REVIEW ARTICLE

Drugs 1998 May; 55 (5): 621-630
0012-6667/98/0005-0621/$10.00/0

Colloid Volume Expanders

Problems, Pitfalls and Possibilities

Joan S. Roberts[1] and *Susan L. Bratton*[2]

1 Paediatric Intensive Care, Department of Anaesthesiology, University of Washington School of Medicine, and Children's Hospital and Regional Medical Center, Seattle, Washington, USA

2 Department of Anaesthesiology, University of Washington School of Medicine, and Children's Hospital and Regional Medical Center, Seattle, Washington, USA

Contents

Summary

Colloid solutions have been developed and used over the past 70 years as expanders of the intravascular space, based on an understanding of Starling's law. Increasing osmotic pressure with colloidal products has remained an attractive theoretical premise for volume resuscitation. Indeed, colloids have been shown to increase osmotic pressure in clinical practice; however, the effects are short-lived. Lower molecular weight colloids exert a larger initial osmotic effect, but are rapidly cleared from the circulation. Larger molecules exert a smaller osmotic pressure that is sustained longer.

The main drawback to colloid therapy lies in pathological states with endothelial injury and capillary leak, precisely the clinical scenario where colloids are commonly given. The colloid solution may leak into the interstitium and remain there exerting an osmotic gradient, pulling additional water into the interstitium.

There are 4 general types of colloid products available for clinical use. Albumin is the predominant plasma protein and remains the standard against which other colloids are compared. Albumin, pooled from human donors, is in short supply and remains expensive. Dextrans have been used to prevent deep venous thrombosis and to lower blood viscosity during surgery. Hetastarch has been widely used as a plasma volume expander. It provides equivalent plasma volume expansion to albumin, but has been shown to alter clotting parameters in studies (prolonging the activated partial thromboplastin time and prothrombin time). Although severe coagulopathies have been reported in sporadic cases, hetastarch

has not been shown to increase postoperative bleeding compared with albumin therapy, even in large doses (3 L/day).

Despite some theoretical advantages compared with crystalloid therapy, colloid administration has not been shown to decrease the risk of acute lung injury or to improve survival. Specific indications for colloid products include hypoproteinaemic or malnourished states, patients who require plasma volume expansion who are unable to tolerate larger amounts of fluid, orthopaedic and reconstructive procedures requiring prevention of thrombus formation and leukapheresis.

Intravascular volume resuscitation can be essential in critically ill patients. Debate over the merits of crystalloid versus colloid solutions has continued for decades without a clear resolution. Advocates for colloid administration maintain that smaller volumes of these agents can be used for intravascular resuscitation, avoiding large volumes of crystalloid administration.

Colloids are expensive, and have allergic risks and coagulopathic adverse effects that are not seen with crystalloids. Furthermore, many critical illnesses lead to increased vascular permeability which limits the ability of colloid solutions to remain in the vascular space and exert additional osmotic pressure (table I). Capillary leak can then increase the colloid in the interstitial space leading to increased oedema formation.

Several colloid solutions have been developed and used in clinical practice worldwide. Wise use of colloid solutions requires an understanding of both the chemical properties of colloids and the unique features of each solution.

1. Ideal Colloid Solution

The ideal colloid fluid for intravascular fluid resuscitation would be free of antigenic or allergic properties, exert a sustained intravascular osmotic pressure and pose no infectious risks. It would not require cross-matching, would have a long shelf-life with simple storage requirements and, of course, be very inexpensive. Needless to say, there is no colloid fluid that fulfils all these criteria.

2. Colloid Osmotic Pressure

The osmotic pressure of a solution is due to the number of particles in solution. Each particle, regardless of its mass, exerts on average the same pressure because they have approximately the same kinetic energy. Larger particles move at slower velocities, while smaller particles move more quickly. Thus, on average, each particle has approximately equal kinetic energy.

The proteins are the only dissolved substances in the plasma that do not diffuse readily through capillary membranes. Because of this, the dissolved proteins in the interstitium and plasma exert the 'colloid' osmotic pressure at the capillary membrane. Colloid osmotic pressure is most commonly measured by a membrane transducer system, which detects volume of flow across a semipermeable membrane. The pore size of the membrane, the molecular weight of the colloid and the surface area of the venous capillary bed affect the volume of flow across the capillary membrane.[1,2]

