A Survey

Hematologic Complications

of extra-corporeal by-pass

PART I

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Hematologic complications are common during and following heart-lung bypass. In part these are related to the massive amounts of blood generally transfused (in effect, an exchange transfusion). In part these result from the intimate exposure of both donor and patient blood to the foreign surfaces and traumatic effects of the extracorporeal pump-oxygenator.

In the interest of brevity, the comments to follow will be somewhat dogmatic and based to a considerable extent on our own experience.

Donor Blood, Procurement:

The Irwin Memorial Blood Bank of the San Franscisco Medical Society provided 84,123 units of blood for 6,295 patients for open heart surgery performed at seven hospitals from 1956 through March 1969. The average amount of blood used per case was 12 units, but it is not unusual to receive an emergency request for 10 or 20 further units during the hours following surgery. Adequate supplies of fresh blood of the appropriate ABO and Rh types can be assured only if the blood bank receives sufficient advance notice of each scheduled operation. Even if it is intended to prime the extracorporeal circuit with electrolyte solutions or with heparinized, recalcified ACD (acid-citrate-dextrose) blood, the blood bank must be alerted in order to be prepared for unexpected blood loss.

Donor Blood, Compatibility:

Donor units need be compatible with the recipient only for the ABO factors and the major Rh factor (Rh_0 or D). It is impractical to require more complete correspondence of blood types (1). Donor bloods are tested for irregular (non-ABO) antibodies by technics approved by the Standards of the American Association of Blood Banks (2). Donor units which contain irregular antibodies are not used.

The sera of the patients are also tested for irregular antibodies by similar technics. If an irregular antibody is found, donor blood must be provided which lacks the corresponding antigenic determinant. It is obviously advantageous to test patient sera as soon as surgery is contemplated so that ample time will be available to secure rare types of donor blood, if necessary. It is also important to repeat the antibody screening test when the patient enters the hospital for surgery because of the possibility that an irregular antibody may have formed since the original sample was obtained for testing.

Priming Solutions, Heparinized Blood:

The extracorporeal circuit is usually filled (primed) with whole blood before bypass is initiated. This blood, which will be perfused through the tissues (including myocardium) of the patient, must have normal calcium ion activity. Without free calcium ions, cardiac standstill will occur. The simplest way to provide blood with free calcium ions is to collect it into heparin. Heparinized blood has the following advantages (Table 1): It is ready to use without further modification. It provides normal concentrations of ionized calcium. It avoids the excess acid and water of the standard ACD blood bank anticoagulant.

The disadvantages of heparinized blood are the requirement to use it within 48 hours of collection (3) and the need to recruit donors of the required ABO and Rh types for collection of their blood into a special container. Therefore, although heparinized blood was the first priming solution employed for heart-lung bypass, there is an increasing trend away from it to the use of either electrolyte solutions (with deliberate hemodilution) or heparinized recalcified ACD blood or both.

Priming Solutions, ACD Blood:

The obvious advantage of priming with ACD blood is that it is readily available with no need to recruit special donors. Disadvantages include the need to heparinize and then recalcify the units as they are added to the pump-oxygenator. Heparin must be added first and mixed well so that clotting will not occur on addition of calcium to the citrate of the ACD solution. Then the calcium is added and also must be mixed well. Very high local concentrations of calcium can clot heparinized blood (4-5).

The correct amount of calcium to be added to a unit of ACD blood to restore a normal level of free calcium is still somewhat uncertain. Foote, Trede and Maloney (4) recommended addition of 6 ml of 10% calcium chloride to each unit of blood, based on dog studies in which ventricular

contractility and other physiologic parameters were monitored. This recommendation has been confirmed in our laboratory using as a guide the concentration of calcium which resulted in the shortest clotting time. We have confirmed it further by assays of ionized calcium activity after heparinization and recalcification (5). Our calcium ion assays, however, demonstrated that six ml of 10% calcium chloride, while correct on the average, resulted in highly variable calcium ion activities in individual units.

