Cell salvage does not minimize perioperative allogeneic blood transfusion in abdominal vascular surgery: a systematic review

[La récupération de sang ne réduit pas la nécessité d'une transfusion allogénique périopératoire en chirurgie vasculaire abdominale : une revue systématique]

Gonzalo G. Alvarez MD, Dean A. Fergusson PhD, David T. Neilipovitz MD, Paul C. Hébert MD

Purpose: To determine whether the use of cell salvage reduces the proportion of patients receiving at least one unit of allogeneic packed red blood cells during the perioperative period of an elective vascular surgery.

Source: We identified all relevant articles through the combined use of electronic searches of the MEDLINE and EMBASE databases, the Cochrane library as well as hand searching of all randomized clinical trials and review articles. The electronic search included articles published between 1966 and April 2001. The search included textword searches using "autotransfusion," "cell salvage," "device," or Medical Subject Headings "autologous blood transfusion" or a "randomized controlled trials" filter.

Principal findings: Five randomized controlled trials (RCT) were identified involving cell salvage and vascular surgeries. In infra renal abdominal aortic aneurysm surgery the risk ratio (the risk of receiving at least one unit of allogeneic red cells) was 0.37 [95% confidence intervals (CI) of 0.06 to 2.36]. In elective aorto-femoral bypass surgery the risk ratio was 0.97 (95% CI of 0.66 to 1.42). The pooled risk ratio for cell salvage in vascular surgery was 0.67 (95% CI of 0.35 to 1.28).

Conclusion: Cell salvage, a commonly used technique to recover red cells from the operative field, has been the subject of several studies in vascular surgery. There is insufficient evidence to recommend the routine use of cell salvage in elective abdominal aortic aneurysm and aorto-femoral bypass surgeries. A large RCT would elucidate whether cell salvage is effective as a blood conservation technique.

Objectif : *Déterminer si la récupération de sang réduit le nombre de patients qui recevront au moins une unité de concentré de globules rouges allogènes en période périopératoire d'une intervention chirurgicale vasculaire réglée.*

Source : *Les articles pertinents ont été repérés par des recherches électroniques combinées dans MEDLINE et EMBASE, la bibliothèque Cochrane et une recherche manuelle des essais cliniques randomisés et des exposés de synthèse. La recherche électronique comprend des articles publiés entre 1966 et avril 2001 à partir des termes «autotransfusion», «cell salvage», «device» ou de mots clés du domaine médical comme «autologous blood transfusion» ou d'un filtre sur les «randomized controlled trials».*

Constatations principales : *Nous avons trouvé cinq études randomisées et contrôlées (ERC) comportant la récupération de sang et la chirurgie vasculaire. L'opération d'un anévrysme aortique abdominal infrarénal présentait un taux de risque (le risque de recevoir au moins une unité de globules rouges allogènes) de 0,37 [intervalle de confiance (IC) de 95 % de 0,06 à 2,36]. Le risque lié au pontage aorto-fémoral réglé était de 0,97 (IC de 95 % de 0,66 à 1,42). Le risque commun en chirurgie vasculaire était de 0,67 (IC de 95 % de 0,35 à 1,28).*

Conclusion : *La récupération de sang, couramment utilisé pour conserver les globules rouges provenant du champ opératoire, a fait l'objet de quelques études en chirurgie vasculaire. Il n'y a pas de preuve suffisante pour recommander la récupération régulière de sang lors d'opérations pour anévrysme aortique abdominal et de pontages aorto-fémoraux. Une importante ERC pourrait préciser si la récupération de sang est efficace comme technique de conservation du sang.*

From the University of Ottawa, Centre for Transfusion Research, Ottawa, Ontario, Canada.

Address correspondence to: Dr. Paul C. Hébert, Centre for Transfusion and Clinical Epidemiology Program, Ottawa Health Research Institute, General Campus, 501 Smyth Road, Box 201, Ottawa, Ontario K1H 8L6, Canada. Phone: 613-737-8197; Fax 613-739-6266; E-mail: phebert@ohri.ca

Dr. Hébert is a Career Scientist of the Ontario Ministry of Health.

