

Review Article

A Comparative Review of Crystalloid, Albumin, Pentastarch and Hetastarch as Perfusates for Cardiopulmonary Bypass

Gerard J. Myers RRT, CCP

Department of Cardiovascular Perfusion, Queen Elizabeth II Health Sciences Center, Halifax, Nova Scotia, Canada

Keywords: perfusate, cardiopulmonary bypass, albumin, cryofibrinogen, pentastarch, cold agglutinins

ABSTRACT

A comparative review is made of the four most common asanguineous solutions used for the priming of cardiopulmonary bypass equipment. Increasing health care costs and concerns over the administration of blood derived products has cardiac programs examining their practice of using albumin as a routine part of the priming solution for bypass. Emphasis is being placed on the use of crystalloids with synthetic colloids, or crystalloids alone, as the priming agents for extracorporeal circulation.

However new evidence has shown that the use of these solutions, without the addition of albumin, may be associated with the development of a cold induced agglutination. The data reviewed suggests that the ideal priming fluid may still not be available and recommendations are made.

Address correspondence to:
Gerard J. Myers RRT, CCP
27 Stewart Harris Drive
Dartmouth, Nova Scotia
Canada B2W 3Z4
e-mail: edit@ra.isisnet.com

INTRODUCTION

In preparation for cardiopulmonary bypass (CPB) one of three combinations of priming solutions is used to prime and de-air the extracorporeal circuit. These are: 1) crystalloids alone, 2) a combination of crystalloids plus synthetic volume expanders, 3) crystalloids plus albumin. All appear to be effective for the purpose of CPB and have little adverse effect on patient outcome. In this review we examine why some perfusate combinations may be more beneficial than others.

HISTORICAL PERSPECTIVE

In 1969, Saltzman (1) discovered that platelets did not adhere *in vitro*, to surfaces that were precoated with albumin. As a result of this and other observations, in an attempt to preserve platelets during CPB, the practice of adding albumin to the perfusate developed. Several reports indicated that using albumin as a priming agent minimized the adhesion of platelets and fibrinogen to polyvinylchloride (PVC) surfaces (2-5). At that time, the effects of albumin coating were thought to last for several hours (4). However, several other reports demonstrated that the benefits of albumin coating of CPB equipment only worked during *in vitro* circulation of the perfusate. Explanations offered included the fact that when heparinized blood contacted precoated synthetic surfaces, plasma proteins were rapidly adsorbed and the platelet protective effects of albumin were lost (5-7).

Other reasons suggested for the addition of albumin to the priming solution included the maintenance of an acceptable colloid osmotic pressure (COP) during bypass (8, 9) and the reduction of postbypass lung water (10). A COP below 17 mmHg was found to increase complications and decrease recovery (11). However, other researchers found colloid osmotic pressures to be as low as 12 mmHg in adults, without the development of postoperative complications (8, 9).

Concern over albumin's cost and the fact that it is a blood derived product led to the development of synthetic colloids such as Hespan®. This became the first real alternative to the use of albumin as a priming agent for CPB. Use of this volume expander was slowed when it became linked to postoperative bleeding concerns (3, 12-14). Recent studies with the use of Pentaspan®, the latest plasma volume expander, have demonstrated excellent results in the clinical setting and it has recently gained popularity as a priming agent for CPB (12, 15, 16).

CRYSTALLOIDS

It is very likely that the majority of cardiac centers worldwide continue to use crystalloid solutions alone as perfusates for CPB (17), as demonstrated in a British survey of 38 centers, which found that 56% of these centers used crystalloid primes only (10). These solutions are readily available, considerably

cheaper than their colloid counterparts and rapidly eliminated through the renal system. The most desirable crystalloid solutions for CPB primes are those that are free of calcium and dextrose and possess a balanced pH of 7.4.

Allergic reactions and viral transmission of disease are almost completely avoided when using crystalloid solutions only as a CPB prime. As well, crystalloid hemodilution is reported to provide superior brain and kidney perfusion (18). The major adverse effect of crystalloid primes is that there is a significant reduction in the patient's COP.