The variation is explained by the relatively small increment of calcium required for normal ionic activity as compared with the large amount required to neutralize the excess citrate in the unit of ACD blood. The calcium requirement is also affected by differences in total volume and in hematocrit of individual units of bank blood. Moreover, these recalcified units provide the patient with a huge excess of calcium citrate and, prior to studies carried out in this laboratory (6), there was no direct published evidence regarding the relative rate at which the calcium and citrate were cleared.

In repeated instances of human heart-lung bypass, addition of ACD blood to the circuit during extracorporeal circulation did not lower the ionized calcium level of the patient, whereas subsequent addition of five ml 10% calcium chloride resulted in a significant rise. With each subsequent addition of ACD blood followed by calcium there was a further increment in the ionized calcium activity of the patient's serum. It thus appeared that restoration of the optimal calcium level in the donor container was not an adequate guide; the patient removed citrate faster than calcium.

Since high calcium levels increase myocardial irritability, this appears to be worthy of concern. Exchange transfusion in dogs under more controlled conditions confirmed the patient data and have led to the tentative recommendation that 3 ml of 10% calcium chloride per unit of added ACD blood is more than adequate to prevent hypocalcemia in the patient. It must be emphasized that the human data mentioned above were obtained by the addition of blood and calcium during bypass. We have not yet tested the effect on the ionized calcium level of total priming with ACD blood recalcified with different amounts of calcium chloride.

Another disadvantage of ACD blood is the additional acid load provided. Some of the citrate is in the form of citric acid. The pH of ACD solution is 4.5, and the pH of fresh ACD blood is approximately 7.0, with a further fall during storage. If the acid-base status of the patient is frequently monitored and deviations from normal are corrected, this may be of little importance. ACD solution also provides more sodium and water than the heparin solution, but this is probably of little concern, especially since many teams priming with whole blood add some electrolyte solution to it.

Priming Solutions, Frozen Red Blood Cells:

A third form in which red cells may be provided in the priming solution is as cells which have been stored in the frozen state. The primary advantage of these is to provide rare types of red cells not otherwise available.

Priming Solutions, Dextran (Table 2):

Dextran has been used as a blood substitute in the priming of extracorporeal circuits, usually in the form of low molecular weight dextran (mean molecular weight 40,000). Dextran of this low molecular weight has been shown to have the properties of decreasing red cell aggregation and improving flow in the micro-circulation (7). This could be an important advantage in heart-lung bypass where low flows can make adequate tissue perfusion difficult.

The disadvantages of dextran include coating of blood platelets, which impairs their ability to maintain hemostasis (8), and coprecipitation with two clotting factors (fibrinogen and anti-hemophilic factor) (9). These effects appear to increase blood loss during and after surgery (10, 11). Large amounts of dextran can also result in difficulties in red cell compatibility testing.

Priming Solutions, Hemodilution (Table 2):

Hemodilution with glucose or electrolyte solutions may be able to accomplish as much as low molecular weight dextran without its disadvantages. The primary gain is minimizing use of donor blood with all of its potential complications. Improvement of the microcirculation also results. Five per cent glucose has been widely used for this purpose, but this may aggregate red cells and decrease their life span. It also results in dilution of essential electrolytes. Sodium chloride solution avoids most of these objections, but may still cause dangerously low levels of serum potassium, and a balanced salt solution seems more logical.

Many groups who prime with electrolytes believe it necessary to add colloid in the form of albumin to hold fluid within the circulation. It is possible to prime the pump-oxygenator with electrolytes alone, avoiding the use of any blood at this point. There is a limit, however, to how far the hematocrit of the patient may be safely lowered, and this is usually not reduced much below 25%. Thus, hemodilution works best with a small volume pump-oxygenator and an adult patient.

With a larger heart-lung machine or a smaller patient, it may be necessary to use some blood in the priming solution. Total hemodilution is usually carried out with the small volume bubble oxygenator, but has been used with a rotating disk oxygenator (12). Those groups who believe bubble oxygenators are less desirable generally use at least some blood in their priming solution.

