Intravenous Artesunate for Transfusion-Transmitted
Plasmodium vivax Malaria in a Preterm Neonate

abstract

Transfusion-transmitted malaria (TTM) in neonates is rare. TTM can occur in both endemic and nonendemic areas because the current tests used to screen the donor blood for malaria are unreliable when there is low parasitemia. Malaria must be considered as an important differential diagnosis for neonatal sepsis after exchange transfusion. Management strategy in TTM in the neonatal period is not standardized; exchange transfusion is often considered. We used intravenous artesunate in a case of severe malaria caused by Plasmodium vivax in a 30-week preterm neonate after packed red blood cell transfusion on day 19 of life. This is the first clinical report of parenteral artesunate successfully used in the neonatal period. We emphasize the need for further investigation of the safety and efficacy of intravenous artesunate in the treatment of severe neonatal malaria.

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KEY WORDS
artesunate, neonatal malaria, transfusion-transmitted malaria, Plasmodium vivax

ABBREVIATIONS
pLDH—parasite lactate dehydrogenase
PRBC—packed red blood cells
TTM—transfusion-transmitted malaria
WHO—World Health Organization

Dr Prashanth conceived, did literature search, and prepared the draft; Drs Maralihalli and Bagalkot helped in acquisition of data and preparation of the manuscript; Dr Joshi reviewed the manuscript and provided critical comments on important intellectual content; all authors were involved in the management of the case and approved the final version of the draft; Dr Prashanth will act as the guarantor for the work.

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No reliable estimate is available regarding the incidence and spectrum of transfusion-transmitted infections in the neonatal period. Transfusion-transmitted malaria (TTM) in neonates is unusual. Most recent data suggest that, in the United States, transfusion-transmitted malaria occurs at a rate of 0.23 per million transfusions in all age groups. In contrast, malaria can be transmitted in as many as 300 cases per million transfusions in malaria-endemic countries. Transfusion-transmitted malaria in neonates in endemic and nonendemic areas alike is known to be severe, and management strategy is not standardized. A recent report suggested effectiveness of oral artesunate in a neonate with acquired chloroquine-resistant Plasmodium vivax malaria. We report a case of severe malaria in a preterm neonate after packed red blood cell transfusion successfully treated with intravenous artesunate. This is probably the first clinical report of intravenous artesunate safely used in the neonatal period.

**PATIENT PRESENTATION**

An appropriate for gestational age preterm female infant weighing 1320 g born at 30 weeks' gestation was admitted to the tertiary level NICU in our center with respiratory distress soon after birth. Chest radiograph was suggestive of moderate respiratory distress syndrome. The infant needed ventilator support in the fourth hour of life; surfactant replacement therapy was not possible because of parental financial constraints. After 5 days of mechanical ventilation, the baby was extubated to nasal continuous positive pressure ventilation. She was gradually weaned from respiratory support and shifted to head-box oxygen by day 15. Nasogastric feeding of expressed breast milk was initiated and by day 20 of life, full enteral feeding was established. In view of continued minimal oxygen dependency and lack of appropriate weight gain, packed red blood cell (PRBC) transfusion was planned at a hemoglobin level of 9.5 g/dL on day 18 of life. Compatible, cross-matched "O" positive PRBCs were arranged from the in-house blood bank and transfused (10 mL/kg; followed by IV frusemide 1 mg/kg per dose). The infant remained hemodynamically stable post-transfusion.

