Erythropoietin therapy and preoperative autologous blood donation in children undergoing open heart surgery

V. Sonzogni[1], G. Crupi[2], R. Poma[3], F. Annechino[2], F. Ferri[1], P. Filisetti[1] and P. Bellavita[3]*

[1]*Department of Anesthesiology, Ospedali Riuniti di Bergamo, Bergamo, Italy.* [2]*Department of Cardiac Surgery Ospedali Riuniti di Bergamo, Bergamo, Italy.* [3]*Blood Transfusion Service, Ospedali Riuniti di Bergamo, Bergamo, Italy*

Corresponding author: Blood Transfusion Service, Ospedali Riuniti di Bergamo, Largo Barozzi n.1, I-24100 Bergamo, Italy

We assessed the feasibility and efficacy of subcutaneous erythropoietin alpha (EPO) therapy and preoperative autologous blood donation (ABD) in children undergoing open heart surgery. Thirty-nine children were treated consecutively with EPO (100 U kg^{-1} s.c. three times a week in the 3 weeks preceding the operation and i.v. on the day of surgery) and two ABDs were made (Group 1). As controls to compare transfusion requirements, 39 consecutive age-matched patients who had undergone open heart surgery during the two preceding years were selected (Group 2). In a mean time of 20 (SD 5) days, 96% of scheduled ABDs were performed and only three mild vasovagal reactions were observed. The mean volume of autologous red blood cells (RBC) collected was 6 (1) ml kg^{-1} and the mean volume of autologous RBC produced as a result of EPO therapy before surgery was 7 (3) ml kg^{-1}, corresponding to a 28 (11)% increase in circulating RBC volume. The mean volume of autologous RBC collected was not different from that produced [6 (1) *vs* 7 (3) ml kg^{-1}, *P*=0.4]. Allogenic blood was administered to three out of 39 children in Group 1 (7.7%) and to 24 out of 39 (61.5%) in Group 2. Treatment with subcutaneous EPO increases the amount of autologous blood that can be collected and minimizes allogenic blood exposure in children undergoing open heart surgery.

Concerns raised by the risks that are associated with receiving allogenic blood transfusion have made preoperative autologous blood donation (ABD) a useful adjunct in elective surgery.[1 2] It reduces the risks of exposure to allogenic blood and is accepted by most physicians as the safest blood component.

Great efforts have been made in recent years to develop blood-saving techniques so that open heart surgery can be performed without allogenic blood transfusion.[3] This goal is more difficult to achieve in children. They often have iron deficiency anaemia, which is made worse by repeated blood sampling. Moreover, their blood is diluted to a greater extent than in adults by extracorporeal circulation. Blood transfusion is therefore more frequent in children during cardiac surgery.[4] Storage of autologous blood before surgery would help to reduce exposure to allogenic blood in children.

The use of recombinant human erythropoietin alpha (EPO), the primary growth factor for red blood cells, is safe and effective in the treatment of anaemia associated with chronic renal failure, human immunodeficiency virus infection and cancer.[5] Knowledge of the scientific and physiological basis of EPO[6 7] has supported its use in patients undergoing elective surgery. As a result, EPO therapy has been approved in the USA, Japan, Europe and Canada for use in patients donating autologous blood before surgery.[8]

At our institution, the blood conservation programme for children undergoing open heart surgery is based on the use of intraoperative tranexamic acid, intraoperative and post-operative transfusion of shed mediastinal blood and the use of prudent transfusion guidelines.[9–11] More recently, treatment with preoperative subcutaneous EPO to facilitate ABD has been adopted. This study was performed to assess the

Table 1 Characteristics of children treated with EPO and ABD before operation (Group 1) and controls (Group 2). Where applicable, data are shown as mean (standard deviation) (range). AVC=atrioventricular canal, VSD=ventricular septal defect, ASD=atrial septal defect

	Group 1	Group 2	P
Male/female (*n*)	26/13	20/19	0.25
Diagnosis (*n*)	1 AVC/3 VSD/35 ASD	5 VSD/34 ASD	
Age (yr)	6.3 (3.1) (2–14)	6.6 (3.3) (2–14)	0.68
Body weight (kg)	22.2 (8.9) (12–40)	23.6 (11) (12–53)	0.54
Total blood volume (ml)	1551 (621) (900–3000)	1652 (760) (840–3710)	0.52
Cardiopulmonary bypass time (min)	40 (36) (14–176)	31 (15) (17–84)	0.15
Aortic cross-clamp time (min)	22 (21) (5–108)	17 (9) (7–54)	0.18

feasibility and efficacy of such treatment and its effect on allogenic blood transfusion in children undergoing open heart surgery.

