Mashed Potatoes and Maize

Are the Starches Safe?

IN 1831 during the European cholera epidemic, Latta[1] was the first to report on a patient who was successfully resuscitated with intravenous fluids. He injected 60 ounces of warm saline intravenously to a pulseless cholera patient. According to the author's report, on receiving the fluid resuscitation, every symptom of cholera was removed. About 80 yr later, fluid resuscitation with colloids was introduced to clinical medicine for treatment of severe hemorrhage. In his case series report published in *JAMA* in 1915, Hogan[2] noted that although salt solutions give a temporary rise in blood pressure (and improvement in the general symptoms resulting from hemorrhage), he could obtain a more permanent rise with gelatin, a hydrophilic colloidal solution. In the same report, Dr. Hogan included the caveat that resuscitation with colloids is insufficient to treat toxemic shock despite the initial effects of colloid resuscitation on blood pressure. This differential effect on outcome of patients presenting with hemorrhagic and septic shock should be kept in mind when interpreting the results from current trials.

"… clinical studies have not only failed to conclusively demonstrate the expected benefits, but have also suggested the possibility of harm from the starches."

Hydroxyethyl starches (HES) are the most commonly used colloids in many parts of the world;[3]however, recent studies suggest that HES may be associated with worse outcomes, when given for fluid resuscitation to patients with sepsis.[4,5] Outcome data on the topic of colloid resuscitation are sparse, which is probably why it still raises strong opinions from key opinion leaders in the field.

In this issue of ANESTHESIOLOGY, two groups of researchers provide important new data on the safety and potential benefits of modern 6% HES. Silva *et al.*[6] show in a preclinical model of hemorrhage and lung injury that potato-derived 6% HES resuscitation compares favorably with crystalloid and gelatin–based fluid resuscitation in terms of variables reflecting pulmonary and renal injury. The meta-analysis of Martin *et al.*[7] reports on the absence of renal toxicity of maize-derived HES given to 1,230 patients undergoing a variety of surgical procedures.

Structure-Action Relationship of Different HES Products

Available HES products differ in their mean molecular weight, molar substitution, substitution pattern, and raw material, and this information is incorporated in the nomenclature of HES given in the product information. Six percent HES 130/0.40 indicates a 6% solution of HES (iso-oncotic) with a mean molecular weight of 130 kd and a substitution ratio of 0.4 (hence the term "tetrastarch"). Older generations of HES with substitution ratios of 0.5, 0.6, and 0.7 are known as penta-, hexa-, and hetastarches, respectively.[8] Newer generation tetrastarches are derived from two sources. The raw material is either waxy maize starch in 6% HES 130/0.4 (Voluven® or Volulyte®, Fresenius Kabi, Bad Homburg, Germany) or potato starch in 6% HES 130/0.42 (*e.g.,* Venofundin® or Tetraspan®, B. Braun Melsungen, Germany; VitaHES® or Vitafusal®, Serumwerk Bernburg, Germany; PlasmaVolumeRedibag®, Baxter, Unterschleißheim, Germany), and some including Martin *et al.*[7] believe that maize- and potato-derived 6% HES 130 are not biologically equivalent.

Potato starch—in contrast to waxy maize starch preparations—contains several thousand parts per million of esterified phosphate groups, which are located predominantly at the C6 (60–70%) and C3 positions (30–40%) of the

◆ This Editorial View accompanies the following articles: 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; and Silva PL, Güldner A, Uhlig C, Carvalho N, Beda A, Rentzsch I, Kasper M, Wiedemann B, Spieth PM, Koch T, Capelozzi VL, Pelosi P, Rocco PRM, Gama de Abreu M: Effects of intravascular volume replacement on lung and kidney function and damage in nonseptic experimental lung injury. ANESTHESIOLOGY 2013; 118:395–408.

Photo: ©ThinkStock.

Accepted for publication November 14, 2012. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

 Anesthesiology 2013;118:244-7

glucose units.[9] Adding more negative charges to the starch molecule affects the tertiary structure and contributes to the higher viscosity of potato-derived starch. In addition, these negative charges may contribute to the formation of inclusion complexes of amylose-containing starch preparations with endogenous lipid molecules, such as prostanoids or free fatty acids.[10] To the best of our knowledge, however, we do not know at this point whether the differences in molecular structure between potato- and maize-derived starch translates into differences in efficacy and drug safety when these colloids are used in perioperative medicine.

The Physiology of Resuscitation

Resuscitation involves much more than volume expansion. Indeed, one can argue that skillful resuscitation lies at the heart of the specialties of anesthesia and critical care. Fundamentally, resuscitation is the restoration of cellular perfusion and oxygenation. Therefore, an ideal resuscitation fluid would accomplish long-lasting volume expansion, while improving microcirculation in the absence of immunosuppression and toxic effects (fig. 1). In addition, we would like our fluids to be inexpensive and have a long shelf life. The potential advantages of colloids over crystalloids include more efficacious volume expansion, decreased extravascular lung water, decreased edema, and improved microcirculation. Although synthetic colloids are significantly cheaper than albumin, they have potential drawbacks, such as the risk of allergic reactions, impaired coagulation and renal function, as well as long-term retention in the reticuloendothelial system, which may differ among compounds. Third-generation of HES preparations (the tetrastarches, characterized by degrees of substitution of 0.40 and 0.42) are widely considered to be the safest of the synthetic colloids,[11] although robust data to substantiate this claim are limited.[12]

What Do the Clinical Data Suggest?

The Saline versus Albumin Fluid Evaluation study showed that in most intensive care unit patients (except in those with traumatic brain injury) 4% albumin did not increase death from any cause during the 28-day period compared with normal saline.[13] The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis trial in 2008[4] suggested a strong association between the use of HES and renal failure and mortality in septic patients. However, it was criticized for using a less favorable HES formulation (a hyperoncotic pentastarch, 10% HES 200/0.5), as well as for using large volumes of HES, well in excess of the manufacturer's recommendation. The recently published 6S trial was performed in response to these critiques.[5] This randomized, blinded trial used moderate doses of a third-generation tetrastarch (derived from potato—6% HES 130/0.42) in patients with severe sepsis, and found that the tetrastarch was associated with worse outcomes (risk of death and risk of requiring renal replacement therapy) than crystalloid. This study, too, needs to be criticized, because the effective volume replacement effect was grossly unbalanced between groups, leading to differences in red blood cell transfusion requirements.[14] It is also important to underscore that we do not understand clearly the mechanisms that underlie HES-mediated nephrotoxicity. In contrast, two small studies looking at the use of tetrastarches in trauma (the Fluids in Resuscitation of Severe Trauma study)[15] and in sepsis (Effects of Voluven on Hemodynamics and Tolerability of Enteral Nutrition in Patients with Severe Sepsis study)[16] failed to find any deleterious effect in terms of renal function or mortality—but they were not powered to rigorously address renal safety and mortality. In a large randomized study of waxy maize-derived tetrastarch (the Crystalloid versus Hydroxyethyl Starch trial, with an enrollment of 7,000 intensive care unit patients), the authors did not find a difference in mortality, which was the criterion the study was powered for.[17] However while there was no difference in the incidence in renal failure, patients treated with HES had a higher rate of renal replacement therapy. Importantly, the authors did not find evidence of adverse outcome in the subset of patients with sepsis, although the patients in this study were less sick than in the VISEP and 6S studies. In addition, more patients who received 6% HES 130/0.4 had adverse events.[17] Accordingly, although the final answer on whether or not HES should be used in critically ill patients has still not been given, considerations regarding its safety profile in these heterogeneous patients continue to be a concern, and it would seem prudent to avoid its use in patients with severe sepsis.

What Do the Present Studies Add?

