Base EM, Lassnigg A, et al. Comparison of the effects of albumin 5%, hydroxyethyl starch 130/0.4 6%, and Ringer's lactate on blood loss and coagulation after cardiac surgery. Br J Anaesth. 2014;112:255-64.

37. Yates DR, Davies SJ, Milner HE, Wilson RJ. Crystalloid or colloid for goal-directed fluid therapy in colorectal surgery. Br J Anaesth. 2014;112:281-9.

38. Martin C, Jacob M, Vicaut E, Guidet B, Van Aken H, Kurz A. Effect of waxy maize-derived hydroxyethyl starch 130/0.4 on renal function in surgical patients. Anesthesiology. 2013;118:387-94.

39. van der Linden P, James M, Mythen M, Weiskopf RB. Safety of modern starches used during surgery. Anesth Analg. 2013;116:35-48.

40. Gillies MA, Habicher M, Jhanji S, et al. Incidence of postoperative death and acute kidney injury associated with i.v. 6% hydroxyethyl starch use: systematic review and meta-analysis. Br J Anaesth. 2014;112:25-34.

41. Farag E, Argalious M, O'Hara J, Doyle DJ. Safety of HES 130/0.4 not yet settled. Anesth Analg. 2013;117:528-9.

42. Groeneveld AB, Navickis RJ, Wilkes MM. Hydroxyethyl starch 130/0.4 and postoperative acute kidney injury. Anesthesiology. 2013;119:733-5.

43. Takala J, Hartog C, Reinhart K. Safety of modern starches used during surgery: misleading conclusions. Anesth Analg. 2013;117:527-8.

44. Wiedermann CJ. Hydroxyethyl starch 130/0.4: safe for the kidney in surgical patients? Anesthesiology. 2013;119:735-6.

45. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013;310:1809-17.

46. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8:R204-R12.

47. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.

48. van der Linden P, James M, Mythen M, Weiskopf RB. In response. Anesth Analg. 2013;117:530-1.

49. Steppan J, Hofer S, Funke B, et al. Sepsis and major abdominal surgery lead to flaking of the endothelial glycocalix. J Surg Res. 2011;165:136-41.

50. Bellmann R, Feistritzer C, Wiedermann CJ. Effect of molecular weight and substitution on tissue uptake of hydroxyethyl starch: a meta-analysis of clinical studies. Clin Pharmacokinet. 2012;51:225-36.

51. Wiedermann CJ, Joannidis M. Accumulation of hydroxyethyl starch in human and animal tissues: a systematic review. Intensive Care Med. 2014;40:160-70.