Material and methods

Between January 1997 and June 1999, 39 consecutive paediatric patients were managed with EPO and ABD (Group 1). Inclusion criteria were: elective open heart surgery for atrial and/or ventricular septal heart defect; a pretreatment haemoglobin concentration between 10 and 14 g dl^{-1}; good haemodynamic status (NYHA class I or II); no concomitant infections or haematological disease; and suitable venous access. This study was approved by the ethics committee of our hospital and written informed consent was obtained from the parents.

Group 1 children received EPO (Eprex, Janssen-Cilag, High Wycombe, UK) 100 U kg^{-1} s.c. three times a week during the 3 weeks preceding the operation and 100 U kg^{-1} i.v. on the day of surgery, to a total dose of 1000 U kg^{-1}. Oral iron sulphate supplementation was given (60 mg day^{-1}) during the 3 weeks preceding the operation and during the entire hospital stay. Blood for the first and second ABDs was collected 3 and 2 weeks preoperatively respectively, provided that the haematocrit exceeded 33%.

Phlebotomies were performed by the anaesthetist on an outpatient basis. The patients underwent cardiac monitoring (pulse oximetry, blood pressure, ECG) during the procedure. An 18-gauge needle was inserted in the antecubital vein of the arm and connected to the collection bag by a three-way tap to allow infusion of small boluses of saline to prevent needle occlusion. At each phlebotomy, blood (9 ml kg^{-1}) was drawn and saline was then infused for volume replacement. The blood was collected in a single 450 ml bag containing 14 ml anticoagulant solution per 100 ml of whole blood (CPDA-1) and stored by the blood transfusion service. The maximum length of storage was 35 days.

As a control for the transfusion requirement, 39 consecutive age-matched patients who had undergone open heart surgery for atrial and/or septal defect at our institution between July 1995 and December 1997 were selected (Group 2). During this 4-yr period, all the children were followed by the same surgical and anaesthetic team and underwent the same blood conservation programme.

For all the children, cardiopulmonary bypass (CPB) was performed using a membrane oxygenator with a prime volume of 700 ml for a body weight of less than 25 kg (Lilliput 2, Dideco D 902, Dideco, Mirandola, Italy) or 900 ml for a body weight more than 26 kg (Midiflo, Dideco D 705). Myocardial protection was performed with a cold, intermittent hyperkalaemic infusion. Tranexamic acid (10 mg kg^{-1}) was given before bypass followed by continuous infusion at 2 mg kg^{-1} h^{-1} to prevent fibrinolysis.

Our blood conservation protocol included the use of a cell-saving device (Compact A, Dideco). Depending on the patient's haematocrit, the blood remaining in the circuit was returned to the patient as whole blood, directly or after ultrafiltration, or as red blood cell (RBC) concentrate, after washing and concentration in the cell-saving system. Postoperative shed mediastinal reinfusion was performed if 300 ml autologous blood or more was present in the containers at 3 and 6 h.

The decision to give blood was based on each patient's clinical condition, with a haematocrit transfusion trigger of 18% during CPB and of 26% in the intensive care unit.

The following laboratory variables were measured: RBC count, haemoglobin concentration, haematocrit, white blood cell count and platelet count. In Group 1, blood samples were drawn before the beginning of EPO therapy; before the second ABD; immediately before surgery; after surgery; and on postoperative days 1 (POD1) and 7 (POD7). In Group 2, these variables were taken from clinical records, but only the preoperative values, the postoperative values and the values on POD1 were always available.

