Comparison of the Hemostatic Effects of Fresh Whole Blood, Stored Whole Blood, and Components After Open Heart Surgery in Children


In a double-blind study, we compared the postoperative (post-op) blood loss in 161 children undergoing open heart surgery with cardiopulmonary bypass whose immediate post-op transfusion requirements were met with either very fresh whole blood (VFWB), 24- to 48-hour-old whole blood or reconstituted whole blood (packed red blood cells, fresh frozen plasma [FFP], and platelets). Assignment to treatment groups was not strictly random but dependent, in part, on the ability of families to provide directed donors for fresh blood. The three patient groups were comparable with respect to patient age, pre-op coagulation profiles (bleeding time, prothrombin time, activated partial thromboplastin time, platelet count, fibrin split products, fibrinogen, and platelet aggregation tests) difficulty of operative procedures and time spent on CPB. Mean 24-hour post-op blood loss in milliliters per kilogram was 50.9 ± 9.3 in the VFWB group, 44.8 ± 6.0 in the 24- to 48-hour-old group, and 74.2 ± 8.9 in the reconstituted group (P = .03). When blood loss was compared in the 93 children less than 2 years of age, mean blood loss was 52.3 ± 10.8 in the VFWB group, 51.7 ± 7.4 in the 24- to 48-hour-old group, and 56.2 ± 10.7 in the reconstituted group (P = .001). For subjects who had received reconstituted blood, 30-minute and 3-hour post-op platelet aggregation responses to adenosine diphosphate (10 μmol/L) and 30-minute aggregation response to epinephrine (2.5 μmol/L) were more depressed than in the VFWB and 24- to 48-hour groups (P < .001, P = .005, and P = .02). Comparison of other post-op coagulation tests could not explain the increased blood loss in the reconstituted group. We conclude that the transfusion of < 48 hours old whole blood is associated with significantly less post-op blood loss than the transfusion of packed red blood cells, FFP, and platelets in children under 2 years old who underwent complex cardiac surgery. The blood losses associated with the transfusion of VFWB and 24- to 48-hour-old blood are comparable and may be, in part, due to better functioning platelets.

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met with either: Group I: very fresh whole blood administered less than 6 hours after donation (VFWB); Group II: whole blood administered 24 to 48 hours after donation; Group III: a combination of packed red blood cells (RBCs), fresh frozen plasma (FFP), and platelets. These components, usually transfused individually, were combined for study purposes only.

We also compared post-op coagulation values and results of platelet function studies to see if these measures of hemostasis differed among the treatment groups.

MATERIALS AND METHODS

Informed consent was obtained from the parents of each patient before entry into the study. The experimental protocol was approved by the Committee for the Protection of Human Subjects at the Children’s Hospital of Philadelphia and reviewed by the Compliance Branch of the Sterile Drugs and Biologics Branch of the Food and Drug Administration (FDA) in Rockville, MD. All children (newborn to 21 years old) scheduled for OHS with CPB were eligible for study. The patients had congenital heart disease who required palliative or reparative surgery of varying degrees of surgical difficulty. The technical difficulty and operative risk of all surgical procedures were graded by the attending surgeon as simple, intermediate, or complex (see Table 1).

Randomization

Because of limited availability of VFWB from the Blood Bank and the need to enroll equal numbers of subjects into each treatment group, the following randomization schedule was devised. For patients whose parents agreed to participate in the study and were able to provide directed blood donors, two thirds were assigned to Group I (VFWB) and one third were assigned Group II (24- to 48-hour-old whole blood) using a series of sealed envelopes. For patients whose parents agreed to participate in the study but were unable to provide directed blood donors, one third were assigned to Group II (24- to 48-hour-old blood) and two thirds were assigned to Group III (reconstituted). For infants transported to this institution for emergency surgery, assignment to the three treatment groups was made on an equal basis using a separate system of sealed envelopes. For these infants, blood was from non-directed donors.

Preparation of Study Units

Blood or blood components were collected into standard blood collection units containing citrate-phosphate-dextrose-adrenaline-1 (CPDA-1) solution. Typing and cross-matching were performed in standard fashion. A sample of donor’s blood underwent requisite screening tests for infectious disease transmission including rapid plasma reagin (RPR), hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), human immunodeficiency virus antibody (anti-HIV), and alanine aminotransferase (ALT) level. Human T-cell leukemia virus type I-II (HTLV-I/II) antibody testing was added in June 1989.

