

Safety and Efficacy of Methods for Reducing Perioperative Allogeneic Transfusion: A Critical Review of the Literature

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A number of pharmacologic and nonpharmacologic technologies are in current use to minimize perioperative homologous blood use. Clinical trials, many of them randomized controlled trials, have been done evaluating these approaches and have demonstrated their efficacy. However, data on safety has relied mostly on case reports, uncontrolled studies, and, for the pharmacologic agents, extrapolation from the nonsurgical setting. In this review I analyze the data from the randomized trials and the lower-level evidence studies to provide the best estimates in safety with these alternatives. In general, these alternatives are safe with proper dosing and monitoring of effects. With aprotinin, the primary concern is anaphylaxis, and this predominantly with re-exposure. With aprotinin and with the anti-fibrinolytics, increased venous thromboembolic risk has not been a consistent finding. Tranexamic acid use intraoperatively is advantageous, but postoperative use appears to have no advantage and may be associated with renal dysfunction. DDAVP is low-risk, provided it is not overused, which can induce hyponatremia. Autologous predonation probably has similar risks as homologous blood with respect to transfusion errors and bacterial infection. As with most medical interventions, we must be vigilant to prevent human error.

Keywords: perioperative transfusion; erythropoietin, aprotinin, antifibrinolytics, tranexamic acid, autologous predonation, DDAVP, safety, adverse events.

INTRODUCTION

Adverse effects of allogenic blood products have contributed to the continuing demand for alternative products and blood conservation methods. Both pharmacologic and nonpharmacologic technologies are available to minimize perioperative transfusion. The clinical trials that have been performed evaluating these approaches have been concerned primarily with their efficacy; information regarding the safety of these strategies has relied mostly on case reports, uncontrolled studies, and, for the pharmacologic agents, extrapolation from the nonsurgical setting. This review is an attempt to synthesize the evidence available in the literature concerning the safety of

these blood conservation methods in adults undergoing elective surgery.

PHARMACOLOGIC TECHNOLOGIES TO MINIMIZE TRANSFUSION

Aprotinin

Aprotinin is a naturally occurring serine proteinase inhibitor. It is a powerful inhibitor of plasmin, trypsin, kallikrein, chymotrypsin, activated protein C, and thrombin.¹ The efficacy of aprotinin in reducing the need for perioperative allogeneic blood transfusion in cardiac surgery was clearly established with numerous randomized trials and was confirmed in the recent International Study of Peri-Operative Transfusion (ISPOT) meta-analysis, which included 45 trials with a total of 5805 patients.² Combining all doses of aprotinin, the overall odds ratio (OR) was 0.31 (range: 0.25–0.39; $P < 0.0001$). Aprotinin was also found to be efficacious when given in high doses (6 mU) (OR = 0.28; range: 0.21–0.36; $P < 0.001$), intermediate doses (2–6 mU) (OR = 0.35; range: 0.22–0.58; $P < 0.0001$),

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and low doses (<2 mU) (OR = 0.49; range: 0.33–0.73; $P = 0.0006$).