Despite erythropoietin treatment, RBC counts usually decreased during the period of ABD in Group 1. Preoperative autologous RBC production in these patients was therefore estimated from the total volume of RBC collected minus the change in circulating RBC between the first donation and the day of surgery.[12] (In the few patients in whom the RBC count increased during this period, the increase was added to the volume of RBC donated.) The volume of autologous RBC collected at each phlebotomy was determined by multiplying the peripheral venous haematocrit by the volume of blood drawn. Circulating RBC volume was determined by multiplying the patient's

Table 2 Details of preoperative autologous donation In children treated with EPO and ABD before operation (Group 1). Where applicable, data are shown as mean (standard deviation)

ABD variables	Group 1
Number scheduled/number performed	78/75
Collection time before surgery (days)	20 (5)
Whole blood collected (ml/patient)	366 (121)
Whole blood collected (ml kg^{-1})	17 (3)
RBC volume collected (ml kg^{-1})	6 (1)
RBC volume produced (ml kg^{-1})	7 (3)

Table 3 Perioperative blood conservation measures and RBC loss in children undergoing elective open heart surgery: children treated with EPO and ABD before operation (Group 1) and retrospective controls (Group 2). Where applicable, data are shown as mean (standard deviation)

	Group 1 (n=39)	Group 2 (n=39)	P
Number receiving blood remaining in CPB circuit	25	28	0.63
Intraoperative shed mediastinal blood reinfused	14	7	0.13
Total intraoperative blood salvaged (ml)	249 (49)	258 (170)	0.75
12 h chest tube drainage (ml)	157 (105)	253 (193)	0.008
Postoperative shed mediastinal reinfusion (n)	0	1	
Perioperative RBC loss (ml kg^{-1})	11.4 (7.2)	13 (8.6)	0.38

total blood volume by the body haematocrit. Total blood volume was determined by multiplying body weight in kilograms by 75 ml kg^{-1},[13] and was assumed not to change during the period of treatment. Body haematocrit was determined by multiplying the peripheral venous haematocrit by 0.91.[14]

The perioperative RBC loss was estimated from the difference in circulating RBC on the day of surgery and the first postoperative day, plus the RBCs transfused in the same period. A standard unit of allogenic packed RBC was considered to contain 200 ml of RBC[15] and the amount of allogenic RBC transfused was therefore determined by multiplying the number of allogenic RBC units transfused by 200.

Statistical analysis

Differences between the two groups were analysed by two-tailed Student's t-test for unpaired data. Intragroup analysis was performed by means of two-tailed Student's t-test for paired data, when indicated. Proportions were compared with the two-sided Fisher exact test or the χ^2 test, as indicated. Differences were considered to be significant if the P value was less than 0.05. All values are expressed as mean (standard deviation) unless specified otherwise.

Results

Patient characteristics are shown in Table 1. The two groups were similar with regard to physical characteristics, blood volume and surgical operating time (Table 1). Age was 6.3 (SD 3.1) (range 2–14) and 6.6 (3.3) (2–14) yr in Groups 1 and 2 respectively. In Group 1 subcutaneous EPO injections were well tolerated without adverse systemic or local reactions. Seventy-five per cent of the 78 scheduled ABD collections (96%) were performed over 20 (5) days. The second ABD was not performed in three patients because they were living a long way from the hospital (two cases) or because of inadequate venous access (one case). Donations were well tolerated, with the exception of three mild vasovagal reactions. Each procedure was performed in 1 h, between the arrival of the patient and discharge from the hospital.

Data on the collection and production of autologous RBC are shown in Table 2. The mean volume of whole blood

donated was 17 (3) ml kg^{-1}, which corresponds to 6 (1) ml kg^{-1} RBC volume. Mean preoperative autologous RBC production was 7 (3) ml kg^{-1}, an increase of 28 (11)% over the circulating RBC volume at baseline. The volume of RBC collected was not different from that produced [6 (1) vs 7 (3) ml kg^{-1}, P=0.4]. The mean volume of autologous units was 183 (60) (range 90–300) ml, corresponding to a mean RBC volume per autologous unit of 68 (25) (35–122) ml.

All children had an uncomplicated perioperative course and were extubated within 8 h after surgery. In one patient in Group 1, a second period of CPB was required for the repair of left atrioventricular valve stenosis. In one patient in Group 2, reopening was necessary 3 h after surgery because of mediastinal bleeding. No statistically significant differences were found between the two groups with regard to recovery of blood remaining in the CPB circuit, intraoperative shed mediastinal blood reinfusion or total intraoperative blood salvage (Table 3).

