

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

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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 glycocalyx. 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 heterogeneous, 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 reli-

able 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 homogeneously 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 fac-

tors. 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 glycocalyx 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.

WISEP STUDY

The WISEP (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 WISEP — 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.

References:

1. Weiser TG, Regenbogen SE, Thompson KD et al.: An estimation of the global volume of surgery: a modeling strategy based on available data. *Lancet* 2008; 372: 139–144.
2. Pearse RM, Moreno RP, Bauer P et al.: Mortality after surgery in Europe: a 7 day cohort study. *Lancet* 2012; 380: 1059–1065.
3. Kehlet H: Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* 1997; 78: 606–617.
4. Lassen K, Soop M, Nygren J et al.: Consensus review of optimal perioperative care in colorectal surgery: enhanced recovery after surgery (ERAS) group recommendations. *Arch Surg* 2009; 144: 961–969.
5. Jacob M, Chappell D, Hofmann-Kiefer K, Conzen P, Peter K, Rehm M: Determinants of insensible fluid loss. Perspiration, protein shift and endothelial glycocalyx. *Anaesthesist* 2007; 56: 747–764.
6. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M: A rational approach to perioperative fluid management. *Anesthesiology* 2008; 109: 723–740.
7. Jacob M, Chappell D: Reappraising Starling: the physiology of the microcirculation. *Curr Opin Crit Care* 2013; 19: 282–289.
8. Hamilton MA, Cecconi M, Rhodes A: A systematic review and meta-analysis on the use of preemptive haemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesth Analg* 2011; 112: 1392–1402.

