Red Blood Cell Exchange Transfusion as an Adjunct Treatment for Severe Pediatric Falciparum Malaria, Using Automated or Manual Procedures

Fouad N. Boctor, MD, PhD

ABSTRACT. Pediatric falciparum malaria is associated with high morbidity and mortality rates. Cerebral malaria and renal failure are common among children with a high percentage of malaria-infected red blood cells. We report 3 cases of imported pediatric falciparum malaria with central nervous system involvement and/or renal failure that were treated initially with intravenous antimalarial therapy, with no clinical improvement. Red blood cell exchange transfusion (RBCET) was started; this resulted in decreases in the percentages of parasitized red blood cells of 80% to 90%. The RBCET was performed with either an automated 1-blood volume or manual 1.5-blood volume exchange. Most cases of falciparum malaria can be treated with intravenously administered antimalarial agents alone. However, for children who have high percentages of parasitized red blood cells with central nervous system involvement and/or renal failure, the use of RBCET as an adjunct treatment should be considered. Pediatrics 2005;116:592–595. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0314; cerebral malaria, imported tropical diseases, red blood cell exchange.

ABBREVIATIONS. RBCET, red blood cell exchange transfusion; LDH, lactate dehydrogenase.

The incidence of Plasmodium falciparum malaria is increasing in western countries because of migration from and travel to countries where malaria is endemic. Of the 1337 malaria cases reported in the United States in 2002, all except 5 were imported.1 Forty-one percent of the world’s population lives in areas where malaria is transmitted. An estimated 700,000 to 2.7 million persons die as a result of malaria each year, 75% of them African children.1,2 P falciparum is the most dangerous of the 4 species causing malaria and is associated with significant morbidity and mortality rates. The mortality and morbidity rates usually correspond to the degree of parasitemia.3 The estimated mortality rate among patients with cerebral malaria exceeds 30% and, when the course is complicated by renal failure or respiratory failure, it may approach 80%.3 Antimalarial drugs act relatively slowly and are not always effective, because of the presence of drug resistance of P falciparum.4 An alternative emergency therapy, red blood cell exchange transfusion (RBCET), decreases the parasitic burden quickly and effectively, removes toxic substances, reduces microcirculatory sludging, and increases the oxygen-carrying capacity of the blood.5,6 Exchange transfusion as an adjunct treatment for the most-severe cases was introduced in 1974.7 Several reports described the use of whole-blood exchange transfusion or RBCET as an adjunctive therapy for adult patients with cerebral malaria or high-percentile parasitemia.7–22 However, limited trials of exchange transfusion in P falciparum-infected pediatric populations have been reported.17,18,21 We describe 3 Africa-born children who visited the United States with high levels of P falciparum parasitemia and cerebral malaria/renal failure; they were initially treated with intravenously administered antimalarial drugs without clinical improvement but were successfully treated with a combination of RBCET and oral antimalarial therapy. Both manual RBCET and automated RBCET were used successfully, and examples are presented.

METHODS

All 3 patients tested negative for sickle cell disease and initially received intravenously administered quinidine gluconate and clindamycin or doxycycline. When this treatment did not result in clinical improvement, RBCET was performed for 2 patients with the COBE Spectra apheresis system (COBE Laboratories, Lakewood, CO). The parasitized red blood cells were replaced by citrate phosphate dextrose amine anticoagulant-preserved solution, leukoreduced, sickle cell-negative, red blood cells and E, C, and K antigen-negative, matching red blood cells. COBE Spectra software determined the volume of blood needed, on the basis of the patient’s height, weight, and hematocrit value. One-blood volume exchanges were performed for the 2 patients (Table 1) once, and the fluid balance was maintained at 100%. The COBE Spectra system was primed with 300 mL of red blood cells before the exchange. The third patient received a manual exchange because of the lack of an available apheresis system and the urgency of the clinical situation. On the basis of the patient’s weight of 25 kg, 1800 mL of reconstituted packed red blood cells (equivalent to 1.5 blood volumes), with a hematocrit value of 33%, were used. Five units of leukoreduced, additive solution anticoagulant-preserved packed red blood cells were reconstituted after removal of the supernatant and were mixed with fresh frozen plasma to adjust the final hematocrit level to 45%. Manual blood exchange was started with 2 intravenous arm lines. Between 100 and 150 mL of blood were withdrawn manually and replaced with an equivalent volume of constituted donor blood. The process required ~4 hours.

