

Voluven, A New Colloid Solution

Anna Mizzi, MD^a, Thanh Tran^b, Rachel Karlnoski, PhD^{b,c,*},
Ashley Anderson, BS^b, Devanand Mangar, MD^b,
Enrico M. Camporesi, MD^{b,d,e}

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A variety of fluid solutions can be used as intravascular replacement for surgical volume loss, and to avoid or delay blood transfusions. Crystalloid solutions, such as Ringer lactate, are typically administered at a rate of 3 or 4 times the volume of blood loss caused by continuous rapid extravasations. Approximately 20% of the volume initially administered remains in the intravascular space hours later. Therefore, rapid infusion of large amounts of crystalloid solutions can cause problems in elderly patients with limited cardiovascular reserve, and can lead to pulmonary and systemic edema. Alternatively, a commonly used synthetic colloid, hydroxyethyl starch (HES), readily allows for a 1:1 replacement ratio of intravascular volume to shed blood, and remains in the intravascular space longer compared with crystalloid solutions. However, HES can induce coagulopathy during prolonged surgical procedures because of the reduced release of factor VIII, von Willebrand Factor (vWF), and impaired platelet function.

There are many types of HES according to molecular weight (MW) and degree of substitution (DS). In general, HES with a low MW and low DS is preferred because HES solutions with a high MW and high DS are harder to metabolize and eliminate from the intravascular space. This prolonged stay results in extended adverse effects on coagulation. Six percent HES with a MW of 130 kDa and a DS of 0.4 in a saline medium (Voluven, Fresenius Kabi, Germany) has the lowest MW/DS ratio among other HES on the market and therefore is purported to induce less coagulation impairment. This review of crystalloid and colloid fluid replacement alternatives explores recently published evidence of the clinical utility of Voluven.

^a Department of Cardiothoracic and Vascular Anesthesia, San Raffaele Hospital, "Vita e Salute" University, Milan, Italy

^b Florida Gulf-to-Bay Anesthesiology Associates, 1 Tampa General Circle Suite A327, Tampa, FL 33606, USA

^c Department of Plastic Surgery, University of South Florida, Tampa, FL, USA

^d Department of Surgery, University of South Florida, Tampa, FL, USA

^e Department of Anesthesiology, University of South Florida, Tampa, FL, USA

* Corresponding author. Florida Gulf-to-Bay Anesthesiology Associates, 1 Tampa General Circle Suite A327, Tampa, FL 33606.

E-mail address: rkarnoski@fgtba.com

FLUID REPLACEMENT

Use of fluid replacement to retain bodily fluid balance requires knowledge of water, sodium, and colloid distribution in the body. Total body water includes approximately 28 L of intracellular fluid and 14 L of extracellular fluid. Plasma volume comprises approximately 3 L; and red blood cell volume comprises 2 L. The body as a whole depends on maintaining this balance in total body water. Therefore, efficient usage of fluid replacement with surgical blood loss is critical.

Blood transfusions offer the advantages of increased tissue oxygenation and reduced bleeding, but there are also associated risks, such as allergic reactions and infection. Although blood transfusions are beneficial, this method is costly and not always readily available. Another effective method in responding to surgical blood loss is the injection of crystalloid and/or colloid solutions to increase the intravascular volume rather than adding the amount lost directly.^{1,2} Perioperative physiologic alterations and anesthesia can also lead to changes in fluid balance. Anesthesiologists must be able to respond and manage the balance, corresponding to fluid therapy.

COLLOIDS VERSUS CRYSTALLOIDS

Colloids and crystalloids are classifications of substances based on their diffusion rates through capillary membranes. In 1861, a study was performed by Thomas Graham observing different substances and classifying them into 2 categories of colloids and crystalloids based on their abilities to diffuse through parchment paper, which acted as a capillary membrane.³ Substances that passed through the parchment paper readily were classified as crystalloids, whereas substances that passed through slowly were classified as colloids. Even today, the distinction between colloids and crystalloids is not completely clear for a specific substance because the phase can change in different conditions; for example, soap in water is considered a colloid, whereas soap submerged in alcohol is a crystalloid. However, the original hypothesis regarding the different capabilities when passing through a membrane still holds. Therefore, intravenous fluids are distinguished based on their abilities to diffuse through the capillary membrane and to distribute properly between the intravascular and extravascular spaces.⁴

