SIGNA VITAE 2014; 9 (Suppl 1): 15 - 20

HES solutions in critical illness, trauma and perioperative period

ROBERT BARONICA • DINKO TONKOVIĆ • DANIELA BANDIĆ PAVLOVIĆ • ŽELJKO DRVAR • SANJA SAKAN • KORALJKA BAČIĆ BARONICA

ROBERT BARONICA (✉) •
DANIELA BANDIĆ PAVLOVIĆ •
ŽELJKO DRVAR •
SANJA SAKAN
Department of Anaesthesiology
Reanimatology and Intensive Care
University Hospital Centre Zagreb
Kišpatićeva 12, 10 000 Zagreb, Croatia
Phone/Fax: +38512367858
E-mail: rbaronica@gmail.com

DINKO TONKOVIĆ
University Department of Anaesthesiology
University Hospital Sveti Duh, Zagreb, Croatia

KORALJKA BAČIĆ BARONICA
University Department of Neurology
University Hospital Sveti Duh, Zagreb, Croatia

ABSTRACT

In the last few years, many studies and meta-analyses have demonstrated that hydroxyethyl starch (HES) solutions increase the risk of acute renal failure and mortality in critically ill patients. Some studies suggest complete avoidance of HES solutions in patients of all categories. On the other hand, recent studies and analyses suggest that HES solutions may be used in hypovolemic critically ill patients and in the perioperative setting. The main problem in everyday clinical practice and in a rational fluid management approach is that treatment with alternatives to HES solutions is not always pathophysiologically justified (crystalloids) or confirmed in randomised controlled trials (gelatins, albumins).

Key words: hydroxyethyl starches, critical illness, perioperative period

Introduction

The synthesis of hydroxyethyl starch (HES) solutions of the third generation should have relieved anxiety concerning the adverse effects of older generations of HES solutions, in particular coagulation disorders, renal injuries and allergic reactions. (1) However, in the past few years many studies and meta-analyses have demonstrated that HES solutions, regardless of their basic properties, increase the risk of acute renal failure (ARF) and mortality in critically ill patients. Based on these findings, recommendations have recently appeared in literature suggesting that HES solutions should be avoided in cases of critical illness and in the perioperative setting. The "Surviving Sepsis Campaign" guidelines (SSCG) from 2012 support a high recommendation grade against the use of HES solutions and suggest that crystalloid solutions should be used in the resuscitation of severe sepsis and septic shock. The SSCG suggest the use of albumin when patients require substantial amounts of crystalloids. (2) At the end of 2012, the European Medicines Agency (EMA) evaluated the safety, benefits and risks of solutions which contain HES. In June 2013, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) suggested that the benefits of HES solutions no longer exceed their risks and that HES solutions should be suspended in all patient populations. After an additional analysis, PRAC agreed that HES solution could continue to be used in some populations such as hypovolemic patients with acute blood loss when treatment with alternative solutions such as crystalloids is not considered to be sufficient. (3)

HES solutions in severe sepsis and septic shock

The German multicentre, prospective, randomised study (VISEP) investigated the effects of intensive and conventional insulin therapy, of 10% HES 200/05 solution and of modified Ringer's lactate in patients with severe sepsis. (4) The study was terminated early for safety reasons concerning an elevated rate of severe hypoglycaemia in patients on intensive insulin therapy and higher rates of ARF and RRT associated with the HES solution therapy. Patients in the HES group had a lower median platelet count and received more units of packed red cells. The mortality rate within 28 days was similar in both groups. A trend toward higher 90-day mortality rate was observed in the HES group. The main limitation of the study was that the older hyperoncotic HES solution was administered without a proper