In either the manual or automated procedure, the extracorporeal volume did not exceed 15% of the total blood volume. The 3 patients received leukocyte-reduced RBCs. For 1 patient (patient 3), the additive solution anticoagulant-preservation solution was

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removal and red blood cells were reconstituted with plasma. The other 2 patients received only citrate phosphate dextrose adenine anticoagulant-preservative solution red blood cells.

CASE REPORTS

Patient 1
A 9-year-old, black, male patient had returned 4 days earlier from a trip to Ghana. Two days after his return, he presented with fever, chills, and headache. Stained blood smears showed 44% parasitemia with *P. falciparum*. The patient was examined by his pediatrician, who prescribed chloroquine (750 mg total dose). The patient was later brought to the emergency department with a rigid abdomen. Quinidine gluconate was administered intravenously at a loading dose of 10 mg/kg over 2 hours, followed by a continuous drip at 0.02 mg/kg per minute, and clindamycin was administered intravenously at a loading dose of 10 mg/kg, followed by 5 mg/kg every 8 hours. The patient did not exhibit clinical improvement during the next 12 hours and developed oliguria and elevated creatinine and blood urea nitrogen. The patient was alert, and his physical examination revealed temperature of 37°C, pulse of 104 beats per minute, respiration of 30 breaths per minute, weight of 29 kg, and height of 53 inches. His sclera and sublingual soft tissue showed yellow coloration (icterus). Laboratory data included the following: hemoglobin, 8.1 g/dL; hematocrit, 23%; platelet count, 32 × 10^5^ platelets per μL; white blood cell count, 12.1 × 10^9^ cells per μL; sodium, 122 mEq/L; potassium, 5 mEq/L; chloride, 97 mEq/L; bicarbonate, 20 mEq/L; total bilirubin, 13.1 mg/dL; indirect bilirubin, 8.9 mg/dL; lactate dehydrogenase (LDH), 1264 IU/L; blood urea nitrogen, 64 mg/dL; creatinine, 2.1 mg/dL; aspartate aminotransferase (serum glutamic-oxaloacetic transaminase), 185 U/L; alanine aminotransferase (serum glutamic-pyruvic transaminase), 105 U/L. Coagulation values were normal. The patient began automated RBCET and tolerated the procedure very well. Postexchange blood smears showed a decrease of infected red blood cells to 4%. Later, the patient also underwent hemodialysis because of hyponatremia, acidosis, and oliguria. Oral treatment with quinidine (10 mg/kg) and clindamycin (5 mg/kg every 8 hours) for a total of 7 days was started the next day. Three days after apheresis, the patient recovered from the acute renal failure, his laboratory values returned to normal, and blood smears were negative for malaria. The patient was discharged 5 days after admission, with no sequelae.