Mean perioperative RBC loss was similar in Group 1 and Group 2 (11.4 (7.2) and 13 (8.6) ml kg^{-1} respectively; P=0.38) (Table 3).

Chest tube drainage was significantly reduced during the first 12 h after surgery in Group 1 compared with Group 2 patients (7.8 (4.8) and 12 (8.7) ml kg^{-1} respectively; P=0.01). In one case in Group 2, chest tube drainage exceeded 100 ml for three consecutive hours and the blood was transfused (Table 3). There were no perioperative deaths and all children were discharged from hospital well. The length of hospital stay was 6.7 (0.8) and 6.4 (0.9) days in Group 1 and Group 2 respectively (P=0.12).

In Group 1, the pretreatment and preoperative haemoglobin concentrations were similar (Table 4). The haemoglobin concentration fell after surgery from 12.4 (1.4) to 10 (1.6) g dl^{-1}; it was 10.9 (1.4) g dl^{-1} after discharge from the intensive care unit on POD1 and it remained unchanged during the subsequent 7 days. The preoperative platelet count in Group 1 increased significantly during the treatment period, from 245 × 10^3 (61 × 10^3) to 326 × 10^3 (95 × 10^3) ml^{-1} preoperatively, decreased after surgery to 188 × 10^3 (52 × 10^3) ml^{-1} and returned to the pretreatment value within a week after the operation (Table 4).

Table 4 Haemoglobin concentration (Hb) and platelet count before and after open-heart surgery in children treated with EPO and ABD before operation (Group 1) and in controls (Group 2). Where applicable, data are shown as mean (standard deviation). *P=0.15 *vs* preoperative, intragroup; not significant. †P=0.22 *vs* POD7, intragroup; not significant. ‡P<0.001 *vs* preoperative, intragroup. §P=0.01 *vs* POD7, intragroup

	Group 1	Group 2	P
Pretreatment Hb (g dl^{-1})	12.2 (0.9)*		
Preoperative Hb (g dl^{-1})	12.4 (1.4)	12.7 (0.9)	P=0.26
CPB Hb (g dl^{-1})	7.2 (1.1)	7.7 (0.9)	P=0.03
Postoperative Hb (g dl^{-1})	10 (1.6)	10.8 (1.6)	P=0.03
Hb (g dl^{-1}) on POD1	10.9 (1.4)†	10.9 (1.5)	P=1.00
Hb (g dl^{-1}) on POD7	11.1 (1.5)		
Pretreatment platelets (10^3 ml^{-1})	245 (61)‡		
Preoperative platelets (10^3 ml^{-1})	326 (95)	264 (51)	P<0.0001
Postoperative platelets (10^3 ml^{-1})	188 (52)	172 (46)	P=0.15
Platelets (10^3 ml^{-1}) on POD1	212 (57)§	193 (43)	P=0.10
Platelets (10^3 ml^{-1}) on POD7	231 (62)		

In Group 2, the preoperative haemoglobin concentration was similar to that observed in Group 1 (Table 4). The haemoglobin concentrations in Group 2 were higher during CPB and postoperatively than those in Group 1 (P=0.03), while the concentrations on POD1 were similar (Table 4). The preoperative platelet count was significantly lower in Group 2 than in Group 1 and the postoperative and POD1 platelet counts were slightly reduced, although not significantly (Table 4).

Children in Group 1 received all the ABD collected during the operative or the postoperative period. Three of the 39 children (7.7%) required allogenic blood during surgery: one patient required 1 unit, a second patient required 2 units and the third patient 3 units. Only one of these children needed fresh frozen plasma and none of them needed platelet transfusion.

A total of 33 units of allogenic packed RBC was administered to 24 out of 39 (61.5%) children in Group 2 during the operative or postoperative period. Eighteen of the 24 patients (75%) required 1 unit of packed RBC, four patients required 2 units and two patients required 3 and 4 units respectively. In addition, four of these children needed fresh frozen plasma but no patient needed platelet transfusion. In the control group, allogenic blood transfusion was needed during CPB in 13 out of 39 children (33%).

