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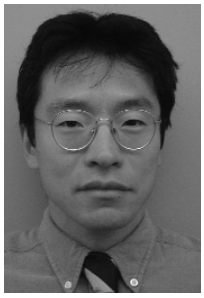
The Efficacy of Preoperative Administration of a Single Dose of Recombinant Human Erythropoietin in Pediatric Cardiac Surgery



Dr. Ootaki

Yoshio Ootaki, MD, PhD, Masahiro Yamaguchi, MD, PhD, Naoki Yoshimura, MD, PhD, Shigeteru Oka, MD, PhD, Masahiro Yoshida, MD, Tomomi Hasegawa, MD

Department of Cardiothoracic Surgery, Kobe Children's Hospital, Kobe, Hyogo, Japan

ABSTRACT

Background. Preoperative autologous blood donation with recombinant human erythropoietin (rHuEPO) is effective in adults. However, there are problems concerning the blood access, cost, and blood storage in children. The purpose of this study was to evaluate the efficacy of administering a single dose of rHuEPO without blood donation in children undergoing pediatric cardiac surgery.

Methods. Eighty-two children (72 with noncyanotic heart disease, and 10 with cyanotic heart disease) whose hematocrit values were less than 45% were included in this prospective, nonrandomized study. The children were divided into 3 groups: group E0 (n = 20) was not treated with rHuEPO and iron sulfate; group E2 (n = 27) was treated with 200 IU/kg of rHuEPO and 2 mg/kg of iron sulfate; and group E4 (n = 35) was treated with 400 IU/kg of rHuEPO and 4 mg/kg of iron sulfate. Administration of rHuEPO was performed subcutaneously 7 days before the operation. The hematological and iron parameters were measured perioperatively.

Results. A lower proportion of children treated with rHuEPO (group E2, 14.8%; group E4, 22.9%) than children without rHuEPO (group E0, 40.0%) were exposed to RBC transfusions; however, there was no significance. The elevations of the hematocrit levels were 0.7% in group E0, 1.3% in group E2, and 1.9% in group E4. The elevation of the hematocrit was greater in patients with anemia (hematocrit ≤37%).

Conclusions. Although the effectiveness for avoiding transfusion was not clear, the administration of a single dose of rHuEPO without autologous blood donations had an effect by increasing hematocrit levels.

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Correspondence: Yoshio Ootaki, MD, PhD, 1-1-1 Takakuradai, Suma-ku, Kobe, Hyogo, 654-0081, Japan; 81-78-732-6961; fax: 81-78-735-0910 (e-mail: y.ootaki@nifty.ne.jp).

INTRODUCTION

Anemia remains one of the main problems seen after cardiac surgery. For the treatment of anemia, whole blood and blood products are used. However, they can potentially cause a variety of complications, such as transfusion reactions, volume overload, infections [Kuehnert 2001], and increased hospital mortality [Michalopoulos 1999], and they have poor effects on long-term survival [Engoren 2002]. Because of these risks, clinicians and surgeons are strongly motivated to minimize or avoid allogeneic transfusion. Intraoperative blood salvage with a cell-saver system and postoperative autotransfusion of shed blood have been reported to be effective [Hardy 1996]. Pharmacological agents, such as aprotinin, are also useful to prevent fibrinolysis caused by cardiopulmonary bypass (CPB) [Bidstrup 1989]. Preoperative autologous blood donation with recombinant human erythropoietin (rHuEPO) is effective and has been established as a treatment for cardiac surgery in adults [Watanabe 1991; Kiyama 1999]. As life expectancy is long for children, the lifetime risk of overt infection, liver cirrhosis, or neoplasm caused by viral transmission due to transfusion is comparatively higher than in adults.

However, there are several restrictions in children because their blood volume is severely diluted during extracorporeal circulation, and it is not easy to collect sufficient amounts of autologous blood from these diseased children for storage [Masuda 1995; Fukahara 1997]. Furthermore, there are problems associated with the cost of rHuEPO therapy and blood storage [Strauss 1994; Coyle 2000]. Therefore, a simple and inexpensive blood-conserving technique is needed for children.

In this study, we sought to investigate the clinical efficacy of administering a single preoperative, subcutaneous dose of rHuEPO without autologous blood donations.