Group I. VFWB was whole blood less than 6 hours old. VFWB was collected on the day of surgery from a donor who, the day before donation, was prescreened and passed all required donor testing. Study units were kept at room temperature until used or for a maximum of 6 hours. Each transfused unit was screened in the same manner. However, testing was not always completed before transfusion. Release of VFWB before completion of screening tests on that unit was approved by the FDA for study purposes only and is not a routine procedure at this institution.

Group II. Twenty-four- to 48-hour-old blood was whole blood collected 24 to 48 hours before transfusion and was stored at 4 to 6°C until used.

Group III. Reconstituted whole blood contained components of whole blood (one unit each of packed RBCs, platelets, and FFP) which were combined to produce a unit of blood that was visually indistinguishable from standard whole blood. A unit of packed RBCs (≤5 days old) was brought from 4 to 6°C to room temperature over a period of 2 hours. The unit was placed on a platelet agitator (Heimer Labs, St Paul, MN) for 10 to 20 minutes before reconstitution. A unit of 2- to 5-day-old random donor platelets that had been collected and stored in conventional fashion was transferred into a thawed unit of FFP using a plasma separator set (Fenwal Labs, Deerfield, IL, code 4C2243) to prepare platelet-rich plasma. The platelet bag was rinsed with plasma to reduce the loss of platelets. Platelet-rich plasma was then transferred into an 800-mL size transfer pack unit (Fenwal Labs, code 4R2005). Finally, a unit of RBCs was transferred into the platelet-rich bag. After the transfer was completed and components were well mixed by hand, residual air was expressed into the empty RBC

**Table 1. Classification of Operative Procedures**

<table>
<thead>
<tr>
<th>Simple</th>
<th>Intermediate</th>
<th>Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valvuloplasty</td>
<td>Closure of primum ASD with mitral valve replacement</td>
<td>Arterial switch</td>
</tr>
<tr>
<td>ASD patch repair (closure of ASD)</td>
<td>ASD repair with mitral valve replacement</td>
<td>Fontan procedure†</td>
</tr>
<tr>
<td>Blalock-Taussig shunt*</td>
<td>ASD/VSD patch repair</td>
<td>Modified Glenn shunt§</td>
</tr>
<tr>
<td>Repair partial anomalous pulmonary venous return</td>
<td>Incomplete AV canal repair</td>
<td>Separation of aorta and pulmonary artery with VSD patch repair (Truncus arteriosus repair)</td>
</tr>
<tr>
<td>Resection subaortic membrane</td>
<td>Complete AV canal repair</td>
<td>Stage I palliation for hypoplastic left heart syndrome</td>
</tr>
</tbody>
</table>

*Subclavian to pulmonary artery anastomosis.
†An operation used in children with transposition of the great vessels that redirects the venous return using an intra-atrial baffle of autologous tissue. The baffle directs the pulmonary venous blood across the tricuspid valve into the right ventricle and to the aorta; the systemic venous blood is directed across the mitral valve into the left ventricle and to the pulmonary artery.
§An operation used in children with a single ventricle that separates the pulmonary from the systemic circulation. This procedure is based on the principle that the right atrial pressure is adequate to drive blood through the lungs, making a ventricle unnecessary.

§Superior vena cava to right pulmonary artery anastomosis.

Palliative procedure consisting of (1) transection of main pulmonary artery, (2) creation of neoaorta, and (3) creation of systemic to pulmonary artery shunt.

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Administration of Study Units

Two units of RBCs were prepared for each subject. The CPB pump was primed with balanced electrolyte solution and whole blood calculated to produce a final hematocrit of 25% during CPB. At the termination of bypass, heparin effect was reversed with protamine sulphate. From this point on, all volume requirements as determined by blood loss and hemodynamic measurement were met with the assigned study blood. The amount of study blood administered varied according to individual patient needs, and was not a predetermined dose. All study blood was passed through a warmer to bring the temperature to 37°C. The surgeon was blinded to the nature of the blood but the anesthesiologist was not. If clinical complications arose, only the surgeon could ask to break protocol before both study units had been administered.