Discussion

Although allogenic blood is safer than ever, the reasons for avoiding blood transfusion remain valid, including the preservation of a limited resource.[16] During open heart surgery, allogenic blood transfusion is frequently required. Consequently, great efforts have been made in recent years to develop blood-saving techniques and treatments to allow open heart surgery to be performed without blood transfusion.[3] However, it is more difficult to avoid allogenic blood transfusion in children undergoing open heart surgery, particularly because their blood is diluted to a great extent during CPB.[4] Although allogenic blood transfusion in children undergoing open heart surgery has declined dramatically over the last three decades, the number of patients still exposed to it remains high.[4 17–19] In the present study, one in every three transfused patients in the control group needed allogenic blood during CPB because of blood dilution. Most of these patients needed 1 standard unit of allogenic packed RBC. Because 1 standard unit of packed RBC contains 200 ml of RBC, this strongly suggests that most of these children could have avoided transfusion of allogenic blood if they had donated at least 2 units of autologous blood.

This study assessed the feasibility and safety of preoperative EPO and ABD, its effectiveness in augmenting autologous RBC count and its effect on allogenic blood transfusion in children undergoing open heart surgery. Complications of blood donation, including syncope, has been described in 2–5% of healthy blood donors.[20] Although the consequences of such events could have been more serious in patients with cardiovascular disease, the risk of autologous blood donation is probably overestimated. In a report of autologous donation in patients awaiting heart transplantation, the haemodynamic effects of ABD were not different from those observed in a control population without cardiac disease.[21] Available data indicate that ABD is safe and feasible and can be used for children of a wide range of age and weight and in a variety of surgical procedures.[22–25] Although venous access may be more difficult preoperatively, the benefits of avoiding allogenic blood transfusion are greater in children because of their longer life expectancy, as the possible consequences of blood-borne infections are more serious and long-lasting in younger patients.

In the present study, donations were well tolerated, with only a low incidence of vasovagal reactions (4%). In addition, 96% of the scheduled collections were performed and none cancelled because of refusal by the children or their parents.

The safety of EPO therapy in patients undergoing elective surgery has been demonstrated in more than 1000 patients in placebo-controlled trials.[8] Thrombotic events described in patients with chronic renal failure have not been seen with EPO therapy in the surgical setting.[26] In our series we did not observe any side-effects of EPO therapy, such as thrombotic events or hypertensive attacks, which is in accordance with the data available in the literature.[8] On the other hand, we observed a significant (30%) increase in platelet count from baseline during treatment in children in Group 1 (Table 4). As a result, the preoperative platelet count was significantly higher in children treated with EPO and remained higher after surgery, without the difference reaching significance compared with controls.

The effect of EPO on platelet count remains controversial. In a recent review, Beguin[27] suggested that moderate stimulation by EPO causes a moderate elevation of the platelet count, whereas intense EPO stimulation causes some degree of thrombocytopenia, probably as a result of

inhibition of platelet production. The two groups of patients reported in this study were not randomized, so our observations should be taken with caution. However, if confirmed in a randomized study, our results could be of some value. In fact, a report on haemostasis in children undergoing open heart surgery found a significant inverse association between platelet count and blood loss.[17] In our experience, the perioperative blood loss was not different in the two groups, and the chest drainage after operation in patients treated with EPO was 35% less than in the control group. Though not randomized, the two groups were similar with regard to physical and operative characteristics, were followed by the same surgical and anaesthetic team and underwent the same blood conservation programme. It is tempting to speculate that the higher preoperative platelet count might be considered beneficial rather then a harmful collateral effect of EPO administration, favouring haemostasis in the immediate postoperative period.

It has been suggested that the most effective way to minimize the use of allogenic blood is the combination of preoperative EPO therapy with the procurement of autologous blood by acute normovolemic haemodilution or donation.[8] Several studies have addressed the use of EPO to facilitate ABD[28 29] and, though it is expensive, general agreement exists on its utility in anaemic autologous donors.[30] Few data have been published on the use of EPO, either alone or associated with ABD, in adult cardiac surgery. Nonetheless, EPO seems to be adequate therapy for increasing mean haemoglobin concentrations by approximately 1 g dl^{-1} per week of treatment, and is effective in allowing ABD collection and reducing exposure to allogenic blood.[31–35] Even fewer data are available on the use of EPO in paediatric cardiac surgery[4 36] and, to our knowledge, no data exist on EPO therapy associated with ABD in children.