determination of the patients' volume status. The baseline patients' characteristics at the time of randomisation suggested that they were not hypovolemic. High volumes of HES solutions were administered at the beginning of randomisation, when the kidneys are more sensitive to oncotic load. (1) In the French multicentre, prospective, controlled, randomised and double-blinded study (CRYSTMAS) on 174 patients with severe sepsis, hemodynamic effects and a safety evaluation of 6% HES 130/04 and 0.9% NaCl solutions were compared. (5) Results of the study demonstrated that hemodynamic stability could be achieved using lower volumes of HES solutions in a shorter time period. Differences between groups in the Acute Kidney Injury Network classification and the Risk, Injury, Failure, Loss, End-Stage Kidney Disease criteria were not found. There were no differences in the coagulation parameters or in the 90-day mortality rate. A notable criticism of the SSCG is that the CRYSTMAS study was underpowered and that there was a 6% higher mortality in the HES group that was not referred to as statistically important. In the Scandinavian multicentre, randomised, parallel-group and double-blinded study (6 S) carried out on 798 patients with severe sepsis, the effects of the balanced HES 130/0.42 solution concerning the mortality rate or end-stage kidney failure were compared to those of a balanced crystalloid solution. (6) The study design enabled a proper evaluation of the molecular effects of HES because Ringer's acetate was a carrier for HES and a comparable crystalloid solution. The volume of administered solutions was similar in both groups, as were the hemodynamic parameters. The 90-day mortality rate was significantly higher in the HES group. More patients in the HES group were treated with the RRT, had severe bleeding and received blood products. The main limitation of the study was that patients in both groups were not hypovolemic at the time of the randomisation. Volume management in both groups was guided by clinical endpoints, without objective hemodynamic monitoring. The design of the study enabled clinicians to administer high amounts of the investigated solutions without knowing their basic properties. It is a questionable approach in terms of rational volume management. Patients with ARF were randomised in both groups and precise indications for the RRT were not established in the study protocol. In the prospective, multicentre, randomised, parallel group, controlled and blind study (CHEST) conducted in 32 hospitals in Australia and New Zealand on 7,000 patients, the effects of HES solutions or saline were compared concerning 90-day mortality, ARF and RRT, as well as concerning new organ failures for cardiovascular, respiratory, coagulation and liver systems. (7) The results of the study demonstrated similar 28-day and 90-day mortality in both groups. A larger proportion of patients who where resuscitated with HES solutions were treated with RRT. HES treatment was associated with lower volumes of resuscitation fluid and increased the use of blood products. There was no significant difference in rates of new respiratory or coagulation organ failure. A lower incidence of new cardiovascular organ failure along with less frequent use of vasopressors, and a higher incidence of new hepatic organ failure were noticed in the HES group. HES was associated with significantly more adverse events, mostly pruritus and rush. There are few limitations of the study. Patients were randomised 11 hours after they were admitted to the ICU and at the time of the randomisation they were not hypovolemic. The study solutions were administered without objective hemodynamic monitoring. Similarly to the 6 S study, rational volume administration was prevented by the fact that clinicians did not know the basic properties of solutions they administered. Although the clinicians were unaware of study-group assignments, the lack of precise indications for RRT might affect the study results.

HES solutions in critically ill, surgical and trauma patients

Gattas et al. performed a meta-analysis of 35 randomised and controlled studies with 10,391 patients. (8) The main goals of the analysis were to investigate effects of 6% HES solutions (130/0.4 and 130/0.42) on mortality and RRT in acute illness. The authors concluded that fluid resuscitation of acutely ill adults with 6% HES 130 is associated with an increased risk of death and treatment with RRT.

Zarychanski et al. performed a meta-analysis of 38 studies and 10,880 critically ill patients and compared HES solutions with crystalloid, albumin and gelatine solutions. (9) The results of the analysis demonstrated a higher mortality rate, ARF and RRT frequency associated with the administration of HES.

In the Perel et al. review, the effects of colloid and crystalloid solutions in the volume management of critically ill patients were analysed. (10) The authors concluded that there is no evidence from randomised controlled trials that colloids reduce the risk of death in patients with trauma, burns or following surgery and that use of HES solutions might even increase mortality. As colloids are more expensive than crystalloids their use in clinical practice is unjustified.

The main goals of the Mutter et al. meta-analysis were to compare the effects of HES and other solutions in various patient categories. (11) The analysis included 42 studies with 11,399 patients. The results of the analysis showed that HES solutions, irrespective of their molecular weight (MW), degree of substitution (DS) or substitution pattern, increase the risk of ARF and RRT in all patient categories.