Administration of a colloid free solution as a perfusate may lead to an increase in fluid shifting from the intravascular to the extravascular spaces. However, when looking at the kinetics of albumin in the human model, the intravascular space normally contains only one third of the exchangeable albumin while the extravascular spaces contain the other two thirds. During CPB, approximately 40 % of the extravascular albumin may be transferred to the intravascular space to maintain acceptable COP's (19), suggesting that reductions of COP may have detrimental effects due to water accumulation in the various organs, including the myocardium. Several investigators have suggested that the optimal level of COP during cardiopulmonary bypass is around 16 mmHg (12, 20). However, in a study of COP during bypass by Beshere and co-workers (8), they found osmotic pressures dropped to less than 12.5 mmHg with no evidence of complications in the intraoperative or postoperative period.

The use of crystalloid solutions only, as perfusates for CPB, appears to avoid all of the allergic, religious, renal and cost factors involved with the composition of a perfusate. In a report by Scott and co-workers (21), urine output was significantly enhanced with the use of crystalloids alone as a perfusate, and hematocrits were higher when compared with other perfusate compositions (17, 21, 22). However, this translates to a greater amount of crystalloid requirements during the bypass period. Reducing some of this positive intraoperative fluid balance can be achieved by the use of therapeutic doses of 20% mannitol (23) during the bypass period.

There appears to be a significant increase in the positive fluid balance of those patients undergoing CPB with crystalloid primes (20-22). At the same time there is also an increase in their urine output and no adverse effects on hemodynamic management or extubation times. In a paper by London and co-workers (12), they concluded that any of the disadvantages of crystalloid primes are compensated for by the patient's intrinsic physiological mechanisms or by intense clinical care.

ALBUMIN

Albumin is a naturally occurring plasma volume expander, with a plasma volume expansion of 1:1 of infused volume. It has an initial plasma half life of around 16 hours, with an average molecular weight (Mw) of 60,048 (Table 1). Albumin is a protein that is extracted from human plasma and is then sterilized, eliminating the need for cross matching but providing the

colloid necessary for plasma volume expansion.

While the addition of albumin to the bypass priming solution is useful not only for its excellent effects on COP, plasma volume expansion capabilities and its reduction in post bypass lung water, one of its main advantages in extracorporeal circulation is its protein surface coating capabilities when used as a priming fluid in circuits with PVC and silicone surfaces. Due to the fact that PVC surfaces carry a negative charge, positively charged albumin proteins tend to bind to their surface if left to recirculate for approximately 30 minutes (24). The effect of this protein layer is a delay in the adsorption of circulating fibrinogen. Whether this matter applies to in vivo situations is a matter of debate (5, 6).

During commercial processing, albumin is heated to 60°C for a period of 10 hours to destroy all viruses and is then filtered to remove any remaining bacteria. The frequency of anaphylactoid reactions to the commercially available albumin ranges from 0.011% (22) up to 0.015% (25). It is believed to be a relatively safe volume expander, but recently there have been some concerns regarding the possible transmission of viruses such as Creutzfeldt-Jacob Disease (26). To address these concerns various agencies, including the Red Cross, have developed improved testing and predonation screening of potential blood donors.

As with all volume expanders, albumin has a hemodilutional effect on all blood components, but appears to have no adverse effects on postoperative coagulation profiles. When compared to other priming solutions, its relative cost doubles that of equal volumes of synthetic volume expanders (Table 1). There are no maximum dosages for the administration of albumin, except for the reported deleterious effects on renal function when the clinician attempts to restore high COP values during CPB (17, 20).