Accepted for publication August 26, 2003.

Revision accepted February 13, 2004.

THE medical community has been investigating new approaches aimed at reducing the amount of allogeneic blood transfused in the perioperative period for several decades. Recently, the impetus to avoid blood transfusions has been based upon the many adverse consequences including the transmission of transfusion-related viral infections such as hepatitis B and C as well as the human immunodeficiency virus.[1–6]

Cell salvage is a blood conservation technique developed and adopted in the past 20 years as a means of decreasing blood transfusions. The technique recovers blood lost in the operative field, purifies it and returns the recovered red blood cells (RBCs) to the patient thereby potentially avoiding exposure to blood products. Many hospitals have included cell salvage as part of the procedures made available to surgical teams that undertake interventions with large anticipated blood losses.[7]

The cell salvage technique is widely used in orthopedic surgery where evidence suggested a reduction in exposure to blood products, however a similar benefit was not observed in cardiac surgery.[7] In vascular surgery, there are many published studies that support the use of cell salvage. However, a significant proportion of these studies make use of historical controls or are observational in nature. In addition, the results of a recent randomized controlled trial[8] did not observe any decrease in red cell transfusions using cell salvage. The authors concluded that this technique should no longer be considered standard of care. Given genuine uncertainty regarding the use of cell salvage in vascular surgery, we conducted a systematic review of published studies to determine if cell salvage reduced the exposure of red cells.

Methods

Identification and selection of studies

In this systematic review, we identified all relevant articles through the combined use of electronic searches of the MEDLINE and EMBASE databases, the Cochrane library as well as hand searching of all randomized clinical trials and review articles. The electronic search included articles published between 1966 and April 2001. The search included textword searches using "autotransfusion," "cell salvage," "device," or Medical Subject Headings "autologous blood transfusion" or a "randomized controlled trials" filter.

We selected studies that met the following criteria. The article was required to state that the study: 1) used a form of random allocation; 2) incorporated a control group that did not receive blood products recovered from a cell salvage device; 3) enrolled patients who underwent an elective abdominal vascular surgery (infra renal abdominal aortic aneurysm or a aorto-bifemoral bypass); and 4) reported the proportion of patients receiving at least one unit of allogeneic blood (the primary outcome). Studies were excluded from the meta-analysis if: 1) they were duplicate publications; 2) primarily involved patients under the age of 18 yr; and 3) allocated patients in the postoperative period.

One of the investigators (G.A.) examined all titles and abstracts obtained in these searches to determine eligibility of the randomized trial in this review. References of retrieved articles were also identified and examined to find additional studies. All randomized controlled trials identified were critically appraised.

Data extraction and synthesis

Once identified, the abstracted data included the proportion of patients receiving at least one unit of allogeneic packed RBCs as a primary outcome. We also gathered data on the mean number of RBC units transfused,[9] the number of patients receiving autologous predonation, the quantity of red cells transfused in millilitres as well as clinical outcomes including complication from surgery and mortality rates. Information related to cell salvage technique included the model of the cell saver, the type of blood collection (washed *vs* unwashed) and the length of time of cell saver use. Other pertinent information related to the study itself included baseline demographics, exclusion criteria, as well as the number of study participants enrolled in the trial. Finally, we assessed indicators of the quality of the studies, specifically blinding, method of randomization and the completeness of follow-up once randomized.

The effect of cell salvage on the proportion of patients who received allogeneic blood was summarized with an overall estimate of the relative risk (RR) and 95% confidence intervals (CI) by using a Mantel and Haenszel's fixed-effects model.[10] In this report, a RR with 95% CI incorporating 1.0 suggests that there is no difference between groups or insufficient data to conclude that cell salvage decreased overall exposure to red cells. A RR with a point estimate and 95% CI less than 1.0 suggests that fewer patients in the cell salvage group received at least one unit of allogeneic red cells while a RR greater than 1.0 suggests that more patients in the cell salvage group received at least one red cell transfusion.

