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EDITORIAL

Fluid resuscitation with hydroxyethyl starch in perioperative acute hemorrhagic shock

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Introduction

Recently, several large studies have demonstrated that intraoperative hypotension can induce myocardial injury, worsening postoperative morbidity and mortality [1, 2]. Not only the degree of hypotension, but also the duration of intraoperative hypotension, can contribute to deteriorating postoperative outcomes [2]. Since acute massive hemorrhage can cause intraoperative hypotension, optimal fluid resuscitation should be performed immediately and appropriately to preserve blood pressure, peripheral perfusion and oxygen delivery to vital organs. Although a compatible blood transfusion might be the most suitable therapy for acute hemorrhage, colloids and crystalloids are usually administered first as intravascular replacement regimens for preservation of hemodynamics, to limit transfusion product and transfusion-related complications [3]. Colloids have been shown to maintain intravascular volume and hemodynamics better than crystalloids through preservation of colloid osmotic pressure [4, 5]. Several studies have demonstrated that fluid resuscitation with colloids compared to crystalloids might improve the outcomes of acute hemorrhagic shock [6, 7]. Moreover, recent studies have elucidated the detailed effects of fluid resuscitation with hydroxyethyl starch (HES) on microcirculation and micro-vessels in subjects with acute hemorrhagic shock [8, 9]. These studies have shown that fluid resuscitation with HES can maintain adequate tissue oxygenation and peripheral perfusion [8], and suppress vascular permeability via protection of glycocalyx layer in acute hemorrhagic shock [9].

Conversely, many randomized controlled studies focusing on patients with septic shock have shown that the advantages of fluid resuscitation with colloids, including HES and albumin, remain controversial [10, 11]. In particular, many studies have shown harmful effects of HES on the kidneys in various patients [12]. Moreover, the high molecular weight HES can cause coagulopathy [13]. These disadvantages of HES mainly in patients with septic shock have limited its use even in patients with hemorrhagic shock.

The author briefly summarized recent demonstrated advantageous effects and clinical concerns of the fluid resuscitation with HES in acute hemorrhagic shock.

Fluid resuscitation in septic shock or hemorrhagic shock

Perioperative physicians might have noted that most previous studies demonstrating the disadvantages of HES have focused on patients with septic shock, rather than those with hemorrhagic shock. In septic subjects, pro-inflammatory cytokines are activated, and the resultant inflammatory responses damage endothelial cells and/or the glycocalyx layer, leading to enhanced capillary leakage [14]. Therefore, the fluids administered, including the colloids, leak from the vessel to the interstitium, decreasing the desired volume expansion effect. Previous studies have shown that vascular endothelial growth factors (VEGFs) are associated with increased vascular permeability [15, 16] as part of the inflammatory response. VEGFs were reported to contribute to increased microvascular leak in acute respiratory distress syndrome [16]. Conversely, acute hemorrhagic shock itself might have less effect on VEGF levels [17]. Ganter et al. reported that VEGFs were not increased and their levels did not correlate with severity of injury and tissue hypoperfusion in the early stages after trauma [17]. In another

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animal study, fluid resuscitation with HES did not increase VEGF levels and hence, did not lead to capillary leakage [7]. Although prolonged hypoperfusion and hypoxia caused by hemorrhagic shock can induce inflammatory responses leading to enhanced vascular permeability and capillary leaks [18], earlier hemodynamic stability by fluid resuscitation with HES can attenuate the inflammatory responses [19, 20]. Thus, immediate fluid resuscitation with HES might be effective in preventing capillary leaks, which could be a new aspect of the fluid resuscitation strategy in acute hemorrhagic shock.