Our protocol of s.c. administration of EPO at a total dose of 1000 U kg^{-1} during the 3 weeks preceding operation allowed the collection of 6 (1) ml kg^{-1} of autologous RBC without reduction in the haemoglobin concentration and with a net production of new autologous RBC corresponding to nearly 30% of the circulating RBC volume at baseline. This net gain in autologous RBC allowed a reduction in allogenic RBC transfusion compared with controls. The amount of autologous blood collected was generally adequate, because almost 92% of children treated with EPO and ABD received no allogenic blood.

Though effective, this treatment is expensive.[37 38] In our experience, the approximate cost of 1000 units of erythropoietin corresponds to about 10 US dollars and that of one ABD unit to about 70 US dollars. For a child weighing 20 kg, the cost of the treatment (20 000 EPO units plus 2 ABD units, manpower and indirect costs excluded) would be almost 340 US dollars. The adoption of weekly regimens with lower doses of EPO will reduce the cost.[8] Nonetheless, this treatment should be reserved for carefully considered circumstances in which the cost is offset by well-defined clinical benefits. We think that this regimen is apposite for young patients undergoing open heart surgery, in whom mild preoperative anaemia is frequent, life expectancy is long and a substantial blood requirement is expected, mainly related to haemodilution during CPB.

References

1 Consensus conference. Perioperative red blood cell transfusion. *J Am Med Assoc* 1988; **260**: 2700–3

2 Goodnough LT, Vizmeg K, Verbrugge D. The impact of autologous blood ordering and blood procurement practices on allogenic blood exposure in elective orthopedic surgery patients. *Am J Clin Pathol* 1994; **101**: 354–7

3 Cooley DA. Conservation of blood during cardiovascular surgery. *Am J Surg* 1995; **170**: 53–9

4 Shimpo H, Mitzumoto T, Onoda K, *et al.* Erythropoietin in pediatric cardiac surgery. Clinical efficacy and effective dose. *Chest* 1997; **111**: 1565–70

5 Goodnough LT, Anderson KC, Kurtz S, *et al.* Indications and guidelines for the use of hematopoietic growth factors. *Transfusion* 1993; **33**: 944–59

6 Krantz SB. Erythropoietin. *Blood* 1991; **77**: 419–34

7 Adamson JW, Spivak JL. Physiologic basis for the pharmacologic use of recombinant human erythropoietin in surgery and cancer treatment. *Surgery* 1994; **115**: 7–15

8 Goodnough LT, Monk TG, Andriole GL. Current concepts: erythropoietin therapy. *N Engl J Med* 1997; **336**: 933–8

9 Welch HG, Meehan KR, Goodnough LT. Prudent strategies for elective red blood cell transfusion. *Ann Intern Med* 1992; **116**: 393–402

10 Robertie PG, Gravlee GP. Safe limits of isovolemic hemodilution and recommendations for erythrocyte transfusion. *Int Anaesthesiol Clin* 1990; **28**: 197–204

11 Goodnough LT, Despotis GJ, Hogue CH, Ferguson TB. On the need for improved transfusion indicators in cardiac surgery. *Ann Thorac Surg* 1995; **60**: 473–80

12 Goodnough LT, Price TH, Rudnick S, Soegiarso RW. Preoperative red cell production in patients undergoing aggressive autologous blood phlebotomy with and without erythropoietin therapy. *Transfusion* 1992; **32**: 441–5

13 Russell SJM. Blood volume studies in healthy children. *Arch Dis Child* 1949; **24**: 88–93.

14 Chaplin H Jr, Mollison PL, Vetter H. The body/venous haematocrit ratio: its constancy over a wide haematocrit range. *J Clin Invest* 1953; **32**: 1309–16

15 Goodnough LT, Brittenham GM. Limitations of the erythropoietic response to serial phlebotomy: implications for autologous blood donor programs. *J Lab Clin Med* 1990; **115**: 28–35

16 Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine. *N Engl J Med* 1999; **340**: 438–47

17 Williams GD, Bratton SL, Ramamoorthy C. Factors associated with blood loss and blood product transfusions: a multivariate analysis in children after open-heart surgery. *Anesth Analg* 1999; **89**: 57–64

18 Despotis GJ, Skubas NJ, Goodnough LT. Optimal management of bleeding and transfusion in patients undergoing cardiac surgery. *Semin Thorac Cardiovasc Surg* 1999; **11**: 84–104