Starling[3] noted that, under normal circumstances, the fluid filtered in the arterioles was nearly equal to the fluid reabsorbed in the venules. The fluid exchange across a capillary membrane is given by the Starling Equation:[3]

$$Q = kS[(P_c - P_i) - \sigma(\Pi_c - \Pi_i)]$$

where Q is the flow of fluid, k is the hydraulic conductivity of the endothelium, S is the surface area, P is the hydrostatic pressure of the capillary (P_c) and interstitium (P_1), σ is the Staverman re-

flection coefficient and Π is the osmotic pressure of the capillary (Π_c) and interstitium (Π_i). The Staverman coefficient ranges from 0 to 1 and represents the transfer of colloid across the membrane. Zero indicates free passage, while 1 is totally impermeable to colloid transfer. The pulmonary capillaries have a value of 0.7, while most of the systemic circulation has a value of 0.95.[4]

The major contribution to the osmotic gradient is the difference in protein on each side of the endothelium. The concentration of protein in the plasma is approximately 7.3 g/dl, while the figure for the interstitial fluid is 2 to 3 g/dl. In healthy volunteers the colloid concentration in the interstitium is about one-third the plasma concentration; however, when the capillary permeability is increased in some pathological states, the osmotic gradient between the capillary and interstitium is decreased and the net flux of fluid into the interstitium increased. Measured colloid osmotic pressure deviates from calculated pressure. The calculated colloid osmotic pressure of plasma is 15mm Hg, while the measured pressure ranges from 25 to 30mm Hg.[5] These differences can be explained in part by both the Donnan equation and the excluded volume effect.

Table I. Conditions associated with increased capillary leak

Acute respiratory distress syndrome
Anaphylaxis
Aspiration pneumonia
Bacterial or viral pneumonia
Burns
Cardiopulmonary bypass
Disseminated intravascular coagulation
Drug overdose (salicylates, cocaine, opioids)
Inhalation injury
Head injury
Massive blood transfusion
Near drowning
Pancreatitis
Sepsis
Thromboembolism
Trauma
Venom exposures

If a colloid has a net charge, then an electrical potential will occur across the membrane. The Donnan equation requires that the sum of the charges on each side of the membrane be equal. To achieve this there must be an imbalance of electrolytes across the membrane, which generates an electrical potential in addition to the osmotic gradient, exerted by the nondiffusing colloid.

Furthermore, the predicted osmotic pressure is based on solutions of infinite dilution. When a new colloid solution is added to an existing solution, the concentration of the original colloid is decreased less than would be expected. This excluded volume effect is because the new total solute volume is less than the solute volume of the 2 independent solutions.

Albumin, globulins and fibrinogen are the primary plasma proteins. Normal concentrations of these proteins are 4.5 g/dl, 2.5 g/dl and 0.3 g/dl, respectively. Because albumin has a relatively small molecular weight (69 000D) compared with the globulins, 1g of albumin contains more molecules and thus exerts a greater colloid osmotic pressure. A normal colloid osmotic pressure of human plasma is 28mm Hg and the partial pressure due to albumin is 21.8mm Hg, while the pressure due to the globulins is only 6mm Hg.

3. Colloid Solution Molecular Weight and Size

Colloids are described by both molecular weight and size. In monodisperse solutions all the molecules have the same molecular weight and size, while in polydisperse solutions there is a wide range of molecular size and shape. The number averaged molecular weights is the arithmetic mean of the weights of all the molecules, while the weighted average molecular weight is the sum of the number of molecules at each molecular weight divided by the total weight of all the molecules. The weighted average molecular weight is more affected by the small proportion of very heavy molecules than the number averaged molecular weight. An index of polydispersity is given by the ratio of the weighted average and the number

Table II. Comparison of colloid solutions

	Albumin		Dextran in normal saline		Hetastarch	Pentastarch	Gelofusine
	5%	25%	Dextran 40	Dextran 70			
Average molecular weight (D)	70 000	70 000	40 000	70 000	450 000	260 000	30 000
Sodium level (mEq/L)	130-160	130-160	154	154	154	154	154
Osmolality (mOsm/L)	300	1500	308	308	310	326	NA
Plasma volume expansion (ml/500ml infused)	500	1700	500-1000	500-700	500-700	600-800	500
Duration of volume expansion	<24h	<24h	<6h	<24h	<36h	<12h	<4h
Dose limitation			≤2 g/kg/day	20 ml/kg/day	20 ml/kg/day		
Approximate cost per litre in US[a] ($US)	360	400	200	150	130	150	NA
Incidence of allergic reaction (%)	0.011	NA	0.007	0.069	0.085	NA	0.066

a *Drug Topics Red Book*. Montvale (NJ): Medical Economics Co., Inc., 1996.

