Effects of Autologous Platelet Concentrate Reinfusion After Open Heart Surgery in Patients With Congenital Heart Disease

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Background. **Plsma pheresis and reinfusion of platelet-rich plasma has not been shown to reduce blood loss in cardiac patients. Recently, freshly prepared autologous platelet concentrates (PC) can be made from patient's blood and has a higher concentration than conventional platelet rich plasma. In this study, the effects of autologous PC reinfusion were examined after open heart surgery in patients with congenital heart disease.**

Methods. **Eight patients with noncyanotic congenital heart disease, who underwent open heart surgery and reinfusion of autologous PC, were classified as the PC group. Eight other patients with noncyanotic congenital heart disease, who underwent only open heart surgery, were defined as the control group. Ages ranged from 2 to 24 years and were not significantly different between the two groups (9.3 ± 5.1 years in the PC group and 12.6 ± 7.9 years in the control group, $p = 0.33$). In the PC group, blood was collected from the femoral vein through a 6F catheter introducer; 9 to 20 U (13.0 ± 5.4 U, 0.42 ± 0.22 U/kg) of autologous PC were prepared and were reinfused after protamine administration. The time course of platelet counts was examined until postoperative day 7. Aggregation responses to adenosine diphosphate; (4 μmol/L and 8 μmol/L), collagen (1 μmol/L and 5 μmol/L), and epinephrine (5 μmol/L and 10 μmol/L) were evaluated after induction of anesthesia (individual references), after protamine administration, at the end of the operation; these responses were shown as recovery ratios.**

Results. **Blood loss during surgery in the PC group was significantly less than in the control group (4.8 ± 3.0 mL/kg versus 7.8 ± 1.7 mL/kg, $p = 0.044$). Similarly blood loss on postoperative day 1 in the PC group was significantly less than in the control group (3.6 ± 1.2 mL/kg versus 7.2 ± 3.1 mL/kg, $p = 0.013$). The platelet counts in the PC group were larger than those in the control group until postoperative day 5, after reinfusion of prepared autologous PC. The recovery ratios of the aggregation responses to adenosine diphosphate, collagen, and epinephrine after protamine administration were not significantly different between the two groups. However, recovery in the PC group after reinfusion of the prepared autologous PC was greater than in the control group.**

Conclusions. **Reinfusion of the freshly prepared autologous PC was followed by good aggregation responses and low blood loss in patients with noncyanotic congenital heart disease after open heart surgery. This procedure may be useful in pediatric open heart surgery without blood transfusion or with little administration of homologous blood products.**

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Effects of plasma pheresis before surgery and reinfusion of platelet-rich plasma (PRP) have been reported in patients undergoing open heart surgery, including decreased blood loss and decreased administration of homologous blood [1, 2]. Transfusion of autologous PRP is very attractive, since the predictable coagulopathy associated with cardiopulmonary bypass (CPB) and risk of homologous blood products can be prevented. However, the effects of plasma pheresis and reinfusion of PRP have not yet been sufficiently established, and few studies are available on the effects in patients with congenital heart disease undergoing open heart surgery [1, 2].

Recently, freshly prepared autologous platelet concentrates (PC) with higher platelet concentration than conventional PRP have been used [3]. In the present study, we investigated the effects of autologous PC freshly prepared from blood collected from patients with congenital heart disease, during open heart surgery, when reinfused immediately after heparin reversal.

Patients and Methods

Eight patients with noncyanotic congenital heart disease (7 with ventricular septal defect and 1 with the incom-

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plete form of common atrioventricular canal) who underwent open heart surgery and were reinfused with prepared autologous PC comprised the autologous PC reinfusion group (PC group). Other eight patients with noncyanotic congenital heart disease (6 with ventricular septal defect, 1 with the incomplete form of common atrioventricular canal, and 1 with partial anomalous pulmonary venous drainage) who underwent open heart surgery alone comprised the control group. Ages ranged from 2 to 24 years and were not significantly different between the PC group (9.3 ± 5.1 years, median 7.5 years) and the control group (12.6 ± 7.9 years, median 10.5 years) ($p = 0.330$).

Permission to perform this study was given by the Ethical Committee of Tokyo Women's Medical University, and informed consent was obtained from each patient or from the respective parents.