In a nonseptic porcine model of acute lung injury, Silva *et al.*[1] found that goal-directed volume expansion with HES (derived from potato) was more effective at restoring circulating blood volume compared with crystalloid (the ratio of HES to crystalloid was 1: 2.7). They also found that HES preserved lung function better than crystalloid, and surprisingly, that HES was less damaging to the kidneys than gelatin, the other colloid tested. It should be noted that functional renal impairment has not been evaluated. The strengths of this study include a well-described model of lung injury and hypovolemia

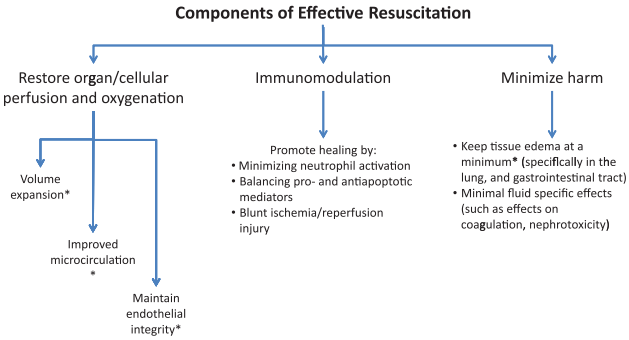


Fig. 1. Goals of effective resuscitation. A *star* indicates potential advantages of colloids over crystalloids from a conceptional point of view. However, dedicated outcome trials need to confirm these findings in entity-based collectives of patients.

in a large mammal, and the relatively sophisticated endpoint (intrathoracic blood volume index) for resuscitation in hypovolemic shock. Some limitations need to be considered: their model does not incorporate infection, and the study period was limited to 4 h, which may explain the better colloid to crystalloid ratio compared with recent clinical studies.[4,5,13,16] The meta-analysis by Martin *et al.*[7] is driven by the consideration that the biological effects of the newer tetrastarches (specifically the HES derived from waxy maize) significantly differ from older-generation starches, and are less likely to be nephrotoxic when used in the perioperative setting. They included data from 17 studies showing that waxy maize-derived HES (6% HES 130/0.40) is not associated with a greater risk of renal damage (as measured by serum creatinine) compared with the fluids it was tested against in these studies in the general surgical population. Martin *et al.*[7] point out in their discussion that unfavorable results generated using HES from potato (as in the 6S trial) may not be applicable to HES derived from waxy maize. Although the high heterogeneity (I^2 = 68.5% for baseline creatinine values, and 79.8% for extreme creatinine values) may be a concern, their data support the view that waxy maize-derived HES (6% HES 130/0.40) can be safely used for treatment of blood loss in the operating room. This finding is in accordance with another recently published analysis on randomized controlled trials using tetrastarches, suggesting that the intraoperative use of modern HES preparations during surgery is not associated with postoperative renal failure.[18]

What Is the Take-Home Message?

The tension between supporters and detractors of the starches largely stems from the fact that the starches seem to have a very compelling physiologic rationale for their use; unfortunately, clinical studies have not only failed to conclusively demonstrate the expected benefits, but have also suggested the possibility of harm from the starches. In addition, colloids are more expensive than crystalloids.

In which patient groups should we consider the use of HES preparations? The two studies that appear in this issue support the view that the new tetrastarches are well suited to short-term resuscitation, for example, in the perioperative or preclinical period, where their demonstrated efficacy at volume expansion may be used to the patient's benefit. However, we do not have robust data that examine the utility of HES in patients undergoing high-risk surgery, such as major vascular surgery and surgery in patients with sepsis. A study using older HES preparations in brain-dead kidney donors found evidence of increased renal dysfunction in the recipients.[19] Although we cannot automatically extrapolate those findings to the newer starches, we would recommend using HES with caution in renal transplants.

Given the available data on HES during surgery and in the intensive care unit, we find ourselves still pretty much in line with the conclusions that Dr. Hogan[2] came to approximately 100 yr ago, that is, resuscitation with colloids is more effective than saline to treat a hypovolemic shock, but insufficient to treat toxemic (septic) shock, despite the initial effects of colloid resuscitation on blood pressure.

Aranya Bagchi, M.B.B.S.,* Matthias Eikermann, M.D., Ph.D.† *Department of Anesthesiology, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. †Department of Anesthesiology, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, and Klinik fuer Anaesthesiologie und Intensivmedizin, Universitaetsklinikum Essen, Dusiburg-Essen University, Essen, Germany. meikermann@partners.org

References

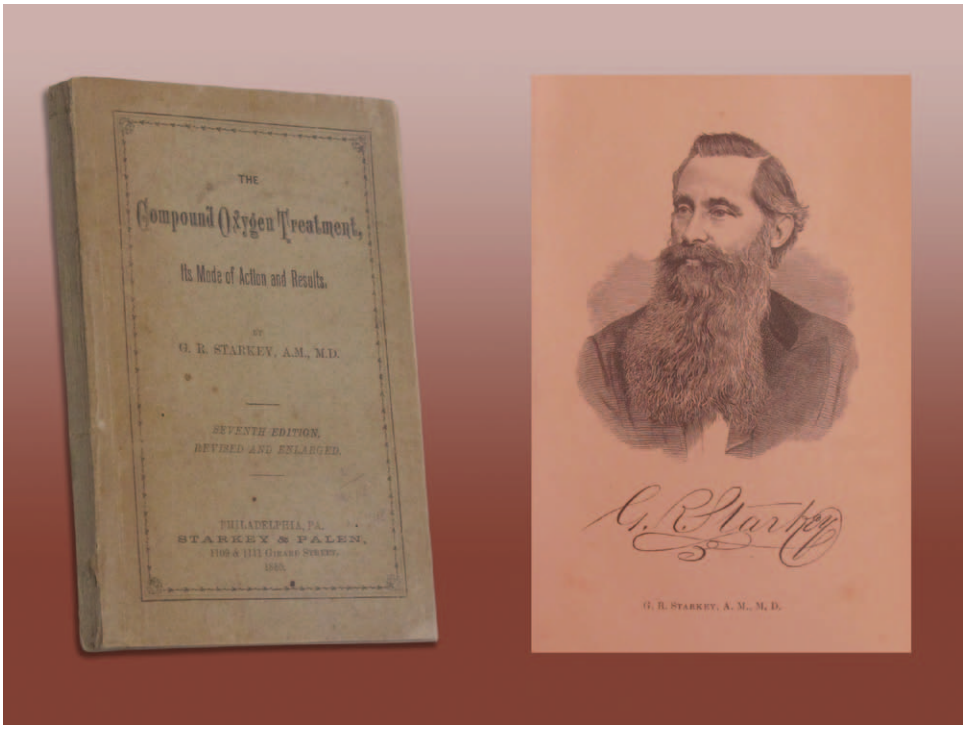
1. Latta T: Saline venous injection in cases of malignant cholera, performed while in the vapour-bath. Lancet 1832; 19:173–6
2. Hogan JJ: The intravenous use of colloidal (gelatin) solutions in shock. JAMA 1915; 64:721–6
3. Finfer S, Liu B, Taylor C, Bellomo R, Billot L, Cook D, Du B, McArthur C, Myburgh J; SAFE TRIPS Investigators: Resuscitation fluid use in critically ill adults: An international cross-sectional study in 391 intensive care units. Crit Care 2010; 14:R185
4. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K; German Competence Network Sepsis (SepNet): Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008; 358:125–39
5. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard AL, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J; 6S Trial Group; Scandinavian Critical Care Trials Group: Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012; 367:124–34
6. Silva PL, Guldner A, Uhlig C, Carvalho N, Beda A, Rentzch I, Kasper M, Wiedemann B, Spieth PM, Koch T, Capelozzi VL, Pelosi P, Rocco PRM, de Abreu MG: Effects of intravascular volume replacement on lung and kidney function and damage in nonseptic experimental lung injury. Anesthesiology 2013; 118:395–408
7. Martin C, Jacob M, Vicaut E, Guidet B, Von 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
8. Mizzi A, Tran T, Karlnoski R, Anderson A, Mangar D, Camporesi EM: Voluven, a new colloid solution. Anesthesiol Clin 2011; 29:547–55
9. Tabata S, Hizukuri S: Studies on starch phosphate. Part 2. Isolation of glucose 3-phosphate and maltose phosphate by acid hydrolysis of potato starch. Starch/Starke 1971; 23:267–72
10. Godet MC, Tran V, Colonna P, Buleon A: Inclusion/exclusion of fatty acids in amylose complexes as a function of the fatty acid chain length. Int J Biol Macromol 1995; 17:405–8
11. Ertmer C, Rehberg S, Van Aken H, Westphal M: Relevance of non-albumin colloids in intensive care medicine. Best Pract Res Clin Anaesthesiol 2009; 23:193–212
12. Hartog CS, Kohl M, Reinhart K: A systematic review of third-generation hydroxyethyl starch (HES 130/0.4) in resuscitation: Safety not adequately addressed. Anesth Analg 2011; 112:635–45
13. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R; SAFE Study Investigators: A comparison of albumin and

saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004; 350:2247–56

14. Chappell D, Jacob M: Protocols, physiology, and trials of hydroxyethyl starch. N Engl J Med 2012; 367:1266; author reply 1267
15. James MF, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS: Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: The FIRST trial (Fluids in Resuscitation of Severe Trauma). Br J Anaesth 2011; 107: 693–702
16. Guidet B, Martinet O, Boulain T, Philippart F, Poussel JF, Maizel J, Forceville X, Feissel M, Hasselmann M, Heininger A, Van Aken H: Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study. Crit Care 2012; 16:R94
17. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SA; the CHEST Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012; 367:1901–11
18. Van Der Linden P, James M, Mythen M, Weiskopf RB: Safety of Modern Starches Used During Surgery. Anesth Analg 2012; DOI: 10.1213/ANE.0b013e31827175da
19. Cittanova ML, Leblanc I, Legendre C, Mouquet C, Riou B, Coriat P: Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. Lancet 1996; 348:1620–2

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Starkey's Compound Oxygen as a Hygienic for Ailments Chronic



Following Quaker schooling in Rhode Island and college in his native Maine, George Rogers Starkey (1823–1896) graduated from the Homeopathic Medical College of Pennsylvania in 1855. By 1869 frail health forced Starkey to abandon teaching anatomy and surgery at his medical *alma mater,* which had since been renamed Hahnemann Medical College. As a general cure for chronic diseases, the "Compound Oxygen" he peddled would evolve from the inhaling of dilute concentrations of nitrous oxide to the imbibing of bottled aqueous nitrate solutions of ammonia and lead. Delighted to sell his Compound to both homeopaths and allopaths, Starkey considered Compound Oxygen as a system of hygiene supplementing whatever other physicians prescribed.

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.

Effect of Waxy Maize-derived Hydroxyethyl Starch 130/0.4 on Renal Function in Surgical Patients

Claude Martin, M.D.,* Matthias Jacob, M.D.,† Eric Vicaut, M.D.,‡ Bertrand Guidet, M.D.,§ Hugo Van Aken, M.D., Ph.D.,‖ Andrea Kurz, M.D.#

ABSTRACT

Background: The aim of this meta-analysis was to evaluate renal safety with the active substance of the latest generation of waxy maize-derived hydroxyethyl starch in surgical patients. The authors focused on prospective, randomized, controlled studies that documented clinically relevant variables with regard to renal effects of waxy maize-derived hydroxyethyl starch 130/0.40.

Materials and methods: The authors carefully searched for all available prospective, randomized studies and evaluated the greatest delta from baseline values in renal safety variables (serum creatinine values, calculated creatinine clearance, incidence of renal replacement therapy, and acute renal failure). The authors included 17 studies that analyzed patients (n = 1,230) undergoing a variety of surgical procedures.

Results: For maximum serum creatinine values, the effect size estimate was 0.068 (95% CI = −0.227 to 0.362), P = 0.65. For calculated creatinine clearance values, pooled risk difference was 0.302 (95% CI = −0.098 to 0.703), P = 0.14. For incidence of acute renal failure, pooled risk difference was 0.0003 (95% CI = −0.018 to 0.019), P = 0.98. For incidence of renal replacement therapy, pooled risk difference was −0.003 (95% CI = −0.028 to 0.022), P = 0.85.

Conclusions: The authors found no evidence for renal dysfunction caused by modern waxy maize-derived hydroxyethyl starch 130/0.40 in surgical patients.

What We Already Know about This Topic

- The use of hydroxyethyl starches has been associated with nephrotoxicity and increase in mortality in the critically ill
- The renal safety of modern hydroxyethyl starches 130/0.40 in nonseptic surgical patients remains unclear

What This Article Tells Us That Is New

- In a meta-analysis of 17 randomized studies (n = 1,230) evaluating renal safety of waxy maize-derived hydroxyethyl starches 130/0.40 in surgical patients no evidence for renal dysfunction was observed

HYDROXYETHYL starches (HES) are colloidal solutions used for prevention and treatment of hypovolemia. During the past decades, the molecular weight and molar substitution (proportion of hydroxyethylated glucose subunits) of these molecules have been optimized, leading to an average molecular weight of approximately 130 kDa and a molar substitution of approximately 0.4. Between the different generations of starches there are clear clinical differences in terms of coagulation effects[1–6] or effects on renal function.[7,8] Nevertheless, it has recently been suggested to exclude starches from volume resuscitation in the critically ill patient.[9] This led to great uncertainty about general use of

◆ This article is accompanied by an Editorial View. Please see: Bagchi A, Eikermann M: Mashed potatoes and maize: Are the starches safe? Anesthesiology 2013; 118:244–7.

* Professor, Département d'Anesthésie et de Réanimation, CHU Nord, Assistance Publique-Hôpitaux de Marseille, Marseille cedex, France. † Associate Professor, Department of Anaesthesiology, University Hospital Munich, Munich, Germany. ‡ Professor, Hôpital Fernand Widal, Service Biophysique et Traitement de l'Image, Laboratoire de Biophysique, Paris, France. § Professor, Hôpitaux de Paris, Hôpital Saint-Antoine, Service de Réanimation Médicale, Paris, France. ‖ Professor, Department of Anesthesiology, Intensive Care and Pain Medicine, University Hospital Münster, Münster, Germany. # Professor, The Cleveland Clinic, Department of Outcomes Research, Cleveland, Ohio.

Received from the Département d'Anesthésie et de Réanimation, CHU Nord, Assistance Publique-Hôpitaux de Marseille Marseille cedex, France. Submitted date for publication March 14, 2012. Accepted date for publication November 14, 2012. The study received a grant from Fresenius Kabi (Bad Homburg, Germany). The authors had access to the Fresenius Kabi study tracking system for literature research. Dr. Martin received honoraria from Fresenius Kabi (Paris, France) for consultancy or for giving lectures. Dr. Jacob received honoraria and funding from Baxter (Unterschleißheim, Germany), B. Braun (Melsungen, Germany), Fresenius Kabi (Bad Homburg, Germany), Serumwerk Bernburg (Bernburg, Germany), ZLB Behring (Marburg, Germany). Dr. Vicaut received honoraria and funding from Sanofi-Aventis (Paris, France), Lilly Pharma (Suresnes, France), Pfizer (Paris, France), Servier (Paris, France), Abbott (Rungis Cedex, France), and Amgen (Neuilly sur Seine Cedex, France). Dr. Guidet received honoraria for lectures and for advisory board of Fresenius Kabi France (Paris, France) as well as honoraria from Grifols (Meyreuil, France). Dr. Van Aken received honoraria and travel reimbursement from Vifor Pharma Ltd. (Glattbrugg, Switzerland), Abbott Germany (Wiesbaden, Germany) and Fresenius Kabi (Bad Homburg, Germany). Dr. Kurz declares that she participates in a study on volume therapy sponsored by Hospira.