TABLE I Characteristics of the randomized controlled trials included in analysis

Authors	*Year*	*Surgery type*	*No. of patients*	*Type of CS*
Clagett *et al.* (1)*	1999	Elective infra renal AAA	50	Hemonetics
Spark *et al.*	1997	Elective infra renal AAA	50	COBE
Kelley-Patteson *et al.*	1993	Elective AFB	36	Hemonetics
Clagett *et al.* (2)*	1999	Elective AFB	50	Hemonetics
TOTAL			186	

AAA = abdominal aortic aneurysm; AFB = aorto-bi-femoral bypass; CS = cell saver. All cell saver units were washed. *The Clagett group studied both AAA and AFB concurrently.

TABLE II Surgical and anesthesia times during elective infra renal AAA

Study	*Cross clamp time (minutes)*		*Anesthesia time (minutes)*	
	Cell salvage	*Control*	*Cell salvage*	*Control*
Clagett*	75 ± 27	80 ± 37	324 ± 60	342 ± 96
Spark**	40(35–60)	43(27–55)	150(120–240)	144(135–225)

AAA = abdominal aortic aneurysm; Clagett * results presented as mean ± standard deviation; Spark** results presented as mean (range).

Results

The electronic literature searches done in this study yielded 120 citations from the MEDLINE database and 117 citations from the EMBASE database. Five randomized controlled trials compared cell salvage to control in abdominal vascular surgical procedures.[8,11–14] Two additional trials were excluded because allocation did not make use of randomization but rather alternately assigned patients to either cell salvage or no cell salvage.[11,14] The three remaining trials, made use of sealed opaque envelopes as a means of concealment of randomization.[8,12,13] None of these studies made use of blinding. It would have been technically difficult if not impossible to mask cell salvage from the anesthesiologist and surgeon. Of these three randomized trials, one involved both elective infra renal abdominal aortic aneurysm surgery and aorto-femoral bypass surgery, the second was only elective infra renal abdominal aortic aneurysm surgery and the third was only aorto-femoral bypass surgery (Table I).

The combined or pooled risk ratio for a decreased exposure to red cells with cell salvage in infra renal aortic aneurysm repair and aorto-femoral bypass was 0.67 (95% CI from 0.35 to 1.28). Only two of the four randomized controlled trials involving elective infra renal aortic abdominal aneurysm repair met the inclusion criteria. The study from Thompson and colleagues[14] could not be evaluated since it did not report the proportion of patients who were transfused red cells. In addition, details regarding the surgical procedures and the use of cell salvage were not reported. Similarly, Varga *et al.*[11] did not report the proportion of patients transfused. The two remaining studies met all inclusion criteria.[8,13] Clagett and colleagues[8] demonstrated that cell salvage did not reduce the proportion of patients exposed to allogeneic blood (RR = 0.89, 95% CI from 0.63 to 1.27). Results reported by Spark and colleagues[13] were in the opposite direction. The investigators observed a significant decrease in exposure to red cells favouring cell salvage (RR = 0.14, 95% CI from 0.05 to 0.39). The combined risk ratio for cell salvage in infra renal abdominal aortic aneurysm surgery was 0.37 (95% CI from 0.06 to 2.36). There were insufficient data extracted from the two publications to compare differences between mean units transfused.

We identified two randomized controlled trials in patients undergoing elective aorto-femoral bypass surgery.[8,12] Neither study demonstrated a clinically important decrease in the number of patients exposed to red cells following the use of cell salvage. The Clagett study reported a RR of 0.94 (95% CI from 0.63 to 1.40) and the Kelley-Patteson study reported a RR of 1.50 (95% CI from 0.28 to 7.93). The pooled RR was 0.97 (95% CI from 0.66 to 1.42). There were insufficient data from both studies to compare and analyze the differences between mean units transfused.