In another systematic review, with meta-analyses of randomised clinical trials on patients with sepsis, Haase et al. assessed the effects of fluid therapy with HES 130/0.38-0.45 solutions versus crystalloid or albumin solutions on mortality, kidney injury, bleeding and serious adverse events. The authors concluded that HES 130/0.38-0.45 increased the use of RRT and transfusion with red blood cells and increased the frequency of serious adverse events. (12)

The multicentre, prospective, randomised and open label trial (CRISTAL)

was conducted in 57 ICUs in France, Belgium, North Africa and Canada and included 2,857 patients with hypovolemic shock due to sepsis, trauma and other causes. (13) The main goals of the study were to compare the effects of colloid and crystalloid solutions on 28-day and 90-day mortality in patients with hypovolemic shock and days alive and not receiving RRT, mechanical ventilation or vasopressor therapy. In the crystalloids group, about 86% of patients were resuscitated with isotonic saline and about 17% with buffered solutions. In the colloids group, about 70% of patients received HES and about 35% received gelatins. Patients in the crystalloids group received higher volumes of fluids to accomplish the same hemodynamic goals as patients in the colloids group. A difference in the 28-day mortality rate was not found. Within 90 days, the mortality rate was lower in the colloids group. There were no differences in the number of patients treated with the RRT. Patients in the colloids group had more days alive without mechanical ventilation and vasopressor therapy. Unlike other similar studies, the CRISTAL study included only hypovolemic patients. The different hemodynamic parameters at the start of the randomisation and the lower total dose of administered starches might have positively affected the mortality and RRT risks in this trial. In addition, patients with severe chronic renal failure were not included in the study. The reduced cardiovascular and respiratory failure in the colloids group may have contributed to renal protection. The possible limitations of the study include the administration of open-labelled fluids, a recruitment period of nine years and protocol violations in both groups. The knowledge of allocation of the investigated solutions by physicians might have influenced the requirements of RRT.

In the Martin et al. meta-analysis, which included 17 studies and 1,230 surgical patients, renal safety with the active substance of the latest generation of waxy maize-derived HES was evaluated. The authors found no evidence of renal dysfunction caused by HES 130/0.40. (14)

In the Van Der Linden et al. analysis, which included 59 studies and 4,529 patients, the safety of modern HES solutions was evaluated during the perioperative period. (15) Tetrastarches did not induce adverse renal effects (39 trials; 3,389 patients), increased blood loss (38 trials; 3280 patients), erythrocyte transfusion (20 trials; 2,151 patients) or mortality. The authors concluded that modern HES solutions did not induce any adverse effects intraoperatively or in the immediate postoperative period. The main limitation of the analysis was that the follow-up period was limited in the evaluated trials and possible long-term adverse effects could not be estimated. The authors argued that the main differences between their analysis and other similar studies and analyses concerned the population investigated and patients' endovascular function. Critical and septic patients have damaged glycocalix and endovascular barrier that promote the extravasation of HES molecules into the extracellular compartment, the loss of intravascular colloid function and the administration of additional volumes of solutions. An increased amount of HES molecules in the extracellular compartment could be responsible for the increased late mortality and the frequency of ARF in critically ill and septic patients. (15) The presumable mechanisms may include intake of starch into epithelial cells of the proximal renal tubules and tubular obstruction associated with hyperviscose urine and inflammation of the renal interstitium. (16) A lower volume of HES solutions administered during the first 48 hours was not associated with ARF or increased ICU mortality in an observational retrospective study on 363 patients. (17) Beside the patients' characteristics, different structures of HES solutions concerning MW, DS, origin of the starch, amylopectin percentage and C2/C6 substitution pattern may be responsible for different outcomes and adverse effects.