Address correspondence to Dr. Martin: Département d'Anesthésie et de Réanimation, CHU Nord, Assistance Publique-Hôpitaux de Marseille, 13915 Marseille Cedex 20, France. claude.martin@ap-hm.fr. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. Anesthesiology's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

 Anesthesiology 2013;118:387-94

HES, especially in European countries where many clinicians routinely use HES preparations to stabilize cardiac preload.

The clinical trials that have raised concerns about the renal safety of HES[10–14] showed a higher frequency of acute renal failure (ARF) and some even higher mortality in critically ill patients, using different isotonic and hypertonic HES preparations. A retrospective trial[15] and two prospective randomized studies[16,17] performed with waxy maize-derived HES 130/0.40 in intensive care unit patients found no significant signs of renal dysfunction or differences in mortality.

Several reviews and meta-analyses have addressed the safety of HES before. But first, most analyses did not usually take into account different HES generations and the raw material.[1,18]

Second, within the latest meta-analyses[19–21] two also focused on HES 130 but did not differentiate between the products derived from waxy maize and potato.[20,21] Also, they included surgical patients and/or critically ill or septic patients. Currently, many small studies in surgery supporting HES 130/0.4 face a small number of relatively large studies in critically ill patients, which showed negative effects. Thus, one might argue that surgical studies were just underpowered to show the adverse effects observed in the critically ill. To test this hypothesis, the current meta-analysis evaluates renal safety with the most modern HES 130/0.40 derived from waxy maize in nonseptic, surgical patients.

We evaluated studies that reported renal effects of waxy maize-derived HES 130/0.40. Furthermore, we included only prospective, randomized interventional studies and analyzed the largest changes from baseline values in renal safety variables within these studies.

Materials and Methods

Eligibility Criteria

We selected only prospective, randomized controlled trials and included all available surgical procedures to achieve as much generalizability of our results as possible.

Inclusion criteria for eligible studies were:

1) The use of waxy maize-derived HES 130/0.40, the latest (third) generation starches, in at least one intervention group. Due to the heavy imbalance in study evidence and proven differences of the products[22–24] we refrained from including data about HES 130/0.42.
2) Reporting on one of the following variables as primary endpoint, secondary endpoint or safety data:
3) Blood urea, serum creatinine, calculated creatinine clearance, glomerular filtration rate, α1-microglobulin, neutrophil gelatinase-associated lipocalin, N-acetyl-β-(D)-glucosaminidase, Risk, Injury, Failure, Loss, End stage kidney disease classification[25], Acute Kidney Injury Network classification, or ARF.
4) The use of a colloidal or crystalloidal solution other than HES 130/0.40 in one intervention group of the study as a control. Studies conducted exclusively in septic or critically ill patients were excluded.

Search Strategy

We searched PubMed for studies with the following terms in all fields: HES 130, HES 130/0.4, and one of the terms "creatinine," "renal function," "renal failure," or "renal replacement therapy." Because many randomized, controlled trials might not be listed in common databases,[26] we performed an additional manual search *via* the Fresenius Kabi study tracking system, using the same search terms. This approach yielded 10 further studies. All studies found in addition to the initial search were also listed in PubMed.**

Study Selection and Data Extraction

The selection criteria mentioned above were developed and studies screened by all authors. The inclusion and exclusion criteria for retrieved studies were *a priori* jointly discussed and agreed upon. The study flow diagram is shown in figure 1. The initial search *via* PubMed resulted in 48 hits. A manual search using the Fresenius Kabi tracking system yielded 10 additional studies.

Thirty-four publications had to be excluded as they were conducted on critically ill patients (*e.g.*, sepsis, trauma, n = 6), review articles (n = 7), experimental studies (n = 5) (*e.g.*, using MP4OX, which is an experimental drug with an unknown safety profile [n = 2][27,28]), retrospective or observational without control group (n = 10), or without adequate control group (comparison of 2 HES 130/0.4) (n = 2).[29,30] In addition, we excluded studies in kidney transplant patients (n = 2),[31] because effects of kidney transplantation on creatinine will very likely mask any effects of HES as creatinine values typically improve after a transplant. Thus, we avoided introducing a falsely positive signal for HES by excluding these studies. We also excluded a nonretracted study published by Boldt[32] due to the retraction of nearly all other relevant studies from this author. For an overview of all included studies and numbers of patients see table 1.

Data were extracted from the individual studies and, in addition to the variables mentioned above, intensive care unit length of stay, hospital length of stay, and mortality were recorded, if available. For renal function, we extracted baseline values for each variable as well as the highest or lowest value after HES administration. This indicated the greatest impact on renal function, independent of the point in time it had been recorded.

Calculated creatinine clearance was directly measured in two studies[33,34] but not specified in the others. Thus, we expect that most of the data presented are calculated or estimated creatinine clearances.

ARF was defined according to Risk, Injury, Failure, Loss, End stage kidney disease [25] criteria when available. In case Risk, Injury, Failure, Loss, End stage kidney disease classification was not reported, the definition of ARF was considered according

** Or at www.clinicaltrial.gov. Accessed December 20, 2012.

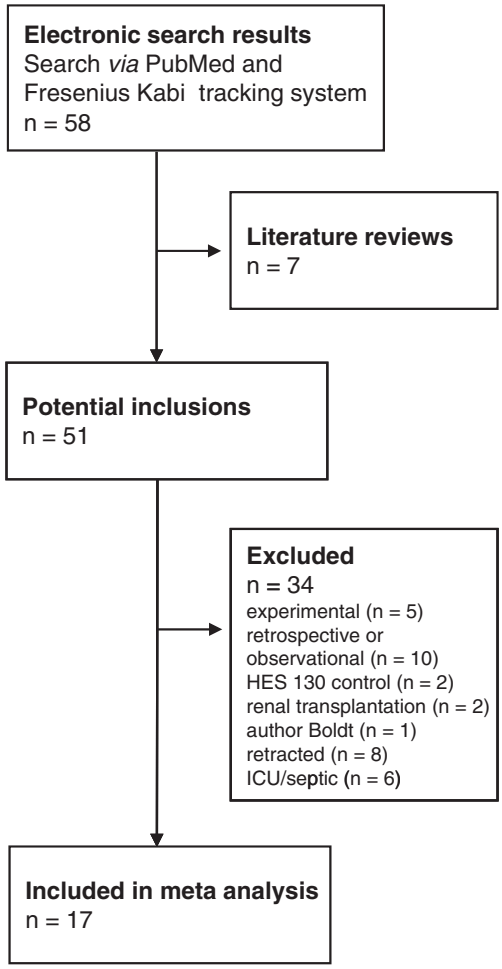


Fig. 1. Study flow diagram. HES = hydroxyethyl starch; ICU = intensive care unit.

to the definition mentioned in the original article. This definition may vary slightly from one publication to another.

