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Modern approaches to avoid allogeneic blood transfusion

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INTRODUCTION

During major surgery (e.g. cardiovascular surgery, orthopedic surgery, transplantation) patients may loose a substantial amount of blood, that traditionally has been corrected by transfusion of stored allogeneic blood. Transfusion of whole blood once seemed to be the best therapy for patients requiring transfusion. Component therapy, e.g. transfusion of packed red blood cells (PRBC), platelets, and fresh frozen plasma (FFP) essentially replaced the earlier practice of whole blood transfusion.

It has been estimated that there are more than 12 million units of PRBCs transfused annually in the United States[1]. The transfusion of allogeneic blood is associated with risks and side-effects that include transfusion-transmitted infectious diseases, transfusion reactions, alloimmunization, and transfusion-associated graft-versus-host reactions[2,3]. The acquired immunodeficiency syndrome (AIDS) has substantially heightened medical and publical awareness of transfusion risks. As a consequence guidelines for blood transfusion have been issued by several organizations[4,5]. Stricter transfusion indication and the realization that patients will tolerate lower hemoglobin values than previously thought have decreased the demand for bank blood. Despite recent improvements in the safety of allogenic blood supply and growing economic concerns associated with the transfusion of blood, the driving force to develop alternatives to allogeneic blood transfusion is still the fear of transfusion-transmitted infectious diseases. The simplest method to avoid this risk is the decrease of the requirement for transfusion. This may be accomplished by judiciously selecting alternatives to transfusion.

Although the degree of blood loss during surgery is primarily dependent on the nature of the procedure and the abilities of the surgical team, the anesthetist may have a considerable impact on intraoperative bleeding by choosing appropriate blood conservation techniques (Table I). Some factors influencing intraoperative blood loss that are under control of the anesthetist, are the choice of the anesthetic regimen (regional *vs* general anesthesia), the depth of anesthesia, and the control of intravascular pressure, cardiac output, or carbon dioxide level.

1. AUTOLOGOUS TRANSFUSION

1.1 Preoperative autologous blood donation

Predonation of autologous blood (PAD) has become an often used technique for patients undergoing major elective surgery[6]. PAD should be considered for patients whose surgical procedure is likely to require blood transfusion. The number of units of autologous blood obtained preoperatively is most commonly based on the number of units that would be crossmatched before surgery when allogeneic blood would be used[7]. Patients are requested to donate two to four units of blood up to four weeks before surgery. Donations are usually made at the

Table I. Techniques for reducing blood loss.

Non-Pharmaceutical Methods		
	Positioning of the patient	
	Autologous transfusion	
		Preoperative autologous donation (PAD)
		Acute normovolemic hemodilution (ANH)
	Hypervolemic hemodilution	
	Cell salvage	
	Controlled hypotension	
	Preoperative plasmapheresis	
Pharmaceutical Methods		
	Aprotinin	
	Tranexamic acid	
	Desmopressin	
	Erythropoietin	
	Perflourochemical emulsions	
	Modified hemoglobin solutions	

rate of one unit per week. The last donation should be collected not later than 72 hours before surgery to allow for restoration of blood volume. Routinely, patients are placed on iron therapy during PAD. Preoperative hematocrit values of 33% are acceptable and well tolerated. PAD is contraindicated in patients with preexisting anemia, severe coronary and valvular heart disease, and those with preoperative arterial desaturation that causes inadequate oxygen delivery. PAD units must be tested for ABO and Rh but need not to be tested for infectious diseases in several countries. The transfusion of autologous blood may prevent transfusion-transmitted diseases, but does not eliminate the risk of bacterial contamination or volume overload[8].

PAD units may provide some or all of the blood needed. In a multicenter study, the proportion of patients undergoing primary total hip arthroplasty who received allogeneic blood was reduced from 60% among non-donors to 15% among donors[9]. Similar numbers are reported as a result of a multicenter study in patients undergoing major orthopedic procedures[10]. Only 9% of autologous blood donors received allogeneic blood in this study. Given the current emphasis on medical cost-containment, use of PAD is not without financial consequences. The most obvious costs of PAD are associated with the collection of autologous blood units, which is relatively labor-intensive process. Besides material and staff costs, which might be substantial, PAD requires the commitment of patient time, transportation, loss of work, and donor screening. Furthermore, approximately 50% of autologous blood units that have been collected are discarded and not transfused. This is partly due to overcollection of autologous blood and makes autologous donation inherently wasteful. Several studies have demonstrated that PAD might not be cost-effective and of questionable benefit[10,11].

1.2 Acute normovolemic hemodilution

An alternative approach to autologous blood procurement is the use of acute normovolemic hemodilution (ANH). In patients undergoing major elective surgery, ANH is a simple means to obtain fresh whole blood containing coagulation factors and platelets. As ANH has been shown to reduce the need for allogeneic transfusion in several elective surgical procedures and to be more cost-effective than PAD, it has become an important blood conservation technique[12]. ANH offers several practical advantages over PAD for the collection of autologous blood. Unlike PAD ANH may be performed immediately on the day of surgery in the operating rooms. As ANH units are stored next to the patient and being retransfused before the patient leaves the operating room, administrative errors that could lead to an ABO-incompatible blood transfusion are eliminated.

