

daily dose" or "safe recommended dose" as some have erroneously argued.

For most of the starches, and certainly for hydroxyethyl starch 670/0.75 (Hextend®) and hydroxyethyl starch 600/0.7 (Hespan®, B. Braun Medical Inc., Irvine, CA), it is impossible to designate any safe maximum dose. No dose-finding randomized trials (or observational studies) have ever been done that demonstrate that 20 ml/kg is "safe" but 21 ml/kg causes a clinically significant worse outcome. Observational studies are very confounded in this setting because patients who receive larger volumes of these starches invariably have more extensive surgery and/or bleeding or may require more blood and blood products. Therefore, in the absence of data from well-designed randomized trials, it is impossible to know whether the larger volume of starch is a cause of bleeding or a marker for more complex surgeries with an expected increased blood loss. Multivariate analysis is an imperfect science and cannot control for this level of confounding. *In vitro* studies, which assess the impact of dose *via* increases in percent hemodilution, cannot be used to define a clinical "maximum safe dose." Finally, it is possible that even if larger doses have theoretical effects on bleeding risk, these effects may be balanced by theoretical benefits of starch related to decreased tissue edema.

In summary, we are not arguing that there is not a provable maximum safe dose for some of these fluids. However, based on existing data, it is impossible at this time to cite a maximum daily dose for some of these fluids, as has been published.^{1,2}

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In Reply:

The intention of our review article was to describe pharmacologically and clinically important differences of hydroxyethyl starch (HES) products.¹ We appreciate the interest in this article and take the opportunity to comment on the points raised in the letters.

In 2007, the Sepsis Occurrence in Acutely Ill Patients study group, with Dr. Reinhart as coauthor, reported that the use of HES had no influence on renal function or the need for renal replacement therapy in critically ill patients.² After the publication of the Volume Substitution and Insulin

Therapy in Severe Sepsis trial,³ which failed its coprimary endpoints, that is, differences in the rate of death at 28 days and the mean score for organ failure, Dr. Reinhart and associates have vigorously argued against the use of HES. They repeatedly and polemically stated that all HES types are the same.^{4,5} This claim may reflect flaws in the Volume Substitution and Insulin Therapy in Severe Sepsis study design and considerable protocol violations that accounted for renal dysfunction and death of 26 patients treated with a hyperoncotic pentastarch solution. To date, the authors of the Volume Substitution and Insulin Therapy in Severe Sepsis trial have not provided a pharmacologic justification why HES 200/0.5 (10%), with known accumulation in the plasma and tissue was used, although the more modern and more rapidly metabolizable HES 130/0.4 (6%) was available since 1999. In this context, it is especially noteworthy that acute kidney injury after administration of hyperoncotic colloids had repeatedly been shown before.^{6–9}

Although Reinhart *et al.* refer to the importance of cumulative doses of starches, they refrain from quantitative pharmacologic considerations. For example, kidney storage after 52 days in the cited rat model amounted to 0.019% of the given cumulative dose of 12,600 mg/kg, merely reflecting continued renal excretion and amounting to 2.4 mg/kg body weight HES substance in the organ, a small proportion of the total dose given, which can hardly be interpreted as relevant accumulation.¹⁰ Hagne *et al.*¹¹ describe a case report of a patient who received repetitive HES infusions, although suffering from dialysis-dependent renal failure, which is a well-documented contraindication for HES. In the study cited for coagulopathy,¹² and in another trial,¹³ chest tube drainage was not higher after HES 130/0.4 than after albumin (means: 895 *vs.* 990 ml, *P* = 0.98). Data reporting less blood loss and transfusion needs after HES 130/0.4 compared with HES 200/0.5^{14–16} have been ignored.

Although pruritus is a known side effect of all HES preparations, it is strongly dependent on dose and storage characteristics.^{17,18} Notably, the patient referred to in the case report¹⁹ received a cumulative dose of 1.2 kg of different HES types. The liver trauma animal experiment of Zaar *et al.*²⁰ is cited and interpreted incorrectly. The HES animals were not lost before the end of the experiment but were followed up longer than Ringer's lactate animals. Fixed doses of crystalloid *versus* colloid were applied in the early phase, with expectedly stronger hemodilution and higher mean arterial pressures in the colloid group, and with consecutive larger bleeding in the colloid group. In the setting of uncontrolled hemorrhage, however, higher mean arterial pressure values are not necessarily beneficial, even when using crystalloids only.²¹ In the isolated kidney model of Hüter *et al.*,²² the authors reported significant differences of HES 200/0.5 (10%) and HES 130/0.4 (6%), showing a more proinflammatory effect of HES 200/0.5 and less tubular damage for both Ringer's lactate and HES 130/0.4 (6%) compared with HES 200/0.5 (10%).

The documentation of Food and Drug Administration approval has been cited selectively. In fact, the Food and

Drug Administration concluded that compared with hetastarch, HES 130/0.4 (6%) was similarly effective but associated with less side effects, for example, fewer bleeding events. Importantly, no safety signal for worsening renal function was apparent.*

In the retrospective analysis of Schabinski *et al.*,²³ it was shown that a change of a predominantly HES 130/0.4 (6%)-based volume therapy to a predominantly gelatin-based therapy did not change the rate of renal failure of renal replacement therapy. For both colloids, there was a similar association of high cumulative amounts with renal events, which by no means can be interpreted as proof of causation, especially because of the lack of an explanatory mechanism for gelatin. Ongoing large studies with third-generation starches in critically ill patients† will hopefully settle these areas of disagreement.