Abbreviation: NA = not available.

averaged molecular weights.[6] The number averaged molecular weight is lower than the weighted average molecular weight for polydisperse colloids.

Solutions with small size or low molecular weight particles will be retained in the circulation for a relatively shorter time than larger particles. Particles are lost from the circulation by both renal clearance and losses into the interstitium. For a given concentration of colloid, solutions with small particles will exert a greater oncotic effect for a shorter period than larger particles. Similarly, for a given concentration (weight/volume) of a larger molecular weight colloid there are relatively fewer particles, so the osmotic effect is less but the duration of effect is more sustained.

4. Colloid Solutions

4.1 Albumin

The function of albumin in the blood is to maintain normal oncotic pressure and act as a carrier of various metabolites. Its use as the first natural colloid product dates back to World War I, and it has remained the standard colloidal agent for comparison. Albumin is a monodisperse solution, has an average molecular weight of 69 000D and at physiological pH has a net charge of –17. Albumin is the predominant protein in human plasma and comprises 75 to 80% of the normal colloid oncotic pressure, and about 50 to 60% of plasma protein. The normal transcapillary leak rate of protein is about 5% per hour but increases up to 60-fold during sepsis.[7] Approximately 10% of the albumin in the body is broken down daily; however, the site of metabolism is uncertain but is probably the reticuloendothelial system.[8]

Commercially available albumin is prepared from pooled human plasma, then heated for 10 hours at 60°C for sterilisation. It can be stored at normal room temperature (not to exceed 30°C). Currently, a worldwide shortage of albumin exists and the average wholesale price is $US360 per litre of 5% albumin (table II). Given as a 5% solution, albumin has colloid oncotic pressure of 19mm Hg, providing an increase in intravascular volume equal to the volume infused. 25% albumin solution contains 12.5g albumin in 50ml of buffered normal saline, with an oncotic pressure of 100mm Hg, producing an increase of 300 to 500ml in intravascular volume for 100ml of infused solution.[9] The effect of infused albumin on plasma volume is variable, depending on volume deficits, initial oncotic pressure, vascular permeability and the adequacy of the volume resuscitation. The expansion of the plasma volume primarily depends on the amount of albumin given, not on the concentration of the solution.[10]

Although albumin has been used safely for decades as a volume expander, many studies have

demonstrated possible complications with its use. Albumin, a derivative of blood, may cause adverse reactions similar to other transfusion reactions such as chills, urticaria, fever and vasodilatation, with a 0.011% incidence of allergic reaction.[11] Another important complication is hypocalcaemia. A study of trauma patients resuscitated with albumin demonstrated normal serum albumin and total calcium levels but significantly reduced ionised calcium levels. Such a reduction, due to binding by albumin, may depress myocardial function.[12] A study in trauma patients receiving albumin for fluid resuscitation reported that intravascular volume requirements were higher, urine output lower and renal function decreased compared with patients who received crystalloid resuscitation.[13]

Other studies have also shown a paradoxical effect on urine output with albumin therapy.[14] Investigation of glomerular filtration rates (GFR) in burn patients given 25% albumin found a substantial decrease in GFR, despite a 40% increase in plasma volume. These findings suggested that the anticipated increase in urine output usually associated with colloid expansion of the intravascular space did not occur because of a decrease in glomerular filtration. Although the mechanism for the decreased glomerular filtration is not clearly known, it may be caused by increased oncotic pressure within the peritubular vessels, causing a decrease in excretion of sodium and water.[15] Albumin solutions contain small amounts of aluminium and in the past some have been contaminated with greater amounts. Premature infants and patients receiving long term parenteral nutrition are at risk for aluminium toxicity.[16]

4.2 Dextrans

Dextrans are glucose polymers of various lengths, produced by bacteria grown on sucrose media. The solutions are polydisperse. Dextran 40 and dextran 70 are commercially available in the US and differ according to the weighted average molecular weight (40 000 and 70 000D, respectively). Dextran 40 is a 10% solution in normal saline, while dextran 70 is available as a 6% solution in normal saline. They can be stored at room temperature between 15 and 30°C. The average wholesale price for 1L of dextran 40 is $US200, while the same amount of dextran 70 costs $US150.

Both dextrans initially produce intravascular volume expansion due to increased osmotic load, but the effect is temporary. Smaller glucose polymers rapidly escape from the vascular compartment into the interstitial space or are excreted by the kidney. The plasma volume is usually increased 1- to 2-fold over the volume of dextran 40 infused; however, 50% of the dextran is lost after 3 hours, 60% within 6 hours.[9] The remaining large glucose polymers are slowly eliminated by enzymatic degradation. Dextran 70, with a preponderance of larger polymers, is less rapidly lost from the intravascular space; within 12 hours, 35% of the polymers are cleared.