PENTASPAN®

Pentaspán® (pentastarch) is a synthetic plasma volume expander that is made up of 10% hydroxyethyl starch in normal saline. It is similar in its class to a more familiar volume expander called Hespan®, but with several distinct differences. These synthetic volume expanders are derived from a waxy starch composed almost entirely of a substance called amylopectin (25). Pentaspán® has an average molecular weight (Mw) of 264,000 and an average half life of 2.5 hours (Table 1). Molecules below a Mw of 50,000 are rapidly eliminated through renal excretion. Anaphylactoid reactions to the use of hydroxyethyl starches are rare, but are in the reported range of 0.007% (25) up to 0.085% (22).

Use of pentastarch as an addition to the priming solutions for CPB derives from its role as an excellent plasma volume ex-

Table 1

| | Pentaspán ^a (500 ml) | Hespan ^a (500 ml) | Albumin ^b (25 g) | Normosol R ^c (500 ml) |
|-------------------------|------------------------------------|---------------------------------|--------------------------------|-------------------------------------|
| Mw (Average) | 264,000 | 450,000 | 60,048 | 734 |
| Plasma Half Life (hr) | 2.5 | 25.5 | 16 | Nil |
| Average Cost* | \$36.66 | \$96.66 | \$70.30 | \$1.74 |
| Maximum Dose (24 hr) | 28 ml/kg | 20 ml/kg | Unknown | Unknown |

* = Canadian dollars

pander (1.5:1.0 of infused volumes [15]), its lower cost compared to similar volumes of albumin (Table 1) and its favorable effects on COP and postoperative coagulation stability (12, 16). However, in a randomized clinical study by London et al (12), they found a lower intraoperative hemoglobin and the greatest degree of intravascular hemodilution when compared to the use of either albumin plus crystalloid or crystalloids alone.

To date there have been no published reports of the platelet protective effects of hydroxyethyl starches during in vitro or in vivo extracorporeal circulation (13). Most studies focus on the role of synthetic volume expanders in regards to weight gain, COP and coagulation effects (25, 27). Pentastarch has been reported to prolong the activated partial thromboplastin time (aPTT) in relation to other priming agents and lowers platelet counts on CPB due to the increased hemodilutional effects (12, 17). However, neither had any adverse effects on the outcome of coagulation stability when compared to other priming agents. The maximum recommended dosages for the administration of pentastarch is 2000 ml over a 24 hour period, or approximately 28 ml/kg of body weight.

HESPAN®

Hespan® (hetastarch) is a synthetic plasma volume expander that is made up of 6% hydroxyethyl starch. It was the predecessor to pentastarch, having experienced some use as a priming additive for CPB. This artificial colloid has an average Mw of 450,000 and a half life of 25.5 hours (Table 1).

During CPB, intraoperative and postoperative platelet counts were found to be lower when compared to the use of other priming solutions containing albumin plus crystalloid or crystalloid alone (28). Explanations for these lowered platelet counts appear to be centered around the dilutional effects of synthetic colloid solutions. However, adverse effects on coagulation of a nondilutional nature, such as enhancement of fibrinolysis, minor prolongation of bleeding times and increased needs for blood

- a Du Pont Merck Pharma - Mississauga, Ontario
 b Bayer Corporation - Elkhart, Indiana
 c Abbott Laboratories Ltd - Saint-Laurent, Quebec

transfusions in the postoperative period (12, 13) were also observed.

Clinical experience using hetastarch has shown variable effects ranging from its use as a safe and effective agent (28, 29), to reports of potential problems with postoperative coagulation and hemostasis management (3, 13, 14). It was considered to be safe in doses up to 20 ml/kg/day. Dosages above 20 ml/kg have demonstrated clinically significant coagulopathies (16).

CRYOFIBRINOGENATION

As previously stated, depending on the attending staff, hospital and country in which CPB is carried out, the use of crystalloids alone, may be the most widely used and universal solution. However, a potentially severe problem with the use of crystalloids alone is not that of fluid accumulation or a lowered COP, but the process described as cryofibrinogenation, leading to cryoprecipitate and platelet deposits on heat exchangers during hypothermic CPB.

