BLOOD TRANSFUSION REACTIONS DURING ANAESTHESIA: A CLINICAL STUDY*

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O God! that bread should be so dear,
And Flesh and blood so cheap!

The Song of the Shirt, Thomas Hood (1798–1845)

It is the anaesthetists' responsibility to decide whether or not blood is to be given during surgery. That this is indeed a responsible decision may be clearly seen from the following facts: 4.5 million transfusions are given each year in the continental United States. In 1958, one in ten of all hospital patients received blood. Varying reactions occurred in 3 to 5 per cent of those transfused. One death resulted from every 1,000 to 3,000 administrations.¹ From these figures a yearly minimum of 1 500 deaths attributable to this procedure can be estimated. This is an annual mortality higher than that from acute appendicitis.²

The anaesthetist should be aware of the problems associated with blood transfusion reactions under anaesthesia, so that morbidity and mortality rates may be reduced.

THE PHYSICO-CHEMICAL COMPOSITION OF STORED CITRATE WHOLE BLOOD

In order to appreciate clinical manifestations of blood transfusion reactions during anaesthesia, an outline of the physico-chemical composition of stored refrigerated citrate whole blood is informative (Table I). A unit of refrigerated citrate whole bank blood contains 120 c.c. of acid citrate dextrose (A-C-D) solution which contains 2.5 gm. di-sodium hydrogen citrate and 3.0 gm. dextrose. The final concentration of citrate is approximately 2 gm./500 ml. unit of blood.³ The physical characteristics of bank blood when administered are: a temperature between 4°C. and 10°C.,⁴ a hematocrit determination between 40 and 60 per cent⁵ and a pH of approximately 6.6 to 7.1,⁶ a shift of the oxygen dissociation curve to the left,⁶ an increase in free hemoglobin⁷ and potassium,⁸ and a depleted unbound calcium in the plasma.⁹ There is a deficiency of platelets, antihemophilic globulin, and the labile factor.¹⁰ The white blood cells are non-functioning.

It is apparent that stored citrate whole blood is not the ideal physiological solution.

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TABLE I
STORED REFRIGERATED CITRATE WHOLE BLOOD
(ONE UNIT)

A-C-D	120 c.c.
Citrate	2 gm.
Temperature	4-10° C.
Haematocrit	40-60 per cent
pH	6.6-7.1
O ₂ dissociation	shift to left
Free HBG	increased
K ⁺	increased
Ca ⁺⁺ (unbound)	decreased
Platelets	decreased
AHG	decreased
Labile factor	decreased
WBC	non-functioning

DIAGNOSIS AND MANAGEMENT OF BLOOD TRANSFUSION REACTIONS DURING ANAESTHESIA

The incidence of transfusion reactions has been creditably reduced owing to the development of increasingly sensitive methods^{11, 12} for cross-matching and better understanding of physico-chemical components. Despite this improvement, however, when reactions do occur they carry an unfortunate morbidity and mortality. This is particularly true for those occurring under general anaesthesia, since recognition and hence management is often delayed because of masked classical clinical presentation. Thus, a variety of blood transfusion reactions continue to occur. This can be appreciated by a perusal of Table II.

TABLE II
BLOOD TRANSFUSION REACTIONS

Early	Late
Most common	transmission of disease
allergic	
pyrogenic	isosensitization
haemolytic	
mechanical	transfusional siderosis
Less common	
biochemical	
hypothermia	
bacterial contamination	
transfusional haemorrhagic diathesis	
legal	

The anaesthetist is concerned primarily with the group of early reactions but should also be aware of the fact that late untoward effects may occur as a result of the transfusion of blood. It is significant that all early reactions may present diagnostic clinical manifestations under anaesthesia. This aspect of these reactions will be emphasized in the following discussion.

Early Reactions

Most common.

ALLERGIC. During anaesthesia these reactions are characterized by wheals and

facial oedema. Severe asthma or anaphylactoid shock are rare under anaesthesia.³ The cause of most allergic reactions may be on a basis of sensitivity.¹³ In most of the mild reactions it is not necessary to halt the administration of blood. An antihistamine such as phenergan, pyribenzamine, benadryl, or chlor-trimeton may be given intravenously. If a more alarming reaction such as bronchial asthma or laryngeal oedema should occur, the emergency treatment of that condition is indicated, using epinephrine, aminophylline, and corticosteroids (Solu-cortef). It may be advisable prior to transfusion to administer an antihistamine to patients with a strong history of allergy, or who have previously experienced allergic reactions to transfusions.^{14, 15}

PYROGENIC (FEBRILE) REACTIONS are characterized by chills and fever. This reaction may be described as any temperature rise during anaesthesia considered to be caused by an infusion of blood and unaccompanied by haemolysis. Four main causes are recognized: (i) exogenous (bacterial) pyrogens, mainly in the equipment (use of disposable sets has reduced the incidence of these reactions); (ii) endogenous pyrogens. Recently, several workers have demonstrated the association of febrile reactions with the presence of (iii) leuko and (iv) platelet agglutinins in the recipient's serum.¹⁶ These reactions were demonstrated only in patients who had received multiple transfusions.

