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Review Article

IS THERE A PLACE FOR CRYSTALLOIDS AND COLLOIDS IN REMOTE DAMAGE CONTROL RESUSCITATION?

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ABSTRACT—Crystalloids and colloids are used in prehospital fluid resuscitation to replace blood loss and preserve tissue perfusion until definite surgical control of bleeding can be achieved. However, large volumes of fluids will increase bleeding by elevating blood pressure, dislodging blood clots, and diluting coagulation factors and platelets. Hypotensive fluid resuscitation strategies are used to avoid worsening of uncontrolled bleeding. This is largely supported by animal studies. Most clinical evidence suggests that restricting fluid therapy is associated with improved outcome. Remote damage control resuscitation emphasizes the early use of blood products and restriction of other fluids to support coagulation and tissue oxygenation. Controversy regarding the optimal choice and composition of resuscitation fluids is ongoing. Compared with crystalloids, less colloid is needed for the same expansion of intravascular volume. On the other hand, colloids may cause coagulopathy not only related to dilution. The most important advantage of using colloids is logistical because less volume and weight are needed. In conclusion, prehospital fluid resuscitation is considered the standard of care, but there is little clinical evidence supporting the use of either crystalloids or colloids in remote damage control resuscitation. Alternative resuscitation fluids are needed.

KEYWORDS—Military, trauma, coagulopathy, hemorrhage, RDCR, plasma

INTRODUCTION

Crystalloids and colloids are used in prehospital fluid resuscitation to replace lost blood volume and provide preload for circulation. This is done with the intention to improve tissue perfusion, delay time to exsanguinations, and provide a bridge to surgical hemostasis. However, large volumes of fluids will increase blood pressure and may increase bleeding. Increased blood pressure could also dislodge blood clots and further increase bleeding. Furthermore, colloids and crystalloids are capable of diluting the concentration of coagulation factors, platelets and red blood cells, causing coagulopathy. Clinical data suggest that prehospital fluid resuscitation could be harmful, particularly in penetrating trauma (1–3). Administration of fluids in the prehospital setting to a bleeding patient is considered a "standard of care" (4). Because of this, it will not be possible to conduct clinical trials comparing fluid resuscitation with no resuscitation. In remote damage control resuscitation (RDCR), the aim is to combat the lethal triad of hypothermia, acidosis, and coagulopathy by means of hypotensive resuscitation, the use of blood products, and aggressive (re)warming of the patient. This review explores the limited role of crystalloids and colloids in the RDCR setting. The use of crystalloids and colloids for resuscitation has been extensively reviewed elsewhere (5–7).

Hypotensive resuscitation

To balance the risk of increased bleeding with the risk of circulatory collapse, various hypotensive resuscitation strategies are used. Usually, small aliquots of fluids (e.g., 50 – 100 mL of hydroxyethyl starch (HES) or 250 mL of Ringer's lactate solution) are given in repeated doses to maintain a palpable radial pulse or a systolic blood pressure of 90 mmHg. The concept of hypotensive resuscitation has been extrapolated from "delayed fluid resuscitation" and is largely supported by animal data. The relationship between mortality and the amounts of fluids given is U-shaped in animal models of uncontrolled hemorrhage (8). Too much and too little fluids both result in increased mortality, suggesting that an ideal amount of fluid can be lifesaving. However, this "ideal amount of fluids" is difficult to determine in the clinical setting because it would depend on unknown factors such as rate of bleeding and clot strength. The landmark article by Bickell et al. (1) reported improved survival in patients sustaining penetrating truncal trauma when fluid therapy was delayed. However, patients who died during transport were excluded from the analyses, making the interpretation of these results difficult. Two clinical trials on hypotensive resuscitation have been published, both in-hospital. Dutton et al. (9) randomized 110 patients to a protocol with a target systolic blood pressure of either 70 or 100 mmHg. With four deaths in each group, the study was not powered to show a benefit. The authors conclude that hypotensive fluid resuscitation is safe. Preliminary data from an ongoing randomized clinical trial have shown a significant reduction in the use of blood products and intravenous fluids with a hypotensive resuscitation strategy (10). The patients receiving hypotensive fluid resuscitation had less postoperative coagulopathy and a lower early postoperative mortality.