Patient 2
A 3.5-year-old, black, female patient from Nigeria, who had arrived in the United States 4 days earlier, presented with a fever of 40.5°C. She had experienced a generalized convulsion that lasted 15 minutes, with postural drowsiness and weakness. She was treated with intramuscularly administered penicillin for streptococcal pharyngitis and sent home. The child was brought to the emergency department 2 days later with fever accompanied by prolonged generalized seizures, which resolved with antiseizure treatment. Laboratory data included the following: hemoglobin, 7.2 g/dL; hematocrit, 22%; platelet count, 32 × 10^5^ platelets per μL; white blood cell count, 1.4 × 10^9^ cells per μL; glucose, 53 mg/dL; bilirubin, 2.9 mg/dL; LDH, 700 IU/mL. Other chemistry and coagulation values were normal. The patient’s hypoglycemia responded to 50 mL of 10% dextrose. Stained blood smears showed 20% *P. falciparum* parasitemia. On the basis of the clinical diagnosis of cerebral malaria, the patient was admitted to the PICU. Quinidine gluconate was administered intravenously at a loading dose of 10 mg/kg over 2 hours, followed by a continuous drip at 0.02 mg/kg per minute, and clindamycin was administered intravenously at a loading dose of 10 mg/kg, followed by 5 mg/kg every 8 hours. Because of a lack of clinical improvement, RBCET was started 24 hours later. During the RBCET, urine output was normal and the urine was clear. Vital signs were stable. Blood chemistry, urine, and coagulation parameters were within normal ranges. After the transfusion, the patient showed marked improvement and a reduction of parasitemia to 4%. Quinidine (10 mg/kg) and clindamycin (5 mg/kg every 8 hours) were administered orally for 7 days. The patient was discharged on the 5th day after admission, with blood smears negative for malaria. The oral administration of antimalarial drugs was continued after the patient’s discharge.

Patient 3
A 9-year-old, black, female patient from Ghana, who had arrived in the United States 10 days earlier, presented with fever, chills, abdominal pain, and vomiting of 5-day duration. Her vital signs were as follows: oral temperature, 38.1°C; pulse, 120 beats per minute; respiration, 18 breaths per minute; blood pressure, 105/64 mm Hg. The patient was also presented with dehydration (estimated at 10%). The patient was lethargic but arousable. She demonstrated scleral icterus and jaundice on her palms and on the soles of her feet. The spleen was palpable. Laboratory data included the following: hemoglobin, 11.5 g/dL; hematocrit, 33.2%; platelet count, 30 × 10^5^ platelets per dL. The chemistry results were normal except for an elevated LDH level of 800 U/L (normal: 120–240 U/L). Stained peripheral blood smears showed that 32% of the red blood cells were infected with *P. falciparum*, and many contained multiple rings. The clinical diagnosis was cerebral malaria. Quinidine gluconate was administered intravenously at a loading dose of 10 mg/kg over 2 hours, followed by a continuous drip at 0.02 mg/kg per minute, and doxycycline was administered intravenously at a loading dose of 10 mg/kg, followed by 5 mg/kg every 8 hours. However, 20 hours later this treatment had produced little improvement in the patient’s condition.

Manual whole blood exchange was started. During the procedure, the urine was clear, urine output was normal, and vital signs were stable. Plasma chemistry, urine, and coagulation parameters were within normal ranges. Blood smears obtained after completion of the exchange showed 2% parasitized red blood cells (a 94% reduction). Quinidine (10 mg/kg) and clindamycin (5 mg/kg every 8 hours) were administered orally for 7 days. One day after the exchange, a blood smear showed no parasitized red blood cells. The patient was discharged on the 5th day after admission. The oral administration of antimalarial drugs was continued after the patient’s discharge.

RESULTS
A dramatic clinical improvement was noticed for all 3 children after RBCET. The parasite count decreased to <5% after 1 exchange (Table 1). With these low counts, the patients did not need another exchange. All patients continued to receive orally administered antimalarial agents for another 5 to 7 days. After the oral antimalarial treatment, all patients achieved complete cure, with normal neurologic, hematologic, and renal functions and laboratory results. These cases showed that 1-volume RBCET is adequate to reduce the infected cell count by 80% to 90% (Table 1).