This febrile reaction must be accurately differentiated from the more serious haemolytic reaction. Examine the patient's plasma. If it is clear, there has been no significant haemolysis. After a febrile reaction has begun, the administration of aspirin or antihistamines¹⁴ will lessen the intensity and duration of the episode.

HAEMOLYTIC TRANSFUSION REACTION is defined as a reaction accompanying or occasioned by the infusion of blood in which there is a shortening of the survival time of the red cells of the donor or of the recipient. It may result from one of three principal causes: specific antigen-antibody reactions, nonspecific destruction of red cells, faulty administration of blood.

It is pertinent to emphasize that many of the reported fatal haemolytic transfusion reactions have occurred when blood was administered to anaesthetized patients. This seems reason enough in itself for avoiding the practice of giving one bottle of blood during anaesthesia "just in case it is needed".¹⁷ It also indicates the desirability of adequate preparation of the patient with regard to preoperative blood volume replacement and, if possible, delaying the administration of blood until the patient is conscious. If there is severe bleeding during surgery, many units of blood will by necessity be given, but giving a "unit of blood" routinely during an uncomplicated operation is unwarranted and not without risk.

Hypotension, petechiae, unexplained oozing sudden in onset, fever, and tachypnoea are signs of a haemolytic reaction which are not altered by anaesthesia. The bleeding accompanying this type of reaction is caused by marked intravascular clotting. This intravascular clotting results in hypoprothrombinemia and hypofibrinogenemia in addition to the thrombocytopenia which accompanies a haemolytic transfusion reaction.^{18, 19} In the majority of case reports²⁰ of incompatible blood transfusion reactions during anaesthesia, hypotension was by far the most common and frequently was the only sign present. Hypertension was possibly an early manifestation, under general anaesthesia, in one of our patients.

When a blood transfusion is complicated by massive intravascular haemolysis, plasma haemoglobin levels may easily exceed 300 mg./100 ml. At plasma levels above 150 mg./100 ml., haemoglobin will appear in the urine.³ This haemoglobinuria will continue until the plasma haemoglobin level has fallen to about 75 mg./100 ml. From a practical viewpoint, for the anaesthetist, a visual inspection for plasma haemoglobin is a simple and extraordinarily valuable procedure. Haemoglobin levels of plasma from blood drawn in a standard manner will seldom exceed 5 to 10 mg./100 ml. This concentration is insufficient to be detected by the unaided eye. Levels of 25 mg./100 ml. appear pink in a test tube and levels of 100 mg./100 ml. are red.³ Thus, any significant haemolysis can be discovered by the simple procedure of prompt inspection of the plasma.

The first step in the treatment of a haemolytic transfusion reaction is to stop the transfusion. Later, intravenous normal saline and corticosteroids may be required.

Fatalities from haemolytic reactions most commonly follow renal damage with anuria. Death may also result from cardiac arrest due to K^+ overload.

The pathogenesis of renal failure following transfusion of incompatible blood has not been satisfactorily explained. Mueller^{21, 22} concludes that inasmuch as haemoglobinuria *per se*, hypotension *per se*, and a combination of these two factors seem to be ineffective in consistently producing experimental renal failure, it seems that some other component of the anaphylactic-like reaction to incompatible blood might have an aetiological relation to the renal disease. Such a component has not as yet been identified.

MECHANICAL DISTURBANCES.

(1) *Circulatory overload reactions.* In normal individuals the intravenous administration of fluids increases blood volume, raises venous and intra-auricular pressures, and increases cardiac output. Patients with reduced cardiac reserve, such as the aged or those with pneumonia, coronary heart disease, and anaemia, are particularly susceptible to circulatory overload reactions, as are patients undergoing pneumonectomy or multiple lobectomy.²³ In these patients the cardiac output may decrease, resulting in hypotension, if blood is given too rapidly or in too large quantities.²⁴ Acute circulatory failure manifested as pulmonary oedema may be precipitated.²⁵ Use of packed red cells, clinical observation of the venous pressure, a slow rate of infusion, and placing the recipient in the semi-Fowler position will reduce the likelihood of pulmonary oedema.