Measurement of Blood Loss

Total blood loss was measured for 24 hours after the study blood was administered. In the operating room, blood loss was determined by weighing sponges and measuring suction and chest tube drainage. In the intensive care unit (ICU), blood loss was assessed by measuring chest tube drainage.

Laboratory Assessment of Coagulation

Bleeding times (Simplate; Organon-Teknika, Durham, NC) were performed on the volar surface of the forearm immediately pre-operatively, and 30 minutes and 3 hours after administration of protamine sulphate. Blood samples were collected through a flushed arterial line. The following laboratory tests were performed immediately before CPB, and 30 minutes and 3 hours after administration of protamine sulphate: platelet count, prothrombin time, activated partial thromboplastin time (aPTT), fibrinogen, fibrin split products (FSP), FVIII:RAg, and platelet aggregation in response to adenosine diphosphate (ADP) (2 μmol/L), epinephrine (2.5 μmol/L), collagen (.047 mg/mL), and ristocetin (6 mg/mL).

Platelet counts were determined on a Coulter Plus IV electrical cell counter (Hialeah, FL) from blood collected in EDTA. Prothrombin time and aPTT were measured on a Coag-A-Mate X2 (Organon-Teknika). Fibrinogen was measured by the dilute thrombin time method of Clauss.26 FSP were detected by latex agglutination technique (Thrombo-Wellcotest Kit; Burroughs-Wellcome, Greenville, NC). vWF:Ag was measured by an adaptation of the station technique (Thrombo-Wellcotest Kit; Burroughs-Wellcome, Greenville, NC). vWF:Ag was measured by an adaptation of the station technique (Thrombo-Wellcotest Kit; Burroughs-Wellcome, Greenville, NC). vWF:Ag was measured by an adaptation of the station technique (Thrombo-Wellcotest Kit; Burroughs-Wellcome, Greenville, NC). vWF:Ag was measured by an adaptation of the station technique (Thrombo-Wellcotest Kit; Burroughs-Wellcome, Greenville, NC).

Platelet aggregation induced by ADP (Bio/Data Corporation, Hatboro, PA), epinephrine, collagen (Bio/Data), ristocetin (Aggre- ceton; Bio/Data), and epinephrine were studied using platelet-rich plasma anti-coagulated with 3.8% sodium citrate, stored at room temperature and tested within 60 minutes of collection. Platelet concentration was adjusted to 200,000/μL. Changes in optical density of the platelet-rich plasma were measured on a platelet aggregation profiler (Bio/Data). Results are expressed as percent maximum aggregation recorded within 5 minutes of adding standard concentrations of the agonist.

Statistical Analysis

Distributions of age, sex, surgical complexity (simple, intermediate, complex), length of time on bypass, and length of time in circulatory arrest in the treatment groups were compared by χ² tests. Mean blood loss and mean pre-op coagulation studies were compared among the three treatment groups by analysis of variance. When the analysis of variance was significant, (ie, the null hypothesis that the means for the three groups were the same was rejected), pairwise comparisons of the groups were performed using t-tests and the Bonferroni method of adjusting for multiple comparisons. Multiple linear regression was used to investigate the effects of several factors simultaneously on blood loss. Statistical significance was set at .05. All analyses were performed with statistical analysis systems.22

RESULTS

Patient characteristics for each of the treatment groups are found in Table 2. A total of 161 patients were enrolled between March 1987 and July 1989. Fifty-two subjects were in Group I, 57 subjects were in Group II, and 52 subjects were in Group III. Four children who died within the first 24 postoperative hours were not included in this analysis. One of these patients died in the operating room and the other three died in the ICU; none of these patients died of overwhelming hemorrhage. Each of the three treatment groups were comparable with respect to age, sex, and percentage of cases in each category of surgical difficulty. The groups were similar in terms of mean bypass time, time of circulatory arrest, and the mean amount of blood transfused per kilogram in the first 24 postoperative hours. Comparison of the means for pre-op coagulation tests (bleeding time, platelet count, prothrombin time, partial thromboplastin time, fibrinogen, FSP, FVIII:RAg, platelet aggregation studies) showed the groups were similar.