Replacement of Blood Lost by Hemorrhage:

Replacement of blood lost during bypass can be accomplished either by transfusing the patient or by adding blood to the reservoir of the pump-oxygenator. Heparinized blood can be used for this purpose, but ACD blood is effective and appears equally safe. If ACD blood is used, 2,500 units of heparin should be added to the circulating blood as well as three ml 10% calcium chloride.

Changes in Donor Blood on Storage:

The effect of the large volumes of donor blood on the patient varies with its length of storage. In ACD blood, platelet viability is rapidly lost and the activities of two clotting factors

[antihemophilic factor (Factor VIII) and factor V] progressively decrease. Potassium leaks from red blood cells into the plasma, and the breakdown of glucose to lactic acid further depresses the pH. In our experience donor blood mixed in the extracorporeal circuit 24 hours after collection has normal levels of fibrinogen, prothrombin and factor V, but only 50% of the original level of factor VIII (antihemophilic factor), whether collected in heparin or ACD solution.

Red cells collected in heparin alter far more quickly than in ACD. Rapid rises in plasma potassium and plasma hemoglobin limit the acceptable period of storage to 48 hours. In addition, small clots may appear in heparinized blood held for longer periods. This is caused, not by disappearance of heparin but, by the liberation of thromboplastic materials from damaged red blood cells and platelets which overcome the anticoagulant effect of heparin (13).

Platelet viability is markedly reduced in ACD blood stored 24 hours and all but absent after 48 hours. There is no information on platelet viability in heparinized blood, but the increased tendency to platelet clumping and alteration in platelet shapes in heparinized as compared with ACD blood suggests that platelet preservation is probably even poorer in heparinized blood.

In any case, the courses of platelet counts in patients who undergo open-heart surgery with pump-oxygenators primed with ACD blood, with heparinized blood (4, 24, or 48 hours old), and with platelet-free blood substitutes are identical (13, 14), indicating that the priming mixtures do not significantly contribute platelets to help the patient maintain an adequate platelet count.

It also indicates that the volume of priming solution is not large enough to dilute patient platelets to a dangerous level. It appears, therefore, that there is no need to pay attention to the viability of platelets in priming solutions. Other parameters dictate use of heparinized blood within 48 hours of collection. ACD blood is generally used within 5 days of collection; but if relatively small amounts of ACD blood are used, the storage age may be of no importance.

Our routine procedure supplies blood which has been collected on the day before the operation (or two days in advance, at the most) in response to advance requisitions. The average request from our surgeons has been for 15 units of blood, some in heparin and some in ACD solution. We have not seen thrombocytopenia severe enough to result in abnormal bleeding with the use of this blood supplemented by another five or six units of blood from routine storage. With additional use of refrigerated blood, severe thrombocytopenia may result from dilution of patient blood with blood stored too long to have viable platelets. Our experience indicates that blood collected within the past 24 hours will have enough viable platelets to maintain the platelet count of the recipient at safe, although low, levels. We, therefore, recommend to our surgeons that they request blood which has been collected within the past 24 hours if they have used the original 15 units of fresh blood and anticipate a need for more than five or six further units.

(TO BE CONTINUED)

REFERENCES

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TABLE 1

Blood to Prime Extracorporeal Circuit

	Heparin	*ACD*
1. Ready to use without modification	Yes	No
2. Extra acid	No	Yes
3. Added water per 450 ml blood	27 ml	67.5 ml
4. Interference with ionized calcium balance	No	Yes
5. Permissible storage period	48 hours	21 days
6. Available routinely	No	Yes

TABLE 2

Priming with Blood Substitutes

	Low Molecular Weight Dextran	5% Glucose in Water	Normal Saline	Balanced Salt Solution
Reduces Use of Blood	Yes	Yes	Yes	Yes
Improves Microcirculation	Yes	Yes	Yes	Yes
Interference with Hemostasis	Yes	No	No	No
Interference with Red Cell Compatibility Tests	Possible	No	No	No
Damage to Red Blood Cells	No	Yes	No	No
Dilution of Sodium	Depends on whether in glucose or in saline	Yes	No	No
Dilution of Potassium, etc.	Yes	Yes	Yes	No
Colloid Osmotic Effect	Yes	No	No	No