VIA MEDICA

REVIEWS

Anaesthesiology Intensive Therapy
2014, vol. 46, no 5, 336–341
ISSN 1642–5758
DOI: 10.5603/AIT.2014.0057
www.ait.viamedica.pl

Why hydroxyethyl starch solutions should NOT be banned from the operating room

Stefan De Hert, Luc De Baerdemaeker

Department of Anaesthesiology, Ghent University Hospital, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium

Abstract

This review summarises the new insights into the physiology of perioperative fluid therapy and analyses recent studies of the safety of the use of HES solutions in the fluid management of critically ill patients. This analysis reveals a number of methodological issues in the three major studies that have initiated the recommendation of the European Medicine Agency to ban hydroxyethyl starches from clinical practice. It is concluded that, when used in the proper indication, and taking into account the recommended doses, hydroxyethyl starches continue to have a place in perioperative fluid management.

Key words: hydroxyethyl starches, perioperative period, safety

Anaesthesiology Intensive Therapy 2014, vol. 46, no 5, 336–341

All things are poison, and nothing is without poison; only the dose permits something not to be poisonous

Paracelsus (1493–1541)

About 230 million patients undergo surgery each year. Reported mortality rates for elective non-cardiac surgery range between 1 and 4% [1, 2]. For many years there has been great interest in the development of strategies that may help to reduce perioperative morbidity and mortality [3, 4]. An important part of this so-called Enhanced Recovery After Surgery (ERAS) strategy relates to perioperative fluid management.

Initially, no clear distinction was made between the different types of fluids used for perioperative fluid management. But during the last decade, a clear differentiation has been established between crystalloid substitution of extracellular losses and stabilisation and optimisation of cardiac preload [5–7]. In the perioperative setting, a goal-directed approach to the latter has been shown to reduce morbidity [8] and has been implemented in the British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP) [9].

In recent years, a number of publications have warned against the potential adverse effects of long-term use of hydroxyethyl starches (HES) in high cumulative doses, especially in septic patients. Although the clinical implications of such reports are controversial and discussion among experts is ongoing [10–13], on 14 June 2013 the risk assessment committee of the European Medicines Agency (EMA) recommended suspending marketing authorisations for HES for all indications [14]. After extensive discussions, this recommendation was adapted later that year to say: "HES solutions must no longer be used to treat patients with sepsis (bacterial infection in the blood) or burn injuries or critically ill patients because of an increased risk of kidney injury and mortality. HES solutions may continue to be used in patients to treat hypovolaemia (low blood volume) caused by acute (sudden) blood loss, where treatment with alternative infusion solutions known as 'crystalloids' alone are not considered to be sufficient" [15].

The present review aims to summarise the new insights into the physiology of perioperative fluid therapy and to critically analyse recent studies of the safety of the use of HES solutions in the fluid management of critically ill patients.

PHYSIOLOGY OF PERIOPERATIVE FLUID LOSS

In normal conditions, about two-thirds of the total body water content is located intracellularly. The remainder is

located extracellularly, of which about 80% is located in the interstitial compartment and the remaining 20% in the intravascular compartment. Both latter subcompartments are separated by the vascular barrier. In normal conditions, this barrier retains the macromolecules within the intravascular space but it is freely permeable to water and electrolytes. For this reason, administration of isotonic crystalloids during the resuscitation of a bleeding patient will result in an even distribution of the infused amount over the entire extracellular space, which is 20% intravascular and 80% interstitial [16].

A normal healthy vascular endothelium is coated by the endothelial glycocalix. This layer, together with the endothelial cells, constitutes a sort of double barrier both of which oppose unlimited extravasation [17]. In addition to its role as physiological endothelial permeability barrier, it prevents leucocyte and platelet adhesion, thereby mitigating inflammation and tissue oedema [6].