We thank Dr. Bennett-Guerrero *et al.* for their letter, which allows some further clarification regarding the complex topic of maximum doses of starches, beyond the restricted possibilities of a table. For hetastarch, regulatorily approved maximum doses by health authorities in Europe have always been restricted to 20 ml/kg.‡ U.S. Food and Drug Administration-labeled texts for hetastarches including Hextend (Hospira Inc., Lake Forest, IL) are less strict, but the dosage recommendation§ is usually 500–1000 ml, and volumes in excess of 1,500 ml/day have been used where severe blood loss has occurred, although generally only in conjunction with the administration of blood and blood products and with a reference to warnings in the patient information. Because there is no adequate high-dose study available for Hextend, we regard this as confirmation that 20 ml/kg should not be exceeded without a good reason. In the absence of a regulatory limit, this could be a pragmatic medical definition of “maximum dose” for the clinician. Given the 20–30 times lower clearance and consecutive plasma accumulation of hetastarch, including Hextend, in comparison with HES 130/0.4,²⁴ we see no good reason to recommend higher Hextend doses. However, we agree that the exact value of approved maximum doses may be somewhat arbitrary and is clearly dependent on individual drug history. Despite potential side effects and disadvantages when compared with third-generation starches,^{25,26} there is no approved maximum dose for gelatins. For newer starch products, such as HES 130/0.4 (6%), regulatorily approved maximum doses (*i.e.*, up to 50 ml/kg) are based on clinical data. Doses higher than these approved maximum doses (70

ml/kg for several days) have already been used successfully in a study of patients with cerebral trauma.²⁷

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† NCT00464204 (CRYSTMAS), NCT00935168 (CHEST). <http://clinicaltrials.gov>. Accessed October 7, 2009.

‡ SmPC Hextend. <http://www.hospira.com/Files/Hextend-PI.pdf>. Accessed October 7, 2009.

§ FI Plasmasteril. <http://ch.oddb.org/de/gcc/resolve/pointer/!fachinfo,437>. Accessed October 7, 2009.

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The Evidence Shows That Allogeneic Transfusion Is Associated with Reduced Survival after Coronary Artery Bypass Surgery

To the Editor:

Beginning with the 2002 landmark publication by Engoren *et al.* on the effect of transfusion on survival after cardiac surgery, multiple investigators have shown an association between transfusion and adverse events including short- and long-term mortality.¹⁻⁷ All these studies included larger numbers of patients than in the study by Weightman *et al.* in *ANESTHESIOLOGY*. This large body of studies is remarkably consistent in the finding that transfusion in a dose-dependent manner confers an increased risk of short- and long-term mortality in cardiac surgery. Contrary to these earlier findings, the recent study by Weightman *et al.*⁸ concludes by stating “Patients who have undergone coronary artery sur-

gery and who have received moderate amounts of blood . . . should be reassured that they are unlikely to experience a reduction in long-term survival.” This statement reaches far beyond what the data in their study show.

How should we interpret the findings of Weightman *et al.* in the context of the previously published evidence? In a variety of well-designed, although nonrandomized, studies, tallying more than 30,000 cardiac surgery patients, there is a consistent “hazard signal” regarding the effect of erythrocyte transfusion on short- and long-term outcomes in cardiac surgery. None of the previously published evidence suggests that erythrocyte transfusion is either safe or effective therapy for anemia in patients undergoing cardiothoracic surgery. One possible explanation offered by the author is that previous studies failed to include preoperative anemia as a mortality risk factor in their analysis. Preoperative anemia is a marker for transfusion; it may also independently predict reduced long-term survival in patients with coronary artery disease.⁹ However, it is highly unlikely that decreased short- and long-term survival in transfused cardiothoracic surgery patients simply reflect the risk of preexisting anemia.

Examination of the data of Weightman *et al.* suggests a number of serious limitations. The data are stratified into four groups based on the number of units transfused: no transfusion, 1–2 units, 3–6 units, and >6 units. Stratification severely dilutes the conclusions and leads to a type II error. Furthermore, the 95% confidence limits for the point estimates for the groups receiving 1–2 units or 3–6 units are very wide and only powered to exclude hazard rates greater than 40%; the possibility of a hazard rate less than 40% may have been falsely rejected. This is a significant limitation to this study given the size of earlier studies and should limit the breadth of any conclusions. As Weightman *et al.* state, this study was inadequately powered.

Plasma, platelet, and cryoprecipitate units transfused were included in the data in equal weight to erythrocyte transfusions. This confounds the analysis and is different from any previous study. It is unlikely that the short-term or any long-term consequences of platelet transfusion, and especially transfusion of acellular blood components such as plasma and cryoprecipitate, will be identical to that of erythrocytes. These products should not have been included in the analysis.

The authors state that “There were 250 subjects who died during follow-up who did not have a history of malignant disease at the time of surgery, comprising 77 subjects in group 1 and 183 in the transfused groups.” Because this total is 260 rather than 250, one or both of these numbers is incorrect. (The total number of deaths stated elsewhere in the article is 266. The number of deaths occurring in patients who reported a history of malignancy before surgery and subsequently died during the follow-up is stated to be 16, leaving 250 deaths in patients without a history of malignancy, not 260).

Finally, there is the influence of new malignant conditions on the cumulative hazard of mortality by (the) transfu-