In fluid therapy, there is much debate about the effectiveness of colloid versus crystalloid solutions. Colloid advocates argue that use of crystalloid solution attenuates the plasma oncotic pressure leading to fluid movement from the intravascular space to the interstitial space.⁵ On the other hand, crystalloid advocates suggest that albumin molecules penetrate easily into the pulmonary interstitial space and exit through the lymphatic system returning to systemic circulation.²

CRYSTALLOIDS

Crystalloid fluids are often composed of salt solutions such as sodium chloride; therefore, they are inexpensive and readily accessible. These solutions are classified as isotonic, hypertonic, or hypotonic. As crystalloids consist of salts, their ions are small and capable of moving freely across the semipermeable capillary membrane. As a result of this free movement, crystalloid fluids tend to distribute evenly throughout the intravascular and extravascular space. This increases the interstitial volume rather than the plasma volume, which is the main component of extravascular fluid.¹ The required replacement of crystalloid is threefold or fourfold of the lost blood volume. The distribution of crystalloid is 1:4, meaning 3 L intravascularly and 12 L extravascularly. This distribution also indicates that the crystalloid would likely expand more in

the extravascular space rather than the intravascular space.² Thus, injecting crystalloid fluids would likely result in expansion of the interstitial volume. As a consequence, large amounts need to be injected for the crystalloid fluids to remain in the intravascular space, increasing the plasma volume.⁴

Examples of Crystalloids

Some of the common crystalloids include normal or isotonic saline, lactated Ringer solution, Normosol or PlasmaLyte, hypertonic salt solutions, and dextrose.

Normal saline is a 0.9% sodium chloride solution. Because its chloride content is higher than that of plasma, hyperchloremic metabolic acidosis may occur.⁴ Normal saline has no buffer or other electrolytes, and can be administered in patients with renal dysfunction because it contains no potassium.²

Lactated Ringer solution consists of potassium and calcium in a sodium chloride diluent. British physician Sydney Ringer's initial solution was developed in 1880 to induce heart contractions in frogs. Later, American pediatrician Alexis Hartmann proposed adding sodium to the solution to treat metabolic acidosis in the 1930s.⁶ From then on the solution became popular in intravenous therapy. Because of the calcium content, lactated Ringer solution is not likely to be mixed with blood transfusions as the calcium binds to certain drugs, making them less effective (specifically anticoagulants). Lactated Ringer solution has not been seen to have any advantage over normal saline.⁶

Normosol or PlasmaLyte has the advantage of a buffer capacity making its pH equal to the pH of plasma. It is also advantageous in patients who show reduction in magnesium. However, this could be a disadvantage in patients with renal deficiency, inducing hypermagnesemia, when the kidney fails to excrete magnesium leading to high levels retained in the blood.⁴

Hypertonic salt solutions have concentrations ranging from 250 to 1200 mEq/L. Their required volumes are less than those of the other solutions due to greater sodium concentration. The reduced water injection, due to the osmotic pressure forcing water from the intracellular to extracellular space, may lead to edema reduction. Another major advantage of hypertonic saline is its effectiveness in field triage with trauma as it is inexpensive, easily stored, and capable of expanding the plasma volume quickly.² However, they are used less frequently than the other solutions.

Dextrose is often added to intravenous solutions to enhance osmolarity. When added to Ringer solution or normal saline, dextrose generates hypertonic infusion. Because dextrose is glucose, administering dextrose could cause cell dehydration in patients with glucose impairment. On the other hand, a useful adjunct of glucose infusion is suppression of muscle protein catabolism as suggested by Mikura and colleagues.⁷

COLLOIDS

Colloids are composed of large molecules, such as proteins, that cannot pass through a semipermeable membrane. Therefore, the solute concentration inside the cell is higher than that outside the cell, increasing the flow of water into the cell, thus building up a pressure called the oncotic pressure or colloid osmotic pressure. This oncotic pressure leads to an increase in volume of the intravascular section, specifically the plasma volume, rather than the interstitial space of the extravascular section. As a result, lesser amounts need to be injected for the colloid fluids to stay in the intravascular section compared with crystalloid fluids. The capability of each colloid solution to expand the volume of plasma is proportional to the oncotic pressure. When the

oncotic pressure of the colloid solution exceeds the oncotic pressure of plasma, the expansion exceeds the volume of infusion. Colloid solutions, however, are more expensive than crystalloid solutions due to their content, such as protein extracted from the body.¹ Another advantage of colloids is that there is minimal to no risk of infection or transmission of viral diseases.²

Examples of Colloids

Colloids that are often used include different percentages of albumin, hetastarch, pentastarch, and dextran.¹