In the Kozek-Langenecker et al. analysis, which included seven studies and 449 major surgical patients, the impact of HES 130/04 solutions on coagulation parameters, blood loss and transfusion volumes was significantly decreased in comparison to HES 200/05 solutions. (18) Mechanisms associated with increased bleeding after the administration of HES solutions include hemodilution, thrombocyte dysfunction, actions on GP IIb-IIIa receptors, increased fibrinolytic reactivity, decreased levels of factor VIII and von Willebrand factor and fibrine polymerisation. (18,19) In healthy volunteers, the repeated administration of HES 130/0.42 showed no accumulation and fewer tendencies to time-dependent changes in pharmacokinetic parameters than HES 200/0.5. (20)

The Bellmann et al. meta-analysis did not support the hypothesis that lower MW and DS decrease the tissue uptake of HES. (21) In terms of colloid osmotic and hemodilution effects, HES 130/0.42 showed an equivalency with HES 130/0.4 and had the fastest clearance from the circulation. (22) The effects of both HES solutions on coagulation were similar. In comparison to crystalloids, more severe hemostatic defects were noticed, mostly expressed as an impairment of fibrin polymerization. (23)

The administration of HES solutions in trauma was evaluated in a randomised, controlled, double-blinded study on 109 patients (FIRST). In patients with penetrating trauma, a significantly lower volume of HES solutions was administered in comparison to the 0.9% NaCl. In patients with blunt trauma, differences in volume administration were not found. Patients with blunt trauma received significantly more erythrocyte concentrates, probably because of higher median Injury Severity Score (ISS). The administration of HES in patients with penetrating trauma was associated with a significantly lower serum lactate levels and_decreased frequency of ARF. Hemodynamic parameters, return of the bowel function and mortality rate were comparable in both groups. (24)

In a retrospective study on 1,867 patients with blunt trauma, an increased exposure to blood products was noticed when HES 130/0.4 was admini-

stered in comparison to 0.9% NaCl. The reason for such a finding might be due to more extensive microvascular injury caused by blunt trauma. (25) Nevertheless, the study results were not conclusive because patients in the HES group had higher ISS and worse initial coagulation parameters. The authors concluded that the incidence of coagulopathy is associated with the severity of traumatic injury, not with volume management.

Alternatives to HES solutions

Although the SSCG suggest the use of crystalloids in severe sepsis and septic shock, it is questionable whether such an approach can be applicable to all critically ill and perioperative patients. From the pathophysiologic point of view, indications for crystalloid administration should be the contraction of the extracellular compartment related to inappropriate fluid intake, insensible perspiration, diuresis and surgical drainage. (26) When the intravascular volume is decreased, it is not logical to use crystalloids that mostly extravasate into the interstitial compartment. (27) A large amount of crystalloids needed for the expansion of intravascular compartment could be associated with numerous adverse effects such as pulmonary oedema, increased excretory renal function, inhibited gastrointestinal motility, intestinal mucosa oedema, increased intra-abdominal pressure and hypercoagulability. (28) According to the "loss-oriented" fluid management approach, izoonotic, balanced and colloid solutions should be used in hypovolemic patients because those solutions remain in the circulation and maintain fluid homeostasis.(1,2,6) Colloids should not be administered in hypervolemic conditions. In the "context sensitivity of colloidal volume effects" theory, two-thirds of colloid solutions will be distributed in the interstitial compartment during the hypervolemia. (1,2,9)

The SSCG suggest the use of albumin solutions when patients with severe sepsis or septic shock require substantial amounts of crystalloids. (29) Albumin solutions are obtained from pooled human plasma and have theoretical advantages in comparison to synthetic colloids. Nevertheless, the use of albumins did not show convincing results in controlled, randomised studies or meta-analyises. (1) The largest randomised study (SAFE) compared the administration of 4% albumins and 0.9% NaCl in 6,997 critically ill patients. (30) The results of the study demonstrated similar 28-day mortality in both groups. A subgroup analysis of patients with severe sepsis showed a benefit trend associated with the administration of albumins. A subgroup analysis of patients with traumatic brain injuries showed increased risk of dying in the albumin group. (31) The main limitation of the SAFE study was that albumin solutions were used as a general fluid substitute, not as volume replacement therapy.