Study Protocol

All patients were anesthetized by intravenous administration of diazepam (0.2 mg/kg) and muscle relaxants, and fentanyl was used for maintenance. No inhalation anesthetic agents were used. Plasma pheresis was begun immediately after induction of anesthesia and was completed before heparinization. The COBE Spectra System (GAMBRO BCT, Inc, Lakewood, CO) was used to perform plasma pheresis [4]. Blood was collected from the femoral vein at a rate of 30 to 50 mL/min through a 6F catheter introducer (Baxter, Irvine, CA). Autologous PC, 9 to 20 (13.0 ± 5.4) units (1 U = 10 mL; 0.42 ± 0.22 U/kg, platelet count 2.60 ± 1.08 × 10^{11}), were prepared by centrifugation at 2,400 rpm and the remains of blood were returned to each patient from the peripheral venous line simultaneously. Central venous pressure, mean arterial pressure, and the electrocardiogram were monitored according to routine anesthetic factors during plasma pheresis. A crystalloid solution (lactated Ringer's solution) was administered to maintain intravascular volume constant (4.2 ± 2.2 mL/kg) in the PC group during plasma pheresis. This amount was equivalent to the prepared autologous PC and the serum hematocrit level was 24.7% to 44.0% (32.4% ± 6.0%) during pheresis. The average pheresis time was 53 ± 5 minutes, and the collected autologous PC counts ranged from 62.0 to 131.1 (80.6 ± 35.6) × $10^4/\mu$L.

After preparation of the autologous PC, heparin was administered, and conventional CPB was performed with aortic cross-clamping and administration of a multiple-dose cardioplegia (glucose-insulin-potassium solution). A roller pump (Tonokura Inc, Tokyo, Japan) and a hollow-fiber membrane oxygenator (COBE Laboratories, Inc, Lakewood, CO) were employed with lactated Ringer's solution as the filler during the CPB procedure. The perfusion flow rate was 2.2 to 2.4 L/m^2/min under moderate hypothermia (rectal temperature 28°C to 30°C). The serum hematocrit level was 17.0 to 33.9 during CPB. No homologous blood transfusions were performed during or after surgery. The duration of the CPB was 52 to 141 minutes (102 ± 31 minutes in the PC group and 91 ± 18 minutes in the control group), and the aortic cross-clamping time was 26 to 104 minutes (67 ± 29 minutes in the PC group and 57 ± 16 minutes in the control group); there were no significant differences between the two groups ($p = 0.422$ and 0.428, respectively). Dopamine, 4 to 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$, was administered after the CPB. The prepared autologous PC was reinfused into the patients in the PC group after protamine administration. All of the blood in the pump was reinfused slowly until the end of the open heart surgery.

Platelet counts were measured in both groups before CPB (after preparation of autologous PC in the PC group), after CPB, after reinfusion of the autologous blood, or after reinfusion of the pump blood, 6 hours after CPB, and on postoperative days 1, 3, 5, and 7. Aggregation responses to adenosine diphosphate (ADP, 4 μmol/L and 8 μmol/L), collagen (1 μmol/L and 5 μmol/L), and epinephrine (5 μmol/L and 10 μmol/L) were evaluated immediately after induction of anesthesia (individual references), immediately after protamine administration, and at the end of the operation (activated clotting time was confirmed to have returned to the normal range). The recovery ratios of the aggregation responses to ADP, collagen, and epinephrine after protamine administration and at the end of the operation were calculated dividing by the reference value.

All values were statistically analyzed and are shown as mean ± standard deviation (SD). Data were compared using the two-tailed unpaired Student's t test or repeated-measures, two-way analysis of variance (ANOVA). A p value of less than 0.05 was considered significant.

Results

Blood Loss

Blood loss during surgery in the PC group was significantly less than that in the control group (4.8 ± 3.0 mL/kg vs 7.8 ± 1.7 mL/kg, $p = 0.044$). Similarly, blood loss on postoperative day 1 in the PC group was significantly smaller than in the control (3.6 ± 1.2 mL/kg vs 7.2 ± 3.1 mL/kg, $p = 0.013$).

Time Course of Platelet Counts

Table 1 depicts the time course of platelet counts. The platelet counts immediately after induction of anesthesia were similar in both groups (24.1 ± 5.3 × $10^4/\mu$L in the PC group and 23.3 ± 5.6 × $10^4/\mu$L in the control group), and were used as the reference values in their respective groups. In the PC group the platelet counts after preparation of the autologous PC had decreased to 17.7 ± 6.0 × $10^4/\mu$L. The platelet counts after CPB decreased significantly to 13.3 ± 4.1 × $10^4/\mu$L in the PC group and 13.4 ± 4.1 × $10^4/\mu$L in the control group, compared with their respective reference values (analysis of variance, $p < 0.01$). The platelet counts in the PC group increased after reinfusion of the prepared autologous PC, and were significantly larger than in the control group until postoperative day 5. On postoperative day 7, there was no significant difference between the two groups.