Fluid shifting out of the intravascular space does normally not occur at a body core temperature of between 33 and 37°C. Below 30°C, a significant decrease in plasma volume is observed, accompanied by a decrease in central venous pressure, an increase in pulmonary and systemic vascular resistance, and an increase in haematocrit [18]. As a consequence, the phenomenon of fluid shifting should not be a common intraoperative problem in noncardiac surgery. Nevertheless, fluid shifting is a commonly seen phenomenon during and after surgical procedures. Perioperative weight gain is considered to be a reliable marker of fluid storage outside the vascular compartment. It has been shown that this weight gain is strongly related to patient mortality [19]. Other studies have confirmed that aggressive crystalloid infusion leading to a positive fluid balance is associated with poor postoperative outcomes such as prolonged ventilator dependency and intensive care unit stay, and increased mortality [20, 21]. These observations were the start for a multitude of randomised trials comparing liberal fluid therapy to more restricted fluid administration strategies. An important consideration with these studies however is that both the restrictive and the liberal fluid regimens are ill-defined, and that methodology is very heterogenous, making global evidence-based recommendations difficult [22]. Nevertheless, the majority of systematic reviews and meta-analyses indicate that the application of a goal-directed therapy is associated with better outcomes than a liberal fluid strategy [23, 24]. Goal-directed therapy implies that the amount of volume to be administered is assessed based on the analysis of specific variables. It is now widely accepted that urine output, pressure correlates of volume status, and other static variables are unreliable to assess the intravascular volume status and fluid need of patients. Instead dynamic variables such as pulse pressure variation and stroke volume variation may give a more reliable idea of the patient's intravascular volume status [25]. However, a number of drawbacks need to be taken into account for these indices for the assessment of volume status and fluid responsiveness [26, 27].

PERIOPERATIVE FLUID HANDLING

From a physiological point of view, perioperative fluid administration basically needs to replace two entirely different kinds of losses: (i) losses occurring all the time (primarily urine production and insensible perspiration); and (ii) losses occurring exclusively during trauma and surgery (mainly blood losses).

LOSSES OCCURRING AT ALL TIME

The extent of these losses may differ from normal both in the perioperative setting and in the critically ill patient. However, there are some common beliefs with regard to these losses that need to be put in perspective.

There is a general tendency to overestimate preoperative fluid deficit and perioperative insensible losses. This results in a liberal fluid administration strategy with recommendations of basal crystalloid infusion rates up to 15 mL kg^{-1} h^{-1} as a perioperative standard measure for major intra-abdominal surgery [28]. It is obvious that such strategies may easily end up with positive fluid balances of up to 10 L. The observation of a concomitant parallel perioperative increase in body weight however suggests that the contribution of insensible perspiration to perioperative fluid needs should be minimal [6]. Direct measurements of insensible perspiration have indeed indicated that the latter is highly overestimated and that the basal evaporation of approximately 0.5 mL kg^{-1} h^{-1} in the awake adult increases at the most to 1 mL kg^{-1} h^{-1} during large abdominal surgery even with maximal bowel exposure [29]. In addition, also the impact of preoperative fasting is seriously overestimated. It has indeed been demonstrated that even after a period of extended fasting, intravascular blood volume seems to remain within normal ranges [30]. Moreover, the current fasting guidelines have substantially decreased the preoperative period of fasting and also the routine use of bowel preparation is now questioned.

Another point of interest is the practice of compensation by fluid administration of the decreased circulatory state during and after induction of general or neuraxial anaesthesia. It should be noted that this transient decrease actually constitutes a state of *relative* hypovolemia due to a decrease of sympathetic tone. So treatment should consist of restoring sympathetic tone with small doses of vasopressors, instead of the administration of various amounts of fluids.

Finally, perioperative fluid management still is frequently based on urine output measurements, where an output of 0.5 mL kg^{-1} h^{-1} is considered to be a minimum. However,

urine output may be a very poor and unreliable indicator of circulatory filling status in the perioperative period. Indeed, the perioperative period should be considered as a period of general stress and the body reacts accordingly by — among others — the release of antidiuretic hormone and the activation of the renin-angiotensin-aldosterone axis resulting in sodium and water retention. As a consequence, decreased urinary output in the perioperative phase merely constitutes a physiological response to surgical trauma and is not necessarily an indication of impaired circulating volume or imminent acute renal failure.

