TWENTY-FIVE YEARS ago, an eye-catching double-page advertisement ran in medical journals, trumpeting that “Albumin & PPF* are no safer or more effective than Hespan (hetastarch)... they’re simply double the price.” Messages like this promoting Hespan and other 6 percent hydroxyethyl starch products strongly resonated at that time with hospitals eager to take advantage of a relatively cheap resuscitative colloid solution available in essentially unlimited supply.

Decades and millions of infusions later, a surge of recent evidence from well-designed prospective trials and meta-analyses has swept away the presumption that starch products, including Hespan, Hextend and Voluven, are safe in critically ill patients who require volume resuscitation. Clinical specialists and drug regulators are now left to ponder the missteps that led to untold numbers of serious complications and deaths over so many years. But, in essence, it boils down to

* Plasma protein fraction (a human plasma-based product in which albumin accounts for about 88 percent of total protein content)
a failure at the outset to ask the right questions and demand answers.

**Not Looked For, Not Found**

Hespan, a synthetic maize-derived starch product featuring high molecular weight and molar substitution ratios (450/0.7), was licensed in 1972 for “treatment of hypovolemia when plasma volume expansion is desired.” Hespan was promoted as an effective, lower-cost alternative to human albumin. The U.S. Food and Drug Administration (FDA) approved the product based on a handful of very small clinical studies, conducted in a variety of treatment settings, comparing it to albumin; unsurprisingly, no differences in safety or efficacy were detected in these underpowered trials.

By the 1990s, numerous reports had described adverse effects of Hespan and other starches on coagulation function. Yet, curiously, in the absence of any large-scale clinical studies to assess its safety, roughly one-half of starch products purchased in the U.S. were being administered in lieu of human albumin or crystalloids to patients undergoing cardiopulmonary bypass (CPB) surgeries — a surgical population at particularly high risk for surgical bleeding complications.1

Finally in 2002, several published look-back studies2-4 documenting excessive hemorrhage in CPB surgery patients switched to starch from albumin were brought to the attention of the FDA.5 A year later, the FDA added specific warnings against use of licensed starch products in this surgical population. A very recent meta-analysis of 18 small clinical trials confirmed that, compared with albumin, starch-based colloids increased postoperative bleeding by 33.3 percent, increased red blood cell transfusions by 28.4 percent, and more than doubled the risk of reoperation; all findings were highly significant.6

**Newer Starch Product, Same Old Toxicities**

Tinkering with starch crosslinking chemistry to try to reduce its effects on coagulation function, several manufacturers came up with starch solutions featuring a lower mean molecular weight and reduced molar substitution ratios. In particular, 200/0.4-0.5 (pentastarch) and 130/0.38-0.45 products are thought to interfere less with coagulation function than the older 450/0.7 products, including Hespan and Hextend. These and other synthetic colloids have significantly displaced the use of albumin in European intensive care settings.

By 2007, a 130/0.4 starch product (Voluven) was approved in the U.S. with a very broad indication — “treatment and prophylaxis of hypovolemia” — and an adult dosage limit two-and-one-half times higher than Hespan or Hextend. The basis for that approval included a U.S. elective orthopedic surgery study randomizing just 100 patients to Voluven or conventional 450/0.7 starch, and three small non-U.S. studies evaluating Voluven against pentastarch products not licensed for use in the U.S. for treatment of hypovolemia.7 Estimated blood loss was not different between Voluven and older starch groups in the U.S. trial. But, inexplicably, the study design permitted doses exceeding 3,000 mL — twice the recommended dose limit for Hespan and other 450/0.7 starch products. Unsurprisingly, three cases of serious coagulopathy occurred in the 450/0.7 arm.

One might question why the pivotal U.S. licensing study evaluated Voluven against Hespan at upper dosage limits far above the 1,500 mL recommended limit in the Hespan labeling and known to induce coagulopathy. Or why, given the investigators’ interest in testing Voluven at doses up to 3,500 mL for a 70 kg adult, regulators did not insist on a comparison against 5% human albumin, the body’s natural circulating colloid that, of course, is not coagulopathic (apart from a dilutional effect) at any dose.

Fortunately, not one but two well-designed and adequately powered trials published last year finally put Voluven and its class of 130/0.4 starch products to the test. The Crystalloid Versus Hydroxyethyl Starch Trials (CHEST) in Australia and New Zealand randomized a heterogeneous mix of 7,000 intensive care unit (ICU) patients to receive fluid resuscitation with Voluven or saline.6 The relative risk (RR) of requiring renal replacement therapy (RRT) was 1.21 in the Voluven arm versus the saline control arm; serum creatinine was persistently elevated, implying a progressive

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**INDUSTRY INSIGHT**

Renal function impairment appears to be associated with starches of varying molecular weights, plainly implying a class effect.

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**450 refers to a mean molecular size of 450 kD, and 0.7 refers to molar substitution (the percentage of hydroxyethyl groups substituted per glucose monomer)**
reduction in creatinine clearance and more severe acute kidney injury. Remarkably, these findings occurred in the context of a massive study in which a mean of just 526 mL and 626 mL of Voluven and saline were respectively administered in the first four days.

A more tightly focused Scandinavian 6S trial randomized 798 patients with severe sepsis to receive either a 130/0.4 starch product or Ringer’s acetate. At 90 days, 51 percent of those assigned to starch had died, as compared with 43 percent of those assigned to Ringer’s (RR, 1.17; P = 0.03). Starch administration was also associated with significantly increased risk of RRT and a strong trend toward increased severe bleeding risk (Table 1).

This same group’s meta-analysis of studies of 130/0.4 starches used in sepsis, published earlier this year, confirmed its findings. In a predefined analysis of five trials with low risk of bias, the risk of requiring RRT was higher in the starch group (RR, 1.36; P = 0.009), as were risks of needing red blood cell transfusion and experiencing serious adverse events.