The most common side effects reported with aprotinin include hypersensitivity reactions, renal dysfunction, and arterial thrombosis. Aprotinin is a naturally occurring protein isolated from bovine (95%) or porcine (5%) lung. Therefore, it is not surprising that hypersensitivity reactions are reported. Since its initial use in the 1960s for acute pancreatitis, aprotinin has been linked to more than 30 case reports of anaphylactoid reactions, ranging from mild to severe. Several case reports of severe anaphylactic reactions have been published, with the common link between them being previous exposure to aprotinin.^{3–6} In several cases, aprotinin-specific IgE antibodies have been documented, indicating previous sensitization.^{4,5} Dietrich et al⁷ retrospectively analyzed the prevalence of anaphylactic reactions in 248 patients re-exposed to aprotinin during cardiac surgery. A total of seven reactions (2.8%) occurred, but the prevalence was 4.5% in those re-exposed within 200 days, and it dropped to 1.5% ($P < 0.05$) in those re-exposed after more than 200 days. Four of the seven reactions were moderate to severe, but no deaths were attributable to aprotinin. Dietrich et al⁸ further explored the issue of anaphylactic reactions to aprotinin on re-exposure in cardiac surgery. The aim of the second study was to establish the ability to predict which patients would have anaphylactic reactions. They evaluated the aprotinin prick test, the timing of aprotinin exposure, and the presence of IgG and IgE antibodies. In this study,⁸ they enrolled 118 patients, and 3 patients had a moderate to severe anaphylactic reaction. Three of 29 patients who had been exposed within 6 months had an anaphylactic reaction versus none of the other 92 exposures in patients who had more than 6 months since exposure. All these reactions occurred in patients with high levels of IgG antibodies to aprotinin. These reactions occurred despite the use of H₁ and H₂ (histamine) receptor blockers and corticosteroid use in most of the patients. The skin prick test was of no value in predicting anaphylactic reactions. Casati et al⁹ demonstrated that anaphylaxis is rare (1 reaction in 518 patients) in patients who have not previously been exposed to aprotinin. Two series ($n = 1573$) in patients undergoing cardiac surgery reported a prevalence of allergic reaction between 0.3% and 0.6%.^{10,11} In summary, anaphylaxis is uncommon in patients without prior exposure, and both histamine blockade and corticosteroids seem to have limited effectiveness for prevention of anaphylaxis.

Aprotinin has a high affinity for renal tissue, and there are concerns that it can cause postoperative renal failure. It is rapidly eliminated by renal excretion, with

a serum half-life of 1 to 2 hours. After 4 hours, 80% to 90% is stored in the proximal tubule cells and excreted over 12 to 24 hours.^{12,13} It is hypothesized that aprotinin causes a reversible overload of the tubular reabsorptive mechanisms, resulting in transient renal dysfunction.^{13,14} Aprotinin may also have a direct toxic effect on the proximal tubule cells or alter intrarenal blood flow through inhibition of renin and kallikrein activity.^{13,15} Although several randomized studies in patients undergoing both cardiac and liver surgery have shown no adverse effects of aprotinin on postoperative renal function, many other studies implicate aprotinin use with the development of postoperative renal dysfunction.^{10,16–19} Three randomized trials that used high-dose aprotinin in cardiac surgery patients reported a trend of a mild to moderate increase in postoperative serum creatinine (~ 0.5 mg/dL) but no increase in clinically important adverse outcomes such as irreversible renal failure or need for dialysis.^{15,20,21} Follow-up at 4 to 6 weeks in one study suggested that the effect is transient.¹⁵

As with most hemostatic agents, the primary concern with the use of aprotinin is the potentiation of a prothrombotic state. Isolated case reports of graft thrombosis and pulmonary artery catheter thrombosis after the use of aprotinin in cardiopulmonary bypass surgery have led to an ongoing debate concerning the safety of aprotinin.^{22,23} In the ISPO meta-analysis, the perioperative myocardial infarction rate was 8% in the aprotinin group versus 5.6% in the placebo group (OR = 1.15; range: 0.82–1.53; $P = 0.48$).² Although this difference was not statistically significant, there were not enough patients to exclude a small but clinically important increase in myocardial infarction in the aprotinin-treated patients. The possibility that low-dose aprotinin (generally 50% of the high-dose protocol or pump-prime only) might lead to more thrombotic events than the high-dose regimen is controversial.²⁴ In the largest randomized controlled trial involving 704 patients and comparing three different dose regimens, Lemmer et al¹⁸ reported a significant increase in postoperative myocardial infarctions in the pump-prime only aprotinin group (16%) versus the placebo group (9%; $P = 0.045$). A pooled analysis using individual patient data from four published American trials and two unpublished trials found a nonsignificant increase in cardiac mortality in patients who received the half-dose regimen (5.4%) compared with placebo (3.8%).²⁴ Interpretation of this analysis is difficult, however, because different doses were not directly compared with each other and many trials that used other dose regimens were not included. Alderman et al²⁵ demonstrated no difference between 436 patients who used high-dose aprotinin and 434 treated with a