After 24 hours of PRBC transfusion, the baby became lethargic, had multiple episodes of apnea necessitating bag-and-mask ventilation. On examination, there was generalized hypotonia with diminished reflexes. Anterior fontanel was depressed and pulsatile. She had mild pallor; icterus was present up to the lower abdomen. No significant liver or splenic enlargement was present. There was no hypothermia, hypoglycemia, or electrolyte imbalance. Hemoglobin concentration was 10.8 g/dL, total leukocyte count was 10 × 10^9/L, absolute neutrophil count was 4000, band forms were 50, and platelet count was 160 × 10^9/L. C-reactive protein was weakly positive (titers 1:8). Blood culture for bacteria and fungi showed no growth after 8- and 48-hour incubation. However, peripheral blood smear examination done as part of complete hemogram showed multiple ring-formed hemoparasites. Giemsa staining of a fresh, repeat blood sample confirmed *P. vivax* schizonts and gametocytes. Malaria card tests for parasite lactate dehydrogenase and histidine-rich protein were positive for non-*Plasmodium falciparum* species. Peripheral blood smear showed evidence of hemolysis, and the serum LDH level was elevated (750 U/L). Qualitative glucose-6-phosphate dehydrogenase blood test results were normal. Serum bilirubin concentration was 20 mg/dL with 18% conjugated fraction. Liver enzymes and blood coagulation profile were normal. A diagnosis of severe transfusion-induced malaria was made in view of the poor general condition, low platelet counts (85 × 10^9/L in a repeat sample), hyperbilirubinemia, and absence of strong evidence in favor of sepsis. Transfusion-transmitted malaria was confirmed by positive *P. vivax* antigen assay in the donor blood; peripheral smear was negative for the malarial parasite. Malaria status of the infant's mother was reconfirmed as negative.

Considering the severity of illness, intravenous artesunate was started at a dose of 2.4 mg/kg diluted in 5 mL normal saline, on day 1 (60 mg artesunate dissolved in 5 mL normal saline and 5 mL sodium bicarbonate to prepare 6 mg/mL solution), followed by 2.4 mg/kg per day for 6 days along with clindamycin (20 mg/kg per day in 2 divided doses as intravenous infusion) given for a total of 7 days. The infant's clinical condition improved 24 hours after the initiation of artesunate therapy. Laboratory parameters during intravenous artesunate therapy are shown in Table 1. Parenteral antibiotics (cefotaxime 150 mg/kg per

<table>
<thead>
<tr>
<th>Day of Illness</th>
<th>Serum Sodium, mEq/L</th>
<th>Parasite Density, parasites/μL</th>
<th>Gametocytes, parasites/μL</th>
<th>Neutrophils, cells/μL</th>
</tr>
</thead>
<tbody>
<tr>
<td>D0</td>
<td>132</td>
<td>18,874</td>
<td>3580</td>
<td>4000</td>
</tr>
<tr>
<td>D1</td>
<td>130</td>
<td>366.6</td>
<td>260.6</td>
<td>4850</td>
</tr>
<tr>
<td>D2</td>
<td>136</td>
<td>10.2</td>
<td>0</td>
<td>4680</td>
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<tr>
<td>D3</td>
<td>NA</td>
<td>0.8</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>D7</td>
<td>135</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>D14</td>
<td>NA</td>
<td>0</td>
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<td>NA</td>
</tr>
<tr>
<td>D21</td>
<td>130</td>
<td>0</td>
<td>0</td>
<td>4520</td>
</tr>
<tr>
<td>D28</td>
<td>132</td>
<td>0</td>
<td>0</td>
<td>4880</td>
</tr>
</tbody>
</table>

* Parasite density was assessed on a stained thick film by counting parasites against leukocytes (100 or more), then multiplying by the patient's own leukocyte count.
d and amikacin 15 mg/kg per day) were given for 7 days. Initial and after-7-day incubation blood cultures were both sterile. There were no further episodes of apnea. Feeding was restarted after 48 hours, and the infant was gradually weaned off oxygen. Bilirubin and hemoglobin levels normalized over the next week. Thereafter, the infant showed consistent weight gain until discharge on day 40 of life (weight at discharge: 1820 g). Neurosonography results at discharge were normal. Neurologic assessment at 6 months corrected age, including muscle tone, head growth, and motor milestones, was within normal limits. Ophthalmologic evaluation and hearing screening results were normal. The infant, currently under follow-up, is asymptomatic with no malarial parasites detectable in peripheral smear.

**DISCUSSION**

In the United States, there have been 2 to 3 TTM cases reported per year over the 40-year period from 1958 through 1998. The current occurrence rate is figured at 1 per 4,000,000 red blood cells transfused with an estimated fatality rate of 11%. TTM in the neonatal period is rare. Review of literature suggested that, in the neonatal period, malaria due to *P. vivax* is more common than *P. falciparum*. Clinically, neonatal malaria mimics bacterial sepsis. A high index of suspicion is therefore needed for making the diagnosis. Severe cases of neonatal malaria often require exchange transfusion. With the use of parenteral artesunate, we could avoid exchange transfusion in our case. This report, therefore, emphasizes the need for investigating the safety and efficacy of intravenous artesunate in the treatment of severe neonatal malaria.