Blood Loss

Mean 24-hour blood loss in milliliters per kilogram was 50.9 ± 9.3 in Group I, 44.8 ± 6.0 in Group II, and 74.2 ± 8.9 in Group III (P = .03) (Table 3). Differences in mean blood loss varied among the groups according to the age of the patient. Comparison of mean 24-hour blood loss for the 93 children less than 2 years old showed the transfusion of reconstituted whole blood was associated with 85% more blood loss than either of the other products (P = .001). Comparison of mean 24-hour blood loss for the 68 children greater than 2 years old did not show a significant difference among treatment groups (P = .41). Differences in blood loss among the groups also varied according to the difficulty of the surgical procedure. For patients whose surgery was simple or of intermediate complexity, no significant differences in blood loss occurred. However, for those undergoing complex surgery, blood loss differed significantly, patients in Group III having the highest blood loss (P = .01). This difference was even more pronounced when the children less than 2 years old with complex surgery were considered (P = .002); those
COMPARISON OF HEMOSTATIC EFFECTS

Table 2. Patient Characteristics for the Three Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Group I VFWB</th>
<th>Group II 24-48 h Old</th>
<th>Group III Reconstituted Whole Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. subjects</td>
<td>52</td>
<td>57</td>
<td>52</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Male</td>
<td>32</td>
<td>32</td>
<td>36</td>
</tr>
<tr>
<td>Ages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± S.E. (y)</td>
<td>2.8 ± 0.4</td>
<td>3.9 ± 0.6</td>
<td>3.8 ± 0.8*</td>
</tr>
<tr>
<td>Range</td>
<td>(0-8.2)</td>
<td>(0-19)</td>
<td>(0-20)</td>
</tr>
<tr>
<td>No. &lt; 2 y</td>
<td>27</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>No. &gt; 2 y</td>
<td>25</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td>Surgical difficulty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple (no. subjects)</td>
<td>11</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Intermediate</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Complex</td>
<td>29</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td>Mean time ± SE on bypass (min)</td>
<td>86.8 ± 6.2</td>
<td>86.1 ± 5.8</td>
<td>84.2 ± 5.1†</td>
</tr>
<tr>
<td>Mean time ± SE of circulatory arrest</td>
<td>38.1 ± 4.3</td>
<td>43.6 ± 4.6</td>
<td>37.2 ± 3.7‡</td>
</tr>
<tr>
<td>Mean volume blood given (Cm³/kg) in 24 h</td>
<td>72.3 ± 9.9</td>
<td>75.5 ± 7.8</td>
<td>97.4 ± 8.6§</td>
</tr>
<tr>
<td>No. of subjects with circulatory arrest</td>
<td>41</td>
<td>42</td>
<td>39</td>
</tr>
</tbody>
</table>

*P = .37.
†P = .94.
‡P = .51.
§P = .11.

in Group III experienced about twice the blood loss of the other two groups.

When the effects of blood loss of age, surgical complexity, and type of blood product were investigated simultaneously using multiple linear regression, blood product and surgical complexity were statistically significant predictors (P = .02 and P < .001, respectively). Reconstituted blood was associated with an 18 mL/kg increase and 24- to 48-hour-old blood with a 3 mL/kg decrease in blood loss compared with VFWB. Compared with simple surgery, complex surgery increased blood loss by 38 mL/kg and intermediate surgery by 4 mL/kg.

Laboratory Evaluation

Changes in bleeding time, platelet counts, prothrombin time, aPTT, fibrinogen, FSP, and FVIII:RAg, which are expected following surgery with CPB, were seen in all