Discussion

In this meta-analysis of randomized controlled trials, we were unable to demonstrate that cell salvage decreased exposure to allogeneic red cell cells. Our

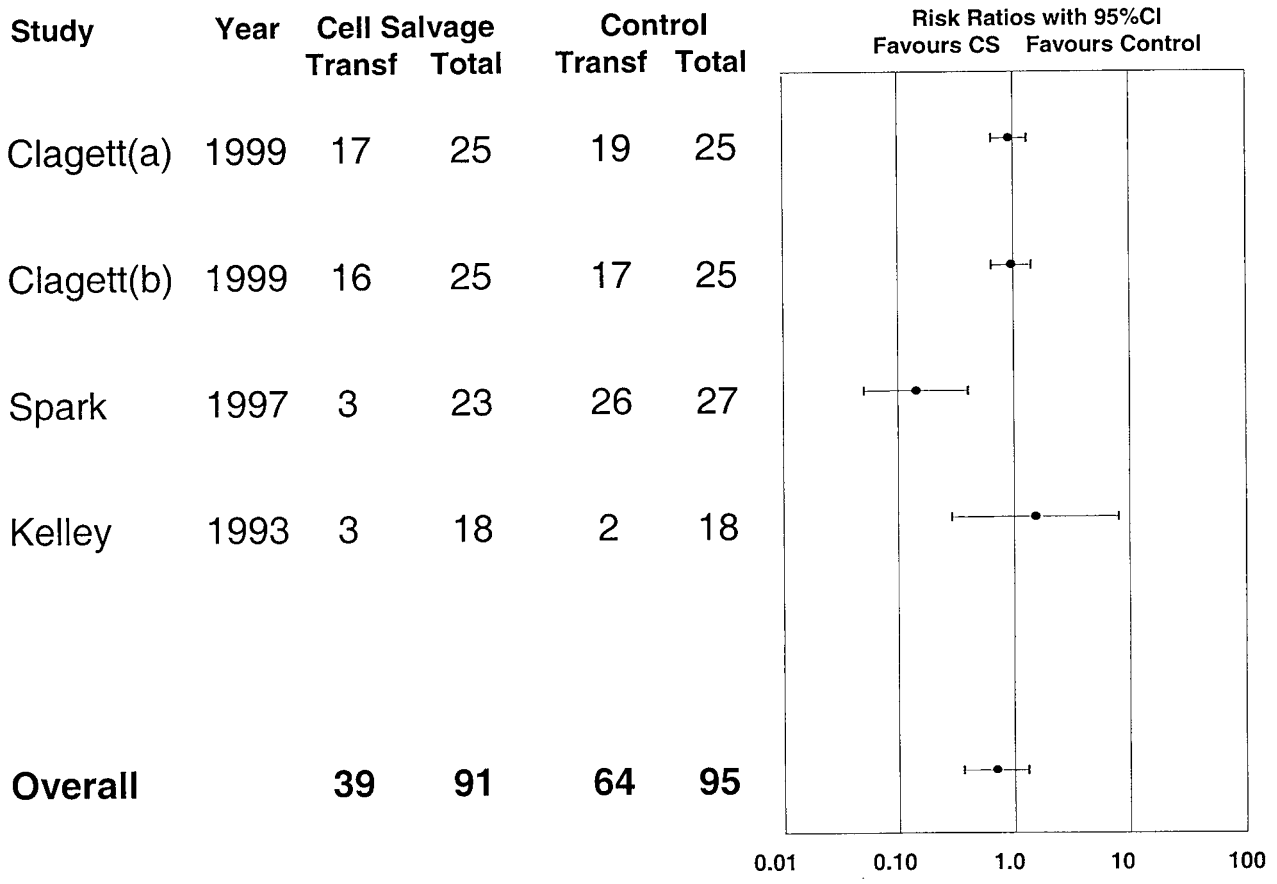

FIGURE 1 Overall risk of transfusion in 186 patients
This figure illustrates that the overall risk of transfusion in the 186 patients from four published clinical trials. The pooled odds ratio was 0.67 with 95% confidence interval of 0.35 to 1.28.

inability to detect a clinically important benefit may be because the technique is truly ineffective or as a consequence of the few patients in small studies included in this review. The few small trials generated a combined RR of 0.35 with large 95% confidence boundaries ranging from 0.35 to 1.28. Similarly, there were too few data to determine whether cell salvage decreased the mean number of RBC units transfused during abdominal aortic surgical procedures.