More recently, several reports have linked the absence of albumin, as part of the perfusate, to the occurrence of platelet mediated clots around the heat exchangers of several brands of oxygenators. The formation of these gel-like clots may be due to the actions of cold reactive proteins called cryofibrinogens, which react strongly with platelets in a temperature dependent fashion in some patients' blood (30, 31). The overall incidence of cold reactive proteins in cardiac patients is around 0.4% to 4.0% (32). In the classification of cold reactive proteins, cryofibrinogens are but one of four members. The others are cold agglutinins, Donath-Landsteiner antibodies and cryoglobins. During the normal course of CPB, it appears that the absence of the protein coating provided by albumin allows fibrinogen from the patient's blood to readily deposit around the heat exchanger of an oxygenator. In those patients who have cryofibrinogens in their blood (cryofibrinogenemia), there is a potential to trigger a cold agglutination process which results in the formation of cryoprecipitates, containing large amounts of factor VIII, von Willibrand factor, fibronectin, fibrinogen and factor XIII (31). It is highly probable that these fibrinogen and cryoprecipitate deposits trigger the platelet and coagulation activation process, leading to the formation of fibrin gel networks around the heat exchanger.

In those reported cases of oxygenator clotting there were many variables in regards to disease state, hematology and therapeutic regimen. However, all cases had three factors in common. There was active cooling below 30°C, albumin was not used as part of the priming solution and abnormal increases in premembrane pressures and pressure differentials were recorded (30, 32).

As stated, in those rare patients that exhibit cryofibrinogenemia, platelet/fibrinogen deposits may be triggered by the start of active cooling through the oxygenator's heat exchanger and the absence of albumin in the priming solution. Nevertheless, this course of action may be transient because it was found

that warming of the patient's blood tended to reverse the process (30). This was demonstrated by the reduction of premembrane/postmembrane pressure gradients as the temperature approached 37°C. However transient, cryoprecipitate and platelet deposits have the ability to reduce the oxygen transfer capabilities of a membrane oxygenator, acutely elevate premembrane pressures and increase the possibility of microemboli release. This then becomes of great concern and an increased diagnostic challenge for those who are responsible for the safe and effective delivery of extracorporeal circulation. Excessively increased premembrane pressure could indicate one of several problems: 1) excessively high flows and viscosity problems at decreasing temperatures, 2) interference with the membrane's fluid path due to manufacturing defect or blood clotting, 3) impending hemolysis and membrane failure, 4) a reduction of oxygen transfer and 5) subsequent reductions of blood flow that may not provide adequate perfusion for the patient's demands.

When looking at the relationship between such cold reactive proteins as cryofibrinogens and heat exchangers, a question comes to mind. Why is this problem being recognized now? After all, non-albumin primes and cold reactive proteins have been around for a long time.

The answer to this question may be found in the expense, technique and technology. First may be in the fact that albumin, being an expensive blood derived product, is being replaced by synthetic colloids for routine CPB by an ever increasing number of cardiac centers. Secondly, many centers do not find it necessary to routinely measure premembrane pressures during CPB. Finally, membrane manufacturers are producing smaller and more efficient membranes and heat exchangers as technology steadily improves.

PRACTICAL CONSIDERATIONS

We have had the opportunity to use all three agents as perfusates for CPB. Crystalloids only and crystalloids plus albumin are by far the easiest perfusates to use to debubble and prime bypass tubing, oxygenators and filters. Priming with crystalloid plus pentastarch requires a great deal of care and gentle handling of the arterial line filter. If microbubbles are generated in these filters during priming with pentastarch, they become very difficult to remove and tend to become very adherent to the filter wall. Flushing the filters with CO₂ prior to priming does seem to help with the removal of microbubble adherence but it does not eliminate it.

The use of albumin preparations in CPB perfusates appears to also be a safe and reliable source of colloid replacement. The advantages of coating the bypass components with proteins is unique to albumin. Recent reports have recommended the use of some albumin in all CPB primes (30, 31). In an attempt to completely eliminate fluid retention during CPB, as much as 175 g of albumin have been added to perfusates with no success.