placebo in the incidence of perioperative acute myocardial infarction and mortality. Several investigators have analyzed the effects of aprotinin on graft patency. Six randomized controlled trials have reported on vein graft patency with aprotinin.²⁶⁻³¹ Only one showed a concerning trend to increased graft occlusion in the aprotinin group (8.0%) versus the placebo group (4.9%).³⁰ Graft occlusion was not accompanied by an increase in the incidence of myocardial infarction in any study. As a subgroup analysis of Alderman et al's study,²⁵ it was demonstrated that there is an increased probability of early occlusion of venous grafts in vessels less than 1.5 mm in diameter or of poor quality (aprotinin group [15.4%] versus controlled group [10.9%]; $P = 0.03$). This was not the primary hypothesis of the study, however, and this subgroup analysis is merely hypothesis generating and needs to be further tested.

Concern about the possibility of developing an increased rate of deep vein thrombosis (DVT) has also been raised. In a recent study comparing placebo with three different doses of aprotinin in patients undergoing unilateral total hip replacement, there was no increased risk of DVT.³² Patients in this study were evaluated by color-Doppler imaging at the time of discharge and with clinical follow-up for development of DVT. There were slightly more than 70 patients in each of the four arms of this trial. The studies assessing the use of aprotinin in cardiac surgery patients have not specifically screened for DVT, but in those that have reported on this outcome, there has not been an increased risk associated with aprotinin use.

EPSILON-AMINOCAPROIC ACID AND TRANEXAMIC ACID

ϵ -aminocaproic acid (EACA) and tranexamic acid (TXA) are synthetic lysine analogues that inhibit plasminogen/plasmin-mediated fibrinolysis.³³ Both bind to the plasminogen lysine-binding site and prevent plasminogen binding to its substrate fibrin. They also prevent plasmin degradation of platelet glycoprotein 1b receptors, thus preserving platelet function. TXA is 10 times more potent than EACA. The synthetic antifibrinolytics EACA and TXA have been used prophylactically to prevent blood loss and to limit allogeneic transfusions in patients undergoing cardiac surgery. They have also been used in prostate surgery, where bleeding has been attributed partly to primary fibrinolysis. More recently, the synthetic antifibrinolytics have been used in orthopedic surgery and liver transplantation surgery to decrease blood loss. A recent meta-analysis of 12 randomized trials in patients

undergoing cardiac surgery showed that TXA decreased the proportion of patients receiving allogeneic red blood cell transfusions, with an OR of 0.50 (95% confidence interval [CI]: 0.34–0.76; $P = 0.0009$).² Much less information is available for EACA. In the same meta-analysis, only three studies of EACA (a total of 118 patients) were eligible, and the OR of 0.20 was not statistically significant (CI: 0.04–1.12; $P = 0.07$), although there was a strong trend toward EACA being efficacious.

Side effects of these synthetic antifibrinolytics include gastrointestinal symptoms, myonecrosis, and thrombosis (cerebral, disseminated intravascular coagulation [DIC], cardiac, and venous). Gastrointestinal side effects such as nausea, diarrhea, and abdominal cramping have been reported primarily with oral forms of EACA and TXA and have not occurred in the perioperative setting, in which they are usually given intravenously (except in prostate surgery, in which both oral and intravenous forms have been used). Between 1972 and 1995, 31 cases of EACA-induced myonecrosis and myoglobinuria were reported in the literature.³⁴ All patients received high doses of oral EACA for more than 28 days. There are no reports of myonecrosis associated with the intravenous use of EACA in the perioperative setting, and myonecrosis with TXA has not been described.

A major concern regarding the perioperative use of the synthetic antifibrinolytics is the possibility of an increase in thrombosis as a result of unopposed fibrin generation. Numerous case reports of thrombosis associated with TXA and EACA date back to the 1960s, when these drugs were first introduced. In the ISPO meta-analysis, which included 12 cardiac trials, there was no increased risk of myocardial infarction (0.4% for TXA versus 1.8% for control; OR = 0.48; CI: 0.12–1.93; $P = 0.3$).² Of 17 randomized controlled trials in adult cardiac surgery (not limited to perioperative transfusion as an outcome), 10 mentioned adverse events, including thrombosis.³⁵⁻⁴⁴ The incidence of myocardial infarction in the TXA-treated patients was 0.36% versus 1.5% in the placebo group (OR = 0.51; CI: 0.18–1.46; $P = 0.21$). There was a nonsignificant increase in the incidence of stroke (OR = 1.27; CI: 0.49–3.27; $P = 0.62$). Although the data from randomized controlled trials are much more limited for EACA, our pooled analysis of 4 trials in cardiac surgery (total of 548 patients) shows a statistically significant increase in perioperative myocardial infarction (OR = 2.5; CI: 1.06–5.86; $P = 0.035$).

