Symposium Report

Blood and blood substitutes

Methods of reducing blood loss and non-blood substitutes

James G. Ramsay MD
Department of Anesthesiology, Emory University Atlanta, Georgia

A variety of techniques can aid the anaesthetist in reducing requirements for perioperative blood products. These include careful preoperative assessment of the patient, and employing techniques during surgery which reduce the blood pressure and help preserve the normal haemostatic mechanism. If the level to which haematocrit will be permitted to decrease is decided, then physiological crystalloid and/or colloid solutions may be used to maintain circulating volume. Where large volumes of fluids are required cardiac filling pressures should be monitored because of the complex nature of the fluid shifts which occur. There is no evidence that any one fluid (physiological crystalloids, colloids) is better than any other in terms of the incidence of perioperative morbidity.

L'anesthésiste dispose de plusieurs outils lui permettant de minimiser les besoins en dérivés sanguins en période périopératoire. Après une évaluation préopératoire serrée, il peut employer une technique qui diminue la pression artérielle tout en préservant les mécanismes de l'hémostase. Après avoir déterminé l'hématocrite minimale acceptable, l'anesthésiste peut se servir de solutions de cristalloïdes ou de colloïdes afin de maintenir un volume circulant normal. S'il doit en utiliser de grandes quantités, il est préférable de mesurer les pressions de remplissage cardiaques car il est difficile de prédire avec exactitude les flux liquidiens. Par ailleurs, que l'on emploie des cristalloïdes ou des colloïdes ne semble faire aucune différence quant à la morbidité péri-opératoire.

Key words
BLOOD: anaemia, haemodilution, loss, replacement, stored;
TRANSFUSION: autotransfusion, complications, stored blood.

Report of Symposium at C.A.S. Annual Meeting, June 1991, Vancouver.
Accepted for publication 20th January, 1991.

As the level of concern about transfusion-related infection has increased exponentially in the last ten years, so has interest in means of reducing requirements for blood products. Other speakers in this symposium will address current criteria for administering blood transfusion, as well as techniques of autotransfusion and the use of autologous blood. This discussion will focus on simple perioperative means of reducing blood loss, and the use of intravenous solutions which restore intravascular volume without restoring oxygen carrying capacity.

Means of reducing blood loss

Preoperative preparation

A carefully obtained history for bleeding tendency is a simple sensitive test to detect patients who might experience excessive perioperative bleeding due to underlying disorders of coagulation. When there is a positive history then a preoperative coagulation screen is indicated (PT/PTT, platelet count). However, there is no evidence that routine preoperative screening with these coagulation tests is useful.[1]

Patients who are receiving anticoagulants may be at increased risk for bleeding if these agents are not discontinued well before surgery. Coumarin interferes with the production of vitamin K-dependent coagulation factors, and can be reversed in 6 to 12 hours by vitamin K. Urgent surgery requires the administration of fresh frozen plasma until the PT is normal. Heparin present at the time of surgery may be measured by performing an activated clotting time (ACT) or heparin assay ("Hepcon"), and reversed with intravenous protamine.

The ASA derivatives irreversibly inhibit platelet adhesiveness for the life of the platelet (approximately ten

days). The implications of ASA-induced platelet dysfunction are not clear for all types of surgery because only in certain patients does the presence of ASA prolong the bleeding time and increase the risk of bleeding.[2] Many patients take ASA, have normal or slightly elevated bleeding times and do not have increased risk of bleeding. It may be appropriate to measure the bleeding time in a patient about to undergo major surgery who is taking ASA, and enquire about availability of platelets when it is prolonged.