In the subgroup of patients who underwent infra renal abdominal aortic aneurysm surgery, the pooled RR for cell salvage was 0.37 with 95% CI ranging from 0.06 to 2.36. In this instance, the very large CIs were primarily a function of divergent study results. In addition to the limited information available for review, there were a number of clinical and methodological differences between the trials. These differences may also offer plausible explanations for our inability to observe benefits from this blood conservation technique. Key differences between studies included referral patterns that may have caused differences in surgical complexity and severity of illness, surgical technique, cell salvage techniques, the type and frequency of complications, approach to randomization as well as other factors.

In the Clagett study, the greater use of re-transfused salvaged red cells was associated with an increased use of allogeneic blood required to maintain comparable hemoglobin concentrations. In an accompanying editorial, Ouriel noted that despite two additional red cell units recovered from the cell salvage procedure, postoperative hematocrit levels were com-

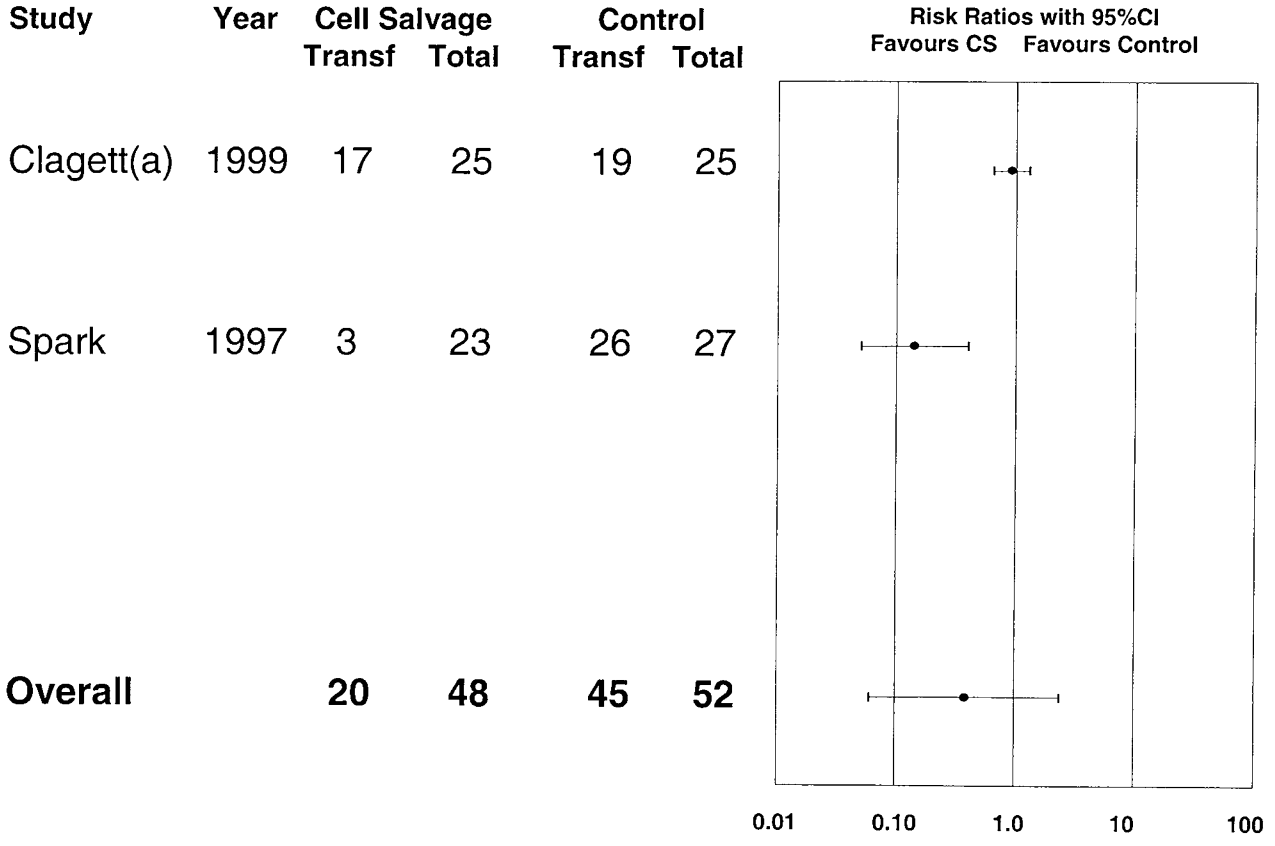

FIGURE 2 Risk of transfusion in infra renal abdominal aortic aneurysm
This graph illustrates the risk of transfusion for the two published trials involving a total of 100 patients. The pooled risk ratio was 0.37 with 95% confidence interval of 0.06 to 1.48.