<table>
<thead>
<tr>
<th>By age</th>
<th>Group I VFWB</th>
<th>Group II 24-48 h</th>
<th>Group III Reconstituted Whole Blood</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages (n = 161)</td>
<td>50.9 ± 9.3</td>
<td>44.8 ± 6.0</td>
<td>74.2 ± 8.9 (n = 52)</td>
<td>.03†</td>
</tr>
<tr>
<td>&lt; 2 y (n = 52)</td>
<td>52.3 ± 10.8</td>
<td>51.7 ± 7.4</td>
<td>96.2 ± 10.7 (n = 36)</td>
<td>.001‡</td>
</tr>
<tr>
<td>≥ 2 y (n = 109)</td>
<td>49.4 ± 15.6</td>
<td>37.2 ± 9.7</td>
<td>24.6 ± 6.0 (n = 16)</td>
<td>NS</td>
</tr>
<tr>
<td>By surgical difficulty</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple (n = 36)</td>
<td>16.3 ± 4.6</td>
<td>31.2 ± 15.2</td>
<td>15.8 ± 7.0 (n = 9)</td>
<td>NS</td>
</tr>
<tr>
<td>Intermediate (n = 36)</td>
<td>24.9 ± 6.3</td>
<td>33.5 ± 6.0</td>
<td>32.9 ± 7.2 (n = 12)</td>
<td>NS</td>
</tr>
<tr>
<td>Complex (n = 99)</td>
<td>74.8 ± 15.0</td>
<td>57.1 ± 7.6</td>
<td>107.1 ± 11.2 (n = 31)</td>
<td>.01§</td>
</tr>
<tr>
<td>By age and surgical difficulty</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple &lt; 2 y (n = 8)</td>
<td>27.9 ± 9.2</td>
<td>39.8 ± 7.9</td>
<td>36.2 ± 9.8 (n = 7)</td>
<td>NS</td>
</tr>
<tr>
<td>Intermediate ≥ 2 y (n = 19)</td>
<td>62.8 ± 14.3</td>
<td>56.1 ± 9.6</td>
<td>110.7 ± 11.6 (n = 29)</td>
<td>.002</td>
</tr>
<tr>
<td>Complex ≥ 2 y (n = 11)</td>
<td>16.3 ± 4.5</td>
<td>31.2 ± 15.2</td>
<td>15.8 ± 6.9 (n = 9)</td>
<td>NS</td>
</tr>
<tr>
<td>Intermediate &lt; 2 y (n = 4)</td>
<td>18.9 ± 4.8</td>
<td>21.0 ± 5.0</td>
<td>28.4 ± 11.4 (n = 5)</td>
<td>NS</td>
</tr>
<tr>
<td>Complex ≥ 2 y (n = 2)</td>
<td>98.0 ± 34.2</td>
<td>60.1 ± 10.4</td>
<td>54.8 ± 0.2 (n = 2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.

*Significant pairwise differences by the method of Bonferroni were as follows:
†II v III.
‡II v II, III v III.
§I v III.
||I v II, III v III.
\|I v III, II v III.

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blood loss for children older than 2 years old did not show a
time on CPB. These factors result in larger blood losses.

optimizes hemostasis and thereby decreases blood loss will
putting the patients at higher risk for hemodynamic instabil-
ity. Although our pediatric patients always require RBC
transfusions following surgery, the use of a product that
reconstituted blood was associated with a longer aPTT at 30
minutes in

There were small differences in the mean age and sex
distributions of unknown patient characteristics among the
patient groups and may have affected the outcome.

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Table 4. Mean Laboratory Values: All Ages

