# BLOOD SUBSTITUTES*

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SUBSTITUTES for whole blood include fractions of blood, such as plasma, serum albumin, and true substitutes such as the plasma volume expanders and intravenous crystalloid solutions.

## BACKGROUND

Czerny reported in 1894[1] on the intravenous injection of colloids in animals, after giving gum arabic or gelatin to dogs, cats, and rabbits. He found an increase of blood viscosity after giving gum arabic and decreased RBC count after colloid injection. Hogan in 1915 first used colloidal gelatin intravenously with improvement in blood pressure of patients in shock.[2] In 1918 Bayliss treated wound shock for the first time with gum acacia.[3] Many of the patients improved; those who did not also did not respond to transfusion of blood. Gronwall and Ingelman reported their work with dextran in 1945 and advocated it as appropriate for treatment of shock.[4] It has been in clinical use ever since.

## ESSENTIALS OF AN ACCEPTABLE PLASMA SUBSTITUTE

Major considerations[5] are that it must maintain a satisfactory colloidal osmotic pressure, be capable of manufacture at a constant composition and reasonable price, be stable in storage and on exposure to wide variations in temperature, be easily sterilized by autoclaving and have a suitable viscosity for intravenous administration. It must be pyrogen free, be excreted or metabolized without damage to tissues and not be antigenic. Another factor is that it should remain in the vascular compartment for 12 to 24 hours.[6] It should not produce haemolysis, red blood cell agglutination, or increased sedimentation rate. It should not alter other functions of the blood, or impair haemostasis.

### *Advantages of Plasma Substitutes*

Substances capable of expanding plasma volume are of critical importance in dealing with disasters involving many casualties and with less emergent needs in remote areas where blood is not available.[7] Non-biological substitutes for blood can be manufactured in large quantities and stored for long periods of time. In many cases of shock there is need for increase of circulating volume, while sufficient red cells are still present for adequate carriage of oxygen. The risks of blood transfusion are the advantages of plasma substitutes: avoidance of bacterial or viral infection, transfusion reactions and Rh sensitization. With plasma substitutes, one

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can evade transfusion of whole blood when the loss is not massive, or when the plasma protein portion of blood only is depleted.

*Types of Substitutes*

Various kinds of plasma volume expanders exist: blood derivatives (albumin, protein fraction, plasma), modified proteins (gelatin, oxypolygelatin) polymerized carbohydrates (dextran, levan) plastics (polyvinylpyrrolidone [PVP]) and intravenous crystalloid solutions (glucose, electrolytes).

*Effects of Plasma Substitutes in Man*

The primary aim in administration of plasma substitutes is to increase plasma volume, and this effectively occurs. Plasma volume has been found to expand 50 per cent of the infused volume when measured two hours after giving one liter of PVP; the haematocrit fell 5 volumes per cent, but returned to normal in 24 hours.[8] As expected from enlarging blood volume, dextran infusion increases cardiac output, stroke volume, and systemic arterial pressure.[9] However, right atrial pressure and blood volume can increase without a rise in stroke volume.

Impaired haemostasis is a detrimental effect, particularly with dextran. Jacobaeus found that Macrodex® prolonged bleeding time and decreased prothrombin, proaccelerin and proconvertin in proportion to the haemodilution. No decrease in platelets occurred, but their activity was inhibited. PVP also has this effect, but gelatin and albumin are quite innocuous. Most of the effects on blood constituents have been attributed to dilution. Plasma proteins and haematocrit decrease and the haematrocrit stays low for five or six weeks afterward; the proteins rise above normal in two to three weeks.[10] The sedimentation rate increases after infusion of PVP.[11] Plasma expanders have no discernible effect on the liver. Similarly 6 per cent dextran produces no marked changes in glomerular filtration rate or PAH clearance by the kidneys.[12]

*Clinical Usefulness of Plasma Volume Expanders*

Anaesthetists should have a thorough knowledge of blood substitutes and of their usefulness in comparison to whole blood.[13]

*I. Plasma*

The only preparation of plasma now made in Canada is fresh frozen plasma. It is most useful because it contains nearly all the clotting factors in normal concentrations, excepting platelets. The risk of viral hepatitis is the same as for whole blood. It must be stored in a deep-freeze unit and requires special handling, including thawing before administration.

*II. Plasma Protein Fractions*

These are produced by partially fractionating a large plasma pool to prepare albumin and several globulin fractions.[14] These are effective plasma volume expanders, can be handled as a pharmaceutical, and are hepatitis-virus free. However, both Bland *et al.*[15] and Torda *et al.*[16] report arterial hypotension from rapid infusion of plasma protein fractions, due to arteriolar dilatation.