An additional characteristic of dextran solutions with clinical implications is their haematological effects. The dextrans alter blood viscosity. The changes in viscosity depend on the molecular weight of the dextran. Above 60 000D the dextrans tend to aggregate red cells *in vitro*; however, below this weight, the tendency is to disaggregate them. The main advantage of the dextrans over other colloids is their proven benefit of deep venous thrombosis prevention and lowering of blood viscosity.[17] Dextran administration is associated with a dilutional coagulopathy as well as decreased fibrin clot formation and reduced factor VIII activity.[18,19]

Allergic reactions to dextrans include an anaphylactoid reaction to high molecular weight dextrans with multiple branches and a true allergic reaction with preformed antibodies. Risk for anaphylactic reaction can be decreased by pretreatment with monovalent hapten-dextran which binds the antibodies.[20] Pretreatment with hapten-dextran reduces the rate of allergic reaction from 1.1% to 0.1%.[20]

4.3 Starches

Hetastarch (hydroxyethyl starch, HES), is a very polydisperse solution of ethoxylated amylopectin. It is produced by partial hydrolysis of insoluble amylopectin, followed by substitution of hydroxyethyl groups at the C2, C3 and C6 positions on the glucose molecules. The greater the number of substitutions, the more soluble hetastarch becomes. The molar substitution is the number of substitutions per glucose molecule. Although the maximum possible is 3, the molar substitution of hetastarch used in clinical practice ranges from 0.5 to 0.7. The weighted average molecular weight is 450 000D. The molecular weights range from 1000 to 3 000 000D. Hetastarch can be stored at room temperatures up to 40°C. The average wholesale price in the US for 1L of hetastarch is $US130. The 6% solution commonly in use ('Hespan', Du Pont Merck Pharmaceuticals) generates an osmotic pressure of 28mm Hg. Hetastarch closely resembles 5% albumin; both are isotonic and increase the intravascular volume by about the amount infused. The half-life of hetastarch in the plasma space is longer, decreasing after 24 to 36 hours both by renal excretion of smaller molecules and by the action of amylase.[21] The added alcohol groups prevent enzymatic degradation, so products vary in half-life, depending on the number of alcohol moieties.

Hetastarch administration has been associated with rare allergic reactions (0.085% incidence)[11] and alteration of haemostasis.[22-24] Increases in prothrombin time, partial thromboplastin time and bleeding time, and decreased levels of factors VIII:C and VIII:Ag, have been reported in patients receiving hetastarch. Hetastarch primarily alters coagulation by haemodilution,[23] and it accelerates the conversion of fibrin to fibrinogen causing less stable thrombus formation, reduces factor VIII activity and alters platelet adhesiveness.[22,25] A maximum daily adult dosage of 1500ml is recommended, and the maximum daily dosage recommended for children is 20 ml/kg.[26] Excessive bleeding has been reported in elderly patients receiving conventional doses of hetastarch after heart surgery.[27] Accumulation of hetastarch, demonstrated by liver biopsy, has been reported in renal failure patients who developed ascites after hetastarch infusions. The role of hetastarch in development of ascites on the basis of morphological hepatic changes is unclear, but should be considered.[28]

Pentastarch ['Pentaspan', DuPont Merck Pharmaceuticals, Wilmington (DE), US] is another polydisperse formulation of hydroxyethyl starch with a lower weighted average molecular weight (264 000D). Its molecular weight distribution ranges from 10 000 to 1 000 000D. The average US wholesale price per litre of pentastarch is $US150. Pentastarch has a greater colloid osmotic pressure (40mm Hg) than hetastarch. This leads to greater expansion of the intravascular space, nearly twice that of the volume infused. However, the average half-life is only 2.5 hours. 60% of an administered dose is excreted in the urine in 24 hours and blood concentrations are undetectable within 96 hours.[21] Thus, pentastarch may provide greater plasma volume expansion for the volume infused, with faster onset and more rapid elimination, than albumin or hetastarch.[29] Pentastarch administration is associated with haemodilution and decreased factor VIII von Willebrand complex.[30]

Pentastarch increases the erythrocyte sedimentation rate and is used to enhance white cell separation by centrifugal means during leukapheresis. It is approved only for leukapheresis in the US, but has been used in other countries as a plasma volume expander.