Yet another systematic review and meta-analysis published this year documented increased risks of renal complications and mortality associated with administration of a spectrum of starch products in critically ill patients (Table 2). The authors carefully excluded a number of discredited studies by German anesthesiologist Dr. Joachim Boldt, who for years was a tireless proponent of newer-generation starch solutions. Much of this man’s prolific body of starch-related clinical research was retracted in 2011 after the discovery of systematic scientific misconduct.

Renal function impairment appears to be associated with starches of varying molecular weights, plainly implying a class effect. Both higher and lower molecular weight 130/0.4 starches are taken up and stored in cells throughout the body. It tends to concentrate in the kidneys, which is thought to be a factor in the increased risk of acute kidney injury versus crystalloids.

### Table 1. Key Clinical Outcomes in a Trial Comparing 130/0.4 Hydroxyethyl Starch (HES) and Ringer’s Acetate in 798 Subjects with Severe Sepsis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>130/0.4 HES (N = 398)</th>
<th>Ringer’s Acetate (N = 400)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead at day 90 (%)</td>
<td>201 (51%)</td>
<td>172 (43%)</td>
<td>1.17 (1.01-1.36)</td>
<td>0.03</td>
</tr>
<tr>
<td>Severe bleeding</td>
<td>38 (10%)</td>
<td>25 (6%)</td>
<td>1.52 (0.94-2.48)</td>
<td>0.09</td>
</tr>
<tr>
<td>Use of renal replacement therapy</td>
<td>87 (22%)</td>
<td>65 (16%)</td>
<td>1.35 (1.01-1.80)</td>
<td>0.04</td>
</tr>
</tbody>
</table>


### Table 2. Findings from a Meta-Analysis of Studies Comparing Hydroxyethyl Starch (HES) to Crystalloids, Albumin or Gelatin in Critically Ill Patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trials</th>
<th>Patients</th>
<th>Risk Ratios all Favoring Control Fluid Over HES</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>28</td>
<td>10,290</td>
<td>1.09</td>
<td>1.02 to 1.17</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>5</td>
<td>8,725</td>
<td>1.27</td>
<td>1.09 to 1.47</td>
</tr>
<tr>
<td>Use of renal replacement therapy</td>
<td>10</td>
<td>9,258</td>
<td>1.32</td>
<td>1.15 to 1.50</td>
</tr>
<tr>
<td>Red cell transfusion</td>
<td>5</td>
<td>1,482</td>
<td>1.42</td>
<td>1.15 to 1.75</td>
</tr>
</tbody>
</table>

**Albunin Resuscitation for Sepsis: A Closer Look**

Some favor colloid solutions in sepsis resuscitation for their ability to obtain rapid and lasting circulatory stabilization. Many others prefer use of crystalloids, arguing that evidence for superiority of more costly colloids is lacking. Results from the landmark 2004 Saline Versus Albumin Fluid Evaluation (SAFE) trial would appear to support the former fluid choice. In a subset of 1,218 ICU severely septic patients randomized to albumin or saline, a strong mortality trend favored albumin (RR, 0.87; P=0.07). At that time, it was pointed out that if this finding is robust, more than one of every 10 lives of septic ICU patients now lost could be saved simply by resuscitating them with 5% albumin instead of saline.14

Seven years later, the SAFE investigators decided to take a closer look at their findings. Conducting multivariate regression analysis adjusting for baseline factors in 919 patients with complete baseline data, the adjusted odds ratio for death for albumin versus saline was 0.71 (95% confidence interval, 0.52-0.97; P = 0.03).15

This mortality difference favoring albumin should not come as a surprise. A landmark Spanish trial more than 10 years ago found that plasma volume expansion with albumin in addition to antibiotic treatment yielded a nearly three-fold lower in-hospital death rate than antibiotic alone (10 percent versus 29 percent; P = 0.01) in patients with cirrhosis and spontaneous bacterial peritonitis (SBP). Closely matching this was a dramatic renal protective effect: 10 percent in the albumin arm suffered renal impairment versus 33 percent of patients in the antibiotic-only arm.16 The investigators pointed out that cirrhosis with SBP has many features of the sepsis syndrome; albumin may be protecting kidneys by enhancing circulatory function. But they also suggested that the beneficial effects of this multifunctional protein could involve other mechanisms as well, such as inhibition of apoptosis and scavenging of reactive oxygen species.13

**Colloids and Crystalloids: Time to Think Anew**

For resuscitation of patients with sepsis, the verdict is in: Hydroxyethyl starch products increase the risk of acute kidney injury and death. A logical question that follows is whether operative patients at meaningful risk for developing sepsis should be administered a starch product when the physician decides that colloid resuscitation is appropriate.

At last, well-designed and adequately powered clinical trials are revealing why resuscitative fluids—including crystalloids—should be thought of as drugs. Today, for critical care patients in particular, the fluid chosen for a specific patient can and should be the one for which the best available evidence points to the most benefit and the least harm.

If albumin is the resuscitative fluid you prefer for some patients, you may also appreciate knowing that frustrating supply shortages and pricing instability are things of the distant past. Since the late 1990s, a dramatic expansion in plasma supply and processing capacity—driven by surging demand for intravenous immunoglobulin—has created a structural, long-term surplus capacity to produce 5% and 25% albumin. The inflation-adjusted price of albumin has fallen by nearly one-half since the mid-1990s, and has consistently remained in good supply for more than a decade.1

It may be worthwhile to have a conversation with your critical care pharmacist about your resuscitative fluid strategy, as a wealth of important new information invites us all to think anew about the age-old colloid-crystalloid debate.

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**References**


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