Three randomized controlled trials have evaluated TXA in orthopedic surgery.⁴⁵⁻⁴⁷ All showed a significant decrease in transfusion requirements. None showed any increase in DVT or pulmonary embolus;

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there were 6 of 97 (6.2%) events in the TXA patients versus 9 of 94 (9.6%) events in the placebo patients (OR = 0.71; CI: 0.26–1.96; $P = 0.51$).

Three trials in patients undergoing liver transplantation used TXA prophylactically to reduce blood loss; there were no thrombotic complications in the TXA or control groups.^{48–50} Although thrombosis in major vessels is not uncommon in patients with liver disease, there have remained concerns that EACA may exaggerate this tendency, because the fibrinolytic state in liver transplantation is usually self-limited. Kang et al⁵¹ gave EACA to 20 patients undergoing liver transplantation; no thrombotic episodes were observed in this study compared with three events in 77 (3.9%) control patients.

Several controlled studies in the 1960s and 1970s showed a reduction in blood loss with EACA administered in patients undergoing prostatectomy.^{52–54} Enthusiasm for EACA has been tempered by isolated reports of EACA causing diffuse thrombosis after treating hemorrhage after prostatectomy, indissoluble blood clot formation in the bladder with TXA, and occasional reports of fatal pulmonary embolus after prostatectomy.^{55–58} Despite these concerns, no controlled study in prostate surgery has reported an increase in thrombotic events with the use of either synthetic antifibrinolytic. Two early studies reported no increase in venous thromboembolic complications (20 of 309 [6.5%] events in EACA-treated patients versus 19 of 281 [6.8%] events in control patients), but neither study mentioned the method of diagnosis.^{57,58} Two subsequent randomized controlled trials used ¹²⁵I-fibrinogen uptake after surgery to screen for DVT. Although the absolute rates of DVT were high in both studies (up to 50%), there were no statistically significant observed differences between the two groups.^{59,60}

With respect to renal toxicity from the use of TXA, there is little to suggest concern. Renal function was reported on in a prospective, randomized, double-blind, placebo-controlled trial in elective cardiac surgery patients who were treated with TXA during surgery and in the postoperative period.⁶¹ In this study, patients were randomized to one of three treatment groups after surgery: saline or two doses of continuous infusion of TXA for 12 hours. Not only was there no benefit with respect to reduction in bleeding and the number of allogeneic transfusions, but there was a tendency to development of renal dysfunction. Although statistical significance was not achieved and this was a subgroup analysis, 6% of patients in the high-dose TXA subgroup developed a doubling of baseline creatinine versus 2.4% in the placebo group. This study certainly suggests that there is no advan-

tage to providing TXA in the immediate postoperative period and that added toxicity is possible.

DESMOPRESSIN

1-Desamino-8-D-arginine vasopressin (DDAVP) is an analogue of the hormone arginine vasopressin with enhanced antidiuretic and decreased vasopressor activity. Use of DDAVP reduces the prolonged bleeding time characteristic of various hemostatic disorders. When given at the usual dose of 0.3 µg/kg (subcutaneously or intravenously), factor VIII levels, von Willebrand factor levels (especially the high-molecular-weight multimers), and tissue plasminogen activator levels increase by 2- to 20-fold.¹ DDAVP has been used as a hemostatic agent in cardiac surgery to reduce perioperative blood loss and transfusion requirements, although results from two recent meta-analyses suggest that DDAVP has no significant effect on decreasing the proportion of patients receiving allogeneic red blood cell transfusions (OR = 0.98; CI: 0.64–1.50; $P = 0.92$ and OR = 1.0; CI: 0.9–1.1).⁶²

