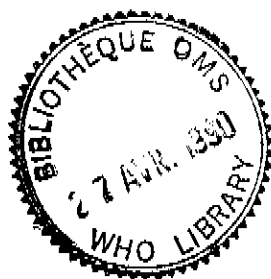

GLOBAL BLOOD SAFETY INITIATIVE

USE OF PLASMA SUBSTITUTES AND PLASMA IN DEVELOPING COUNTRIES

GENEVA
20-22 MARCH 1989



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The Global Blood Safety Initiative (GBSI) is a cooperative endeavour to support the development of safe and effective blood transfusion services in all countries. Core participants are the World Health Organization's Global Programme on Aids (WHO/GPA) and unit of Health Laboratory Technology (LAB), the League of Red Cross and Red Crescent Societies (LRCS), the United Nations Development Programme (UNDP) and the International Society of Blood Transfusion (ISBT). The Initiative is also supported by the World Federation of Hemophilia and other bilateral and multilateral development agencies and nongovernmental organizations.

This document was reviewed and endorsed by the GBSI Consultation on Developing and Strengthening Blood Transfusion Services, held in Geneva from 20 to 22 March 1989. A total of 19 specialists in blood transfusion medicine and haematology from 16 countries participated in the consultation. The participants are listed on the last page.

1. Introduction

This document provides information and guidance on the use of plasma substitutes (crystalloids, synthetic and human colloids) and plasma. The indications for the use of plasma substitutes for correction of hypovolaemia due to haemorrhage are discussed here. The reader should consult WHO/CDD/SER/80.2/Rev.1¹ for a discussion of the indications for their use in patients with diarrhoea. Paediatric, surgical and medical texts and WHO handbooks² discuss the indications for their use in the management of patients whose hypovolaemia is caused by other gastro-intestinal disorders, burns, extensive soft tissue infections and acute abdominal disorders (e.g., peritonitis, pancreatitis, perforated peptic ulcer).

Plasma should rarely be used, if at all, for correcting hypovolaemia. Plasma substitutes are safer and preferable. It is useful for the management of some patients who have disorders of haemostasis and also in some cases of acute plasma protein loss (e.g., burns).

2. Crystalloids

Sterile pyrogen-free physiological saline (0.156 mol/l; 9.0 g/l) is the most widely used crystalloid and is useful in the management of haemorrhage and burns. Other crystalloids, such as Ringer's lactate, are usually not as readily available.

Crystalloids diffuse rapidly through the capillary walls into the interstitial fluid space and only one-third of the infused volume is retained in the plasma space. Thus, three volumes of crystalloids are required to replace one volume of blood or plasma. Because part of the administered load is excreted in the urine, the duration of their effect

depends on the rate of urinary output. Additional crystalloid solutions may therefore be required within a few hours.

2.1 Side effects

The fraction of the infused volume which passes into the interstitial space may cause tissue oedema, and the debate on the merits and disadvantages of crystalloids and colloids centres mainly on this. Transient interstitial oedema is acceptable, except possibly in high-risk patients, e.g., with severe anaemia or cardiopulmonary dysfunction. Even large volumes of crystalloids used for resuscitation seldom produce pulmonary oedema in the absence of heart failure.

Contamination with pyrogens or trace compounds, e.g., in lactate used to produce balanced salt solutions, or due to poor packaging or handling of solutions, has been described.

3. Synthetic colloids

Colloid solutions exert an oncotic pressure because of the macromolecules they contain; this retains water and thus volume within the circulation. The oncotic pressure increases with the number of molecules and with the concentration of the colloid. The size of the molecules is also important, because larger molecules leave the circulation more slowly.

It is important to note a fundamental difference between albumin and the synthetic colloids. Albumin, which has a molecular weight of 6600 daltons and accounts for two-thirds of the normal oncotic pressure of 26-28 mm Hg, is a "monodisperse" colloid; that is, all albumin molecules have the same size and weight. By contrast, the synthetic

¹WHO/CDD/SER/80.2/Rev.1 (1984), A Manual for the treatment of acute diarrhoea.