MATERIALS AND METHODS

Seventy-two children with noncyanotic heart disease and 10 children with cyanotic heart disease whose hematocrit values were less than 45% were included in this prospective, nonrandomized study. The study was approved by the local

Table 1. Patient Profile*

	Group E0 (n = 20)	Group E2 (n = 27)	Group E4 (n = 35)	*P*
Age, y	4.8 ± 3.3	6.9 ± 4.1	6.6 ± 3.8	.133
Sex, male/female	10/10	14/13	21/14	.718
Weight, kg	17.2 ± 12.0	22.8 ± 12.4	21.3 ± 11.5	.266
Previous operation	0/20 (0%)	3/27 (11%)	5/35 (14%)	.219
CPB time, min	146 ± 46	139 ± 51	132 ± 74	.728
Blood loss, mL				
6 h	71 ± 27	77 ± 40	78 ± 68	.931
24 h	172 ± 75	167 ± 81	183 ± 168	.918

*Data are expressed as mean ± standard deviation. CPB indicates cardiopulmonary bypass.

institutional review board, and all parents gave written informed consent. The patients were classified as cyanotic or noncyanotic based on the anatomy of the cardiac defect. All cyanotic patients had a history of cyanosis or cyanotic spells after the birth; however, the children with cyanotic heart disease included in this study had mild cyanosis on the day of admission to the hospital. The children were divided into 3 groups: group E0 (n = 20) was not treated with rHuEPO and iron sulfate; group E2 (n = 27) was treated with 200 IU/kg of rHuEPO (Kirin Brewery, Tokyo, Japan) and 2 mg/kg of iron sulfate; and group E4 (n = 35) was treated with 400 IU/kg of rHuEPO and 4 mg/kg of iron sulfate. Administration of rHuEPO was performed subcutaneously 7 days before the operation. Administration of iron sulfate was performed orally daily for 7 days prior to the operation.

Patients were placed on CPB with bicaval cannulations and a single aortic cannula. CPB was performed with a roller pump, and a hollow-fiber membrane oxygenator was used for gas exchange (Exceran HPO-20HC; Mera, Tokyo, Japan). The circuit was primed with 550 to 900 mL of crystalloid solutions depending on the patient's weight. The CPB was instituted at a flow rate of 2.4 to 2.6 L/min per m^2, and the perfusate was cooled to induce moderate hypothermia (30 to 32°C). Before CPB was initiated, 15 mL/kg of autologous blood was collected from the right atrial cannula and replaced with the same amount of hydroxyethylated starch. The autologous blood was returned to the patient after modified ultrafiltration (MUF). Myocardial preservation was achieved with intermittent cold blood cardioplegia using a crystalloid cardioplegic solution and oxygenated blood from the oxygenator. The blood cardioplegic solution was aspirated to the cardiotomy reservoir during CPB. Conventional ultrafiltration (CUF) and MUF were carried out using a polymethylmethacrylate hemofilter (Hemofeel-CH-0.3SL; Toray, Tokyo, Japan). CUF was begun during the rewarming phase of CPB with a rate adjusted to reach a cardiotomy reservoir level that approached 0 at the termination of CPB. MUF was performed as we previously reported [Ootaki 2002]. The heparinization was neutralized by protamine sulfate until the activated coagulation time had normalized. The residual blood in the CPB circuit was returned to the patient within the operative day. Postoperative drainage was collected in a water-sealed drainage system; however, the shed blood was not reinfused.

Criteria for red blood cell (RBC) transfusion included anemia with a hematocrit level less than 15% during CPB and 20% after CPB [Ootaki 2004]. We monitored mixed venous oxygen saturation during CPB and kept the value above 50%. In cases in which we had difficulty maintaining the mixed venous oxygen saturation above 50%, despite increasing the pump flow or oxygen concentration during CPB, we decided to transfuse the autologous blood or homologous blood. In cases of postoperative hemodynamic instability despite sufficient inotropic support, we decided to transfuse RBC even when the hematocrit level was above 20%. We did not transfuse platelets or fresh frozen plasma prior to RBC transfusion in this study.