Albumin is a blood-derived, transport protein that is prepared by heating methods, and is available as albumin 5% and 25% in normal saline diluent. Albumin at 25% is given in smaller volumes compared with 5% albumin because the amount of associated sodium is less. The oncotic pressure of 25% albumin is greater than the oncotic pressure of 5% albumin at 70 mmHg and 20 mmHg, respectively. Therefore, 25% albumin expands plasma volume more than 5% albumin. For example, when 100 mL of 25% albumin is infused, the plasma volume is said to expand to 400 to 500 mL. Heat-treated albumin eliminates any associated viral transmission, such as human immunodeficiency virus, which makes the patient more susceptible to infections.^{4,8}

Hetastarch is commonly prepared as a 6% solution in normal saline. Hetastarch consists of amylopectin molecules, one of the constituents of starch. Amylopectin molecules are glucose polymers in plants that range in size from 100 to 1,000,000 Da. Hetastarch is a synthetic colloid that has a similar MW and effect to 5% albumin; but it is lower in cost and stronger because its higher oncotic pressure allows it to expand the plasma volume to 30 mmHg versus 20 mmHg with 5% albumin. To be excreted by kidneys, hetastarch molecules must first be cleaved by amylase enzymes, which can lead to an increase in amylase levels. These colloids can also affect the coagulation cascade; hetastarch can produce dilutional results like other volume expanders and decrease factor VIII and vWF levels. Hetastarch can also reduce the accessibility of glycoprotein IIb/IIIa on the surface of platelets.⁹ All these effects on coagulation parameters can result in severe coagulopathy.

Pentastarch is a form of hetastarch that is lower in MW and consists of smaller molecules. As pentastarch has higher quantity and smaller molecules than hetastarch, it results in higher oncotic pressure and better expansion. Pentastarch is prepared as 10% in normal saline. It is often preferred over hetastarch because it is less likely to lead to the same undesirable effects, such as coagulopathy.² Pentastarch is mainly used in Europe, not the United States.

Dextrans are polymers of glucose from the bacterium *Leuconostoc*, developed in a medium made up of sucrose. Dextrans are available as 10% dextrans 70 and 40 in normal saline. Dextran 70 is a volume expander, whereas dextran 40 is used to increase blood flow. Both dextrans have an oncotic pressure of 40 mmHg, greater than that of plasma at 20 mmHg. Dextran 40 is a better short-term volume expander than dextran 70, particularly for a few hours compared with the lengthened effect of dextran 70. Thus, dextran 70 is often preferred over dextran 40. Dextran can be antigenic and can lead to anaphylactoid reactions, but the incidence of such severe reactions has been reduced dramatically from about 5% to 0.032% in the past 20 years. Dextrans can disable the crossmatch for blood by coating red blood cells and increasing the erythrocyte sedimentation rate. Dextrans are also considered as a cause of acute renal failure because their oncotic pressure is higher than plasma, reducing filtration pressure in the kidneys.^{2,10}

HES 130/0.4 (Voluven, Fresenius/Hospira, Germany): A New Colloid

HES is derived from amylopectin, a polysaccharide from maize, and is similar to glycogen. HES is prepared by hydrolysis, *in vivo*, by serum α -amylase and amylopectin hydroxyethylation. Hydroxyethylation, which is also known as molar substitution, helps to identify the different starches. Hydroxyethyl substitution causes the solubility of starch to increase and delays hydrolysis, thus delaying the degradation of starch molecules and excretion.¹¹

HES is excreted by the kidneys and the rate of decomposition of starch is based on the molar substitution and C2/C6 ratio, which is the substitution of hydroxyethyl at the C2 or C6 location. The higher the molar substitution and C2/C6 ratios, the slower the decomposition, ultimately leading to plasma accumulation. The higher molar substitution means a larger molecule; so the larger the molecule, the slower the degradation in the body.¹²

Another form of starch that is now in favor as an alternative to older HES is Voluven. The United States Food and Drug Administration approved the use of Voluven for intravenous treatment of blood loss in December 2007.¹³ **Table 1** compares Voluven pharmacokinetics with hetastarch (Hespan, B. Braun Medical) and albumin. Voluven, like hetastarch and pentastarch, consists of artificial starch that is insoluble in water. Voluven is also mixed in a salt solution so that its salt concentration is similar to that in blood. Also like the older starches, this newly introduced starch acts as a plasma volume expander.¹¹

The average MW of Voluven is 130,000 Da. The ratio of hydroxyethyl group substitution to the glucose units, or molar substitution, in the Voluven structure is 0.4. From these properties, Voluven is usually presented as hydroxyethyl starch 130/0.4. Hetastarch is usually seen as 450/0.7; and pentastarch appears as 200/0.5.¹¹

Voluven molecules are smaller than those of hetastarch and pentastarch, and the molecular decomposition of Voluven is faster. Thus, Voluven is likely excreted from the body faster and is less likely to cause plasma accumulation. These characteristics make Voluven less likely to cause the same undesirable effects as the other starches.¹²

A problem associated with HES is possible hemostasis impairment, specifically on vWF. However, the problem seems to be associated more with the higher substituted HES that have medium to high MW.¹¹ An increasing number of prospective studies have compared Voluven with other starches (**Table 2**).