Intraoperative measures

Avoidance of intraoperative hypertension plays an important role in reducing surgical haemorrhage. A simple way of reducing arterial pressure at the site of surgery, while at the same time reducing venous pressure in order to facilitate venous drainage, is to position the surgical site uppermost. For example, surgery of the head and neck should be performed with the bed in the reversed Trendelenberg position. Deliberate hypotension induced by anaesthetic agents or specific vasodilating or myocardial depressant drugs is an effective way to reduce intraoperative blood pressure and perioperative blood loss. However, patients with cerebral or coronary artery disease may not be candidates for this technique. Many studies have attested to the safety and effectiveness of deliberate hypotension in patients undergoing both major and minor surgical procedures.[3]

There is some evidence that the use of regional anesthesia can reduce intraoperative blood loss.[4] This may simply be due to a reduction in the arterial blood pressure.

The clinician must weigh the benefits and disadvantages of these intraoperative techniques (Table I) in each patient before deciding to employ any one of them to reduce intraoperative blood loss.

Specific pharmacological agents

It is now possible to administer synthetic human erythropoeitin preoperatively in order to increase the haemoglobin concentration. This is an extremely expensive medication; however, we may hope that within the next few years the cost will decrease. Use of erythropoeitin preoperatively may allow the patient to donate more blood before his surgical procedure if autotransfusion is employed. Its use before surgery in anaemic patients may result in reduced transfusion requirements.

Two other agents which have been used in an attempt to reduce blood loss are *1-desamino-8-D-arginine vasopressin (desmopressin or DDAVP)* and *aprotinin*. The former is a synthetic form of the hormone vasopressin which releases factor VIII and Von Willebrand's factor from endogenous sites. Desmopressin is useful in the management of medical bleeding in selected patients with haemophilia, Von Willebrand's disease, and renal disease.[5] A reduction in perioperative blood loss during major orthopaedic surgery[6] and complicated valvular surgery[7] has also been demonstrated. However, a recent report suggests that routine coronary artery bypass patients derive no benefit from this agent, as they have high levels of Von Willebrand factor both preoperatively and postoperatively.[8] The role of desmopressin in perioperative bleeding requires further evaluation.

TABLE I Intraoperative techniques to reduce blood loss

Position surgical site uppermost
Avoid hypertension and venous congestion
Controlled hypotension
Regional anaesthesia

In 1989, Bidstrup *et al.* reported the use of high-dose *aprotinin* in patients undergoing cardiac surgery.[9] An impressive reduction in both intraoperative and postoperative bleeding was observed. Aprotinin is a serine protease inhibitor known to inhibit human plasmin, trypsin, and tissue kallikrein. It is postulated that aprotinin prevents the activation of plasma proteins and platelets during cardiopulmonary bypass, and thereby helps preserve normal coagulation. A large multicentre trial is currently under way in the United States to investigate this medication during valvular heart surgery.

After cardiac surgery some centres utilize antifibrinolytic agents (*epsilon aminocaproic acid*, or the newer *tranexamic acid*) in the belief that better haemostasis is achieved. These agents are not without risk, and their use is at present controversial.

Thrombelastograph

While this is not a means of reducing blood loss, it presents an exciting new application of an old technique to detect coagulation disorders rapidly. Although still under investigation, the thrombelastograph assesses qualitatively and semiquantitatively the stages of clot formation and retraction. It may identify the presence of an abnormality as well as the most likely cause for the abnormal coagulation. Reports of its use during liver transplantation[10] and cardiac surgery are promising.[11]

Non-blood substitutes

Despite the use of techniques to minimize intraoperative blood loss, intravascular volume replacement must be undertaken by the anaesthetist to counteract preoperative dehydration, insensible intraoperative losses, sequestration of fluid around the site of surgery, and intraoperative loss of body fluids including blood. Guidelines from a consensus conference on perioperative red cell transfu-

sion suggest that a large percentage of patients may tolerate an haematocrit of <30% without adverse effects on morbidity or mortality.[12] While this discussion is not intended to focus upon the optimum haematocrit, it is necessary to decide in each patient what level of haematocrit is acceptable. Once this decision has been made then non-blood solutions may be used to maintain volume status until haemodilution has brought the haematocrit to the predetermined value. Fluid resuscitation from hypovolaemia restores cardiovascular stability and oxygen delivery, even without the administration of red cells.