The following laboratory parameters were assessed: hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), reticulocyte count, serum iron, ferritin, and total iron-binding capacity (TIBC). The transferring saturation (TS) was calculated as follows: TS (%) = (iron/TIBC) × 100. The hematological parameters were determined on the first day that iron sulfate was administered, just before the surgery, pre-CPB, every 20 minutes during CPB, before MUF, after MUF, just after the surgery, and 1, 2, 4, and 7 days after the surgery. The iron parameters were determined on the day of iron sulfate administration and just before surgery. In group E2 and group E4, the hematocrit values were further analyzed in patients with anemia (hematocrit ≤37%) and without anemia (hematocrit >37%).

All values were expressed as mean ± standard deviation (SD). A paired Student *t* test was used to assess the difference between data from before the administration of rHuEPO and immediately before the operation. A chi-square test for independence and 1-factor analysis of variance were used to assess the differences between the 3 groups. A 1-way repeated-measures analysis of variance was used to assess the differences in hematological and iron parameters. When the differences were determined by the 1-factor repeated-measures analysis of variance to be significant, the differences were further analyzed by the Fischer test. Differences were considered significant at $P < .05$.

RESULTS

All children experienced an uncomplicated intraoperative course, and no perioperative death occurred. There was no reoperation because of postoperative bleeding in this study. All children were discharged from the hospital in

Table 2. Hematological and Iron Parameters of Each Group before and after Administration*

	Group E0	Group E2	Group E4	*P*
Number	20	27	35	
Hematocrit, %				
Baseline	38.6 ± 4.6	38.6 ± 3.0	37.7 ± 2.5	.469
Preop	39.3 ± 4.1	39.9 ± 2.6†	39.6 ± 3.0†	.778
MCV, fL				
Baseline	81.5 ± 2.9	82.5 ± 3.9	80.6 ± 4.3	.184
Preop	82.5 ± 5.0	83.4 ± 4.0†	81.9 ± 4.3†	.447
MCH, pg				
Baseline	28.0 ± 1.3	28.1 ± 1.4	27.6 ± 1.6	.402
Preop	27.7 ± 2.1	28.1 ± 1.4	27.8 ± 1.7†	.612
Reticulocytes, %				
Baseline	15.5 ± 4.4	12.9 ± 6.8	13.4 ± 5.0	.709
Preop	16.2 ± 5.3	23.8 ± 12.3†	27.8 ± 8.5†‡	.028
Ferritin, ng/mL				
Baseline	29.8 ± 11.9	31.2 ± 18.7	34.6 ± 24.9	.807
Preop	32.7 ± 25.2	30.1 ± 16.1	36.3 ± 17.9	.428
TS, %				
Baseline	25.9 ± 5.1	26.5 ± 11.2	25.5 ± 13.0	.949
Preop	27.8 ± 21.2	33.6 ± 12.3†	30.2 ± 21.5	.695

*Data are expressed as mean ± standard deviation. Baseline indicates before administration; Preop, immediately before the operation; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; TS, transferring saturation.

†$P < .05$, Baseline versus Preop.

‡$P < .05$, group E0 versus group E4.

good condition. rHuEPO and iron sulfate caused no adverse reactions. The patients in group E0 tended to be younger in age and weigh less compared with the other groups; however, there were no differences between the 3 groups with regard to age, sex, weight, previous operation, CPB time, and blood loss (Table 1). A lower proportion of children treated with rHuEPO (group E2, 4/27, 14.8%; group E4, 8/35, 22.9%) than children without rHuEPO (group E0, 8/20, 40.0%) were exposed to allogeneic RBC transfusions; however, there was no significance. The total volume of the transfusions was higher in children without rHuEPO (group E0, 203 ± 285 mL) than in children with rHuEPO (group E2, 40 ± 113 mL, $P = .005$; group E4, 81 ± 173 mL, $P = .025$). The main factor for a homologous RBC transfusion was a hemodilution during CPB due to low body weights.

The changes in hematological and iron parameters in the 3 groups are summarized in Table 2. The hematocrit levels and reticulocyte counts significantly increased in group E2 and group E4. Although there was no significant difference in the hematocrit value between the 3 groups, group E4 (27.8 ± 8.5‰) had higher reticulocyte counts than group E0 (16.2 ± 5.3‰) immediately before the operation ($P = .011$). The ferritin and TS did not decrease after administration of rHuEPO. The hematocrit values in patients with anemia and without anemia are shown in Table 3. In group E4, the hematocrit values increased in both patients with anemia and without anemia, whereas the hematocrit values increased only in patients with anemia in group E2.