Crystalloids

Crystalloids are solutions of electrolytes used as volume expanders. Crystalloids contain no macromolecules and diffuse

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freely out of the vascular compartment. The simplest crystalloid is normal saline, containing 9 mg/mL of NaCl. Saline is isotonic, but infusion of large volumes will cause electrolyte disturbances, such as hyperchloremia (5). The most frequently used crystalloid in Europe is lactated or acetated Ringer's solution. Ringer's content resembles the electrolyte concentrations in plasma and is buffered by lactate or acetate. The latter has a theoretical advantage because less energy is needed to metabolize acetate than lactate. It might also be better to avoid infusion of lactate while the patient is in a state of lactic acidosis. Crystalloids cause edema, compartment syndromes, acute respiratory distress syndrome, dilution coagulopathy, and hyperchloremic acidosis (saline) when large volumes are used (5, 6). Balanced crystalloids such as Ringer's acetate cause less electrolyte and acid/base disturbances than saline (11) and are recommended for trauma patients (7). Crystalloids are used to replace blood in a ratio of 1:3. This represents a logistical burden in the prehospital setting, especially for the military medics who need to carry several liters of resuscitation fluids.

Colloids

Artificial colloids are macromolecular solutions based on glucose polymers, gelatins, or amylopectin. They are mainly used as plasma substitutes. Albumin is the only natural colloid of human origin. The molecules of colloids have a high molecular weight and are relatively incapable of crossing the healthy capillary membrane (7). Colloids have the advantage of staying longer in circulation. Less colloid is needed for the same expansion of intravascular volume. Consequently, colloids cause less edema. In a military setting, there is a logistical advantage of using colloids because less volume and weight need to be carried. One liter of colloid will roughly replace 3 L of crystalloids at a third of the weight. However, artificial colloids cause varying degrees of coagulopathy (12, 13). Anaphylactic reactions have also been described (14).

Dextran is a glucose polymer used mainly for prevention and treatment of deep vein thrombosis. It is not suitable for trauma patients because it causes coagulopathy in relatively low concentrations (15). Dextran infusion leads to a drop in concentration of von Willebrand factor (vWF) and FVIII not only related to dilution, causing a state similar to von Willebrand disease type I (12, 13). Von Willebrand factor binds to subendothelial collagen and platelets, facilitating platelet adhesion to the injured vessel wall. Consequently, lack of vWF impairs primary hemostasis. Dextran accelerates clot fibrinolysis by altering the polymerization of fibrin (13). Clots formed in the presence of dextran are bulky, with less tensile strength, and are more easily disrupted (12).

Hydroxyethyl starch solutions are synthesized from amylopectin. They are classified by their mean molecular weight and by their rate of molar substitution of glucose by hydroxyethyl-groups. High-molecular-weight HES solutions are typically 450 to 670 kd, with a substitution rate of 0.6 to 0.75. Medium-molecular-weight HES solutions are 200 to 260 kd, with a substitution rate of 0.45 to 0.62. Low-molecular-weight HES are characterized by a molecular weight of 70 to 130 kd, with a substitution rate of 0.5. The interference of HES solutions on the coagulation system is related to their molecular weight, with the high-molecular-weight HES solutions causing more interference and the low-molecular-weight solutions causing less. Like dextrans, administration of HES solutions is also associated with a drop in vWF and FVIII, mimicking von Willebrand disease type 1 (13). Fibrinogen, FII, FXIII, and FX activities are all reduced, but the acquired reduction of fibrinogen is probably most important in developing coagulopathy (16). Hydroxyethyl starch molecules are incorporated into clots, making them weaker and accelerate fibrinolysis. Clinically, prolonged bleeding times have been observed with high- and, in some studies, with medium-molecular-weight HES (12, 13). Recently, the general safety of HES solutions has been questioned. Results from large clinical trials showed increased mortality (17) and increased risk of kidney failure (17–19) when resuscitated with HES. The European Medicines Agency's Pharmacovigilance Risk Assessment Committee has recommended withdrawal of marketing license for all HES-containing solutions.

