

Mashed Potatoes and Maize

Are the Starches Safe?

IN 1831 during the European cholera epidemic, Latta¹ 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, Hogan² 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.

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



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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

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 “tetra starch”). 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 tetra starches are derived from two sources. The raw material

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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 2008⁴ 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

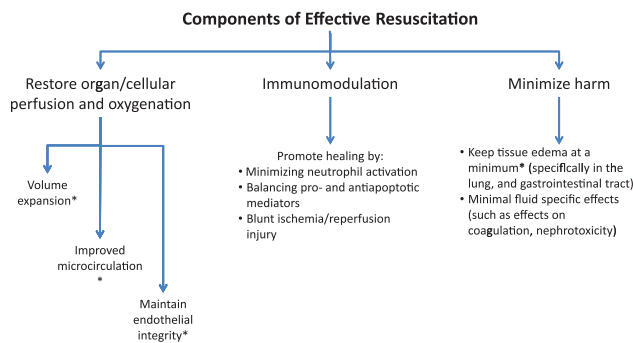


Fig. 1. Goals of effective resuscitation. A *star* indicates potential advantages of colloids over crystalloids from a conceptual point of view. However, dedicated outcome trials need to confirm these findings in entity-based collectives of patients.

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. Hogan² 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.

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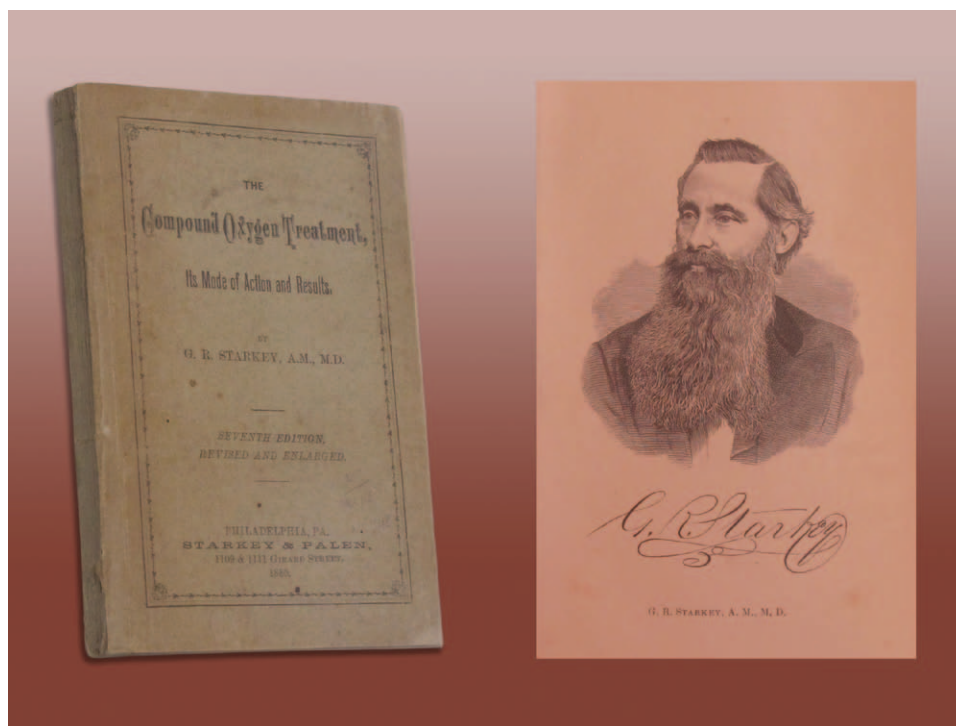
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Starkey's Compound Oxygen as a Hygienic for Ailments Chronic



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. (Copyright © the American Society of Anesthesiologists, Inc.)

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