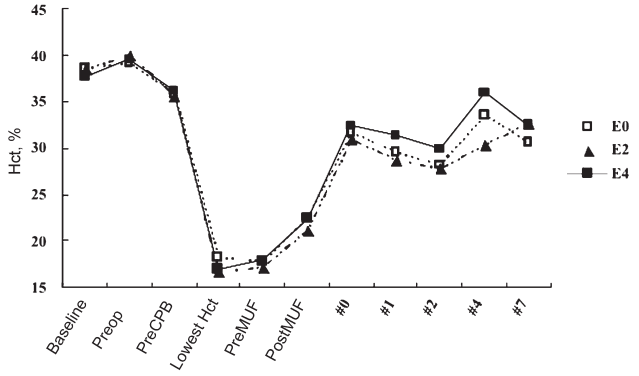
The perioperative changes in the hematocrit levels are shown in the Figure. The hematocrit levels were significantly

Table 3. Hematocrit Levels in Each Group with Anemia (Hematocrit ≤37%) and without Anemia (Hematocrit >37%)*

	Group E2		Group E4	
	Anemia (+)	Anemia (–)	Anemia (+)	Anemia (–)
Number	11	16	20	15
Hematocrit, %				
Baseline	36.1 ± 1.3	40.4 ± 2.5	35.7 ± 1.1	39.2 ± 2.3
Preop	38.5 ± 2.0†	40.9 ± 2.5	38.1 ± 3.1†	40.7 ± 2.4†

*Data are expressed as mean ± standard deviation. Baseline indicates before administration; Preop, immediately before the operation.

†$P < .01$, Baseline versus Preop.



Perioperative changes in hematocrit (Hct) levels. There was no significant change between the 3 groups. CPB indicates cardiopulmonary bypass; MUF, modified ultrafiltration.

increased during MUF. After the surgery, the hematocrit levels decreased in 2 days, and then increased. However, there was no significant change between the 3 groups.

DISCUSSION

Erythropoietin was isolated by Miyake in 1977 [Miyake 1977]. This hormone is a glycoprotein that is produced by the kidneys, and its concentration is increased by hypoxia. In 1985, Jacobs and associates [Jacobs 1985] produced rHuEPO by cloning the erythropoietin gene. The mass production of rHuEPO subsequently became possible using gene technology. At present, rHuEPO has become the main agent in treating anemia caused by reduced erythropoiesis, which is seen in chronic renal insufficiency and some hematological diseases. Recently, much interest has arisen regarding the use of rHuEPO preoperatively in cardiac surgery. Previous studies have demonstrated that autologous blood donation and administration of rHuEPO reduce the need for transfusion by increasing preoperative hemoglobin and enhancing postoperative erythropoietic recovery. In Japan, the donation of autologous blood with rHuEPO therapy has been approved, and it is usually performed in elective cardiac operations in adults. However, in the case of children with congenital heart disease, the donation of autologous blood before scheduled surgery is limited by the difficulties of the phlebotomy, blood storage, and the patient's low weight [Masuda 1995; Fukahara 1997]. Recent advances in pediatric cardiac surgery have helped to lower the age for the correction of cardiac anomalies. As a result, there is increasing interest in blood conservation to avoid the need for homologous blood transfusions. In this study, we evaluated the efficacy of administering a single dose of rHuEPO without autologous blood donation in patients undergoing pediatric cardiac surgery.