Side effects of DDAVP include facial flushing, headache, hypotension, hyponatremia, water intoxication, seizures, and anecdotal reports of thrombotic events. Hypotension is caused by a direct vasodilating effect and an indirect effect via prostacyclin release from endothelial cells. Although two early trials reported no adverse effects on blood pressure during or shortly after DDAVP infusion, several more recent trials have clearly documented a significant decrease in mean arterial pressure and systemic vascular resistance lasting up to 30 minutes after infusion in a substantial portion of patients.^{63–69} The hypotension is responsive to a combination of fluids and vasopressors. No studies have reported electrocardiogram-documented ischemic changes, arrhythmias, or myocardial infarction directly attributable to the hypotension.

Severe hyponatremia and water intoxication resulting from the antidiuretic activity of DDAVP have been reported rarely. Although the postoperative period is conducive to the development of hyponatremia as a result of the stimulation of antidiuretic hormone caused by pain and the use of analgesic agents, few trials have systematically looked for this side effect of DDAVP. Four trials in cardiac and orthopedic surgery patients provided data on serum sodium.^{64,70–72} Only one trial reported a significant difference in mean postoperative serum sodium in the DDAVP group (131.8 mmol/L) versus the placebo group (133.9 mmol/L); the clinical relevance of this difference is likely insignificant.⁷²

The primary concern with DDAVP is induction of a potentially prothrombotic state through enhanced platelet aggregation and increased factor VIII activity. Several isolated case reports of coronary and cerebral thrombosis have been described in nonsurgical settings.⁷³⁻⁷⁵ A recent meta-analysis of 12 randomized controlled trials using DDAVP in cardiac surgery reported an incidence of myocardial infarction of 4.4% in the DDAVP-treated group versus 1.6% in the placebo-treated group (OR = 2.07; CI: 0.74-5.85; $P = 0.19$).² Cattaneo and Mannucci pooled data from double-blind placebo-controlled trials that evaluated the hemostatic efficacy of DDAVP in cardiac, vascular, and orthopedic surgery.⁷⁶ Total thrombotic events (i.e., myocardial infarction, stroke, arterial thrombosis, venous thromboembolism) were reported in 3.4% of the DDAVP-treated patients and 2.7% of the placebo-treated patients ($P = 0.38$). We pooled data from 17 randomized controlled trials in cardiac ($n = 15$) and vascular ($n = 2$) surgery that specifically mentioned the presence or absence of thrombotic events. The incidence of myocardial infarction was 3.9% (28 of 716 patients) in the DDAVP-treated group and 3.1% (20 of 646 patients) in the placebo group for an OR of 1.25 (CI: 0.72-2.14; $P = 0.43$).

In orthopedic surgery, only three of the five published randomized controlled trials were assessed for DVT. There were four cases of DVT/pulmonary embolism in the DDAVP group (3.7%) and five in the placebo group (4.3%), for an OR of 0.82 (CI: 0.24-2.78; $P = 0.75$).^{71,77,78}

PREOPERATIVE AUTOLOGOUS DONATION

Preoperative autologous donation is being used with increased frequency as a method of reducing allogeneic transfusions. A recent meta-analysis of six randomized trials and nine concurrent control cohort studies found that patients who predonated autologous blood were less likely to be exposed to allogeneic blood (OR = 0.17; CI: 0.08-0.32; $P < 0.00001$ for the randomized trials and OR = 0.19; CI: 0.14-0.26; $P < 0.0001$ for the cohort studies).⁷⁹ The same meta-analysis also showed that autologous donors were more likely to receive any transfusion (OR = 3.03; CI: 1.70-5.39; $P < 0.00001$ for the randomized trials and OR = 12.32; CI: 5.90-25.40; $P < 0.00001$ for the cohort studies). This latter finding, corroborated by others, is thought to be attributable to a combination of a more liberal transfusion practice and lower preoperative hemoglobin levels in patients who predonate autologous blood.