Fluid resuscitation focusing on vascular permeability and the glycocalyx

Previous studies have shown that the effects of fluid resuscitation on vascular endothelial permeability depend on the type of fluids administered [21, 22]. Fresh frozen plasma (FFP) was reported to have protective effects on vascular permeability [21] and the glycocalyx layer [22] after hemorrhagic shock. However, the use of FFP may be limited in emergent situations since it can cause several adverse effects [23]. Recent studies have shown that fluid resuscitation with a third-generation HES (HES 130/0.4) in acute hemorrhagic shock can preserve micro-vessel integrity [8] and protect the glycocalyx layer, leading to better outcomes in animal models of acute hemorrhage [9]. Komori et al. have demonstrated that fluid resuscitation with HES 130/0.4 effectively maintained adequate tissue oxygenation and peripheral perfusion compared to that with crystalloids in a rabbit model of hemorrhagic shock [8]. By examining the micro-vessel and perfusion status of the sublingual mucosa and an ear chamber using intravital microscopy, their study clearly showed that HES rather than crystalloids preserved hemodynamics and the microcirculation. Their results indicated that better recovery of central venous oxygen saturation and the central venous-to-arterial carbon dioxide gap could be achieved after fluid resuscitation with HES 130/0.4. Uzawa et al. also studied the efficacy of HES 130/0.4 on the microcirculation in a mouse model of acute hemorrhage [9]. They focused on modulation of the glycocalyx, which plays a crucial role in the preservation of vascular wall integrity and prevention of capillary leak, before and after fluid resuscitation in acute hemorrhagic shock. They found that fluid resuscitation with HES 130/0.4 but not the crystalloids (normal saline) could preserve glycocalyx thickness in acute hemorrhagic shock. They also found that an increased concentration of syndecan-1, which is a component of the glycocalyx and is released into the blood under hyper-permeability, was not observed in subjects treated with fluid resuscitation using HES 130/0.4. They confirmed preservation of the glycocalyx by HES 130/0.4 by linking it to the suppression of capillary leak of fluorescein isothiocyanate-labeled agents. On the basis of this evidence, fluid resuscitation with HES 130/0.4 in acute hemorrhagic shock might improve not only hemodynamics and macro-circulation, but also microcirculation, via preservation of vessel integrity and prevention of capillary leak. Further studies are desired to reveal the association between glycocalyx status and the degree of inflammatory responses during fluid resuscitation with colloids or crystalloids in acute hemorrhagic shock, and the effects of hemodilution through prevention of capillary leak on oxygen delivery to vital organs. Nevertheless, recent evidence suggests that the strategies for fluid resuscitation in acute hemorrhagic shock should be different from those in septic shock.

Clinical concerns on fluid resuscitation with HES in acute hemorrhagic shock

Previous studies have pointed out harmful effects of older generation of HES on the kidneys in various patients [12]. However, recent evidences have shown that a third-generation HES did not contribute to the renal dysfunction in subjects with hemorrhagic shock [6–8] and in surgical patients [24, 25], it preserved renal function through maintenance of microvascular oxygenation [6, 26].

While earlier fluid resuscitation with HES has advantageous effects on vascular permeability in acute hemorrhagic shock, prevention of capillary leak can induce hemodilution leading to coagulopathy. HES and albumin produced greater hemodilution and interfered with coagulation [27, 28]. Moreover, high molecular weight HES could induce coagulopathy via decreased plasma levels of coagulation factor VIII and Von Willebrand factor [28, 29]. Although the effects of a third generation of HES on coagulation factors have never been proved, and modern 6% HES 130/0.4 does not increase blood loss and transfusion requirements are the same as the older generation of HES [28, 29], perioperative physicians should consider dilution coagulopathy during fluid resuscitation with HES 130/0.4 in acute hemorrhagic shock.

Compliance with ethical standards

Conflict of interest The author has no financial interests in products related to this review.

References

1. Puelacher C, Lurati Buse G, Seeberger D, Sazgary L, Marbot S, Lampart A, Espinola J, Kindler C, Hammerer A, Seeberger E, Strebel I, Wildi K, Twerenbold R, du Fay de Lavallaz J, Steiner