Voluven was compared with the standard HES 200/0.5 (pentastarch) in 59 coronary artery bypass patients and was found to be similar in efficacy.¹⁴ The mean infusion volume of HES was comparable between the 2 groups (2550 ± 561 mL in the group

Table 1
Single-dose pharmacokinetics of plasma expanders (data provided by Voluven Fresenius/Hospira)

	Voluven (130/0.4)	Hespan (600/0.75)	Albumin
Clearance	17–31.4 mL/min	0.98 mL/min	—
Half-life	12–16 h	46.4 h	15 d
Elimination in urine	62% within 72 h	33% within 24 h 46% after 2 d 64% after 8 d	No renal elimination
Plasma concentrations of HES	14% of peak at 6 h <0.5 mg/mL in 24 h	10% of peak at 2 wk <0.5 mg/mL in 2 wk	—

Table 2
Investigations of Voluven (HES 130/0.4) compared with other colloids (HES 200/0.5, HES 670/0.75) or human albumin

Study: First Author, Year	Patient Population	Design	Number of Patients Enrolled	Outcomes
Gallandat Huet et al, ¹⁴ 2000	Cardiac surgery	Prospective, randomized, double-blinded, parallel-group, multicenter cohort	59	Compared HES 130/0.4 with HES 200/0.5 and found similar infusion volume requirements in both groups. A lower mean total blood loss was experienced with the HES 130/0.4 group and was reflected by a significantly lower use of packed RBCs
Jungheinrich et al, ¹² 2002	Renal dysfunction	Prospective cohort	19	HES 130/0.4 total plasma clearance depended on renal function. Residual concentrations found 24 h after 500 mL were small, even in patients with severe renal dysfunction. C _{max} and terminal half-life were not dependent on renal function
Boldt et al, ¹⁵ 2007	Cardiac surgery with compromised renal function	Prospective, randomized cohort	50	Compared HES 130/0.4 with 5% human albumin to determine the effects of Voluven on renal function. No differences were seen in any of the outcome parameters after 48 h of volume resuscitation. The parameters examined included volumes infused on several markers of kidney function, serum creatinine, glomerular filtration rate, and cystatin C plasma levels. A 6-month follow-up showed that none of the patients developed acute renal failure
Gandhi et al, ¹¹ 2007	Major orthopedic surgery	Prospective, controlled, randomized, double-blinded, multicenter cohort	100	Compared HES 130/0.4 with HES 670/0.75. No differences were found in fluid replacement volumes. Nadir factor VIII activity and vWF concentration was lower in hetastarch group than Voluven group within 2 h of end of surgery
Standl et al, ¹⁶ 2008	Pediatric, noncardiac surgery	Prospective, controlled, randomized, open, multicenter pilot cohort	82	Compared HES 130/0.4 with 5% human albumin. No differences in hemodynamics, coagulation profiles, fluid input or output, intensive care unit stay or length of hospital stay

receiving Voluven and 2446 ± 516 mL in the control group). Blood loss was found to be lower in patients receiving Voluven (1301 ± 551 mL) than in those receiving control (1821 ± 1222 mL), $P = 0.046$. This reduced blood loss was reflected in a lowered need for transfusion of packed red blood cells in patients receiving Voluven (241 ± 419 mL in the Voluven group versus 405 ± 757 mL in the control group). vWF increased to supranormal levels in both groups, but the increase was higher with Voluven.

In a study by Boldt and colleagues,¹⁵ Voluven was compared with 5% human albumin to examine the effects on kidney function in a group of 50 patients who underwent coronary artery bypass. Voluven was given perioperatively until the second postoperative day to keep pulmonary artery occlusion pressure or central venous pressure between 12 and 14 mmHg. There were no significant differences with fluid input or output between the 2 groups. The use of diuretics and catecholamines, and hemodynamics were also comparable. Neither conventional measures of kidney function such as serum creatinine and glomerular filtration rate nor more sensitive measures such as cystatin C or kidney-specific proteins were significantly increased with Voluven compared with albumin. Sixty-day postoperative follow-ups showed no difference in kidney function between the Voluven and human albumin groups. There was also no difference in the occurrence of renal failure between the 2 groups.