*III Serum Albumin*

Advantages of serum albumin are that it can be concentrated and made salt poor: it does not transmit serum jaundice and can be handled conveniently as a pharmaceutical. Albumin is more stable than other plasma proteins and due to its major contribution to oncotic pressure, most valuable in expanding plasma volume. The 25 per cent solution can be given quickly since it is relatively non-viscous. Other intravenous fluids must be given rapidly with it if dehydration is present, since albumin draws fluid from the interstitial space. While there is no dose limit, large amounts will dilute endogenous clotting factors, requiring fresh frozen plasma or whole blood to be given. Serum albumin is the best of the presently available substitutes and should be used first. However, it is expensive and scarce.

*IV Dextrans*

Dextrans are branched polysaccharides made up of glucose units and come in three varieties, depending on molecular weight: low (Rheomacrodex) averaging 40,000, medium (Macrodex, Commercial Dextran) averaging 75,000, and high (British Dextran) averaging 150,000. The dextrans are free of hepatitis virus, inexpensive, and readily available. A coagulation defect occurs if a large amount is given, but not if the volume is no more than 1,000 ml of 6 per cent dextran. A small incidence of sensitivity to dextran is seen in people receiving it for the first time. Elimination from the body is primarily by the kidneys. The effects of dextran vary with the molecular weight.[17]

Low molecular dextran is satisfactory for volume expansion, but the effect does not last long. It has a beneficial effect on the microcirculation by preventing or abolishing sludging and platelet aggregation. It has the least relative increase in viscosity of RBC suspension in dextran.

Medium molecular dextran is capable of expanding intravascular volume for several hours. It has only slight effect on the microcirculation and platelet aggregation, with moderate relative increase in viscosity of RBC suspension in dextran.

High molecular dextran produces adequate prolonged plasma volume expansion. Its effect on the microcirculation is detrimental since it causes platelet aggregation. There is marked relative increase in viscosity of RBC suspension in dextran.

Neither low nor medium molecular weight dextran have been associated with major toxicity except the rare anaphylactoid reaction to the medium type.

The tendency to increased bleeding may be attributed to:

(1) the high molecular weight type, no longer used clinically. It prolongs bleeding and coagulation times, reduces fibrinogen and other clotting factors, and causes thrombocytopenia due to platelet aggregation and consequent intravascular coagulation;[18]

(2) rapid infusion or large doses of the low and medium types. Even 1,000 ml of low molecular weight dextran given to a healthy man in two hours causes a slight transient fall in platelets and prolongs bleeding time;[19]

(3) administration of dextran along with heparinization, the two effects on clotting potentiating each other.

*V Polyvinylpyrrolidone*

This product was developed in Germany during World War II. However, it has

not been used since Dextran became available, since it remains indefinitely in the tissues.

*VI Intravenous Crystalloid Solutions*

Administration of sodium chloride intravenously, as a blood volume expander, was first tried nearly a century ago. It was soon found that it did not remain in the vascular compartment. However, about 10 years ago Shires and associates[20] pointed out a valid reason for giving electrolyte solutions in blood loss, burns and trauma, to wit: the body's response to blood loss is to draw interstitial fluid into the blood stream to restore circulating volume. This depletes extracellular volume, and secondarily intracellular fluid volume, since these spaces equilibrate with each other. Unless intravascular and extravascular volumes are restored within a short time, cellular metabolism is irreversibly compromised and shock becomes refractory. Other factors such as endotoxins and metabolic acidosis are also involved.

Because of this philosophy, Lactated Ringer's Solution has become almost universally used for fluid replacement in hypovalaemia, and electively during operation. Over-enthusiastic administration of fluids has led to postoperative pulmonary dysfunction from water retention.[21]

Another effect of reduced blood pressure and circulating blood volume is a deficient oxygen supply to cells. The anaerobic production of adenosine triphosphate (ATP) produces lactate, and lactic acidosis. Hence, restoring intravascular, interstitial, and intracellular fluid volumes with a solution containing lactate seems far less than ideal. Lactate is a metabolic dead-end that must be changed to pyruvate with oxygen, which must then go through the Krebs Cycle in the liver to produce ATP. We have found[22] that giving lactated Ringer's is metabolically the same as giving no solution during abdominal operations. The body mobilizes and uses glycogen and energy, and ketosis is present in the Recovery Room.

The same study[22] documented that 5 per cent glucose either in water, or in Ringer's solution (300 ml/hour) during major operations avoided ketosis, i.e. less lipid was metabolized. Blood glucose was higher than in the patients who did not receive glucose. Pyruvate and lactate levels were also higher, presumably due to metabolism of the extra glucose.