parable between groups immediately following surgery.[8] One would have expected a measurable increase in red cell mass given that patients received extra salvaged red cells. A plausible explanation for the inability to detect a rise in postoperative hemoglobin concentrations elaborated in the editorial was excess hemolysis of salvaged red cells in study participants. Unfortunately, markers of hemolysis were not measured by Clagett and colleagues. Other potential explanations may include differences in fluid administration resulting in dilutional anemia in the postoperative period.

Hemolysis from cell salvage procedures may occur because of suction pressures in the collection of shed red cells that increase shear stress in the plastic tubing and filters in the device, as well as the centrifugation process.[15] In their trial Spark and colleagues standardized the suction pressures not to exceed 150 mmHg and filter sizes used during surgery. As a consequence, they did not observe significant differences in biochemical and morphological markers of hemolysis. Differences in the type of device may also have caused different rates of clinically important hemolysis observed in the two trials.

The marked difference in reported cross clamp time and the length of time required for the operative intervention may indicate differences in the selection of study participants or surgical techniques. Indeed, reported results from the Clagett trial averaged almost twice the amount of time patients were anesthetized, doubled the length of time of cross clamp and operation time when compared to Spark *et al.* (Table II). The longer cross-clamp times[16] or the re-infusion of hemolyzed red cells may have resulted in an increased rate of complications such as nosocomial infections, lengths of stay and perioperative mortality.