However, as little as 50 g has shown a significant decrease in fluid accumulation during bypass (20). As of yet, there is no research indicating how much albumin is required to avoid the potential cryofibrinogen problem, but those centers reporting as little as 12.5 g of albumin in the prime have yet to report the occurrence of a problem that resembles the cryofibrinogen process. At current market prices for albumin, this may be an acceptable alternative for those centers utilizing synthetic colloids as part of their perfusates. In utilizing larger volumes of albumin, synthetic colloids like pentastarch have been gaining popularity as an inexpensive replacement for the albumin in CPB perfusates. As noted in the Pentaspan® monograph (25), special care should be taken in the presence of impaired renal function. Our center has adopted a policy not to use pentastarch as a priming additive in those patients who have serum creatinines above the normal value. It has yet to be reported that any of the synthetic colloids can provide the platelet protective effects of serum albumin, however short lived.

CONCLUSIONS

The ideal solution for priming the extracorporeal circuit would alleviate all of the potential adverse reactions, debubbling problems, and increased costs associated with current priming solutions. It would also reduce the risk of spreading transmissible disease, maintain acceptable colloid osmotic pressures and reduce the activation of platelets and the coagulation cascade from foreign surfaces. Unfortunately, such a solution does not exist.

However, until the ideal perfusate is found, further research and investigation should be carried out on the process of cryofibrinogenation and the potential for adverse outcome during CPB. In the meantime, to avoid confusion regarding the potential causes for abnormal changes in premembrane pressures during hypothermic CPB, we suggest that it may be appropriate to add some amount of albumin to precoat extracorporeal surfaces and prevent the possibilities of cold induced blood reactions. Also, to alert the clinician to potential problems within the oxygenator, we suggest the monitoring of premembrane as well as postmembrane pressures.

ACKNOWLEDGEMENT

I greatly appreciate Dr. Richard Hall, Cardiac Anaesthesia, for his tremendous help and in depth critique of this manuscript.

REFERENCES

- 1 Saltzman E, Merrill E, Binder A, et al. Protein-platelet interaction on heparinized surfaces. *J Biomed Mat Res.* 1969; 3:69-81.
- 2 Martin J, Carson F, Race G. Calcium containing platelet granules. *J Cell Biol.* 1974; 60:775.
- 3 Bartlett R, Gazzanigo A. Physiology and pathophysiology of extracorporeal circulation. In: *Current Techniques in Extracorporeal Circulation.* Ionescu, Woller eds. London: Butterworths; 1981; 27.
- 4 Lee R, Kim S. Adsorption of platelets onto hydrophobic polymer surfaces: adsorption isotherms and kinetics. *J Biomed Mater Res.* 1974; 8:251.
- 5 Kurusz M, Schneider B, Conti V. Albumin pretreatment of autotransfusion apparatus. *J Extra-Corpor Technol.* 1982; 14: 467-69.
- 6 Gravlee G, Davis R, Utley J. *Cardiopulmonary Bypass Principles and Practice.* Baltimore: Williams and Wilkins; 1993; 419.
- 7 Saunders C, Carlisle L, Bick R. Hydroxyethyl starch versus albumin in cardiopulmonary bypass prime solutions. *Ann Thorac Surg.* 1983;36:532-39.
- 8 Beshere G, Camerlengo L, Dearing J. Estimation of colloid osmotic pressure during hemodilutional cardiopulmonary bypass. *J Extra-Corpor Technol.* 1982;14(3): 381-84.
- 9 Blackwell M, Riley J, McCall M, et al. An evaluation of three methods for determining colloid osmotic pressure. *J Extra-Corpor Technol.* 1994; 26(1):18-22.
- 10 Hett DA, Smith DC. A survey of priming solutions used for cardiopulmonary bypass. *Perfusion.* 1994;9:19-22.
- 11 Morissette MP. Colloid osmotic pressure : Its measurement and clinical values. *CMA J.* 1977 ;116:897-900.
- 12 London M, Franks M, Verrier E, et al. The safety and efficacy of 10% pentastarch as a cardiopulmonary bypass priming solution. *J Thorac Cardiovasc Surg.* 1992; 104:284-96.
- 13 Kerins P, Vertrees R, Finn K, et al. Comparison of two colloid constituents in prime solutions and the effect on blood loss following CPB. *AmSECT Proceedings.* 1989; 11-14.
- 14 Strauss R. Volume replacement and coagulation: A comparative review. *J Cardiothorac Anesth.* 1988; (Suppl 1) 2(6): 24-32.
- 15 Quon, C.. Clinical pharmacokinetics and pharmacodynamics of colloid plasma volume expanders. *J Cardiothorac Anesth.* 1988; (Suppl 1) 2(6):13-23.
- 16 London M, Ho J, Triedman J, 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;97:785-97.
- 17 Sandrelli L, Alfieri O, VanOeveren W. The problem of priming solutions? The solution of priming problems. *Perfusion.* 1992;7: 217-21.
- 18 Sade R, Stroud M, Crawford F, et al. A prospective randomized study of hydroxyethyl starch, albumin and lactated Ringers solution as a priming fluid for CPB. *J Thorac Cardiovasc Surg.* 1985; 89:713-22.
- 19 Beattie H, Evans G, Garnett E, et al. Albumin and water fluxes during cardiopulmonary bypass. *J Thorac Cardiovasc Surg.* 1974; 67:926.