Table 1. Time Course of Platelet Counts

Time	Control Group Mean ± SD/10^4 μL	PC Group Mean ± SD/10^4 μL	*p* Value[a]
Before CPB	24.6 ± 6.5	23.8 ± 5.7	0.778
After CPB	11.7 ± 4.4	11.5 ± 4.0	0.926
After PC or pump blood	15.7 ± 4.0	22.5 ± 5.5	0.012
6 Hours after CPB	14.3 ± 4.2	19.2 ± 4.2	0.034
POD 1	14.1 ± 3.4	19.7 ± 4.2	0.006
POD 3	13.9 ± 2.4	22.3 ± 6.1	0.012
POD 5	20.7 ± 3.2	29.0 ± 4.7	0.047
POD 7	33.6 ± 6.2	34.9 ± 4.5	0.457

Data at each time point were compared using two-tailed unpaired Student's *t* test.

[a] The *p* values for time, group, and interaction effects of repeated-measures two-way analysis of variance analysis were < 0.0001, 0.0474, and 0.0090, respectively.

CPB = cardiopulmonary bypass; PC = platelet concentrates; POD = postoperative day.

Aggregation Responses to ADP, Collagen, and Epinephrine

Figures 1 through 3 show platelet aggregation responses. The recovery ratios of the aggregation responses to ADP (4 μmol/L and 8 μmol/L) after protamine administration demonstrated no significant differences between the two groups. However, recovery in the PC group after reinfusion of the prepared autologous PC was greater than in the control group. Similarly, the recovery ratios of the aggregation responses to collagen (1 μmol/L and 5 μmol/L) and epinephrine (5 μmol/L and 10 μmol/L) after protamine administration also demonstrated no significant differences between the two groups. However, recovery in the PC group after reinfusion of the prepared autologous PC was also greater than in the control group.

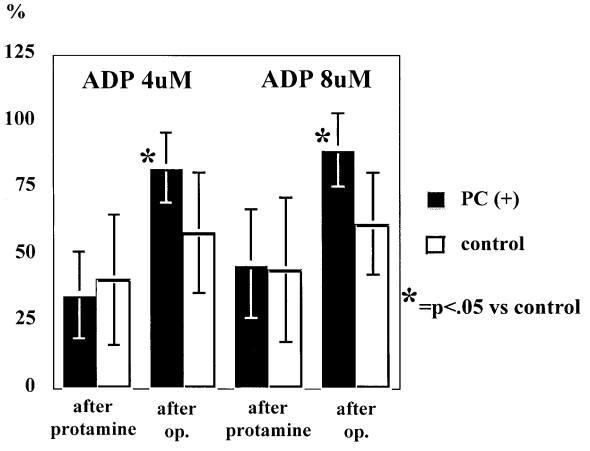

*Fig 1. Platelet aggregation responses to ADP (4 μmol/L, 8 μmol/L). (*ADP = *adenosine diphosphate;* op. = *operation;* PC = *platelet concentrates.)*

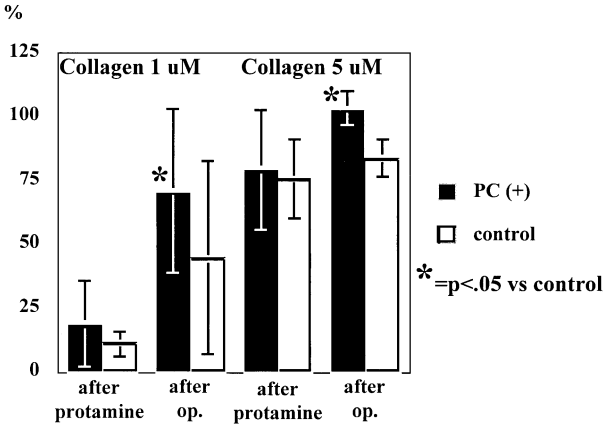

*Fig 2. Platelet aggregation responses to collagen (1 μmol/L, 5 μmol/L). (*op. = *operation;* PC = *platelet concentrates.)*

Comment

During CPB, platelets are activated by contact between the blood and the tubing in the extracorporeal circuit. The activated platelets aggregate and form microemboli, resulting in thrombocytopenia and platelet-aggregating dysfunction [5]. Reinfusion of prepared autologous PRP is very attractive as a means of preventing the predictable coagulopathy associated with CPB and the risk of homologous blood products in patients undergoing open heart surgery with CPB. In the present study, reinfusion of the freshly prepared autologous PC after open heart surgery in patients with congenital heart disease was followed by good aggregation responses and lower levels of blood loss. However, plasma pheresis and reinfusion of PRP in patients undergoing open heart surgery have never sufficiently decreased blood loss [1, 2].