L, Gurke L, Breidthardt T, Rentsch K, Buser A, Gualandro DM, Osswald S, Mueller C, BASEL-PMI Investigators. Perioperative myocardial injury after noncardiac surgery: incidence, mortality, and characterization. Circulation. 2018;137:1221–322.
2. Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, Kurz A. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: a retrospective cohort analysis. Anesthesiology. 2017;126:47–65.
3. Ferraris VA, Davenport DL, Saha SP, Austin PC, Zwischenberger JB. Surgical outcomes and transfusion of minimal amounts of blood in the operating room. Arch Surg. 2012;147:49–55.
4. Jacob M, Chappell D, Hofmann-Kiefer K, Helfen T, Schuelke A, Jacob B, Burges A, Conzen P, Rehm M. The intravascular volume effect of Ringer's lactate is below 20%: a prospective study in human. Crit Care. 2012;16:R86.
5. Rehm M, Haller M, Orth V, Kreimeier U, Jacob M, Dressel H, Mayer S, Brechtelsbauer H, Finsterer U. 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;95:849–86.
6. 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;107:693–702.
7. Roger C, Muller L, Deras P, Louart G, Nouvellon E, Molinari N, Goret L, Gris JC, Ripart J, de La Coussaye JE, Lefrant JY. Does the type of fluid affect rapidity of shock reversal in an anaesthetized-piglet model of near-fatal controlled haemorrhage? A randomized study. Br J Anaesth. 2014;112:1015–23.
8. Komori M, Samejima Y, Okamura K, Ichikawa J, Kodaka M, Nishiyama K, Tomizawa Y. Effects of crystalloids and colloids on microcirculation, central venous oxygen saturation, and central venous-to-arterial carbon dioxide gap in a rabbit model of hemorrhagic shock. J Anesth. 2019;33:108–17.
9. Uzawa K, Ushiyama A, Mitsuda S, Ando T, Sawa M, Miyao H, Yorozu T. The protective effect of hydroxyethyl starch solution on the glycocalyx layer in an acute hemorrhage mouse model. J Anesth. 2019. https://doi.org/10.1007/s00540-019-02692-8.
10. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, Madsen KR, Moller MH, Elkjaer JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard AL, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J, 6S Trial Group, Scandinavian Critical Care Trials Group. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367:124–34.
11. Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, Fanizza C, Caspani L, Faenza S, Grasselli G, Iapichino G, Antonelli M, Parrini V, Fiore G, Latini R, Gattinoni L, ALBIOS study investigators. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014;37:1412–21.
12. Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database Syst Rev. 2013;23:CD007594.
13. Treib J, Haass A, Pindur G. Coagulation disorders caused by hydroxyethyl starch. Thromb Haemost. 1997;78:974–83.
14. Steppan J, Hofer S, Funke B, Brenner T, Henrich M, Martin E, Weitz J, Hofmann U, Weigand MA. Sepsis and major abdominal surgery lead to flaking of the endothelial glycocalix. J Surg Res. 2011;165:136–41.
15. Pickkers P, Sprong T, Eijk Lv, Hoeven Hv, Smits P, Deuren Mv. Vascular endothelial growth factor is increased during the first 48 hours of human septic shock and correlates with vascular permeability. Shock. 2005;24:508–12.
16. Thickett DR, Armstrong L, Christie SJ, Millar AB. Vascular endothelial growth factor may contribute to increased vascular permeability in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2001;164:1601–5.
17. Ganter MT, Cohen MJ, Brohi K, Chesebro BB, Staudenmayer KL, Rahn P, Christiaans SC, Bir ND, Pittet JF. Angiopoietin-2, marker and mediator of endothelial activation with prognostic significance early after trauma? Ann Surg. 2008;247:320–6.
18. Lee CC, Chang IJ, Yen ZS, Hsu CY, Chen SY, Su CP, Chiang WC, Chen SC, Chen WJ. Delayed fluid resuscitation in hemorrhagic shock induces proinflammatory cytokine response. Ann Emerg Med. 2007;49:37–44.
19. Wang P, Li Y, Li J. Protective roles of hydroxyethyl starch 130/0.4 in intestinal inflammatory response and oxidative stress after hemorrhage shock and resuscitation in rats. Inflammation. 2009;32:71–82.
20. Chen G, You G, Wang Y, Lu M, Cheng W, Yang J, Zhao L, Zhou H. Effects of synthetic colloids on oxidative stress and inflammatory response in hemorrhagic shock: comparison of hydroxyethyl starch 130/0.4, hydroxyethyl starch 200/0.5, and succinylated gelatin. Crit Care. 2013;17:R141.
21. Pati S, Matijevic N, Doursout MF, Ko T, Cao Y, Deng X, Kozar RA, Hartwell E, Conyers J, Holcomb JB. Protective effects of fresh frozen plasma on vascular endothelial permeability, coagulation, and resuscitation after hemorrhagic shock are time dependent and diminish between days 0 and 5 after thaw. J Trauma. 2010;69:S55–63.
22. Torres Filho IP, Torres LN, Salgado C, Dubick MA. Plasma syndecan-1 and heparan sulfate correlate with microvascular glycocalyx degradation in hemorrhaged rats after different resuscitation fluids. Am J Physiol Heart Circ Physiol. 2016;310(11):H1468–H14781478.
23. Pandey S, Vyas GN. Adverse effects of plasma transfusion. Transfusion. 2012;52(Suppl 1):65S–79S.
24. Van Der Linden P, James M, Mythen M, Weiskopf RB. Safety of modern starches used during surgery. Anesth Analg. 2013;116:35–48.
25. Kabon B, Sessler DI, Kurz A, Crystalloid-Colloid Study Team. Effect of intraoperative goal-directed balanced crystalloid versus colloid administration on major postoperative morbidity: a randomized trial. Anesthesiology. 2019;130:728–44.
26. Konrad FM, Mik EG, Bodmer SI, Ates NB, Willems HF, Klingel K, de Geus HR, Stolker RJ, Johannes T. Acute normovolemic hemodilution in the pig is associated with renal tissue edema, impaired renal microvascular oxygenation, and functional loss. Anesthesiology. 2013;119:256–69.
27. Skhirtladze K, Base EM, Lassnigg A, Kaider A, Linke S, Dworschak M, Hiesmayr MJ. Comparison of the effects of albumin 5%, hydroxyethyl starch 130/0.4 6%, and Ringer's lactate on blood loss and coagulation after cardiac surgery. Br J Anaesth. 2014;112:255–64.
28. Kozek-Langenecker SA, Jungheinrich C, Sauermann W, Van der Linden P. The effects of hydoxyethyl starch 130/0.4 (6%) on blood loss and use of blood products in major surgery: a pooled analysis of randomized controlled trials. Anesth Analg. 2008;107:382–90.
29. Jungheinrich C, Sauermann W, Bepperling F, Vogt NH. Volume efficacy and reduced influence on measures of coagulation using hydroxyethyl starch 130/0.4 (6%) with an optimised in vivo molecular weight in orthopaedic surgery: a randomised, double-blind study. Drugs R D. 2004;5:1–9.