Statistical Analysis

All values extracted from the individual studies were transformed to mean values and SD. If mean value and SD were not reported, they were estimated from median values and ranges, or interquartile ranges.[35] If studies included more than one control group,[34,36] the respective data were pooled (weighted estimate). Two studies did not provide a baseline value for serum creatinine[36] or blood urea.[37,38] Nevertheless, the respective highest or lowest values were included in the meta-analysis. We calculated the effect size using the nonbiased method proposed by Hedges and Olkin.[39] Finally, the effect size for continuous variables or relative risk for binary variables was pooled *via* a meta-analysis with random effects based on DerSimonian-Laird using the Statdirect software (StatDirect Ltd., Altrincham, United Kingdom). Begg-Mazumdar and Egger variables were used for testing bias within publications. Heterogeneity was estimated by the I^2 index proposed by Higgins and Thomson.[40] *P* values were two-tailed and a *P* value of less than 0.05 was considered as statistically significant.

Results

In total, 17 studies were included in the analysis. These comprised patients undergoing elective surgical procedures like cardiopulmonary bypass,[37,38,41,42] cardiac surgery,[2,3,43–45] other surgical procedures,[33,34,36,46–49] or liver transplantation.[50] Most studies provided data about serum creatinine or calculated creatinine clearance, whereas other variables like neutrophil gelatinase-associated lipocalin or β-acetyl-β-(D)-glucosaminidase were reported only rarely. The extracted extreme values for serum creatinine occurred on average 2 days after surgery. None of our funnel plots showed significant heterogeneity. The bias indicators for serum creatinine extreme values were −0.099 (0.5906) for Kendall tau (Begg-Mazumdar) and 0.735 (95% CI = −5.395 to 3.925); *P* = 0.74 for the Egger bias indicator. We found no significant difference for the effect of waxy maize-derived HES 130/0.40 on serum creatinine as compared with the respective controls for baseline (pooled d+ = −0.021 [95% CI = −0.261 to 0.219], *P* = 0.86, I^2 = 68.5% [95% CI = 35.8 to 80.9%]) and for extreme values (pooled d+ = 0.068 [95% CI = −0.227 to 0.362], *P* = 0.65, I^2 = 79.8% [95% CI = 65.2 to 86.6%]) (fig. 2, A and B). Two studies differed in their results: for Tiryakioglu *et al.*,[38] the HES group showed significantly higher serum creatinine values 24 h after the procedure (97 ± 9 to 124 ± 21 μmol/l). In Gallandat-Huet *et al.*,[2] the serum creatinine concentration did not differ significantly between the study groups. Yet it increased slightly in the HES 130 group (96 ± 14 to 109 ± 17 μmol/l), whereas it decreased in the HES 200 control (98 ± 14 to 94 ± 21 μmol/l).

In terms of ARF (n = 701, fig. 3), none of the selected studies showed a significant difference in risk. The pooled risk difference for random effects was 0.0003 (95% CI = −0.018 to 0.019), *P* = 0.98, I^2 = 0% (95% CI = 0–56.3%). We did not find significant differences between HES and control groups for calculated creatinine clearance (n = 344), urea (n = 390), mortality (n = 834), and the need for renal replacement therapy (n = 531) (table 2). Furthermore, there was no significant difference in intensive care unit or hospital length of stay (n = 723 and 940 respectively, table 2).

Discussion

The present meta-analysis on the renal effects of third-generation waxy maize-derived hydroxyethyl starch 130/0.40 shows no evidence for renal impairment caused by this colloidal solution in surgical patients.

Only three of the included studies showed a slight increase in serum creatinine to approximately 124 μmol/l. With respect to calculated creatinine clearance, incidence of ARF and mortality, our results showed no significant differences for HES 130/0.40 and the respective comparators. However, especially data with regard to ARF are limited due to a low number of patients with ARF and different

Table 1. Overview of Studies with Surgery Patients (N = 1,230)

Study, Year	N (Total)	Clinical Setting	Comparator	Most Important Renal Parameter	Creatinine Data (µmol/l)*			
					HES 130		Comparator	
					BL	Worst	BL	Worst
Fenger-Eriksen *et al.*, 2005[49]	11	Spine surgery	Isotonic saline	Serum creatinine	73 (54–89)	71 (64–75)	77 (50–98)	65 (51–72)
Gallandat-Huet *et al.*, 2000[2]	59	Cardiac surgery	HES 200	Serum creatinine	96 ± 14	109 ± 17	98 ± 14	94 ± 21
Godet *et al.*, 2008[33]	65	Vascular surgery	Gelatin solution	Serum creatinine, calculated creatinine clearance	108 ± 29	123 ± 62	111 ± 24	127 ± 62
Hanart *et al.*, 2009[45]	119	Cardiac surgery	Human albumin	Serum creatinine	28 (24–34) (IQR)	27 (22–35) (IQR)	24 (21–28) (IQR)	26.5 (20–32) (IQR)
Harten *et al.*, 2008[46]	29	Abdominal surgery	"Standard care"	Serum creatinine	85 (55–160)	85 (60–150)	100 (70–260)	95 (60–300)
Ickx *et al.*, 2004[47]	40	Abdominal surgery	HES 200	Serum creatinine	93 ± 11	84 ± 17	102 ± 11	90 ± 11
Jover *et al.*, 2009[48]	29	Abdominal laparoscopic surgery	Ringer solution	Calculated creatinine clearance			—	
Kasper *et al.*, 2003[3]	117	Cardiac surgery	HES 200	Serum creatinine	80 ± 18	88 ± 35	80 ± 18	97 ± 53
Lee *et al.*, 2011[43]	106	Cardiac surgery	Isotonic saline	ARF			—	
Mahmood *et al.*, 2007[36]	62	Vascular surgery	Gelatin solution, HES 200	Serum creatinine	96 ± 1 (SEM)	95 ± 2 (SEM)	101 ± 2 (SEM)	138 ± 24 (SEM)
Mukhtar *et al.*, 2009[50]	40	Liver transplantation	Human albumin	Serum creatinine, calculated creatinine clearance	97 ± 9	133 ± 31	93 ± 18	115 ± 34
Ooi *et al.*, 2009[41]	90	Cardiopulmonary bypass	Gelatin solution	eGFR			—	
Shabazi *et al.*, 2011[42]	70	Cardiopulmonary bypass	Ringer solution	Serum creatinine, calculated creatinine clearance	85 ± 16	111 ± 31	88 ± 13	107 ± 40
Tiryakioglu *et al.*, 2008[38]	140	Cardiopulmonary bypass	Ringer solution	Serum creatinine, Calculated creatinine clearance	97 ± 9	124 ± 21	88 ± 18	97 ± 27
Van der Linden *et al.*, 2005[44]	132	Cardiac surgery	Gelatin solution	Serum creatinine	93 ± 20	88 ± 27	96 ± 26	103 ± 65
Yang *et al.*, 2011[34]	81	Liver surgery	Ringer solution, human albumin	Serum creatinine	78 ± 20	73 ± 22	RL: 77 ± 15HA: 73 ± 11	RL: 71 ± 18HA: 67 ± 16
Yap *et al.*, 2007[37]	40	Cardiopulmonary bypass	Gelatin solution	Serum creatinine	—	96 ± 23	—	118 ± 51

* Values are expressed as mean ± SD or median (range) if not stated differently (IQR = median + interquartile ranges, SEM = standard error of the mean).

ARF = acute renal failure; BL = baseline; eGFR = estimated glomerular filtration rate; G = gelatin; HA = human albumin; HES = hydroxyethyl starch; RL = Ringer´s lactate.