Potential side effects of preoperative autologous donation include those that result from the donation process itself and those incurred as a result of the autologous transfusion. The incidence of reactions occurring around the time of donation in allogeneic donors is 2% to 5% and is similar in autologous donors.^{80,81} Most reactions are mild and of vasovagal origin. First-time donation (OR = 2.4), female gender (OR = 1.9), and decreasing age (10-year increment, OR = 1.2) are predictors of donor reaction for both autologous and allogeneic donors.⁸² Reactions severe enough to require hospitalization were reported in 1 of 16,783 autologous donations (13 of 218,190 donations) by the American Red Cross from July 1993 to March 1995.⁸³ Of these, 67% were classified as vasovagal, and angina was reported in only 4 patients (of more than 4 million autologous and allogeneic donors).

In a series of 5660 autologous donors at 25 blood centers in the United States, AuBuchon and Popovsky⁸¹ reported reactions in 4.3% of the 886 donors who did not qualify for allogeneic donation and in 2.7% of those who met the criteria for allogeneic donation. This suggests that a subset of autologous donors may be more susceptible to experiencing a reaction during donation. Hillyer et al⁸⁴ examined reaction rates in 207 donations from high-risk patients (i.e., coronary artery disease, cerebrovascular disease, hypertension requiring two or more medications, symptomatic dyspnea, seizures, arrhythmia, congestive heart failure, diabetes, valvular or congenital heart disease) and 665 donations from patients who were not at high risk. There was no difference in reaction rates (3.9% in the high-risk group versus 3.3% in the group not at high risk). In addition, there were no severe reactions (defined as unconsciousness with seizures) in the high-risk group.⁸⁴

Few studies have properly assessed the safety of autologous donation in high-risk patients awaiting cardiac surgery. Studies have also excluded patients in whom donation is clearly believed to be dangerous, including patients with critical aortic stenosis, left main coronary artery disease, ventricular arrhythmia, unstable angina, or hypertrophic cardiomyopathy. In a prospective cohort of patients undergoing cardiac surgery, 12% (10 of 82) of the patients with coronary artery disease experienced worsening angina with predonation.⁸⁵ Although 4 of these patients were hospitalized and required emergency coronary bypass surgery, 4 of the control patients who did not predonate (4 of 111) also required earlier surgery because of a worsening of their angina. Because there is a small but definite preoperative mortality in patients awaiting cardiac bypass surgery, it is difficult to establish a

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causal relation between autologous donation and the development of angina or myocardial infarction. In a recent European series of patients awaiting cardiac bypass surgery (no autologous predonation), 2.2% (25 of 1124) died of cardiac-related causes.⁸⁶ Two of 288 (0.7%) patients on the medium priority list with a waiting period of 39 days (similar to the collection period of autologous predonation) died before surgery. These deaths might have been considered a complication of predonation if they had occurred during the collection interval.

The risks of perisurgical anemia resulting from a combination of predonation and surgical blood loss are not clear. No trial of autologous predonation has shown an increase in perioperative myocardial infarction. Goodnough and Monk⁸⁷ reported a case of myocardial infarction 1 day after surgery in a patient undergoing radical suprapubic prostatectomy. The patient had predonated 3 U of blood, and his postoperative hematocrit was 22%. There is no way of knowing whether the low hematocrit contributed to the myocardial infarction, but this case emphasizes the importance of appropriate transfusion practice, regardless of the type of blood available.

It has been suggested that a state of hemodilution resulting from preoperative donation might prevent DVT because of a decrease in blood viscosity.⁸⁸ Anders et al⁸⁹ analyzed the effect of predonation of autologous blood on postoperative DVT in a retrospective cohort study of 237 patients undergoing total hip or knee arthroplasty. DVT (diagnosed by routine venography) developed in 17% (28 of 161) of the patients who predonated compared with 34% (26 of 76) of the patients who did not predonate ($P = 0.006$). The patients who predonated had a significantly lower mean preoperative hemoglobin level (132 g/L) than those who did not predonate (140 g/L) ($P < 0.001$). The association between preoperative hemoglobin and DVT was of borderline significance, however; the mean hemoglobin level was 138 g/L in patients who developed DVT compared with 133 g/L in those who did not ($P = 0.07$). This finding has not been confirmed in a randomized controlled trial. Indeed, in a randomized trial in patients undergoing hip surgery, Elawad et al⁹⁰ reported venous thromboembolism events in 13% of controls (2 of 15) and in 13% of patients who predonated autologous blood (6 of 45). Stowell et al⁹¹ studied almost 500 patients scheduled for total joint arthroplasty who were mildly anemic. These patients were randomized to weekly doses of erythropoietin or to participate in a preoperative autologous donation (PAD) program. There was no difference in the risk of allogeneic transfusion in this study. Similarly, from the safety point of view, there was no difference be-