(2) *Air embolism.* Blood transfusion under pressure presents a potential source of this complication. Once it occurs, hypotension, tachycardia, cyanosis, and death may result. The mechanism of death is acute right heart failure. The right heart fills with air, and the entrance of blood into the pulmonary circulation through the outflow tract of the right ventricle stops. Diagnosis is made by recognizing the source of the air. Auscultation of the heart reveals the characteristic crunching murmur, often described as a "mill-wheel" murmur. Treatment is by the removal of air from the right ventricle between the second or third ribs to the right of the sternum, with the patient left side down. These manoeuvres relieve the cardiac airlock and improve patency of the pulmonary artery.

Less common.

BIOCHEMICAL DISTURBANCES.

(1) "*Citrate intoxication.*" There are clinical situations where the controversial "citrate intoxication" might feasibly occur: (i) in the presence of any factor which might impair body metabolism of citrate, for example, cirrhosis of the liver; (ii) hypothermia, where there is a decreased rate of metabolism; (iii) avitaminosis, hypoparathyroidism, and osteoporosis, where calcium is not mobilized from bone; (iv) in the child or newborn, where there are inadequate calcium stores; (v) in shock, where there is little or no blood supply to bone.

The administration of calcium is the specific therapy. It is estimated that, in the normal adult weighing 60 kg., as much as 2 L. of citrated blood can safely be given in 20 minutes.^{4, 5} If more than this is given it would seem wise to inject 10 ml. of 10 per cent calcium gluconate for every litre of citrated blood administered.

(2) *Potassium intoxication.* During the storage of blood the potassium content of the red cells decreases and that of the plasma increases. The normal potassium plasma level of 4 to 5 meq./L. rises to about 20 meq./L. after 14 days storage.³ In adults with good renal function, potassium toxicity from stored citrated blood probably presents no problem, except in massive blood transfusion. However, when transfusing patients with oliguria or anuria, blood stored for less than two or three days should be utilized whenever possible, since not only does the potassium level of plasma rise during storage, but from older stored blood there is an increased number of red cells broken down on infusion, which adds further potassium load.

HYPOTHERMIA. We have seen this more commonly in the newborn, infant, or child. However, the adult as well as the child, during deliberately induced hypothermia, may have a precipitous drop in temperature by 3° to 5° C. following transfusion of refrigerated stored blood.

BACTERIAL CONTAMINATION. Reactions from infected blood are uncommon. The bacteria are usually cold-growing or psychrophilic Gram-negative pseudomonads, coliforms, or achromobacters which may produce lethal endotoxins. In these reactions there is usually immediate circulatory collapse which responds poorly to emergency measures.^{5, 26} Cortisone and levarterenol have been effective in the treatment of these reactions. Confirmation of the cause of the reaction rests mainly on the demonstration of bacteria, in residual blood, as shown by direct smear and by culture.²⁶

TRANSFUSIONAL HAEMORRHAGIC DIATHESIS. Clotting defects⁴ have been attributed to decreased platelets, decreased ionized calcium, increased plasma citric acid levels, fibrinolysis, decreased labile factor, and hypothermia. The recommended treatment for decreased platelet clotting defect is the administration of fresh drawn blood; for decreased Ac globulin or labile factor, fresh bank blood or lyophilized plasma (antihaemophilic plasma); for decrease in fibrinogen, whole blood which contains 250 mg. per cent fibrinogen, or fibrinogen *per se*.

LEGAL. This aspect has been discussed extensively in several recent reviews,^{27, 28} and is not to be elaborated upon here.

Late Untoward Effects

Transmission of disease. The most common disease transmitted by transfusion

is homologous serum hepatitis (1 in 200–500 transfusions). Its mortality is reported to be from 0.2 to 10 per cent.²⁹ No way to sterilize whole blood has yet been found.

Isosensitization. Even with the most careful selection of blood, every transfusion carries a certain risk of inducing isosensitization. The danger of isosensitization increases with the number of transfusions. There is no product available deserving designation as “universally” safe blood, that is, one which can be given without any risk to a patient without preceding pretransfusion test. For this purpose, the routine addition of corticosteroids to blood should be condemned.³⁰ Admittedly there are surgical situations in which the need for replacement of blood volume is so urgent and critical that no waiting period can be interposed before giving the blood. The anaesthetist requesting this procedure must realize that such a step represents a definite calculated risk. For one, the patient may already have antibodies for the blood administered. At the Vancouver General Hospital, 2 per cent of those patients requiring transfusion have abnormal circulating antibody.³¹ In 1 to 2 per cent of cases, the patient may become sensitized as a result of the transfusion.² This fact is especially important in the female in childbearing age since it may place in jeopardy the fate of subsequent offspring.