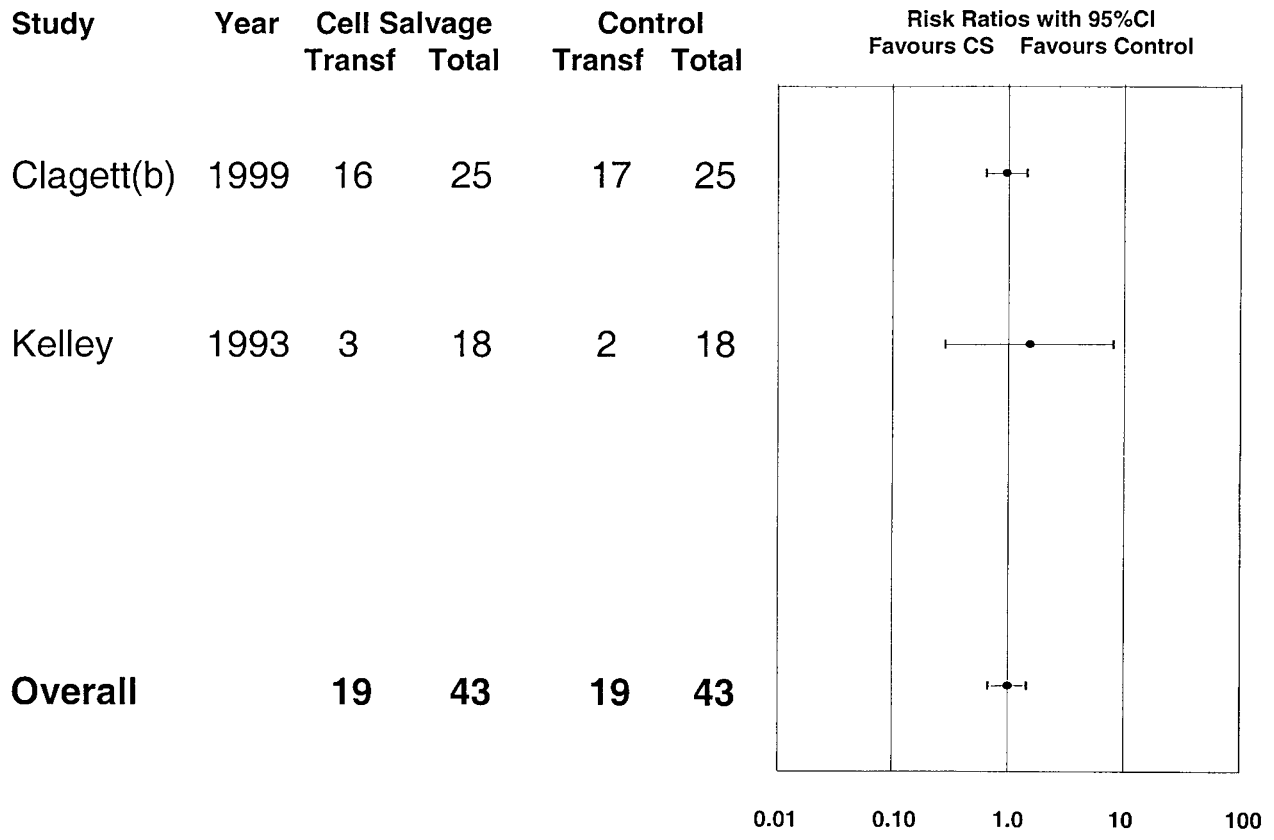

FIGURE 3 Risk of transfusion in aorto-bifemoral bypass
This graph illustrates the risk of transfusion in the 86 patients from two trials. The risk ratio was 0.97 with 95% confidence interval of 0.66 to 1.42.

Unfortunately, both studies were not large enough to detect changes in most clinically important outcomes.

Although both major trials used random allocation, the cell salvage group may well have been healthier than the control group in the study reported by Clagett. The control group had almost twice as many patients with chronic obstructive pulmonary disease (14% *vs* 26%) and three times as many patients with chronic renal failure patients (8% *vs* 22%). Both major co-morbidities may have increased the rates of transfusion in the control group thereby potentially resulting in a bias favouring cell salvage. Indeed there were twice as many "unusual bleeding" episodes in the control group as compared to the cell salvage group (46% *vs* 20%). These results are consistent with sicker patients being enrolled in the control group.

The randomized trials also included patients undergoing aorto-femoral bypass surgery.[8,12] This surgical intervention requires significantly less RBC transfusions as compared to aortic aneurysm surgery. Both major studies[8,12] evaluating cell salvage during aorto-femoral bypass were not able to document any savings in allogeneic RBC use with this technique. Inferences from these studies and the resultant meta-analysis are weak given the small sample size of both individual studies and the pooled results. The use of cell salvage for surgical procedures with low blood loss such as aorto-femoral bypass will likely not reduce or eliminate exposure to allogeneic RBCs.