A new hydroxyethyl starch, pentrafraction, which has been divested of most of the highest and lowest molecular weight components present in other starch preparations, provides a medium molecular weight range starch that has been used in animal studies.[31-32] Pentrafraction has a number averaged molecular weight of 110 000D, but the range of molecular weights is less than in the case of hetastarch or pentastarch (100 000 to 500 000D). Elimination of the very low molecular weight molecules provides a more sustained colloid osmotic effect, and should reduce fluid flux and oedema formation compared with pentastarch.

4.4 Gelatins

Currently 2 types of gelatins are produced from bovine collagen. Both are initially treated with alkali which causes the collagen to swell and hydrolyses ester and peptide links, followed by suspension in aqueous solution. The urea-linked gelatins (e.g. 'Haemaccel', Braun Ltd, Aylesbury, Bucks, UK) are prepared by cross-linking polypeptide chains with hexamethyl di-isocyanate, resulting in a weighted average molecular weight of 35 000D. The succinylated gelatins (e.g. 'Gelofusine', Hausmann Laboratories, Switzerland) use slightly higher weight polypeptide chains which are treated with succinic acid anhydrase, which replaces amino groups with a negatively charged COO- group. The increased negative charge results in reduced coiling and increased size of the molecule. The weighted average molecular weight of 'Gelofusine' is 30 000D and the number averaged molecular weight is 22 600D. The colloid osmotic pressure is 465mm H_2O.

Both types of solutions are polydisperse. The small particles exert a large initial osmotic effect, but are rapidly lost from the circulation by glomerular filtration. The volume expanding effect lasts approximately 3 hours in a healthy circulation but is shortened during sepsis.[17] Urea-linked gelatin ('Haemaccel') has much higher calcium (6.26 mmol/L) and potassium (5.1mmol/L) levels than succinylated gelatin ('Gelofusine') – 0.4 mmol/L for both elements. This higher calcium level can lead to clotting if the urea-linked gelatin is infused with blood.[33] The modified gelatins have no effect on coagulation other than haemodilution,[34] but are associated with allergic reactions, with an incidence of 0.066% for 'Gelofusine' and 0.146% for 'Haemaccel'.[11]

5. Pulmonary Oedema

Two major points of contention in the debate over fluid choice for intravascular volume expansion are the volume of fluid required and the consequent risk of pulmonary oedema. Which fluid will restore haemodynamic stability with the least contribution to extravascular lung water?

In studies of shock patients with intact microvascular permeability, no increase in intravascular lung water has been demonstrated after fluid loading, even after massive crystalloid infusion.[35] On the other hand, in shock patients with increased microvascular permeability (from various insults, including trauma, sepsis, burns or anaphylaxis), most studies have demonstrated increased amounts of serum proteins, primarily albumin, in the lung interstitium.[36-38] In contrast, one study demonstrated no increase in lung water with colloid administration compared with crystalloid as long as pulmonary vascular pressures were not elevated in patients with increased microvascular permeability.[39] In general, most studies suggest that smaller amounts of colloid are required for fluid resuscitation compared with crystalloid therapy; however, the colloid can leak into the interstitium where it is not reabsorbed well, potentially causing a more prolonged increase in extravascular lung water. Careful monitoring of haemodynamic parameters during fluid resuscitation is prudent in patients with shock or lung injury with either fluid therapy.[40]

An interesting study[41] evaluated the clearance of fluid from the lung airspaces in animals who had resuscitation fluid and plasma given through an endotracheal tube. Saline and dextran 70 were cleared the most rapidly. The clearance of hetastarch was approximately half the rate of saline and dextran 70. The study was remarkable in that essentially no plasma was cleared within the 3-hour study period. Colloid osmotic forces are clearly not the only important gradient driving reabsorption because saline and dextran 70 were cleared at similar rates. The clearance mechanism for alveolar fluid is most likely one involving active sodium transport.[42,43]

Despite many studies comparing resuscitation solutions, there are no clear data which suggest improved survival when colloid therapy is compared with crystalloid therapy.[44] A meta-analysis of clinical studies that compared mortality based

on crystalloid or colloid fluid resuscitation demonstrated no statistically significant differences. The meta-analysis showed a 5.7% relative improvement in mortality with crystalloid therapy across all patient groups. The improvement increased to 12.3% when only trauma patients were considered. When the nontrauma patients were evaluated separately there was a 7.8% difference in mortality favouring colloid use.[45] The lack of a consensus confirms that there is no ideal fluid for all patients. Most authors agree that crystalloid therapy for previously healthy trauma or surgical patients is the best choice. The use of colloids appears to have more of a role in the hypoproteinaemic patient and in those unable to withstand larger fluid volumes.