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VFWB</td>
<td>24-48 h</td>
<td>Reconstituted</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Whole Blood</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding time (s)</td>
<td>Pre-op</td>
<td>308.0 ± 22.2</td>
<td>252.7 ± 20.6</td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td>353.2 ± 25.6</td>
<td>346.4 ± 30.8</td>
</tr>
<tr>
<td></td>
<td>3 h</td>
<td>377.9 ± 30.7</td>
<td>363.4 ± 32.2</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Pre-op</td>
<td>304.0 ± 14.3</td>
<td>291.6 ± 17.0</td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td>145.6 ± 7.2</td>
<td>163.4 ± 8.4</td>
</tr>
<tr>
<td></td>
<td>3 h</td>
<td>174.4 ± 9.0</td>
<td>182.6 ± 9.3</td>
</tr>
<tr>
<td>Prothrombin time (s)</td>
<td>Pre-op</td>
<td>11.4 ± 0.1</td>
<td>11.4 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td>12.2 ± 0.2</td>
<td>12.7 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>3 h</td>
<td>11.6 ± 0.2</td>
<td>12.3 ± 0.2</td>
</tr>
<tr>
<td>aPTT (s)</td>
<td>Pre-op</td>
<td>35.4 ± 0.9</td>
<td>35.3 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td>39.7 ± 3.4</td>
<td>43.3 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>3 h</td>
<td>33.0 ± 1.1</td>
<td>36.4 ± 1.4</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>Pre-op</td>
<td>214.2 ± 8.0</td>
<td>197.0 ± 7.8</td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td>195.1 ± 5.6</td>
<td>184.0 ± 4.8</td>
</tr>
<tr>
<td></td>
<td>3 h</td>
<td>209.0 ± 6.1</td>
<td>195.1 ± 6.3</td>
</tr>
<tr>
<td>FSP (mg/mL)</td>
<td>Pre-op</td>
<td>2.3 ± 1.2</td>
<td>1.8 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td>8.2 ± 3.1</td>
<td>7.0 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>3 h</td>
<td>6.0 ± 1.7</td>
<td>6.8 ± 1.5</td>
</tr>
<tr>
<td>F VIII: Ag (%)</td>
<td>Pre-op</td>
<td>115.5 ± 8.2</td>
<td>116.9 ± 15.5</td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td>165.2 ± 8.3</td>
<td>145.5 ± 8.4</td>
</tr>
<tr>
<td></td>
<td>3 h</td>
<td>246.8 ± 14.3</td>
<td>214.0 ± 16.4</td>
</tr>
</tbody>
</table>

Mean ± standard error.

treatment groups (Table 4). Mean activated clotting times
measured 30 minutes after protamine were similar in all
treatment groups (P = .92). Thirty minutes after pro-
amine, subjects in Group III had a longer mean aPTT and a
lower mean fibrinogen concentration (P = .06 and .07) in
comparison with the other groups. Comparison of other
mean post-op laboratory values at 30 minutes and 3 hours
showed differences among the groups (platelet counts at
both times, prothrombin time at 3 hours, and FSPs at 3
hours). Reconstituted blood was also associated with the
most abnormal platelet aggregation studies at 30 minutes in
the presence of the agonists ADP, epinephrine, and colla-
gen (P < .001, P = .02, and P = .007). ADP-induced aggre-
gation at 3 hours was also significantly reduced in the
reconstituted group (P = .005).

DISCUSSION

Avoiding excessive hemorrhage after OHS with CPB in
children is an important factor in improving surgical out-
come. Although many approaches to limiting post-op hem-
orrhage have been tried, no single approach has proven
uniformly successful. In our study, children less than 2 years
old who had complex surgery derived the greatest benefit
from whole blood less than 48 hours old. Compared with the
repair of simpler defects, complex congenital heart
defects require more extensive reconstruction and more
time on CPB. These factors result in larger blood losses,
putting the patients at higher risk for hemodynamic instabil-
ity. Although our pediatric patients always require RBC
transfusions following surgery, the use of a product that
optimizes hemostasis and thereby decreases blood loss will
lessen the amount of blood replacement required following
surgery and help to reduce donor exposure. Comparison of
blood loss for children older than 2 years old did not show a
difference among the treatment groups. However, this
result may be a reflection of an inadequate sample size. The
finding for young children was highly significant and corrob-
orated the impression of some cardiac surgeons. However,
as a larger effect on young children was not a formally
stated hypothesis a priori, this finding should be interpreted
cautiously.

The randomization method used in this study was forced
by institutional practicalities and was adopted to provide
study units and to allow enrollment of equal numbers of
patients in each treatment arm. Enrollment into Group I
required that families provide directed donors of the study
blood product and enrollment in Group III was restricted to
the donor pool at this institution provided these study units.
We observed prolongation of the mean protime and mean aPTT in all of our
treatment groups after CPB. However, the transfusion of reconstituted blood was associated with a longer aPTT at 30
minutes and prothrombin time at 3 hours than either other
treatment group. Because the transfusion of FFP is ex-
pected to deliver amounts of plasma coagulation factors analogous to those found in whole blood,27 the cause of these differences is not clear. Although the comparison of mean post-op platelet counts at 30 minutes and 3 hours, prothrombin time at 3 hours, and FSP at 3 hours showed significant differences among the groups, the pattern of these differences does not help to explain increased bleeding observed in Group III, as thrombocytopenia was more pronounced in Group II, prothrombin times equally prolonged in Groups I and III, and FSP was higher in Group I.