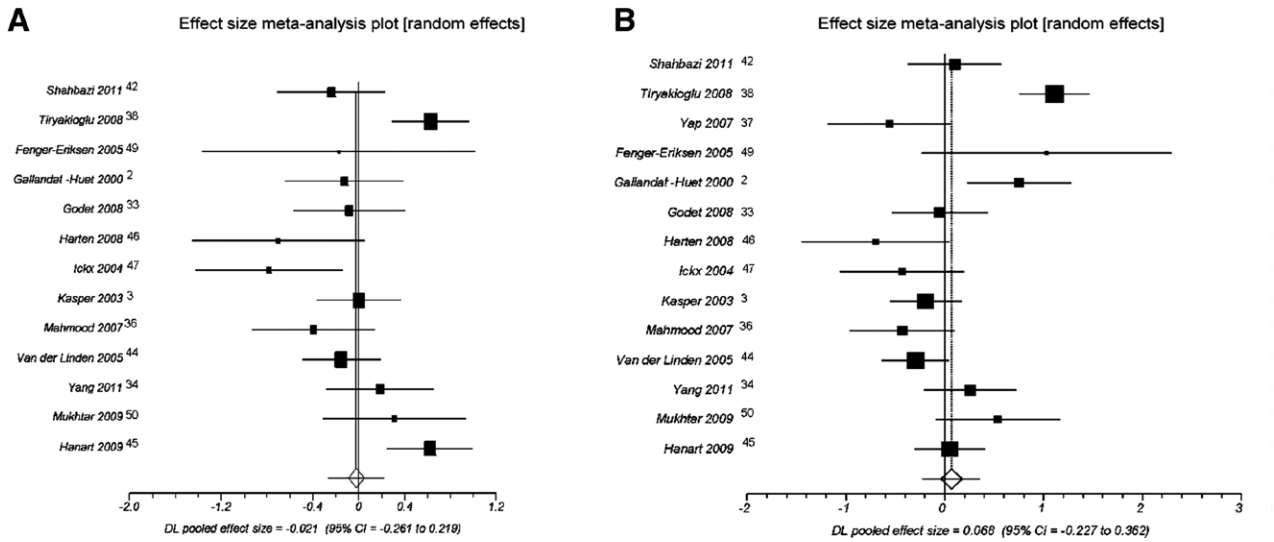


Fig. 2. Surgical patients. (*A*): Serum creatinine baseline values; random effect pooled d+ = –0.021 (95% CI = –0.261 to 0.219), Z (test d+ differs from 0) = –0.172, *P* = 0.86. (*B*): Serum creatinine extreme values; random effects (DerSimonian-Laird), pooled d+ = 0.068, (95% CI = –0.227 to 0.362), Z (test d+ differs from 0) = 0.45, *P* = 0.65. No significant differences were found between extreme values and baseline. d+ effect size = difference; DL = DerSimonian-Laird; FK = Fresenius Kabi; HES = hydroxyethyl starch; N = number of patients.

definitions of ARF among the studies. The results of one study[48] for calculated creatinine clearance indicated a potentially positive effect of waxy maize-derived HES 130/0.40. However, in this study the clearance of the control group corresponding to the worst value for waxy maize-derived HES 130/0.40 was exceptionally low whereas it increased for the HES group. Additionally, the number of patients in this study was very low; it was only 29. Within the last years, several other authors performed meta-analyses or literature reviews on safety aspects of HES. Unfortunately, no analysis so far has provided a stringent and transparent inclusion of the best available data sets about surgical patients only.

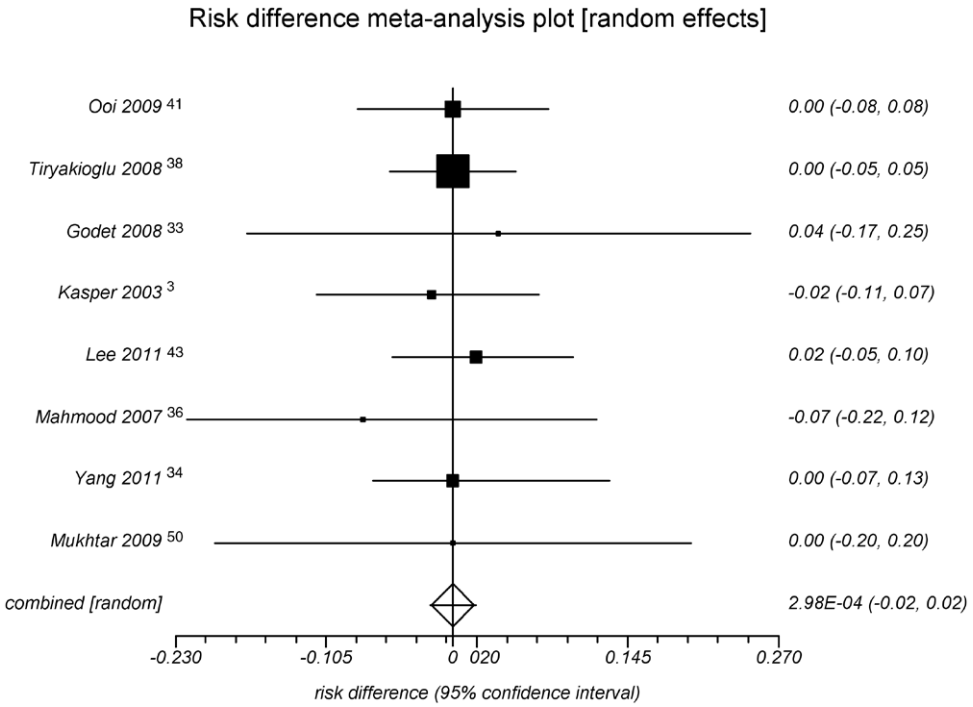


Fig. 3. Risk difference of acute renal failure; random effects (DerSimonian-Laird): Pooled risk difference = 0.000298 (95% CI = –0.018 to 0.019), Chi^2 (test risk difference differs from 0) = 0.000992 (df = 1), *P* = 0.98. No significant risk difference was found. df = degree of freedom.

Table 2. Results of the Meta-analysis

Parameter	Results (Model: Random Effects (DerSimonian-Laird))	
Calculated creatinine clearance (n = 344)	Baseline	Extreme value
	Pooled d+ = 0.302 (95% CI = −0.098 to 0.703)	Pooled d+ =0.783 (95% CI = −0.229 to 1.795)
	Z (test d+ differs from 0) = 1.482; *P* = 0.14	Z (test d+ differs from 0) = 1.517; *P* = 0.13
	I^2 = 67.8% (95% CI = 0% to 85.4)	I^2 = 93.8% (95% CI = 88.9 to 95.9%)
Urea (n = 390)	Baseline	Extreme value
	Pooled d+ = −0.068 (95% CI = −0.371 to 0.236)	Pooled d+ = −0.148 (95% CI = −1.077 to 0.782)
	Z (test d+ differs from 0) = −0.437; *P* = 0.66	Z (test d+ differs from 0) = −0.311; *P* = 0.76
	I^2 = 12.3% (95% CI = 0% to 76.1)	I^2 = 94.3% (95% CI = 90.2 to 96.2%)
Renal replacement therapy (n = 531)	Pooled risk difference = −0.003 (95% CI = −0.028 to 0.022)	
	Chi^2 (test risk difference differs from 0)=0.037 (df=1); *P* = 0.85	
	I^2 = 0% (95% CI = 0 to 58.5%)	
ICU length of stay (n = 723)	Pooled d+ = 0.113 (95% CI = −0.172 to 0.398)	
	Z (test d+ differs from 0) = 0.775; *P* = 0.44	
	I^2 = 80.1% (95% CI = 62.6% to 87.4)	
Hospital length of stay (n = 940)	Pooled d+ = 0.212 (95% CI = −0.035 to 0.46)	
	Z (test d+ differs from 0) = 1.68; *P* = 0.09	
	I^2 = 73.9% (95% CI = 48.1 to 83.9%)	

ICU = intensive care unit.