To sum up then, as outlined in Table III, blood transfusion reactions during anaesthesia can be differentiated on the basis of key clinical manifestations and confirmations made by simple laboratory procedures.

TABLE III
DIAGNOSIS OF BLOOD TRANSFUSION REACTIONS DURING ANAESTHESIA

Clinical manifestation	Differential diagnosis	Confirmation
wheal	allergic	
fever	haemolytic	plasma haemoglobin urine haemoglobin direct coombs bilirubin
	pyrogenic	coombs' consumption test
	bacterial contamination	direct smear bacterial culture
petechiae	haemolytic	
unexplained oozing	haemolytic	
	bacterial contamination	
	massive transfusion	coagulogram
hypotension	haemolytic	
	circulatory overload	venous pressure haematocrit blood volume $K^+ \uparrow$ citrate $\uparrow$ $NH_3 \uparrow$ $Ca^{++} \downarrow$
	bacterial contamination	
	air embolism	auscultation
pulmonary oedema	circulatory overload	
arrhythmia	massive transfusion	ECG, $K^+ \uparrow$
	air embolism	
	haemolytic	

SUMMARY

Inescapably the anaesthetist is responsible for the decision as to whether or not blood is to be given during the surgical period. That this decision is, indeed, a responsibility, may be seen by the fact that there is an estimated annual death rate of 1 in 1,000 to 3,000 administrations in the U.S.A. This gives a yearly minimum of 1,500 deaths attributable to blood transfusions in the continental United States alone. Moreover, despite increasingly sensitive methods of cross-matching blood and a better knowledge of physico-chemical factors, a variety of reactions with a 3-5 per cent incidence continue to occur. Unfortunately, they still carry a significant morbidity and mortality rate. Particularly is this true during anaesthesia, where late recognition and management may result because of masked classical clinical presentation. The anaesthetist should be wary when giving blood to patients with any history of previous reaction or known allergies. The more common early reactions are allergic, pyrogenic, haemolytic, and circulatory overload; less common are air embolism, potassium and citrate intoxication, hypothermia, transfusional haemorrhagic diathesis, and bacterial contamination. Late untoward effects of blood can also occur. These are, mainly, transmission of disease, isosensitization, and transfusional siderosis. It is significant that all early blood transfusion reactions present key diagnostic clinical manifestations under anaesthesia. These are readily confirmable by simple laboratory procedures. An awareness of these features of blood transfusion reactions during anaesthesia will lead to their prompt recognition and management, thereby reducing morbidity and preventing mortality.

RÉSUMÉ

Indiscutablement, l'anesthésiste est responsable de la décision à prendre s'il faut donner ou non du sang durant l'opération. Que cette décision constitue une responsabilité de démontre par le fait que, aux Etats-Unis, le taux annuel des morts est de 1/1000 à 1/3000 transfusions de sang. Cela donne un minimum annuel de 1500 morts attribuables aux transfusions sanguines dans les Etats-Unis continentaux seulement. En dépit de méthodes de plus en plus ensembles pour faire les groupements sanguins et une meilleure connaissance des facteurs physico-chimiques, il survient encore dans 3 à 5% des cas des réactions variées. Malheureusement, elles entraînent un taux important de morbidité et de mortalité. Cela est particulièrement vrai au cours de l'anesthésie, alors que le tableau clinique classique est masqué, et que le diagnostic et le traitement sont retardés. L'anesthésiste doit avoir l'œil ouvert lorsqu'il donne du sang à des malades qui ont une histoire de réactions antérieures ou d'allergies connues. Les réactions précoces les plus fréquentes sont des réactions allergiques, pyrogéniques, hémolytiques et une surcharge circulatoire; les réactions moins fréquentes sont : l'embolie gazeuse, l'intoxication au potassium et au citrate, l'hypothermie, la diathèse hémorragique transfusionnelle, et la contamination bactérienne. Il peut exister également des accidents tardifs. Ils consistent surtout en la transmission de maladie, l'isosensitisation, et la sidérose transfusionnelle. Il faut noter que toutes les réactions précoces aux transfusions, sous anesthésie, présentent des manifestations cliniques clés pour faire un diagnostic. Elles peuvent être confirmées

instantanément par de simples examens de laboratoire. La surveillance de ces signes des réactions transfusionnelles au cours de l'anesthésie va aider au diagnostic et au traitement précoces et réduire ainsi la morbidité, et éviter la mort.

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