6. 'Best' Colloid Therapy

Colloids have been used to maintain intravascular volume with blood loss from surgery and from other causes of shock. Most studies have compared a single colloid versus crystalloid therapy or compared 2 colloids, so definite recommendations on the 'best' colloid therapy remain elusive. Furthermore, 'best' can be defined by haemodynamic effects, cost effectiveness or complications of colloid administration. The incidence of allergic reaction to a blood transfusion is greater than with any colloid therapy.[11]

Albumin remains a very expensive colloid therapy. A study of intensive care unit patients compared the use of 4.5% albumin and 3.5% gelatin for volume replacement.[46] Length of stay and mortality did not differ according to treatment group. Several studies have compared 5% albumin and 6% hetastarch for volume resuscitation after cardiac surgery.[26,47,48] Hetastarch and albumin both provided reliable volume expansion and stable haemodynamic responses; however, hetastarch use was associated with a prolonged activated partial thromboplastin time (PTT)[26,47] and prothrombin time (PT)[47] in some studies. Of note, patients who received hetastarch did not bleed more than patients who received albumin. Similarly, a study comparing 5% albumin and 6% hetastarch in patients with trauma again reported a prolonged PTT, but no increased risk of bleeding in patients who received hetastarch.[49] Although the recommended daily dose of hetastarch is 1500ml for an adult, some studies have evaluated doses up to 3000ml and did not report increased blood loss compared with 5% albumin.[49,50]

Given the much lower cost and equal efficacy of hetastarch, this agent appears to be a superior choice over albumin in patients who are not coagulopathic. If large doses are needed, then bleeding and coagulation tests should be monitored closely. Hetastarch has also been compared with Ringer's lactate for volume expansion during surgery.[51] Hetastarch was superior for expansion of plasma volume and cardiac output during surgery. Although this superiority of performance is short-lived, some clinical situations require rapid intravascular volume expansion. Similarly, dextran 60 has been compared with Ringer's lactate for plasma volume expansion, and provided superior cardiac output during surgery.[52] However, the improved haemodynamic effects of colloid over crystalloid appear to be short-lived, and colloid can increase fluid retention and weight in patients after a few days compared with crystalloid infusions.[53]

Hetastarch and pentafraction have been studied for burn resuscitation.[31,54] Although both colloids reduced the initial resuscitation needs and decreased oedema in burned tissues in comparison with crystalloid therapy, neither was superior to 5% albumin. Hetastarch has a greater volume effect than 3% gelatin but was associated with increased bleeding after hip replacement.[55]

Although the 'best' colloid debate will continue, there are no definitive studies that demonstrate improved survival or reduced risk of acute lung injury with a specific therapy. Certainly the cost of the solutions makes the starches, dextrans and gelatins compare favourably with albumin. However, crystalloid therapy remains the least expensive method of plasma volume expansion. Specific indications for colloid products include hypoproteinaemic or malnourished states, patients who require plasma volume expansion who cannot tolerate larger amounts of fluid, orthopaedic and reconstructive

procedures requiring prevention of thrombus formation and leukapheresis. Colloid therapy appears to be indicated in selected clinical situations where the patient requires rapid plasma expansion and does not have significant endothelial injury.