The effect of CPB on platelets has been intensively studied. CPB is responsible for a transient decrease in platelet count because of dilution and mechanical platelet damage.9 Platelets become activated as they pass through the bypass apparatus. Clinical bleeding has been reported in association with platelet alpha granule release and decrease in levels of platelet secretory ADP.28 In vitro abnormalities include loss of fibrinogen receptors from the platelet surface as well as defective aggregation to ADP, collagen, and ristocetin.29,30 Some children with congenital heart disease have decreased platelet aggregation responses to ADP and collagen when studied outside of the peri-op period.7 For the group of patients we studied, in vitro platelet function was normal in all groups before surgery and deteriorated most significantly in the patients who had received reconstituted blood. Mean pre-op bleeding times were all within the normal range; the means increased in the post-op period but remained in the normal range. The acquired dysfunction of these already impaired platelets probably contributes to bleeding from sites of surgical damage, despite normal bleeding times.

Mohr et al have suggested that blood loss following CPB is the same when patients are transfused with either one unit of fresh blood or 10 units of platelet concentrates.17 Lavee et al have shown that transfusion of fresh whole blood after CPB gives the same increase in platelet count as six units of platelet concentrates and that the platelets in fresh blood retain better function than those in concentrates.31 The platelets contained in VFWB are not subject to the damage inherent in concentrate preparation and storage.27 The platelets in our reconstituted product had been prepared and stored as platelet concentrate and undoubtedly lost some of their function. The standard approach to blood replacement after OHS is to give the element of blood which is lacking. In this study, reconstituted blood contained the components of whole blood that are usually administered separately. The purpose of creating this product was to offer a standard therapy arm while blinding the observer to the nature of the blood product. We acknowledge that this product may not have contained platelets in equal number or with equal function to the platelets in fresher whole blood. Although the platelets in 24- to 48-hour-old blood have not undergone centrifugation and concentration, they have been refrigerated at 4°C for at least 1 day and their function is presumably significantly impaired.18 Our study shows that the blood loss associated with the transfusion of VFWB and 24- to 48-hour-old whole blood are the same.

Concern over the use of directed fresh blood has been raised by recent reports of fatal graft-versus-host disease (GVHD) in immunocompetent adult patients who have received viable lymphocytes in a transfusion of fresh blood from a close relative.19,20 The American Association of Blood Banks has suggested that directed blood donations from first degree relatives be routinely irradiated to minimize the threat of GVHD.32 Because the bulk of VFWB is drawn from directed donors and processing of this product must occur within 6 hours of donation, the routine procurement of directed fresh blood is difficult and, occasionally, incompletely screened blood is requested. Meeting post-op cardiac surgery transfusion needs with 24- to 48-hour-old blood eliminates the need for release of untested, very fresh blood. Day-old fresh blood can be screened for infection and supplied to the operating room more easily and from sources other than directed donors. GVHD is not a risk following transfusion of blood whose lymphocytes have been inactivated with irradiation33 and this procedure could be routinely accomplished for directed 24- to 48-hour-old fresh blood.

In summary, the transfusion of whole blood less than 48 hours old in children less than 2 years old who had complex OHS was accompanied by significantly less post-op hemorrhage in comparison with stored blood components. The benefit of fresh blood may be because of the presence of better functioning platelets. We have also found that whole blood less than 6 hours old and whole blood that is between 24 and 48 hours old have a similar hemostatic effect. Older fresh blood can be thoroughly screened for infection, stored for routine and emergency transfusion, and could be irradiated to eliminate the risk of GVHD inherent in very fresh blood from directed, family donors. Our current practice is to use screened, refrigerated 24- to 48-hour-old whole blood for early blood replacement requirements following complex OHS with CPB in children. Another approach to decreasing blood loss after OHS suggested by the results of this study might include finding ways to improve the function of the platelets in stored platelet concentrates.

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