Losses related to urine output and perspiration insensibilis affect the entire extracellular space, which includes the intravascular plus the interstitial space. This loss does not normally lead to a decrease in the colloid osmotic force of the intravascular space. In normal conditions, these are replaced by the absorption of colloid-free fluid and electrolytes from the gastrointestinal tract. In the fasted patients, this compensation mechanism may fail and has to be replaced artificially. Theoretically, the best solution is the administration of crystalloids, ideally in a balanced form, to prevent acid-base disorders. Because crystalloids are not retained by the vascular barrier they are homogenously distributed within the entire extracellular compartment. There is no place for colloids to compensate for these fluid losses since they will primarily compensate only the intravascular compartment. However, it is important to note that the volume effects of colloids have been shown to be context-sensitive. A simultaneous infusion of iso-oncotic colloids during acute bleeding has a volume effect of more than 90%. In contrast, in a normovolemic patient, approximately 60% of the same preparation will leave the vasculature towards the interstitial space within minutes. The reason for this phenomenon is a hypervolemia-related impairment of the vascular barrier functioning [31]. Volume effects of colloids therefore depend on the context, which is the volume and hydration state of the patient [32]. As a consequence, treating relative hypovolemia secondary to vasodilation with colloids carries the inherent risk of later inducing relative hypervolemia with pulmonary oedema once the vascular tone restores at the end of surgery and anaesthesia.

LOSSES OCCURRING EXCLUSIVELY DURING TRAUMA AND SURGERY

This type of loss induces primarily an isolated intravascular deficit, including losses of all blood components. In substituting acute blood losses there is no physiological correlate that can be mimicked. The primary goal to account for these losses is to maintain the circulatory volume in order to maintain haemodynamic stability. Theoretically, this could be achieved by the substitution of the blood elements and the plasma components including the clotting factors. However, because of infection and incompatibility risks, and financial and logistical implications, the administration of blood products and plasma components will mainly be driven to correct specific deficits in these components.

Since the primary goal of fluid replacement with these losses is a prompt and longlasting restoration of the intravascular volume, the ideal solution should have a good volume expansion effect and preferably have no side effects. Table 1 summarises the properties of the different available solutions. Since isotonic crystalloids distribute within the whole extracellular compartment, about 80% of the amount of fluid will leave the intravascular compartment within a short time. As a consequence, this type of fluid is inappropriate when the goal is to expand specifically the intravascular space. The recommendation [33] and still widely applied strategy to substitute the first 1,000 mL of blood loss with a three- or fourfold dose of isotonic crystalloids has no physiological rationale. Similarly, there are no arguments to increase crystalloid infusion rates when patients seem to be clinically hypovolemic during surgery despite an intact extracellular fluid balance [6]. Colloids, on the other hand, remain intravascularly, and in the specific setting of acute bleeding have a volume effect of more than 90% [25].

PERIOPERATIVE FLUID SHIFTS

Fluid shifting towards the interstitial space can be divided into two types. *Type 1* is the physiological shift which occurs at all times. It refers to an almost colloid-free shift of fluid and electrolytes out of the intravascular space. This type of shift occurs even when the vascular barrier is intact. *Type 2*, on the other hand refers to a pathological fluid shift in which fluid containing protein close to the plasma concentration crosses a functionally altered vascular barrier. This type of fluid shift occurs with alteration of the endothelial glycocalix and the endothelial cells by, for instance, mechanical stress, endotoxin exposure, and ischaemia-reperfusion injury or inflammation, but may also occur in the context of acute hypervolemia [6].

Part of the perioperative fluid management strategies should be directed towards minimising the extent of both types of fluid shifting. Minimising *type 1* shifting implies the use of crystalloids only to replace urine production and insensible perspiration and use iso-oncotic colloids for replacement of acute blood loss. Minimising *type 2* shifting implies avoiding any cause of endothelial barrier damage. Several approaches can be considered [6] but a key element is to carefully maintain intravascular volume and avoid any hypervolemic peak. Once a type 2 shifting has occurred, this means that there is a leakage of protein rich fluid. Causal treatment of the intravascular hypovolemia due to a protein-rich type 2 shift should aim at restoring as much as possible the intravascular colloid osmotic force, hence the

administration of colloids. Using crystalloids in this situation will only aggravate the clinical picture by a massive increase of the physiological type 1 shift, which will further increase the interstitial load.