²Dobson M.B. *Anaesthesia at the district hospital*. Geneva, World Health Organization, 1988. *Surgery at the district hospital: obstetrics, gynaecology, orthopaedics and traumatology* (in preparation).

colloids are "polydisperse", that is, mixtures of various molecular fractions with substantially differing sizes and weights. They are therefore characterized by average molecular weight.

Gelatin solutions (e.g., succinylated gelatin and urea-linked gelatin), dextran 70 and hydroxyethyl starch (HES) are the most widely used synthetic colloids. Dextran and HES are true plasma expanders, i.e., the intravascular volume effect exceeds the infused volume by withdrawing fluid from the extravascular space, which becomes dehydrated. The gelatins have no expanding effect because of their relatively low concentration, and because some of their smaller molecules escape rapidly from the circulation. The initial intravascular volume effect is roughly equal to the infused volume.

The volume effect of dextran 70 and HES is more prolonged than that of the gelatins. Gelatins act as osmotic diuretics because they pass rapidly into the extravascular space and through the kidneys into the urine. Therefore, when they are administered, one or two litres of supplementary crystalloid solutions should be given in addition to the daily metabolic requirement. Alternatively, the urine output should be measured and the excess replaced, preferably by fluids given orally.

3.1 Side effects

Synthetic colloids may cause circulatory overload but this risk is smallest with the gelatins. Anaphylactoid reactions have been described in association with all synthetic colloids, varying from cutaneous rashes to lethal shock. The total incidence varies between 0.07% and 0.25%, depending upon the colloid used but the incidence of severe reactions is less than 0.02%. Severe reactions usually occur shortly after the start of the infusion. Close observation of the patient and meticulous monitoring of the vital signs are therefore particularly important during this period, and facilities must be readily available for prompt resuscitation of patients with anaphylactic shock.

Synthetic colloids may cause red cell aggregation but this is not a significant problem with the products currently available, particularly if a blood sample for cross-matching is obtained before they are transfused.

Dextran 70 interferes with platelet and factor VIII function. This may cause abnormal bleeding if more than 1000-1500 ml are given to an adult within 24 hours. It is contraindicated in patients with pre-existing haemostatic abnormalities.

HES also interferes with haemostatic mechanisms though less so than dextran. There is concern about prolonged tissue storage of the high molecular weight fractions and its possible long-term effect. After a single infusion of HES 450 in man, small quantities of the

material are still demonstrable in the circulation after one and a half months and repeated administration has a cumulative effect.

The gelatins do not show clinically relevant interference with haemostasis and even severe thrombocytopenia is not a contraindication to their use.

4. Albumin and plasma protein fraction (PPF)

The concentration of albumin in albumin solutions and PPF preparations varies between 50 and 250 g/l. Depending on the recipient's disease, the albumin infused has a physiological half-life of approximately 18 days. These preparations do not contain any coagulation factors. They are pasteurized to inactivate human immunodeficiency virus (HIV), and the hepatitis and other viruses. Albumin preparations are more stable and produce fewer adverse reactions than PPF but are more expensive. Production of albumin and PPF requires complex manufacturing techniques with rigid quality control.

4.1 Side effects

Both albumin and PPF can cause circulatory overload with left ventricular failure and pulmonary oedema, especially in anaemic patients. This risk is increased considerably when the more concentrated albumin preparations (e.g., 250 g/l) are used.

Hypotension due to vasoactive kinin and kininogen may occur during rapid infusions of PPF. Anaphylactoid reactions occur with both types of preparation but are less frequent than with the synthetic colloids.

5. Plasma

The major therapeutic value of plasma is in its haemostatic properties. Despite its importance physiologically for maintaining oncotic pressure, it is not the first choice for correction of hypovolaemia, because of the risk of transmitting infections. Crystalloids, synthetic colloids, or albumin or PPF if they can be afforded, are preferable.

Plasma is used for the preparation of cryoprecipitate, which is rich in factor VIII and fibrinogen and is useful for the management of haemophilia A, von Willebrand's disease and disseminated intravascular coagulation. Cryosupernatant may be used for the management of factor IX deficiency and of haemostatic disorders complicating liver disease. Frozen fresh plasma (FFP) thawed at or below 37°C is useful for correcting single or multiple coagulation deficiencies, when concentrated preparations are not available or appropriate.