As per the World Health Organization (WHO), artemisinin-based compounds (artemether, artesunate, arteether, etc) are the first-line treatment of severe malaria in infants and young children, because they are superior to chloroquine in terms of schizonticidal activity, prevention of drug resistance, and early reduction of malarial transmission. However, there are no specific guidelines available for the treatment of severe malaria among neonates. We preferred parenteral artesunate over chloroquine and oral artesunate considering the sickness level of the preterm neonate, the inherent risks associated with exchange transfusion, and the recent reports of chloroquine resistance among *P. vivax* in India and the surrounding region. The use of artesunate in our case was consistent with the WHO policy to promote artemisinin-based combination therapy to treat malaria. No data are available about the safe dose of artesunate in neonates; the doses of parenteral artesunate and clindamycin used in our case were according to the most recent WHO malaria treatment guidelines. Radical treatment was not considered because this case involved transfusion-associated malaria.

Artesunate is soluble in water but has poor stability in aqueous solutions at neutral or acidic pH. A separate ampoule of 5% sodium bicarbonate solution, therefore, is provided with 60 mg anhydrous artesunic acid ampoule for intravenous injection. Plasma clearance of artesunate is rapid, with a mean half-life of 1 to 5 minutes, whereas that of dihydroartemisinin, its active metabolite, is 45 minutes to 1 hour. Artesunate has diuretic and natriuretic effects on kidneys, and it may also increase endogenous nitric oxide production. No drug interactions are known. Potentially serious adverse effects include type-1 hypersensitivity reactions in ∼1 in 3000 patients, and dose-dependent neutropenia documented in adults and HIV-infected children. The preterm infant in our case had no alterations in serum electrolyte levels and neutrophil counts during therapy (Table 1).

We simultaneously treated the infant with parenteral antibiotics. Routine use of antibiotics in severe malaria is debatable, albeit recent reports suggesting frequent Gram-negative bacterial coinfection in malaria. Severe *P. falciparum* malaria coexisting with bacteremia may increase the case fatality substantially. Although no similar data exist in *P. vivax* malaria, it is known that, among neonates, clinical syndromes of sepsis and severe malaria often overlap. We restarted antibiotics in the present case considering this possibility.

Currently, there is a paucity of pharmacokinetic data for antimalarial drugs formulated specifically for use in neonates. Also, there have been no studies looking specifically at the safety of these drugs in the neonatal period. Additional studies focusing on dose optimization and pharmacokinetics of antimalarial drugs, including artesunate-based compounds in neonates and young infants, are warranted.

Our case report also intends to bring to the fore the unresolved issue concerning the donor screening for malaria. Current tests used to screen the donor blood, including polymerase chain reaction-based techniques, are unreliable when there is low parasitemia in the donor. Because of the lack of unequivocal guidelines for donor screening, TTM remains a significant problem in endemic areas. At our blood bank, we routinely screen donors by using Giemsa-stained blood smears and immunochromatographic methods detecting antigens histidine-rich protein- *P. falciparum* and parasite lactate dehydrogenase- *P. vivax*. Structure of surveillance programs for monitoring transfusion-transmissible infections in industrialized countries varies considerably. In the United States, prevention of TTM rests on the exclusion of potentially infected donors.
based on the donor interview; whereas, in Europe, immunologic tests are used for screening. Stringent donor screening strategies, paradoxically, may result in unnecessary high discarding of collected blood units in industrialized countries. Currently, no donor test for malaria screening has been recommended by the Food and Drug Administration. Special leukoreduction filters designed to purify malaria-infected blood are being evaluated.22

CONCLUSIONS
Malaria is one unusual infection in neonates acquired through blood products. It must be considered as an important differential diagnosis for suspected sepsis after exchange transfusion. No standardized management protocols are currently available. We found intravenous artesunate effective and safe in a preterm neonate with severe P. vivax malaria. Comparative studies are needed to examine whether enteral artesunate can be recommended over exchange transfusion in severe malaria, and in cases of uncomplicated malaria in sick preterm neonates.

REFERENCES
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