Another factor now emerging as important in selecting an intravenous solution is osmolality. Plasma osmolality (normal 280–290 m Osmol/kg $H_2O$) is the solute concentration of the plasma (the solution), and a major determinant of water movement across vascular walls. One can envision that a large amount of hypo-osmolar intravenous solution could reduce plasma osmolality below normal, allowing more water loss from the vascular compartment. Ringer's solution has an osmolality of 260, and 5 per cent Dextrose in water is 265. Every 100 mg per cent rise in blood sugar raises plasma osmolality 5 milliosmols. Hence, a balanced electrolute solution containing 5 per cent dextrose, with an elevated osmolality, will help to maintain plasma osmolality, and retain more water intravascularly.

In essence, for elective para-operative volume replacement, or emergency replenishing of body fluids, a balanced electrolyte solution with glucose is more likely to maintain closer-to-normal plasma osmolality and energy metabolism. Normal plasma osmolality should decrease fluid retention outside the vascular compartment, which tends to occur as a response to surgical stress.

In summary there is a variety of useful agents for expansion of plasma volume, available to substitute for whole blood. Circumstances such as the location and nature of the emergency need, and the speed and volume of replacement required should dictate the choice of product to be given.

## Summary

Substitutes for whole blood include blood fractions such as plasma, serum albumin and other fluids of various kinds which are not derived from blood but are used as plasma volume expanders; these include the usual crystaloid intravenous solutions. Since in comparison to blood far more of these latter solutions are given intravenously, a thorough knowledge of plasma volume expanders is essential. The first use of such expanders in human patients was by Hogan in 1915. He used colloidal gelatin and noted an improvement in blood pressure of patients in shock. In 1945, Gronwall and Ingelman advocated the use of dextran in shock.

The requirements for an acceptable plasma substitute are: a satisfactory colloidal osmotic pressure, constant composition at reasonable cost, a viscosity suitable for intravenous administration, stability in prolonged storage at variable temperatures, and sterilization by autoclaving. Such substances must be either fully excreted or metabolized, and must cause no early or late tissue damage. They must be non-antigenic and pyrogen free. They must cause no change in the blood such as haemolysis, R.B.C. agglutination, increased sedimentation rate and no impairment of haemostasis.

The presently available plasma expanders include blood derivatives (plasma, albumin), modified protein (gelatin, oxypolygelatin), polymerized carbohydrates (dextran) and plastics (polyvinyl pyrrolidone-PVP). All these substances expand plasma volume, decrease haematocrit and plasma proteins, increase sedimentation rate and blood pressure. Dextran, PVP and gelatin do not alter hepatic function. Dextran and gelatin have no deleterious effects on renal function.

Features of the clinically used plasma expanders are:

1. *Fresh Frozen Plasma*

Fresh frozen plasma contains all clotting factors except platelets. The risk of the transmission of hepatitis is present as it is with whole blood.

2. *Plasma Protein Fractions*

Plasma protein fractions are free of hepatitis virus, but may cause arteriolar dilatation and hypotension.

3. *Serum Albumin*

Serum albumin is a concentrated blood protein fraction. It is salt poor, stable and does not transmit the virus of hepatitis. Since it has a high oncotic pressure it is necessary to give significant quantities of clear fluids with it. It is expensive, scarce, and dilutes the clotting factors. It is, however, a first choice for emergency treatment of shock.

4. *Dextran*

The dextrans may be of medium or low molecular weight. They are inexpensive and readily available, and do not transmit the virus of hepatitis. In large amounts they cause a coagulation defect and may be antigenic. The main advantage of low molecular weight dextran is that it abolishes red blood cell sludging in the microcirculation in low flow states.

5. *P.V.P.*

This was developed in Germany in World War II. It is no longer acceptable as an expander because it is stored indefinitely in tissues.

*Crystalloid Solutions*

The most commonly administered plasma expanders are the clear (crystaloid) intravenous solutions. These are blood substitutes that temporarily expand plasma volume, supply water, electrolytes and energy substrate for the needs of the fasting or hypovolaemic patient. Lactated Ringer's solution has become widely accepted for fluid replacement because it contains electrolytes in plasma concentrations. However, it is hypo-osmolar and contains no readily available energy substrate. The effects of Ringer's solution with and without dextrose and 5 per cent dextrose in water have been compared during and after operation. Plasma concentrations of electrolytes were little different in patients receiving Ringer's solution or dextrose 5 per cent in water at the rate of 300 ml/hour. Patients receiving 5 per cent dextrose, either in water or in Ringer's solution, gave evidence of greater glucose metabolism and less lipid utilization than did those patients receiving Ringer's Solution alone.