Tobe and colleagues [1] reported that preparation of autologous platelets (average 3 U or less, pheresis time 15 minutes) in patients undergoing coronary artery bypass followed by reinfusion of the prepared autologous platelets had little or no significant therapeutic effect. How-

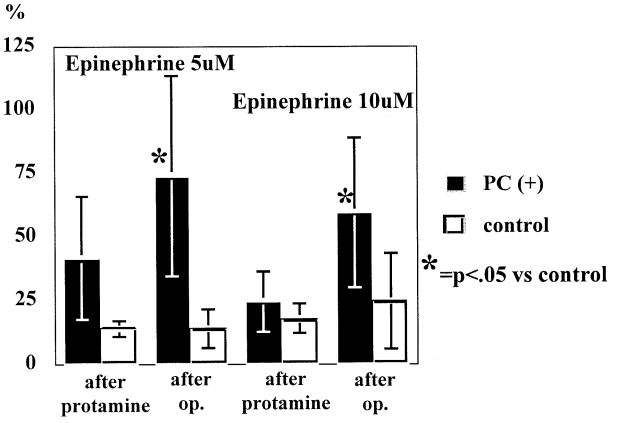

*Fig 3. Platelet aggregation responses to epinephrine (5 μmol/L, 10 μmol/L). (*op. = *operation;* PC = *platelet concentrates.)*

ever, Ereth and associates [6] doubted that reinfusing 3 U or less of prepared autologous platelets would have any effect. They suggested that the autologous platelets be prepared before CPB, and that an average of 5 U or more of prepared autologous platelets would have a significant therapeutic effect. In our study, the autologous PC with high concentration (average 13 U, and average pheresis time 53 minutes) was prepared by using the COBE Spectra system (GAMBRO BCT, Inc, Lakewood, CO) before CPB. Masuda and colleagues [7] reported preparing 5 to 20 U of autologous PC with the same system in patients undergoing adult open heart surgery, but the amount of blood loss did not decrease. However, they collected the blood within 2 or 3 days before surgery. Because the aggregating ability of platelets decreases by one half after 6 hours of storage, as shown by Silver and coworkers [8], the autologous PC should be prepared during surgery and should be reinfused rapidly after heparin reversal. In our study, the time between collection of the blood immediately after induction of anesthesia and the complete reinfusion of the autologous PC was within 3 hours. As a result, the use of the freshly prepared autologous PC was followed by good aggregation responses and low blood loss.

After reinfusion of the prepared autologous PC, the platelet counts in the PC group were significantly larger than in the control group until postoperative day 5. This longlasting effect on platelet counts is mainly explained as follows. The platelet counts in the PC group were kept in the almost same before CPB level, whereas those in the control group remained lower than before CPB level until postoperative day 3. However, the platelet counts gradually increased by the rebound effects of bone marrow in both groups due to open heart surgery without blood transfusion, and there was no significant difference between the two groups on postoperative day 7.

Although the lower body weight limit of this autologous PC collecting system was unclear, 16.5 kg was the lowest body weight of any patient in our study, and 9 U of autologous PC could be prepared from this child. We think that this autologous PC collecting system is applicable to children with a body weight of 10 kg, as a 6F catheter introducer can be inserted into their central venous line and sufficient blood flow can be obtained.

Problems of oozing from the anastomosis, dissecting parts, or retrosternal space are encountered during open heart surgery without homologous blood transfusion. The reinfusion of the freshly prepared autologous PC in our study seemed to be especially effective in preventing this oozing.

The present study has several limitations. First, the duration of CPB was relatively short. Second, the study was based on patients with noncyanotic congenital heart disease alone. In the near future we will examine the effects of reinfusion of the freshly prepared autologous PC in patients with cyanotic congenital heart disease. Preparation of a large quantity of autologous platelets requires a long time for plasma pheresis. Reoperations such as redo-Rastelli due to conduit stenosis, seems to be good indication of this autologous PC collecting system, as they require a relatively long time to complete the dissection before CPB.

In summary, our study suggests that reinfusion of freshly prepared autologous PC in patients with congenital heart disease results in good aggregation responses to ADP, collagen, and epinephrine, increased platelet counts until postoperative day 5, and decreased amounts of blood loss after open heart surgery. We believe that this procedure is useful in pediatric open heart surgery without blood transfusion or with little administration of homologous blood products.

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