Research is being conducted into the use of non-blood, oxygen carrying solutions. Examples include modified haemoglobin and perfluorochemicals ("fluosol"). These preparations are not presently suitable for clinical use but may be available in the future.

Replacement crystalloid

In a 70-kg man there are approximately 22 L of intracellular water and 14 L of extracellular water. The latter is divided into 11 L of interstitial fluid and 3 L of plasma. Depending on its composition, fluid administered into the vascular compartment may be distributed to one, two, or all of these body fluid compartments.

Dextrose in solution (e.g., 5% dextrose) is taken up and metabolized, leaving "free water" which is distributed to all body fluid compartments. Thus, one litre of 5% dextrose is distributed to 36 L of body water leaving 3/36 (3/36 × 1 L = 83 ml) intravascular. Large volumes of 5% dextrose administered postoperatively to gynaecological patients have been associated with irreversible brain damage.[13] Other replacement solutions include one-quarter or one-half normal saline, sometimes with dextrose added. These solutions are meant for long-term replacement (i.e., days) in patients who are not taking fluid by mouth. When given in large quanities to restore the circulation from hypovolaemia they may induce electrolyte abnormalities.

Physiological crystalloid solutions

Crystalloid solutions with the osmolality of plasma (normal saline or Ringer's lactate) are distributed only to the extracellular water: the vascular wall allows almost free passage of water and electrolytes, but cell membranes are impermeable to electrolytes. One litre of Ringer's lactate will be distributed in 14 L, leaving 3/14 (3/14 × 1 L = 214 ml) intravascular. When given rapidly, equilibration between the vascular and interstitial compartments takes less than one hour. Only these physiological crystalloid solutions should be used for large-volume replacement during hypovolaemia.

Colloids

Solutions containing large molecules which cannot pass immediately from the vascular compartment to the interstitial space are "colloids." They exert an "oncotic" pressure (COP) which holds on to a volume of water and electrolytes. In man, the plasma proteins act as colloids, albumin being the most important. Some capillary beds (brain) are impermeable to protein while others (liver) are freely permeable; the majority are slightly permeable. When the capillaries are damaged as in sepsis the intravascular retention of administered proteins or other large molecules may be greatly reduced. Similarly, in malnourished or hypercatabolic states administered albumin is removed more quickly from the vascular compartment.

Specific colloids

ALBUMIN

Human albumin is heat-treated and noninfective. Until recently the cost of albumin was considerably in excess of the synthetic colloid solutions, but the cost has come closer for some of these products. Albumin is prepared either as a 5% or 25% solution. As the former has the same concentration as in plasma, the intravascular volume is increased by the volume that is given. In contrast, 25% albumin contains five times the concentration of protein normally present in plasma. Administration of this solution results in absorption of interstitial fluid into the vascular compartment. For this reason, when the patient has generalized hypovolaemia (interstitial depletion) as often occurs intraoperatively, concentrated albumin should be administered along with crystalloid solution. There appear to be few risks to the administration of albumin apart from overhydration and pulmonary oedema and this may be prevented by carefully monitoring cardiac filling pressures.

HETASTARCH ("hespan")

Hetastarch is a polymerized molecule of dextrose units prepared as a mixture of molecules ranging from the size of less than that of albumin to several times the size of albumin. The small molecules are filtered at the glomerulus and may induce a small osmotic diuresis. The large molecules stay intravascular and are gradually absorbed by the reticuloendothelial system. Hetastarch can be measured in the body several weeks after its administration, but this does not appear to be a problem. A new smaller form of this molecule ("pentastarch") has a slightly different structure and is metabolized and eliminated.