tween the two groups with respect to serious or unexpected events. Interestingly, in this study, pulmonary embolism was more common in the PAD group; indeed, the only two deaths in the study were a consequence of postoperative pulmonary emboli in the PAD group. These differences were not statistically significant, however, and lack of comparison to a placebo group precludes any firm conclusion.

Regarding the risks of transfusion itself, autologous blood may be contaminated with bacteria; may cause circulatory overload (estimated risk of 1%); or may be associated with clerical, laboratory, or ward error (causing transfusion of the wrong unit of blood).⁹² The risk of clinically significant bacterial infection from a unit of blood is less than 1 in 1 million, and the risk of death is 1 in 9 million. There are several case reports of bacterial sepsis resulting from autologous blood transfusion, but there is no reason why this remote risk should be any different from that with allogeneic blood.⁹³⁻⁹⁶ A recent study from France demonstrated that transfusion-associated bacterial contamination occurred at a rate of 7.4 per million U of allogeneic blood transfused and at a rate of 1.9 per million U of autologous transfusion.⁹⁷ These data demonstrated that half of the cases of transfusion-associated bacterial contamination may not cause significant clinical problems. The true proportion of patients with mild transfusion-associated bacterial contamination is likely higher than reported in their series. Their observed death rate was 1 in 6 patients who were transfused with bacterial contaminated blood, similar to other case series.

The frequency of ABO (A, B, or O antigen) incompatibility and fatal acute hemolytic transfusion reactions attributable to transfusion error has been reported as 1 in 33,000 and 1 in 600,000, respectively.⁹⁸ The risk of transfusion error for autologous donors is not known. A survey of autologous donation errors in Canadian Red Cross Society blood centers between 1989 and 1996 reported that 1 U of autologous fresh-frozen plasma was transfused to 1 wrong patient in 70,351 donations.⁹⁹ This was a retrospective survey, and it is possible that some events were not reported. In a survey of transfusion errors in New York State, Linden reported that 2 patients who donated autologous blood received the blood of another patient (2 of 124,601 units).¹⁰⁰

CELL SALVAGE

Cell salvage, a form of autologous transfusion, consists of the collection and transfusion of blood that has been shed within the operative field. Numerous

randomized and nonrandomized studies have reported a clinically important decrease in the frequency of allogeneic transfusion, whereas a smaller number have found no decrease in the transfusion requirement. We are not aware of any published meta-analyses of the efficacy of cell salvage.

The safety of cell salvage devices has improved markedly since they were first introduced in the late 1960s, and this review concentrates on the adverse effects associated with the devices currently in use.^{101,102} The main side effects consist of air embolism, coagulation abnormalities, and DIC. There continues to be concern about the use of cell salvage in patients with sepsis as well as in patients with cancer.

Although air embolism was a relatively frequent complication of the earliest cell salvage devices, it is now a rare complication. The best information about the frequency of air embolism comes from a study of 127,586 cell salvage procedures performed in New York State between 1990 and 1995.¹⁰³ Five fatal cases of air embolism occurred, a frequency of 1 in 30,000 procedures for intraoperative cell salvage and 1 in 38,000 procedures for postoperative cell salvage. In all cases, the salvaged blood was transfused under pressure. Methods of avoiding air embolism include only transfusing blood under pressure if bleeding is life threatening, avoidance of direct transfusion from the recovery container (the blood should be transferred to a reinfusion bag before administration), automated and human vigilance to detect air that might have entered the system, and appropriate training and testing of personnel operating the devices.

