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. 

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 adenine anticoagulant-preservative 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-preservative 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-preservative solution was
removed 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. Quinine 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 levels. Laboratory data included the following: hemoglobin, 8.1 g/dL; hematocrit, 23%; platelet count, 32 × 10^9 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 was lethargic but arousable. He demonstrated scleral icterus and jaundice on his 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 × 10^9 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. Quinine 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 98% reduction). Quinine (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.

**Patient 2**

A 3.5-year-old, black, female patient from Nigeria, 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 child 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 × 10^9 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. Quinine 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 98% reduction). Quinine (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,
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. Quinine 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.

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. 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.

The question of who would receive the maximal benefit from this treatment was addressed by White and Breman, 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. 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. 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. Erythrocytapheresis was also found to be safer and faster and avoids changes in levels of electrolytes and coagulation factors. 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, and 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.

ACKNOWLEDGMENTS

I thank Drs John A. Smith and William Benjamin for reviewing and editing the manuscript, Dr Margot S. Kruskall for her advice and encouragement, and Lisa Sosebee for her help with typing and formatting.

REFERENCES

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

Fouad N. Boctor

Pediatrics 2005;116;e592
DOI: 10.1542/peds.2005-0314 originally published online September 15, 2005;
Red Blood Cell Exchange Transfusion as an Adjunct Treatment for Severe Pediatric Falciparum Malaria, Using Automated or Manual Procedures
Fouad N. Boctor
*Pediatrics* 2005;116:e592
DOI: 10.1542/peds.2005-0314 originally published online September 15, 2005;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/116/4/e592