Starch molecules are effective plasma volume expanders and have a low incidence of allergic reactions. When transfused in large quanities it is possible to measure abnormalities in coagulation tests; however, clinical

TABLE II Some crystalloid and colloid preparations

	Normal saline	*Lactated ringers*	*5% Albumin*	*Dextran 70 6% NS*	*Hetastarch 6% NS*
Na ($mOSm \cdot L^{-1}$)	154	147	130–160	154	154
Cl ($mOSm \cdot L^{-1}$)	154	109		154	154
Osmolality ($mOSm \cdot L^{-1}$)	308	278	300	308	310
Plasma expansion (per 500 ml) (ml)	100	100	500	500–700	500–700
Large molecule size (mean)	—	—	62–69,000	20–200,000 (70,000)	10–1,000,000 (70,000)
Elimination	—	—	(hepatic)	plasma hydrolysis renal	reticuloendothelial system renal
Duration of Expansion (approximate)	(very transient)		24 hr	24 hr	36 hr
Effect on coagulation	—	—	—	impaired	?
Allergic reactions	—	—	0.011	0.03–4.7	0.85
Anaphylaxis	—	—	—	0.08–0.6*	0.006
Recommended maximum dose	—	—	—	$20 ml \cdot kg^{-1}$ 24 hr	$20 ml \cdot kg^{-1}$ 24 hr
Cost to Emory Univ. Hospital Pharmacy $US	0.60 per litre	0.74 per litre	36.00 per 500 ml	7.22 per 500 ml	38.45 per 500 ml

*Preventable by prior administration of dextran 1 ("Promit").
In Canada the cost of albumin is absorbed through the funding of the Red Cross, thus only dextran and hetastarch use will be reflected in the hospital or departmental budget.

bleeding is rarely reported unless the maximum recommended dose ($20 ml \cdot kg^{-1}$) is exceeded. There is some hope that pentastarch will be less likely than hetastarch to induce coagulation abnormalities.[14]

DEXTRAN

Dextran is a polymer of dextrose similar to hetastarch, with a slightly different configuration. It is available as a preparation with a mean molecular size of 40,000 (dextran 40) or 70,000 (dextran 70). Dextran 40 is filtered at the kidney and in oliguric states has been found to be deposited in the tubules causing renal damage. This solution is therefore not recommended in hypovolaemia. The larger size of the dextran 70 molecules prevents this problem. Unfortunately, both the incidence of severe allergic reactions and interference with coagulation are more common with dextran than with hetastarch. The former has been largely solved by the introduction of dextranil ("Promit") which when given immediately before dextran, complexes with dextrose-reactive immunoglobulin.

While there is considerable discussion and a large, conflicting literature on the choice of fluid, if therapy is monitored appropriately and fluids are given at an appropriate rate, any physiological crystalloid or colloid solution will restore the circulation from hypovolaemia due to any cause (Table II).

Fluids and the lung

Much attention has been paid to the importance of plasma COP in preventing pulmonary oedema. If COP is dramatically reduced when permeability is normal then the hydrostatic pressure required to produce oedema is also reduced. Unless the hydrostatic pressure is elevated above the normal range oedema does not accumulate. This is because even with extreme reductions in COP, when pulmonary artery occlusion pressure (PaOP) is kept in the normal range a large increase in lymphatic drainage prevents oedema.[15] An elevation in CVP, into which the lymph drains, can reduce the ability of lymphatic drainage to increase. Thus, during crystalloid resuscitation, pulmonary oedema may develop at a PaOP less than the usual 25 mmHg. Regardless of the fluid chosen monitoring of filling pressures is the most important method of preventing oedema.

References

1 *Roizen MF.* Routine preoperative evaluation. *In*: Miller RD (Ed.). Anesthesia, 2nd ed., London, New York: Churchill Livingstone 1986; 247–8.
2 *Ferraris VA, Gildengorin V.* Predictors of excessive blood use after coronary artery bypass grafting. J Thorac Cardiovasc Surg 1989; 98: 492–7.
3 *Miller ED.* Deliberate hypotension. *In*: Miller RD (Ed.). Anesthesia, 2nd ed., London, New York: Churchill Livingston, 1986; 1949–70.

