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EDITORIAL

Is the literature inconclusive about the harm from HES? Yes

Christian Ertmer[1*], Djillali Annane[2] and Philippe Van Der Linden[3]

One major burden of modern intensive care medicine is the so-called negative trial disease [1]. Many promising new interventions in animal models of critical illness and in phase II/III trials were killed off by large pragmatic phase III trials (randomized controlled trials, RCTs). One of the reasons for this dilemma may be a lack of consensus and standardization, and thus a large variability, in the very basic therapy approaches to critically ill patients. In this context, physicians have struggled with the indication, amount, and choice of fluids for resuscitation since the time of the great cholera epidemic of the nineteenth century, when Thomas Latta pioneered modern fluid therapy as he infused fluids to a hypovolemic, somnolent women who—"after six pints of fluid"—"began to glow with returning animation" [2]. Since this birth of intravenous fluid therapy it has been argued that it "affords wonderful temporary relief but no permanent benefit" [3] and "effusion from the exhalent vessels" will accrue [4]. Who would have thought that 185 years later we still struggle with exactly these issues!

Although there is still no consensus when to start and stop fluid therapy, how to guide it, and how much to give, most if not all previous trials specifically addressed only the issue of the type of fluid to be used. Most of these studies compared crystalloids with colloids or albumin with synthetic colloids in shock or perioperative patients. Hydroxyethyl starch (HES) solutions have been investigated in many of these studies. Notably, there are a broad variety of HES solutions depending on molecular weights, molar substitutions, raw materials (waxy maize vs potato starch), and parent solutions (balanced vs saline-based) [5]. Likewise, trials of fluid therapy had very different designs. To understand shortcomings in the design of most of these trials, the rationale for fluid therapy in shock states needs to be considered.

In the initial phase of hypovolemic shock states, immediate fluid therapy is life-saving. This has never been formally proven in RCTs, but is globally recognized as a fact. However, the total amount of fluids given and the positive fluid balance throughout the intensive care unit stay may be associated with morbidity and mortality. In fact, early positive fluid balance (first 24 h) may be associated with improved survival, whereas later on in the critical illness course, positive fluid balance may correlate with mortality [6]. These findings are in line with the "golden hour" concept in trauma and with the recently published "four phases" model of fluid resuscitation [7]. In this model, the "rescue" and "optimization" phases are characterized by a positive fluid balance and the subsequent "stabilization" and "de-escalation" phases are characterized by even or negative fluid balance, respectively. Thus, timing is of paramount importance for the response to fluid therapy and its effects on outcome.

Recent trials on HES in intensive care medicine (i.e., VISEP, 6S, CHEST) lacked a rational protocol for fluid therapy [8–10]. Indications for fluid resuscitation included either the clinical judgment of the physician in charge or poorly reliable static hemodynamic parameters, e.g., central venous pressure. In these trials, experimental fluids were given for periods ranging from 21 to 90 days and patients could be enrolled as much as 24 h after the onset of severe sepsis (in 6S and VISEP) [8, 9]. The rescue and optimization phases were already likely completed by time of randomization in these trials. Accordingly, observed global hemodynamic data in the trials suggested hemodynamic stability with adequate mean arterial pressure, low lactate levels, etc. None of

*Correspondence: ertmer@anit.uni-muenster.de
[1] Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital of Muenster, Albert-Schweitzer-Campus 1, Bld. A1, 48149 Muenster, Germany
Full author information is available at the end of the article

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these trials reported on peripheral perfusion, microcirculation, or dynamic preload markers. Therefore, it is reasonable to assume that in a non-negligible fraction of patients, fluids were given in the absence of formal indication. In this situation, the likelihood for harm is greater than that of benefit. The volume effect of HES solutions is likely greater than the volume effect of crystalloids, even in the setting of severe capillary leakage [11]. Thus, the harm associated with inadequate infusion may be higher for HES than for crystalloids. The large RCTs may therefore indicate that the signal of harm from HES is a result of merely inadequate use of the substance. This is especially the case of the VISEP study, where very high amounts (quite above the recommended dose) of hyperoncotic pentastarch were used [8].

The only large study which investigated the effects of therapy with crystalloids versus colloids in the initial rescue and optimization phases was the recently published CRISTAL trial [12]. In this study patients were included very early in the disease process, when arterial hypotension, hypovolemia, and tissue perfusion abnormalities were still present. Notably, in this study HES was given only on ICU days 0–2 in most of the patients, and the median cumulative amount of HES over 7 days was only 1500 mL. These findings suggest that the CRISTAL protocol was more likely to reflect "rational" fluid therapy than the former trials. The lack of difference in 28-day mortality (primary endpoint) and the significantly lower 90-day mortality in the colloid group suggest that there was no harm but (if anything) a small benefit associated with the early use of low doses of colloids.

Whereas the timing of fluid therapy is intrinsically complex in intensive care medicine, where organ failure and microcirculatory compromise often precede overt hemodynamic shock signs, it is less complex in the perioperative setting where the insult usually starts with the onset of surgery. Notably, none of perioperative fluid trials with modern HES solutions (mainly waxy maize-based 6 % HES 130/0.4) showed clinically relevant harm. In practice, several meta-analyses confirmed the safety of HES solutions with regard to renal function and other adverse outcomes in the perioperative setting [13–17]. However, further studies are required to confirm long-term safety of modern HES solutions, e.g., long-term renal outcome.

In summary, the design of fluid trials in critically ill patients did not rely on a convincing underlying pathophysiologic concept. Then, the true finding from these trials is that misuse of colloids may be more harmful than misuse of crystalloids. Before we further think about *what* to infuse in our patients, we should first have consensus on *how* we will perform fluid therapy in future trials.

Author details
[1] Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital of Muenster, Albert-Schweitzer-Campus 1, Bld. A1, 48149 Muenster, Germany. [2] General ICU, Raymond Poincaré Hospital (APHP), Laboratory of Inflammation and Infection U1173 INSERM and University of Versailles SQY, 104 Boulevard Raymond Poincaré, 92380 Garches, France. [3] Department of Anaesthesiology Centr-hospitalo-universitaire Brugmann, Universite Libre de Bruxelles, Brussels, Belgium.

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None.

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