The dependency on pharmacokinetics and the preservation of the volume effect of HES 130/0.4 on renal function were studied in 19 volunteers with nonanuric renal dysfunction.¹² These patients were given a single infusion of 500 mL of Voluven (HES 130/0.4) over 30 minutes. HES peak concentration and terminal half-life were not affected by renal impairment. The mean MW of HES in plasma showed lower values with increased renal impairment ($P = 0.04$). This study concluded that Voluven can be safely administered in patients with renal impairment, as long as urine flow is preserved, without plasma accumulation.¹²

The equivalence and efficacy of Voluven was compared with hetastarch (HES 670/0.75 in saline) in a study that investigated intravascular volume replacement therapy during major orthopedic surgery (with an expected blood loss of 500 mL or more) in 100 patients.¹¹ Colloid administration was guided by central venous pressure (CVP) and arterial blood pressure: infusion of colloids with CVP less than 10 mmHg, colloids administration or vasoactive agents used with CVP 10–15 mmHg and unacceptable blood pressure, and vasoactive agents administered with CVP greater than 15 and unacceptable blood pressure. No colloids were infused after the end of surgery.

The primary end points included the total volume of colloid solution required during surgery (efficacy) and calculated total perioperative erythrocyte loss, nadir factor VIII activity and vWF antigen concentration within 2 hours of completion of surgery, and use of fresh frozen plasma (safety). Secondary end points were total fluid input and output and use of vasoactive drugs for efficacy, and hemodynamic stability and adverse events for safety.

In patients undergoing major orthopedic surgery (most involving the spine or hip), the mean volumes of colloids administered were similar in the 2 HES groups (1613 ± 778 mL in the Voluven group versus 1584 ± 958 mL in the control group).¹¹

The nadir factor VIII activity within 2 hours of the end of surgery was lower for hetastarch than for Voluven ($P = .0499$), and a higher fraction of patients presented vWF values less than the lower limit 2 hours after surgery in the hetastarch group ($P = .027$). At 24 and 48 hours, values of factor VIII activity and vWF antigen were significantly higher for the Voluven group ($P < .0001$). Three serious coagulopathy events occurred in the hetastarch group, and none in the Voluven group.

In conclusion, this study showed that Voluven and hetastarch are equally effective plasma volume expanders, but Voluven has a lesser effect on coagulation.

In a prospective, controlled, randomized, open, multicenter pilot study, children younger than 2 years undergoing noncardiac surgery were treated with either Voluven (16.0 mL/kg) or human albumin 5% (16.9 mL/kg).¹⁶ A total of 81 patients were treated and no differences in hemodynamics, coagulation parameters, or other laboratory values were detected between the 2 groups. Blood loss was significantly less in the group treated with albumin compared with the Voluven-treated group. However, there were no differences in the amount of red blood cells, fresh frozen plasma, or platelet concentrates between the groups. Albumin and Voluven were both effective for hemodynamic stabilization in pediatric noncardiac surgery, with no adverse impact on coagulation.¹⁶

In a recent study, 2 similar, low MW colloids were compared in 54 patients who underwent prolonged multilevel spinal surgeries (PLIF) involving 3 vertebrae or less. Voluven, previously regarded as the most benign toward coagulation, and a new saline-based HES, Hextend, were investigated.¹⁷ Hextend (Biotime, United States) is a new type of HES with a physiologic pH and balanced electrolytes including calcium, which is beneficial to coagulation. For both groups, 15 mL/kg of solution were administered during surgery. Blood loss, coagulation, and electrolyte profiles were checked before infusion and 5 minutes, 3 hours, and 24 hours after infusion. The Hextend group showed slightly better electrolyte balance, however, more coagulation impairment and postoperative transfusions (37% vs 11%) compared with the Voluven group. The effect of Hextend on coagulation lasted until 24 hours after infusion. In conclusion, if coagulopathy is a concern during PLIF, then an HES with low MW/DS in a saline-based medium (Voluven) may be a better alternative than a HES with high MW/DS in a balanced salt medium (Hextend).

SUMMARY

Voluven is a new volume expander that can effectively replace fluids during major surgical procedures, has useful properties compared with albumin and the traditional hetastarch Hespan, and is more versatile for general clinical use.

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