4 *Chin SP, Abou Madi MN, Eurin B et al.* Blood loss in total hip replacement: extradural vs phenoperidine analgesia. Br J Anaesth 1982; 54: 491–5.
5 *Mannucci PM.* Desmopressin: a nontransfusional form of treatment for congenital and acquired bleeding disorders. Blood 1988; 72: 1449–55.
6 *Kobrinsky NL, Letts MR, Patel LR.* 1-desamino-8-D-arginine vasopressin (Desmopressin) decreases operative blood loss in patients having Harrington rod spinal fusion surgery. Ann Int Med 1987; 107: 446–50.
7 *Salzman EW, Weinstein MJ, Weintraub RM et al.* Treatment with desmopressin acetate to reduce blood loss after cardiac surgery. N Engl J Med 1986; 314: 1402–6.
8 *Hackman T, Gascoyne RD, Naiman SC et al.* A trial of desmopressin (1-desamino-8-D-arginine vasopressin) to reduce blood loss in uncomplicated cardiac surgery. N Engl J Med 1989; 321: 1437–43.
9 *Bidstrup BP, Royston D, Sapsford RN et al.* Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin (Trasylol). J Thorac Cardiovasc Surg 1989; 97: 364–72.
10 *Kang YG, Martin DJ, Marquez J et al.* Intraoperative changes in blood coagulation and thromboelastographic monitoring in liver transplantation. Anesth Analg 1985; 64: 888–96.
11 *Spiess BD, Tuman KJ, McCarthy RJ, Ivankovich AD.* Thromboelastography as an indication of post-cardiopulmonary bypass coagulopathies. J Clin Monit 1987; 3: 25–30.
12 Consensus conference on perioperative red blood cell transfusion. JAMA 1988; 260: 2700–3.
13 *Arieff AI.* Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. N Engl J Med 1986; 314: 1529–35.
14 *London MJ, Ho JS, Triedman JK.* 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.
15 *Zarins CK, Rice CK, Peters RM et al.* Lymph and pulmonary response to isobaric reduction in plasma oncotic pressure in baboons. Circ Res 1978; 43: 925–30.

Blood product utilization and management in Canada

Gershon H. Growe MD
Department of Medicine (Pathology), Transfusion Service, Vancouver General Hospital, University of British Columbia

The utilization of blood for transfusion in Canada has remained at 900,000–950,000 units p.a. for the past six years. Donation has decreased slightly from a peak of 1,200,000 units p.a. in 1989. The use of fresh plasma and cryo-precipitate has decreased while the use of platelets has doubled in the past six years. The increased use of albumen cannot be explained. In Vancouver, all anaesthesia residents take a compulsory transfusion medicine rotation which appears to be successful in rationalizing transfusion practice.

Aux fins de transfusions, on a utilisé de 900 000 à 950 000 unités de sang par an au Canada au cours des six dernières années. Les dons de sang ont un peu fléchi après un maximum de 1 200 000 unités atteint en 1989. L'usage de plasma frais et de cryoprécipité a diminué mais la demande en plaquettes sanguines a doublé en six ans. L'engouement récent pour l'albumine est surprenant. A Vancouver, tous les résidents en anesthésie font un stage en hématologie transfusionnelle ce qui semble contribuer à une attitude rationnelle envers les transfusions.

Since 1983 there has been an unique stress on the blood transfusion systems of the world including that of Canada because of the concern about HIV and other viral infections. Not only has this made patients and doctors less enthusiastic about transfusing blood and blood products, but it has also had an unusual effect in some communities of discouraging blood donors. There has been a vigorous attempt to educate people in this regard. In Canada between 1983 and 1989 there was a slight increase in total blood collections from approximately 1,100,000 to 1,200,000. With the introduction of HIV testing, donor self-exclusion at site, and now hepatitis C and HTLV-I testing there has been a decrease of 5% of usable blood once drawn. Red cell utilization in Canada has remained stable between 900,000 and 950,000 units over the six years despite the introduction of many new transplant and aggressive trauma programs. Therefore, this pattern likely reflects a more judicious use of red