9. Powell-Tuck JG, Lobo DN, Allison SP et al.: British consensus guidelines on intravenous fluid therapy for adult surgical patients. 2011. http://www.bapen.org.uk/pdfs/bapen_pubs/giftasup.pdf
10. Reinhart K, Perner A, Sprung CL et al.: Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. *Intensive Care Med* 2012; 38: 368–383.
11. Zacharowski K, Van Aken H, Marx G et al.; *Comments on Reinhart*: Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. *Intensive Care Med* 2012; 38: 1556–1557.
12. Meybohm P, Van Aken H, De Gasperi A et al.: Re-evaluating currently available data and suggestions for planning randomized controlled studies regarding the use of hydroxyethyl starch in critically ill patients — a multidisciplinary statement. *Crit Care* 2013; 17: R166.
13. Coriat P, Guidet B, De Hert S, Kochs E, Kozek S, Van Aken H: Counter statement to open letter to the executive director of the European Medicines Agency concerning the licensing of hydroxyethyl starch solutions for fluid resuscitation. *Br J Anaesth* 2014; 113: 194–195.
14. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Hydroxyethyl_starchcontaining_medicines/human_referral_prac_000029.jsp&mid=WC0b01ac05805c516f
15. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Hydroxyethyl_starchcontaining_medicines/human_referral_prac_000029.jsp&mid=WC0b01ac05805c516f
16. Jacob M, Chappell D, Hofmann-Kiefer K et al.: The intravascular volume effect of Ringer's lactate is below 20%: a prospective study in humans. *Crit Care* 2012; 16: R86.
17. Rehm M, Zahler S, Lotsch M et al.: Endothelial glycocalyx as an additional barrier determining extravasation of 6% hydroxyethyl starch or 5% albumin solutions in the coronary vascular bed. *Anesthesiology* 2004; 100: 1211–1223.
18. Hammersborg SM, Farstad M, Haugen O, Kvalheim V, Onarheim H, Husby P: Time course variations of haemodynamics, plasma volume and microvascular fluid exchange following surface cooling. An experimental approach to accidental hypothermia. *Resuscitation* 2005; 65: 211–219.
19. Lowell JA, Schifferdecker C, Driscoll DF, Benotti PN, Bistrain BR: Postoperative fluid overload: not a benign problem. *Crit Care Med* 1990; 18: 728–733.
20. Humphrey H, Hall J, Sznajder I, Silverstein M, Wood L: Improved survival in ARDS patients associated with a reduction in pulmonary capillary wedge pressure. *Chest* 1990; 97: 1176–1180.
21. Schuller D, Mitchell JP, Calandrino FS, Schuster DP: Fluid balance during pulmonary edema: is fluid gain a marker or a cause of poor outcome? *Chest* 1991; 100: 1068–1075.
22. Bundgaard-Nielsen M, Secher NH, Kehlet H: Liberal vs restrictive perioperative fluid therapy — a critical assessment of the evidence. *Acta Anaesthesiol Scand* 2009; 53: 843–851.
23. Giglio MT, Marucci M, Testini M, Brienza N: Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials. *Br J Anaesth* 2009; 103: 637–646.
24. Corcoran T, Rhodes JEJ, Clarke S, Myles PS, Ho KM: Perioperative fluid management strategies in major surgery: a stratified meta-analysis. *Anesth Analg* 2012; 114: 640–651.
25. Guerin L, Monnet X, Teboul JL: Monitoring volume and fluid responsiveness: from static to dynamic indicators. *Best Pract Res Clin Anaesthesiol* 2013; 27: 177–185.
26. De Hert SG: Assessment of fluid responsiveness: insights in a “gray zone”. *Anesthesiology* 2011; 115: 229–230.
27. De Hert S: Noninvasive haemodynamic monitoring devices: new tools or just another toy? *Anesthesiology* 2014; 120: 1065–1066.
28. Campbell IT, Baxter JN, Tweedie IE, Taylor GT, Keens SJ: IV fluids during surgery. *Br J Anaesth* 1990; 65: 726–729.
29. Lamke LO, Nilsson GE, Reithner HL: Water loss by evaporation from the abdominal cavity during surgery. *Acta Chir Scand* 1977; 143: 279–284.
30. Jacob M, Chappell D, Conzen P, Finsterer U, Rehm M: Blood volume is normal after preoperative overnight fasting. *Acta Anaesthesiol Scand* 2008; 52: 522–529.
31. Rehm M, Haller M, Orth V et al.: Changes in blood volume and hematocrit during acute preoperative volume loading with 5% albumin or 6% hetastarch solutions in patients before radical hysterectomy. *Anesthesiology* 2001; 85: 849–856.
32. Jacob M, Chappell D, Rehm M: Clinical update: perioperative fluid management. *Lancet* 2007; 369: 1984–1986.
33. Kaye AD, Kucera AJ: Fluid and electrolyte physiology. In: *Miller RD (ed.): Anesthesia*. 6th ed., Philadelphia, Churchill Livingstone 2005: 1763–1798.
34. Salmon JB, Mythen MG: Pharmacology and physiology of colloids. *Blood Rev* 1993; 7: 114–120.
35. Vercueil A, Grocott MPW, Mythen MG: Physiology, pharmacology, and rationale for colloid administration for the maintenance of effective haemodynamic stability in critically ill patients. *Transfus Med Rev* 2005; 19: 93–109.
36. Van der Linden PJ, De Hert SG, Deraedt D et al.: Hydroxyethyl starch 130/0.4 versus modified fluid gelatin for volume expansion in cardiac surgery patients: the effects on perioperative bleeding and transfusion needs. *Anesth Analg* 2005; 101: 629–634.
37. Gondos T, Marjanek Z, Ulakcsai Z et al.: Short-term effectiveness of different volume replacement therapies in postoperative hypovolaemic patients. *Eur J Anaesthesiol* 2010; 27: 794–800.
38. Laxenaire MC, Moneret-Vautrin DA et al.: Anesthetics responsible for anaphylactic shock. A French multicenter study. *Ann Fr Anesth Reanim* 1990; 9: 501–506.
39. Laxenaire MC, Mertes PM: Anaphylaxis during anaesthesia. Results of a two-year survey in France. *Br J Anaesth* 2001; 87: 549–558.
40. Finfer S, Liu B, Taylor C et al.: Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. *Crit Care* 2010; 14: R185.
41. Rivers E, Nguyen B, Havstad S et al.: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345: 1368–1377.
42. Chappell D, Jacob M: Hydroxyethyl starch — the importance of being earnest. *Scand J Trauma Resusc Emerg Med* 2013; 21: 61.
43. Brunkhorst FM, Engel C, Bloos F et al.: Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; 358: 125–139.
44. Dellinger RP, Levy MM, Rhodes A et al.: Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2013; 41: 580–637.
45. Perner A, Haase N, Guttormsen AB et al.: Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; 367: 124–134.
46. Myburgh JA, Finfer S, Bellomo R et al.: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; 367: 1901–1911.
47. James MF, Michell WL, Joubert IA, Navsaria PH, Gillespie RS: Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). *Br J Anaesth* 2011; 107: 693–702.
48. Guidet B, Martinet O, Boulain T et al.: Assessment of haemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study. *Crit Care* 2012; 16: R94.
49. Annane D, Siami S, Jaber S et al.: Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock. The CRISTAL randomized trial. *JAMA* 2013; 310: 1809–1817.
50. Martin C, Jacob M, Vicaud E, Guidet B, Van Aken H, Kurz A: Effect of waxy maize-derived hydroxyethyl starch 130/0.4 on renal function in surgical patients. *Anesthesiology* 2013; 118: 387–394.
51. Van der Linden P, James M, Mythen M, Weiskopf RB: Safety of modern starches during surgery. *Anesth Analg* 2013; 166: 35–48.

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Received: 16.09.2014

Accepted: 28.10.2014