HES: A DEBATE OR KILLING OF A MOLECULE?

When the decision is taken — based on the physiological arguments elaborated above — to administer colloids in a fluid administration strategy, the choice of agent should be based on considerations of volume expansion vs safety concerns.

While the immediate plasma-extending properties are similar between gelatins and HES solutions, the latter tend to remain longer in the circulation [34–37]. In addition, the incidence of allergic reactions, though very small, has been reported to be higher with gelatins than with HES solutions [38, 39]. Administration of the older HES preparations with higher molecular weight has been associated with an increased blood loss and need for blood transfusion, but this phenomenon seems to be absent with the newer preparations with lower molecular weight [36].

As a consequence, according to a recent international cross-sectional study in 391 intensive care units, HES preparations seemed to be fairly popular as resuscitation fluid in critically ill adults [40].

Meanwhile, a number of studies have been published that have started to question the safety of the use of HES preparations concerning adverse effects on mortality but also on morbidity and more specifically increased renal dysfunction and failure. These concerns have resulted in the negative advice given by the EMA with regard to the use of HES solutions in patient care [14, 15]. Despite the fact that these different studies were all published in prestigious journals, they all contain some methodological flaws that hamper the drawing of conclusions and in fact bring into question the recommendations concerning the banning of HES solutions from clinical practice.

There is an important consideration to be made with regard to the issue of fluid resuscitation, which is that failure to early haemodynamically stabilise patients in acute shock makes it very difficult to compensate for this failure at a later stage [41]. In haemodynamic resuscitation, two phases need to be distinguished: an initial (six hours) resuscitation phase which is followed by a maintenance phase. During the initial phase, volume therapy is an important part of an outcome-relevant causal therapy. During the maintenance phase, fluid therapy is only one measure within a multifactorial supportive strategy, and therefore any causal relationship between this single strategy and patient outcome is extremely hazardous [42]. This needs to be taken into account when evaluating the different studies that have resulted in the EMA recommendations with regard to HES solutions.

VISEP STUDY

The VISEP (volume substitution and insulin therapy in severe sepsis) compared the use of Ringer's lactate to that of 10% HES 200/0.5 for volume replacement in 537 septic patients [43]. The colloid-treated patient group showed an increased incidence of renal failure and a 'trend' ($P = 0.09$) towards higher 90-day mortality. However, it should be noted that in this trial, the start of the study treatment was delayed for up to 24 hrs after diagnosis of severe sepsis. This implies that, for the majority of patients, at this time initial stabilisation of haemodynamics was already completed. Indeed, when looking at the baseline values at randomisation, it appears that all target values for resuscitation, as defined by the Surviving Sepsis Campaign Guidelines [44], were already reached before randomisation. The result is that 58% of the patients in the *crystalloid* group who had already successfully been stabilised haemodynamically before randomisation did receive up to 1 L HES for initial resuscitation (remarkably, a further 33% in this group received colloids during the trial). Conversely, the patients in the *colloid* group received an outdated hyperoncotic solution over a prolonged period of time in the absence of a proper (physiological) indication and in daily cumulative doses beyond the recommendations.

This point is important, because apparently the subgroup of patients who received the HES solution in daily amounts within the recommended range showed a *lower* mortality than the crystalloid group.

6S STUDY

The 6S (Scandinavian Starch for Severe Sepsis/Septic Shock) trial compared the use of Ringer's acetate to the administration of 6% HES 130/0.42 for fluid resuscitation in 800 septic patients [45]. The authors observed an increased need for renal replacement therapy and a significantly higher 90-day mortality in the patients randomised to the HES group. However, also in this study, patients were once again only randomised up to 24 hrs after the diagnosis of sepsis or septic shock. The consequence of this approach was that — similar to VISEP — 60% of patients in the *crystalloid* group had already received up to 1 L of colloid for initial resuscitation and that in the colloid group the majority of patients were already stabilised with target values better than those of the Surviving Sepsis Guidelines [44]. This implies that, also in this study, the patients randomised to the HES group were, once again, tested for a non-indicated drug compared to the rational and well established strategy for fluid maintenance with crystalloids in stable patients. In