To calculate the amount of blood that can be removed by ANH in a specific patient, formula as given by Gross may be helpful[13]. Hemodilution starts with the withdrawal of one unit (approximately 450 ml) of whole blood into a standard blood bag containing anticoagulant (citrate-phosphate-dextrose-adenosine) before or after induction of anesthesia. The blood bag is placed on a scale to prevent insufficient or excessive blood withdrawal in relationship to the anticoagulant of the collection bag. The procedure entails withdrawal of 1.5 to 2.0 liters of blood with the simultaneous infusion of colloid or crystalloid to maintain intravascular volume. ANH is usually performed with the aim of strict normovolemia. Therefore volume restitution has to proceed at a rate similar to blood withdrawal. Considerable controversy exists regarding the optimal diluent. Hemodiluents must maintain circulatory volume without adversely altering either oxyhemoglobin dissociation, the rheological properties of blood, or coagulation. Crystalloids are replaced at a ratio of 3 to 4 ml for every ml of withdrawn blood, whereas colloids are given at a ratio of 1:1. A combination of colloids and crystalloids may also be used. Colloids have the advantage of better sustaining plasma colloid oncotic pressure (COP) and of requiring smaller amounts of infused volume. When retransfusion of the collected ANH units is anticipated within 6 hours, the blood should be stored at ambient temperature next to the patient. When major blood loss ceases or when the patient's hematocrit level drops below a predetermined minimum, the initially collected unit, which has the highest hematocrit and platelet concentration, is returned. Because ANH units are routinely reinfused at the end of surgery, the wastage associated with predonated autologous blood is minimized. The whole procedure of ANH is performed immediately next to the patient, to minimize procedure time and decrease costs. Therefore ANH has been advocated as a point-of-care method of autologous blood procurement[12]. The blood conservation benefit of ANH results from the fact that loss of red-cell volume is reduced during perioperative blood loss because of lowering of preoperative hematocrit levels.

The two major consequences of hemodilution are a reduction in arterial oxygen content and an augmentation in blood flow due to reduced viscosity. The major contraindication of ANH is a limited capacity to compensate reduced oxygen delivery by augmentation of cardiac output and coronary perfusion. Therefore ANH is contraindicated in patients with severe coronary artery or valve disease, severe ventricular dysfunction, and patients showing significant carotid artery stenosis. Hemoglobin concentration > 120 g/l is a prerequisite for ANH, otherwise insufficient amounts of autologous blood may be procured.

The efficacy of ANH for reducing use of allogeneic blood is a much debated issue. A recent meta-analysis of more than twenty randomized, prospective trials of ANH concluded that acute hemodilution reduced the likelihood of allogeneic exposure and the total units of blood transfused[14]. These is confirmed by Monk and colleagues, who found that ANH was a safe, effective and inexpensive method of blood conservation[12]. However, in two other trials ANH failed to show a significant benefit[15,16]. Nash et al. showed that in a group of patients undergoing ANH, 20% of the patients required allogeneic blood, a similar number as an untreated control group[15]. Data from another recent randomized, prospective study in patients undergoing radical retropubic prostatectomy confirmed that ANH had a beneficial, but only limited effect on reduction of the use of allogeneic blood; 60% of control patients needed PRBC, whereas 45% of ANH patients received allogeneic blood[16].

2. CONTROLLED HYPOTENSION

Lowering mean arterial blood pressure (MAP) is a rather old method of reducing blood loss and there is a considerable renewal of interest in this strategy. Controlled hypotension has been proven efficacious in decreasing blood loss and transfusion requirements in many surgical procedures[16,17]. The results of a recently published prospective study indicate that patients undergoing radical prostatectomy with an intraoperative MAP of 50 mmHg have a significantly lower blood loss and needed less PRBC than a control group with an intraoperative MAP of > 70 mmHg[16].

Hypotension can be achieved by reduction in cardiac output (CO), systemic vascular resistance (SVR), or both. During hypotension a blood flow sufficient to maintain adequate tissue oxygenation and metabolism must be provided. For this reason controlled hypotension is usually achieved primarily by decreasing SVR and not by lowering CO.