In our study, the administration of a single dose of subcutaneous rHuEPO was performed safely and had no adverse effect. The elevation of the hematocrit levels was 1.3% with 200 IU/kg rHuEPO and 1.9% with 400 IU/kg rHuEPO. These elevations were similar to the reports of Shimpo [1997] and D'Ambra [1997]. Shimpo and associates used 2 doses of 150 IU/kg rHuEPO and 300 IU/kg rHuEPO intravenously, and hemoglobin concentration increased 0.7 g/dL with 150 IU/kg rHuEPO and 0.9 g/dL with 300 IU/kg rHuEPO during the 7 days before surgery. D'Ambra and associates used 8 doses of 150 IU/kg rHuEPO and 300 IU/kg rHuEPO subcutaneously, and hematocrit levels increased 0.07% with 150 IU/kg rHuEPO and 0.90% with 300 IU/kg rHuEPO during the 5 days before the operation. Yazicioglu and associates [2001] also reported marked erythropoiesis with rHuEPO. They used a single dose of 100 IU/kg rHuEPO intravenously, and hemoglobin concentrations increased 2.4 g/dL during the 4 days before the surgery. However, they also reported that rHuEPO treatment in healthy patients who had hemoglobin levels of more than 13.5 g/dL experienced no significant changes. De Andrade and associates [1996] reported that pretreatment hemoglobin level is an important predictor of transfusion risk and that patients who benefited most from perioperative rHuEPO had a pretreatment hemoglobin level greater than 10 g/dL but less than or equal to 13 g/dL. In addition, Sowade and associates [1997] reported that epoetin beta was most beneficial in patients with a perioperative blood loss of more than 750 mL, a baseline hematocrit lower than 42%, and in those 60 years of age or older. In our study, 31 children (50%) with rHuEPO had a pretreatment hematocrit level less than or equal to 37.0%. The elevations of the hematocrit levels in these anemic children were 2.4% in group E2 and 2.4% in group E4, whereas the elevations of the hematocrit levels in patients without anemia were 0.5% in group E2 and 1.5% in group E4. These results suggest that preoperative rHuEPO was more effective for anemic children than nonanemic children. The results also suggest that 400 IU/kg of rHuEPO was effective in patients without anemia. While the effectiveness to avoid transfusion was not clear in this study, further studies should be conducted to evaluate the safety and efficacy of alternative rHuEPO treatment regimens, such as the optimal method of administration, the optimal time for and benefit of more frequent administration prior to surgery, an optimal higher dose, and the ideal patients to receive this drug.

To our knowledge, our study was the first time rHuEPO was administered preoperatively to children with cyanotic congenital heart disease. Others reported that the serum erythropoietin in most children with cyanotic congenital heart disease was normal [Haga 1987; Tyndall 1987]. Although the benefit of rHuEPO to avoid transfusion was still unclear for those patients, our results suggest that erythropoiesis in children without polycythemia in cyanotic heart disease was not impaired.

In our study, the administration of a single dose of rHuEPO did not affect the postoperative hematocrit levels. If the cost of rHuEPO will permit, additional administration might be effective for the postoperative hematocrit levels, as in other studies [D'Ambra 1997, Shimpo 1997]. The problems relating to the costs associated with rHuEPO have been discussed by other authors [Strauss 1994; Coyle 2000]. However,

our simple method does not require a high cost. While the costs in Japan and the United States may differ, the Japanese cost of 6000 units of rHuEPO is ¥11,181 ($93), and the cost of one unit of irradiated RBC is ¥6255 ($52). Avoiding allogeneic blood transfusion is more important and has greater long-term cost effectiveness in children, because the life expectancy is longer for children.

There have been some reports that cardiac surgery was performed with significant hemodilution, around 15% [Masuda 1995]. Cook and associates [1997] also reported a limiting hematocrit level for normothermic CPB in dogs. We had no incidents of brain damage associated with the hemodilution. However, we must be reminded that cerebral injury continues to be one of the most important sources of morbidity after CPB, particularly when there are extreme manipulations such as deep hypothermic circulatory arrest [Kurth 1997].

Significant adverse effects after administration of rHuEPO are rare; however, pure red-cell aplasia was recently reported in patients who had undergone treatment with rHuEPO [Bennett 2004]. These patients were treated for anemia with chronic kidney disease. Although there was no report of pure red-cell aplasia related to preoperative administration of rHuEPO, postoperative follow-up will be necessary for the patients who received rHuEPO.

In conclusion, although the effectiveness of avoiding transfusion was not clear, administration of a single dose of rHuEPO without autologous blood donations had an effect by increasing the hematocrit levels. The effect of the increased hematocrit level was limited to the preoperative period. Further studies are needed to confirm the optimal dose, route of administration, frequency of rHuEPO administration, method of patient selection, and the low and high hematocrit limits for pediatric cardiac surgery.

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