addition, at study onset 36% of the randomised patients had renal failure, which is an established contraindication for HES administration. Finally, 32% of the patients allocated to the *crystalloid* group received colloids *during* the trial and in 216 patients (27%) the trial fluid was discontinued during the study. Despite these methodological issues, all patients were included into the follow-up. Of note, the RIFLE score, which allows for objective reporting of the grade of renal function impairment and failure, is only reported in the supplement. Interestingly, there seems to be no significant difference between groups [42]. It is therefore impossible to grasp the potential implications on outcome when the picture is blurred by a multitude of methodological issues [42].

CHEST STUDY

The CHEST (Crystalloid versus HydroxyEthyl Starch Trial) randomised 7,000 patients at mean 11 hours after admission on the intensive care unit, to receive either saline or 6% HES 130/0.4 for fluid resuscitation [46]. No difference was observed between groups in 90-day mortality or renal function according to the RIFLE criteria. However, the authors reported an increased incidence in renal replacement therapy. It is unclear why a group of patients with better renal function nevertheless had a higher need for renal replacement therapy. In the absence of well-defined criteria for the use of renal replacement therapy, it is very likely that the higher incidence of renal replacement therapy simply reflects the situation that more patients received this therapy but that this by no means implies that this therapy was indeed required. Instead, an independent analysis of the data even indicates that due to an improved kidney function and no differences in renal replacement therapy, CHEST shows an advantage over HES [42]. In addition, also in this study haemodynamic targets for initial fluid resuscitation were already met at the time of inclusion, suggesting haemodynamic stability and no need for additional colloid therapy. Also, similar to the VISEP and 6S, 36% of patients had renal failure at randomisation and should have been excluded. Finally, 508 patients of the saline group had received HES prior to randomisation. Of note, 30% of the patients were septic and in this subgroup no difference in mortality, renal failure or need for renal replacement therapy was observed.

HES: PUTTING THE FACTS TOGETHER

It seems therefore that of the three main papers that have questioned the safety of HES solutions in the fluid management of critically ill patients, one showed no relevant differences [46] and two suffered from major methodological issues [43, 45]. These issues include treatment strategies not reflecting clinical reality, ignoring contraindications and maximum recommended daily doses, overinterpretation of results, and selective biased analysis of data [42]. It is also important to note that these three studies failed to address the initial resuscitation phase after the diagnosis of sepsis and septic shock. Actually, in all trials, colloids were administered to a majority of patients during this phase. As a consequence, one can only conclude that specifically in a group of patients treated with HES, the wrong fluid was administered at the wrong time (after haemodynamic stabilisation crystalloids are to be administered) in an inappropriate amount (exceeding daily recommended doses) in the wrong patients (pre-existing acute renal failure at randomisation). In addition, the results of these trials — especially taking into account the abovementioned shortcomings — do not allow the provision of recommendations on the indications of these compounds in the setting of acute need for volume replacement. Indeed, when used in the proper indication as early stage resuscitation fluid, it has been shown that 6% HES 130/0.4 could have a superior risk/benefit ratio and improved outcome compared to crystalloids [2, 47–51].

CONCLUSIONS

In the discussion about fluid management strategies, it is of prime importance that intravenous fluids should be treated as foreign substances that are introduced into the body. Therefore, their administration should be guided by the same concerns as the administration of drugs, taking into account strict indications and the necessary precautions with respect to side effects and potential adverse reactions. It seems that the debate about the place of HES in the treatment of critically ill patients is blurred by a clash of strong opinions. It is therefore essential that currently available data is evaluated in an objective manner with respect to the underlying physiology and pathophysiology of fluid treatment in various disease states [12]. Only in this way can evidence-based clinical recommendations be provided.

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Corresponding author:
Stefan De Hert, MD, PhD
Department of Anaesthesiology
Ghent University Hospital
De Pintelaan 185
B-9000 Ghent, Belgium
email: stefan.dehert@ugent.be

Received: 16.09.2014
Accepted: 28.10.2014