The Delaney et al. meta-analysis of 17 studies and 1,977 patients with severe sepsis and septic shock showed that treatment with albumins in comparison to other solutions reduced mortality. (32) The Alderson et al. meta-analysis of 38 studies and 10,842 critically ill patients with hypovolemic shock demonstrated no benefit on survival when albumins were administered in comparison to other solutions. (33) Although studies that investigated albumin administration as volume replacement therapy did not show clear benefits, studies in hypoalbuminemic patients demonstrated positive effects of their use concerning a fluid balance and haemodynamics, better tolerance to enteral feeding and improved organ function. (34,35)

Gelatin solutions are produced from animal collagen. There are conflicting results in literature about the volume effectiveness of gelatin solutions. Most studies demonstrated lower intravascular volume expansion, increased extravasation of infused gelatins and less expressed effects on cardiac and stroke volume indices in comparison to HES solutions. (36,37,38) Although kidneys eliminate gelatin solutions very rapidly, the effects on kidney function are currently unclear. (37) Compared to HES solutions, gelatines have reduced effects on fibrin polymerisation. (1) An impairment of the clot strength after cardiac surgery was noticed with both colloids. (39) A considerably higher risk for anaphylactic reactions is associated with the use of gelatin solutions, and the transfer of the bovine spongiform encephalopathy cannot fundamentally be excluded. (40)

Dextrans solutions have major side-effects that include anaphylactoid reactions, renal damage and impaired hemostasis. (37) They have lost their role in modern volume replacement therapy.

Conclusion

The majority of studies published in the past few years have pointed to the possibility that in critical illness HES solutions are associated with increased ARF and RRT and some studies have demonstrated a higher mortality rate. On the other hand, recent studies and analyses suggest that HES solutions may be used in hypovolemic critically ill patients and in the perioperative setting. The use of HES solutions in the future will probably depend on revised indications, doses and the duration of the treatment made by regulatory boards and manufacturers. Untill then we must use them cautiously and in accordance with strict therapeutic indications.

REFERENCES

1. Kozek-Langenecker SA. Colloidal Volume Replacement Therapy. 1st ed. Bremen: UNI-MED, 2011.
2. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013 Feb;41(2):580-637.
3. http://www.ema.europa.eu/ema//809470/2013 Hydroxyethyl starch solutions (HES) no longer to be used in patients with sepsis or burn injuries or in critically ill patients.
4. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008 Jan 10;358(2):125-39.
5. Guidet B, Martinet O, Boulain T, Philippart F, Poussel JF, Maizel J, et al. Assessment of hemodynamic 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 May 24;16(3):R94.
6. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367(2):124-34.
7. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, at al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012 Nov 15;367(20):1901-11.
8. Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S. Fluid resuscitation with 6 % hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: systematic review of effects on mortality and treatment with renal replacement therapy. Intensive Care Med 2013;39(4):558-68.
9. Zarychanski R, Abou-Setta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, Fergusson DA. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA. 2013;309(7):678-88.
10. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients.Cochrane Database Syst Rev. 2013;2:CD 000567.
11. Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database Syst Rev. 2013;7:CD 007594.
12. Haase N, Perner A, Inkeri Hennings L, Siegemund M, Lauridsen B, Wetterslev M, Wetterslev J. Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis: BMJ 2013;346:f839.
13. Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declčre AD, 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 Nov 6;310(17):1809-17.
14. Martin C, Jacob M, Vicaut 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 Feb;118(2):387-94.
15. Van Der Linden P, James M, Mythen M, Weiskopf RB. Safety of modern starches used during surgery. Anesth Analg. 2013;116(1):35.
16. Claus RA, Sossdorf M, Hartog C. The effects of hydroxyethyl starch on cultured renal epithelial cells. Anesth Analg 2010; 110:300-301.
17. Boussekey N, Darmon R, Langlois J, Alfandari S, Devos P, Meybeck A, et al. Resuscitation with low volume hydroxyethylstarch 130 kDa/0.4 is not associated with acute kidney injury. Crit Care. 2010;14(2):R40.
18. Kozek-Langenecker SA, Jungheinrich C, Sauermann W, Van der Linden P. The effects of hydroxyethyl starch 130/0,4 (6%) on blood loss and use of blood products in major surgery: a pooled analysis of randomized clinical trials. Anesth Analg 2008;107:382-90.
19. Westphal M, James MF, Kozek-Langenecker S, Stocker R, Guidet B, Van Aken H. Hydroxyethyl starches: different products-different effects. Anesthesiology 2009; 111:187-202.
20. Lehmann GB, Asskali F, Boll M, Burmeister MA, Marx G, Hilgers R, Förster H. HES 130/0.42 shows less alteration of pharmacokinetics than HES 200/0.5 when dosed repeatedly. Br J Anaesth. 2007;98(5):635-44.
21. Bellmann R, Feistritzer C, Wiedermann CJ. Effect of molecular weight and substitution on tissue uptake of hydroxyethyl starch: a meta-analysis of clinical studies. Clin Pharmacokinet. 2012 Apr 1;51(4):225-36.
22. Lehmann G, Marx G, Förster H. Bioequivalence comparison between hydroxyethyl starch 130/0.42/6:1 and hydroxyethyl starch 130/0.4/9:1. Drugs R D. 2007;8:229-40.
23. Godier A, Durand M, Smadja D, Jeandel T, Emmerich J, Samama CM. Maize or potato derived hydroxyethyl starches: is there any thromboelastometric difference? Acta Anaesthesiol Scand 2010; 54:1241-1247.
24. James MF, Michell WL, Joubert IA, Nicol AJ, 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 Nov;107(5):693-702.
25. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma 2003;54:1127-30.
26. Chappell D, Jacob M, Hofmann-Kiefer K, Conyen P, Rehm M. A rational approach to perioperative fluid management. Anesthesiology 2008;109:723-740.
27. Jacob M, Chappell D, Hofmann-Kiefer K, Helfen T, Schuelke A, Jacob B, et al. The intravascular volume effect of Ringer's lactate is below 20%: a prospective study in humans. Crit Care. 2012 May 16;16(3):R86.
28. Holte K, Sharrock NE, Kehlet H. Pathophysiology and clinical implications of perioperative fluid excess. Br J Anaesth 2002;89:622–32.
29. Rehm M, Haller M, Orth V, Kreimeier U, Jacob M, Dressel H, 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;95:849-56.
30. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004; 350:2247-56.
31. Myburgh J, Cooper DJ, Finfer S, Bellomo R, Norton R, Bishop N, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N England J Med 2007;357:874-84.