When albumin or PPF are not available cryosupernatant or FFP may be used in the management of patients with acute protein depletion (e.g., burns).

5.1 Side effects

FFP may cause circulatory overload, particularly in children, and when it is infused rapidly for the correction of haemostatic disorders. FFP, cryoprecipitate and cryosupernatant may transmit infectious agents such as HIV and the hepatitis viruses. Methods for treating cryoprecipitate to inactivate viruses have been described but the technology is not yet widely available.

The risk of contamination with microorganisms is increased if a closed system (e.g., double or multiple plastic packs) has not been used for collection of the blood and harvesting of plasma. Incompatible transfusion reactions may occur if ABO-specific or compatible plasma is not transfused. Anaphylactic reactions range from cutaneous rashes to severe hypotension and shock.

6. Practical guidelines for the management of haemorrhage

- 6.1 Prompt control of external haemorrhage and urgent restoration of blood volume are the most important steps to be taken.
- 6.2 Treatment with oral rehydration salt solution - sodium chloride (table salt) 3.5 g, sodium bicarbonate (baking soda) 2.5 g, potassium chloride 1.5 g and glucose 20 g, dissolved in one litre of potable water - may be started immediately, provided there is no suspicion of a gastro-intestinal lesion and surgery is not imminent.
- 6.3 An intravenous infusion should be started if the pulse rate exceeds 100 per minute and/or the systolic blood pressure is less than 90 mm Hg.
- 6.4 Depending on the amount of blood lost, initial pulse and blood pressure and the patient's response, treatment should begin with 1000 - 2000 ml of crystalloids e.g., physiological (0.156 mol/l) saline or Ringer's lactate. This is infused intravenously within 15-30 minutes, or until the pulse is less than 100 and systolic blood pressure is 90-100 mm Hg. The urinary output should reach at least 30 ml per hour. The rate of the infusion is adjusted to maintain these levels.³
- 6.5 If circulatory stability is not achieved by 2000 ml of crystalloids (or proportionately less in children), the patient should be transferred as soon as possible to a treatment centre where blood is available and haemorrhage

can be controlled. If this is not immediately possible it is preferable to continue with 500-1000 ml of a synthetic colloid. If colloids are not available, proceed with crystalloids up to 7000 to 8000 ml within 24 hours provided that renal output remains satisfactory.

- 6.6 The adequacy of treatment is assessed by serially monitoring skin temperature, urinary output, venous filling, blood pressure and pulse.
- 6.7 If internal haemorrhage is suspected, and in order to minimize reactivation of bleeding, the systolic blood pressure should not be raised above 90 mm Hg. Such patients must be rapidly transferred to an institution with the facilities for appropriate treatment.
- 6.8 It is important that records of the clinical condition and all treatment given be kept and that they accompany the patient on transfer to another treatment facility.
- 6.9 **Notes**
 - (i) Ringer's lactate and some gelatins contain calcium ions and may therefore induce clotting in the giving set when blood is administered subsequently through the same set. Intravenous infusion sets and lines must first be flushed out with physiological saline or, preferably, blood or plasma should be transfused through a different set. Modifications of Ringer's lactate with low calcium ion concentrations are available in some centres.
 - (ii) The volumes given above are suitable for adults. Children less than two years old should not receive more than 30 ml/kg physiological saline within six hours because of the danger of precipitating congestive cardiac failure.
 - (iii) Gelatin is usually given in doses of up to 50 ml/kg within 24 hours but up to 5 litres may be given in 24 hours if urinary output is satisfactory. Doses of dextran 70 or HES should not exceed 20 ml/kg per 24 hours.
 - (iv) The rate of infusion of albumin (50g/l) and of PPF varies with the clinical situation. Fast rates may be necessary to maintain adequate tissue perfusion. Occasionally PPF may cause hypotension. The patient must be monitored closely and another plasma substitute should be used if this occurs.
 - (v) Solutions containing dextrose should not be mixed with blood in the same giving set as they may cause haemolysis.