RÉSUMÉ

Les substituts du sang entier comprennent les fractions sanguines telles que le plasma, l'albumine sérique et les divers autres liquides qui, n'étant pas des composés du sang, servent à accroître le volume plasmatique; parmi ceux-ci nous pouvons inclure les solutions électrolytiques habituellement en usage. Puisque ces solutés sont donnés par voie intraveineuse en quantité beaucoup plus grande par rapport au sang, il devient nécessaire de posséder une connaissance approfondie des expanseurs du volume plasmatique. Pour la première fois chez l'humain, de telles substances ont été employées par Hogan en 1915. Il se servit de gélatine colloïdale et nota une amélioration de la tension artérielle chez les patients en choc. En 1945, Gronwall et Ingelman préconisèrent l'empli du dextran dans le choc.

Les exigences relatives à un substitut plasmatique adéquat sont: une pression osmotique colloïdale satisfaisante; un composé fiable à un coût raisonnable; une viscosité compatible avec l'administration intraveineuse; la stabilité après storage prolongé à des températures variées; la stérilisation possible à l'autoclave. De telles substances doivent être soit entièrement excrétées, soit métabolisées, ne doivent causer de dommages tissulaires ni précoces, ni tardifs. Elles doivent être exemptes de pouvoir antigénique et libres de corps pyrogènes. Elles ne doivent être la cause d'aucune altération du sang tel que l'hémolyse, l'agglutination des G.R., l'accélération de la vitesse de sédimentation ou d'une altération de l'hémostase.

Les expanseurs plasmatiques actuellement disponibles comprennent des dérivés du sang (plasma, albumine), des protéines modifiées (gélatine, oxypolygélatine),

des polymères d'hydrates de carbone (dextran) et des plastiques (polyvinyl pyrrolidone-PVP). Toutes ces substances accroissent le volume plasmatique, abaissent l'hématocrite et les protéines du plasma, augmentent la vitesse de sédimentation et la pression sanguine. Le dextran, le PVP et la gélatine n'altèrent pas la fonction hépatique. Le dextran et la gélatine n'ont pas d'effet nocif sur la fonction rénale.

Particularités des solutions colloïdales employées en clinique pour augmenter le volume plasmatique :

1– *Plasma frais congelé*

Le plasma frais congelé contient tous les facteurs de coagulation à l'exception des plaquettes. Le risque de transmission de l'hépatite est égal à celui du sang entier.

2– *Fractions protéiniques plasmatiques*

Les fractions de protéines plasmatiques sont exemptes du virus de l'hépatite, mais peuvent causer une dilatation artériolaire et de l'hypotension.

3– *Albumine sérique*

L'albumine sérique est une fraction protéinique sanguine concentrée. Elle est pauvre en sel, stable et ne transmet pas le virus de l'hépatite. Puisqu'elle a une pression oncotique élevée, il est nécessaire de l'accompagner d'une grande quantité de solutés. Elle est dispendieuse, rare et elle dilue les facteurs de coagulation. Elle est cependant la substance de premier choix dans le traitement d'urgence du choc.

4– *Dextran*

Les dextrans peuvent être de poids moléculaire moyen ou bas. Ils sont peu coûteux et facilement disponibles; ils ne transmettent pas le virus de l'hépatite. Lorsque donnés en grande quantité, ils causent des troubles de coagulation et peuvent devenir antigéniques. Le principal avantage du dextran à poids moléculaire bas est de s'opposer à la formation de rouleaux "sludging" des hématies dans la microcirculation lorsque le débit sanguin est lent.

5– *P.V.P.*

Celui-ci fut développé en Allemagne au cours de la seconde guerre mondiale. Il n'est plus acceptable comme substitut plasmatique parce qu'il est emmagasiné définitivement dans les tissus.

*Les solutés crystalloïdes*

Les substituts plasmatiques les plus communément employés sont les solutés clairs (crystalloïdes). Ils sont les substituts du sang capables d'accroître temporairement le volume plasmatique et de fournir de l'eau, des électrolytes et un substratum énergétique pour les besoins d'un patient à jeun ou hypovolémique. La solution de lactate Ringer est largement acceptée comme liquide de remplacement car elle contient des électrolytes en concentration semblable à celle du plasma. Toutefois, elle est hypo-osmolaire et ne contient pas de substratum énergétiques. Les effets de la solution Ringer avec et sans glucose, et du soluté glucosé à 5 pour cent dans l'eau ont été comparés, durant et après l'opération.

Les concentrations plasmatiques en électrolytes furent quelque peu différentes chez les patients qui recevaient de la solution Ringer ou du soluté glucosé à 5 pour cent dans l'eau, à une vitesse de 300 cc/hre. Les patients qui recevaient du glucosé, soit dans l'eau, soit dans la solution Ringer, démontrèrent un métabolisme glucidique supérieur ainsi qu'un catabolisme lipidique moins important que les patients recevant uniquement la solution Ringer.

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