References

1. Weil MH, Morissette M, Michaels S, et al. Routine plasma colloid osmotic pressure measurements. Crit Care Med 1974 Sep-Oct; 2 (5): 229-34
2. Webb AR, Barclay SA, Bennett ED. *In vitro* colloid osmotic pressure of commonly used plasma expanders and substitutes: a study of the diffusibility of colloid molecules. Intensive Care Med 1989; 15 (2): 116-20
3. Starling EH. On the absorption of fluids from the connective tissues spaces. J Physiol 1896; 19: 312-26
4. Taylor AE. Capillary fluid filtration: Starling forces and lymph flow. Circ Res 1981 Sep; 49 (3): 557-75
5. Barclay SA, Bennett ED. The direct measurement of plasma colloid osmotic pressure is superior to colloid osmotic pressure derived from albumin or total protein. Intensive Care Med 1987; 13 (2): 114-8
6. Billmeyer FW. Measuring the weight of giant molecules. Chemistry 1966; 39: 8-14
7. Fleck A, Raines G, Hawker F, et al. Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. Lancet 1985; Apr 6; I (8432): 781-4
8. Mishler JM. Synthetic plasma volume expanders – their pharmacology, safety and clinical efficacy. Clin Haematol 1984 Feb; 13 (1): 75-92
9. Nearman HS, Herman ML. Toxic effects of colloids in the intensive care unit. Crit Care Clin 1991 Jul; 7 (3): 713-23
10. Lamke LO, Liljedahl SO. Plasma volume expansion after infusion of 5%, 20% and 25% albumin solutions in patients. Resuscitation 1976; 5 (2): 85-92
11. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet 1977 Feb; I (8009): 466-9
12. Kovalik SG, Ledgerwood AM, Lucas CE, et al. The cardiac effect of altered calcium homeostasis after albumin resuscitation. J Trauma 1981 Apr; 21 (4): 275-9
13. Ledgerwood AM, Lucas CE. Postresuscitation hypertension, etiology, morbidity and treatment. Arch Surg 1974 Apr; 108 (4): 531-8
14. Gore DC, Dalton JM, Gehr TW. Colloid infusions reduce glomerular filtration in resuscitated burn patients. J Trauma 1996 Mar; 40 (3): 356-60
15. Lucas CE. Renal considerations in the injured patient. Surg Clin North Am 1982 Feb; 62 (1): 133-48
16. Klein GL. The aluminum content of parenteral solutions: current status. Nutr Rev 1991 Mar; 49 (3): 74-9
17. Salmon JB, Mythen MG. Pharmacology and physiology of colloids. Blood Rev 1993 Jun; 7 (2): 114-20
18. Bergqvist D. Dextran and haemostasis: a review. Acta Chir Scand 1982; 148 (8): 633-40
19. Aberg M, Hedner U, Bergentz SE. Effect of dextran on factor VIII (antihemophilic factor) and platelet function. Ann Surg 1979 Feb; 189 (2): 243-7
20. Laubenthal H, Messmer K. Allergic reactions to dextrans. In: Baron JF, editor. Plasma volume expansion. Paris: Arnette Blackwell, 1992
21. Mishler JM, Hester JP, Heustis DW, et al. Dosage and scheduling regimens for erythrocyte-sedimenting macromolecules. J Clin Apheresis 1983; 1 (3): 130-43
22. Strauss RG, Stump DC, Henriksen RA, et al. Effects of hydroxyethyl starch on fibrinogen, fibrin clot formation, and fibrinolysis. Transfusion 1985 May-Jun; 25 (3): 230-4
23. Alexander B, Odake K, Lawlor D, et al. Coagulation, hemostasis, and plasma expanders: a quarter century enigma. Fed Proc 1975 May; 34 (6): 1429-40
24. Stump DC, Strauss RG, Henriksen RA, et al. Effects of hydroxyethyl starch on blood coagulation, particularly Factor VIII. Transfusion 1985 May-Jun; 25 (4): 349-54
25. Gold MS, Russo J, Tissot M, et al. Comparison of hetastarch to albumin for perioperative bleeding in patients undergoing abdominal aortic aneurysm surgery: a prospective, randomized study. Ann Surg 1990 Apr; 211 (4): 482-5
26. Brutocao D, Bratton SL, Thomas JR, et al. Comparison of hetastarch with albumin for postoperative volume expansion in children after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1996 Apr; 10 (3): 348-51
27. Villarino ME, Gordon SM, Valdon C, et al. A cluster of severe postoperative bleeding following open heart surgery. Infect Control Hosp Epidemiol 1992 May; 13 (5): 282-7
28. Dienes HP, Gerharz CD, Wagner R, et al. Accumulation of hydroxyethyl starch (HES) in the liver of patients with renal failure and portal hypertension. J Hepatol 1986; 3 (2): 223-7
29. London MJ, Ho JS, Triedman JK, et al. A randomized clinical trial of 10% pentastarch (low molecular weight hydroxyethyl starch) versus 5% albumin for plasma volume expansion after cardiac operations. J Thorac Cardiovasc Surg 1989 May; 97 (5): 785-97
30. Rackow EC, Mecher C, Astiz ME, et al. Effects of pentastarch and albumin infusion on cardiorespiratory function and coagulation in patients with severe sepsis and systemic hypoperfusion. Crit Car Med 1989 May; 17 (5): 394-8
31. Brazeal BA, Honeycutt D, Traber LD, et al. Pentafraction for superior resuscitation of the ovine thermal burn. Crit Care Med 1995 Feb; 23 (2): 332-39
32. Yeh T, Parmar JM, Rebeyka IM, et al. Limiting edema in neonatal cardiopulmonary bypass with narrow-range molecular weight hydroxyethyl starch. J Thorac Cardiovasc Surg 1992 Sep; 104 (3): 659-65
33. Saddler JM, Horsey PJ. The new generation gelatins. Anaesthesia 1987 Sept; 42 (9): 998-1004
34. Lundsgaard-Hansen P, Tschirren B. Clinical experience with 120,000 units of modified fluid gelatin. Dev Biol Stand 1980; 48: 251-6
35. Tranbaugh RF, Elings VB, Christensens J, et al. Determinants of pulmonary interstitial fluid accumulation after trauma. J Trauma 1982 Oct; 22 (10): 820-6
36. Weaver DW, Ledgerwood AM, Lucas CE, et al. Pulmonary effects of albumin resuscitation for severe hypovolemic shock. Arch Surg 1978 Apr; 113 (4): 387-92
37. Holcroft JW, Trunkey DD. Pulmonary extravasation of albumin during and after hemorrhagic shock in baboons. J Surg Res 1975 Feb; 18 (2): 91-7
38. Robin ED, Carey LC, Grevik A, et al. Capillary leak syndrome with pulmonary edema. Arch Intern Med 1972 Jul; 130 (1): 66-71
39. Appel P, Shoemaker WC. Evaluation of fluid therapy in advanced respiratory failure. Crit Care Med 1981 Dec; 9 (12): 862-9
40. Imm A, Carlson RW. Fluid resuscitation in circulatory shock. Crit Care Clinics 1993 Apr; 9 (2): 313-33