Table 1. **Effects on coagulation and volume expansion of different crystalloids and colloids**

Volume expander	Commercial name	Volume expansion, %	Effect on hemostasis	Mechanism of coagulopathy
Plasma	LyoPlas	100	0	None
Albumin 4%	Albunorm	80	(+)	Dilution only
Albumin 20%	Flexbumin	200 – 400	(+)	Dilution only
Saline	Natriumklorid	25 – 33	(+)	Dilution only
Ringer's	Ringer-Acetat	20 – 30	(+)	Dilution only
Gelatins	Haemaccel	70 – 90	+	Impaired platelet aggregation
Low-molecular-weight HES	Voluven	130	+	Acquired fibrinogen deficiency
Medium-molecular-weight HES	Hestril	100	++	Acquired fibrinogen deficiency
High-molecular-weight HES	Hextend	100	++ (+)	Acquired fibrinogen deficiency
Dextran	Macrodex	120 – 200	+++	Reduction of vWF and FVIII Accelerated fibrinolysis
Hypertonic saline (7.5%) with HES 200/0.5	HyperHAES	200 – 300	+	As medium-molecular-weight HES, but small dose
Hypertonic saline (7.5%) with Dextran 70	RescueFlow	200 – 300	++	As Dextran, but small dose

Effect on hemostasis: +, weak; ++, moderate; +++, significant.

Gelatins are polypeptides synthesized from bovine collagen. Two forms are produced, a succinylated and a urea-linked form. It was generally believed that gelatins did not impair hemostasis, except by dilution. However, both forms of gelatins have been shown to impair platelet aggregation, resulting in prolonged bleeding time (12, 13). Clots formed in the presence of gelatins may also have reduced strength. The clinical consequences of these findings are uncertain because most authors report no increased perioperative bleeding (12, 13).

Hypertonic–hyperoncotic solutions

Small amounts (4 mL/kg body weight) of hypertonic 7.2% to 7.5% saline (HTS) or hypertonic–hyperoncotic solutions can be used for rapid restoration of blood pressure, cardiovascular function, and tissue perfusion (20). Hypertonic saline causes plasma expansion by mobilizing fluids from intracellular to the interstitial and intravascular spaces (21). From a military perspective, HTS is advantageous logistically because 250 mL of HTS will provide the same volume expansion as 3 L of crystalloids (22). Animal studies were promising, showing attenuated inflammation, enhanced organ function, and improved survival in rats resuscitated after hemorrhage (23, 24). However, human clinical trials have so far been disappointing—with no documented survival benefit (25–27). Hypertonic saline remains a useful tool for controlling intracranial pressure in the critical care setting (28).

Crystalloids versus colloids

Controversy regarding the optimal choice and composition of resuscitation fluids is ongoing (Table 1). Two systematic reviews have compared crystalloids with colloids, without finding any survival benefit of using colloids (29, 30). It is known that most colloids interfere with the coagulation system and that coagulopathy is associated with increased mortality in trauma patients (31). The side effects of crystalloids, such as acute respiratory distress syndrome and compartment syndromes, are usually not fatal immediately and can be handled in the intensive care unit. With the latest controversy regarding the safety of HES in mind, it is difficult to justify the use of colloids from a pure medical point of view. However, the logistical advantage of only having to carry one third of the weight is hard to ignore, especially in austere environments. Some military forces, including the United States, are using Hextend (a HES solution) as their primary resuscitation fluid for this reason.