19 Guay J, Rivard GE. Mediastinal bleeding after cardiopulmonary bypass in pediatric patients. *Ann Thorac Surg* 1996; **62**: 1955–60

20 McVay PA, Andrews A, Kaplan EB, *et al*. Donation reactions among autologous donors. *Transfusion* 1990; **30**: 249–52

21 Klapper E, Pepkowitz SH, Czer L, *et al*. Confirmation of the safety of autologous blood donation by patients awaiting heart or lung transplantation. *J Thorac Cardiovasc Surg* 1995; **110**: 1594–9

22 Tasaki T, Ohto H, Noguchi M, *et al*. Autologous blood donation in elective surgery in children. *Vox Sang* 1994; **66**: 188–193

23 Masuda M, Kawachi Y, Inaba S, *et al*: Preoperative autologous blood donations in pediatric cardiac surgery. *Ann Thorac Surg* 1995; **60**: 1694–7

24 Mayer MN, de Montalembert M, Audat F, *et al*. Autologous blood donation for elective surgery in children weighing 8–25 kg. *Vox Sang* 1996; **70**: 224–8

25 Fukahara K, Murakami A, Ueda T, *et al*. Scheduled autologous blood donation at the time of cardiac catheterization in infants and children. *J Thorac Cardiovasc Surg* 1997; **114**: 504–5

26 Goodnough LT, Price TH, Friedman KD, *et al*. A phase III trial of recombinant human erythropoietin therapy in nonanaemic orthopedic patients subjected to aggressive removal of blood for autologous use: dose, response, toxicity and efficacy. *Transfusion* 1994; **34**: 66–71

27 Beguin Y. Erythropoietin and platelet production. *Haematologica* 1999; **84**: 541–7

28 Goodnough LT, Rudnick S, Price TH, *et al*. Increased preoperative collection of autologous blood with recombinant human erythropoietin therapy. *N Engl J Med* 1989; **321**: 1163–8

29 Mercuriali F, Adamson J. Recombinant human erythropoietin enhances blood donation for autologous use and reduces exposure to homologous blood during elective surgery. *Semin Hematol* 1993; **30** (Suppl. 6): 17–21

30 Price TH, Goodnough LT, Vogler WR, *et al*. The effect of recombinant human erythropoietin on the efficacy of autologous blood donation in patients with low haematocrits: a multicenter, randomized, double-blind, controlled trial. *Transfusion* 1996; **36**: 29–36

31 Watanabe Y, Fuse K, Naruse Y, *et al*. Subcutaneous use of erythropoietin in heart surgery. *Ann Thorac Surg* 1992; **54**: 479–483

32 Schmoeckel M, Nollert C, Mempel M, *et al*. Effects of recombinant human erythropoietin on autologous blood donation before open heart surgery. *Thorac Cardiovasc Surg* 1993; **41**: 363–8

33 Sowade O, Warnke H, Scigalla P, *et al*. Avoidance of allogenic blood transfusions by treatment with epoetin beta (recombinant human erythropoietin) in patients undergoing open-heart surgery. *Blood* 1997; **89**: 411–8

34 Walpoth B, Galliker B, Spirig P, *et al*. Use of epoetin alfa in autologous blood donation programs for patients scheduled for elective cardiac surgery. *Semin Hematol* 1997; **33** (2 Suppl. 2): 75–6

35 Baron JF. Autologous blood donation with recombinant human erythropoietin in cardiac surgery: the Japanese experience. *Semin Hematol* 1997; **33** (2 Suppl. 2): 64–7

36 Shaddy RE, Bullock EA, Tani LY, *et al*. Epoetin alfa therapy in infants awaiting heart transplantation. *Arch Pediatr Adolesc Med* 1995; **149**: 322–5

37 Marchetti M, Barosi G. Cost-effectiveness of epoetin and autologous blood donation in reducing allogenic blood transfusion in coronary artery bypass graft surgery. *Transfusion* 2000; **40**: 673–81

38 Coyle D, Lee KM, Fergusson DA, *et al*. Cost effectiveness of epoetin-alpha to augment preoperative autologous blood donation in elective cardiac surgery. *Pharmacoeconomics* 2000; **18**: 161–71