The characteristics of an ideal agent for inducing hypotension include ease of administration, a predictable and dose-dependent effect, rapid onset of action and recovery from effects, and maintenance of an adequate blood flow to vital organs at low levels of blood pressure. Many techniques, including manipulating body positioning, using anesthetic techniques such as spinal and epidural anesthesia, deeping general anesthesia, and use of vasoactive drugs have been advocated to induce controlled hypotension (Table II). Hypotension achieved by epidural or subarachnoid anesthesia techniques causes pharmacological sympathectomy, which produces arteriolar dilatation. These effects are enhanced by venous blood pooling that decreases venous return and cardiac output. The unpredictable degree of hypotension and the necessity for large infusions of fluid are the principle drawbacks of this method. It was recently demonstrated by Williams-Russo and coworkers that if hemodynamic stability is maintained by low-dose epinephrine infusion, this technique can be used safely even in geriatric patients[18]. Over 200 elderly adults (mean age 72 years) with comorbid medical illness undergoing primary total hip replacement with epidural anesthesia were included in this randomized, controlled clinical trial. The patients were assigned to intraoperative MAP management levels of either 45-55 mmHg or 55-70 mmHg. The overall incidence of major cardiovascular complications was surprisingly low, despite the high incidence of comorbid vascular risk factors in the study population. The epinephrine infusion used routinely in this study did not directly affect MAP, but maintained normal stroke volume. This was associated with increased cardiac index and might have prevented significant bradycardia. However, this trial did not find any evidence of relevant differences in intraoperative blood loss or transfusion of blood products. This might be due to the fact that both levels of intraoperative MAP were relatively low compared to the patients' preoperative MAP. Volatile anesthetics, particularly isoflurane and desflurane, were also used for performing controlled hypotension[19]. Volatile anesthetics produce hypotension by a dose-dependent decrease in systemic vascular resistance while maintaining cardiac output and peripheral perfusion. Cerebral metabolism and autoregulatory mechanisms are well preserved at concentrations less than 1 MAC. However, at higher concentrations volatile anesthetics may increase cerebral blood flow and intracranial pressure and impair cerebral autoregulation. These effects are particularly important in patients who showed reduced intracranial compliance. Thus, volatile anesthetics should only be used with caution as a sole agent to induce hypotension in patients with intracranial disease. Combining volatile anesthetics with alpha- or beta-adrenergic blocking drugs might attenuate these undesirable effects[20]. The most commonly used agents to lower blood pessure is sodium nitroprusside (SNP). The technique is simple to perform but practiced not nearly as often as it might be. SNP produces vasodilation by release of nitric oxide, which stimulates accumulation of cyclic guanosine monophosphate in vacular smooth muscle cells. SNP acts primarily on arteriolar tone with a rapid onset of action and recov-

Table II. Drugs and techniques used to induce controlled hypotension.

Regional anesthesia	
	Spinal anesthesia
	Epidural anesthesia
General anesthetics	
	Isoflurane
	Desflurane
	Sevoflurane
Direct vasodilators	
	Sodium nitroprusside
	Nitroglycerine
	Hydralazine
Alpha/Beta adrenergic blocking drugs	
	Trimetophan, Phentolamin, Urapidil
	Esmolol, Propranolol
Other	
	Adenosine, prostaglandin E1,

ery of blood pressure[21]. SNP dose-dependently reduces systemic vascular resistance (SVR), pulmonar vascular resistance (PVR), and right arterial pressures (RAP), while the effect on cardiac output (CO) is dependent on initial left ventricular end-diastolic pressure. The circulatory effects of SNP depend upon circulating blood volume. In the presence of normovolemia CO remains unchanged, while it decreases in hypovolemia. No direct myocardial effects of SNP have been demonstrated[21]. Because SNP contains five cyanide groups, toxicity might be of concern. Nonenzymatical breakdown in red cells and plasma produces free cyanide, which rapidly diffuses into the tissue, where it binds with high affinity to cytochrome oxidase. This may cause tissue hypoxia. Cyanide is also metabolized in the liver by rhodanase to thiocyanate which undergoes renal excretion[21]. Cyanide toxicity can be treated by infusion of sodium thiosulfate. SNP requires careful administration to appropriately selected patients. Most experience with this technique has been gained in orthopedic and urologic surgery[16,17]. The margin of safety for lowering MAP has been set at 50 mmHg based on the assumption that autoregulatory mechanisms in vital organs (e.g. brain and myocardium) are still active. Strict exclusion criteria must be applied before using controlled hypotension. It is contraindicated in patients with coronary or valvular cardiac disease, myocardial ischemia, ischemic cerebrovascular disease or stroke, hypovolemia, and severe untreated systemic hypertension. Relative contraindications include hepatic or renal dysfunction, pregnancy, and diabetes. However, with appropriate patient selection and monitoring, the risk of performing controlled hypotension as a blood conservation technique is relatively low.

3. COST-CONSIDERATIONS

Cost-effectiveness is an extremely important factor in the present climate of cost constraints. ANH is less costly than PAD[12] and does not require cumbersome logistics. In a cost analysis comparing ANH with controlled hypotension for reducing the use of allogeneic blood, not only more patients did not receive allogeneic blood, cost savings were documented only in the group of patients who underwent intraoperative controlled hypotension[16]. Although cost calculations did not include hospital overhead costs, staff costs, or costs for treatment of possible adverse effects of allogeneic blood, these data suggest that controlled hypotension is a more cost-effective alternative to reduce use of allogeneic blood than ANH. This makes controlled hypotension an economically attractive concept and the use of this technique may further promote the trend towards bloodless surgery.

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