Although only three randomized controlled trials met inclusion criteria, each study adequately described the study population, the cell salvage techniques and their complications, the transfusion protocols as well as important surgical and anesthetic benchmarks. In addition, the reports adequately described the use of standard concealment of randomization technique,

reported on all major objective outcomes and major co-interventions. The reporting of outcomes and co-interventions is all the more important in studies where blinding is not possible.

In conclusion, the results of this meta-analysis did not find sufficient evidence that cell salvage decreases exposure to allogeneic red cells in abdominal vascular surgeries. Unfortunately, there are too few studies involving too few patients to draw inferences regarding the benefit of therapy. Indeed, the fact that three randomized controlled trials documented divergent outcomes underscores the need for further research. In addition, we identified even fewer data examining the consequences of this blood sparing technique on clinically important outcomes such as infections, organ failure and mortality. Given the substantial cost associated with this technique, we believe that it is all the more important to conduct a large randomized controlled trial in this patient population.

References

1 *Carson JL, Russell LB, Taragin MI, Sonnenberg FA, Duff AE, Bauer S.* The risks of blood transfusion: the relative influence of acquired immunodeficiency syndrome and non-A, non-B hepatitis. Am J Med 1992; 92: 45–52.

2 *Coffin CM.* Current issues in transfusion therapy. 1. Risks of infection. Postgrad Med 1986; 80: 219–24.

3 *Crosby ET.* Perioperative haemotherapy: II. Risks and complications of blood transfusion. Can J Anaesth 1992; 39: 822–37.

4 *Faust RJ, Warner MA.* Transfusion risks. Int Anesthesiol Clin 1990; 28: 184–9.

5 *Warner MA, Faust RJ.* Risks of transfusion. Anesthesiol Clin North America 1990; 8: 501–17.

6 *Regan FA, Hewitt P, Barbara JA, Contreras M.* Prospective investigation of transfusion transmitted infection in recipients of over 20 000 units of blood. TTI Study Group. BMJ 2000; 320: 403–6.

7 *Huet C, Salmi LR, Fergusson D, et al.* A meta-analysis of the effectiveness of cell salvage to minimize perioperative allogeneic blood transfusion in cardiac and orthopedic surgery. International Study of Perioperative Transfusion (ISPOT) Investigators. Anesth Analg 1999; 89: 861–9.

8 *Clagett GP, Valentine RJ, Jackson MR, Mathison C, Kakish HB, Bengtson TD.* A randomized trial of intraoperative autotransfusion during aortic surgery. J Vasc Surg 1999; 29: 22–31.

9 *Lemmer JH Jr.* Reporting the results of blood conservation studies: the need for uniform and comprehensive methods. Ann Thorac Surg 1994; 58: 1305–6.

10 *Normand SL.* Meta-analysis: formulating, evaluating, combining, and reporting. Stat Med 1999; 18: 321–59.

11 *Varga ZA, Thompson JF, Locke-Edmunds JC, Baird RN, Farndon JR.* Clinical and experimental studies of intraoperative autotransfusion using a new filtration device. Br J Surg 1995; 82: 765–9.

12 *Kelley-Patteson C, Ammar AD, Kelley H.* Should the cell saver autotransfusion device be used routinely in all infrarenal abdominal aortic bypass operations? J Vasc Surg 1993; 18: 261–5.

13 *Spark JI, Chetter IC, Kester RC, Scott DJ.* Allogeneic versus autologous blood during abdominal aortic aneurysm surgery. Eur J Vasc Endovasc Surg 1997; 14: 482–6.

14 *Thompson JF, Webster JH, Chant AD.* Prospective randomised evaluation of a new cell saving device in elective aortic reconstruction. Eur J Vasc Surg 1990; 4: 507–12.

15 *Adan A, Brutel de la Riviere A, Haas F, van Zalk A, de Nooij E.* Autotransfusion of drained mediastinal blood after cardiac surgery: a reappraisal. Thorac Cardiovasc Surg 1988; 36: 10–4.

16 *Gelman S.* The pathophysiology of aortic cross-clamping and unclamping. Anesthesiology 1995; 82: 1026–57.