- 20 Utley J, Stephens DB. Fluid balance during cardiopulmonary bypass. In: Utley J, ed. *Pathophysiology and Techniques of Cardiopulmonary Bypass Vol. II*. Baltimore: Williams & Wilkins. 1983; 31-33.
- 21 Scott D, Cannata J, Mason K, et al. A comparison of albumin, polygeline and crystalloid priming solutions for cardiopulmonary bypass in patients having coronary artery bypass graft surgery. *Perfusion*. 1995; 10:415-24.
- 22 McGrath L, Gonzalez-Lavin L, Neary M. Comparison of Dextran 40 with albumin and Ringer's Lactate as components of perfusion prime for cardiopulmonary bypass in patients undergoing myocardial revascularization. *Perfusion*. 1989; 4:41-49.
- 23 Jenkins I, Curtis A. The combination of mannitol and albumin in priming solutions reduces positive intraoperative fluid balance during cardiopulmonary bypass. *Perfusion*. 1995; 10:301-05.
- 24 Gurjar Y, Bowman J. Prevention of platelet adhesion to extracorporeal surfaces. *J Extra-Corpor Technol*. 1984; 16: 104-07.
- 25 Pentaspan Monograph. DuPont Pharma, Mississauga, Ontario; February 1992.
- 26 Myers, G. Editorial. *Canadian Perfusion Canadienne*. 1995; 8(1):6.
- 27 Sade R, Crawford F, Dearing J, et al. Hydroxyethyl starch in priming fluid for cardiopulmonary bypass. *J Thorac Cardiovasc Surg*. 1982; 84:35-38.
- 28 Palanzo D, O'Neill M, Williams D, et al. Hetastarch as a clear prime for cardiopulmonary bypass. *J Extra-Corpor Technol*. 1984;16(2): 55-57.
- 29 London M. Plasma volume expansion in cardiovascular surgery: practical realities, theoretical concerns. *J Cardiothorac Anesth*. 1988; (Suppl 1) 2:39-49.
- 30 Blomback M, Kronlund P, Aberg B, et al. Pathological fibrin formation and cold-induced clotting of membrane oxygenators during cardiopulmonary bypass. *J Cardiothorac Vasc Anesth*. 1995; 9(1): 34-43.
- 31 Bearss M, Ericson D, Parks P, et al. The puzzling case of the cryoprecipitates. *AmSECT Today*. 1996; 5: 21-25.
- 32 Agarwal SG, Ghosh PK, Gupta D. Cardiac surgery and cold reactive proteins. *Ann Thorac Surg*. 1995; 60: 1143-50.