41. Mackersie RC, Durelle J. Differential clearance of colloid and crystalloid solutions from the lung. J Trauma 1993 Sep; 35 (3): 448-53
42. Goodman BE, Kim KJ, Crandall ED. Evidence for active sodium transport across the alveolar epithelium of isolated rat lung. J Appl Physiol 1987 Jun; 62 (2): 2460-6
43. Goodman BE, Anderson JL, Clemens JW. Evidence for regulation of sodium transport from airspace to vascular space by cAMP. Am J Physiol 1989 Aug; 257 (2 Pt 1): 86-93
44. Ratner LE, Smith GW. Intraoperative fluid management. Surg Clin North Am 1993 Apr; 73 (2): 229-41
45. Velanovich V. Crystalloid versus colloid fluid resuscitation: a meta-analysis of mortality. Surgery 1989 Jan; 105 (1): 65-71
46. Stockwell MA, Sone N, Riley B. Colloid solutions in the critically ill: a randomized comparison of albumin and polygeline. 1: outcome and duration of stay in the intensive care unit. Anaesthesia 1992 Jan; 47 (1): 3-6
47. Kirklin JK, Lell WA, Kouchoukos NT. Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. Ann Thorac Surg 1984 Jan; 37 (1): 40-6
48. Boldt J, Knothe C, Schindler E, et al. Volume replacement with hydroxyethyl starch solution in children. Br J Anaesth 1993 Jun; 70 (6): 661-5
49. Shatney CH, Deepika K, Militello PR, et al. Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. Arch Surg 1983 Jul; 118 (7): 804-9
50. Vogt NH, Bothner U, Lerch G, et al. Large-dose administration of 6% hydroxyethyl starch 200/0.5 for total hip arthroplasty: plasma homeostasis, hemostasis, and renal function compared to use of 5% human albumin. Anesth Analg 1996 Aug; 83 (2): 262-8
51. Marcus MAE, Vertommen JD, Aken HV. Hydroxyethyl starch versus lactated Ringer's solution in the chronic maternal-fetal sheep preparation: a pharmacodynamic and pharmacokinetic study. Anesth Analg 1995 May; 80 (5): 949-54
52. Dawidson IJA, Willms CD, Sandor ZF, et al. Ringer's lactate with or without 3% dextran as volume expanders during abdominal aortic surgery. Crit Care Med 1991 Jan; 19 (1): 36-42
53. So KW, Fok TF, Wong WW, et al. Randomized controlled trial of colloid or crystalloid in hypertensive preterm infants. Arch Dis Child 1997; 76: F43-6
54. Guha SC, Kinsky MP, Button B, et al. Burn resuscitation: crystalloid versus colloid versus hypertonic saline hyperoncotic colloid in sheep. Crit Care Med 1996 Nov; 24 (11): 1849-57
55. Mortelmans YJ, Vermaut G, Verbruggen AM, et al. Effects of 6% hydroxyethyl starch and 3% modified fluid gelatin in intravascular volume and coagulation during intraoperative hemodilution. Anesth Analg 1995 Dec; 81 (6): 1235-42

Correspondence and reprints: Dr *Susan L. Bratton*, Department of Anaesthesia and Critical Care, CH-05, Children's Hospital and Regional Medical Center, P.O. Box 5371, Seattle, WA 98105, USA.
E-mail: bratton@u.washington.edu