A very extensive meta-analysis on HES by Dart *et al.*[18] addressed the question of renal safety. Yet, it did not take into account the existence of differences between HES generations and pooled data for all HES preparations, concentrations, and different oncotic properties. It is thus not surprising that this review article—like others before—highlights the negative effects of some very old starches like HES 650. Unfortunately, the authors extend their results to all HES. Additionally, the analysis was dominated by the VISEP trial,[13] in which critically ill patients received a hyperoncotic 10% HES 200/0.5, whereas the vast majority of studies with colloids used isooncotic preparations. Groeneveld *et al.*[19] distinguished between different HES generations. Still this analysis has several limitations: First, the incidence of ARF and the need for renal replacement therapy were the primary outcome. Yet, as discussed before, the definitions of ARF varied largely among studies. Renal replacement therapy is also subject of controversy, because the decision when to start it differs considerably among studies and centers and is generally not defined by the study protocol. Therefore, this specific outcome is highly variable among studies. Second, the included data were incomplete. Notably, three available studies[38,41,50] and several others regarding nonrenal outcomes were not taken into account.

Another recent analysis by Hartog *et al.*[20] also extensively reviewed the literature on HES 130/0.40. However, with regard to renal outcome, the authors considered only a limited number of trials and excluded several others by using criteria that seem to be weakly defined. Most important, data from small trials were classified as "random findings" and, therefore, excluded from the analysis. This seems questionable as the main merit of a meta-analysis or a literature review is its ability to gain evidence from pooling small studies that fulfill basic requirements in study design.

The most recent review article in critically ill patients was published by Gattas *et al.*,[21] and critically it analyzed whether the recent retraction of studies by Boldt[34] substantially changed the evidence concerning clinical use of HES 130/0.40. In fact, the authors found that this was not the case. Gattas *et al.* only considered studies reporting the need for renal replacement therapy and urine output and concluded that there were insufficient data to draw definite conclusions about the renal safety of HES 130/0.40.

Our meta-analysis includes all available randomized controlled trials analyzing waxy maize-derived HES 130/0.40 effects on renal safety in elective surgical patients. We chose serum creatinine as our main outcome as this was available in all studies. Furthermore, monitoring serum creatinine, as well as changes in serum creatinine, has been reported to be a valid and sensitive variable in predicting patient outcome.[25,51] As with all clinical markers, serum creatinine has inherent limitations that might not reflect small but long-term damages that could become relevant after repeated or very high dose administration of HES.

The present meta-analysis includes the comparison of waxy maize-derived HES 130/0.40 to various control solutions, including products that are known as being safe for renal function like crystalloid solutions. For subanalysis of data comparing waxy maize-derived HES 130/0.40 with, for example, crystalloids or specific colloids, the number of patients is too small to draw meaningful conclusions. The estimates of heterogeneity (I^2) between studies may represent substantial heterogeneity, which should be kept in mind when interpreting the data. Given the range of different

settings and comparators analyzed for this meta-analysis, this is not surprising and is a trait that has even been reported even for many Cochrane meta-analyses.

We are also aware that our analysis does not allow the drawing of any conclusions about critically ill patients.

A limitation of any meta-analysis as of ours potentially is sample size and power of the study. Also, not all variables used to assess renal function were available in all the analyzed studies. Furthermore, our findings cannot be extrapolated to the use of hypertonic HES,[52] the use in patients undergoing kidney transplantation[53] even if waxy maize-derived HES is used during the resuscitation of the donors and the recipients.

In summary, our meta-analysis provides evidence that there is currently no verifiable association between the administration of waxy maize-derived HES 130/0.40 and changes of serum creatinine and calculated creatinine clearance or the incidence of ARF in patients undergoing surgical procedures.

References

1. Westphal M, James MF, Kozek-Langenecker S, Stocker R, Guidet B, Van Aken H: Hydroxyethyl starches: Different products–different effects. Anesthesiology 2009; 111:187–202
2. Gallandat Huet RC, Siemons AW, Baus D, van Rooyen-Butijn WT, Haagenaars JA, van Oeveren W, Bepperling F: A novel hydroxyethyl starch (Voluven) for effective perioperative plasma volume substitution in cardiac surgery. Can J Anaesth 2000; 47:1207–15
3. Kasper SM, Meinert P, Kampe S, Görg C, Geisen C, Mehlhorn U, Diefenbach C: Large-dose hydroxyethyl starch 130/0.4 does not increase blood loss and transfusion requirements in coronary artery bypass surgery compared with hydroxyethyl starch 200/0.5 at recommended doses. Anesthesiology 2003; 99:42–7
4. Langeron O, Doelberg M, Ang ET, Bonnet F, Capdevila X, Coriat P: Voluven, a lower substituted novel hydroxyethyl starch (HES 130/0.4), causes fewer effects on coagulation in major orthopedic surgery than HES 200/0.5. Anesth Analg 2001; 92:855–62
5. Gandhi SD, Weiskopf RB, Jungheinrich C, Koorn R, Miller D, Shangraw RE, Prough DS, Baus D, Bepperling F, Warltier DC: Volume replacement therapy during major orthopedic surgery using Voluven (hydroxyethyl starch 130/0.4) or hetastarch. Anesthesiology 2007; 106:1120–7
6. Kozek-Langenecker SA: Benefits of fluid therapy on the hemostatic system of intensive care patients. J Coagul Disorders 2010; 2:41–8
7. Jungheinrich C, Scharpf R, Wargenau M, Bepperling F, Baron JF: The pharmacokinetics and tolerability of an intravenous infusion of the new hydroxyethyl starch 130/0.4 (6%, 500 mL) in mild-to-severe renal impairment. Anesth Analg 2002; 95:544–51
8. Blasco V, Leone M, Antonini F, Geissler A, Albanèse J, Martin C: Comparison of the novel hydroxyethylstarch 130/0.4 and hydroxyethylstarch 200/0.6 in brain-dead donor resuscitation on renal function after transplantation. Br J Anaesth 2008; 100:504–8
9. Reinhart K, Perner A, Sprung CL, Jaeschke R, Schortgen F, Johan Groeneveld AB, Beale R, Hartog CS; European Society of Intensive Care Medicine: Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. Intensive Care Med 2012; 38:368–83
10. Schortgen F, Lacherade JC, Bruneel F, Cattaneo I, Hemery F, Lemaire F, Brochard L: Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: A multicentre randomised study. Lancet 2001; 357:911–6
11. Bayer O, Reinhart K, Sakr Y, Kabisch B, Kohl M, Riedemann NC, Bauer M, Settmacher U, Hekmat K, Hartog CS: Renal effects of synthetic colloids and crystalloids in patients with severe sepsis: A prospective sequential comparison. Crit Care Med 2011; 6:1–8
12. Schortgen F, Girou E, Deye N, Brochard L; CRYCO Study Group: The risk associated with hyperoncotic colloids in patients with shock. Intensive Care Med 2008; 34:2157–68
13. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K; German Competence Network Sepsis (SepNet): Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008; 358:125–39
14. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard AL, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J; 6S Trial Group; Scandinavian Critical Care Trials Group: Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012; 367:124–34
15. Boussekey N, Darmon R, Langlois J, Alfandari S, Devos P, Meybeck A, Chiche A, Georges H, Leroy O: Resuscitation with low volume hydroxyethylstarch 130 kDa/0.4 is not associated with acute kidney injury. Crit Care 2010; 14:R40
16. Guidet B, Martinet O, Boulain T, Philippart F, Poussel JF, Maizel J, Forceville X, Feissel M, Hasselmann M, Heininger A, Van Aken H: Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study. Crit Care 2012; 16:R94
17. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SA; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012; 367:1901–11
18. Dart AB, Mutter TC, Ruth CA, Taback SP: Hydroxyethyl starch (HES) versus other fluid therapies: Effects on kidney function. Cochrane Database Syst Rev 2010; 20:CD007594
19. Groeneveld AB, Navickis RJ, Wilkes MM: Update on the comparative safety of colloids: A systematic review of clinical studies. Ann Surg 2011; 253:470–83
20. Hartog CS, Kohl M, Reinhart K: A systematic review of third-generation hydroxyethyl starch (HES 130/0.4) in resuscitation: Safety not adequately addressed. Anesth Analg 2011; 112:635–45
21. Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S; CHEST Management Committee: Fluid resuscitation with 6% hydroxyethyl starch (130/0.4) in acutely ill patients: An updated systematic review and meta-analysis. Anesth Analg 2012; 114:159–69
22. Jamnicki M, Zollinger A, Seifert B, Popovic D, Pasch T, Spahn DR: The effect of potato starch derived and corn starch derived hydroxyethyl starch on in vitro blood coagulation. Anaesthesia 1998; 53:638–44
23. Lehmann G, Marx G, Förster H: Bioequivalence comparison between hydroxyethyl starch 130/0.42/6: 1 and hydroxyethyl starch 130/0.4/9: 1. Drugs R D 2007; 8:229–40
24. Sommermeyer K, Cehc F, Schossow R: Differences in chemical structures between waxy maize- and potato starch-based hydroxyethyl starch volume therapeutics. Transfus Altern Transfus Med 2007; 9:127–33

25. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup: 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:R204–12
26. Wieland LS, Robinson KA, Dickersin K: Understanding why evidence from randomised clinical trials may not be retrieved from Medline: comparison of indexed and non-indexed records. BMJ 2012; 344:d7501
27. van der Linden P, Gazdzik TS, Jahoda D, Heylen RJ, Skowronski JC, Pellar D, Kofranek I, Górecki AZ, Fagrell B, Keipert PE, Hardiman YJ, Levy H; 6090 Study Investigators: A double-blind, randomized, multicenter study of MP4OX for treatment of perioperative hypotension in patients undergoing primary hip arthroplasty under spinal anesthesia. Anesth Analg 2011; 112:759–73
28. Olofsson CI, Górecki AZ, Dirksen R, Kofranek I, Majewski JA, Mazurkiewicz T, Jahoda D, Fagrell B, Keipert PE, Hardiman YJ, Levy H; Study 6084 Clinical Investigators: Evaluation of MP4OX for prevention of perioperative hypotension in patients undergoing primary hip arthroplasty with spinal anesthesia: A randomized, double-blind, multicenter study. Anesthesiology 2011; 114:1048–63
29. Base EM, Standl T, Lassnigg A, Skhirtladze K, Jungheinrich C, Gayko D, Hiesmayr M: Efficacy and safety of hydroxyethyl starch 6% 130/0.4 in a balanced electrolyte solution (Volulyte) during cardiac surgery. J Cardiothorac Vasc Anesth 2011; 25:407–14
30. Kulla M, Weidhase R, Lampl L: Hydroxyethyl starch 6% 130/0.42 in acetate-buffered Ringer's solution as a part of a balanced-volume resuscitation in abdominal surgery. Anästh Intensivmed 2008; 49:7–18
31. Wu Y, Wu AS, Wang J, Tian M, Jia XY, Rui Y, Yue Y: Effects of the novel 6% hydroxyethyl starch 130/0.4 on renal function of recipients in living-related kidney transplantation. Chin Med J 2010; 123:3079–83
32. Boldt J, Lehmann A, Römpert R, Haisch G, Isgro F: Volume therapy with a new hydroxyethyl starch solution in cardiac surgical patients before cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2000; 14:264–8
33. Godet G, Lehot JJ, 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
34. Yang J, Wang WT, Yan LN, Xu MQ, Yang JY: Alternatives to albumin administration in hepatocellular carcinoma patients undergoing hepatectomy: An open, randomized clinical trial of efficacy and safety. Chin Med J 2011; 124:1458–64
35. Hozo SP, Djulbegovic B, Hozo I: Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5:13
36. 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
37. Yap WW, Young D, Pathi V: Effects of gelatine and medium molecular weight starch as priming fluid in cardiopulmonary bypass–a randomised controlled trial. Perfusion 2007; 22:57–61
38. Tiryakioglu O, Yildiz G, Vural H, Goncu T, Ozyazicioglu A, Yavuz S: Hydroxyethyl starch versus Ringer solution in cardiopulmonary bypass prime solutions (a randomized controlled trial). J Cardiothorac Surg 2008; 3:45
39. Hedges LV, Olkin I: Statistical methods for meta-analysis. London, Academic Press, 1985
40. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21:1539–58
41. 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
42. Shahbazi S, Zeighami D, Allahyary E, Alipour A, Esmaeeli MJ, Ghanele M: Effect of colloid versus crystalloid administration of cardiopulmonary bypass prime solution on tissue and organ perfusion. Iran Cardiovasc Res J 2011; 5:24–31
43. 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
44. Van der Linden PJ, De Hert SG, Deraedt D, Cromheecke S, De Decker K, De Paep R, Rodrigus I, Daper A, Trenchant A: Hydroxyethyl starch 130/0.4 versus modified fluid gelatin for volume expansion in cardiac surgery patients: The effects on perioperative bleeding and transfusion needs. Anesth Analg 2005; 101:629–34, table of contents
45. Hanart C, Khalife M, De Villé A, Otte F, De Hert S, Van der Linden P: Perioperative volume replacement in children undergoing cardiac surgery: Albumin versus hydroxyethyl starch 130/0.4. Crit Care Med 2009; 37:696–701
46. Harten J, Crozier JE, McCreath B, Hay A, McMillan DC, McArdle CS, Kinsella J: Effect of intraoperative fluid optimisation on renal function in patients undergoing emergency abdominal surgery: A randomised controlled pilot study (ISRCTN 11799696). Int J Surg 2008; 6:197–204
47. Ickx BE, Bepperling F, Melot C, Schulman C, Van der Linden PJ: Plasma substitution effects of a new hydroxyethyl starch HES 130/0.4 compared with HES 200/0.5 during and after extended acute normovolaemic haemodilution. Br J Anaesth 2003; 91:196–202
48. Jover JL, García JP, Martínez C, Espí A, Gregori E, Almagro J: [Hydroxyethyl starch to protect renal function in laparoscopic surgery]. Rev Esp Anestesiol Reanim 2009; 56:27–30
49. Fenger-Eriksen C, Hartig Rasmussen C, Kappel Jensen T, Anker-Møller E, Heslop J, Frøkiaer J, Tønnesen E: Renal effects of hypotensive anaesthesia in combination with acute normovolaemic haemodilution with hydroxyethyl starch 130/0.4 or isotonic saline. Acta Anaesthesiol Scand 2005; 49:969–74
50. Mukhtar A, Aboulfetouh F, Obayah G, Salah M, Emam M, Khater Y, Akram R, Hoballah A, Bahaa M, Elmeteini M, Hamza A: The safety of modern hydroxyethyl starch in living donor liver transplantation: A comparison with human albumin. Anesth Analg 2009; 109:924–30
51. Kim KE, Onesti G, Ramirez O, Brest AN, Swartz C: Creatinine clearance in renal disease. A reappraisal. Br Med J 1969; 4:11–4
52. Kerbaul F, Rondelet B, Bénas V, Grisoli D, De Waroquier A, Fesler P, Fusai T, Brimioulle S: Hypertonic saline hydroxyethylstarch restores right ventricular-arterial coupling after normovolemic hemodilution in piglets. Anesthesiology 2011; 115:136–43
53. Cittanova ML, Leblanc I, Legendre C, Mouquet C, Riou B, Coriat P: Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. Lancet 1996; 348:1620–2