Abnormal thromboplastic substances, cytokines, and other molecules such as free hemoglobin are present in unwashed salvaged blood.^{104–107} Free hemoglobin is elevated because of hemolysis associated with vacuum aspiration of blood in the salvage device. Contact of blood with tissue at the surgical site results in initiation of coagulation and subsequent fibrinolysis of blood at the time of salvage.¹⁰² Washing the salvaged blood decreases the frequency of these abnormalities.^{104,108} The clinical importance of these abnormalities is not clear, however, because most patients seem to suffer no serious adverse clinical effects from the transfused blood. Temporary hypotension and hyperthermia occurred in 19% and 6% of patients, respectively, who received unwashed blood salvaged after orthopedic surgery.¹⁰⁹ The most worrisome potential consequence of the coagulation abnormalities present in salvaged blood is DIC. There are a number of case reports of a DIC-like syndrome (also called the “salvaged blood syndrome”) occurring shortly after transfusion of blood collected by means of cell salvage.^{110–114} Some of these patients had catastrophic

underlying illnesses (e.g., trauma, ruptured aortic aneurysm), and the DIC may well have occurred because of profound hypotension, shock, or dilutional coagulopathy. In some instances, however, the DIC syndrome does seem to be related to the transfusion of salvaged blood. The frequency of the DIC syndrome is not clear, although one retrospective study of 36,000 patients reported 18 cases (incidence of 1 in 2000). Most of the patients were extremely ill, and the syndrome seemed to be related to the patients' underlying illness rather than to the transfusion.¹¹²

Although many studies have reported a decrease in allogeneic transfusion requirements in patients in whom cell salvage is used, some studies have reported an increase in postoperative bleeding in patients receiving unwashed blood.^{101,106,115} This is believed to be attributable to initiation of coagulation and fibrinolysis when blood contacts tissue. In operations with large intraoperative blood losses, it is likely that any increase in postoperative bleeding is counteracted by the large amount of autologous blood that can be salvaged and transfused.

There is concern that malignant cells may be transfused in oncologic patients undergoing surgery. Potential transfusion of malignant cells with cell salvage has been shown in experimental models, and it has been shown that filtering the blood decreases but does not entirely remove malignant cells from the transfused blood.^{116,117} A leukocyte filter may be more effective.¹¹⁸ Although some studies have suggested that the prognosis of cancer patients after surgery seems similar to that of patients who did not undergo cell salvage, the studies are small, nonrandomized, and limited to a small number of cancers.^{119–122} Thus, the safety of autotransfusion in patients with cancer has not been firmly established.

Finally, cases of noncardiogenic pulmonary edema and upper airway edema after unwashed cell salvage have been described. They were believed to be attributable to platelet or complement activation or to transfer of antileukocyte antibodies.^{83,123} There have been few recent reports on the use of cell salvage in coronary artery surgery. Kitano et al¹²⁴ recently reported on a small study in 10 patients, which aimed to determine hemodynamic changes with the use of unwashed shed blood reinfusion after surgery. These investigators demonstrated a decrease in the right ventricular ejection fraction that was statistically significant, elevations in thromboxane B₂ and 6-keto-prostaglandin F_{1α}, and an increase in the mean pulmonary artery pressure. These data are provocative, but, unfortunately, there is no ability to determine whether these are clinically relevant changes.

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DISCUSSION

The soundest method of determining the true incidence of side effects attributable to any of these technologies would be careful analysis of adverse events in randomized controlled trials large enough to detect small differences in side effects. Large cohort studies of consecutively treated patients, especially with concurrent controls, also can provide useful data. As our review has shown, much of the available data comes from uncontrolled studies. Therefore, it is difficult to comment definitively on the true incidence of side effects for most of these technologies.

The randomized controlled trials have not consistently reported on adverse effects or have not been large enough to detect small differences in adverse effects attributable to the technology. Nevertheless, given the data that have been presented, it does seem reasonable to conclude that these technologies are quite safe. Severe complications (e.g., fatal air embolism with cell salvage, anaphylaxis with aprotinin) are rare.

The greatest difficulty in evaluating side effects is in determining whether any of the drugs increase thrombotic events, particularly myocardial infarction in cardiac patients. The data are inconclusive, but the accumulating evidence is such that any increased risk, if real, is likely to be of minor clinical relevance.

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