DISCUSSION
Although infections with *Plasmodium vivax*, *Plasmodium ovale*, or *Plasmodium malariae* are rarely fatal, infection with *P. falciparum* can rapidly become lethal,

### TABLE 1. Red Blood Cell Exchange Data

<table>
<thead>
<tr>
<th>Patient 1 (9 y)</th>
<th>Patient 2 (3.5 y)</th>
<th>Patient 3 (9 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infected RBCs before exchange, %</td>
<td>44</td>
<td>20</td>
</tr>
<tr>
<td>Infected RBCs after exchange, %</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Blood volume exchanged</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Method of exchange</td>
<td>COBE Spectra</td>
<td>COBE Spectra</td>
</tr>
</tbody>
</table>

RBCs indicates red blood cells.
with multiple organ failure. Among children, hypoglycemia, convulsions, and severe anemia are fairly common; acute renal failure and pulmonary edema are more common among adults. Cerebral malaria with coma, shock, and acidosis can occur at any age, with high morbidity and mortality rates. Quinidine and quinine derivatives are the major antimalarial drugs. Quinidine is more active than quinine but also is more cardiotoxic and more expensive. In the United States, parenteral quinidine treatment is recommended for severe malaria.1

The use of exchange transfusion as an ancillary treatment in combination with antimalarial agents is controversial because of the associated risks of fluid overload and transfusion reactions, the expense, and the danger of transmission of other blood-borne diseases.2-4 The question of who would receive the maximal benefit from this treatment was addressed by White and Breman,2,3 who recommended RBCET for patients who are seriously ill and have parasitemia exceeding 15%. However, they stated that RBCET should be considered for patients with parasitemia in the range of 5% to 15% if there are other signs of poor prognosis. Riddle et al.,27 in their meta-analysis, found a tendency toward adjunct exchange transfusion benefit among subgroups of patients with partial immunity. It was also suggested that exchange transfusion may be a practical alternative for treatment of young children, because the small amount of blood needed by a child could be obtained from a parent or relative.28 Another question is what blood component needs to be exchanged. Some investigators used whole blood, whereas others suggested plasma exchange to remove toxic substances and cytokines because plasma exchange is somewhat safer.28 Erythrocytapheresis was also found to be safer and faster and avoids changes in levels of electrolytes and coagulation factors.29,30 In our hands, erythrocytapheresis (patients 1 and 2) and whole-blood exchange (patient 3) resulted in the same reductions in parasitized red blood cells. However, erythrocytapheresis was easier and faster. The next question is what volume of blood or blood components should be removed. The minimal effective volume of red blood cells to be exchanged has not been defined. Exchanges of 1 to 2 blood volumes were recommended.20,21 We used between 1 and 1.5 blood volumes for both adult31 and pediatric18 populations. In our experience, a 1-blood volume exchange achieves >80% to 90% removal of parasitized red blood cells. This is higher than the 60%-70% expected from the mathematical models for 1-, 1.5-, and 2-volume exchanges,32 which may raise the possibility of mechanical destruction of infected red blood cells during the exchange or toxicity of the antiagglutinant additive for parasitized red blood cells. White26 and Cook6 recommended that RBCET be conducted in adequate facilities, with a safe blood supply. However, with the recent nucleic acid testing for HIV and hepatitis C virus, blood and blood products are very safe for transfusion in developed countries.33 Also, the expense is much lower than that of keeping patients in ICUs while antimalarial treatment is completed. Unfortunately, RBCET is not proposed for widespread use in developing countries, where the majority of deaths attributable to severe malaria occur and where the lack of automated apheresis availability and blood safety could be a deterrent for erythrocytapheresis. However, as shown for patient 3, the manual method could be used under these circumstances. For most pediatric populations, the volume of blood that is needed for exchange is small. However, the benefits of exchange must be weighed against the risk of pathogen transmission through the available blood supply. The benefits of RBCET for pediatric populations include (1) rapid reduction of parasitized cells, (2) decreased risk of cerebral malaria and renal failure, and (3) improved rheologic features with transfused red blood cells and improved oxygen-carrying capacity.

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