32. Delaney AP, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. Crit Care Med 2011;39(2):386-91.
33. Alderson P, Bunn F, Li Wan Po A, Li L, Blackhall K, Roberts I, Schierhout G. Human albumin solution for resuscitation and volume expansion in critically ill patients. Cochrane Database Syst Rev 2011;(10):CD001208.
34. Dubois MJ, Orellana-Jimenez C, Melot C, De Backer D, Berre J, Leeman M et al. Albumin administration improves organ function in critically ill hypoalbuminemic patients: A prospective, randomized, controlled, pilot study. Crit Care Med 2006;34:2536-40.
35. Fernandez J, Monteagudo J, Bargallo X, Jimenez W, Bosch J, Arroyo V, Navasa M. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology. 2005;42:627-34.
36. Mortelmans YJ, Vermaut G, Verbruggen AM, Arnout JM, Vermylen J, Van Aken H, Mortelmans LA. Effects of 6% hydroxyethyl starch and 3% modified fluid gelatin on intravascular volume and coagulation during intraoperative hemodilution. Anesth Analg. 1995;81(6):1235-42.
37. Ertmer C, Rehberg S, Van Aken H, Westphal M. Relevance of non-albumin colloids in intensive care medicine. Best Pract Res Clin Anaesthesiol. 2009;23(2):193-212.
38. Schramko AA, Suojaranta-Ylinen RT, Kuitunen AH, Raivio PM, Kukkonen SI, Niemi TT. Comparison of the effect of 6% hydroxyethyl starch and gelatine on cardiac and stroke volume index: a randomized, controlled trial after cardiac surgery. Perfusion. 2010;25(5):283-91.
39. Schramko A, Suojaranta-Ylinen R, Kuitunen A, Raivio P, Kukkonen S, Niemi T. Hydroxyethylstarch and gelatin solutions impair blood coagulation after cardiac surgery: a prospective randomized trial. Br J Anaesth. 2010;104(6):691-97.
40. Rehm M. Limited applications for hydroxyethyl starch: background and alternative concepts. Anaesthesist. 2013;62(8):644-55.