Both crystalloids and colloids can replace lost volume but will, at the same time, dilute coagulation factors and red blood cells. When large volumes are used, this will cause coagulopathy and reduced oxygen-carrying capacity. For these reasons, military forces are developing RDCR strategies, where the use of crystalloids and colloids is restricted. Other products for replacing lost blood volume are needed.

What are the alternatives?

Accumulating evidence suggest that warm whole blood might be the optimal resuscitation fluid (32). This is rarely available prehospital at the point of injury and does have some logistical, tactical, and medicolegal challenges. Today, the best alternative is probably reconstituted freeze-dried plasma. It provides volume comparable to colloids, without causing dilution coagulopathy (33). It has a shelf life of more than a year in room temperature and can be reconstituted in 5 min. The value of this product has been known since World War II (34), but so far, there are no human trials exploring its use as a resuscitation fluid for hypotensive resuscitation. Nevertheless, many military units, including the Israeli Defense Forces (35) and Norwegian Special Forces, have included freeze-dried plasma in their RDCR protocols.

CONCLUSIONS

Prehospital fluid resuscitation is considered the standard of care, but there is little clinical evidence supporting the use of either crystalloids or colloids in RDCR. The only reason to choose colloids over crystalloids is logistical because less volume and weight are needed. Alternative resuscitation fluids are needed.

REFERENCES

1. Bickell WH, Wall MJ Jr, Pepe PE, Martin RR, Ginger VF, Allen MK, Mattox KL: Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 331:1105–1109, 1994.
2. Dretzke J, Sandercock J, Bayliss S, Burls A: Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients. *Health Technol Assess* 8:1–103, 2004.
3. Haut ER, Kalish BT, Cotton BA, Efron DT, Haider AH, Stevens KA, Kieninger AN, Cornwell EE 3rd, Chang DC: Prehospital intravenous fluid administration is associated with higher mortality in trauma patients: a National Trauma Data Bank analysis. *Ann Surg* 253:371–377, 2011.
4. Strauss DC, Thomas JM: What does the medical profession mean by "standard of care?". *J Clin Oncol* 27:e192–e193, 2009.
5. Cotton BA, Guy JS, Morris JA, Abumrad NN: The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. *Shock* 26:115–121, 2006.
6. Santry HP, Alam HB: Fluid resuscitation: past, present, and the future. *Shock* 33:229–241, 2010.
7. Myburgh JA, Mythen MG: Resuscitation fluids. *N Engl J Med* 369: 1243–1251, 2013.
8. Hahn RG: Fluid therapy in uncontrolled hemorrhage—what experimental models have taught us. *Acta Anaesthesiol Scand* 57:16–28, 2013.
9. Dutton RP, Mackenzie CF, Scalea TM: Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. *J Trauma* 52:1141–1146, 2002.
10. Morrison CA, Carrick MM, Norman MA, Scott BG, Welsh FJ, Tsai P, Liscum KR, Wall MJ Jr, Mattox KL: Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. *J Trauma* 70:652–663, 2011.
11. Morgan TJ: The ideal crystalloid—what is "balanced"? *Curr Opin Crit Care* 19:299–307, 2013.
12. de Jonge E, Levi M: Effects of different plasma substitutes on blood coagulation: a comparative review. *Crit Care Med* 29:1261–1267, 2001.
13. Van der Linden P, Ickx BE: The effects of colloid solutions on hemostasis. *Can J Anaesth* 53(Suppl 6):S30–S39, 2006.
14. Treib J, Baron JF, Grauer MT, Strauss RG: An international view of hydroxyethyl starches. *Intensive Care Med* 25:258–268, 1999.
15. Petroianu GA, Liu J, Maleck WH, Mattinger C, Bergler WF: The effect of *in vitro* hemodilution with gelatin, dextran, hydroxyethyl starch, or Ringer's solution on thrombelastograph. *Anesth Analg* 90:795–800, 2000.
16. Fenger-Eriksen C, Tønnesen E, Ingerslev J, Sørensen B: Mechanisms of hydroxyethyl starch–induced dilutional coagulopathy. *J Thromb Haemost* 7:1099–1105, 2009.
17. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, et al.: Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 367: 124–134, 2012.
18. Guidet B, Martinet O, Boulain T, Philippart F, Poussel JF, Maizel J, Forceville X, Feissel M, Hasselmann M, Heininger A, 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* 16:R94, 2012.

19. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, et al.: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 367:1901–1911, 2012.
20. Tollofsrud S, Tonnessen T, Skraastad O, Noddeland H: Hypertonic saline and dextran in normovolaemic and hypovolaemic healthy volunteers increases interstitial and intravascular fluid volumes. *Acta Anaesthesiol Scand* 42: 145–153, 1998.
21. Strandvik GF: Hypertonic saline in critical care: a review of the literature and guidelines for use in hypotensive states and raised intracranial pressure. *Anaesthesia* 64:990–1003, 2009.
22. Dubick MA, Atkins JL: Small-volume fluid resuscitation for the far-forward combat environment: current concepts. *J Trauma* 54(Suppl 5):S43–S45, 2003.
23. Angle N, Hoyt DB, Coimbra R, Liu F, Herdon-Remelius C, Loomis W, Junger WG: Hypertonic saline resuscitation diminishes lung injury by suppressing neutrophil activation after hemorrhagic shock. *Shock* 9:164–170, 1998.
24. Deitch EA, Shi HP, Feketeova E, Hauser CJ, Xu DZ: Hypertonic saline resuscitation limits neutrophil activation after trauma-hemorrhagic shock. *Shock* 19:328–333, 2003.
25. Bulger EM, May S, Brasel KJ, Schreiber M, Kerby JD, Tisherman SA, Newgard C, Slutsky A, Coimbra R, Emerson S, et al.: Out-of-hospital hypertonic resuscitation following severe traumatic brain injury: a randomized controlled trial. *JAMA* 304:1455–1464, 2010.
26. Bulger EM, May S, Kerby JD, Emerson S, Stiell IG, Schreiber MA, Brasel KJ, Tisherman SA, Coimbra R, Rizoli S, et al.: Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: a randomized, placebo controlled trial. *Ann Surg* 253:431–441, 2011.
27. Junger WG, Rhind SG, Rizoli SB, Cuschieri J, Shiu MY, Baker AJ, Li L, Shek PN, Hoyt DB, Bulger EM: Resuscitation of traumatic hemorrhagic shock patients with hypertonic saline-without dextran inhibits neutrophil and endothelial cell activation. *Shock* 38:341–350, 2012.
28. Lazaridis C, Neyens R, Bodle J, DeSantis SM: High-osmolarity saline in neurocritical care: systematic review and meta-analysis. *Crit Care Med* 41: 1353–1360, 2013.
29. Choi PT, Yip G, Quinonez LG, Cook DJ: Crystalloids vs. colloids in fluid resuscitation: a systematic review. *Crit Care Med* 27:200–210, 1999.
30. Perel P, Roberts I, Ker K: Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2:CD000567, 2013.
31. Brohi K, Cohen MJ, Davenport RA: Acute coagulopathy of trauma: mechanism, identification and effect. *Curr Opin Crit Care* 13:680–685, 2007.
32. Spinella PC, Perkins JG, Grathwohl KW, Beekley AC, Holcomb JB: Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. *J Trauma* 66(Suppl 4): S69–S76, 2009.
33. Bolliger D, Görlinger K, Tanaka KA: Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. *Anesthesiology* 113: 1205–1219, 2010.
34. Beecher HK: Preparation of battle casualties for surgery. *Ann Surg* 121: 769–792, 1945.
35. Glassberg E, Nadler R, Gendler S, Abramovich A, Spinella PC, Gerhardt RT, Holcomb JB, Kreiss Y: Freeze dried plasma at the point of injury—from concept to doctrine. *Shock* 40:444–450, 2013.