³The containers should have clearly visible markings per 100 ml, so that volume and rate calculations can easily be made e.g.:
 1000 ml/15 minutes = 200 ml/3 minutes
 1000 ml/30 minutes = 100 ml/3 minutes (x 2 for 2000 ml)

7. Training of personnel

Personnel who will use plasma substitutes in the absence of a physician should be trained in at least the following areas:

- 7.1 prompt control of external bleeding;
- 7.2 assessing skin temperature and measuring the pulse rate and systolic blood pressure;
- 7.3 recognition of the clinical signs of hypovolaemia and of the features of impending and manifest shock;
- 7.4 record-keeping, including charting input (type, quantity and time of infused fluids) and urinary output (volume and time of voiding);
- 7.5 preparing and starting an intravenous infusion;
- 7.6 ability to administer doses recommended or consultation of a prepared leaflet;
- 7.7 recognition of signs of circulatory overload and of other reactions attributable to the infusion(s);
- 7.8 recognition of signs of contamination of intravenous fluids and ability to commence corrective action immediately;
- 7.9 recognition of the need for a patient to be transferred to a specialized treatment facility and organization of transport for this purpose.

Ideally, this training should be included in the general curriculum of paramedical health personnel. The details would be decided upon by national health authorities.

8. Availability and supply of plasma substitutes

8.1 Crystalloids

Most countries should be able to produce physiological saline for intravenous administration, provided that there are adequate arrangements for quality assurance, including good manufacturing practice and maintaining sterility.

Physiological saline is stable at ambient temperatures for more than one year and is cheaper than the synthetic colloids. There are few risks associated with its administration (see Section 2.1). Physiological saline should therefore be available at all levels of the health services in any country, including the health clinic, provided that the staff has been adequately trained (see Section 7). Treatment can be started at this level and the patient may be transferred for further management (e.g., to a district hospital) if necessary.

Other crystalloids (e.g., Ringer's lactate) may be used instead of physiological saline. However, because they are more difficult to produce they would probably be imported and therefore more expensive than saline.

8.2 Synthetic colloids

These are more difficult to produce than crystalloids and are usually imported. Apart from HES which is apparently stable at ambient temperatures above 35°C, they are sensitive to temperatures above 30°C. Degradation into smaller molecules begins after one month's storage above 40°C and is very marked after five or six months. They should therefore preferably be stored below 20°C. Treatment with synthetic colloids costs two or three times that of treatment with equivalent amounts of crystalloids. Moreover, a higher level of training is required for people who will administer them because of the risks associated with their use (see Section 3.1).

Since synthetic colloids are useful for managing some patients with haemorrhage (see Section 6.5), they should be available at district hospitals where a doctor will supervise their use and treat complications if necessary. Larger stocks would be required in intermediate and tertiary referral hospitals. Despite their cost, synthetic colloids are useful and safe alternatives to blood transfusion and are less expensive.

8.3 Albumin and PPF

These can be produced only in fractionation plants and very few countries have these facilities. The majority of countries must therefore import these solutions and few can afford the cost which may be 10-15 times that of synthetic colloids. They are stable for several years at refrigeration temperature and for up to three years at temperatures up to 30°C. Apart from the hypotensive episodes which may occur when PPF is infused at more than 10 ml/minute, they are relatively safe. If they are affordable, they are the colloids of choice for management of patients with burns and they may also be useful in the management of major haemorrhage.

8.4 Plasma

Plasma is obtained from blood by centrifugation (preferably), for which a refrigerated centrifuge is required, or by sedimentation. Storage of frozen fresh plasma and cryosupernatant requires a freezer (at least -20°C). Cryoprecipitate can be lyophilized, simplifying its storage and transport, but this technology is not widely available and in most countries it must therefore be stored in a freezer. In addition to these disadvantages and the others already outlined (see Section 5.1), plasma is expensive. It is 7 to 10 times more expensive to

use than equivalent amounts of synthetic colloids. The latter are therefore preferable for the correction of hypovolaemia in patients with hemorrhage. It is reasonable for stocks of cryoprecipitates, cryosupernatant or frozen fresh plasma to be available for management of disorders of haemostasis (see Section 5) and of burns. The storage centre will depend on the state of communications within the country.

Plasma, cryoprecipitate and cryosupernatant should be prepared only from donors who have been shown to be consistently non-reactive in sensitive screening tests for HIV on several occasions. This is particularly important in countries in which the prevalence of HIV infection is high.

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